AU2

a0005

Perfusion MRI

T T Liu, E C Wong, and R B Buxton, University of California, San Diego, La Jolla, CA, USA

s0005

Introduction

p0005 The first demonstration that the signal measured with magnetic resonance imaging (MRI) can be made sensitive to neural activity used an injected intravascular contrast agent that alters the MR signal as it passes through the brain. The investigators compared the dynamics of the agent in visual cortex during a rest condition and, with a second injection, during sustained visual stimulation. Although this contrast agent approach ignited the field of functional neuroimaging with MRI, and has now become a standard technique in clinical practice, it has had only limited applications in basic neuroscience studies of brain function. However, it demonstrated that local perfusion changes associated with neural activity can be detected with MRI and then used to map patterns of activation. Soon after this demonstration, the blood oxygenation level-dependent (BOLD) effect was discovered, and this quickly supplanted the earlier perfusion-based technique. With BOLD imaging, the signal changes associated with neural activity arise from a local increase in blood oxygenation, because the fractional blood flow increase is larger than the fractional change in the oxygen metabolic rate. No injections are needed, because the BOLD effect is an intrinsic change in the MR signal related to magnetic properties of hemoglobin, making experiments easier to perform, and also allowing measurement of dynamic changes.

p0010 Although imaging methods based upon BOLD contrast are currently the predominant method for functional magnetic resonance imaging (fMRI) of the brain, the interpretation of changes in the BOLD signal can be complicated by factors such as age, disease, and medication, because the magnitude of the BOLD response depends on the matching of changes in blood flow and oxygen metabolism. In addition, BOLD methods can only detect changes between two states, and so are insensitive to chronic conditions. A different approach to perfusion fMRI, based upon arterial spin labeling (ASL) methods, offers a useful complement to BOLD fMRI. Like BOLD, the ASL approach requires no injections, and exploits the ability of MRI techniques to selectively 'tag' water in different regions by inverting the proton magnetization, a noninvasive and easily repeatable method to label inflowing blood. It can provide quantitative measures of both resting-state levels of cerebral blood flow (CBF) and of the functional CBF response associated with evoked neural activity. It is also insensitive to slow signal drifts, which can contaminate the BOLD signal. When combined with measures of the BOLD response, measures of functional CBF responses can be used to estimate functional changes in the cerebral metabolic rate of oxygen.

s0010

Cerebral Blood Flow

p0015 Cerebral blood flow, or perfusion, is a measure of the rate of delivery of arterial blood to a capillary bed in tissue. The standard unit of measurement for CBF is milliliters of blood per 100 grams of tissue per minute, and a typical value in the human brain is 60 ml 100 $g^{-1}min^{-2}$. Assuming an average brain tissue density of 1 g ml^{-1}, the average CBF may also be written as 60 ml 100 ml^{-1} min^{-2} = 0.01 s^{-1}. In a typical ASL experiment, about 1 s is allowed for the delivery of blood. This corresponds to 1 ml of blood delivered to 100 ml of tissue. As a result, the overall magnetic resonance signal change due to the delivered blood is only about 1% of the total signal due to the tissue. This small percentage contributes to the low intrinsic signal-to-noise ratio (SNR) of ASL methods.

s0015

Overview of Arterial Spin Labeling

p0020 MRI is based on manipulating the magnetization of protons, primarily in water molecules, to generate a detectable MR signal, and the MR image is then a spatial map of this signal. Initially the magnetic moments of the protons partially align with the main magnetic field of the MRI system to create a local magnetization. When radiofrequency (RF) magnetic fields are applied, this magnetization can be tipped over to create a detectable MR signal, or fully inverted by a 180 degree RF pulse. After an RF pulse the magnetization relaxes back to alignment with the main magnetic field, typically requiring a few seconds, and the magnetization can then be tipped again by another RF pulse to generate a new MR signal. The effects of the RF pulses can be quite selective, exciting only a thin plane or a broad band. Most arterial spin labeling methods measure CBF by taking the difference of two sets of images: tag images, in which the magnetization of arterial blood is inverted or saturated, and control images, in which the magnetization of arterial blood is fully relaxed. In

this way the arterial blood delivered to an image voxel has a positive magnetization in one image and a negative magnetization in the other, while the static protons contribute the same signal to both and so subtract out in the difference image. The basic steps are as follows:

1. Arterial blood flowing toward the region of interest (ROI) is tagged by magnetic inversion or saturation (see **Figure 1**). This tagged blood flows into the imaging slices or volume and also relaxes toward equilibrium with the longitudinal relaxation time constant of blood (see red curves in the bottom half of **Figure 1**).
2. After a delay *TI* (known as the inversion time) to allow for inflow of tagged blood, an image is acquired in the slice(s) or volume of interest. This image is referred to as the tag image.
3. As discussed previously, the delivered blood signal is only about 1% of the static tissue signal. In order to remove the contribution of the static tissue to the tag image, a control image of the same slice is acquired in which inflowing blood is not tagged. The magnetization of this control image is shown by the dashed blue lines in the bottom half of **Figure 1**.
4. Taking the difference of the control and tag images yields an image $\Delta M = M_{control} - M_{tag}$ that is proportional to CBF. This is shown as the difference of the blue and red lines in **Figure 1**.
5. Tag and control images are typically acquired in an interleaved fashion, and the running difference of the control and tag images is used to form a perfusion time series (see later, section titled 'Processing of ASL data').

Arterial Spin Labeling Methods

s0020

There are currently three classes of ASL methods, pulsed, continuous, and velocity selective, as summarized in **Figure 1**.

p0025

Pulsed ASL (PASL) – tagging based on location

s0025

In pulsed techniques, short (5–20 ms) RF pulses are used to saturate or invert a slab of magnetization that is proximal to the region of interest. These techniques have the advantages that they provide high inversion efficiency and use little RF power. Disadvantages are that they depend on the coverage and uniformity of the transmit RF field to determine the geometry of the applied tag.

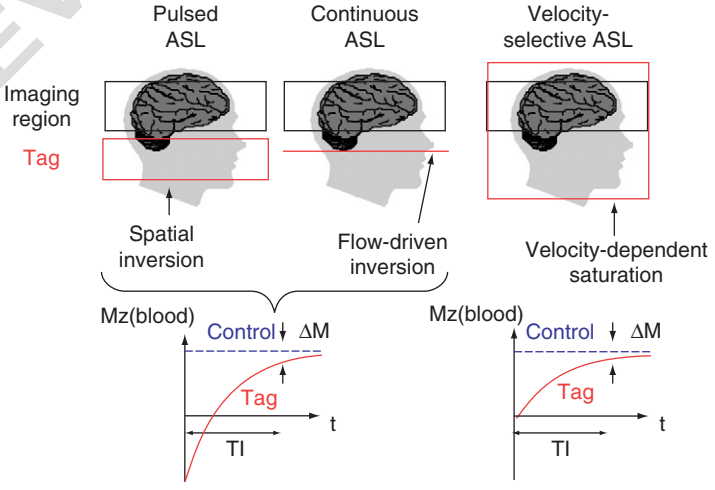
p0030

Continuous ASL (CASL) – tagging based on location and velocity

s0030

In continuous ASL, long (1–3 s) RF pulses are used in conjunction with a static gradient field to irradiate a narrow plane of spins with RF energy. The plane is chosen proximal to the region of interest so that inflowing arterial blood flows through in a direction that is roughly perpendicular to the plane. When the RF amplitude and gradient fields are properly adjusted, flowing blood undergoes adiabatic flow-dependent inversion when traversing the irradiated plane. Because the tag can be applied closer to the region of interest (on average), this can result in a higher overall tagging efficiency than is possible with pulsed techniques. However, this technique requires a large amount of average RF power and

p0035



f0005 **Figure 1** Pulsed, continuous, and velocity-selective arterial spin labeling (ASL) methods use various methods to either invert or saturate the magnetization of arterial blood. The difference, ΔM, between control and tag images is proportional to cerebral blood flow.

can be limited by specific absorption rate (SAR) considerations at higher fields. A recently introduced form of CASL, dubbed pseudo-CASL, uses repeated RF pulses instead of a continuous RF wave.

s0035

Velocity-selective ASL (VS-ASL) – tagging based on velocity

p0040 In the VS-ASL technique, an RF pulse train is applied that selectively saturates flowing spins with no spatial selectivity. Because it tags all blood that is flowing above a selected cutoff velocity, this technique has the advantage that the applied tag is close to all the target tissue. This results in a small and uniform transit delay for the delivery of the tagged blood to the tissues of interest (see below regarding transit delays).

s0040

Perfusion Quantification

p0045 The ASL difference signal ΔM is proportional to CBF but also has a complex dependence on a number of physiological parameters. Variations in these physiological parameters can cause systematic errors in the CBF measurements, and the goal of quantitative ASL methods is to minimize these errors. The primary sources of errors are (1) the transit delay Δt between the tagging region and the imaging slice, (2) the temporal width τ of the arterial bolus in PASL techniques, (3) the presence of tagged intravascular blood that has not yet perfused its target capillary bed, (4) the dependence of relaxation on the exchange of water between blood and tissue compartments, and (5) the clearance of water by outflow.

p0050 Transit delays arise in spatial tagging methods because of the need to place the tagging slab in PASL or the tagging plane in CASL some distance (1–3 cm) from the imaging slice in order to minimize the perturbation of spins in the imaging region. To allow all of the tagged blood to travel from the tagging region to the imaging region, the inversion time TI must satisfy the condition $TI > \Delta t + \tau$, where Δt is the transit delay and τ is the temporal width of the tagged bolus. Although increasing the inversion time reduces the sensitivity to transit delays, it also reduces the magnitude of the difference signal ΔM, which is decaying exponentially with a relaxation time that is of the same order as the transit delay (the T_1 of blood is approximately 1600 ms at a magnetic field of 3 T). Typical inversion times are 1000 and 1400 ms for CASL and PASL, respectively. In contrast to CASL and PASL, transit delays are typically negligible in VS-ASL because the velocity-selective tagging process saturates arterial blood with velocities down to 1–2 cm s^{-1}, corresponding to vessels (roughly 50- to 100-μm arterioles) that are close to the capillary bed and within the imaging region. This insensitivity to transit delay makes VS-ASL a particularly attractive method for functional ASL studies of those individuals, such as stroke patients, who may exhibit long transit delays.

p0055 In CASL methods the temporal bolus width τ is determined by the temporal duration (typically 1–3 s) of the continuous inversion pulse. However, in PASL methods the temporal width depends on the velocity of arterial blood in the tagging region, which typically increases with functional activation. To reduce the sensitivity to the temporal width, a spatial saturation pulse can be applied to the tagging region at a time TI_1 after the inversion pulse. If $TI_1 < \tau$, then the temporal width of the bolus is TI_1, and the measured signal is proportional to the product of CBF and TI_1.

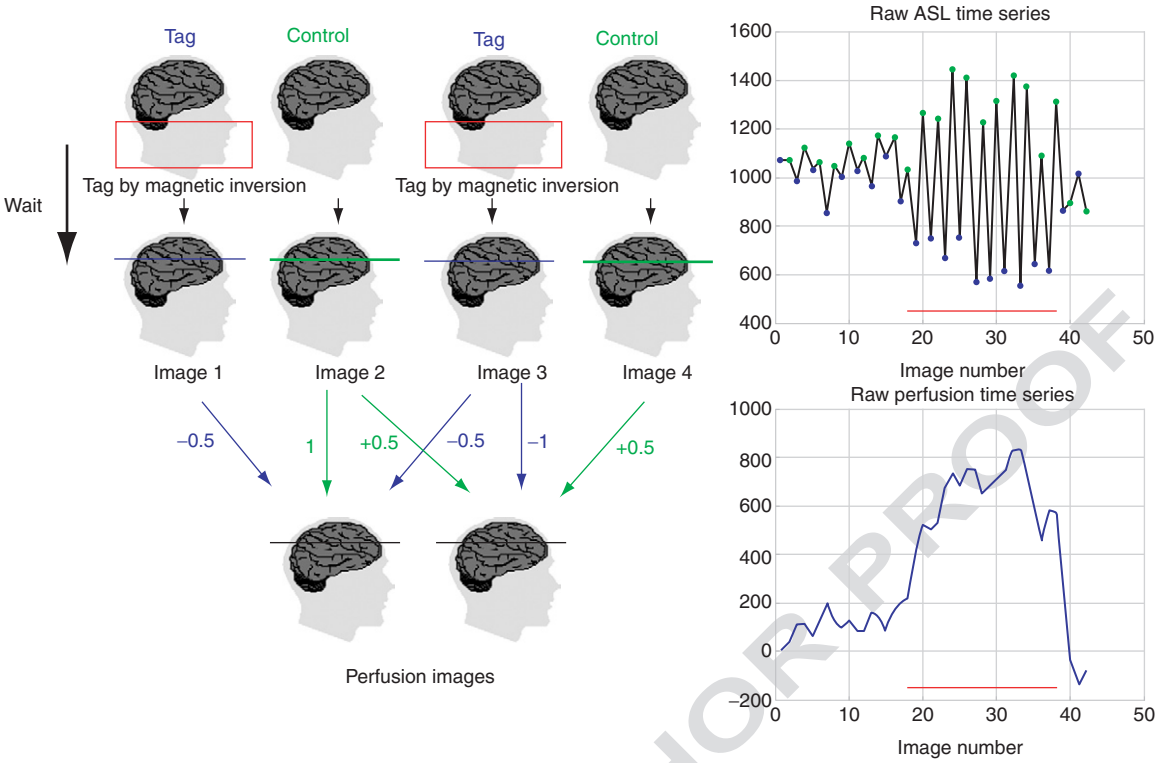
p0060 A related source of error is the presence of tagged blood in the arteries and arterioles that has entered the imaging slice but is destined to perfuse to more distal slices. If the image is acquired before this blood has time to leave the imaging slice, the intravascular signal will contribute to the ASL difference signal and lead to an overestimate of CBF. Typically, this is not a problem when using pulse sequence parameters that also control for transit delays. In addition, flow-weighting gradients can be used to attenuate the intravascular signal, at the cost of a reduction in the SNR of the desired difference signal.

p0065 Improper modeling of the exchange of water between blood and tissue components can lead to significant errors in CBF quantification, especially in tissues with low CBF, such as white matter. For these cases, a simple two-compartment model of exchange can be used to improve accuracy. Finally, errors due to the clearance of water by venous outflow are usually negligible given the inversion times used in most ASL experiments, but may need to be considered in high-flow conditions or when long inversion times are used.

Processing of ASL Data

s0045

p0070 In most ASL fMRI experiments, control and tag images are acquired in an interleaved fashion, as shown in **Figure 2**. A perfusion time series is then formed from the running subtraction of the control and tag images. An example of this process is shown in **Figure 2**, where the perfusion images are formed from the difference between each control image and the average of the two surrounding tag images or from the difference between the average of two surrounding control images and a tag image. The type of differencing shown in **Figure 2** is referred to as



f0010 **Figure 2** Formation of a perfusion time series from the 'surround subtraction' of control and tag images. An example arterial spin labeling (ASL) time series of control (blue) and tag (green) signals is shown in the upper right-hand plot. The perfusion time series created by surround subtraction is shown in the lower right-hand plot. The red bars indicates the time of stimulus.

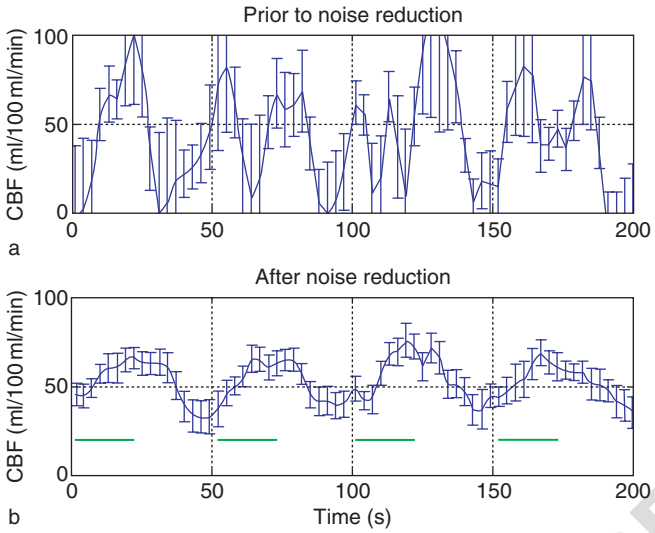
surround subtraction, and represents one specific approach to the filtered subtraction of control and tag images. Other common approaches are pair-wise subtraction and sinc subtraction. These approaches all share the property that they can be modeled as the modulation of the control and tag images (e.g., multiply all control images by +1 and all tag images by −1) followed by convolution with a lowpass filter. For fMRI experiments with block designs (e.g., long periods of on/off), surround and sinc subtraction approaches tend to provide the best performance. In contrast, for randomized event-related experimental designs, pair-wise subtraction can provide better performance (e.g., less filtering of the hemodynamic response function). However, all filtered subtraction approaches lead to inevitable broadening of the hemodynamic response function. Unfiltered approaches based upon general linear models of the ASL experiment can be used to eliminate this broadening and can also provide improvements in statistical power.

p0075 As with BOLD fMRI experiments, cardiac and respiratory fluctuations are a major source of noise in ASL experiments, especially at higher field strengths. Since the inherent SNR of ASL methods is typically much lower than that of BOLD fMRI, the need for methods to reduce physiological noise is especially pronounced. Retrospective image-based methods have been shown to significantly reduce physiological noise in ASL data and should be used whenever possible. An example is shown in **Figure 3**.

Simultaneous Estimates of CBF and BOLD s0050

p0080 ASL data for fMRI are often acquired with single-shot acquisition methods such as echo-planar imaging (EPI) or spiral readouts. In addition to their sensitivity to flow introduced by the tagging process, these images can also exhibit BOLD contrast. For example, with gradient echo readouts, the images exhibit a BOLD weighting. Dual echo acquisitions are particularly useful for simultaneous perfusion and BOLD imaging. Images acquired at a short echo time (e.g., 3 ms) can be used to form a perfusion time series with relatively little BOLD weighting, while images acquired at a later echo time (e.g., 30 ms) can be use to form the BOLD time series.

p0085 A BOLD time series can be formed from the control and tag images through a running average approach that is analogous to the filtered subtraction approach used to form the perfusion time series. In general, the BOLD time series is formed by the convolution of the control and tag images with a lowpass filter. For



f0015 **Figure 3** Example of the hippocampal cerebral blood flow (CBF) response to a memory encoding task before (top panel) and after (bottom panel) the application of physiological noise correction. Mean responses from a population of 10 older individuals (mean age 74 years) are shown with standard error bars. The horizontal green bars denote the times during which novel images were shown.

example, the method analogous to surround subtraction would be a surround average consisting of the average of each image with the average of its two nearest neighbors. The BOLD time series are inherently flow-weighted because of the tagging process. In pulsed ASL experiments the flow-weighting can be reduced by the application of a presaturation pulse applied in the imaging plane either immediately prior to or immediately after the application of the tagging pulse.

s0055 ## Temporal Resolution

p0090 The temporal resolution of perfusion fMRI is inherently poorer than BOLD fMRI because of the necessity to form tag and control images and to allow time for blood to be delivered from the tagging region to the imaging slice. In a typical pulsed ASL experiment, a repetition time (*TR*) of 2 s or more is used, so that one tag and control image pair is acquired every 4 s. By comparison, the temporal resolution of BOLD fMRI is typically 1 to 2 s and can be as low as 100 ms for specialized applications. Methods for improving temporal resolution include turbo-ASL and single-shot ASL. In turbo-ASL, a control image is acquired after the inversion pulse at a delay (typically 100 ms) that is too small for blood to have flowed into the imaging slice. A tag image is then acquired at an interval of *TR* (typically 1 s) after the control image. In single-shot ASL, background suppression is used to suppress static tissue, thus eliminating the need for a control image. While these methods can improve temporal resolution, the quantification of the resultant ASL signals is more complicated than are the more standard methods.

s0060 ## SNR and Contrast-to-Noise Ratio

p0095 As discussed on the first page, the SNR of ASL methods is inherently low because the inflowing blood magnetization is typically only about 1% of the tissue. The low SNR combined with the poor temporal resolution of ASL results in a low contrast-to-noise ratio (CNR) for quantitative ASL fMRI experiments, as compared to BOLD. Due to the low inherent SNR of ASL methods, noise reduction methods (such as the physiological noise reduction method discussed earlier) should be used wherever possible. Background suppression methods that attenuate the static tissue component also have the potential to reduce noise, but their application for simultaneous CBF/BOLD experiments is not straightforward. For functional mapping experiments in which quantification of CBF is not required, nonquantitative versions of ASL, such as turbo-ASL and close-tag CASL, can be used to improve the CNR. For example, the CNR of close-tag CASL at 1.5 T has been shown to approach that of the BOLD signal for a finger-tapping experiment.

p0100 In brain regions such as the orbital frontal cortex, the presence of pronounced magnetic susceptibility gradients can lead to severe signal dropouts in gradient-echo BOLD imaging, due to the long echo times employed. Because perfusion fMRI measures do not require BOLD contrast, these signal dropouts can be reduced through the use of either short echo time

readouts or a refocusing pulse sequence. The relative SNR of perfusion fMRI measures can therefore be higher than that of BOLD measures in these brain regions.

s0065

Spatial Coverage

p0105 At present, most ASL fMRI studies use 2-D multislice acquisition methods in which the data are acquired on a slice-by-slice basis. For CASL and PASL methods, the slices are typically acquired in an inferior-to-superior manner so that slices that are further from the tagging region are acquired at later times. The number of slices that can be acquired depends on the (a) acquisition time for each slice, (b) the time *TR–TI* that is available for slice acquisition, and (c) the need to acquire slices before the difference signal ΔM has decayed away due to the longitudinal relaxation of blood. Due to these considerations, ASL studies typically acquire a smaller number of slices (e.g., 3–15) than do whole-brain BOLD studies (e.g., 30–40 slices), with thicker slices (e.g., 5–8 mm) than would be used in a BOLD study (e.g., 3–4 mm). Recently, ASL fMRI studies with single-shot 3-D acquisitions have been demonstrated. The 3-D acquisition methods with refocusing pulse trains can reduce susceptibility artifacts, are well-suited to the use of background suppression methods, and are a natural match for the nonspatial tagging scheme used in VS-ASL. However, 3-D methods are not as well suited for simultaneous measurements of CBF and BOLD.

s0070

Applications of ASL in Functional MRI

s0075

Quantitative Assessment of Brain Activity

p0110 Because it can provide a quantitative measure of a fundamental physiological quantity (i.e., CBF), ASL has the potential to better reflect neural activity as compared to BOLD, which is a complex function of a number of physiological variables. As compared to BOLD, ASL measures of functional CBF changes have been shown to exhibit decreased interindividual and intersession variability and a more linear relation to neural stimulus, possibly reflecting a more direct link between CBF and neural activity.

p0115 Although the majority of studies using perfusion fMRI have focused on the visual and motor cortices, there has been a growing number of studies aimed at measuring the CBF response to more complex cognitive tasks. Perfusion fMRI has been used to successfully detect CBF responses associated with language generation, visual attention, memory encoding, working memory, and sequence learning.

p0120 When combined with BOLD measures, ASL measures of CBF can be used to derive estimates of functional changes in the cerebral metabolic rate of oxygen ($CMRO_2$), which has been shown in animal studies to be correlated with functional changes in neuronal spiking frequency. In human fMRI studies, the addition of simultaneous measurements of CBF and BOLD responses to a hypercapnic stimulus (administered carbon dioxide) can provide information that is then used to calibrate the BOLD response and estimate functional changes in $CMRO_2$. This approach has been used to demonstrate a linear coupling in the visual cortex between functional changes in CBF and $CMRO_2$. The use of combined CBF and BOLD measures is especially important for fMRI studies of populations, because factors such as medication, age, and disease can complicate interpretation when only BOLD measures are acquired.

p0125 Simultaneous measures of CBF and BOLD with ASL are also useful for understanding the mechanisms underlying the BOLD response. For example, ASL measurements have been used to examine whether poststimulus undershoots in the BOLD signal are due primarily to a slow return to baseline in cerebral blood volume or a prolonged elevation of $CMRO_2$.

s0080

Insensitivity to Low-Frequency Noise

p0130 Low-frequency drifts are present in most fMRI time series data and tend to reduce the statistical power of BOLD experiments. As discussed in a previous section, perfusion time series are formed from the filtered subtraction of control and tag images. This subtraction process greatly attenuates low-frequency drifts and can make ASL more sensitive than BOLD for experimental paradigms with long periods. For example, the insensitivity of ASL to low-frequency drifts has been used to study increases in CBF that persisted for at least 8 min after the completion of a stressful task. In another experiment demonstrating the stability of ASL measurements, patterns of activation were detectable when comparing resting images on one day with activation images on the next day, a comparison that would not be possible with BOLD imaging.

s0085

Spatial Localization

p0135 Because CBF directly measures the amount of arterial blood that has been delivered to the capillary beds, it has been hypothesized that the functional CBF signal may be more localized to the sites of neuronal activation than the BOLD signal. With the quantitative ASL methods described above, the measured CBF signal is

primarily from small arterioles, capillaries, and brain tissue. There is relatively little signal in the arteries because the inversion delays are chosen to allow enough time for the blood to flow to the target tissue. In addition, there is relatively little outflow of the tagged blood into the venous circulation, because (a) the inversion delays are on the order of the T_1 of blood, which is typically less than the capillary transit time, and (b) there is rapid exchange of water between the vascular and tissue compartments, which effectively slows the outflow. By contrast, the BOLD signal derives primarily from veins and their surrounding tissues. In work examining the visual orientation columns in the cat brain, it was found that the ASL signal provided a more convincing functional map of these very high-resolution structures than did the BOLD signal.

s0090

Summary

p0140

Perfusion fMRI using arterial spin labeling offers a useful complement to standard BOLD techniques. ASL methods provide a quantitative measure of CBF that has the potential to better characterize the magnitude and localize the sites of the underlying neuronal activity. Two important drawbacks of ASL techniques for fMRI are that both the temporal resolution and the sensitivity of ASL are lower than those of the BOLD contrast mechanism, so the choice of these methods should be tailored carefully to the biological questions at hand, or used together to provide additional physiological or metabolic information.

See also: Cognition: an overview of neuroimaging techniques (00298); Evoked potentials, recording methods (00318); Positron Emission Tomography (PET) (00323); Statistical tests and inferences (00331).

Further Reading

Aguirre GK, Detre JA, and Wang J (2005) Perfusion fMRI for functional neuroimaging. *International Review of Neurobiology* 66: 213–236.

Buxton RB (2002) *Introduction to Functional Magnetic Resonance Imaging*. Cambridge, UK: Cambridge University Press.

Buxton RB, Frank LR, Wong EC, et al. (1998) A general kinetic model for quantitative perfusion imaging with arterial spin labeling. *Magnetic Resonance in Medicine* 40(3): 383–396.

Calamante F, Thomas DL, Pell GS, et al. (1999) Measuring cerebral blood flow using magnetic resonance imaging techniques. *Journal of Cerebral Blood Flow & Metabolism* 19(7): 701–735.

Detre JA, Leigh JS, Williams DS, et al. (1992) Perfusion imaging. *Magnetic Resonance in Medicine* 23: 37–45.

Detre JA and Wang J (2002) Technical aspects and utility of fMRI using BOLD and ASL. *Clinical Neurophysiology* 113(5): 621–634.

Golay X, Hendrikse J, and Lim TC (2004) Perfusion imaging using arterial spin labeling. *Topics in Magnetic Resonance Imaging* 15(1): 10–27.

Liu TT and Wong EC (2005) A signal processing model for arterial spin labeling functional MRI. *Neuroimage* 24(1): 207–215.

Parkes LM (2005) Quantification of cerebral perfusion using arterial spin labeling: Two-compartment models. *Journal of Magnetic Resonance Imaging* 22(6): 732–736.

Wong EC, Buxton RB, and Frank LR (1998) A theoretical and experimental comparison of continuous and pulsed arterial spin labeling techniques for quantitative perfusion imaging. *Magnetic Resonance in Medicine* 40(3): 348–355.

Wong EC, Cronin M, Wu WC, et al. (2006) Velocity-selective arterial spin labeling. *Magnetic Resonance in Medicine* 55(6): 1334–1341.