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Arterial Spin Labeling Perfusion fMRI With Very Low Task Frequency

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Functional magnetic resonance imaging (fMRI) has become the most widely used modality for visualizing regional brain activation in response to sensorimotor or cognitive tasks. While the majority of fMRI studies have used blood oxygenation level-dependent (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 arterial spin labeling (ASL) perfusion contrast, primarily as a result of successive pairwise subtraction between images acquired with and without labeling. Recent data suggest that ASL contrast shows stable noise characteristics over the entire frequency spectrum, which makes it suitable for studying low-frequency events in brain function. The present study investigates the relative sensitivities of ASL and BOLD contrast in detecting changes in motor cortex activation over a spectrum of frequencies of experimental design, where the alternating period between the resting state and activation is varied from 30 s up to 24 hr. The results demonstrate that 1) ASL contrast can detect differences in motor cortex activation over periods of minutes, hours, and even days; 2) the functional sensitivity of ASL contrast becomes superior to that of BOLD contrast when the alternating period between the resting state and activation is greater than a few minutes; and 3) task activation measured by ASL tends to have less intersubject variability than BOLD contrast. The improved sensitivity of the ASL contrast for low task frequency and longitudinal studies, along with its superior power in group analysis, is expected to extend the range of experimental designs that can be studied using fMRI. Magn Reson Med 49:796–802, 2003. © 2003 Wiley-Liss, Inc.

Key words: arterial spin label; 1/f noise; BOLD contrast; perfusion fMRI; fMRI task design

Over the past decade, functional magnetic resonance imaging (fMRI) methods have become the most popular and economical approach for imaging the neural correlates of cognition in humans. The most widely used fMRI technique, blood oxygen level-dependent (BOLD) contrast, measures dynamic changes in regional magnetic susceptibility. Functional contrast is obtained because several interacting physiologic responses to neural activity alter the concentration of local deoxyhemoglobin, which is paramagnetic and spoils the regional magnetic field (1). However, biophysical factors, such as vessel orientation with respect to the main magnetic field, also influence the observed signal changes (2).

While BOLD contrast has been widely and successfully exploited for imaging task activation, such as in event-related studies that examined the evoked BOLD response to individual cognitive or sensorimotor stimuli (3,4), at the other end of the frequency spectrum slow "drifts" in fMRI signal confound comparisons of activity spaced much more than a minute apart. These drifts can be well characterized as having power that varies inversely with frequency (5), or by a more complicated model such as high-order autoregressive function (6,7). Experiments with longer blocks (lower task frequencies) are most affected, such as studies that involve slowly developing processes (e.g., mood changes or procedural learning) or require comparisons of widely-spaced observations (e.g., drug effects). Drifts have been shown to be a property of the scanning system itself, rather than a physiologic property of the brain, and can be observed in the absence of a temporally structured experimental paradigm, or even with inert phantoms instead of human subjects (5,8). Other evidence has suggested that drift effects may be influenced by spontaneous neuronal events and may be pixel-wise dependent (9).

Perfusion imaging with arterial spin labeling (ASL) contrast uses magnetically labeled arterial blood water as an endogenous tracer to provide quantitative cerebral blood flow (CBF) measurements (10,11). This approach can provide a direct measure of a well characterized physiological parameter (perfusion), and can be sampled using a variety of imaging sequences, including sequences that preserve signal in regions of high static susceptibility, such as the orbitofrontal cortex. With ASL methods, perfusion measurements are typically derived from pairwise subtractions of temporally adjacent images acquired with and without spin labeling. Because of this pairwise subtraction and the subsequent calibration process to produce an absolute measure of CBF, the slow drifts present in BOLD contrast images are eliminated in ASL (12). Resting CBF measurements from ASL have previously been shown to be stable across intervals varying from a few minutes to a few days (13). Functional activation data comparing ASL to BOLD contrast during task activation have indicated that ASL is superior to BOLD contrast for task periods longer than 1–2 min (12). These data also suggest that ASL produces less intersubject variability in task activation compared to BOLD, which is most likely attributable to ASL's ability to measure task-induced flow changes directly and quantitatively. ASL may therefore provide a

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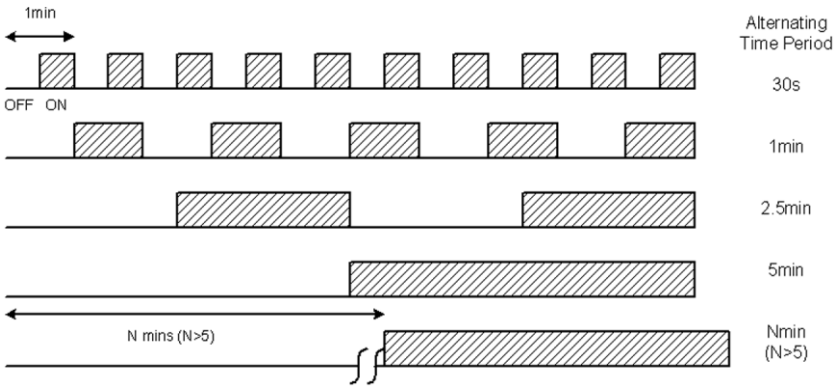

FIG. 1. Skeletal diagram depicting the experimental designs for perfusion fMRI. While the designs of the four conditions with alternating periods of <5 min are relatively straightforward, those of the other four conditions with alternating periods of >5 min require concatenation of separate scans of rest and activation, with corresponding intervals in between.

solution to the fundamental limitations of BOLD methods at low task frequencies, permitting the measurement of changes in neural activity that span longer periods of time—minutes, hours, and even days.

The present study was designed to test the hypothesis that ASL contrast may be used to detect differences in evoked neural activity on time scales much longer than those used for BOLD studies. For this purpose, we employed a simple motor task that produces large task-induced signal changes in relatively well established anatomical regions. A spectrum of frequencies of experimental design were tested, wherein the alternating period between the resting state and activation was varied from 30 s up to 24 hr. We compared both individual and group results from a multislice pulsed ASL (PASL) technique at 4.0 T (14) with both BOLD contrast derived from raw PASL data (12,15) and separately acquired BOLD data with optimized parameters.

METHODS

MR Scanning

Imaging was performed on a GE 4.0T whole-body scanner (GE Medical Systems, Milwaukee, WI) using the product quadrature head coil. Motor cortex stimulation was used as the task activation in all of the studies, which entailed self-paced bilateral finger tapping of sequential thumb-to-digit oppositions. The onset of the activation and resting state was indicated by visually presented cues. Written informed consent was obtained prior to all human studies according to Institutional Review Board guidelines. Perfusion fMRI was performed on six healthy male subjects (22–35 years old, mean 27.2 years) using a PASL sequence that has been described previously (14). The acquisition parameters were: FOV = 24 cm × 16 cm, 64 × 40 matrix, TR/TE = 3000/18 ms, delay time (between the saturation and excitation pulses) = 800 ms, bandwidth = 100 kHz, slice thickness = 8 mm, and interslice space = 2 mm. Eight slices were acquired from inferior to superior in an interleaved order using a gradient-echo echo-planar imaging (EPI) sequence to ensure complete coverage of the motor cortex, and each slice acquisition took about 50 ms.

Eight experimental conditions were tested on two scanning sessions at similar times on consecutive days for perfusion fMRI. Each experimental condition consisted of a 10-min scan of 200 acquisitions, in which the alternating time period between the motor cortex stimulation and resting state was 0.5, 1, 2.5, 5, 10, 20 min, 1 and 24 hr, respectively (see Fig. 1). For conditions with alternating periods longer than 5 min, two 5-min scans of resting state and activation with corresponding intervals in between were concatenated. The first-day scanning session consisted of four 10-min scans of 0.5, 1, 2.5, and 5 min OFF/ON finger tapping preceded by a 5-min scan of baseline, which made up the 1-hr (approximate) period condition concatenated with the last 5-min scan of finger tapping. The second-day scanning session consisted of a 5-min baseline and two 10-min scans of 5-min OFF/ON finger tapping. The first and second 5-min scans of finger tapping made up the 10- and 20-min period conditions concatenated with the baseline scan, respectively. Similarly, the first 5-min scan of finger tapping made up the 24-hr (approximate) period condition concatenated with the 5-min baseline scan acquired on the first day. A 30-s two-point T_1 measurement sequence was carried out after each scan for CBF quantification.

Since a gradient-echo EPI sequence was used for image acquisition in the PASL approach, concurrent ASL and BOLD contrast images could be obtained (15). However, these BOLD contrast data may not be optimal because of the relatively short TE and long TR used, and the reduced raw image intensity that resulted from the inversion recovery acquisitions. Therefore, a gradient-echo EPI sequence with the same FOV and matrix size as the PASL sequence was used for optimized BOLD imaging in a separate set of experiments. Acquisition parameters were: TR/TE = 2000/28 ms (16), bandwidth = 62.5 kHz, and slice thickness = 5 mm without gap. A flip angle of 90° was used to replicate the RF uniformity of the ASL data. This would cause a <3% reduction in raw signal intensity compared to that acquired using the Ernst angle of 75°, assuming a gray matter T_1 of 1.4 s at 4.0T. Twenty-one slices were acquired from inferior to superior in an interleaved order. Six experimental conditions were tested on another six subjects (five males and one female, 22–40 years old, mean 28.0 years) within one scanning session. Each of the experimental conditions consisted of an 8-min scan of 240 acquisitions in which the alternating time period between the motor cortex stimulation and resting state was 0.5, 1, 2, 4, 8 min, and 1 hr, respectively. The scanning session consisted of a 4-min baseline scan followed by four 8-min scans using the paradigms of 0.5, 1, 2, and 4 min of

OFF/ON finger tapping, respectively, and another 8-min baseline scan at the end. The 8-min and 1-hr (approximate) period conditions were formed by concatenating the last 4-min finger-tapping scan with the last and first 4-min baseline scans, respectively. To enable all the experimental conditions to be compared within one scanning session, a scan time of 8 min was used, which would cause an approximately 10% reduction in functional sensitivity as compared to a scan time of 10 min used in perfusion fMRI experiments. During all the above experiments, a 3D inversion-prepared spoiled GRASS sequence was used for T_1-weighted anatomical images.

Data Processing

Data were reconstructed offline and realigned to the first image for each experimental condition, followed by spatial smoothing using a 3D 8-mm FWHM Gaussian kernel. For perfusion, the series of label images were shifted in time by one TR using linear interpolation (average of the two adjacent label images). Perfusion and BOLD contrast images were generated by pairwise subtraction and summation between the time-matched label and control images, respectively (15). CBF, f, can be calculated by (14)

$$f = \frac{\lambda \Delta M}{2\alpha M_0 TI_1 \exp(-\ TI_2/T_{1a})} \quad [1]$$

where ΔM is the difference image between label and control acquisitions, M_0 is the equilibrium brain tissue magnetization, λ is the blood/tissue water partition coefficient, T_{1a} is the longitudinal relaxation time of blood, α is the inversion efficiency, and TI_1 and TI_2 are the tagging bolus duration and image acquisition time, respectively. Conversion to CBF values used assumed values of $\lambda = 0.9$ml/g, $\alpha = 0.98$, $T_{1a} = 1.6$s, and the M_0 image acquired with the T_1 measurement sequence. For concatenated experimental conditions, this procedure was performed separately for the resting-state and activation scans. To minimize the motion artifact between the M_0 and functional images, the M_0 images were also realigned to the precedent functional scan by applying the transformation matrix of the last image of that scan.

Three data sets of image series were analyzed using the VoxBo software package (http://www.voxbo.org), i.e., the simultaneously measured CBF and BOLD data acquired using the PASL sequence (100 images per condition) and the optimized BOLD data acquired using the gradient-echo EPI sequence (240 images per condition). Voxel-wise analysis of the functional data was carried out to identify voxels with a significant response to the motor cortex stimulation for each experimental condition in each subject. This analysis employed the modified general linear model (17) and used an appropriate single covariate function of resting state and activation associated with each experimental condition. t-Tests were performed to evaluate the significance of the variance in the data explained by the model. To account for the temporal autocorrelation of the BOLD data, a 1/frequency ($1/f$) function was fit to the (square root of the) average BOLD power spectrum from each experimental condition for each subject, ignoring those frequencies at which power attributable to task might be expected. The time-domain representation of the $1/f$ curve was placed within the K matrix (the convolution matrix representing all assumed temporal autocorrelation) (5,17) along with a "notch" filter designed to remove the low-frequency confounds and high-frequency noise at the Nyquist frequency, and a low-pass kernel representing the standard hemodynamic function. This procedure was carried out independently for each experimental condition, and the notch filtering was not necessary for conditions with only one cycle of baseline and activation. For experimental conditions with concatenated scans, the BOLD data were normalized (scaled) by the global mean signal from each scan to account for the difference in scanner condition.

CBF data were found not to have any substantial temporal autocorrelation in the power spectrum (12). Therefore, the analysis of these data was able to assume independence of the errors, and did not require modeling of intrinsic temporal autocorrelation, notch filtering, or temporal smoothing. Individual activation maps including the t- and β-values were Talairach-normalized through manually defined landmarks. The random-effects group t-maps were generated by applying the unpaired t-test for the normalized β-values of all the subjects at each voxel for each condition. The region of interest (ROI) of somatosensory motor cortex related to hand movement was defined upon the mean normalized anatomical images based on the "precentral knob" landmark structure (18), and was consistent across all of the subjects. The functional signal-to-noise ratio (SNR) was then measured as the mean t-value within ROI divided by the standard deviation (SD) of the whole-brain t-values for each experimental condition from both normalized individual and group t-maps. No mask, cluster, or threshold was applied on the individual or group t-maps for the comparison of the relative sensitivities of the ASL and BOLD contrast. An arbitrary threshold of $t > 3.5$ ($P < 0.008$, uncorrected) was set on the group t-maps for display purpose.

For statistical analysis the experimental conditions were divided into two categories of high (alternating period $\leq$ 4 min) and low (alternating period $>$ 4 min) task frequency (see Results). The individual functional SNR values of the conditions within the definition range of these two categories were averaged, followed by comparison between the simultaneously measured perfusion and BOLD data using a paired t-test, and comparison between the simultaneously measured perfusion or BOLD data and the optimized BOLD data using an unpaired t-test.

RESULTS

Figure 2 displays the group t-maps of the perfusion and BOLD activation induced by bilateral finger tapping acquired using the PASL and EPI sequences, respectively. The perfusion data shows robust and consistent activation in the bilateral somatosensory motor cortex in all of the conditions, even when the resting state and activation were separated by one day. Supplementary motor cortex activation was also observed in most of the conditions. By contrast, the BOLD group t-maps acquired concurrently using PASL, or separately using EPI, show little activation when the alternating period was longer than 1 or 2 min,

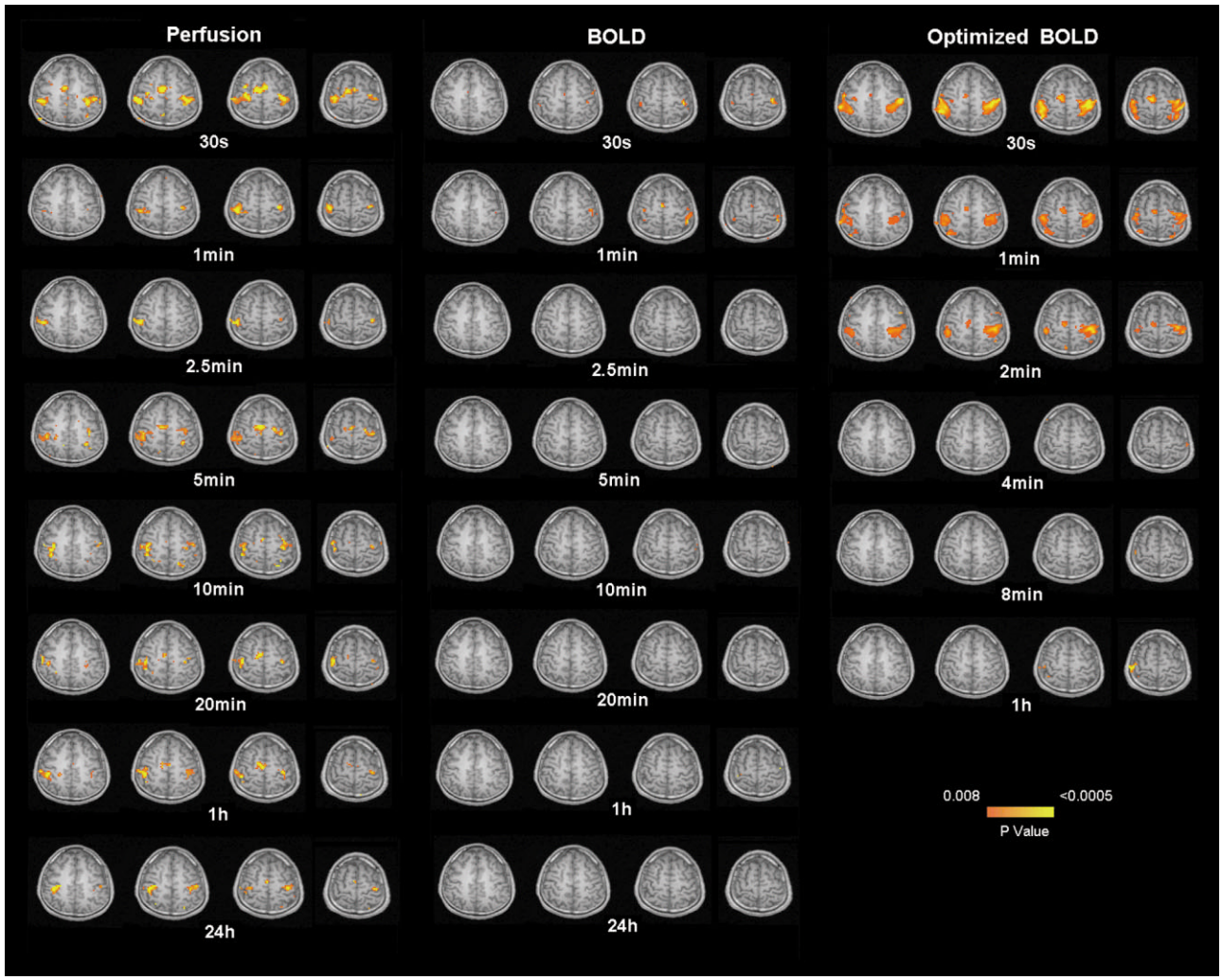

FIG. 2. Talairach-normalized group *t*-maps ($N = 6$) of the perfusion and BOLD activation induced by bilateral finger tapping acquired using the PASL and EPI sequences for each of experimental conditions, showing four axial slices through the motor cortex. A color scale of *t*-values ($7 > t > 3.5$, $0.0005 < P < 0.008$ uncorrected) is overlaid upon normalized anatomical images of a single subject.

respectively. Not suprisingly (given that more images were acquired and more optimal parameters were used), the optimized BOLD data showed improved sensitivity compared to the simultaneously measured BOLD data.

The functional SNRs based on the individual/group perfusion and BOLD data for each experimental condition are plotted in Fig. 3. As displayed by the average within-subject functional SNR (Fig. 3a), the optimized BOLD data show improved sensitivity compared to the perfusion data for conditions with relatively short alternating periods ($P = 0.024$, see Table 1). However, the BOLD method has progressively less power to detect ever slower variations in brain activity, while ASL contrast shows persistent sensitivity throughout all tested frequencies of experimental design ($P = 0.032$ and 0.029 for simultaneously measured BOLD and optimized BOLD data, respectively). The cross-point of task frequency when ASL contrast becomes superior to optimized BOLD contrast is around 0.002 Hz, corresponding to an alternating period of about 4 min. The functional SNR measured on the group *t*-maps of the perfusion and BOLD data (Fig. 3b) shows that the across-subject *t*-values of the perfusion data are slightly greater than those of the optimized BOLD data using short alternating periods, and are almost two times greater than those of the BOLD data with low task frequencies. This observation adds support to the previous finding of lower inter-subject variability in ASL contrast compared to BOLD contrast (12). In addition, the functional SNR of the BOLD data measured simultaneously using the PASL sequence is significantly reduced compared to the optimized BOLD data for conditions with relatively short alternating periods ($P = 0.019$), which suggests that the parameters were indeed suboptimal for detecting functional activation.

In the above analysis, the SD of the whole-brain *t*-values was taken as the index of the noise level that could lead to potential errors due to the inclusion of the activated voxels. The SD of noise was also derived from ROIs that consisted of prefrontal and temporal lobes that have no documented relationship with sensorimotor function, and very similar results were obtained with increased inter-subject variance. The mean quantitative CBF values averaged across six subjects for each condition are displayed in Fig.

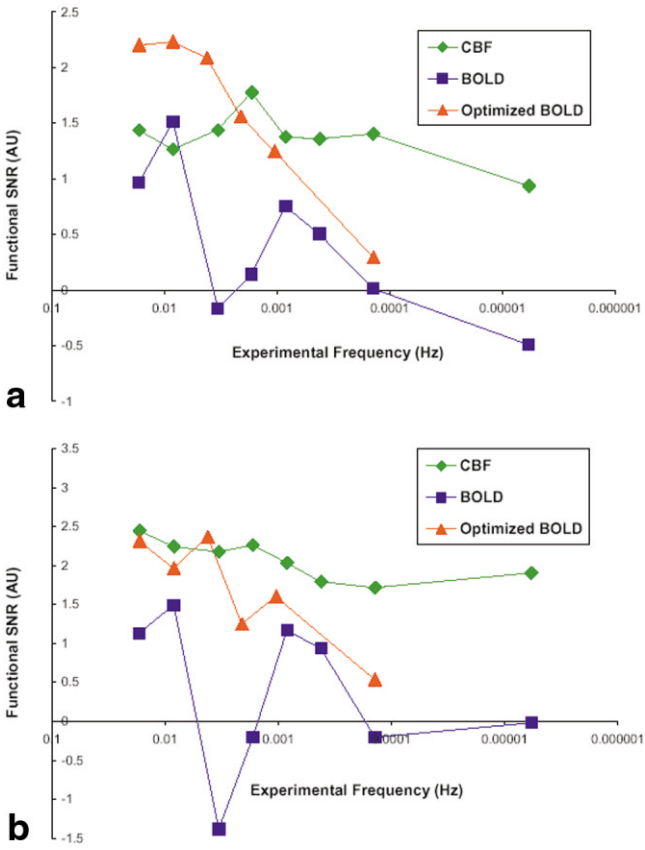

FIG. 3. Functional SNRs based on the individual/group perfusion and BOLD data for each experimental condition, displaying (**a**) the average within-subject functional SNR and (**b**) the functional SNR measured on the group *t*-maps.

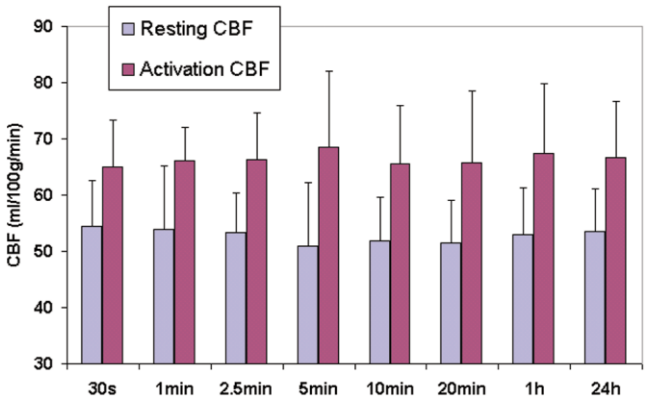

FIG. 4. The mean quantitative CBF values measured from the predefined hand motor ROIs, averaged across six subjects for each of the eight experimental conditions.

4, which shows highly reproducible CBF values over various intervals between task and resting state. The mean CBF values averaged across eight conditions were 52.8 ± 1.2 (mean ± SD) and 66.4 ± 1.1 ml/100 g/min during rest and activation, respectively, with a mean signal change of 25.9% ± 4.3% in the predefined hand motor ROI. The relatively low fractional signal change reflects the fact that it is averaged within the ROI rather than across significantly activated voxels. Nevertheless, the very small variance of the CBF values across conditions reflects the stability of ASL perfusion fMRI.

DISCUSSION

The present study provides experimental confirmation that ASL perfusion fMRI can reliably detect sensorimotor task activation at frequencies well below the range at which BOLD fMRI loses sensitivity due to drift effects. According to the theoretical calculation by Aguirre et al. (12), the relative sensitivity of perfusion contrast will become greater than that of BOLD contrast when the task frequency is lower than 0.006 Hz (an approximately 90-s period). The present results are in good agreement with the theoretical prediction (which was derived from a visual stimulation paradigm with a 31-s alternating period at 1.5T), except that the cross-point between the relative sensitivities of the perfusion and optimized BOLD contrast is at the task frequency of 0.002 Hz (an approximately 4-min period). The reduction in BOLD sensitivity at low task frequency can be understood as a consequence of two effects. First, appropriate statistical modeling of the increased noise present at low temporal frequencies in BOLD data reduces sensitivity for slow changes in neural activity. Second, voxel-to-voxel variability in the degree of

Table 1
Values of Functional SNR Associated With High and Low Task Frequency Categories

		High task frequency (alternating period ≤ 4 min)	Low task frequency (alternating period > 4 min)
Individual	Perfusion	1.38 ± 0.52	1.37 ± 0.49 (0.032 P vs. B)
	BOLD	0.77 ± 0.96 (0.019 B vs. OB)	0.18 ± 0.97
	Optimized BOLD	1.91 ± 0.59 (0.024 OB vs. P)	0.77 ± 0.42 (0.029 OB vs. P)
Group	Perfusion	2.29	1.94
	BOLD	0.41	0.33
	Optimized BOLD	1.97	1.07

Statistical significance (*P* value) is listed in the parenthesis followed by abbreviation representing the pair of data being compared. P, Perfusion; B, BOLD; OB, Optimized BOLD).

low-frequency noise decreases the accuracy of noise modeling and causes inflated false-positive rate (6), thereby increasing intersubject variability and decreasing the power of group studies. Analysis of our BOLD data indicates that the two effects both contribute to the reduced power of BOLD contrast in visualizing slow variation in brain function, which supports previous findings that BOLD data has substantial temporal autocorrelation (5–7).

The long-term stability of the ASL perfusion technique and its sensitivity to slow variations in brain function can be understood in several ways. To a first approximation, pairwise subtraction of adjacent points results in the first derivative of a time series $f(t)$, and the Fourier transform of the first derivative is $i\omega F(\omega)$ (where $F(\omega)$ is the Fourier transform of $f(t)$). If the power spectrum of the intrinsic data is $1/\omega$, the magnitude of the Fourier transform of its derivative will be one, and the removal of low-frequency drift is expected. Second, fractional signal change of task activation is typically in the range of 0.5–5% in the BOLD signal, while it is on the order of 50% in the ASL signal. A change by a few percent in raw image intensity that evolves over a period of several minutes due to subject motion and scanner instability can overwhelm the real activation in BOLD signal. However, because the difference perfusion signal (tag-control) scales with the raw image intensity, such effects will at most cause a few-percent change in the ASL signal, and have little effect on the large percentage signal change with activation (11). Finally, the approach employed in the present study uses M_0 as a calibration factor for CBF quantification, which further reduces the effect of variations in raw image intensity between different scanning sessions. In the current experiment, a steady CBF baseline and robust motor cortex activation were observed despite the relatively large displacement and signal difference between the raw images acquired 24 hr apart (sometimes even after motion correction).

Figure 3 demonstrates the general trend of stable functional sensitivity of perfusion contrast as opposed to decreasing sensitivity of BOLD contrast with ever lower task frequency. A detailed inspection of these data reveals fluctuations, especially in the functional SNR curves of the simultaneously measured BOLD data that display negative excursion. Based on analysis of variance (ANOVA) results, the variation in the perfusion data is most likely due to noise, since the effect of task frequency is not statistically significant, whereas the effect of task frequency is significant ($P < 0.05$) in both the optimized and simultaneously measured BOLD data. Further experiments will be needed to determine whether the apparent oscillations in the BOLD data as a function of task frequency reflects particular temporal characteristics of the BOLD fMRI signal vs. noise. Previous studies have used BOLD contrast to characterize brain responses to prolonged sensorimotor stimuli, with durations of up to about 20 min (19–21), although the brain regions from which the time courses were derived were actually either determined by a separate scan using relative high task frequency (19,21) or constrained by anatomical information (20). It is also possible to improve the sensitivity of BOLD contrast at low task frequency by normalizing the BOLD signal using a global signal or an external reference—an idea borrowed from positron emission tomography studies. In the present study, scaling by the global signal from each separate scan did not show improved functional sensitivity at low task frequencies, probably because temporal autocorrelations in the data may vary spatially. Other possible methods to improve the functional sensitivity in BOLD fMRI at low task frequencies include baseline detrending and absolute measuring of T_2^*.

The present study also provides additional confirmation that ASL perfusion fMRI has less intersubject variability compared to BOLD fMRI, even though the sensitivity for detecting task activation remains markedly lower in individual subjects (12). The reason for this is not yet well understood. Most likely, the reduced intersubject variability reflects the direct measurement of a single physiological parameter (perfusion) with ASL. In contrast, the BOLD signal is not only affected by physiological parameters of CBF, blood volume, and oxygenation consumption (22–24), but is also susceptible to biophysical effects, including small changes in scanner condition (8). These complex endogenous and exogenous effects may add extra noise to the intrinsic variance of the CBF, leading to increased intersubject variability in the BOLD signal. Another possible explanation may lie in the observation that the magnetically labeled blood water is uniformly diffused at the tissue and capillary sites (25,26) and provides more accurate localization than BOLD activation, which depends on tortuous venous vasculature (27). When individual activation maps are normalized and grouped together, the BOLD activation sites may spread around the corresponding anatomical structure, thereby reducing the peak magnitude seen in the group results. These tentative explanations await experimental verification.

In conclusion, the temporal characteristic of ASL perfusion contrast makes it suitable for longitudinal studies and for imaging CBF both at rest and in response to task activation. This important feature of ASL contrast, along with other advantages such as superior power in group analysis, potential for susceptibility-free imaging, and more specific spatial localization, renders ASL perfusion MRI an appealing tool for functional neuroimaging applications.

REFERENCES

1. Thulborn KR, Waterton JC, Matthews PM, Radda GK. Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. Biochim Biophys Acta 1982;714:265–270.
2. Lai S, Glover GH, Haacke EM. Spatial selectivity of BOLD contrast: effects in and around draining veins. In: Moonen CTW, Bandettini PA, editors. Functional MRI. Heidelberg: Springer-Verlag; 1999. p 221–231.
3. Buckner RL, Bandettini PA, O'Craven KM, Savoy RL, Petersen SE, Raichle ME, Rosen BR. Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. Proc Natl Acad Sci USA 1996;93:14878–14883.
4. Josephs O, Turner R, Friston KJ. Event-related fMRI. Hum Brain Mapp 1997;5:243–248.
5. Zarahn E, Aguirre GK, D'Esposito M. Empirical analyses of BOLD fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions. Neuroimage 1997;5:179–197.
6. Friston KJ, Josephs O, Zarahn E, Holmes AP, Rouquette S, Poline J. To smooth or not to smooth? Neuroimage 2000;12:196–208.
7. Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of fMRI data. Neuroimage 2001;14:1370–1386.
8. Smith AM, Lewis BK, Ruttimann UE, Ye FQ, Sinnwell TM, Yang Y, Duyn JH, Frank JA. Investigation of low frequency drift in fMRI signal. Neuroimage 1999;9:526–533.

9. Hyde JS, Biswal BB, Jesmanowicz A. High-resolution fMRI using multislice partial k-space GR-EPI with cubic voxels. Magn Reson Med 2001;46:114–125.
10. Detre JA, Alsop DC. Perfusion fMRI with arterial spin labeling (ASL). In: Moonen CTW, Bandettini PA, editors. Functional MRI. Heidelberg: Springer-Verlag; 1999. p 47–62.
11. Wong EC. Potential and pitfalls of arterial spin labeling based perfusion imaging techniques for MRI. In: Moonen CTW, Bandettini PA, editors. Functional MRI. Heidelberg: Springer-Verlag; 1999. p 63–69.
12. Aguirre GK, Detre JA, Zarahn E, Alsop DC. Experimental design and the relative sensitivity of BOLD and perfusion fMRI. Neuroimage 2002;15: 488–500.
13. Floyd TF, Maldjian JA, Gonzalez-Atavales JB, Detre JA. Test-retest stability with continuous arterial spin labeled (CASL) perfusion MRI in regional measurement of cerebral blood flow. In: Proceedings of the 9th Annual Meeting of ISMRM, Glasgow, Scotland, 2001. p 1569.
14. Wang J, Alsop DC, Li L, Listerud J, Gonzalez-At JB, Schnall MD, Detre JA. Comparison of quantitative perfusion imaging using arterial spin labeling at 1.5 and 4 telsa. Magn Reson Med 2002;48:242–254.
15. Wong EC, Buxton RB, Frank LR. Implementation of quantitative perfusion imaging techniques for functional brain mapping using pulsed arterial spin labeling. NMR Biomed 1997;10:237–249.
16. Yang Y, Wen H, Mattay VS, Balaban RS, Frank JA, Duyn JH. Comparison of 3D BOLD functional MRI with spiral acquisition at 1.5 and 4.0 T. Neuroimage 1999;9:446–451.
17. Worsley KJ, Friston KJ. Analysis of fMRI time-series revisited—again. Neuroimage 1995;2:173–182.
18. Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P. Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain 1997;120:141–157.
19. Bandettini PA, Kwong KK, Davis TL, Tootell RB, Wong EC, Fox PT, Belliveau JW, Weisskoff RM, Rosen BR. Characterization of cerebral blood oxygenation and flow changes during prolonged brain activation. Hum Brain Mapp 1997;5:93–109.
20. Chen W, Zhu XH, Kato T, Andersen P, Ugurbil K. Spatial and temporal differentiation of fMRI BOLD response in primary visual cortex of human brain during sustained visual simulation. Magn Reson Med 1998;39:520–527.
21. Kruger G, Kleinschmidt A, Frahm J. Stimulus dependence of oxygenation-sensitive MRI responses to sustained visual activation. NMR Biomed 1998;11:75–79.
22. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA 1992;89:5675–5679.
23. Mandeville JB, Marota JJ, Ayata C, Moskowitz MA, Weisskoff RM, Rosen BR. MRI measurement of the temporal evolution of relative CMRO(2) during rat forepaw stimulation. Magn Reson Med 1999;42: 944–951.
24. Ogawa S, Menon RS, Tank DW, Kim SG, Merkle H, Ellerman JM, Ugurbil K. Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. Biophys J 1993;64:803–812.
25. Luh WM, Wong EC, Bandettini PA, Ward BD, Hyde JS. Comparison of simultaneously measured perfusion and BOLD signal increases during brain activation with T(1)-based tissue identification. Magn Reson Med 2000;44:137–143.
26. Duong TQ, Kim DK, Ugurbil K, Kim SG. Localized cerebral blood flow response at submillimeter columnar resolution. Proc Natl Acad Sci USA 2001;98:10904–10909.
27. Hoogenraad FG, Pouwels PJ, Hofman MB, Reichenbach JR, Sprenger M, Haacke EM. Quantitative differentiation between BOLD models in fMRI. Magn Reson Med 2001;45:233–246.