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Review

Technical aspects and utility of fMRI using BOLD and ASL

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Abstract

Functional magnetic resonance imaging (fMRI) is an emerging methodology which provides various approaches to visualizing regional brain activity non-invasively. Although the exact mechanisms underlying the coupling between neural function and fMRI signal changes remain unclear, fMRI studies have been successful in confirming task-specific activation in a variety of brain regions, providing converging evidence for functional localization. In particular, fMRI methods based on blood oxygenation level dependent (BOLD) contrast and arterial spin labeling (ASL) perfusion contrast have enabled imaging of changes in blood oxygenation and cerebral blood flow (CBF). While BOLD contrast has been widely used as the surrogate marker for neural activation and can provide reliable information on the neuroanatomy underlying transient sensorimotor and cognitive functions, recent evidence suggests perfusion contrast is suitable for studying relatively long term effects on CBF both at rest or during activation. New developments in combining or simultaneously measuring the electrophysiological and fMRI signals allow a new class of studies that capitalize on dynamic imaging with high spatiotemporal resolution. This article reviews the biophysical bases and methodologies of fMRI and its applications to the clinical neurosciences, with emphasis on the spatiotemporal resolution of fMRI and its coupling with neurophysiology under both normal and pathophysiological conditions.

Keywords: Functional magnetic resonance imaging; Blood oxygenation level dependent; Arterial spin labeling; Perfusion; Combination of neurophysiological measurements and functional magnetic resonance imaging

1. Introduction

The goal of functional neuroimaging is to map the activity of the living brain in space and time. Electrophysiological methods including magnetoencephalography (MEG) and electroencephalography (EEG) offer direct measurements of neural activity with high temporal resolution, but are limited by difficulties in defining the spatial extent of activation. Although more indirect, neuroimaging methods based on metabolic and vascular parameters provide excellent spatial resolution for imaging brain function along with precise matching with anatomical structures. In particular, functional magnetic resonance imaging (fMRI) has enabled imaging of changes in blood oxygenation and perfusion, and has been gaining increasing popularity over other methods for its total non-invasiveness and wide availability. Over the past several years fMRI has become the most widely used modality for visualizing regional brain activation in response to sensorimotor or cognitive tasks, and is now widely used in cognitive, systems and clinical neuroscience.

As compared to positron emission tomographic (PET) scanning, fMRI is completely non-invasive, does not require exposure to ionizing radiation, and is much more widely available. fMRI also provides superior temporal and spatial resolution, and increased sensitivity for detecting task activation in individual subjects through signal averaging. PET still provides a much greater repertoire of image contrasts. Whereas fMRI is primarily sensitive to hemodynamic changes, PET images can reflect blood flow, glucose utilization, oxygen consumption, and receptor binding. The latter occurs at concentrations well below the sensitivity of MRI, and can only be measured in vivo with radioactive tracers, though fMRI can be used to visualize pharmacological effects indirectly (Nguyen et al., 2000; Stein, 2001; Zhang et al., 2001). PET also provides a silent environment that is not affected by electromagnetic interference or the presence of ferrous objects. However, PET scanning is less widely available and significantly more costly than fMRI due to the need for on-line tracer synthesis.

In this review, we will discuss the physiological bases and contrast mechanisms underlying the susceptibility-based and perfusion-based fMRI signals with emphasis on the coupling with neurophysiology and the spatiotemporal reso-

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lution in each modality. A brief review of the applications of fMRI particularly in clinical neuroscience will also be provided.

2. Contrast mechanisms and signal characteristics

2.1. Blood oxygenation level dependent (BOLD) contrast

The primary contrast mechanisms exploited for fMRI are BOLD contrast and perfusion contrast obtained using arterial spin labeling (ASL) techniques. These contrast mechanisms are illustrated schematically in Fig. 1. BOLD signal is the result of a complex interaction between changes in blood flow, blood volume, and oxygenation consumption accompanying neural activity (Kwong et al., 1992; Ogawa et al., 1993; Mandeville et al., 1999). Functional contrast is obtained because the ferrous iron on the heme of deoxyhemoglobin is paramagnetic (Thulborn et al., 1982), producing a local susceptibility induced field shift or field distortion manifested as primarily a change in T2*. With regional brain activation, an increase in T2* is observed, reflecting a decrease in regional deoxyhemoglobin which has been attributed to increases in cerebral blood flow (CBF) that exceed metabolic oxygen demands.

This change in hemoglobin oxygenation can be probed by a variety of pulse sequences, including gradient-echo and offset spin-echo routine or high-speed imaging techniques such as echoplanar (Stehling et al., 1991) and spiral scanning (Meyer et al., 1992), which particularly emphasize T2* effects. The typical BOLD response consists of a 0.5–5% change in regional image intensity, which increases at higher magnetic field strengths. BOLD signal changes may approach 25% with sensorimotor tasks at 4.0 T. Task-specific BOLD signal changes are not directly quantifiable in physiological units, but rather are expressed as a percentage signal change or as a statistical significance level based on a statistical model. Absolute or resting function

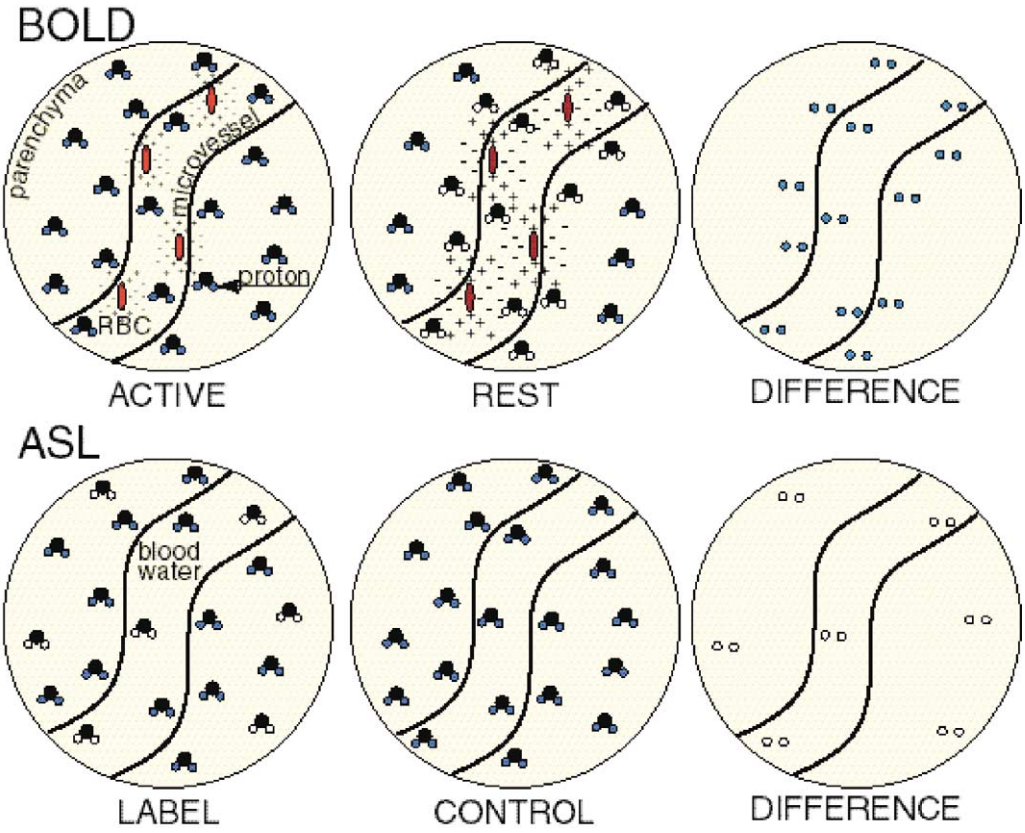

Fig. 1. Schematic diagram illustrating BOLD and ASL perfusion MRI contrast mechanisms. The circular regions indicate brain parenchyma with a vessel. Water molecules containing mobile protons are distributed in the intravascular and extravascular space. Top: BOLD contrast results from magnetic susceptibility effects due to deoxyhemoglobin. Red blood cells (RBC) containing deoxyhemoglobin are indicated, surrounded by a small magnetic field. In the active state, blood supply greatly exceeds oxygen demand and RBCs are relatively oxygenated (bright red), resulting in only a small perturbation of the main magnetic field. In the resting state, RBCs in veins are relatively deoxygenated, and signal from nearby protons is spoiled (indicated by white color). The difference image shows intravascular and perivascular signal changes typical of BOLD contrast acquired with gradient echo imaging. Bottom: ASL perfusion contrast results from proximal inversion of arterial blood water. Because these spins have been labeled prior to image acquisition, they do not contribute to the image (indicated by white color). Because water is diffusible, the ASL signal is distributed evenly throughout the region. With control labeling, there is no effect on the image. The difference image demonstrates the effects of ASL. In contrast to the BOLD difference image, tissue labeling is reduced, but more uniform.

cannot be easily assessed, and for clinical studies it may be difficult to know whether any observed abnormalities are due to baseline or task-specific effects.

The power spectrum of BOLD fMRI data collected from human subjects in the absence of any experimental task or time varying stimuli demonstrate greater power at low frequencies, which can be well characterized by a 1/frequency ($1/f$) function (Zarahn et al., 1997a), or by more complicated modeling with special smoothing techniques (Friston et al., 2000; Woolrich et al., 2001). This temporal autocorrelation causes relative reductions in sensitivity for experimental designs with fundamental frequencies below 0.01 Hz (Aguirre and D'Esposito, 1999). Because the BOLD signal is based on the susceptibility contrast, it is also very sensitive to the bulk static susceptibility effects, leading to signal loss or distortion at tissue–air and tissue–bone interfaces such as the orbital frontal cortex and inferior temporal lobe. This susceptibility induced BOLD signal dropout, if primarily arising from through-plane field gradients, can be largely recovered by Z-shimming techniques which require multiple image acquisitions with different amplitudes of slice refocusing gradient (Constable and Spencer, 1999) or additional k-space coverage (Glover, 1999). As the latest development, single-shot Z-shimming approach is now available without sacrificing the temporal resolution of BOLD fMRI (Song, 2001).

2.2. ASL perfusion contrast

fMRI based on perfusion contrast can also be achieved using the ASL approach, which utilizes magnetically labeled arterial blood water as a diffusible tracer for CBF measurements, in a manner analogous to that used for ^{15}O PET scanning (Detre et al., 1994). In ASL perfusion MRI, arterial blood water is labeled proximal to the tissue of interest, and the effects of this prelabeling are determined by pair-wise comparison with separate images acquired with control labeling. Several ASL strategies exist, including slab pseudo-saturation (Detre et al., 1992), continuous adiabatic inversion (Williams et al., 1992), slab inversion (Edelman et al., 1994; Wong et al., 1998), and selective/non-selective inversion (Kim, 1995; Kwong et al., 1995). The magnetic tracer has a decay time of T1, which is sufficiently long to allow perfusion of the microvasculature and tissue to be detected but short enough to allow dynamic changes to be monitored. Functional contrast is obtained because labeled arterial spins that flow into brain tissue elicit local longitudinal signal changes (either increase or decrease depending on the specific technique), which are proportional to perfusion. While the BOLD contrast primarily detects changes in T2* that indirectly reflect changes in CBF, ASL perfusion contrast is essentially based on alternations in T1 induced directly by changes in regional blood flow. ASL techniques are capable of quantifying CBF in well characterized physiological units of ml 100 g^{-1} min^{-1}, or may be used in a qualitative fashion similar to that used in BOLD fMRI.

ASL perfusion contrast can be sampled with any imaging sequence. Whereas gradient-echo sequences have typically been used for rapid image acquisition in ASL applications, spin-echo methods offer a means of imaging perfusion in brain regions with high static field inhomogeneity which are otherwise difficult to visualize using susceptibility-based modalities (Chen et al., 1997; Crelier et al., 1999; Liu et al., 2001). Because the ASL perfusion signals are obtained by pair-wise subtraction between adjacently acquired tag and control images, motion artifact and baseline drift are effectively reduced in ASL fMRI (Wong, 1999). Performing ASL at higher field strengths provides increased SNR and advantages for labeling both due to increased perfusion signal and a prolonged relaxation time T1 of the labeled blood. However, task-activation perfusion change obtained using ASL may also decrease at high field because of the stronger susceptibility effects on the venous blood (Wang et al., in preparation). A significant factor affecting the accuracy of perfusion quantification using ASL is the transit time for the blood to flow from the tagging region to imaging slices, which is the primary source of vascular artifact in ASL perfusion images (Detre and Alsop, 1999).

Table 1 lists a side-by-side comparison between BOLD and ASL perfusion fMRI. Examples of functional activation data obtained using BOLD and ASL perfusion fMRI are shown in Fig. 2. In general, the application of ASL approaches in functional imaging has been less widespread because they are more difficult to implement, usually have less imaging coverage and produce a lower signal change for activation, typically less than 1%. Nevertheless, ASL contrast has certain advantages over BOLD contrast, especially for clinical studies. The capability of the ASL technique to provide absolute quantification of CBF is very useful for clinical studies and in studies for which normal and patient populations are compared. An example of this is illustrated in Fig. 3. Recent data also demonstrate that task activation measured by ASL shows less inter-subject variability than BOLD contrast, and that ASL contrast shows stable noise characteristics over the entire frequency spectrum, making it suitable for studying slow variation in brain function over periods greater than a few minutes (Aguirre et al., 2002). Functional signal changes detected by ASL may also have superior spatial and temporal resolution as compared to BOLD contrast (Silva et al., 1999; Duong et al., 2001). An increased use of ASL approaches in fMRI is anticipated over the next several years.

3. Spatial, temporal, and cellular localization

3.1. Activation-flow coupling

Most imaging studies of task-specific activation, including BOLD and perfusion fMRI, rely on the existence of a

Table 1
Comparison between imaging characteristics of fMRI using BOLD and ASL perfusion contrasts

	BOLD	ASL perfusion
Signal mechanism	Blood flow, blood volume, oxygenation consumption	Blood flow
Contrast parameter	T2*	T1
Spatial specificity	Venules and draining veins	Capillaries, arterioles
Typical signal change	0.5–5%	<1%
Imaging methods	Gradient-echo Offset spin-echo	Gradient-echo Spin-echo
Optimal task frequency (block design)	0.01–0.06 Hz	<0.01 Hz
Sample rate (TR)	1–3 s per image	3–8 s per perfusion image
Relative contrast-to-noise ratio	>2 with high task frequency <0.5 with low task frequency	1
Intersubject variability	High	Low
Imaging coverage	Whole brain	Part or most of brain cortex
Major artifacts	Susceptibility; motion; baseline drift	Vascular artifact

close coupling between regional changes in brain metabolism and regional CBF, herein termed activation-flow coupling (AFC). Changes in blood flow and metabolism occur with excitatory or inhibitory neurotransmission, both of which are energy consuming processes (Nudo and Masterson, 1986). Since regional CBF changes are used as a surrogate marker for changes in regional brain metabolism which in turn reflects neural function, an uncoupling of either blood flow and metabolism or metabolism and neuronal function could result in false negative or false positive activation.

Studies in both animal models and human subjects using a variety of modalities have shown that in normal brain, blood flow changes occur following a latency of 0.5–1.5 s and build to a peak in approximately 4–8 s, even for stimuli of much shorter duration (Villringer and Dirnagl, 1995). However, there are both regional variations and pathological alterations in AFC, as well as individual variations in AFC, even in normals (Aguirre et al., 1998). For example, in patients with severe stenosis of arteries supplying a given brain region, delayed vascular transit times may be observed along with an attenuation of functionally induced hemodynamic changes (Powers et al., 1988; Stoll et al., 1998).

The AFC phenomenon was originally described in 1890 by Roy and Sherrington (Roy and Sherrington, 1890), yet studies since that time have failed to identify a specific hormonal or metabolic factor which mediates AFC (Villringer et al., 1993). While it is often assumed that a regional CBF increase is required to supply oxygen and nutrients, studies of brain energy metabolism in response to functional activation have not conclusively supported this idea (Fox and Raichle, 1986) and more recent data confirm that CBF changes are not regulated by glycolytic demands (Powers et al., 1996). Additionally, blood flow effects can be pharmacologically decoupled from brain activation without loss of at least electrophysiological responses (Lindauer et al., 1996). An alternative possibility is that regional blood flow increases to remove toxic waste products of metabolism. Several lines of evidence suggest that the oxygen to glucose ratio decreases during functional activation, resulting in lactate accumulation that must be cleared. It has been speculated that this is at least partially attributable to the use of glycogen as an energy source during functional activation (Shulman et al., 2001). Nonetheless, at least in normal subjects, regional blood flow changes have typically co-localized with known functional specialization.

3.2. Functional metabolism

Changes in tissue oxygen and oxygen consumption during functional activation are also poorly understood. Early PET studies during sustained visual stimulation in humans suggested an uncoupling of glycolytic and oxidative metabolism, with both CBF and CMRGlu increasing about 50% with stimulation and CMRO2 remaining minimally changed (Fox and Raichle, 1986), suggesting the preferential recruitment of glycolytic metabolism. Recent work has shown that much of the glucose utilized during glutamatergic neurotransmission is actually consumed by astrocytes (Magistretti and Pellerin, 1999). These cells have glucose transporters on their end-feet directly abutting the capillaries, and terminate neurotransmission through glutamate uptake from the synaptic cleft. Glutamate is cycled back to neurons as glutamine, and lactate is at least partially cycled back to neurons to be oxidized. In other words, the blood oxygen level rises because of an increase in the processing of glutamate in astrocytes after glutamatergic neurotransmission. This explanation was supported by the fact that blood flow in functionally activated brain can be increased by lactate infusion and decreased by pyruvate infusion (Ido et al., 2001).

Infrared optical spectroscopy studies during functional activation indicate an early increase in deoxyhemoglobin which is then washed out by a much larger and less well localized increase in oxyhemoglobin due to increased CBF (Malonek and Grinvald, 1996). Similar early increases in deoxyhemoglobin have also been observed with BOLD fMRI (Menon et al., 1994; Yacoub et al., 1999). Evidence

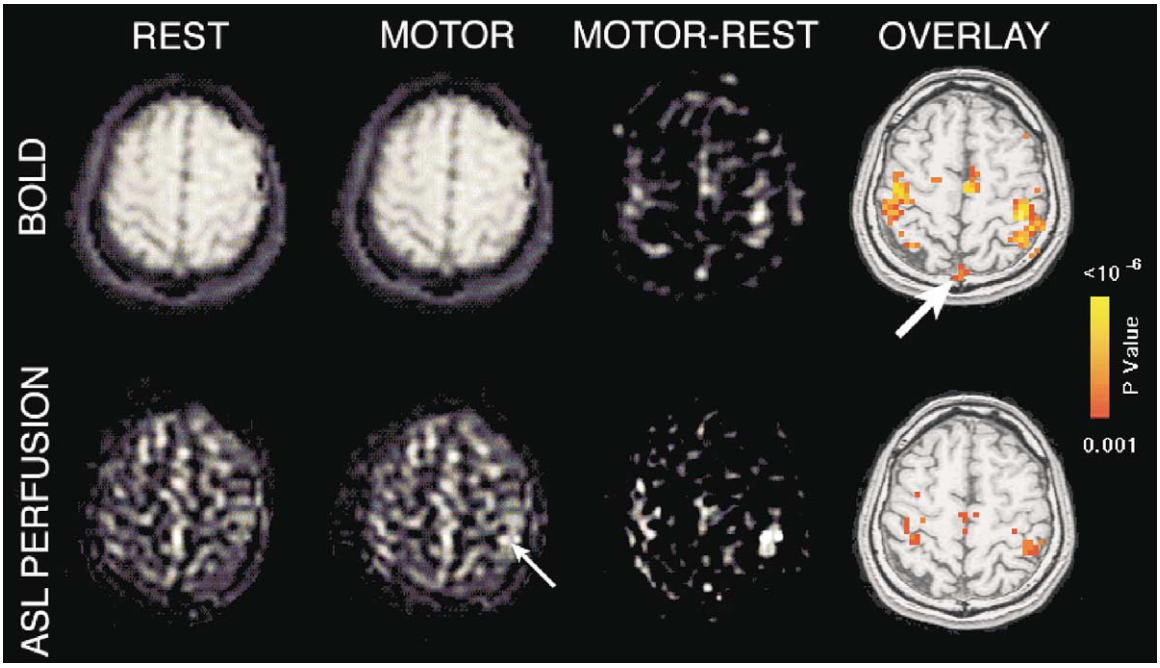

Fig. 2. Examples of functional activation data obtained using BOLD and ASL perfusion contrast with self-paced bilateral finger tapping. A single axial slice through motor cortex is shown. BOLD data are susceptibility-weighted echoplanar images. ASL perfusion data are images of the label-control difference obtained using a similar pulse sequence, and are proportional to perfusion with higher flow observed in gyral gray matter. With motor activation, a focal increase is observable in motor cortex in the ASL perfusion data (small arrow). For both BOLD and ASL perfusion data, signal changes are much more evident in the motor-rest difference images, though these are noisy. Most fMRI data are ultimately presented as an overlay of a thresholded statistical map (e.g. motor-rest difference divided by standard deviation) onto a higher resolution anatomical image. In the overlays, signal changes are observed in bilateral motor cortex and in supplementary motor cortex. BOLD yields more significant changes within an individual subject. However, in BOLD data, signal changes are also observed in the sagittal sinus draining this region (large arrow), whereas ASL perfusion data are localized to the parenchyma.

for an early increase in deoxyhemoglobin and therefore an increase in oxygen consumption has also been obtained using phosphorescence quenching methods (Vanzetta and Grinvald, 1999; Ances et al., 2001a), and more recently by direct oxygen electrode measurements in tissue (Ances et al., 2001b). This latter study also demonstrated even larger decreases in tissue oxygen following prolonged stimulation, which were not accompanied by increases in

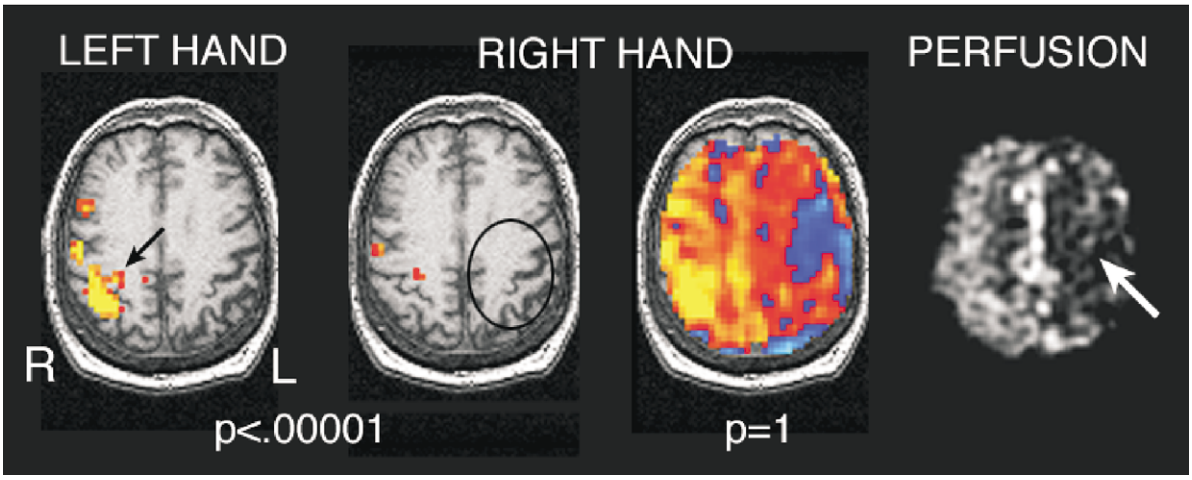

Fig. 3. Motor fMRI and resting perfusion imaging in a patient with left sided cerebrovascular disease and intermittent right sided weakness who was able to perform paced left and right sided ball squeezing. Representative data from a single slice are shown. The first two images show thresholded BOLD activation data during left and right hand tasks, respectively. With left hand ball squeezing, there is strong activation over right motor cortex (black arrow). However, despite right handed ball squeezing, there is no observable left sided activation at the same threshold (black oval). With no thresholding of BOLD data ($P = 1$), paradoxical deactivation over the left hemisphere is observed (blue color). Resting perfusion MRI demonstrates hypoperfusion in the left hemisphere (white arrow) indicative of hemodynamically significant cerebrovascular disease. This provides a basis for the absence of task-correlated BOLD signal increase with right hand function.

flow, suggesting that decreased tissue oxygen is not the signal for blood flow increases. This has also been confirmed in recent PET studies in human subjects in which CBF with visual stimulation did not increase with hypoxia as compared to normoxia (Mintun et al., 2001). The precise timing and extent of glycolytic versus oxidative pathways during functional activation remains uncertain.

3.3. Spatial resolution of fMRI

The spatial resolution limits of fMRI are determined by the technology as well as the contrast mechanism underlying the functional signal. While MRI is capable of imaging structures in the micron range (Johnson et al., 1987), SNR varies directly with voxel size. Various methods have been carried out to achieve the SNR required by high-resolution fMRI, including scanning at high magnetic field and using special coil with high sensitivity. Noise reduction approaches such as cardiac and respiratory gating are often necessary to mitigate image degradation caused by physiological motion which becomes a very significant problem with high-resolution imaging (Guimaraes et al., 1998). In addition, diffusion-weighted images may be acquired to suppress macrovasular signals which would magnify the error of spatial localization in fMRI.

Because BOLD contrast is primarily due to intravascular deoxyhemoglobin changes; signal changes due to functional activation may be observed overlying venous structures draining the activated region. Indeed, careful examination of the sources of the BOLD effect with functional stimulation at 1.5 T has demonstrated that nearly all of the apparent activation occurs proximal to a macroscopic vessel, with susceptibility effects extending into adjacent cortex (Hoogenraad et al., 2001). As noted above, there is evidence of an early and more localized decrease in blood oxygenation with functional stimulation termed the 'initial dip' which could provide better spatial resolution for imaging functional activation since it should occur close to the region of increased parenchymal metabolism. The feasibility of this method has been demonstrated in cat and human visual cortex, where this signal has been used to localize iso-orientation and ocular dominance columns (Menon et al., 1997a; Kim et al., 2000). However, the existence of the 'initial dip' has remained controversial (Fransson et al., 1998; Mandeville et al., 1999; Lindauer et al., 2001).

In contrast to BOLD fMRI, perfusion MRI uses a nominally diffusible tracer (magnetically labeled arterial water) which can exchange with tissue water. In addition, the decay time of this tracer corresponds to the T1 relaxation time, which is approximately 1 s, precluding significant tracer accumulation in venous structures even in the absence of diffusion. Thus, signal changes in perfusion fMRI are not observed over veins, resulting in better localization of signal changes over activated cortex (Silva et al., 1999). It has recently been demonstrated that ASL perfusion fMRI provides equivalent spatial resolution to the 'initial dip' for visualizing iso-orientation columns in cat visual cortex (Duong et al., 2001). These findings suggest that overall the spatial resolution of ASL perfusion fMRI may be superior to that of BOLD contrast.

The spatial resolution limits for functional imaging contrast have begun to be characterized in brain regions with known functional organization. Ocular dominance columns and iso-orientation 'pinwheels' have been imaged in primary visual cortex (Menon et al., 1997a; Kim et al., 2000), lateral geniculate nucleus can be located (Chen et al., 1998), and discrete activation due to stimulation of adjacent vibrissae has been observed in whisker barrel cortex (Yang et al., 1996). While these results provide the possibility to study spatial processing in the brain at millimeter or even sub-millimeter scale, the spatial resolution in hemodynamic response is limited by the smallest vascular unit that adapts independently to brain activity (Villringer, 1999). Although this is still an issue of controversy, a large body of literature suggests that it is at the level of feeding arterioles. The size of the vascular territory of one arteriole is on the order of 1 mm^3, and this is probably the smallest functional unit that can be detected using fMRI.

3.4. Temporal resolution

The temporal resolution limits of fMRI are currently more confined by the vascular-hemodynamic response than the technology itself. Due to the fast imaging techniques like echoplanar and spiral scanning as well as the improvements in gradient hardware, it is possible to image a single slice in less than 100 ms and the whole brain within 2–3 s. The recent development of SENSE imaging with multicoil receivers can further improve the image sample rate, and the acquisition time for a single slice can be on the order of milliseconds (Pruessmann et al., 1999).

As a result of the high imaging speed of fMRI, event-related or even single-trial fMRI is available and has greatly expanded the spectrum of task designs and analytical techniques that can be used in neuroimaging studies (Buckner et al., 1996). The peak latency of several seconds represents a major limiting factor in the temporal resolution of functional imaging methods which rely on AFC, and behaves like a low-pass filter on the input stimulation function (Friston et al., 1994). As a result, conventional blocked designs with an on–off period less than 8 s are undesirable (Bandettini, 1999). Similarly, the stimulus presentation rate in event-related fMRI design with fixed inter-stimulus interval (ISI) should be slower than at least one trial per 10 s to avoid overlapping effects of adjacent trials. Short stimulus presentation rates (one trial per 2 s or less) have recently been proven feasible in event-related fMRI using a jittered ISI followed by deconvolution approaches, analogous to the usage in event-related potential studies (Dale and Buckner, 1997; Zarahn et al., 1997b). However, such event-related approaches rely very strongly on linearity between neural activity and hemodynamic responses. This has been found

to be roughly true in visual (Dale and Buckner, 1997) and prefrontal cortex (Cohen et al., 1997), but not in auditory cortex (Friston et al., 1998) and unclear in other brain regions associated with high-order cognitive functions. Some recent approaches to analyzing event-related fMRI include modeling of the hemodynamic response without a priori assumptions of its form (Ollinger et al., 2001b) and modeling of separate neural processes within each trial (Ollinger et al., 2001a).

As mentioned earlier, ASL perfusion contrast allows exquisite control over the vascular structure being observed, which is primarily capillary site. The impulse response of the ASL signal is expected to reach the peak earlier and have less variance in peak latency compared with that of the BOLD signal. In fact, high-field studies of perfusion activation using ASL contrast indicate that the perfusion signal begins to increase as early as 600 ms after the onset of functional stimulation (Silva et al., 1999), which is earlier than the 'initial dip' in BOLD contrast. The temporal resolution of ASL perfusion fMRI theoretically should be superior to that of BOLD contrast. However, a practical issue in ASL based fMRI is that the sample rate of perfusion images is only half of the actual sample rate because of the pairwise acquisition of label and control images, usually 4–8 s per perfusion image. Some recent developments in perfusion technique have improved the temporal resolution of ASL to be comparable with BOLD fMRI (Wong et al., 2000; Duyn et al., 2001), and event-related perfusion fMRI has been demonstrated using brief visual (Liu et al., 2000) and motor cortex stimulation (Yang et al., 2000).

The temporal resolution limits of fMRI have begun to be characterized by correlating the fMRI signal with behavioral responses, using event-related or even single-trial designs. A recent study has been able to derive the relative onset of activation of supplementary motor cortex relative to primary motor cortex using a delayed motor task following a readiness cue (Richter et al., 1997a). In another study on mental rotation, the width of individual fMRI responses in parietal regions has been demonstrated to be correlated with the duration of the task (Richter et al., 1997b). The capability of fMRI for detecting the across-region difference in the onset and return to baseline of the fMRI signal has also been tested. For example, visual stimuli with a temporal lag as short as 500 ms can be differentiated based on a shift in peak latency (Savoy et al., 1995). These data suggested that the fMRI signal, though blurred and slow, do follow the neuronal activity with some degree of fidelity.

While most efforts have been focused on how to increase imaging speed in fMRI, it is also quite important to improve the stability of the technique over relatively longer periods of time from minutes to hours or even days. The power of BOLD fMRI in detecting gradual variations in regional brain function is poor due to the intrinsic baseline drift (Aguirre et al., 1997), though inter-session effects of functional activation can still be modeled. In contrast, because perfusion fMRI is obtained by pair-wise subtraction, which markedly reduces drift effects, this approach appears to be suitable for imaging sequential changes in regional brain function as well as resting perfusion over periods greater than a few minutes. The quantitative CBF measured using ASL perfusion MRI has been proven to be highly reproducible over sequential scanning sessions at various intervals (Floyd et al., 2001).

3.5. Correlations with neurophysiology

Although fMRI has been widely used to study the operational organization of the human brain, it still remains unclear how accurately the fMRI signal can reflect the underlying neuronal activity. Recent studies comparing functional imaging with neurophysiological measures in experimental animals have begun to shed light on this fundamental question. The amplitude of the hemodynamic response was found to correlate approximately linearly with electrophysiological measures in rats (Yang et al., 1997; Ogawa et al., 2000) and in monkeys (Logothetis et al., 2001). Analysis of microelectrode recordings obtained during BOLD fMRI indicated that BOLD signal changes correlate best with local field potentials, rather than axonal firing patterns (Logothetis et al., 2001), reflecting information input and intracortical processing in a brain region. SNR for neurophysiological responses greatly exceeds that of BOLD contrast indicating the likelihood of 'invisible' sources of brain activation by statistical rejection in imaging experiments where the underlying neuronal activity is highly significant. However, evidences exist supporting that the BOLD signal correlates with axonal firing patterns rather than field potentials (Heeger et al., 2000; Rees et al., 2000), and controversy remains as to whether BOLD contrast reflects afferent, efferent, or possibly both signals in different situations. The spatial extent of activation in fMRI experiments has been found to correlate to a reasonable extent with neuronal activation measured electrophysiologically, considering the differences between these methods. A recent primate study (Disbrow et al., 2000) revealed a 55% concordance between the cortical topography of motor cortex generated using fMRI and microelectrode recordings, and the accuracy of fMRI is within about 1 cm. This is in agreement with clinical findings (see below).

Comparison of fMRI with neurophysiological measures in humans is less direct, primarily relying on EEG and MEG, which reflect summations of activity in individual cells. The most common approach to define the electromagnetic sources underlying the EEG/MEG signals is to assume a relatively small number of focal sources (equivalent current dipole models) (Scherg, 1992) or to explore continuous, weighted estimates of activation over the entire cortical surface (continuous current estimates) (Dale and Sereno, 1993). Source localization of visual evoked EEG/MEG activity showed correspondence with fMRI activation foci, based on the data acquired using interleaved (Bonmassar et

al., 1999) or separate EEG/MEG and fMRI recordings (Ahlfors et al., 1999). Building on the millisecond temporal resolution in EEG/MEG and the millimeter spatial resolution in fMRI, the combination of these two modalities is able to render a powerful tool to explore the complex dynamics of neural processes with high spatiotemporal resolution (Dale and Halgren, 2001). Typically, data from fMRI can be used to spatially constrain or bias (Liu et al., 1998) the EEG/MEG inverse solution toward locations that are hemodynamically active during a specific task. Recent examples of this spatiotemporal imaging technique include applications to target detection (Menon et al., 1997b), motion and shape processing (Wang et al., 1999), auditory 'oddball' (Opitz et al., 1999), and semantic judgement (Dale et al., 2000).

Concurrent EEG and fMRI recording has been available recently with minimum interference from each modality (Allen et al., 2000; Hoffmann et al., 2000). The technical challenges for simultaneously recording electrophysiological signals with MR scanning include the cardioballistogram effects associated with subject's pulse (Pulse Artifact) and dynamic magnetic field interference primarily caused by switching MR gradients. The cardioballistogram artifacts can be minimized by subtracting the average waveform related to pulsation (Allen et al., 1998) or spatial filtering (Bonmassar et al., 1999), and the switching gradient interference can be largely removed by subtracting the average waveform synchronized to gradient switching (Allen et al., 2000) or filtering out certain frequency ranges associated with gradient artifact either in frequency or time domain (Hoffmann et al., 2000).

4. Selected applications of fMRI

The advent of fMRI has greatly expanded opportunities for the application of functional neuroimaging to basic and clinical neuroscience. A comprehensive review of existing applications is well beyond the scope of any single review article, so this section will focus on selected previous and potential future applications of relevance to clinical neurophysiologists. The reader is referred to other reviews for applications in cognitive neuroscience (Cabeza and Nyberg, 2000; D'Esposito, 2000; Hammeke et al., 2000).

4.1. Presurgical localization

Since fMRI provides sufficient sensitivity to map functional activation within a single subject, one of the earliest clinical applications of fMRI was for presurgical localization of functional regions with respect to brain tumors requiring neurosurgical resection. In several studies, fMRI localization of finger tapping paradigms has been compared with intraoperative cortical stimulation. Because cortical stimulation is essentially a 'lesion' study confined to the superficial cortex while BOLD fMRI measures endogenous function throughout the brain, these modalities may be expected to differ somewhat in functional localization. Nonetheless, an excellent correlation has been consistently found between regions of motor activation seen on BOLD-fMRI and intraoperative cortical stimulation (Yetkin et al., 1997). In most studies that have compared sensorimotor localization with fMRI and corticography, agreement has been within 1 cm.

fMRI has also been compared to intracarotid amobarbital testing (IAT) for presurgical lateralization of language and memory. IAT has been the gold standard for identifying lateralization of language and memory function preoperatively, but it is invasive and therefore carries risk. In addition to being completely non-invasive, fMRI offers the capability of spatially resolving functional activation within each hemisphere, potentially guiding tailored resections to spare eloquent cortex. Several groups have reported initial successful functional activation studies for lateralizing language. Binder et al. (1996) reported a cross validation study comparing language dominance determined by both fMRI and IAT in 22 epilepsy patients. A semantic decision task was used to activate a distributed network of brain regions involved in language specialization. Excellent agreement in language laterality with fMRI versus IAT was observed in this and subsequent studies, though there remains some controversy concerning the optimum task for lateralizing language. Covert verbal fluency tasks typically provide excellent activation in Broca's area, but often lack strong activation in posterior language areas and do not provide a measure of subject performance. For this reason, the majority of studies have used semantic decision tasks.

A complex visual scene encoding task has been used to lateralize mesial temporal lobe memory dysfunction in patients with temporal lobe epilepsy (TLE), and showed a good correlation with memory lateralization by IAT in preliminary studies (Detre et al., 1998b), while a mental navigation task successfully lateralized temporal lobe seizure foci (Jokeit et al., 2001). Over the past few years, several additional studies have consistently shown that fMRI provides reliable localization, at least for language lateralization, including one study using real-time analysis methods to provide immediate results (Fernandez et al., 2001). While initial enthusiasm for using fMRI in presurgical lateralization as a non-invasive replacement for IAT persists, these are fundamentally different approaches whose results may be complementary rather than entirely reduplicative (Killgore et al., 2000).

Functional imaging has also contributed to the localization of seizure foci. Lateralization of TLE is predicted by interictal mesial temporal lobe (mTL) hypometabolism using ^{18}fluorodeoxyglucose PET (^{18}FDG-PET), and the presence of interictal abnormalities on PET or SPECT scanning has also been associated with an improved outcome from epilepsy surgery (Duncan, 1997). In some studies, partial uncoupling of CBF and metabolism has been demonstrated in the resting state, with FDG-PET showing better lateralization than $H_2{}^{15}O$-PET measurements of CBF (Leiderman et al., 1992; Gaillard et al., 1995; Fink et al.,

1996). These findings indicated that blood flow based methods might not be useful for lateralizing interictal hypometabolism. However, a recent study successfully demonstrated decreased regional cerebral blood volume (rCBV) on the side of the epileptogenic focus using a bolus-contrast MR perfusion technique in patients with TLE (Wu et al., 1999). Interictal hypoperfusion has also been demonstrated using perfusion MRI with ASL (Wolf et al., 2001). Although such hemodynamic measurements may not provide as good sensitivity as FDG-PET, the ability to combine them with routine clinical MRI suggests a possible role for perfusion MRI in patient screening.

Ictal events have long been known to be associated with marked increases in rCBF and metabolism. In the case of focal seizures, metabolic imaging may demonstrate regional abnormalities that are missed by ictal EEG, presumably reflecting superior spatial resolution for metabolic imaging. Ictal SPECT scanning remains the most commonly employed imaging method for localizing ictal foci, and has the unique logistic advantage of allowing tracer to be administered intravenously during an event with scanning carried out up to several hours later. However, there has also been some success using fMRI to localize ictal metabolic changes at higher spatial resolution. Several groups have scanned patients during clinical or subclinical seizures, and have demonstrated time-dependent alterations in BOLD signal intensity, which have correlated with seizure foci as determined by standard methods (Jackson et al., 1994; Detre et al., 1995). In one case, cross-correlational analysis revealed corticothalamic coupling during focal seizures (Detre et al., 1996), suggesting a potential role for fMRI in identifying networks of seizure propagation. Perfusion MRI can also reveal focal hyperperfusion in epilepsy partialis continua, and in the immediate postictal state. With the recent advent of methodologies that allow concurrent EEG and fMRI, it has been possible to localize regional metabolic changes accompanying spike discharges, either using spike-triggered approaches (Krakow et al., 1999) or using retrospective analysis of continuously acquired data (Lemieux et al., 2001). The approach of concurrent EEG and fMRI recording tends to be a more efficient and accurate way to determine epilepsy foci compared with spike-triggered fMRI approach and allows patient state monitoring during scanning (Krakow et al., 1999). In addition to contributing to clinical localization, these approaches should provide new insights into the anatomical and pathophysiological correlates of unifocal and multifocal spike discharges (Krakow et al., 2001a,b). This application of combined electrophysiology and fMRI represents perhaps the most obvious and attainable opportunity to capitalize upon the temporal resolution of EEG and the spatial resolution of fMRI. This may be of particular value in the presurgical evaluation of neocortical epilepsy where paroxysmal activity on EEG may remain poorly localized. Examples of fMRI results in patients with epilepsy are shown in Fig. 4.

4.2. Differential diagnosis of neuropsychiatric disorders

Intuitively, it would seem that fMRI techniques should be useful in the differential diagnosis of neuropsychiatric disorders, revealing alterations in regional brain function even

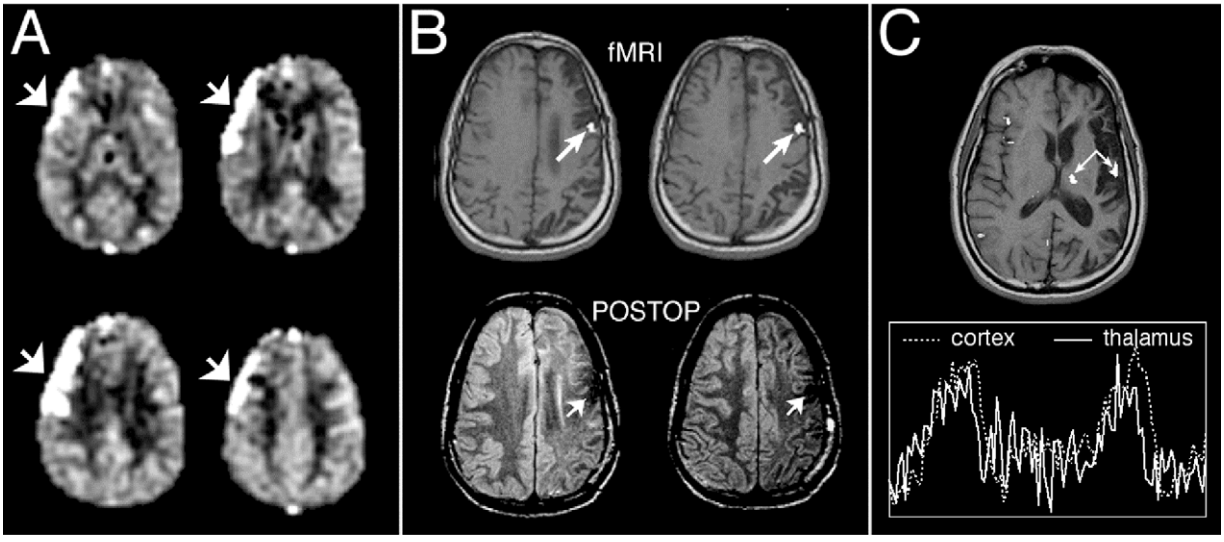

Fig. 4. Examples of functional MRI studies in epilepsy. (A) Quantitative ASL perfusion MRI in a patient with epilepsy partialis continua with left facial twitching. Markedly increased perfusion is seen in the right frontal lobe (arrows). Grayscale shows perfusion from 0 to 150 ml 100 g^{-1} min^{-1}. (B) fMRI and postoperative structural scans from a patient with seizures consisting of right sided weakness, often with speech arrest. fMRI data indicate the location of onset for spontaneous stereotyped increases in BOLD contrast attributed to subclinical seizures (large arrows), in a region of encephalomalacia. The patient subsequently underwent curative epilepsy surgery performed with cortcography. Postoperative scans show that the region of successful subpial transection (small arrows) corresponds to the site of seizure onset detected by fMRI. (C) Cross-correlation analysis of fMRI data from the same patient as in (B), showing corticothalamic coupling during subclinical ictal events (arrows). Graph of signal changes shown below.

prior to any structural changes. fMRI methods are primarily sensitive to flow effects, either at rest using perfusion MRI or in response to task activation with perfusion MRI or BOLD contrast. Certainly, alterations in resting regional cerebral perfusion can be seen in patients with cerebrovascular disorders (Detre et al., 1998a), but for other types of pathology fMRI provides only an indirect measure of neural dysfunction. Perfusion MRI has also demonstrated alterations in resting perfusion in patients with dementia (Alsop et al., 2000), and in TLE as noted above. One group has observed highly localized changes in resting BOLD contrast that correlate with cognitive performance in both patients with Alzheimer's disease and in mutant mice with memory deficits (Small et al., 2000). These changes are thought to reflect alterations in oxygen metabolism, though BOLD contrast reflects a complex interaction between metabolic, hemodynamic, and biophysical factors.

Numerous studies have attempted to demonstrate abnormal responses to task activation in a variety of neuropsychiatric syndromes. Alterations in fMRI responses to primary sensorimotor or cognitive tasks have been observed in some psychiatric syndromes, but these have been relatively non-specific (Callicott and Weinberger, 1999). For cognitive activation, fMRI studies are further confounded by task performance, since patients typically perform worse than controls. Although this seems counter-intuitive at first, it is generally incorrect to assume that fMRI during task activation will contribute to the understanding of an unusual cognitive deficit, particularly in the absence of extensive normative data obtained with parametric variations in task difficulty and performance. Even the direction of expected change in fMRI activation with performance is uncertain. Existing data indicate that activation may increase with performance in certain regions, at least over certain ranges, while in other regions activation may decrease with increasing performance. The latter response has been observed in dorsolateral prefrontal cortex during pharmacological modulation of working memory performance (Furey et al., 2000; Mehta et al., 2000). However, a recent study in patients at risk for Alzheimer's disease demonstrated alterations in activation which correlated with APO-E status and subsequent memory decline (Bookheimer et al., 2000), suggesting that at least in some cases diagnostic or predictive value can be obtained.

4.3. Recovery of function and neuroplasticity

fMRI may also have a role in elucidating mechanisms of neural plasticity. Neural correlates of phantom limb symptoms following amputation have been observed (Borsook et al., 1998), along with an abnormally large region of contralateral motor cortex fMRI activation with stump movement in a patient whose left arm had been amputated at an early age (Dettmers et al., 1999). Differential language lateralization has been observed in deaf patients as compared to hearing subjects (Neville et al., 1998) and activation of visual cortex has been observed with tactile stimulation in a blind individual (Sadato and Hallett, 1999).

Several groups have begun to define changes in functional activation following stroke. Although most of these studies were performed in the chronic phase, the use of functional imaging to predict outcome and in the acute phase would have obvious implications for utilization of rehabilitation services. Cramer et al. (1997) identified increased activation of a motor network in the unaffected hemisphere to a greater extent than found in controls, an increased degree of supplementary motor area activation, and perilesional activation. Similar findings were also reported by Cao et al. (1998). Based on fMRI findings, the location of ipsilateral motor cortex activation both in normals and following stroke appears to be ventrolateral to the region that is activated by contralateral movements (Cramer et al., 1999). Thulborn et al. (1999) and Cao et al. (1999) have applied fMRI to language recovery. Spontaneous redistribution of function to the right hemisphere was observed within days of the stroke and continued for months afterward. However, a similar prospective PET study of language activation in patients with acute left hemispheric stroke concluded that although right hemispheric activation clearly occurred, recovery of useful language only correlated with left hemispheric activation (Heiss et al., 1997). These results highlight the difficulties of interpreting regional activation in terms of being either necessary or sufficient for supporting a given cognitive or sensorimotor function. Similarly, due to the potential confound of vascular reorganization following ischemic brain injury, it remains difficult to conclusively prove that all of the perilesional effects observed with fMRI are functionally significant.

An emerging application of fMRI is in brain bionics. Implantable stimulators are currently used in the management of a variety of neurological syndromes including Parkinson's disease, epilepsy, and chronic pain. fMRI can be used to visualize the hemodynamic effects of neurostimulation (Rezai et al., 1999). fMRI has also been used to guide the placement of electrodes into brain regions under conscious control such as motor cortex (Mao et al., 1999), allowing paralyzed patients to use motor imagery to control robotics devices (Kennedy and Bakay, 1998). fMRI should also be of use in monitoring functional reorganization resulting from brain–electrode interactions.

5. Conclusions

fMRI methods provide a relatively inexpensive and non-invasive means of measuring regional brain function, and is now available widely. Over the past decade, methods for acquiring and analyzing fMRI data have evolved considerably, resulting in improved reliability. fMRI is currently the primary method used for studying regional brain responses to cognitive tasks. An increasing body of evidence indicates

that BOLD fMRI can reliably detect regional task activation due to sensorimotor and language tasks, and that this information can contribute to neurosurgical planning and to neuropsychiatric prognosis. Recent evidence suggest that perfusion MRI using ASL will be useful for longitudinal studies, both for imaging CBF at rest and in response to task activation. The development of methods to allow concurrent fMRI and EEG should allow a new class of studies that capitalize on the spatial and temporal resolution advantages of each modality. Like most other methods for visualizing regional brain function, fMRI utilizes hemodynamic changes as a surrogate marker for neural activity. Ongoing basic research will hopefully provide additional insights into the mechanisms and mediators of the coupling between CBF and neural function. This information will provide added specificity to the interpretation of fMRI studies. The extent to which this coupling remains intact, particularly in clinical populations, needs to be carefully interpreted and may even have diagnostic significance.

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