What's New in Neuroimaging Methods?

Peter A. Bandettini

National Institute of Mental Health, Bethesda, Maryland

The rapid advancement of neuroimaging methodology and its growing availability has transformed neuroscience research. The answers to many questions that we ask about how the brain is organized depend on the quality of data that we are able to obtain about the locations, dynamics, fluctuations, magnitudes, and types of brain activity and structural changes. In this review an attempt is made to take a snapshot of the cutting edge of a small component of the very rapidly evolving field of neuroimaging. For each area covered, a brief context is provided along with a summary of a few of the current developments and issues. Then, several outstanding papers, published in the past year or so, are described, providing an example of the directions in which each area is progressing. The areas covered include functional magnetic resonance imaging (fMRI), voxel-based morphometry (VBM), diffusion tensor imaging (DTI), electroencephalography (EEG), magnetoencephalography (MEG), optical imaging, and positron emission tomography (PET). More detail is included on fMRI; its subsections include fMRI interpretation, new fMRI contrasts, MRI technology, MRI paradigms and processing, and endogenous oscillations in fMRI.

Key words: **functional MRI (fMRI); voxel-based morphometry (VBM); diffusion tensor imaging (DTI); diffusion spectrum imaging (DSI); magnetoencephalography (MEG); electroencephalography (EEG); optical imaging; diffuse optical tomography (DOT); endogenous oscillations; default network; resting state fluctuations; fMRI decoding; multivariate analysis; positron emission tomography (PET); region of interest (ROI)**

Introduction

Many of the questions that we ask about human brain structure and function are dependent on the sophistication of the neuroimaging technology that we use. Neuroimaging has grown into an essential tool for the neuroscientist seeking to understand the brain on the spatial scale ranging from neurons to systems, and on a temporal scale ranging from milliseconds to decades. Recent years have seen rapid growth of neuroimaging methodology and, subsequently, insights into brain organization as well as burgeoning clinical applications. Improvements in technology, methodology, and interpretation continue to arise at an increasing rate. Correspondingly, the general level of sophistication with which neuroimaging tools are used by the wider community is continually being elevated. As thousands of papers per year are published in neuroimaging, it is impossible to keep up with the developments in any area other than one's own subspecialty.

The focus of this review is neuroimaging methods as they have advanced in approximately the past year. Descriptions of these developments are framed by discussions of historical context, specific ongoing issues, and general trends over longer time spans. A breakdown of the number of scientific abstracts submitted to the Organization for Human Brain Mapping (OHBM) meeting in 2007 across research themes shows that neuroimaging methods account for at least one third of the total presentations at OHBM.

Address for correspondence: Peter A. Bandettini, Ph.D., Section on Functional Imaging Methods & Functional MRI Core Facility, National Institute of Mental Health, Building 10, Rm 1D80, 10 Center Dr., Bethesda, Maryland 20894. Voice: +301-402-1333; fax: +301-402-1370. bandettini@nih.gov

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The author's own subspecialty, functional MRI (fMRI), is the most thoroughly described, but the areas of diffusion tensor imaging (DTI), voxel-based morphometry (VBM), magnetoencephalography (MEG), electroencephalography (EEG), and optical imaging are also touched upon. Many other areas of neuroimaging methods are unfortunately completely ignored in this review. The goal of this review article is not to comprehensively cover all advancements in all aspects of neuroimaging methods in the past year, but highlight some of the ongoing themes and corresponding recent work in each of the areas that are described.

Functional MRI

Now in its seventeenth year, fMRI has become the tool of choice for the cognitive neuroscience community. It is essential to those interested in understanding the functional correlates of behavior and disease in populations and, in a growing degree, individuals. Functional MRI has grown largely because of its noninvasiveness, relative ease of implementation, high spatial and temporal resolution, and importantly, signal fidelity. The fMRI signal is robust and for the most part highly reproducible and consistent. Another development that further enabled the rapid spread of fMRI was the introduction in 1996 of echo planar imaging (EPI) as a standard capability on clinical scanners sold by most vendors.

Advancements in fMRI have been defined by higher resolution both in time and space, better understanding of the signal, more robust or sensitive processing methods, new applications, and new neuroscience or clinical findings with fMRI. What fMRI can do in terms of probing brain organization is growing rapidly and in some unanticipated directions. New insights into the limitations of fMRI—or rather, what fMRI cannot do—have been just as important as advances in what fMRI can do. A deepening collective understanding is shared that while fMRI can very effectively answer questions about what brain areas—at a specific spatial scale—are active in association with specific tasks, it cannot as effectively be used to address questions of mechanisms of cognition or provide insights into deep principles of how the brain is organized. It is able, perhaps, to tell us what decisions a person is going to make or what object one is looking at or even how one feels. It can also provide information regarding where in the brain processing related to (but not necessarily essential to) a specific processing task occurs. It might be able to provide sensitive probes, complementary to other clinical techniques on an array of diseases and perhaps provide useful information for predicting future illnesses, including psychological disorders or dementia.

Over the past year or so several exciting advancements have come out—thus continuing to push the horizon of what fMRI can and might do. In addition, the emergence of a "standard practice" in fMRI for performing and reporting studies emerged (Poldrack et al. 2008). Specific cutting-edge findings include insights into the mechanisms of blood oxygenation level-dependent (BOLD) contrast, new hypotheses about hemodynamic contrast, new fMRI contrast mechanisms, higher resolution and increased sensitivity, and new paradigms and methods for analyzing and generating data. All of these have led to surprising new applications and findings. Below, these advancements are discussed in detail.

Functional MRI Interpretation

Over the years, fMRI has been defined by a certain ambiguity about the origins of the functional signal. It is based in hemodynamics and therefore is only an indirect measure of brain activation. Even though it is extremely robust and consistent, it requires that many assumptions be made if more in-depth interpretation of its signal is desired. The field has benefitted from efforts to better understand not only the neuronal correlates of fMRI but the sources of fMRI signal variability. In the past year these

efforts have continued—as indicated by a large number of new fMRI contrast mechanism papers as well as some excellent review articles.

To begin, a recently published opinion piece by Greg Miller in *Science* (Miller 2008) and a review article by Nikos Logothetis in *Nature* (Logothetis 2008) do an excellent job in laying out some limits and misuses of fMRI while also discussing its potential. At the heart of a long-recognized problem with some fMRI studies is the issue of data interpretation. Data interpretation can be confounded on several levels. First, the fMRI signal is based on the complex interaction of neuronal activity, neuronal metabolism, blood flow, and blood volume on a spatial scale that lumps together hundreds of thousands of neurons in each MRI voxel. These factors may vary not only across subject populations, individuals, and regions in the brain but also across voxels and even within voxels. This hemodynamic variability poses a severe limit on how fMRI can be used. This limit prevents an investigator from suggesting that one part of the brain shows "more" activity for one region over another simply because the fMRI signal is greater for that region relative to the other. This interpretation limit applies to individual brains when comparing region to region and between individuals or group-averaged brains when the magnitudes of activation in specific regions are compared across subjects or groups. Among other things this signal intensity is highly weighted by the blood volume in each voxel (Bandettini & Wong 1997). Logothetis goes further in his review to suggest that the limits in our knowledge of precisely what neuronal activity (excitation, inhibition, sub threshold activity, top-down, or bottom-up modulation) is manifest by the hemodynamic response limits, the depth of which we can draw inferences even from parametrically modulated signal within a region. While most researchers have known these caveats all along, this particular one is a potentially significant confound in the interpretation of the many parametric studies that have been performed over the years.

Because of the variability of the timing of hemodynamics, we also have well understood time limits (on the order of seconds) on the inferences of the relative timing of brain activity between regions. Without a clear understanding of the non-neuronal sources of this spread in latency, inferences about causality based on relative timing (below 2-second differences) are inherently weak and likely to be so weighted by the underlying vasculature-influenced timing that they are simply meaningless. Processing techniques such as Granger Causality, used to infer not only connectivity but causality based on relative timing, should be only used with a great deal of caution—keeping in mind that hemodynamic delays (and not neuronal delays) from voxel to voxel dominate the timing differences from region to region. A growing area in fMRI method development is that of hemodynamic calibration—to measure and subsequently account for the hemodynamic variability over space (Ances et al. 2008, Chiarelli et al. 2007, Hoge et al. 1999a, Kida et al. 2007, Thomason et al. 2007). Nevertheless, the problem of parsing excitatory and inhibitory brain activity, for example, remains unable to be "calibrated" with fMRI.

Another perhaps more common problematic level of interpretation in fMRI is not that of inferring the level, degree, or timing of BOLD signal change but that of drawing unsubstantiated inferences about mental states or conditions from assessment of brain activation maps. Functional MRI is not immune to the problem of researchers creating the "just so" story that can explain any pattern of activation shown in the data. (i.e., If the amygdala is active, the subject must be feeling fearful.) The best fMRI studies are those with testable hypotheses, tightly controlled paradigms, appropriate calibrations, and careful inferences. It is typically correct to say "this area is associated with processing visual stimuli." It is much more risky (but not necessarily impossible) to say "Because there is more activation in this area for task A than task B, then this subject recognizes the object in task A."

Regarding fMRI interpretation, a surprising amount of progress has been made in past year. Several papers are worth mentioning. First, an exciting study by Schummers et al. (2008) describes in detail the spatial and temporal behavior of astrocyte activation relative to neuronal activation, and convincingly demonstrates that it is astrocytes that signal blood flow to increase with this activation. Interestingly, this work shows that the spatial tuning of visual cortex astrocytes to orientation column stimulation is sharper than that of neurons. In addition, the activation timing of astrocytes is delayed about 4 sec from that of neurons. To show astrocyte influence on hemodynamics astrocyte activation was selectively modulated using isoflurane, which has less of an effect on neurons. When astrocyte activity was suppressed, the measured hemodynamic response to stimulation was also shown to be suppressed. These findings certainly shed light on the mechanism of fMRI contrast mechanisms and will cause us to refine our models of neurovascular coupling.

As is well known, considerable controversy continues as to the physiologic origin of several specific aspects of BOLD contrast, including BOLD nonlinearity, preundershoot, postundershoot, and fluctuations. Many papers published this year have provided provocative data perhaps shedding light on several of these unknowns. In particular, Devor et al. (2007) provides a unique angle on decreased BOLD signal. Devor and colleagues show, in a rat model that, when the animals were given somatosensory stimulation, a concentric pattern of neuronal depolarization (and corresponding increase in oxygenation) surrounded by hyperpolarization (and corresponding decrease in oxygenation) was created. The most intriguing part of this study was that, in the areas of hyperpolarization (and deoxygenation), which was up to 3 mm away from the central depolarization, there was a clear vasoconstriction. This appears to imply that inhibitory synaptic activity, rather than a decrease in firing rate, drives vasoconstriction. These data appear to contradict the current understanding, supported by a study by Shmuel et al. (2002) that shows a clear decrease in spiking that spatially corresponds to a decrease in BOLD signal. If this turns out to be a general finding, this may not only explain negative signal changes (inhibitory synaptic activity in distinct locations in space) but perhaps also the poststimulus undershoot (inhibitory synaptic activity at distinct times following activation). This group also published an intriguing hemodynamic model called the vascular anatomical network model (VAN) (Boas et al. 2008) that goes beyond the balloon model (Buxton et al. 2004) in that it is based on physically measurable parameters and models effects both in time and over space. It has been able to accurately predict, based on low level input parameters, blood pressure in vascular compartments, and dynamics of blood pressure and hemoglobin saturation.

Regardless of these pieces of interesting data and insightful modeling, controversy still reigns. One clear-cut example, touched on above, is that of the poststimulus undershoot. As is well understood, BOLD signal increases with an increase in blood oxygenation or decrease in blood volume. Three popular hypotheses for the postundershoot exist: The first is that there is a perseveration of increased blood volume, after blood flow and oxygenation have returned to baseline. The second is that there is a perseveration of oxidative metabolic rate after blood flow and volume have returned to baseline, thus reducing blood oxygenation. The third is that there is a poststimulus decrease in flow, causing blood oxygenation to decrease since the time for oxygen to be delivered to active tissue increases, thus enhancing delivery. The work by Devor et al. (2007), mentioned above, may suggest the latter explanation. Other groups have experimental evidence for a blood volume perseveration (Silva et al. 2007), while yet another set of researchers has experimental evidence for oxidative metabolic rate perseveration (Lu et al. 2004) or just against blood volume perseveration (Frahm et al. 2008). There exist different assumptions, experimental conditions, and spatial scales with all of these studies.

As with most fMRI contrast mechanism work, the explanation for an effect, when discovered, is always more complicated than we expect it to be. To most people outside of the subspecialty of fMRI contrast mechanism studies, this seems like a somewhat esoteric discussion since the poststimulus undershoot is typically not even used as a source of contrast. Understanding it fully is nevertheless extremely important as this understanding may lend insight into other aspects of BOLD contrast and potentially lead to an enhanced capability of using BOLD contrast to understand neuronal activity.

We turn to negative signal changes, noting that a common network showing negative signal changes in response to a wide range of cognitive tasks has been termed *the default mode network* (McKiernan et al. 2002; Raichle et al. 2001). An ongoing debate continues with regard to precisely what these negative signal changes imply and what the functional role of this network is. One recent study combined spectroscopy and fMRI to further probe these areas (Northoff et al. 2007). Specifically, relative concentrations of GABA (an inhibitory neurotransmitter) were measured in the anterior cingulate cortex (ACC)—one node of this negative signal change network—during a task that caused a decrease in signal there. The findings demonstrated that a clear negative relationship exists between GABA concentrations and the magnitude of BOLD signal decrease in the ACC. Both the previous study and this seem to be aspects of a similar evolving story—that inhibitory activity apparently leads to negative signal changes in the area showing the inhibitory activity. Another study combined EEG and fMRI data to probe the default mode (Scheeringa et al. 2008). When EEG power at theta frequencies (2 to 9 Hz) was used (a regressor for resting state fMRI signal), only negative correlations were found, which spatially corresponded to the default mode network. The conclusion of this study is that increased frontal theta activity can be seen as an indicator of default mode network activity. There is more on theta activity in the MEG/EEG section of this review.

Functional MRI contrast continues to be compared with that of other modalities, with occasionally curious and surprising results. Spatial location, timing, and magnitude have been studied as they relate to EEG, MEG, optical imaging, and electrophsyiologic measures. Generally, these have been confirmatory studies, showing a general agreement in space, magnitude, and timing between modalities. A recent eye-opening report is not quite so confirmatory. In their study, Muthukumaraswamy and Singh compared fMRI and MEG gamma frequency (40 to 60 Hz) responses to a visual stimulus which was varied in spatial frequency and temporal frequency (Muthukumaraswamy & Singh 2008). While the spatial overlap between brain activation measured with the two modalities was substantial, the parametric dependence of the signals varied between the two. This is shown in Fig. 1. For fMRI, nearly identical temporal frequency dependence curves were generated for both spatial frequencies. With MEG, high spatial frequency showed much higher power across temporal frequency than low spatial frequency. In addition, both temporal frequency dependence curves were generally flatter for MEG than for fMRI. These results strongly suggest that the two measures are tuned to different aspects of neuronal activity.

Taking the investigation of temporal frequency dependence further with high resolution BOLD contrast, Sun et al. demonstrated in a recent study (2007) a dramatic columnar organization in V1 of visual temporal frequency preference. This map is shown in Fig. 2. Thus, the story of frequency dependence is complicated by this fine-grained structure of temporal frequency responsiveness.

New Functional MRI Contrasts

As the imaging community comes to terms with the limits of fMRI, many are busy trying to develop an MRI-based functional contrast that

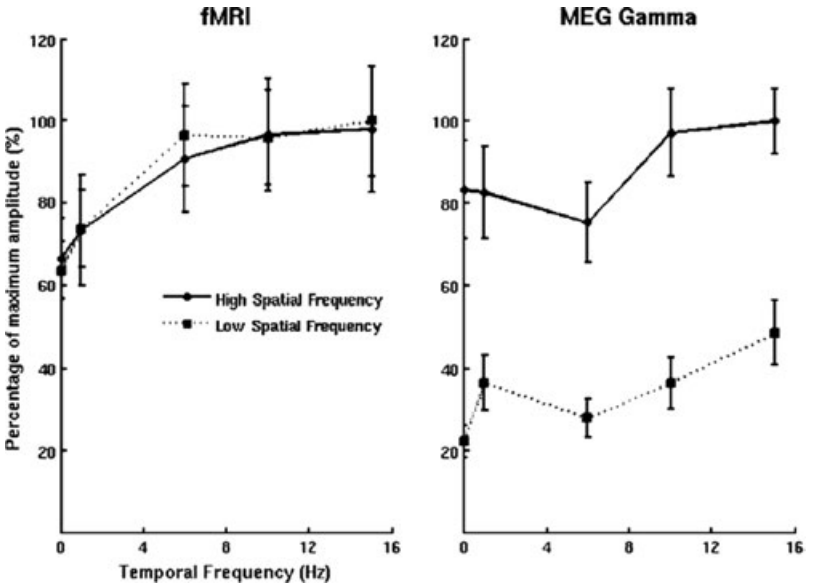

Figure 1. This shows the temporal frequency tuning curves for peak responses in fMRI and MEG gamma frequency (40–60 Hz) data in primary visual cortex, clearly indicating a difference between fMRI and MEG responses. No spatial frequency dependence is seen in fMRI, while with MEG, a strong spatial frequency dependence is demonstrated. In addition, with MEG the tuning curves show a more flat responsivity than do the fMRI curves. Obtained from Muthukumaraswamy & Singh 2008.

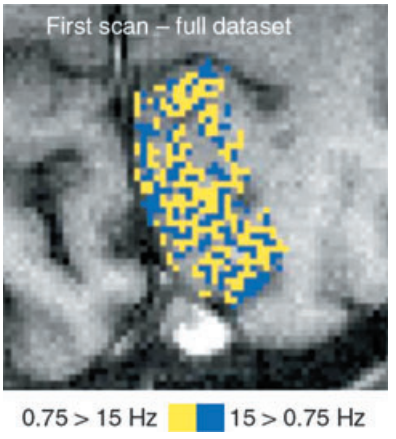

Figure 2. This is *not* an ocular dominance column map. It is an fMRI-derived temporal frequency domain map, showing the fine structure of areas in primary visual cortex that are either selective to high temporal frequency visual stimuli (blue – showing voxels where the response to 15 Hz was greater than to 0.75 Hz) or low temporal frequency visual stimuli (yellow – showing voxels where the response to 0.75 Hz was greater than to 15 Hz). This is the first demonstration of spatial organization of cortex based on temporal frequency. Obtained from Sun et al. 2007.

may somehow be a more direct, sensitive, quantitative measure of neuronal activity. Indeed, many other functional contrasts have been put forward as possible. These include the noninvasive measures of activation-induced changes in perfusion (Detre et al. 1992; Asllani et al. 2008, Rao et al. 2007), blood volume (Lu et al. 2003), diffusion (Le Bihan et al. 2006, Song et al. 2003), $CMRO_2$ (Davis et al. 1998, Hoge et al. 1999b), temperature (Yablonskiy et al. 2000), and presumably magnetic field changes in the vicinity of active neurons (Bandettini et al. 2005). These results have always been met with extreme interest by the imaging community but none have proven superior to BOLD—because the techniques are more technically challenging or, more often, the effect size produced using the specific contrast sensitivity is considerably less than BOLD contrast.

Perfusion imaging has, perhaps, come closest to BOLD in terms of utility and functional contrast. While it generally has less brain coverage, lower temporal resolution, and lower

functional contrast to noise than BOLD, it does have the advantages of higher specificity, baseline information, potentially quantitative information, and less baseline drift. The latter advantage is significant when probing very slow brain activation timing (Aguirre et al. 2002). Overall, the positive aspects of perfusion imaging have not succeeded in outweighing the serious practical disadvantages. Therefore, perfusion imaging remains a niche technique. One potential area of growth in perfusion imaging is that of calibrated fMRI in which the magnitude of activation-induced perfusion changes are compared with the magnitude of simultaneously obtained BOLD changes to obtain a unique and potentially quantitative measure of $CMRO_2$ changes (Ances et al. 2008).

Progress in an area may not always mean that a technique grows in utility or validity but rather that papers are published that increase our understanding of the results. In the past year some progress has been made with regard to two types of new MRI-based brain activation contrast: the measurement of decreases in diffusion coefficient with brain activation and direct measurement of neuronal activity as indicated by MR phase or magnitude changes.

Depending on the degree of sensitization to diffusion, brain activation causes either an increase or decrease in measured diffusion coefficient. If a very small diffusion weighting is used—sensitizing the signal to extremely rapid random motion of spins—specifically that of capillary flow, then, hypothetically, if brain activation causes an increase in flow, this diffusion coefficient will increase and will be manifest as a signal decrease (Song et al. 2002). If the diffusion weighting is much larger the sensitization is weighted toward changes in diffusion in very slow moving spins. Hypothetically, with brain activation, a small amount of cell swelling occurs, increasing the proportion of presumably slower diffusing intracellular spins. Therefore, with brain activation and when a large diffusion weighting is used, the measured diffusion coefficient will decrease, resulting in an increase in this highly diffusion-weighted signal (Le Bihan et al. 2006). It is hypothesized that this contrast is a more direct measure of neuronal activity. In recent years this technique has received a considerable amount of publicity but has been difficult to replicate. Last year, two papers were published which contradicted the hypothesis that the origins of this diffusion coefficient change were in tissue (Jin & Kim 2008; Miller et al. 2007). These papers suggested that the origin of these activation-related diffusion coefficient decreases was in the vasculature. Currently, the story is yet not fully resolved.

A second perhaps more popular potential functional contrast is that which allows detection of neuronal currents directly. Following a few results in phantoms (Bodurka & Bandettini 2002, Konn et al. 2003), preliminary (and nonreplicated) results in humans (Xiong et al. 2003), and some studies with cell cultures (Petridou et al. 2006) and in intact systems (Park et al. 2004)—all suggesting that direct detection of neuronal currents in humans might be possible, researchers in the field are taking a second, more in-depth look at what hypothetically they seek out and what the prospects realistically are for detection. The hypothesis for this effect is as follows: Neuronal activity produces a transient current, presumably in dendrite clusters, setting up transient, small in extent, and very subtle magnetic fields superimposed on the existing magnetic field. The precise timing, extent, and magnitude of these fields are a source of debate and study. These small field inhomogeneities contribute to NMR phase shifts or phase dispersion, depending on the geometry. For larger fields of a single orientation, a predominant phase shift occurs; if they are smaller and more random in orientation, phase dispersion occurs. Optimal contrast weighting for these has, so far, been long TE (TE = $T2^*$ of tissue) gradient echo, which, unfortunately, is also the optimal contrast weighting for BOLD contrast. One of the reasons why clear detection is so difficult is that any hint of BOLD contrast has to be clearly ruled out.

In the past year, several outstanding papers have contributed to this effort to image and understand neuronal current effects in MRI. These include some extremely detailed models of magnetic fields produced by neuronal activity (Cassara et al. 2008, Paley et al. 2008), very carefully executed but, unfortunately, producing negative findings (Tang et al. 2008), some highly innovative pulse sequences that may be more sensitive to periodic neuronal currents (Buracas et al. 2008), and some novel ideas regarding the potential to detect neuronal currents using extremely low magnetic field strength scanners (Cassara & Maraviglia 2008, Kraus et al. 2008). At extremely low fields (i.e., fields like that in which the Larmor frequency is, the same order of magnitude as the predominant brain frequencies, measured with MEG), the hypothesis is that brain activity at specific frequencies (i.e., 10 to 60 Hz) would enhance spin relaxation for spins precessing at a corresponding frequency. This is an intriguing hypothesis that is certainly worth exploring.

A unique paper, tangentially related to fMRI contrast mechanisms, published in 2008 is worth mentioning. Moore and Cao have put forth what they call the "hemo-neural" hypothesis stating that activation-induced hyperemia (increase in blood flow) has a neuromodulatory function (Moore & Cao, 2008). In other words, an increase in neuronal activity increases blood flow, which, in turn further increases the gain of local cortical circuits, perhaps influencing detection and discrimination of sensory stimuli. They propose the following mechanism for this effect: The delivery of blood-borne messengers, mechanical modulation, thermal modulation, or hemodynamic modulation of astrocytes exerts an influence on neuronal activity. Evidence for some of these mechanisms is provided in their study. In general, this highly novel paper is certainly worth taking a look at, as, in the context of creating models of neuronal activity, if hemodynamic changes upregulate neuronal excitability significantly then their effects need to be taken into account.

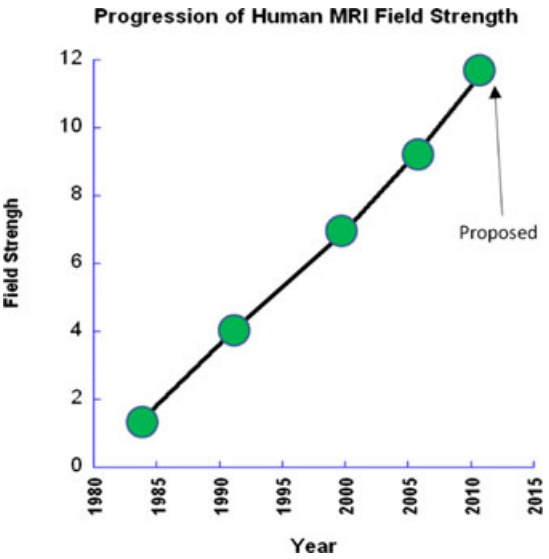

Figure 3. Plot of the highest current MRI field strength used for human imaging as it has increased over the years, showing a surprising linear trend.

MRI Technology

Just about every significant step in the advancement in fMRI applications has been made as a direct result of an advancement in MRI technology. MRI technology includes: magnetic field, RF coil configuration, and acquisition and/or image reconstruction strategies. Advancements in MRI technology include increases in field strength, increases in image signal-to-noise ratio, increases in resolution, and increases in imaging speed. In the past year several dramatic improvements in MRI technology have been published. These are discussed below.

A look at the field strength used for scanning humans over the years reveals a surprising linear trend, as shown in Fig. 3. A new MRI Center, NeuroSpin, has proposed developing a human 11.7 T scanner by the year 2012—thus maintaining the linear trend. In addition, at the time of this review article, there are over 28 human 7 T scanners in operation. A summary of the countries where the 7 T scanners exist is shown in Fig. 4. The push for higher field strength is driven not only by a direct proportionality of sensitivity to field strength, but by

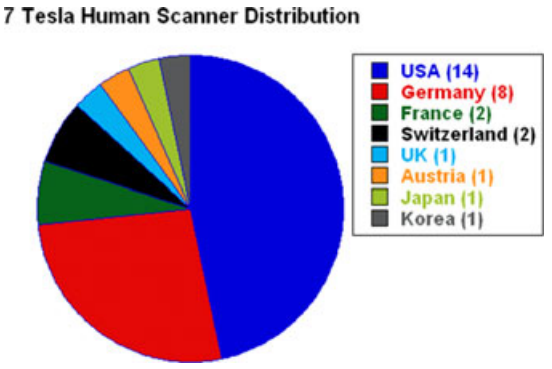

Figure 4. Pie chart showing the current distribution (as of the summer of 2008), by country, of 7 Tesla human scanners.(Data courtesy of Hellmut Merkle, NINDS)

two other, related factors: With this increased sensitivity comes the ability to collect high SNR functional and anatomical images faster and at higher resolution—allowing investigation of more subtle signal changes or anatomic features or allowing scanning of volunteers or patients in a faster time. Also, the images at 7 T are not simply higher signal-to-noise ratio or higher resolution, but qualitatively different in terms of anatomical contrast. Qualitatively new anatomic contrast is apparent in 7 T anatomical images. An example of the qualitative difference in contrast at 7 T is a study by Duyn et al. (2007), which demonstrates that MRI phase is a highly sensitive contrast at 7 T, revealing a 10x improvement in gray matter−white matter delineation over magnitude contrast at lower field strengths, as well as cortical layers, and perhaps even white matter tracts. The authors speculate that the phase shifts are mostly due to differences in susceptibility effects, but other hypotheses have been put forward (Zhong et al. 2008) suggesting that macromolecules play a role. Examples of detailed, high contrast images at 7 T are shown in Fig. 5.

Performance of fMRI at high field is technically extremely challenging. Challenges include magnetic field inhomogeneity, RF power deposition in some sequences, RF excitation inhomogeneity, acoustic noise, increased physiologic noise, and patient discomfort, among others. Nevertheless the benefits are beginning to manifest themselves in fMRI. A recent publication by Yacoub et al. (2008) has shown that activation of human orientation columns (about a third of the size of ocular dominance columns) can be imaged. These results are shown in Fig. 6. To achieve this, scanning was performed at 7 T on a Siemens/Varian console using a four-shot spin-echo sequence, resulting in an in-plane resolution of 0.5×0.5 mm^2. A novel finding from this study is that there is a bias toward processing orientations around the vertical direction. An important point also to be taken from this study is that at 7 T, the intravascular contribution is reduced such that spin echo sequences do not suffer from large vessel intravascular effects—as occurs at lower field strengths. This enables spin-echo sequences to have a smaller functional point spread function than gradient echo sequences (Shmuel et al. 2007; Yacoub et al. 2007), thus being critical for the imaging of orientation columns.

Other technological innovations have been in the direction of faster image acquisition. Currently, almost all functional MRI data involves the collection of a stack of 2D images, which takes about 2 sec. With higher bandwidth receivers, parallel RF coil arrays, stronger gradients, and novel image reconstruction strategies, the goal of obtaining a relatively high resolution volume of data in a single excitation or with a single acquisition is drawing closer. In the past year, two papers have described novel echo volume imaging (EVI) techniques. The first paper, by Lindquist et al. (2008), describes a method by which a central cubic portion of 3D raw data space is sampled in 100 ms, leading to a volume of low resolution ($25 \times 25 \times 17$ matrix size to $46 \times 46 \times 17$ matrix size) but rapidly obtained data. This approach was then used to study transient dynamics of the hemodynamic response. First, the preundershoot, presumably associated with a rapid increase in oxidative metabolic rate before an increase in flow, was observed. Second, in a task that involved motor cortex activation cued by a visual stimulus, a difference in onset time of the preundershoot was observed. The second paper, by

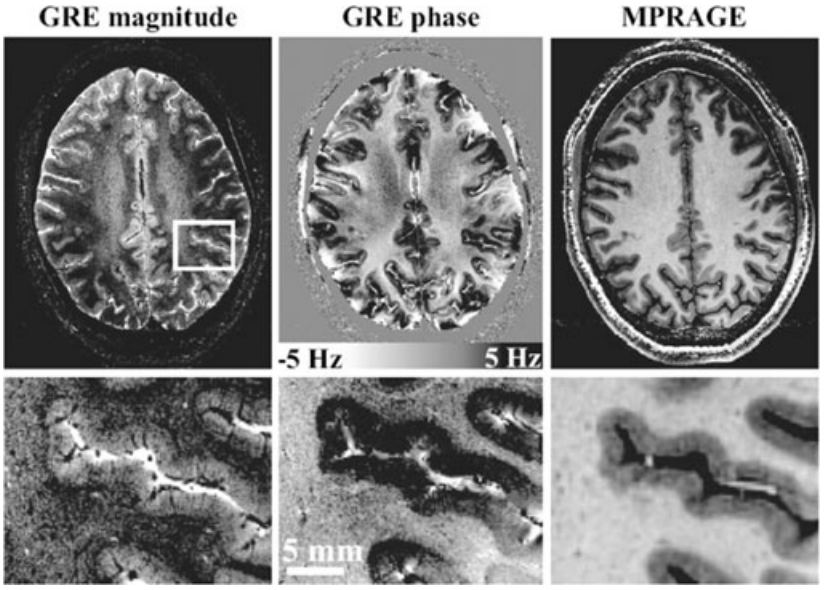

Figure 5. This is an illustration of the image quality of magnitude and phase images obtained at 7 T. The GRE data, left and center, had a resolution of 240 × 240 um with a scan duration of 6.5 min, whereas the MP-RAGE data on the right had a resolution of 480 × 480 um and a scan time of 20 min. The scale bar shows the frequency shifts corresponding to the phase changes. Obtained from Duyn et al. 2007.

Rabrait et al. (2008), demonstrates how parallel acquisition, outer volume suppression, and SENSE reconstruction can be combined to obtain a 20 × 20 × 24 matrix size with a 120 × 120 × 144 mm^3 FOV to create isotropic 6-mm voxel sizes. It is important to note that, in typical fMRI studies with voxel sizes of about 3 mm^3, spatial smoothing, normalization, and multisubject averaging reduces the effective resolution to about this. In fact it is more optimal to acquire images initially at this lower resolution than it is to acquire them at either a higher resolution (and lower SNR) or to be acquired at higher resolution and spatially smoothed. It appears that in the near future, EVI will be a new standard in image acquisition for those researchers performing multisubject averaging or are interested in studying subtle dynamics of the response across the brain.

Lastly, Lin et al. (2008) and Hennig et al. (2007) have taken parallel acquisition to a new level in minimizing the need for time-consuming spatial encoding gradients. Lin and colleagues, using a 32-channel parallel array with the coil configuration resembling EEG or MEG sensor geometries, apply similar source localization algorithms to reconstruct these images. They have named this approach "magnetic resonance inverse imaging" (InI). Hennig et al. have reduced the need for spatial encoding gradients even further with their one-voxel-one-coil (OVOC) imaging method. While the obvious advantage of these methods is the extreme rapidity with which useful volumes are obtained, another advantage is the presumably silent acquisition. This avenue of technology development appears to be just beginning. It is easy to imagine improvement in coil configurations optimized for specific brain areas or more efficient sampling schemes. Higher bandwidth acquisition rates will also lead to further improvements in resolution. Perhaps in the next several years, relatively silent, whole-brain fMRI will be the standard.

fMRI Paradigms and Processing

The powerful approach of analyzing fMRI that involves extraction of subtle voxel-wise

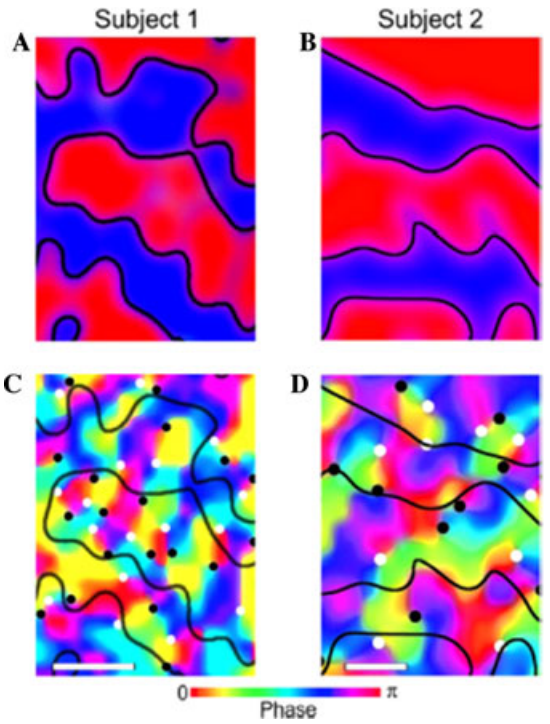

Figure 6. This shows ocular dominance columns for two subjects in panels **A** and **B**. Red and blue represent voxels that showed preference to right and left eye stimulation, respectively. Maps shown in panels **C** and **D** show maps in the same cortical areas of orientation preference. The black and white circles on the orientation preference maps show where multiple preferences converge. These form "pinwheel center." White circles indicate clockwise pinwheels and black circles indicate counterclockwise pinwheels. The white bars at the base of the images are 0.5 mm in length. Obtained from Yacoub et al. 2008.

activation patterns rather than mapping blobs of activation has, in the past few years, seen a tremendous surge of interest due to some of the dramatic results that it has produced (Carlson et al. 2003, Cox & Savoy 2003, Davatzikos et al. 2005, Eger et al. 2008, Hanson et al. 2004, Haxby et al. 2001, Haynes & Rees 2005a,b, 2006, Haynes et al. 2007, Kamitani & Tong 2005, Kriegeskorte & Bandettini 2007a,b, Kriegeskorte et al. 2007, Kriegeskorte et al. 2006, LaConte et al. 2005, Mitchell et al. 2004, Mourao-Miranda et al. 2005, O'Toole et al. 2005, Pessoa & Padmala 2005, 2007, Shinkareva et al. 2008, Strother et al. 2002; Friston et al. 2008). This new class of techniques is generally known as multivariate pattern recognition, classification, or decoding (i.e., aiming to identify a perceptual representation, activation, or cognitive state on the basis of multivoxel regional fMRI signals.) When a perceptual representation can be decoded from the activity pattern, the brain region studied contains information about the stimulus. In general, such "information-based" analysis requires multivariate techniques, but not necessarily decoding. In many instances "decoding" has been performed using univariate techniques.

Multivariate techniques in neuroimaging were introduced over a decade ago (Worsley et al. 1997), but the current interest in the information-based approach is derived from the idea that brain activation patterns reveal information carried by a neuronal population code at the scale of imaging voxels. This idea motivates multivariate analysis in single subjects without smoothing of the data. An information-based analysis determines whether there is a statistical dependency (i.e., mutual information) between the experimental conditions and the regional spatiotemporal activity patterns. Information undetected by activation-based mapping is often present in neuroimaging data. If the information resides in the fine-scale pattern of the activity, the spatial average may be similar between conditions, so no effect may be found by conventional methods with the data spatially averaged for region of interest (ROI) analysis or smoothed for statistical mapping. Information-based analysis can be applied to predefined ROIs. Alternatively, a continuous information-based mapping can be performed with a multivariate searchlight in order to discover regions carrying a particular type of information (Kriegeskorte et al. 2006).

It should be emphasized that this approach to neuroimaging, while, on the surface, appears to approach the brain as a black box from which to extract information about what the subject is doing, can be used as a highly sensitive probe to understand which aspects of

a response are most informative, and therefore most relevant to behavior. In addition, as researchers begin to explore and understand precisely why certain classification algorithms work better in the context of extracting information from messy biological systems, perhaps this information will also be useful in lending insight into brain function that could not be probed any other way. Ultimately, the technique may, at the moment, appear to be a flashy way of doing tricks with fMRI, but in fact, this approach has tremendous potential to pose and answer extremely subtle questions about how the brain is organized.

In the past year, two outstanding studies have further pushed the limits of decoding mental content from brain activity. In previous decoding studies, the experiments have been divided between a training set in which the spatial pattern of brain activity was associated with an object (or object category), orientation, or position; and an experiment set in which the same stimuli used in the training set were used. The training and test set were the same or highly similar stimuli. The two studies described below extend fMRI decoding to allow the accurate identification of brain activation associated with completely novel stimuli or tasks.

An exciting paper by Kay et al. (2008) has demonstrated the ability for fMRI patterns to be used to identify completely novel images that the subject was viewing. A schematic diagram of the principle steps of this study is shown in Fig. 7. This study consisted of a training set in which subjects viewed 1750 natural images. From this training set a quantitative receptive field model for each voxel was created using Gabor wavelets, characterizing tuning dimensions in space, orientation, and spatial frequency. Subjects then viewed 120 completely novel images. The corresponding brain activity patterns were compared with the receptive field models obtained from the training set. Accuracy ranged from 72 to 92%. In addition, the decrease of accuracy was extremely small as the size of the test set increased, providing hope that, with the appropriate training set size

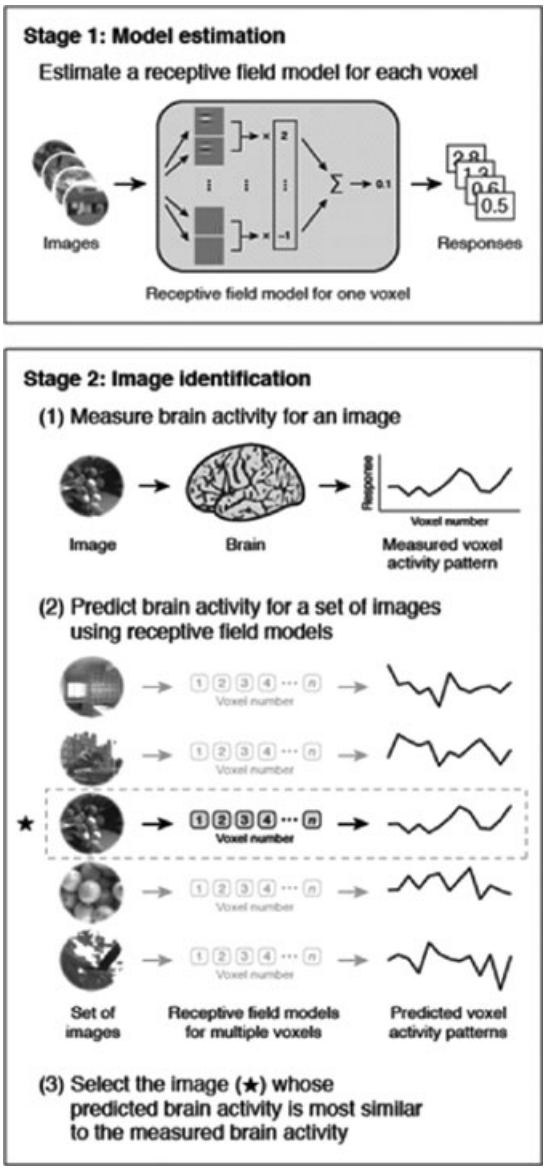

Figure 7. This is a schematic diagram showing the steps in the fMRI decoding experiment. In stage 1, fMRI data were recorded as subjects viewed a large collection of natural images. From these data receptive field models for each voxel were created, based on a Gabor wavelet pyramid. These describe tuning along the dimensions of space, orientation, and spatial frequency. In stage 2 fMRI data were recorded while each subject viewed a collection of novel natural images. For each brain map an attempt is made to identify the image that was seen using the receptive field models. Obtained from Kay et al. 2008.

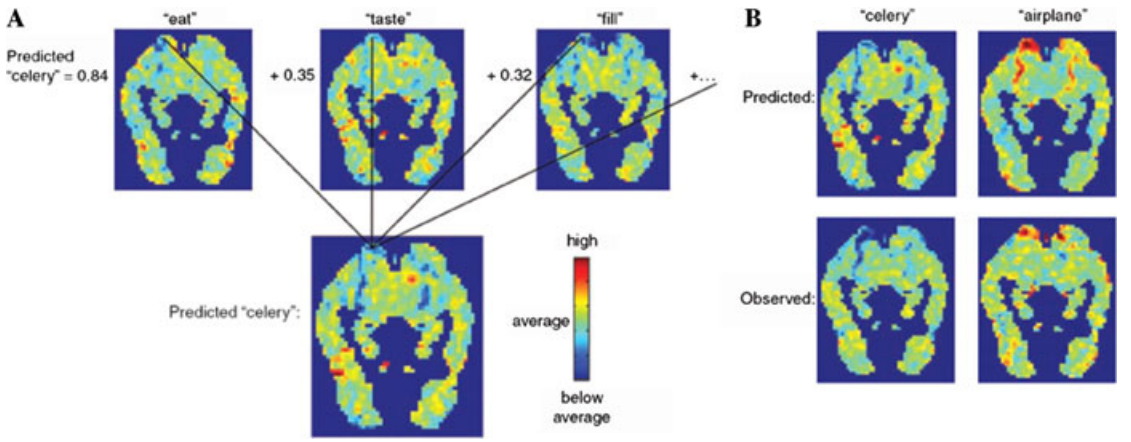

Figure 8. This figure shows the process by which predicted fMRI maps were created for specific stimulus words. The top three maps in **A** are learned spatial coefficients for 3 of the 25 semantic features related to "celery" ("eat," "taste," and "fill"). The co-occurrence in normal speech of each of these features is shown on the left of the images. These weighted images are summed to create the predicted image. In **B** are two examples ("celery" and "airplane") of predicted maps (top panels), showing a clear difference between the two, with observed maps (bottom panels) showing a relatively high level of similarity between predicted and observed. Obtained from Mitchell et al. 2008.

and tuning dimensions, activation for just about any object that exists may be characterized with a high level of accuracy.

In the second study, Mitchell et al. (2008) describe a method by which whole-brain patterns associated with statistical relationships between words representing abstract semantic concepts are determined and used to predict mental states not present in the training set. The essence of this method is shown in Fig. 8. These results establish a direct predictive relationship between the statistics of word occurrences in text and the activation patterns associated with processing word meanings. A new insight into how the brain processes concrete nouns is also put forth in this study. Essentially, the meaningful fMRI patterns for these nouns are distributed across the brain (i.e., also in prefrontal regions) rather than only existing in typical sensory motor regions.

Both of these studies represent an important paradigm shift in fMRI decoding—that of using a large training set focused on more elemental aspects of a brain state (i.e., from visual stimulus or word set) to predict the brain activation pattern associated with novel stimuli or brain states associated with processing novel semantic content. Not only do these studies pave the way for extensive applications of fMRI for "brain reading," but they also lend a unique insight into how the brain is processing information by being able to identify the "most informative" voxels and regions. Similar insights regarding the significance of tuning functions and whole-brain activation patterns would not likely have been uncovered using standard univariate mapping techniques. These studies represent the very beginning of an extremely powerful new approach to fMRI in reading brains and in understanding brain organization.

A related study by Williams et al. (2007) addresses a previously overlooked aspect of pattern information—that which regards which aspects of a specific pattern in the brain are actually used in the processing of a visual stimulus or word and which are nonessential epiphenomena. In their study, subjects were scanned while observing novel objects that belonged in one of three categories. They were asked to decide which category each viewed object fell into. The corresponding fMRI activation patterns in retinotopic and lateral occipital cortex (LOC) were shown to contain category information associated with objects, but only in

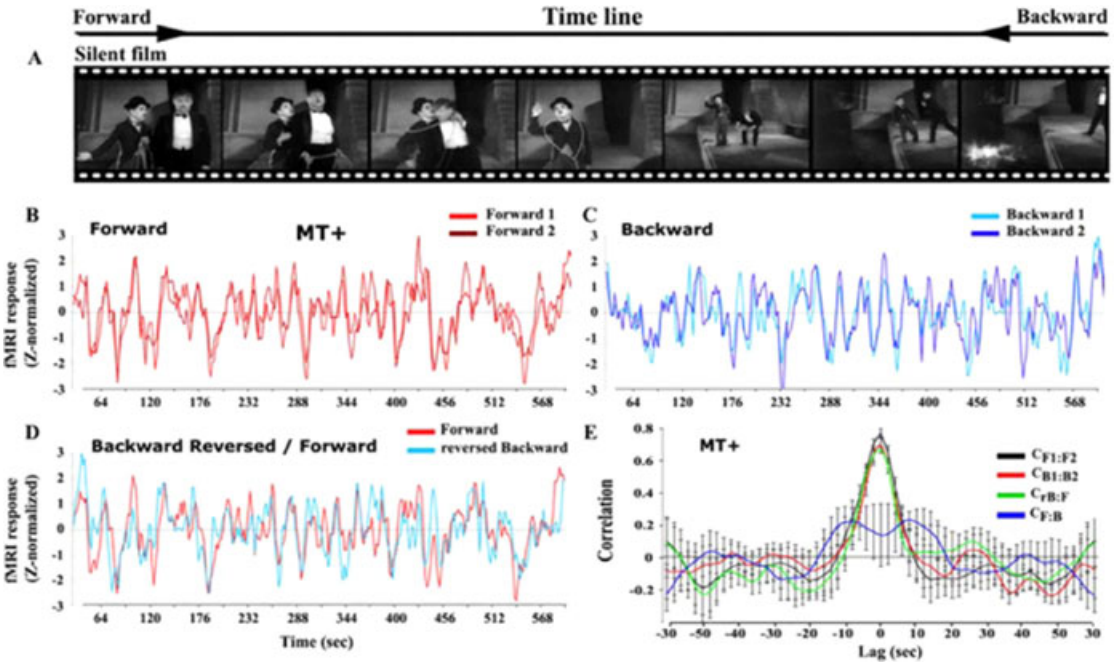

Figure 9. This shows a summary of their clever experiment testing which cortical areas are sensitive and insensitive to time reversals in movie sequences. Plots are from area MT+. (**A**) Representative frames from the silent films used. Average time courses for (**B**) two forward, and (**C**) two backward presentations. (**D**) Superimposed plots of a time-reversed version of the backwards movie time course and the forward time course (both time courses shifted appropriately to account for the hemodynamic delay). (**E**) Cross-correlations of various iterations of the two forward time courses with themselves (black), backward with themselves (red), reversed backward with forward (green), and backward with forward (in blue – as expected, showing minimal correlation) showing that, at least in MT+, temporal order is certainly not critical for activation. Obtained from Hasson et al. 2008.

the LOC were the patterns stronger for correct than for incorrect trials. Put another way, in trials in which the subjects did not correctly categorize the stimulus, the correct stimulus information was present in retinotopic cortex but not in LOC. This work represents an alternative direction in fMRI pattern effect imaging—that of determining pattern representations and then comparing with corresponding behavior to further classify cortical areas as they influence behavior.

Lastly, every so often a paper captures the attention of those in the field simply because of the cleverness and elegance of a paradigm. A recent study by Hasson et al. (2008) does just that. The study sets out to identify brain regions responsive to sensory information accumulated over different temporal windows. The paradigm simply involves viewing of a movie played either forward, backward, or in a scrambled manner. Low-level processing regions such as primary visual (V1) cortex and motion sensitive area (MT+) showed minimal dependence on the direction in which the movie was played, while higher regions such as the superior temporal sulcus (STS), precuneus, posterior lateral sulcus (LS), temporal parietal junction (TPJ), and frontal eye field (FEF) were highly affected by how the movie was played. In addition LS, TPJ, and FEF activation depended on information accumulated over time periods of about 36 sec, while STS and precuneus activation depended on information accumulated over about 12 sec. Using a simple, natural paradigm involving movie viewing, temporal processing scales were elegantly and effectively probed. The summary of this study is shown in Fig. 9.

Endogenous Oscillations in Functional MRI

One area of rapid development in fMRI is that of using endogenous or "resting state" fluctuations or oscillations to explore resting state networks. The basic observation is that when subjects are not performing any task in the scanner, the time series signal consists of fluctuations that are not simply thermal noise of the scanner. Components of these fluctuations include cardiac pulsations of blood and CSF (inflow effects), breathing oscillations (changes in B_o field from chest expansion), bulk motion, scanner instability, vasomotion, BOLD and flow fluctuations that occur with slow changes in end tidal CO_2 variations, and BOLD and flow fluctuations that occur with spontaneous neuronal activity. The last component is, of course, the most interesting to neuroscientists. The predominant frequency component of these "neuronally related" fluctuations is at or below 0.1 Hz.

Research related to this phenomenon has been directed toward determining three avenues: (1) how to most efficiently and robustly extract and map these correlated resting state fluctuations; (2) how to best interpret these fluctuations, as well as to best separate neuronal from physiologic fluctuations; and (3) how to best apply the phenomenon of resting state fluctuations toward neuroscience questions and understanding patient populations. Hundreds of papers have covered these topics in only the past 5 years. In the past year the trend of an explosive interest in endogenous oscillations continues. A recent special issue of the journal *Human Brain Mapping*, (Vol. 29, Issue 7, July 2008) was devoted completely to the publication of studies about endogenous oscillations. Several excellent review articles have also been written in the past year.

Regarding each of the three areas of endogenous oscillations research, the following are some notable advancements in the past year.

Endogenous Oscillation Processing

The current problem in resting state processing is as follows: Given about 60,000 voxels, and 60,000 × 300 = 18 million time points in a single 5-min volumetric fMRI scan, the task of determining the correlation of every voxel time series with every other voxel in the brain is computationally prohibitive. Two alternative solutions have been popular. The first is to choose "seed voxel" regions (Biswal et al. 1995; Greicius et al. 2003) and the second is to use relatively unsupervised model-free approaches such as independent component analysis (ICA) (Damoiseaux et al. 2006). Each of the methods has a limitation. In the seed voxel approach the results are highly dependent on the choice of ROI or voxel from which the "seed" reference time series is chosen from. Within this chosen time series, much of the energy in the signal driving the correlation may also be artifactual. In addition, many correlated areas are, of course, missed, depending on how many "seeds" are chosen. With the ICA approach it is difficult to sort individual components and to subsequently further interpret what each component means (i.e., Which frequency components are correlated? What is to be done about phase offsets over space?). As ICA methodology improves it appears that the problem of robustly extracting a stable set of networks for comparison and clinical use is being solved. Papers that discussed how to process resting state data last year include the following: (Calhoun et al. 2008, Cohen et al. 2008, Duff et al. 2008, Esposito et al. 2008, Salvador et al. 2008, van den Heuvel et al. 2008, Wink et al. 2008, Zhu et al. 2008).

Endogenous Oscillation Interpretation and Separation

A central issue is whether or not the extracted networks actually mean anything neuronal, and if they do contain neuronally relevant fluctuations, how are these separated robustly from data that contain non-neuronal fluctuations? In the past year, several excellent multimodal

studies were carried out to demonstrate the neuronal basis of fMRI-based endogenous oscillations (de Munck et al. 2008; Hamandi et al. 2008; Helmut Laufs 2008; Shmuel & Leopold 2008). In addition, several studies have recently addressed the issue of how physiologic processes such as breathing and cardiac function can influence fluctuations (Birn et al. 2008a,b; Shmueli et al. 2007). Other studies have shown functionally correlated endogenous oscillations in the generally "cleaner signal" perfusion data (Chuang et al. 2008). While identification of potentially confounding artifacts is relatively straightforward, a clear assessment in each subject of what regions show artifactual correlation and which do not is much more difficult. It is problematic to cleanly "regress out" respiration or other variations. Most would agree that there is sufficient evidence that spontaneous and correlated neuronal activity certainly does contribute to signal fluctuations. Work is ongoing, and will be ongoing for quite a few years, to minimize any false positives in the identification of these networks.

One other point that is not discussed as much as other aspects of endogenous oscillations is in regard to what the "purposes" or precise mechanisms of these neuronally mediated oscillations in flow and BOLD are. Are they only epiphenomena of regions being physically connected or functionally related, or do they serve a specific critical function involved in how an individual interacts with the world? In the past year four interesting studies have come out that speak to a functional role—or at least an effect on behavior—of endogenous oscillations.

The first study, carried out by Boly et al. (2007), starts with the observation that baseline signal magnitude in the brain spontaneously varies. They then demonstrate that a temporal variance in perception of identical stimuli is positively correlated with pretrial activity in medial thalamus and lateral frontoparietal network (thought to be associated with vigilance and external monitoring) and negatively correlated with posterior cingulate/precuneus and temporoparietal cortices, which are hypothesized to be related to introspection and, incidentally, the primary areas associated with what has been identified as the "default network." These results are summarized in Fig. 10.

The second study, by Fox et al. (2007), demonstrated not only that endogenous oscillations persist during tasks and that they contribute to a significant fraction of the trial to trial variance of the BOLD response in supplementary motor cortex with a simple finger tapping task, but, amazingly they also affect motor performance. The performance of the task itself (force of a button press) was affected by when the task is performed relative to the phase of the endogenous oscillation. It appears that when the oscillations are at the peak of their cycle at the beginning of activation-induced BOLD changes, the force of the finger tap force is lightest, and vice versa. . .when the trough is at the beginning of the BOLD-signal change, the finger tap force is greatest. About 74% of the behavioral (finger tapping force) variance is attributed to ongoing endogenous oscillations in supplementary motor cortex. These results are shown in Fig. 11.

The third study by Mason et al. (2007) suggests that the default network is most active during mind wandering. In a clever study, the researchers demonstrated a positive correlation between the percent signal change in specific nodes of the default network and the frequency of stimulus-independent thoughts (or mind wandering), suggesting a conscious introspection role of this network. They concluded with a few speculations: Stimulus-independent thoughts may maintain the brain in an optimal state of arousal, thus facilitating performance on mundane tasks. Stimulus-independent thoughts maintain a sense of coherence with one's past and future or may be epiphenomena of the brain's ability to manage multiple tasks.

Fourth, a comparison study of the resting state networks (default, oculomotor,

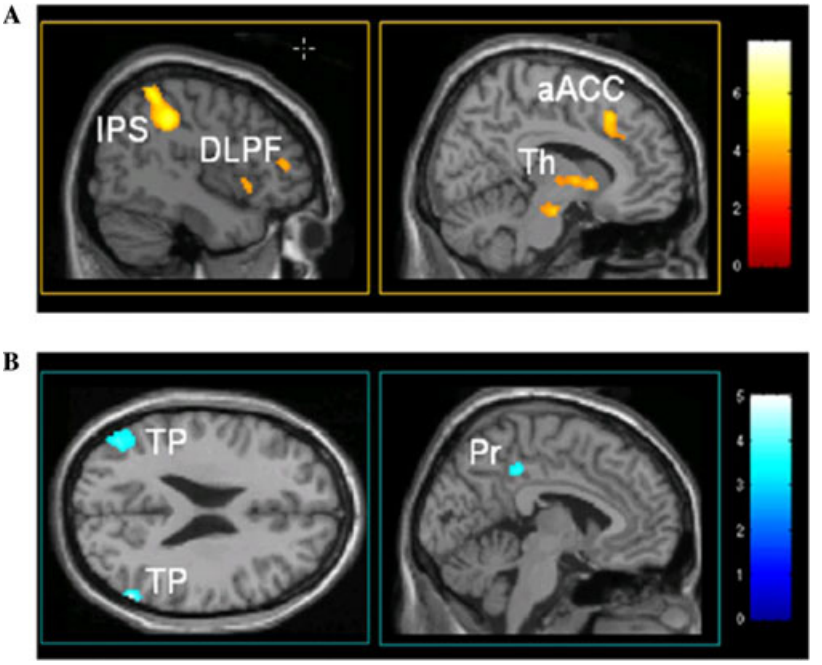

Figure 10. Maps of baseline activity predicting conscious perception of subsequent somatosensory stimuli. (**A**) Increased activity of the medial thalamus (Th), dorsolateral prefrontal cortex (DLPF), intraparietal sulcus/posterior parietal cortex (IPS), and anterior cingulate cortex (aACC) 3 sec before stimulus presentation predicts perception of low-intensity sensory stimuli. (**B**) Decreased baseline activity in the default brain network – posterior cingulate/precuneus (Pr), bilateral temporal/parietal junctions (TP) – exerts an enhancing effect on perception of subsequent somatosensory stimuli. Obtained from Boly et al. 2008.

somatomotor, and visual) in anesthetized monkeys was carried out by Vincent et al. (2007). Not only did they show that the same "default" network was activated in humans and monkey but provided anatomical connectivity and evoked response pattern support for the oculomotor network. This work strongly argues that the "default" network is not dependent on the level of consciousness, as suggested in the study by Mason, mentioned above, nor is it a uniquely human system.

All four of these studies provide intriguing evidence that endogenous oscillations influence how we perceive the world and interact with it. What to make of this information with regard to understanding the functional significance of endogenous oscillations remains to be fully worked out.

Applications of Neuronal Fluctuation Assessment

A surprisingly large number of applications of studies involving endogenous oscillations have been reported in a very short time. In the past year, these have included children and infant studies (Liu et al. 2008, Thomason et al. 2008), populations with multiple sclerosis (Lowe et al. 2008), intelligence (Song et al. 2008), acupuncture (Dhond et al. 2008), sleep (Horovitz et al. 2008), sedation (Greicius et al. 2008), seizure activity (Lui et al. 2008), Alzheimer's (Liu et al. 2008a), schizophrenia (Liu et al. 2008b; Zhou et al. 2008), chronic pain (Baliki et al. 2008), ADHD (Castellanos et al. 2008), depression (Greicius et al. 2007), and consciousness (Boly et al. 2008). For future clinical studies the paradigm that clinicians are

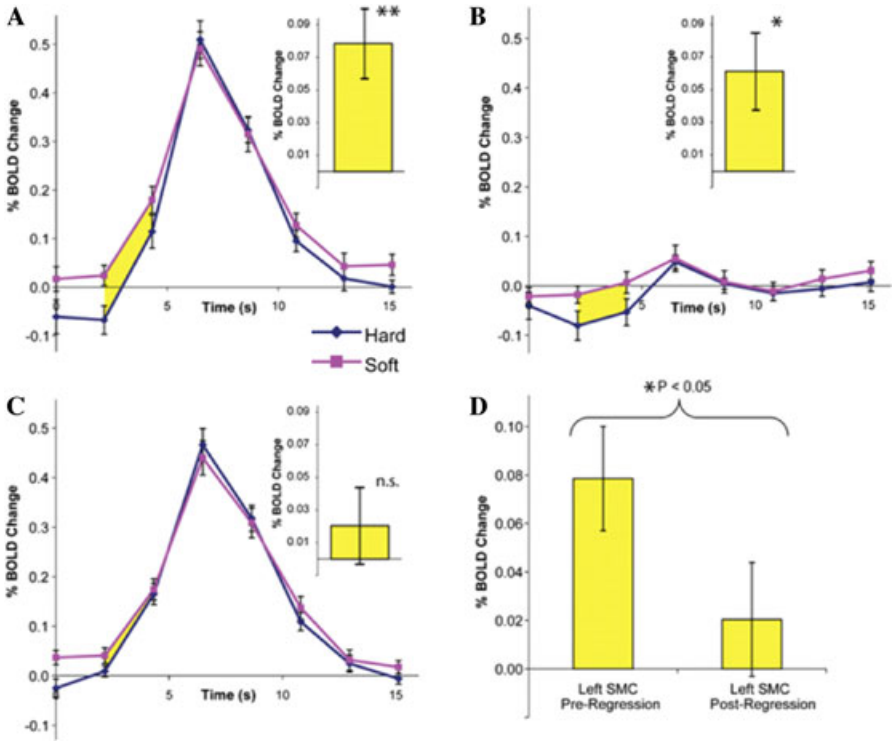

Figure 11. This is a demonstration that coherent spontaneous activity in the motor cortex influences the force with which subjects press a button. (**A**) Average left sensorimotor cortex BOLD time courses for the hard (blue) and soft (red) button presses. Yellow indicates significant differences between them. The same time courses for the right sensorimotor cortex also show a BOLD-behavior effect. (**C**) After spontaneous fluctuations were regressed out, the effect disappears. (**D**) Summary of the comparison of (**A** and **C**). Obtained from Fox et al. 2007.

looking to with hope is one in which fMRI signal changes that do not require a probe task but that are extremely sensitive to patient population and conscious state.

Gray and White Matter Imaging: VBM and DTI

Voxel-Based Morphometry

There is growing evidence that the brain structure changes on a temporal scale that is faster than previously thought—and, potentially, it changes due to a large number of influences. These influences include normal development, aging, drug abuse, psychiatric disorders, stressful or enriching environmental factors, learning, and chronic health problems. Evidence is growing that the brain may exhibit identifiable structural changes within weeks or months in correspondence with these influences. The current method for comparing changes in gray matter is with voxel-based morphometry. VBM is the comparison of local gray matter concentration between groups of subjects. Typically, high resolution MRI scans are compared after segmentation and spatial normalization. This technique started in the mid 1990s (Wright et al. 1995) and has since then increased tremendously in popularity, doubling in the number of publications every 2 years. The prevalent unknowns in VBM are the following: The relationship between gray matter concentration and MRI signal intensity is not clearly established. Secondly, the mechanism and timing by which gray matter concentration changes with learning, experience, or disease

has never been established. Some recent papers suggest that it happens quite rapidly (May et al. 2007). Two excellent review articles (Draganski & May 2008; Johansen-Berg 2007) discuss some possible mechanism of neuronal plasticity and very clearly lay out the problem, but don't provide any conclusive answers regarding the relationship between experience and neuronal rewiring, and then MRI-detectable changes in gray matter density. A third unknown is more related to practical aspects of the fidelity of VBM comparison data. Many variables cause highly nonlinear distortions in MR images making them extremely difficult to register. Any small registration error will lead to errors in VBM comparison data. The field appears to need a comprehensive assessment of the variability in VBM data. When a comparison is made where no changes would be expected, how frequently do changes show up? In general, across-group comparisons suffer considerably from extreme sensitivity to registration errors across groups. Registration errors are ubiquitous—therefore one might argue that all across-group VBM results are highly suspect. Within-group and longitudinal studies are potentially more stable.

In spite of these unknowns and problems, researchers have charged ahead with tremendous optimism and energy in the past 8 years. The field itself has received a considerable boost by the seminal work of Ashburner and Friston, laying out a clear set of methods for performing VBM (Ashburner & Friston 2000). A list of only a small fraction of the applications include: schizophrenia (Wright et al. 1995), aging (Good et al. 2001b), dementia (Mummery et al. 2000, Rosen, Gorno-Tempini et al. 2002), sex and handedness (Good et al. 2001a), headache (May, 2006), sleep apnea (Macey et al. 2002), cocaine abuse (Franklin et al. 2002), mild cognitive impairment (Chetelat et al. 2002), back pain (Apkarian et al. 2004), epilepsy (Woermann et al. 1999), post-traumatic stress disorder (Yamasue et al. 2003), inherited speech and language disorder (Watkins et al. 2002), Huntington's disease (Thieben et al. 2002), developmental stuttering (Sommer et al. 2002), Parkinson's disease (Burton et al. 2004), intelligence (Haier et al. 2004, Wilke et al. 2003), autism (Boddaert et al. 2004, Salmond et al. 2003), bipolar disorder (Lyoo et al. 2004, Wilke et al. 2004), borderline personality disorder (Rusch et al. 2003), chronic smoking (Brody et al. 2004), herpes (Gitelman et al. 2001), study of symphony orchestra musicians (Sluming et al. 2002), marijuana abuse (Matochik et al. 2005), aphasia (Rosen, Kramer et al. 2002), aphasia and apraxia (Josephs et al. 2006), ecstasy (MDMA) abusers (Cowan et al. 2003), multiple sclerosis (Pelletier et al. 2004), tinnitus (Muhlau et al. 2006), and panic disorder (Massana et al. 2003).

VBM is clearly exploding in terms of findings. A seemingly reasonable thing to do with regard to just about any difference in behavior, genetics, development, or experience is to compare the brain structure with a control group using high resolution MRI. While all of the comparisons are fascinating, some of the most attention-grabbing results in recent years have been functional as well as structural changes due to learning or with training (Draganski & May 2008, Kelly & Garavan 2005). A landmark study by Maguire et al. (2000) showing that the hippocampus of London taxi drivers, who perform memory-demanding navigation, was larger than those of controls, was among the first to suggest that MRI-measurable changes in the brain could occur with learning. Other studies followed. These include one by Draganski et al. (2004) demonstrating that those who learned how to juggle obtained a higher concentration of gray matter bilaterally in MT. This same group also investigated changes associated with learning abstract information rather than a skill (Draganski et al. 2006). Images were obtained at three different time points while medical students studied for their medical examination. During the learning period, the gray matter increased significantly in the posterior and lateral parietal cortex bilaterally and did not change significantly toward the third scan 3 months after the exam. The

posterior hippocampus showed a different pattern over time: The initial increase in gray matter during the learning period was even more pronounced toward the third time point.

Lastly, recently published was perhaps the first true longitudinal study in which the same group was imaged with MRI and fMRI both before and after subjects became proficient in mirror reading (Ilg et al. 2008). Mirror reading activated dorsolateral occipital cortex, medial occipital cortex, superior parietal cortex, medial and dorsolateral prefrontal cortex, as well as anterior insula and cerebellum. Daily practice of 15 min for 2 weeks was carried out. Practice-related decrease of activation at the right superior parietal cortex and increase of activation at the right dorsal occipital cortex was found. These results are shown in Fig. 12. The longitudinal VBM analysis showed an increase of gray matter in the right dorsolateral occipital cortex that corresponded to the peak of mirror reading-specific activation. This area which overlaps with the peak of activation in some atlases, curiously appears outside the brain. Nevertheless, this finding is the first of its kind and is the right type of research to be doing to explore these gray matter changes. The mechanism that the authors proposed for the increase in gray matter concentration was synaptic remodeling within specific processing areas. It is clear that many more exciting studies of this kind will be coming out in the very near future.

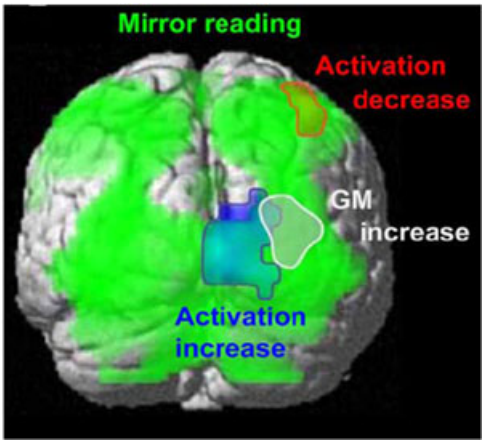

Figure 12. This shows practice related changes in activation and in gray matter density related to performing the task of mirror reading. The green areas indicate the overall activation. The blue area is where the activation-induced signal change increased with practice. The red area is where the activation-induced signal change decreased with practice. Lastly, the white area is where the change in gray matter density was found. Obtained from Ilg et al. 2008.

While interpretation of VBM data is wrought with very serious problems, VBM research is in an exciting stage of development at this point. Precise timings and mechanisms for gray matter changes are still not known. New comparisons are coming out almost daily, even though the sources of variability are not fully characterized. The field also may go in the direction of making comparisons in very high resolution scans of very small regions of the brain, rather than in low resolution images of the entire brain. Another direction that seems relatively unexplored is that of pulse sequence choice for VBM. Perhaps sequences that are weighted toward blood volume, perfusion, or susceptibility effects may be more sensitive to changes and may help researchers to elucidate mechanisms of change. A study by O'Gorman et al. (2008) demonstrates the use of VBM with arterial spin labeling based on resting state perfusion data rather than on anatomical data in the assessment of subjects with ADHD. Clear increases in perfusion for ADHD subjects were shown in the left caudate nucleus and in frontal and parietal regions. Psychomotor stimulation normalized perfusion within the frontal and caudate regions and decreased perfusion below normal levels in parietal and parahippocampal regions. This last study indicates not only a new direction for VBM, but a new direction and potentially enhanced utility of noninvasive quantitative baseline perfusion data.

Diffusion Tensor Imaging

Voxel-based morphometry can be generally thought of as the characterization of any voxel-wise changes in anatomical images. Most

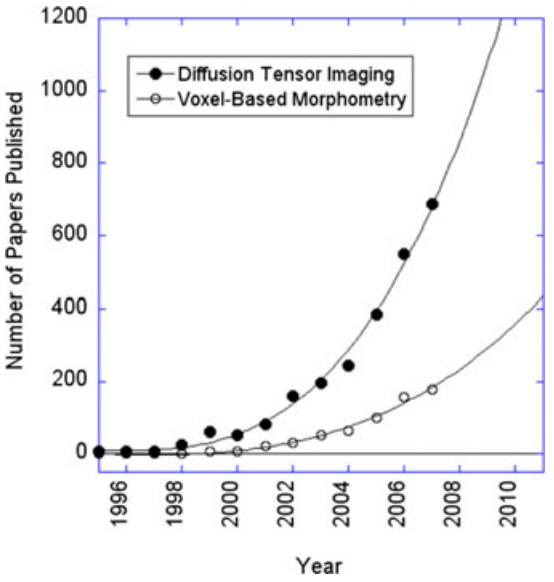

Figure 13. Results of a literature search using the "Scopus" literature search tool(www.scopus.com) of all diffusion tensor imaging and voxel-based morphometry imaging studies published in the past 12 years. A rapid growth in both is seen after 2002.

studies involving VBM, however, focus on characterizing changes in gray matter density. Diffusion tensor imaging (DTI) mostly involves the characterization of white matter, and specifically, the directionality of white matter tracts. DTI-generated maps may be used in the context of VBM, but they do not have to be, as a considerable amount of unique information resides in the maps themselves for individual subjects. DTI involves the use of diffusion gradients sensitized to diffusion in multiple directions to determine the preferential directionality of diffusing spins (Basser & Jones 2002). With the understanding that spins diffuse more rapidly along white matter tracts as opposed to perpendicularly to them, this method can create voxel-wise maps of fractional anisotropy (FA) as well as computed maps of white matter tracts. This avenue of neuroimaging has picked up considerable momentum as methods become more sophisticated and robust. Fig. 13 shows the exponential growth of the number of papers published per year for both DTI and VBM.

Dr. Peter J. Basser, arguably the creator of DTI, having published the first several papers in the field on the topic (Basser 1995; Basser et al. 1994a,b; Basser & Pierpaoli 1995), received in 2008 the International Society for Magnetic Resonance in Medicine Gold Medal for his contribution to the field—the society's highest honor of and certainly well deserved.

DTI has gained popularity in the neuroimaging community because it provides a methodology for assessing unique structures in the brain that were previously one was unable to image noninvasively. Functionally relevant anatomical information may be derived from white matter anisotropy as well as from tract-related connectivity measures. While publications using DTI are reaching about 1,000 per year, the technique itself faces several major technical challenges. These include a high level of sensitivity to subject motion, eddy currents, susceptibility effects, gradient heating, scanner noise, and low resolution. Sensitivity to subject motion and brain pulsation can be reduced by single shot imaging techniques, which then increase the problems of susceptibility effects (longer TR, longer readout window) and also lower the image resolution. These problems are reduced by SENSE acquisition methods which, of course, require multichannel acquisition. Eddy current effects cause image warping and generally remain a problem. Pulse sequence-based solutions as well as post-processing-based unwarping solutions have been proposed and have helped reduce eddy currents. Gradient heating problems have been reduced by new gradient cooling methods involving water circulation through the gradient coil windings themselves. Scanner noise has also been reduced by mechanical stabilization/isolation approaches.

The primary problem of MRI tractography (Conturo et al. 1999; Mori & Van Zijl 2002) is the insufficient resolution it affords to separate crossing fibers from those that approach each other within a voxel and then go in parting directions. One solution is to image at higher spatial resolution, although individual fibers cross at a much finer spatial scale than current

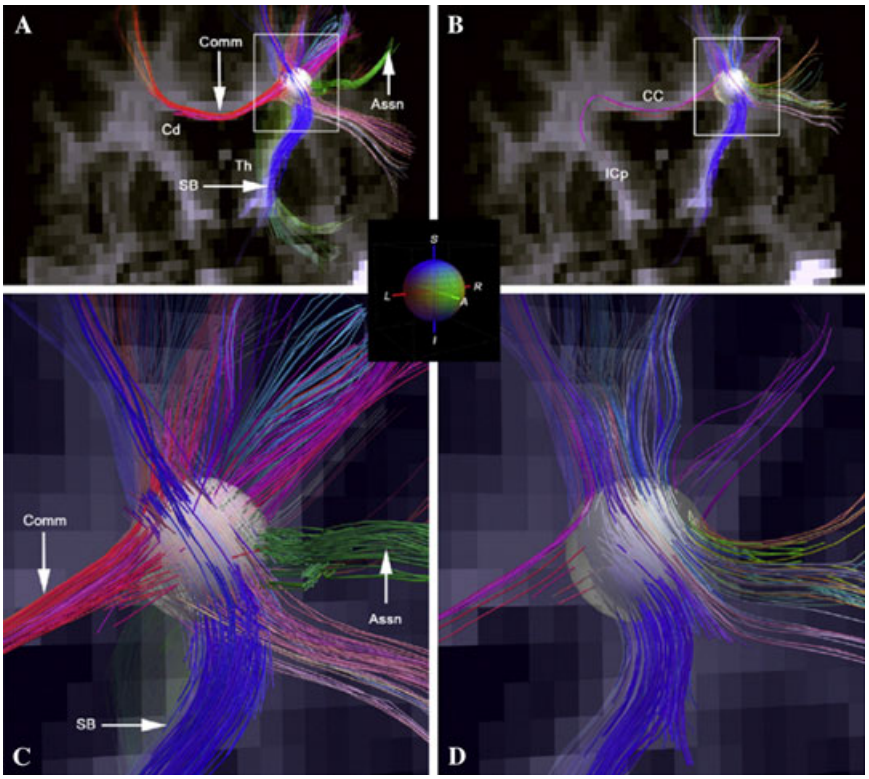

Figure 14. These panels show crossing fibers within the centrum semiovale of *in vivo* human brain using DSI (**A**, **C** – magnification of **A**) and DTI (**B**, **D** – magnification of **B**). Abbreviations: Assn, long association fibers; CC, corpus callosum; Cd, caudate nucleus; Comm, commissural fibers; ICp, posterior limb of internal capsule; SB, subcortical bundle projection fibers; Th, thalamus. DSI shows superior fiber tracking resolution over DTI. Obtained from Wedeen et al. 2008.

techniques can resolve. Other solutions include application of diffusion gradients in more than just the three perpendicular directions, thus performing a more fine-grained directional encoding. Wedeen et al. (2008) have taken (diffusion spectrum imaging) DSI to dramatic new levels of detail in postmortem fixed macaque brain and in healthy human brain. A dramatic image of some of the results from that paper are shown in Fig. 14.

Some developments and applications of DTI and fiber tracking in the past year include automated methods for fiber tracking (Zhang et al. 2008), the use of DTI to predict clinical outcome to traumatic brain injury (Sidaros et al. 2008), the use of DTI to help explain synethesia as an increased structural connectivity (Rouw & Scholte 2007), exploration of the limits of fMRI-guided DTI fiber tracking (Staempfli et al. 2008), and characterization of the microstructural maturation of the human brain from childhood to adulthood (Lebel et al. 2008).

EEG and MEG

Recently, both MEG and EEG have experienced new growth as those performing fMRI seek more direct measures of brain activity to complement their studies. Both MEG and EEG have been useful and challenging in many regards. In terms of utility MEG studies have uncovered specific transient dynamics associated with slower BOLD changes and fluctuations (Furey et al. 2001, Singh et al. 2002; Singh et al. 2003). BOLD changes have helped

confine dipole source estimations, allowing forward solutions, which delineate precise timing between regions (Dale & Halgren 2001, Dale et al. 2000). EEG studies have the distinct advantage of being carried out simultaneously with fMRI studies (Herrmann & Debener 2008, Laufs et al. 2008), allowing the study of nonrepeatable effects in the context of the study of epileptic patients (Jackson 1994, Lemieux et al. 2008, Lemieux et al. 2001) and healthy volunteers (Horovitz et al. 2008, Horovitz et al. 2004, Horovitz et al. 2002). Comparisons of dynamics of MEG and EEG with BOLD contrast have led to insights and additional puzzles regarding the parametric stimulus dependence of BOLD (Muthukumaraswamy & Singh 2008), BOLD dynamics (Tuan et al. 2008) and fluctuations (Goldman et al. 2001, Goldman et al. 2002, Helmut Laufs 2008, Laufs et al. 2007).

An ongoing question in MEG and EEG pertains to the functional significance of the various frequency bands that show relatively high levels of spatially specific spectral power. This is particularly relevant given a growing body of evidence that resting state oscillations in fMRI are functionally important to performance and perception—as mentioned above. The following four studies, published last year, stood out as cutting edge examples of how MEG and EEG oscillations are being used and probed.

The first study (van Dijk et al. 2008) explored the functional role of alpha band (~10 Hz) oscillations in MEG. Subjects performed a subtle visual detection task. Prestimulus alpha power was shown to be inversely correlated with performance. Source modeling found that the location of this performance-related alpha modulation was in the parieto–occipital sulcus. The hypothesis is that this alpha power reflects inhibition of these areas by higher areas, therefore modulating the gain in visual stream. A lower gain effectively "gates" the information passing from occipital to dorsal parietal areas. Consequently, subtle details of a visual stimulus would less likely make their way to conscious perception during high alpha activity. Interestingly, reaction time was not affected, suggesting that alpha power modulations do not modulate vigilance (a potential confound in the study).

The second study concerns gamma (>30 Hz) oscillations. Gamma oscillations have been recently implicated in perceptual binding of multiple inputs within sensory systems and might also reflect functional coupling within distributed cortical networks underlying perceptual or cognitive processes. The spatial and parametric relationship between gamma oscillations and BOLD has been shown to be mostly similar but with some dramatic differences as discussed above (Muthukumaraswamy & Singh 2008). This study used MEG to demonstrate gamma oscillations in primary motor cortex during self-paced movement, peaking at about 100 to 250 ms after movement onset (Cheyne et al. 2008). The hypothesis is that these gamma oscillations are within cortico–subcortical networks and are involved with feedback control of discrete movements.

A third study involves MEG and EEG processing that is along a similar avenue as the growing area of fMRI decoding (Waldert et al. 2008). This type of work is significant in the context of building robust brain computer interfaces. Because of their much higher temporal resolution, these techniques have a greater potential for real time interaction of brain activity with neuroprosthetic devices or with feedback based on brain activity. In this study subjects performed hand movements that caused power modulation of MEG activity in three frequency bands. They observed an increase in power for <7 Hz (low frequency or theta) and for 62–87 Hz (high gamma) and a decrease for 10–30 Hz (beta). Interestingly, only the power modulations of low frequency activity were informative with regard to decoding direction of movement from the MEG data. In addition, the informative decoding time period began just before movement onset.

The last study involves exploring the significance of theta band frequencies with regard to speech discrimination performance (Luo &

Poeppel 2007). The key to this study is that the focus was not on spectral power but on theta band phase. MEG signal was recorded from subjects listening to spoken sentences of varying intelligibility. It was found that theta band phase pattern predominantly in the right hemisphere reliably discriminated spoken sentence signals and that this tracking was correlated with sentence intelligibility. These results suggest that continuous speech is processed through a temporal window of about 200 ms—which is the period of the theta band.

These studies are only a small sampling of the very large and growing areas of MEG and EEG as they relate to BOLD contrast and as they relate to questions regarding the fundamental mechanisms of cortical processing. It is clear that we are just at the very beginning of making sense of the biological significance and the utility of these oscillations. As more robust, sensitive, and perhaps standardized processing methods emerge to explore this highly multidimensional data (Dalal et al. 2008), insights will certainly come more rapidly.

Optical Imaging

Optical imaging is an extremely wide field, extending well beyond neuroscience and medicine. Within neuroscience the techniques range from invasive approaches in animal models with probes directly over brain tissue to noninvasive approaches with probes passing light directly through the skull. The technique is generally based on the observation that activation-related hemodynamic changes and (in a small but growing number of studies) nerve cell changes have been shown to cause localized detectable changes in light absorption. Time courses and maps of deoxygenated, oxygenated, and total hemoglobin can be routinely created. The array of optical imaging techniques have been extremely helpful in elucidating fMRI-based contrast (Huppert et al. 2006a,b, Malonek et al. 1997) as well as fundamental brain organization (Grinvald et al. 2000). Recently, practical clinical applications have been increasing. Specifically, applications in the field of pediatric assessment of development and brain function are a high growth area in optical imaging (Franceschini et al. 2007). Children provide more optimal information than adults for optical imaging, due to their thinner skull. The technique is advantageous over fMRI because of its portability and relative ease of use.

Optical imaging is also a technique that is still rapidly evolving technically. Three cutting-edge papers, published in the past year, highlight areas of impressive technical advancement in the field of optical imaging and provide a glimpse of some of the directions that the field may be going. The first is that of Zeff et al. (2007). In this study, a high-density diffuse optical imaging (DOT) system is shown to be capable of performing retinotopic mapping—something that was a major achievement in the mid 1990s for fMRI. These maps are shown in Fig. 15. The technique is reported to resolve functional responses of 1.7 cm and subtle spatial shifts in responses of less than 1 cm. This dramatic increase in resolution may pave the way to increased usage clinically.

The second study (Liebert et al. 2006) is a bit more radical. Even though it was published in 2006, it is worth mentioning because of its innovative approach. The study is the first demonstration that fluorescence of exogenous dyes introduced intravenously to healthy human volunteers inside the brain can be excited and detected noninvasively. A bolus of indocyanine green was introduced, and the passage of the dye was monitored by detection of the fluorescence signal following a pulsed laser excitation at 780 nm. This technique may evolve into a portable and noninvasive alternative to present day MRI-based techniques involving intravascular susceptibility-based contrast agents to assess blood volume and vascular patency.

The last study is not noninvasive and is not demonstrated on humans or even on brains. The study is a demonstration on stimulated lobster leg nerves of a novel technique for imaging

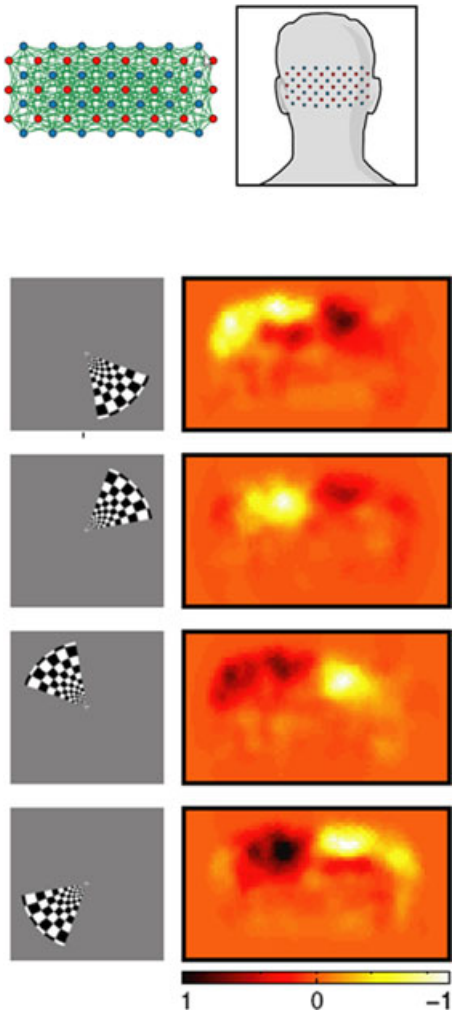

Figure 15. This shows polar angle retinotopic mapping with diffuse optical tomography. Obtained from Zeff et al. 2007.

action potentials at high temporal resolution using near-infrared video microscopy and polarized light (Schei et al. 2008). Biological tissue can alter light polarization through birefringence, light-scattering polarization changes, and absorption of light with specific polar angles. Sodium channel activation causes reorientation of peptide bonds, altering the polarization of scattered light. Nerve shape changes and swelling may also cause changes in polarized light. Action potentials were detected both in transmission and reflection mode. Different parts of the nerve showed different effects in transmission and reflection mode. Movies of action potentials were created, demonstrating a complex interaction of the larger, faster axons and slower, smaller axons. In general, polarization methods appear to be more hopeful than scattering detection methods since polarization provides more specificity to activated neurons. It will be challenging, yet hypothetically possible, to use this technique in intact brains having random nerve cell orientation.

PET

Positron emission tomography (PET), while perhaps taking a back seat to functional MRI with regard to brain mapping, remains a highly influential neuroimaging technique due to its continuing demonstration of advancement in the fields of molecular imaging, and more specifically, neuroreceptor mapping. Currently, fMRI and NMR spectroscopy lack the sensitivity of PET with regard to imaging specific tracers (or biomarkers) *in vivo*. A well attended neuroreceptor mapping meeting where over 200 abstracts presented took place in July 2008. The proceedings of this meeting are published in *NeuroImage* (Vol. 41, Suppl. 2, 2008).

One technical advance of PET that has generated excitement is that of a machine that performs simultaneous PET and fMRI (Judenhofer et al. 2008). This paper outlines a 7 T animal MRI-PET system. The primary challenge that was overcome in creating this system was the fact that conventional PET scanners incorporate photomultiplier tubes that are very sensitive to magnetic fields. One solution is the use of optical fibers that lead scintillation light outside the magnetic field. For this system an alternative solution was used. Here, a novel PET detector based on lutetium oxyorthosilicate scintillation crystals and avalanche photodiodes was used in the MRI bore. This manuscript demonstrates that these scanners work just as well as conventional detectors.

In contrast to the recently introduced PET-CT scanners, PET-MRI has more potential than biomarker tracing and anatomical

imaging. It can synergistically combine fMRI, anatomical MRI, spectroscopy, and PET, opening up new avenues in research involving studies that are extremely difficult to identically reproduce across separate systems.

Conclusions

This review has is an attempt at a very narrow snapshot of the cutting edge of the rapidly moving—accelerating—discipline of neuroimaging methods. The areas of fMRI, DTI, VBM, MEG, EEG, optical imaging, and PET were covered—but, admittedly, with considerably more emphasis on fMRI methods and contrast mechanisms. The hope is that some of the most innovative work and most interesting controversies were highlighted in such a way that the reader can come away not only with a bit more information about specific papers but a general perspective of where the field currently rests and where it is going, from a methodological perspective. It is also hoped that a clear sense of excitement is conveyed, for these methods show no indication of stabilizing any time soon. Methods are continually advanced as new technology comes about, as we understand more of the biophysics and neurophysiology of the signal being measured, and as we come up with ever more clever ways of pulling subtle information from our data. From these advancements, high impact applications inevitably follow. It is clear that many methods described are still in their infancy, and a considerable amount of collaborative work between experts of all disciplines remains to be carried out toward developing better methods, intended not only to better understand the human brain, but to use this ever growing understanding in the most effective way possible.

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Conflicts of Interest

The author declares no conflicts of interest.

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