Published in final edited form as:

Int J Psychophysiol. 2009 July ; 73(1): 33–42. doi:10.1016/j.ijpsycho.2008.12.020.

Current Trends and Challenges in MRI Acquisitions to Investigate Brain Function

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Abstract

Functional magnetic resonance imaging (fMRI) studies using the blood oxygenation level dependent (BOLD) response have become a widely used tool for noninvasive assessment of functional organization of the brain. Yet the technique is still fairly new, with many significant challenges remaining. Capitalizing on additional contrast mechanisms available with MRI, several other functional imaging techniques have been developed that potentially provide improved quantification or specificity of neuronal function. This article reviews the challenges and the current state of the art in MRI-based methods of imaging cognitive function.

Keywords

Functional MRI; Neuroimaging; Cerebral blood flow; Cerebral blood volume; BOLD; Cognitive neuroscience

Functional MRI (fMRI) using the blood oxygenation-level dependent (BOLD) response is by far the most commonly employed method for noninvasive localization of activity in the brain in cognitive psychology investigations. The method is non-invasive, does not employ ionizing radiation, and generally produces reliable depictions of brain activity with reasonable spatial resolution and whole-brain coverage.

fMRI seems to have arrived as an established, appealing method. However, it is in fact a relatively new, even primitive method with considerable upside potential as methods improve. BOLD and other fMRI methods are advancing fairly rapidly, and there is some sentiment that the standard BOLD method is virtually obsolete. Such evolution is typical of new technologies, though not commonly appreciated in the rapid embrace of fMRI in cognitive psychophysiology to date.

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Basics of BOLD

Using the blood oxygenation-level-dependent (BOLD) response, fMRI assesses magnetic susceptibility differences between oxygenated and deoxygenated hemoglobin in microcirculation (Ogawa et al., 1992, Ogawa et al., 1990). fMRI provides a window into the local oxygenation state of hemoglobin, a state which changes depending on a number of parameters, of which blood flow (including blood volume, perfusion, and blood velocity) and oxygen extraction fraction are the primary links to local metabolism and neuronal function. However, the relationship between the oxygenation state through magnetic susceptibility is not direct.

Signal intensity and spatial localization in MRI rely on a uniform magnetic field existing throughout the sample of interest. Much effort is devoted to properly designing and shimming the main magnetic field to achieve uniform intensity. A tiny but detectable fraction of the protons present in water in the body will align with this strong, steady magnetic field. The tissue of interest is occasionally subjected to a brief electromagnetic radio-frequency (RF) pulse, essentially tilting the aligned protons off the axis of the main magnetic field. The protons then precess around the main field axis at a known frequency proportional to the main magnetic field. That field can be manipulated to identify the location of certain types of activity. The rate of precession can be used, for example, to encode the spatial position of the protons for imaging, by creating a gradient in the magnetic field along one direction (Lauterbur, 1973). The protons then precess at different frequencies depending on their location, as the magnetic field that they experience is due to both the main magnetic field and the applied imaging gradient. In the course of precession, the protons can vary in their alignment, characterized as phase relationships among the protons, discussed below.

Efforts to create a uniform magnetic field are limited by the fact that different tissues and materials possess a property called magnetic susceptibility, a property that reflects the magnetizability of a substance. This magnetic susceptibility, denoted by χ , affects the magnetic field that protons experience inside that tissue or material. This disrupts the uniformity of the magnetic field and results in signal loss if the disrupting substance is small compared to an imaging voxel. In particular for functional imaging, the magnetic susceptibility of oxygenated and deoxygenated blood differ, with oxygenated blood having a magnetic susceptibility closer to that of the surrounding tissue. The difference in magnetic susceptibility between oxygenated and deoxygenated blood is small, on the order of tenths of parts per million (ppm) (Weisskoff and Kiihne, 1992). However, the protons in the tissue surrounding the blood vessels are affected by this microscopic field variation, and it results in a loss of coherence in the precession frequency and hence the phase of the protons. With loss of phase coherence comes signal cancellation and ultimately a decrease in signal intensity. Since oxygenated blood has susceptibility close to that of the surrounding tissue, it does not disrupt the magnetic field as much as deoxygenated blood. The signal from MRI increases with increased oxygenation of the blood, providing the fMRI BOLD signal.

A slightly counterintuitive aspect of the fMRI BOLD mechanism is that the oxygenation of the blood supply increases, rather than decreases, under local activation of the parenchyma. The exact mechanism of this increase of oxygenation due to neuronal activation is still under consideration. However, during activation there is a local increase in the oxygen extraction fraction to supply the increased metabolic demands by the activated neural tissue, likely including both neurons and glial cells. In response to this increased oxygen extraction, the vascular system responds with a localized increase in blood flow that more than compensates for the increased utilization. The oversupply results in an overall decrease in deoxygenated blood and an increase in the BOLD fMRI signal.

For an overview of BOLD phenomenon, experimental design, and analysis, see several excellent texts on the topic (Huettel et al., 2004, Buxton, 2001, Jezzard et al., 2001).

Current Challenges in BOLD fMRI

Although BOLD-based fMRI is widely used, several challenges exist that impede absolute determination of functional activity from the detectable signal. These include: venous contributions of the signal, bulk magnetic susceptibility signal losses and distortions, reliability and calibration between sites, and indirect coupling to the neuronal response.

Venous contributions

BOLD-based fMRI relies on changes of the local magnetic field within large vessels (arteries and veins), in microvessels (arterioles, capillaries, venules), and in tissue surrounding large and small vessels. Changes in blood oxygenation at the site of activation can result in apparent activations in veins that drain blood from the activated areas, often resulting in detection of signal in far-removed places or even outside the brain in the draining sinuses (Duong et al., 2003).

Moderate levels of diffusion-weighting have been applied in order to suppress intravascular BOLD signals in vessels potentially far-removed from the site activation (Boxerman et al., 1995, Song et al., 1996, Zhong et al., 1998). Blood has a higher molecular diffusion coefficient than the parenchyma and flows within the vascular network, resulting in a higher apparent diffusion coefficient (ADC) for the flowing blood than the parenchyma. Therefore, the use of diffusion gradients can suppress both small and large vessels' intravascular BOLD signal. The first diffusion-weighted fMRI studies were performed at 1.5 T and showed that a significant portion of the gradient-echo BOLD fMRI signal originates from intravascular protons (Boxerman et al., 1995, Song et al., 1996, Zhong et al., 1998). However, the extravascular component of the BOLD signal arising from the magnetic susceptibility changes around large vessels can be suppressed only by using spin-echo acquisitions. When diffusion-weighting has been added to spin-echo fMRI sequences, the only component of the functional signal that remains unsuppressed is the extravascular contribution arising from susceptibility effects around small vessels. Since the functional signal contribution in a diffusion-weighted spin-echo fMRI experiment is quite small, the diffusion-weighting has to be optimized depending on the magnetic field and the sequence parameters to maximize sensitivity (Michelich et al., 2006). The optimization of diffusion-weighting has been also extremely useful to understand the various functional signal compartments at 3 T (Jochimsen et al., 2004, Jochimsen and Moeller, 2005) and at higher fields (Lee et al., 1999, Jin et al., 2006). For instance, diffusion-weighted spin-echo fMRI experiments at 9.4 T have shown that the large vessel contribution to the functional signal can be considered negligible at this field strength (Lee et al., 1999).

Magnetic Susceptibility Signal Loss and Distortion

BOLD fMRI is acquired with contrast that reflects the magnetic susceptibility signal. However, different tissues also possess different magnetic susceptibility, and this can lead to artifacts during functional imaging. Since this effect disrupts the uniformity of the magnetic field, it is referred to as magnetic field inhomogeneity or bulk magnetic susceptibility (BMS). In the brain, the magnetic susceptibility differences between soft tissues ($\chi = -9 \times 10^{-6}$) and air ($\chi = 0.4 \times 10^{-6}$) result in field inhomogeneity, especially at regions around air/tissue interfaces (Yoder et al., 2004). This makes certain regions in the brain particularly problematic to image, including the orbitofrontal cortex and amygdala, which are of very considerable interest in cognitive, affective, and clinical psychophysiology.

Figure 1 provides an example of the image distortions and signal loss that result from air/tissue magnetic susceptibility differences in fMRI images that are weighted to reflect susceptibility differences in blood. Generally, fMRI images are collected as gradient echo images with fairly long echo times (25–40 ms) and as single-shot acquisitions with long data acquisition windows. These properties contribute to susceptibility-induced signal loss and geometric image distortions, respectively.

High-field systems (≥ 3 T) bring improvement in spatial localization from BOLD fMRI. This is due to the mechanism by which the BOLD contrast is created. In a high field system, the field gradients around the microvasculature are large enough that movement of protons around the vessel during the echo time will create enough variability in phase for dephasing the signal. Due to this mechanism at high field, spin echo sequences for BOLD fMRI are feasible, instead of relying on gradient echo sequences that are used at lower field strengths. Due to the use of spin echo sequences, higher-field systems may not suffer as significantly from magnetic susceptibility-induced signal loss due to gradients of the magnetic field across a voxel. However, since the magnitude of field inhomogeneity scales with the magnetic field, magnetic susceptibility-induced image distortions will worsen.

Several approaches exist to compensate for BMS-induced signal loss and distortions, considered briefly here, in three categories: 1. Interventions in setup of the experiment, 2. Pulse sequence modifications, 3. Post-acquisition image processing approaches.

BMS considerations in experimental setup

Several devices have been built to modify the magnetic field shape in the orbitofrontal region using a dielectric mouth insert (Wilson and Jezzard, 2003, Wilson et al., 2003, Cusack et al., 2005) or a mouth shim coil (Hsu and Glover, 2005). These devices can result in a more uniform magnetic field in the orbitofrontal region but may cause degradations in magnetic field uniformity elsewhere in the brain. In addition, they may be sensitive to subject motion and may require subject-specific customization of the oral insert.

In addition to devices reshaping the magnetic field, a major advance in MRI data acquisition has been the use of parallel receiver networks. Instead of using a single volume receive coil, arrays of receiver coils are arranged around the object with each receiver coil being sensitive to a subset of the object. By taking advantage of the localized sensitivity of the receiver coils, several methods have been developed to acquire data more quickly by subsampling the data space. The full images are reconstructed by considering the spatial sensitivity of the individual coils. By subsampling, data acquisition time for a single image is shorter, resulting in less BMS-induced distortions in the image. Parallel image reconstruction can occur in image space as in SENSE (Pruessmann et al., 1999), k-space as in GRAPPA (Griswold et al., 2002), or other methods (Blaimer et al., 2004). Parallel receivers are just the beginning of the use of arrays in fMRI. Parallel transmit methods are being developed to allow for shaping of the transmit slice profile (magnitude or phase) for combating non-uniform transmit profiles (bias field) or susceptibility-induced signal loss in functional MRI (Katscher et al., 2003).

Pulse sequence modifications to address BMS

Three families of pulse sequence modifications provide means of addressing BMS-induced signal loss due to gradients in the magnetic field through a slice, *i.e.* through-plane dephasing. First, RF pulses have been developed that apply a phase pattern or profile across a slice to exactly cancel the phase profile that results from BMS-induced dephasing (Ro and Cho, 1992, Stenger et al., 2000, Stenger et al., 2002). These methods require that the phase profile of each slice be measured, then they apply a low-resolution 3D RF pulse to the slice of interest, taking advantage of the smoothly varying nature of the magnetic field distribution map. This

is an exceptionally demanding method at acquisition time, with substantial barriers to routine implementation. The recent development of transmit SENSE may make this more feasible (Katscher et al., 2003). However, sensitivity to subject motion and real-time implementation demands will continue to challenge its use.

Second, pulse sequences have been developed that trade acquisition time for improved signal from high-susceptibility regions. The simplest approach to reduce BMS-induced signal loss from through-plane gradients is to reduce the dimensions of the voxel in the slice-select direction – thus, thinner slices (Merboldt et al., 2000, Wadghiri et al., 2001, Bellgowan et al., 2006). Bellgowan et al. compared medial temporal activations from a 4 mm acquisition and from combining successive slices from a 2 mm acquisition and showed gains in functional temporal signal-to-noise ratio and in contrast-to-noise ratio, the latter referring to the ratio of signal change during activation divided by the temporal variability, thus, the discriminability of activation in an fMRI experiment.

A third family of methods using an acquisition modification employs an imbalanced slice-select gradient as a compensation for the induced magnetic field gradient (Frahm et al., 1988, Glover, 1999, Yang et al., 1997, Yang et al., 1998a). Several different imbalanced slice-select gradients are used to compensate for varying BMS-induced gradients within a slice. A single-shot methodology has been developed to measure two functionally weighted images simultaneously, one with a single z-compensating gradient and one without any compensation (Heberlein and Hu, 2004, Song, 2001). When combined, these images provide some recovery from susceptibility-induced signal loss. However, a different imbalanced gradient is needed to address different BMS-induced gradients within a slice. This necessitates multiple acquisitions in order to compensate for several dephasing gradients.

Post-acquisition image processing for BMS

The susceptibility-induced distortion artifact is an effect that has been extensively addressed in the MRI methodology literature. The appearance of the distortion depends on the data acquisition (k-space) trajectory and timing. For a raster-grid Cartesian acquisition, such as in echo planar imaging (EPI), the BMS induces a phase ramp in data space that causes a geometric shift in image space along the slow-acquisition axis, *i.e.* the phase encode axis (Sekihara et al., 1984). When a spiral trajectory is used for acquiring the data, the slow-acquisition axis is in the radial direction, and the BMS-induced distortions result in a blurring in the radial direction (Yudilevich and Stark, 1987). Many correction methods exist to compensate for the BMS-induced off-resonance accrual of phase during the data acquisition. Most methods start with a measurement of the distribution of the magnetic field due to BMS-induced distortions, *i.e.* measurement of a field map. After the field map is formed, correction methods proceed to attempt to compensate for the predicted distortions. For EPI trajectories, a common and effective way to correct for the resulting geometric shift is to form a pixel-shift map that remaps the pixels to their original, undistorted locations (Sekihara et al., 1984, Sumanaweera et al., 1993, Jezzard and Balaban, 1995, Reber et al., 1998). For spiral acquisitions, a method called conjugate phase is usually employed to attempt to undo the phase accrual due to BMS by multiplying the data by the conjugate of the phase accumulated, found from multiplying the field map by the timing during the acquisition (Noll et al., 1991, Man et al., 1997b, Schomberg, 1999). Other methods employ a field map that is also measured in a BMS-distorted acquisition (Kadah and Hu, 1997) or utilize an auto-focusing approach that attempts to refocus the point spread function (Noll et al., 1992, Man et al., 1997a). Recently, iterative image reconstructions have been presented that model the phase accrual due to BMS-induced magnetic field inhomogeneities and result in more accurate image reconstructions in the vicinity of air/tissue interfaces (Harshbarger and Twieg, 1999, Sutton et al., 2003, Twieg, 2003).

In addition to corrections for the distortion artifacts, methods are under development for incorporating the through-plane gradients in the signal model of an iterative image reconstruction framework (Sutton et al., 2004, Liu and Ogawa, 2006). Such post-acquisition methods may allow for compensation of a wide range of through-plane gradients within a slice.

Reliability and Calibration Between Sites

In order for fMRI to be a reliable method of inquiry in cognitive neuroscience, the reliability of the signal needs to be well understood. In light of reports of changes in the BOLD response as a function of caffeine (e.g. (Mulderink et al., 2002)) and neuropathology (e.g. (Pineiro et al., 2002)), one might wonder about the general applicability to distinguish changes in localized function related to a particular population and how results at one research site may relate to another site. In particular, several studies have examined and found high reliability in fMRI acquisition for within-subject, between-subject, and between sites. In light of early promising results from multicenter fMRI studies such as those in (Casey et al., 1998) and (Ojemann et al., 1998), a number of recent studies have been conducted to provide a concerted effort to examine reproducibility of functional MRI responses from different sites. A conservative criterion for the demonstration of multicenter compatibility would be to demonstrate a highly reproducible BOLD response rather than simply similar thresholded activation maps, as has been used in previous studies.

One of the larger efforts in this direction has been conducted by fBIRN (www.nbirn.net), involving 14 different MR laboratories that use magnets of three different field strengths with three different scanner manufacturers as well as different pulse sequences (Zou et al., 2005, Zou et al., 2004, Thomason et al., 2007, Glover et al., 2004, Friedman and Birn, 2004, Friedman et al., 2004). The initial work has highlighted many factors important to ensure compatibility between different sites. For example, the fBIRN group has shown the importance of simple but regular standardized quality control measures to maintain comparability of scanners using both phantoms (Glover et al., 2004) and human data (Stocker et al., 2005). In Friedman and Birn (Friedman and Birn, 2004) and Friedman et al (Friedman et al., 2004), differences in the smoothness and sensitivity of fMRI images were compared among ten sites. Significant smoothness and sensitivity differences were found that related to imaging sequence, gradient performance, image reconstruction and filtering methods, and field strength. Due to different sensitivities to the BOLD response at different sites, these studies have also motivated an effort to calibrate fMRI responses across sites and individuals using a breath-hold task (Thomason et al., 2007). Although the initial results are promising, more work needs to be done to determine protocols for quantitatively assessing functional response across subjects and sites.

Spatial Resolution

Spatial resolution in BOLD fMRI is limited by both the localization of the signal and the physiology of control of blood flow to neural tissue. Issues relating to the venous weighting of BOLD fMRI signals were discussed above and represent a significant limitation of localization. This venous weighting results in a loss of spatial specificity and spatial resolution of the BOLD response. As stated above, higher magnetic field strengths and diffusion weighted acquisitions allow for decreased sensitization to large vessels and better localization to the microvasculature. In addition to the changes in vascular weightings, higher magnetic fields also allow for the combination of high spatial resolution and the detection of an “initial dip” in the biphasic BOLD response (Ugurbil et al., 2000). The initial dip is thought to correspond to a phase lag between the increased oxygen utilization by the parenchyma and the vascular response of increased blood flow. This results in an initial increase in deoxygenated blood and a decrease in the BOLD signal. After a short delay, the vasculature responds with a flow increase causing an increase in oxygenation both at the site of activation and continuing downstream in the veins. The initial dip is thought to be more specific to the site of activation

than the positive BOLD signal. Using this initial dip, Duong et al. (Duong et al., 2000) were able to map submillimeter optical dominance columns in the cat. However, due to the low signal-to-noise ratio of this initial dip, its use in high-resolution studies in humans has been limited.

Even without using the specificity of the initial dip, Shmuel et al. were able to estimate a point spread function for gradient echo BOLD at approximately 2 mm in human visual cortex (Shmuel et al., 2007). Ultimately, with BOLD being coupled to the vasculature, the physiologic control of vascular response limits the spatial and temporal resolution of the BOLD method. Recent advances have approached this physiological limit (Yacoub et al., 2007), but other MR phenomena may offer additional imaging possibilities.

Other Functional MRI Modalities

Several other options exist to use MRI to examine functional changes that accompany neuronal activation. These include perfusion-based techniques, blood-volume-based measures, diffusion-weighted imaging, and several other non-vascular functional imaging methods.

Perfusion-Based Functional MRI

Perfusion-based fMRI can be achieved noninvasively by using the arterial spin labeling (ASL) approach, which utilizes magnetically labeled arterial blood water as a diffusible tracer for CBF measurements, in a fashion similar to that used for ^{15}O PET scanning (Detre et al., 1992, Williams et al., 1992). Whereas traditional perfusion measurements need injection of a tracer, ASL uses water in blood as an endogenous perfusion contrast agent. ASL is a subtraction technique whereby two successively acquired images are subtracted, one with and one without proximal labeling (i.e., magnetization preparation including spoiling or inversion) of arterial water spins. The perfusion contrast is induced by the exchange of these labeled spins with spins within the microvasculature and tissue of interest (Figure 2). ASL reflects directly and quantitatively localized perfusion measures, whereas BOLD reflects a complex interaction of blood flow, blood volume, and oxygen extraction fraction.

Current Techniques in ASL—Currently, there is a large family of ASL methods that can primarily be classified into two categories: continuous arterial spin labeling (CASL) techniques and pulsed arterial spin labeling (PASL) techniques. CASL uses long RF pulses (2–4 seconds) in combination with a slice selection gradient to adiabatically invert the arterial magnetization as it flows through a plane in arteries in the neck. However, the application of long off-resonance RF pulses induces magnetization transfer (MT) effects. In spite of some solutions to control for these effects, CASL is usually limited to single-slice perfusion imaging. In PASL, a short RF inversion pulse is applied to produce a bolus of labeled magnetization at a tagging location proximal to the slice of interest. PASL has met with increasing success due to ease of implementation. The PASL subfamily includes numerous pulse sequences, such as EPISTAR (Echo-Planar Imaging and Signal Targeting with Alternating Radiofrequency) (Edelman et al., 1994), FAIR (Flow-sensitive Alternating Inversion Recovery) (Kwong et al., 1995, Kim, 1995), PICORE (Proximal Inversion with a Control for Off-Resonance Effects) (Wong, Buxton et al. 1997), QUIPSS (QUantitative Imaging of Perfusion using a Single Subtraction) (Wong et al., 1997) and TILT (Transfer-Insensitive Labeling Technique) (Golay et al., 1999). All of these methods share some basic principles, differing in the strategies by which the tagged and control RF pulses are applied.

Benefits and Challenges of ASL

Like BOLD, ASL reflects vascular changes and only indirectly reflects neuronal activity. However, it provides a quantitative measure of cerebral blood flow (CBF) that may be more

closely tied to neuronal function. The primary benefits of ASL fMRI include: it allows for absolute measurement of CBF, it may provide higher spatial specificity of neuronal activity than BOLD, and it is less sensitive to signal baseline drift than BOLD fMRI. Several recent review articles discuss the comparisons between BOLD and ASL methods for functional imaging (Brown et al., 2007, Liu and Brown, 2007, Fernandez-Seara et al., 2007, Federspiel et al., 2006, Mildner et al., 2005). For a quick summary of this comparison, see Table 1 in (Detre and Wang, 2002).

Despite these advantages of ASL fMRI, it is still an emerging technique and has not replaced more invasive procedures for the assessment of cerebral blood flow in patients or replaced BOLD fMRI for mapping functional activation. Obstacles to the adoption of ASL approaches in functional imaging include several challenges: they produce a low signal change for activation with a relatively complex analysis procedure, they are more difficult to implement accurately because of transit delay effects, they usually have less imaging coverage, and they suffer from even lower temporal resolution than BOLD fMRI (which is already low relative to many types of neural events of interest).

Quantification of ASL—ASL fMRI techniques may be used in a qualitative fashion similar to that of BOLD fMRI. However, they are also capable of quantifying CBF in ml/min/100g. In contrast, the BOLD signal reflects a complex combination of CBF, cerebral blood volume (CBV), and oxygen consumption changes (CMRO₂) (Ogawa et al., 1993). The absolute quantification of CBF provided by ASL has shown to be more reproducible across subjects and generally over longer periods of time than the BOLD signal. In addition, it may be useful for individual clinical case studies and in studies for which normal and patient samples are compared (Alsop and Detre, 1996, Ye et al., 1996, Kim and Tsekos, 1997, Yang et al., 1998b, Wong et al., 1998b).

Localization of ASL signal—There is a more direct coupling of local neuronal activity to CBF than to the BOLD contrast, which reflects CBV and CMRO₂ as well as CBF. As discussed above, the ASL signal arises from the delivery of magnetically tagged arterial water into the imaging slice where it exchanges into the tissue. Therefore, ASL techniques target signal changes that are localized to the level of arteries, capillaries, and brain tissue, which are presumably the sites most relevant to neuronal activity. Compared to relatively venous-weighted BOLD methods, ASL has higher inherent spatial resolution and specificity in functional mapping than BOLD (Fernandez-Seara et al., 2007). Again, however, this trades off with generally lower spatial coverage and temporal resolution than BOLD.

Insensitivity to Baseline Drift—In fMRI studies, baseline drift can mask low-frequency neural activations and can result from both physiological and non-physiological changes induced by effects such as subject motion and system instabilities. This slow drift is an important issue because functional maps are calculated from control and task-state signal differences. Given that the vast majority of fMRI studies have used BOLD contrast as a marker for neural activation, baseline drift effects result in poor sensitivity for detecting slow variations in neural activity. By contrast, drift effects are minimized in ASL perfusion contrast, primarily as a result of successive pairwise subtraction between images acquired with and without labeling, which makes it suitable for studying low-frequency events in brain function (Wang et al., 2003), for long-term functional tasks like studies of sleep, habituation, and effects of drugs, and for intersubject or intersession intrasubject comparisons (Aguirre et al., 2002).

Small Signal Changes—The biggest disadvantage of ASL fMRI is its intrinsic low SNR. Since ASL is measuring the perfusion signal, the small blood volume fraction of a voxel limits the signal to noise ratio. A typical functional change in the acquired ASL signal is often on the order of 1% or less and ASL techniques require image subtraction to obtain blood flow

information. This subtraction can lead to increased noise levels in the perfusion images. Also, in functional activation studies, another subtraction is needed to compare blood flow changes between rest and activation states (Wong et al., 1997, Kim and Ugurbil, 1997, Yang et al., 1998b). As a result, ASL studies often require considerable averaging to obtain reliable activation signals and thus are insensitive to phenomena that are difficult to elicit recurrently.

Transit Delay Effects—After the application of the proximal inversion tag in ASL, there is a transit delay before tagged blood begins to enter the imaging slices. This delay is typically between 500 ms and 1500 ms and can be highly variable even within a given imaging slice. In the case of local cardiovascular or neuropathology, this transit delay can be significantly lengthened. During functional activation, the transit delay can shorten due to the increased blood flow (Gonzalez-At et al., 2000). Accurate determination of transit time is critical for quantification of the functional perfusion signal. Several modified ASL techniques have been proposed to decrease sensitivity to the effects of transit delay for CASL (Ye et al., 1997, Alsop and Detre, 1996, Alsop and Detre, 1998) and PASL (Wong et al., 1998b, Wong et al., 1998a, Luh et al., 1999).

Temporal Resolution—ASL signal reflects primarily the vascular response of the capillaries as mentioned earlier, and its temporal resolution theoretically should be superior to that of BOLD contrast. However, because of the pairwise subtraction of tagging and control pulses and the need to wait for recovery of transverse magnetization, the sample rate for perfusion images is lower than BOLD. The TR normally is around 2–4 s, and the effective perfusion image acquiring rate is around 4–8s (Kim and Tsekos, 1997, Yang et al., 1998b, Wong et al., 1998b). This limitation of ASL fMRI, combined with the low signal to noise ratio, makes it less favorable particularly for event-related fMRI.

State of the Art in ASL

High-Field ASL—One of the drawbacks of the ASL method is the relatively low sensitivity compared to BOLD fMRI. The move towards higher-field MR scanners that have inherently better SNR could improve ASL signal sensitivity. An additional gain for ASL from high field systems is that the T_1 relaxation time is longer at higher fields, resulting in slower decay of the labeling signal. It is estimated that the increase in arterial blood $T_{1\text{blood}}$ from 1400ms at 1.5 T to 1680ms at 3 T (Lu et al., 2002, Lu et al., 2004a) will increase the SNR of the images by approximately 20% to 30%. Therefore, a reduction of the scan time or an increased image resolution for identical imaging parameters is expected when going from 1.5 T to 3 T.

These advantages have been well illustrated in ASL studies that focused on baseline blood flow, but functional experiments often show less than the expected improvement in sensitivity (Wang et al., 2002), suggesting that additional factors need to be considered at high field strength. Recent studies have shown that higher magnetic field also introduces new challenges, such as significant contamination from BOLD effects in the quantification of ASL fMRI at 3 T (Lu et al., 2006).

Velocity-Encoded ASL—In conventional ASL techniques, arterial blood is tagged proximal to imaging slices. Therefore, there is necessarily a spatial gap between the tagging location and the imaging slices. This gap results in a transit delay for the delivery of tagged blood. The transit delay can be small for single-slice imaging but is larger for multislice acquisitions. The magnitude and variability of the transit delay in relation to the T_1 decay of the tag causes one of the largest potential sources of error in the quantification of perfusion using ASL in the normal human brain. Transit delay could be much larger than T_1 in the presence of vascular pathology or stroke, rendering conventional ASL as an impractical method for accurately measuring CBF in those patients (Neumann-Haefelin et al., 1999).

To reduce sensitivity to transit delay, a new ASL method named velocity-selective ASL (VSASL) has been introduced (Wong et al., 2006), in which the tag pulse is velocity-selective and not spatially selective. This allows for the tagging of all flowing spins that slow down during an acquisition to slower than a cutoff velocity V_c (2–4 cm/s), regardless of location, and can in principle eliminate the problem of transit delays. The feasibility of VSASL fMRI has been investigated by comparing it with conventional ASL fMRI (Wu and Wong, 2007). The results show that VSASL has comparable spatial specificity in detecting the perfusion change induced by neuronal activity as conventional ASL. Further, one of the great advantages of VSASL is that it labels flowing spins sufficiently close to the imaging slices, thereby avoiding the transit delay issues of the conventional ASL technique. This implies that the VSASL signal mainly reflects local blood flow information, but conventional ASL signal comes from more distant feeding arteries.

Other techniques to examine blood flow are under development, including a new technique named Flow-ENhanced Signal Intensity (FENSI) (Sutton et al., 2007). FENSI has both spatial and velocity localization abilities and reflects blood flow rather than perfusion. The technique hopes to provide mass transport relations to microvascular blood flow that is free of arterial delivery effects.

Blood Volume-Based Functional MRI

The BOLD response reflects changes in cerebral blood volume (CBV) in addition to the changes in blood flow and oxygen extraction. Several techniques have been developed to examine blood volume and to quantify functional changes associated with blood volume. Two classes of methods exist depending on whether or not they use an exogenous contrast agent. Absolute quantitations require an exogenous contrast agent. Without an exogenous contrast agent, relative activation can be assessed.

Exogenous Contrast Agents

CBV-based studies have been widely applied in animal fMRI studies by using exogenous contrast agents that are mainly composed of superparamagnetic particles of a metal, such as short blood-half-time agent gadolinium diethylenetriamine pentaacetic acid (GdDTPA) and the long blood half-time agent, monocrySTALLINE iron oxide nanoparticle (MION). Following the intravenous injection of the contrast agent, the MR signal decreases due to the change in the magnetic susceptibility of vascular space. Consequently, magnetic field inhomogeneities are generated around blood vessels. There are two competing factors that contribute to the observed fMRI signal in experiments employing iron oxide contrast agent: the superparamagnetic effect of the contrast agent and the BOLD effect that results from the susceptibility difference between oxygenated and deoxygenated hemoglobin. The contrast agent causes signal to drop with activation, because a local increase in CBV leads to an increase in the amount of contrast agent within a voxel, whereas the BOLD effect causes signal to increase. With sufficiently high doses of contrast agent, the susceptibility effect of the contrast agent overwhelms the BOLD effect, and the fMRI signal reflects primarily CBV changes (Mandeville et al., 1997).

CBV fMRI with contrast agent injection has been shown to have a much higher sensitivity than BOLD (Mandeville et al., 1998, Vanduffel et al., 2001) and a higher spatial specificity from animal experiments (Lu et al., 2004b, Zhao et al., 2006), provided a sufficient dose of contrast agent. However, the application of contrast-agent-based CBV fMRI in human research has been limited due to invasiveness and dosage considerations.

Endogenous Contrast

In response to the exogenous contrast agent limitations, several noninvasive methods for measuring CBV changes have recently been proposed: vascular space occupancy (VASO) (Lu et al., 2003, Gu et al., 2006), multi-echo gradient-echo/spin-echo (MEGESE) (An and Lin, 2002), modulation of tissue and vessel (MOTIVE) (Kim and Kim, 2005), and venous refocusing for volume estimation (VERVE) (Stefanovic and Pike, 2005). The common point of all these methods is nulling blood or separating blood from tissue signal using inversion recovery techniques.

In the VASO technique, each voxel is assumed to consist of two-compartments: blood and tissue. When a vessel dilates due to functional activation, water will be redistributed between these two compartments. By nulling the blood-water signal, VASO predicts the volume changes in the intravascular compartment by inferring signal changes from tissue water alone. VASO imaging has been used to measure CBV signal changes associated with functional activation in the visual cortex as well as changes in response to hypercapnia in a single slice (Lu et al., 2003, Gu et al., 2006) and whole brain by the technique called multiple acquisitions with global inversion cycling (MAGIC VASO) (Lu et al., 2004c, Scouten and Constable, 2007). The spatial specificity of a VASO-weighted functional map has recently been compared with the traditional exogenous contrast agent technique at 9.4 T (Jin and Kim, 2006). The results show that both functional maps show good localization of functional changes to the middle cortical layer, which has the highest density of vasculature.

Diffusion-weighted functional Imaging

Diffusion-weighted magnetic resonance imaging (DW-MRI) has the unique capability of probing molecular displacements, enabling the characterization of microscopic blood motion within the vascular network and the quantification of water mobility within the cellular space (Le Bihan et al., 1986, Moseley et al., 1990a, Moseley et al., 1990b, Basser et al., 1994). Briefly, diffusion MRI encodes microscopic displacements using magnetic field gradients (the diffusion gradients) (Stejskal and Tanner, 1965). The spatial scale of displacement encoding is given by the b -value, which depends on the timing and strength characteristics of the diffusion gradients (Callaghan, 1991). Microscopic spin motion with an apparent diffusion coefficient ADC, produced because of flow or diffusion, can then be encoded by attenuating the diffusion-weighted MR signal relative to the non-diffusion-weighted signal according to the expression $\exp(-b \text{ ADC})$. In general, diffusion MRI is considered complimentary to fMRI (Mulkern et al., 2006, Mulkern et al., 2007). As discussed above, diffusion-weighting can be added to an existing fMRI sequence to elucidate the BOLD functional signal components (Song et al., 1996, Michelich et al., 2006). However, diffusion weighting can also be employed in the generation of novel functional techniques mapping microvascular flow and volume changes (Song et al., 2002, Song and Li, 2003) as well as cellular volume alterations (Le Bihan, 2007, Darquie et al., 2001, Jasanoff, 2007a) occurring during or after neuronal activation.

DW-MRI mapping CBV and CBF changes

In addition to examining the BOLD functional signal components, the implementation of diffusion gradients on a gradient-echo fMRI technique has been proposed in order to map ADC changes related to microvascular flow and volume alterations in the areas of neuronal activation. This work is based on the proposition of the Intravoxel Incoherent Motion (IVIM) technique (Le Bihan et al., 1986). IVIM models the diffusion signal as having two major compartments: one coming from blood flow within intravascular space and one originating from water diffusion in extravascular space. The intravascular compartment relates to higher mobility and therefore persists only at low b values. The ADC measurement based on signal at low b values has been implemented to map flow and volume changes in the microvascular

networks. Specifically, (Song et al., 2002) showed that the ADC increases in both the case that vessel volume fraction increases as blood flow increases and in the case that vessel volume fraction remains constant as blood flow increases. In general, ADC depicts both blood volume and flow changes at the level of arteries, arterioles, and capillaries, whereas BOLD reflects oxygenation changes in capillaries, venules and veins. The combination of information from the two contrast mechanisms can delineate capillary activation, leading to enhanced spatial localization of the functional signal (Song et al., 2002, Song et al., 2003, Roberts et al., 2007, Song et al., 2007). The time course of the ADC-based functional signal precedes the BOLD signal by about 1 sec, confirming the initial hypothesis that ADC contrast is sensitive to blood volume and flow changes in the arterial and capillary network (Gangstead and Song, 2002). By also varying the employed b values range it was found that the time course in the high b factor range lagged that of the low b factor range showing that different levels of diffusion-weighting can assess sensitivity to vessels of different sizes (Harshbarger and Song, 2004). Further refinement of the ADC-fMRI method by employing flow-moment-nulling to compensate for the effect of blood flow changes has also shown an improvement in the selective sensitivity of the functional signal toward smaller vessels, where volume changes are prevalent (Song and Li, 2003).

DW-MRI mapping cellular changes

High b -value DW-MRI has recently been proposed to measure cellular volume changes occurring upon neuronal activation. This technique potentially provides a direct measurement of neuronal activity, not relying on hemodynamic coupling. From a physiological perspective, cell swelling is considered an important response associated with cerebral neuronal activation (Le Bihan, 2007). Continuing the initial observations of transient decrease in water diffusion observed in human occipital cortex upon visual stimulation (Darquie et al., 2001), Le Bihan et al. claimed that diffusion MRI can map changes in tissue microstructure arising from cell swelling during neuronal activation (Le Bihan et al., 2006). They supported their argument for the origin of the measured signal with two observations. First, they showed an increase in the percentage signal change as b value increased, which is opposite to the observed behavior for the low b value regime. Second, they observed that the diffusion signal response precedes the BOLD response by 2–3 s.

Further explorations of the contrast mechanism and specificity of the technique are needed and the source of the signal is still under debate. A recent study (Miller et al., 2007b) employing mild hypercapnia attacked the fundamental argument for the non-vascular nature of the high b value diffusion fMRI signal. They presented measurements showing a significant high b -value diffusion fMRI signal response during hypercapnia. Hypercapnia induces significant vascular changes and, presumably, has a negligible effect on neuronal activity. Therefore, the authors claimed that if the signal had a non-vascular origin, there should be no signal response during hypercapnia. Although the source of the high b value diffusion fMRI signal remains an open question, the scientific debate around the technique highlights the emerging need for exploring new fMRI methods relying on direct neuronal activation measures.

Future of functional imaging with MRI

BOLD-based fMRI has found a prominent place in the cognitive psychophysiology toolbox and will remain an important means to investigate local neuronal activation for some time to come. It will also continue to find use in discovering networks of activation related to a variety of pathology. However, to develop reliable, quantitative measurements of function that can be compared across individuals, more development is needed. BOLD fMRI signal reflects vascular changes along with the desired signature of changes in neuronal metabolism. Modeling combined with multi-modal approaches that supplement BOLD with blood volume and blood flow measurement techniques can be used to quantify the relative contributions of

the vascular response versus the oxygen extraction fraction and neuronal metabolism (Hyder et al., 2001). Measurements of CBV, CBF, and BOLD can be used to determine CMRO₂ and localized neuronal metabolism.

All of the methods mentioned above rely on neurovascular coupling in order to produce a detectable signal. The relationship between the detectable vascular response and the neural signal is termed hemodynamic coupling or neurovascular coupling. This indirect relationship with the desired measurement of neuronal activity will continue to pose challenges, especially in studying interventions and pathologies that are likely to produce or coincide with vascular effects.

There is a great need for imaging of direct neuronal activity, separate from vascular coupling. Several areas are currently under development that may achieve that: DW-MRI mapping of cellular changes (mentioned above), neuronal current density imaging, functionalized contrast agents, and functional magnetic resonance spectroscopy that allows quantitative imaging of metabolites. Some of these are discussed in an excellent recent review (Jasanoff, 2007a).

Functionalized contrast agents are being developed that can reflect specific biochemistry in neuronal activation, such as calcium sensors to allow visualization of activation (Atanasijevic and Jasanoff, 2007, Jasanoff, 2007b) or Mn²⁺ to trace neural connections and assess calcium channel function (Lin and Koretsky, 1997). These contrast agents allow visualization of cellular-level function with the macroscopic lens of MRI.

While multimodal imaging with MRI using BOLD, CBF, and CBV measures can be used to infer oxygen utilization of tissues (CMRO₂), magnetic resonance spectroscopy (MRS) offers a more direct window into the biochemistry of neurons and glia. Traditional MRI relies on signals from hydrogen protons, but MRS can be used with other nuclei, including ¹³C. MRS of ¹³C can be used to visualize different steps in the metabolic pathway of glucose, resulting in more direct measures of cell metabolism (Hyder et al., 1996, Hyder et al., 2001).

CONCLUSION

This exciting progress augurs well for applications in many domains. Often unappreciated is the technical expertise needed to use MRI methods optimally and to interpret the resulting data appropriately (for discussion of implications for clinical psychology researchers, see (Miller et al., 2007a); on the need for clinical application to catch up with and drive technical advances, see (Sorensen, 2006)). A safe prediction is that the future cognitive scientist will have available a range of brain mapping techniques of MRI to reflect spatially and temporally localized, quantitative changes in neuronal activity. This toolbox will consist of a combination of hemodynamic techniques to provide general mapping and more direct methods such as spectroscopy to provide focused detail. In turn, MRI-based methods will complement established methods such as EEG and MEG, emerging methods such as optical imaging, and, very likely, methods not yet foreseen (Dale and Halgren, 2001, Detre, 2006, Miller et al., 2007a). Because different imaging methods offer different strengths and limitations, the future looks more and more interdisciplinary. The need not only for cross-disciplinary collaboration but cross-training of basic and clinical researchers will grow.

Acknowledgments

The authors acknowledge support from NIDA R21 DA14111, NIMH R01 MH61358, NIMH P50 MH079485, and NIMH T32 MH19554.

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Figure 1.

Two types of image artifact resulting from bulk magnetic susceptibility differences near air/tissue interfaces in the brain. An EPI simulation based on a measured image and field map is shown in (a–c): (a) reference image, (b) geometric distortion (EPI with 0.7 ms echo spacing), (c) signal loss from dephasing (EPI with TE 30 ms).

Figure 2.

Schematic illustration of the principles of ASL. The left panel shows the proximal tagging pulse being applied. The middle panel is included to depict the transit of the bolus of tagged blood from the tagging plane to the imaging plane. The right panel shows the arrival of the tag at the imaging slice after the transit time.