High-Sensitivity Single-Shot Perfusion-Weighted fMRI

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A method is presented for measurement of perfusion changes during brain activation using a single-shot pulsed spin labeling technique. By employing a double-inversion labeling strategy, stationary tissue (background) signal was suppressed while minimally affecting perfusion sensitivity. This allowed omission of the otherwise required reference scan, resulting in twofold-improved temporal resolution. The method was applied to visual and motor cortex activation studies in humans, and compared to standard FAIR-type perfusion labeling techniques. Experiments performed at 1.5T and 3.0T indicate a close to 90% suppression of background signal, at a cost of an 11% and 9%, respectively, reduction in perfusion signal. Combined with the twofold increase in signal averaging, and a reduction in background signal fluctuations, this resulted in a 64% (1.5T, $N = 3$) and a 128% (3T, $N = 4$) overall improvement in sensitivity for the detection of activation-related perfusion changes. Magn Reson Med 46:88–94, 2001. Published 2001 Wiley-Liss, Inc.†

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Perfusion changes in response to neuronal activation can be detected indirectly by functional MRI (fMRI) techniques sensitive to blood oxygen level-dependent (BOLD) contrast (1) or directly by fMRI techniques sensitized to perfusion (2). Both BOLD and perfusion techniques have the potential to provide relatively accurate localization of the activation, provided that signals originating from larger vascular structures are suppressed (3–5). Despite the generally lower sensitivity and anatomical coverage compared to BOLD, the perfusion techniques offer some potential advantages. These include a reduced sensitivity to macroscopic susceptibility effects, and an increased simplicity of the contrast mechanism due to the virtual absence of blood oxygenation effects. This potentially allows fMRI in areas with poor magnetic field uniformity, as well as better reliability and reproducibility.

Perfusion and flow changes with brain activity can be detected using a fast MR scan technique preceded by an inversion pulse that is selective to the imaging slice (2). Unfortunately, single-shot perfusion labeling (SSPL) is prone to contamination by BOLD and motion-related signal changes, because the perfusion changes occur in the presence of a normally much larger background signal. To alleviate this situation, a short echo time can be used, and a control scan with nonselective inversion (flow-sensitive alternating inversion recovery (FAIR) (7)) can be added (3,6) to estimate the magnitude of the background signal as well as to derive and estimate background perfusion levels. Disadvantages of adding this reference scan are a twofold increase in measurement time, and a $\sqrt{2}$ increase in white noise. In the following we propose an alternative approach that reduces contamination of the SSPL signal without the need of a reference scan. By sacrificing the ability to measure baseline perfusion levels, this method allows for a substantial increase in sensitivity for detection of perfusion changes in fMRI.

MATERIALS AND METHODS

Background Suppression

The strategy of our single-shot pulsed labeling method is to suppress signal from nonperfusing (stationary) spins while minimally affecting the perfusion sensitivity. This can be achieved by inserting a second inversion pulse between the standard selective inversion pulse and the image acquisition (see Fig. 1). This method, similar to the double water eliminated Fourier transform (WEFT) water suppression technique used in proton MR spectroscopy (8), allows for good suppression of signal from multiple T_1-species, including gray matter, white matter, and CSF (Fig. 1b). Contrary to alternative background suppression techniques recently introduced for perfusion imaging (9–11), the current method does not require a second (control) acquisition, and only minimally affects perfusion sensitivity. The background suppression can be optimized by adjusting the settings of inversion delay times TI_1, TI_2, and the repetition delay TD. In addition, the perfusion labeling time TL, equal to $TL = TI_1 + TI_2$, can be varied in the commonly used range of 1.5–2.0 s, while allowing for good suppression efficiency. Assuming complete spoiling of the in-slice magnetization during the 90° excitation and crusher of the imaging segment (Fig. 1a), the residual longitudinal magnetization M_z at time of excitation can be calculated as:

$$M_z = M_0 \cdot [1 - (2 - (2 - e^{-TD/T_1}) \cdot e^{-TI_1/T_1}) \cdot e^{-TI_2/T_1}]. \quad [1]$$

Figure 2 shows an example of the stationary signal suppression for TL = 1.5 s, suggesting that suppression factors of 90% are achievable over a wide range of T_1 values.

Perfusion Sensitivity

The sensitivity of pulsed labeling methods to perfusion is proportional to the net amount of label delivered to the imaging slice during the labeling time TL, which is highly dependent on the particular implementation of the labeling scheme. For simplicity, we neglect T_1 differences between arterial blood, venous blood, and tissue, as well as blood volume changes related to perfusion. This allows us to establish a constant decay rate of the label, independent of whether it is arriving in the slice or has arrived at an earlier time. Under this assumption, as with the selective inversion scan in the FAIR experiment, the perfusion sig-

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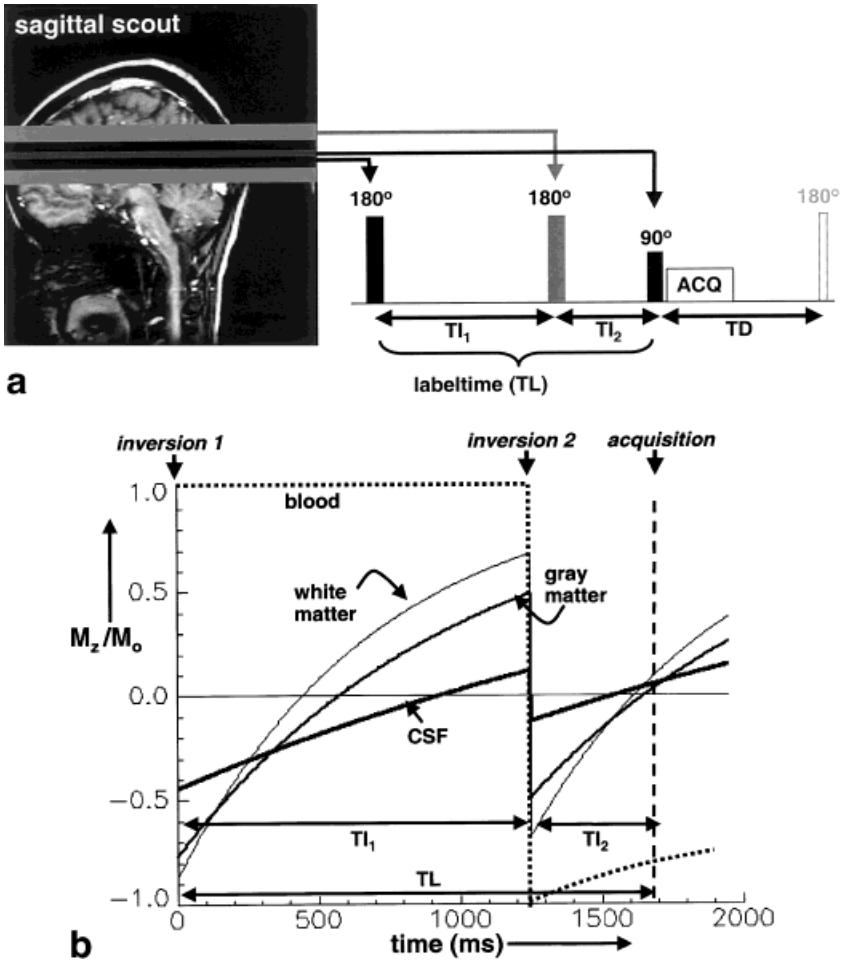

FIG. 1. **a:** MRI pulse sequence for double-inversion single-shot perfusion labeling (SSPL). Following a delay time TI_1 after the initial slice-selective inversion, a second selective inversion is played out to suppress the stationary signal. Another delay time TI_2 later, a 90° image pulse is played out to acquire the image. Following the image acquisition, and prior to a subsequent repetition of the experiment, a delay time TD is used for recovery of the magnetization. **b:** Time course of the longitudinal magnetization of blood, white and gray matter, and CSF (assuming T_1 = 1500, 700, 1000, and 2500 ms, respectively), calculated from Bloch equations, using TI_1 = 1250 ms, and TD = 1500 ms.

nal S(t) in SSPL prior to the second inversion pulse equals the accumulation of label in the imaging slice, corrected for its decay at time of detection:

$$S(t,\ t < TI_1) = 2 \cdot M_0 \cdot (t - \tau) \cdot \frac{Q}{\lambda} \cdot e^{-t/T_1}, \qquad [2]$$

with Q as cerebral blood flow, λ as the partition coefficient of brain water, and τ as the transit time, i.e., the time for the labeled spins to reach the observation slice. If the second inversion pulse at time $t = TI_1$ inverts all inflowing (M_{in}) and outflowing (M_{out}) spins, we have for $t > TI_1$:

$$M_{in} = M_0 - 2 \cdot M_0 \cdot e^{-(t - TI_1)/T_1} \qquad [3a]$$

$$M_{out} = M_0 \cdot [1 - (1 - (-1 + 2 \cdot e^{-TI_1/T_1})) \cdot e^{-(t - TI_1)/T_1}]$$

$$= M_0 \cdot [1 + 2 \cdot e^{-t/T_1} - 2 \cdot e^{-(t - TI_1)/T_1}]. \qquad [3b]$$

Complete inversion of M_{in} and M_{out} can be ensured by making the inversion profile of the second inversion pulse wide enough compared to the imaging slice, to ensure that it inverts all spins that reach the observation slice during interval TI_2. For the perfusion signal we have:

$$S(t,\ t > TI_1)$$
$$= (M_{in} - M_{out}) \cdot (t - \tau) \cdot Q/\lambda$$
$$= -2 \cdot M_0 \cdot (t - \tau) \cdot \frac{Q}{\lambda} \cdot e^{-t/T_1}. \qquad [4]$$

This indicates that, under the assumptions stated above, the SSPL and FAIR perfusion signals are of equal magnitude. However, under realistic conditions, particularly at high field, the dispersion in T_1 values between the various tissue and blood compartments is substantial and can not be neglected. This significantly complicates quantitation of the perfusion signal, which will depend on the resi-

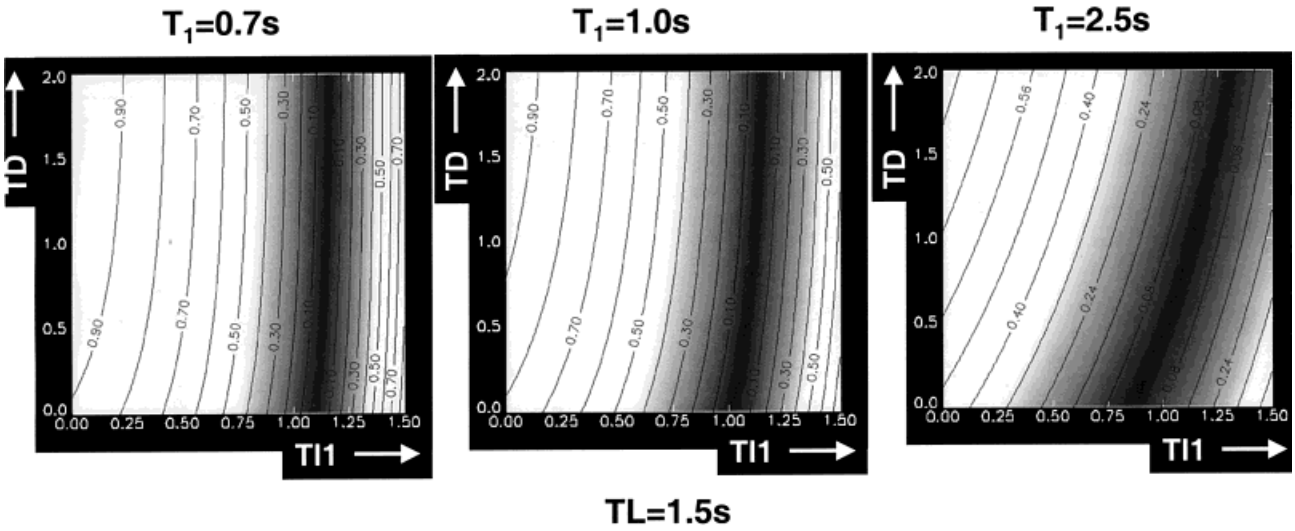

FIG. 2. Suppression of background signal as a function of T_1, TI_1, and TD. The longitudinal magnetization in the SSPL experiment was calculated using the Bloch equations using TL = 1500 ms, and T_1s of 700 ms, 1000 ms, and 2500 ms, which are similar to the T_1s of white and gray matter and CSF at 1.5T. Gray scale indicates the level of remaining longitudinal magnetization at time of acquisition.

dence time of the in-flowing as well as the out-flowing spins in each of the compartments. Equations [2] and [4] should therefore be considered as rough indications of the perfusion-related signal change.

MR Data Acquisition

Experiments were performed on normal volunteers on 1.5T (N = 10) and 3.0T (N = 6) GE scanners. In all experiments, the manufacturer's RF transmit/receive or receive-only coils were used for reception. Image acquisition was performed using single-shot trapezoidal spiral imaging (12). The single-slice acquisitions were performed in dual echo mode, with starting times of the spiral readouts (in the following indicated with TE) occurring at 11 and 35 ms. An image matrix size of 64 × 64 and a field of view of 24 cm were used. Immediately prior to data acquisition, a bipolar crusher gradient was employed on all gradient axes (b-value = 5 s/mm^2) in order to suppress signal from large vessels. Other imaging parameters were: acquisition window duration = 22 ms, and TL/TR = 1.5/3.0 s. Selective frequency offset corrected inversion (FOCI) adiabatic

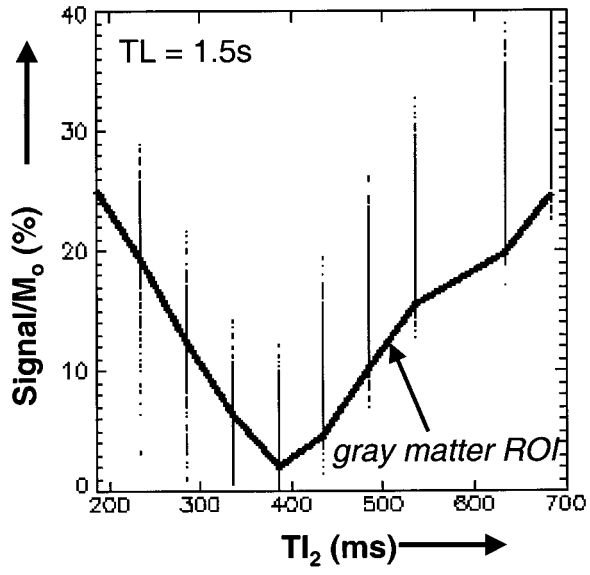

FIG. 3. Suppression of background signal as a function of TI_2. The remaining background signal was measured across an axial brain slice, using TL = 1.5 s, and TD = 1.5 s. Displayed are the signal intensities for individual pixels (dots) and the values for a gray-matter ROI (solid line).

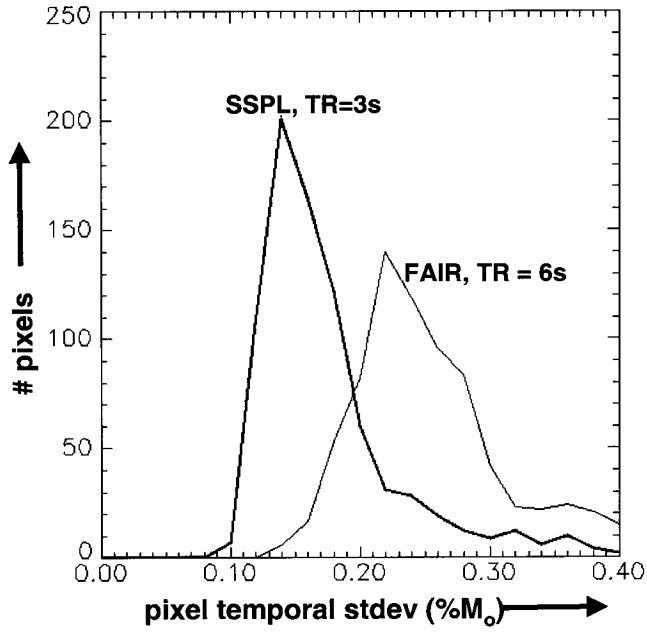

FIG. 4. Signal stability comparison of FAIR vs. SSPL. The standard deviation histogram of single-pixel time-courses indicates a median standard deviation 0.14% for SSPL, which is 57% lower than the 0.22% value found with FAIR.

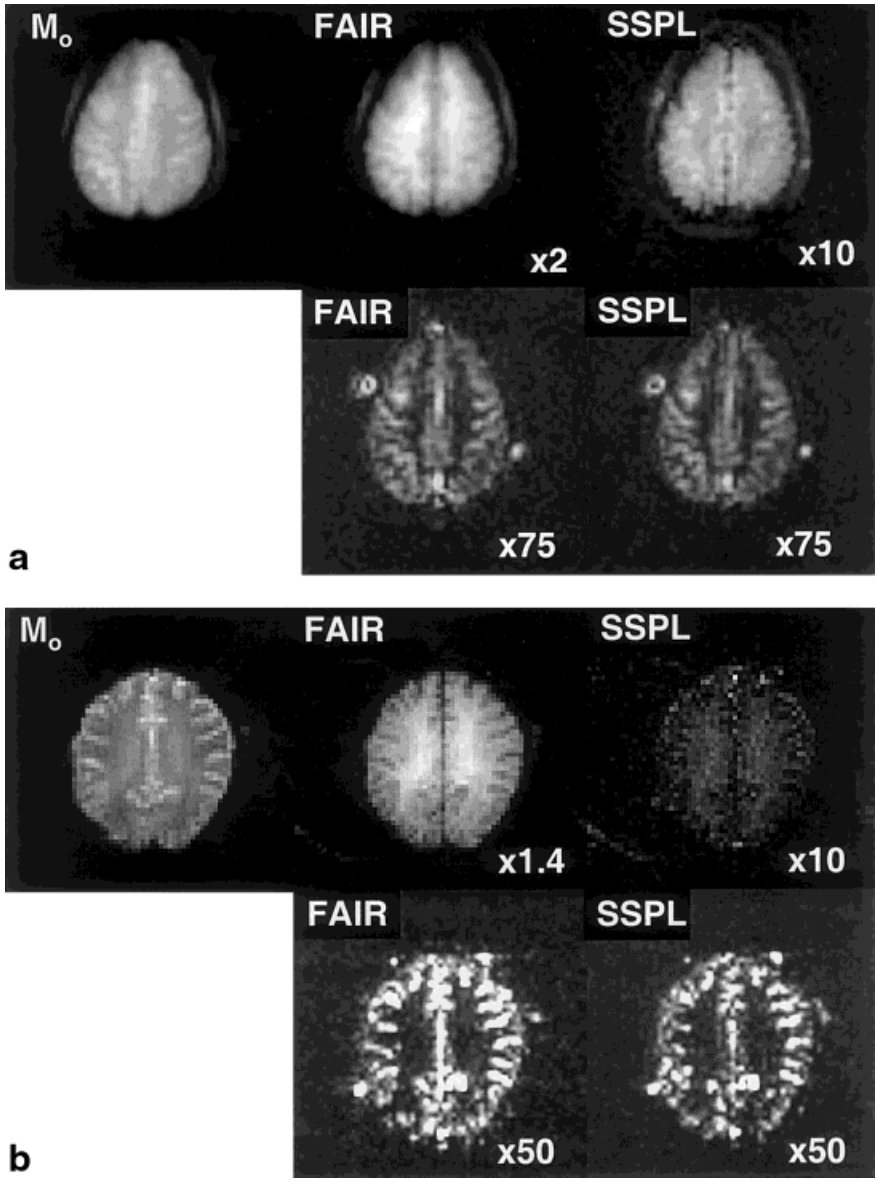

FIG. 5. Baseline perfusion measurement with FAIR and SSPL at (**a**) 1.5T and (**b**) 3.0T. Acquisition parameters were $TI_1/TI_2/TD$ = 1200/250/1500 ms, TE/TR = 11/50 ms, and 5-mm slice thickness. The SSPL perfusion images were generated subtracting a reference scan with nonselective inversion pulses from the selective scan. Perfusion images were qualitatively similar between FAIR and SSPL, although a small drop in perfusion signal was observed with SSPL (see text).

inversions of 30 and 35–1000 mm, respectively, were used. The selectivity of these two pulses was varied by adjusting the amplitude of the selection gradient. After spiral image acquisition, a slice-selective RF saturation was performed over the thickness of the second selective inversion. The purpose of this saturation was to accelerate the recovery of inverted blood spins in this region as preparation for the next repetition of the sequence. A potential additional advantage was the improved magnetization uniformity in the image region, which would reduce temporal image intensity fluctuations in the presence of out-of-slice motion. Baseline perfusion was estimated using a reference scan consisting of 10 averages during rest, with both inversions nonselective. A FAIR sequence was run under similar conditions for comparison. Motor cortex activation studies were performed using a finger-tapping paradigm involving the dominant hand, with eight alternating off-on stages of 30 s each (4-min scan time), at a pace of four taps/s. Visual activation studies were performed with identical timing using an alternating (6 Hz) checkerboard pattern presented using video goggles (Resonance Technologies, Van Nuys, CA). For detection of activation, *t*-test analysis was performed on a pixel-by-pixel basis by correlating with a boxcar-shaped reference. Activation levels were determined by averaging *t*-scores within anatomically chosen ROIs.

RESULTS AND DISCUSSION

Background Suppression

For each SSPL experiment, TI_1 and TI_2 values were fine-adjusted (at fixed TL) to achieve optimal background suppression. Figure 3 shows an example of the effect of this tuning for SSPL at 1.5T. For TL, TD = 1.5 s, the optimal TI_2 value was found in the range of 300–400 ms, and a background suppression of 85–95% of M_0 was achieved. At 3T, the optimal TI_2 value was the range of 250–300 ms, with

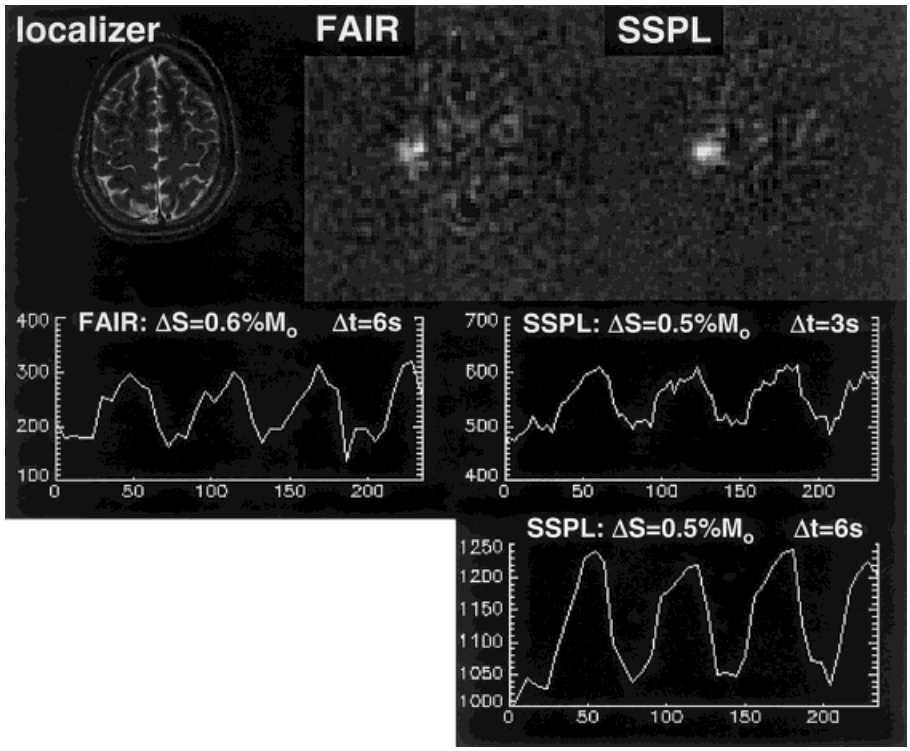

FIG. 6. SSPL and FAIR measurement of perfusion changes during motor cortex activation at 3.0T. Displayed are perfusion difference images (active–rest) and ROI-based time courses. The SSPL time-course data, acquired at a twofold faster rate, showed a small (~20%) reduction in perfusion difference. However, when reformatting the SSPL data to obtain a temporal resolution identical to the FAIR data (6 s), the sensitivity improvement with SSPL becomes apparent.

similar levels of background suppression. To assess the consistency of the background suppression in a repeated (time-series) experiment, the temporal standard deviation of the signal intensity was calculated on a pixel-by-pixel basis, and compared to the FAIR experiment. Figure 4 shows a typical histogram of these standard deviations, derived from a 4-min scan, indicating a 35–40% improved signal stability of SSPL over the subtraction images obtained with FAIR. This is close to the $\sqrt{2}$ improvement expected when assuming white noise as the dominant source of signal instabilities. Observation of the pixel intensity time course in a time-series experiment indicated that the background suppression in SSPL leads to much reduced signal fluctuation.

Perfusion Sensitivity

To compare the magnitude of the perfusion signals in SSPL and FAIR, a control scan was run for the SSPL experiment in which both inversion pulses were made nonselective. This allowed for the remaining background signal to be separated from the perfusion signal. Examples of these experiments, performed at 1.5T and 3.0T, are shown in Fig. 5a and b, respectively. The results indicate that at both field strengths qualitatively similar perfusion images can be obtained for SSPL and FAIR. However, on average, small reductions of 11 ± 10% (N = 5, 1.5T) and 9 ± 6% (N = 6, 3T) in perfusion signal were observed for the SSPL experiment compared to FAIR. A possible explanation is an imperfection in the operation of the additional inversion pulse in SSPL. Another possibility is that some sensitivity is lost because the additional inversion pulse and saturation pulse after image acquisition somewhat reduce the magnetization available in the inferior arteries for the succeeding repetition. This would restrict the use of TRs much shorter than the 3 s used in this study, which is a potential disadvantage of SSPL.

The sensitivity of SSPL was only minimally dependent on selectivity of the second inversion pulses in a limited range. Variation of the inversion width between 75 and 1000 mm showed less than 10% variation in sensitivity. Below 35 mm, more than 50% of the perfusion signal was lost. This is explained by signal cancellation due to mixing of spins with opposite polarities, caused by noninverted spins reaching the image slice. These measurements suggest that SSPL would allow perfusion fMRI without a large volume exciter, possibly with a transmit-receive surface coil.

The relative sensitivity of SSPL and FAIR to perfusion *changes* during neuronal activation was tested with both the visual (N = 2) and motor cortex (N = 5) activation studies. An example of a motor cortex activation study is shown in Fig. 6. As with the baseline perfusion signal in the previous experiment, the magnitude of the SSPL signal change with activation was smaller than that observed with FAIR. The average reduction in activation signal was 17 ± 9% and 10 ± 7% for the 1.5T (N = 3) and 3T (N = 4) data, respectively. However, because of the twofold increased averaging (more repetitions in same scan time), and the reduced temporal fluctuations (Fig. 4), the SSPL activation images (Fig. 6) were markedly improved over the FAIR data. The average gain in t-scores was 64 ± 33% for the 1.5T (N = 3) and 128 ± 29% for the 3T (N = 4) data.

Multislice Acquisition

As with FAIR, multislice acquisition in SSPL leads to varying labeling times over the slices, resulting in varying

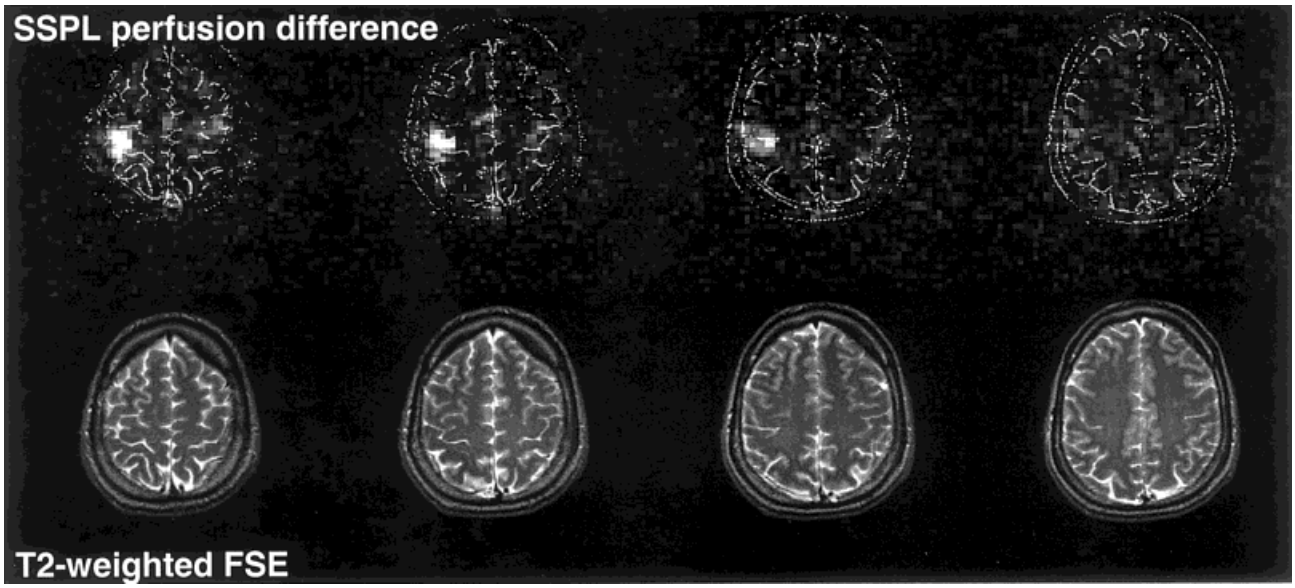

FIG. 7. Example of a four-slice SSPL motor cortex activation experiment. Complex subtraction of activation and rest stages was performed to avoid inadvertent cancellation of perfusion signal due to polarity variations across tissue types.

perfusion sensitivity. In addition, with SSPL, multislice acquisition results in a varying background suppression, because TI_2 varies across slices. An example of a multislice finger-tapping fMRI experiment with M_z polarity correction is given in Fig. 7. This experiment was performed at 3.0T using single-echo acquisition with TI_1 = 1.25 s, TI_2 = 0.2 s, TE = 11 ms, and measurement time = 144 ms for four slices. Background suppression averaged 23%, 13%, 16%, and 25% for slices 1–4, respectively. In this measurement, performed on an experienced volunteer, motion was not an apparent problem, as judged from the excellent subtraction of background signal in the activation (difference) images.

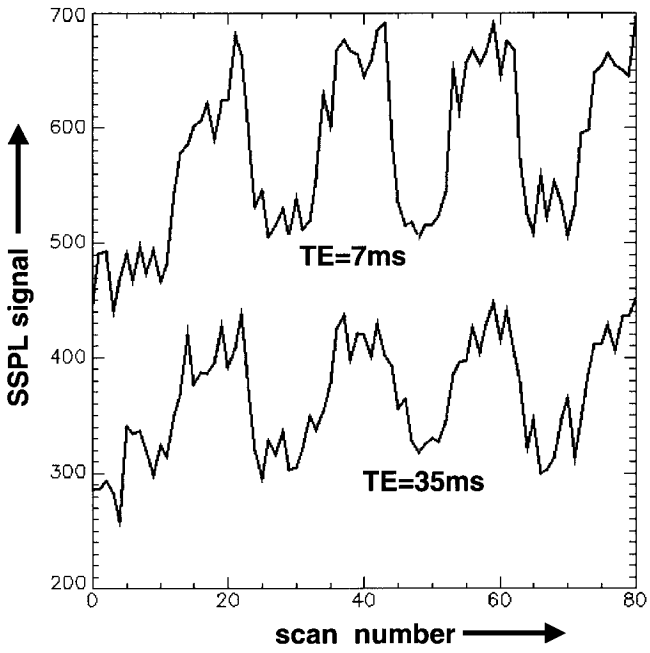

FIG. 8. SSPL time course during motor cortex activation as a function of TE. Dual-echo data, obtained from an ROI in the motor cortex, shows a reduction in activation signal with an increase in TE from 7–35 ms, consistent with a perfusion-dominated contrast mechanism.

Some interesting artifacts were observed in SSPL perfusion images and perfusion activation images obtained with TI_2 values at or larger than the setting for optimum background suppression, a situation easily encountered in multislice protocols. The artifact is related to the M_z polarity of the background signal, which under this circumstance can alternate between being identical or opposite to the perfusion signal. This occurs because the various tissue components do not cross $M_z = 0$ at identical TI_2 values. With magnitude reconstruction of the MR images, this can lead to uncertainty in the sign of the perfusion signal, and sometimes loss of the perfusion signal. In the data presented in Fig. 7, this artifact was resolved by phase correction of the complex data (e.g., in *k*-space) using a reference scan. Alternatively, one could avoid varying polarity of the background M_z by choosing TI_2 slightly shorter than the value for optimal background suppression.

Contribution of BOLD Contrast in Perfusion Data

Despite the significant background suppression in SSPL, as well as in FAIR after subtraction of reference scan, a remaining concern with perfusion fMRI is the potential contamination of the activation signal with effects related to BOLD contrast. Areas prone to contamination by BOLD contrast are the tissue surrounding the capillaries, and the area within and around the large veins. To some extent, these effects can be suppressed by the specific choice of the acquisition parameters. A sufficiently wide selective inversion reduces the venous blood signal, a bipolar crusher reduces large vessel signals, and the short TE

obtained with spiral acquisition leads to an overall reduction of the BOLD effect.

Evaluation of the dual-echo SSPL activation data (Fig. 8) indicates that perfusion is indeed the major contributor to the observed functional signal: the fractional changes are virtually equal at both TEs, indicating a perfusion-dominated contrast. Comparison with a reference SSPL scan with nonselective inversion pulses showed that the BOLD contribution to the perfusion signal was, averaged over a small ROI covering the primary motor cortex, less than 7% for the shortest TE (7 ms) data.

CONCLUSIONS

Using a double-inversion pulsed labeling strategy, single-shot perfusion-weighted fMRI can be performed with a twofold-improved temporal or a close-to-twofold increase in sensitivity as compared to FAIR. In addition, the background suppression in SSPL allows for reduced motion sensitivity. These characteristics make SSPL a promising alternative for BOLD in fMRI, particularly in areas with high susceptibility gradients, where short TE acquisition becomes mandatory. Current work focuses on multislab acquisition protocols to improve volume coverage of SSPL.

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