Functional Brain Imaging Using a Blood Oxygenation Sensitive Steady State

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Blood oxygenation level dependent (BOLD) functional MRI (fMRI) is an important method for functional neuroimaging that is sensitive to changes in blood oxygenation related to brain activation. While BOLD imaging has good spatial coverage and resolution relative to other neuroimaging methods (such as positron emission tomography (PET)), it has significant limitations relative to other MRI techniques, including poor spatial resolution, low signal levels, limited contrast, and image artifacts. These limitations derive from the coupling of BOLD functional contrast to sources of image degradation. This work presents an alternative method for fMRI that may overcome these limitations by establishing a blood oxygenation sensitive steady-state (BOSS) that inverts the signal from deoxygenated blood relative to the water signal. BOSS fMRI allows the imaging parameters to be optimized independently of the functional contrast, resulting in fewer image artifacts and higher signal-to-noise ratio (SNR). In addition, BOSS fMRI has greater functional contrast than BOLD. BOSS fMRI requires careful shimming and multiple acquisitions to obtain a precise alignment of the magnetization to the SSFP frequency response. Magn Reson Med 50:675–683, 2003. © 2003 Wiley-Liss, Inc.

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In the 10 years since its inception, blood oxygenation level dependent (BOLD) functional MRI (fMRI) (1–3) has become a dominant tool for functional neuroimaging. BOLD fMRI has the unique ability to map activity at its source without the use of invasive procedures or tracers. BOLD fMRI also achieves higher resolution than other methods for global mapping.

A number of localized physiological changes accompany neural activity, including increases in blood flow, blood volume, and oxygen metabolism. BOLD imaging senses changes in blood oxygenation by exploiting the paramagnetism of deoxyhemoglobin. During activation the cerebral blood flow increases more than oxygen consumption (4), resulting in a dilution of the deoxyhemoglobin concentration. Because deoxyhemoglobin experiences a resonance frequency shift relative to water (5), the presence of deoxyhemoglobin introduces a spread in resonance frequency that causes the signal to dephase more quickly (6). In BOLD fMRI, data acquisition is delayed following RF excitation (typically by 30–60 ms) to allow signal dephasing to occur, resulting in signal levels that depend on the local concentration of deoxyhemoglobin (1). Since blood has a lower concentration of deoxyhemoglobin during activation, the signal during activation is larger than the signal at rest (7). This signal change is the source of the BOLD contrast.

BOLD fMRI has a number of important limitations that result from the coupling of the BOLD contrast mechanism to image artifacts and signal loss. First, significant signal is lost due to transverse relaxation during the long echo time (TE), resulting in a low signal-to-noise ratio (SNR) (8). Second, sources of off-resonance in the image other than deoxyhemoglobin also cause significant dephasing, resulting in image distortion (9,10) and signal dropout (11). Third, the long delay between excitation and acquisition necessitates the use of long readouts to maintain temporal resolution. Off-resonance and $T_2^*$ decay over the course of these long readouts cause warping and loss of resolution (12). While these artifacts are always present in BOLD imaging, they are particularly pronounced near susceptibility boundaries, such as the sinus cavities in the head. The severity of artifacts in these regions effectively precludes the use of BOLD fMRI in areas adjacent to the sinuses.

This work introduces a new method for fMRI using balanced steady-state free precession (SSFP) imaging (13,14) that may overcome these issues. The balanced-SSFP signal is highly sensitive to resonance frequency (13,15) and can be used to directly detect the deoxyhemoglobin frequency shift associated with brain activity (16). The sequence presented here uses the phase profile of SSFP (17) to invert signal from the deoxyhemoglobin frequency shift relative to water, establishing a blood oxygenation sensitive steady-state (BOSS) signal. This method is intrinsically sensitive to the deoxyhemoglobin frequency shift, and decouples the functional contrast mechanism from sources of artifact. The major difficulty with the BOSS approach is that the resonance frequency of oxygenated blood must be accurately aligned with the balanced-SSFP frequency response. In practice, the accuracy required to cover important regions of interest (ROIs), such as the visual cortex, can be obtained by combining careful linear shimming with acquisition at a small number of frequencies. In addition to a reduction of image artifacts and signal dropout, this method offers higher SNR and greater functional contrast than traditional BOLD fMRI.

THEORY

Balanced SSFP consists of a rapidly repeating series of RF pulses and fully refocused imaging gradients, as shown in Fig. 1. For short repetition times, (TRs), the magnetization
persists from one RF pulse to the next, creating a steady state that is strongly dependent on the amount of phase the magnetization accrues during the TR (13,17). Since all gradients axes have zero total area, the only source of phase accrual between RF pulses is off-resonance precession (i.e., apparent precession due to any difference between the resonance frequency of the magnetization and the transmit frequency of the RF pulse). The balanced SSFP signal is therefore strongly dependent on resonance frequency (18–21).

The frequency response of the balanced-SSFP signal has a unique and fairly complicated dependence on tissue and sequence parameters. One key characteristic of this signal is that certain frequencies experience drastically reduced signal, creating frequency bands of signal attenuation commonly referred to as “nulls.” For example, balanced-SSFP imaging usually uses a large flip angle ($\alpha \approx 30^\circ$) with alternating sign ($\pm \alpha$), resulting in a sharp null for species that precess $180^\circ$ over each TR. If the sign of the RF pulse does not alternate, this null occurs on-resonance (solid line in Fig. 2a).

fMRI With Frequency Nulling

Scheffler et al. (16) previously proposed using the magnitude null at large flip angles to detect the dynamic frequency shifts associated with brain activation. This method carefully places the transmit frequency relative to the unshifted oxyhemoglobin frequency and the shifted deoxyhemoglobin frequency. For example, the signal at the deoxyhemoglobin frequency (which we will refer to as the “deoxygenated” signal) is placed in or near the null, while the signal at the oxyhemoglobin frequency (or “oxygenated” signal) is shifted slightly out of the null, as shown in Fig. 2a. As blood oxygenation levels rise during activation, the fraction of spins dwelling in the null decreases and the signal increases. Alternatively, the oxygenated signal could be placed in or near the null, causing a signal decrease during activation. This contrast mechanism has the advantage of directly detecting the activation-induced frequency shift, whereas BOLD detects the shift indirectly as signal dephasing.

The functional contrast of this sequence can be thought of as the vector difference between the oxygenated and deoxygenated signals, which gives the signal change $\Delta M$ shown in Fig. 2c. This technique favors short, multishot readouts to maintain the steady state, which results in improved image quality over BOLD imaging. This contrast mechanism has three main drawbacks. First, signals are deliberately acquired in the low-signal part of the SSFP signal profile. Second, it requires a very homogeneous magnetic field. Third, because the slope of the null is inversely proportional to the TR, functional contrast is coupled to the TR such that fairly long TRs (20–40 ms) are favored (16).

fMRI With Frequency Inversion

We propose a different but related approach that creates functional contrast based on the phase of the balanced-SSFP magnetization profile. In addition to the magnitude effects described above, the magnetization phase undergoes an abrupt change of $180^\circ$ over a narrow band of frequencies near resonance. At $TE = TR/2$, the phase profile outside this transition band is flat, with positive and negative frequency offsets separated by $180^\circ$ (dashed lines in Fig. 2). These flat regions of the phase profile reflect spin...
echoes on the positive and negative real axes (22). Consequently, the signals for positive and negative frequency offsets have opposing signs. In the region of the transition, the signal phase is extremely sensitive to resonance frequency, while outside the transition the phase is largely independent of off-resonance. At small flip angles, the signal magnitude peaks in the phase transition (15) (solid line in Fig. 2b).

We can use the signal profile in Fig. 2b for functional contrast by placing the oxygenated and deoxygenated signals on opposite sides of the phase change [see Fig. 2b]. In this arrangement, the oxygenated signal has the opposite sign of the deoxygenated signal (see Fig. 2d). Within a voxel, the deoxygenated signal will subtract from the larger oxygenated signal. Activation causes a drop in the fraction of the signal that is deoxygenated (negative) and a rise in the fraction that is oxygenated (positive). Assuming that the majority of the magnetization is oxygenated, the signal increases during activation. If the majority of spins were frequency-shifted to the deoxyhemoglobin frequency, reducing the concentration of deoxyhemoglobin would cause signal loss. We refer to this functional contrast mechanism as BOSS fMRI.

Inversion vs. Nulling

Like the nulling method, BOSS fMRI is intrinsically a multishot acquisition with short readouts. The use of multishot readouts drastically reduces the image artifacts and signal dropout compared to BOLD fMRI. In addition, both methods also require careful shimming and placement of the transmit frequency.

There are two key differences between these methods. First, the BOSS inversion exhibits a larger signal change than the nulling technique. This can be seen by comparing the vector diagrams in Fig. 2c and d, which show deoxygenated signal ($M_{\text{deoxygenated}}$), the oxygenated signal ($M_{\text{oxygenated}}$), and the resulting difference ($\Delta M$) for the two methods. Second, whereas the nulling method couples functional contrast to lower signal levels, the BOSS method allows functional signal to be acquired in the highest-signal portion of the off-resonance profile, resulting in higher SNR.

METHODS

We tested the BOSS fMRI method on a 1.5 T GE Signa scanner with gradients capable of 40 mT/m and 150 mT/m/ms maximum slew rate. The subject was presented with a visual stimulus consisting of a 10-Hz contrast-reversing annulus grating. The stimulation was presented in four 30-s blocks consisting of 15 s of stimulus followed by 15 s of rest. The subject was instructed to fixate at all times on cross-hairs located in the center of the visual FOV. A sagittal slice through the occipital pole (24-cm FOV, 128 × 64, α = 5°) was gathered every 0.5 s during stimulation. A 2DFT trajectory was used with the center of k-space acquired halfway through the TR (TR/TE = 7.8/3.9 ms, chosen to yield an image every 0.5 s). Linear shimming was targeted to the caudal occipital pole. The experiment was repeated three times at each of four frequency offsets spaced 4 Hz apart (where 4 Hz roughly corresponds to the width of the phase transition band for gray matter, as shown in Fig. 2).

Analysis began with motion correction, removal of a fourth-order temporal polynomial, and averaging of the three repetitions of each frequency. The resultant data sets from the four frequency measurements were processed both individually and as a group. The individual frequency measurements were separately processed using standard fMRI analysis methods. Each data set was temporally and spatially filtered (temporal and spatial Gaussian filters with full-width at half-maximum (FWHM) = 1.5 s, and 1.8 × 3.75 mm²). The timecourse for each voxel was then correlated with a simple model for the hemodynamic response to the block stimulus. Activated pixels were identified by thresholding this correlation map and the average timecourse for this ROI was calculated, resulting in four activation masks and timecourses (one for each frequency).

The data at multiple frequencies were also processed as a group, using a custom analysis. Each unfiltered data set was separately correlated as above. For each voxel, the timecourse from the frequency with maximum stimulus correlation was retained (i.e., a maximum intensity projection (MIP) of the multifrequency measurements), resulting in a single data set that was pieced together from the four frequency data sets. This data set was thresholded as above to create an ROI and average timecourse. Because this analysis is unconventional, we minimized the amount of data manipulation by not performing any spatial or temporal filtering.

RESULTS

The results for the single-frequency experiment exhibiting the greatest area of activation are shown in Fig. 3a and c. Stimulus-correlated signal changes of 4–5% were found exclusively in the occipital lobe. These changes are 2–3 times larger than typical BOLD signals (1–2% at 1.5 T) for similar full-contrast visual stimuli (8). The multifrequency analysis identified a similar ROI (Fig. 3b) with even larger signal changes of 7–8% (Fig. 3d). Given that the activation ROIs are largely overlapping, the larger signal changes found by the multifrequency analysis indicate that some voxels activated more strongly at a frequency other than that shown in Fig. 3a and c. Because no temporal or spatial filtering was performed on the data, physiological fluctuations were more prevalent in the multifrequency timecourse. The mean contrast-to-noise ratio (CNR) for individual unaveraged, unfiltered voxels was measured at 1.34, which may reflect stronger sensitivity to physiological fluctuations than BOLD.

The activation masks in Fig. 3 are overlaid on the balanced-SSFP images gathered during the experiment. These images contain no warping or blurring. The signal variation across these images is due to drift of the resonance frequency across the brain. The transmit frequency was set to the resonance frequency of the occipital pole so that the visual cortex was near the phase transition. Consequently, anterior regions of the brain lay in the low-signal portion of the off-resonance profile (see Fig. 2b). This signal variation is not the same type of signal dropout found in BOLD
images. In BOSS, the transmit frequency can be set to give high signal in any desired region of the brain, whereas signal dropout in BOLD is unrecoverable.

In addition to the positively-correlated voxels discussed above, we also observed negatively-correlated voxels, i.e., voxels that lost signal during stimulus periods. Like the positively correlated activations, these voxels had a strong, stimulus-correlated signal change of 6–7% in the multifrequency MIP analysis. These changes were significantly larger than the 1–2% BOLD signal changes at 1.5 T. Temporal filtering was performed in c but not in d, which exhibits larger physiological noise fluctuations. Masks are shown on the balanced-SSFP images from the experiment (the signal variation is due to the magnitude profile in Fig. 2).

BOSS is a new fMRI method that directly senses changes in blood oxygenation by inverting the frequency-shifted deoxyhemoglobin signal relative to the unshifted water signal. Although BOLD and BOSS fMRI both measure signal changes related to the deoxyhemoglobin frequency shift, BOSS fMRI measures this shift directly, whereas BOLD detects the shift indirectly as signal dephasing. This gives BOSS several advantages over BOLD, including improved image quality and higher SNR. In addition, BOSS detects activations in the visual cortex with higher functional contrast than is typically found in BOLD because the BOSS signal change is based on signal inversion rather than attenuation. In the following sections we analyze various aspects of the BOSS signal, and further compare BOSS with BOLD fMRI.

**DISCUSSION**

**Functional Contrast**

BOSS fMRI is expected to have improved functional contrast over BOLD imaging. Since the BOSS signal change is due to a pool of spins that switch from deoxygenated (negative signal) to oxygenated (positive signal), the signal change is roughly twice the size of the exchanging pool (see the vector diagram in Fig. 2d). In comparison, the signal change in BOLD imaging is an attenuation of the exchanging pool, resulting in a smaller percentage signal change. We therefore expect improved functional contrast

**FIG. 3.** Results from the single- and multifrequency analyses of the BOSS activation experiments. The activation masks for the a single- and b multifrequency analyses are strikingly similar. These ROIs have stimulus-correlated signal changes of c 4–5% at a single frequency and d 7–8% for the multifrequency experiment. These changes are significantly larger than the 1–2% BOLD signal changes at 1.5 T. Temporal filtering was performed in c but not in d, which exhibits larger physiological noise fluctuations. Masks are shown on the balanced-SSFP images from the experiment (the signal variation is due to the magnitude profile in Fig. 2).

**FIG. 4.** Positive and negative correlations in BOSS fMRI of visual cortex (zoomed). Comparing voxel correlations at different transmit frequencies, 33 voxels were strictly positively correlated (red), 13 voxels were strictly negatively correlated (blue), and two were positively correlated at one frequency and negatively correlated at a different frequency (green). Positive and negative correlations also tended to occur in distinct locations. Further experimentation will be required to determine the source of the negative correlations.
in BOSS fMRI over BOLD imaging. This prediction was supported by our initial results, which revealed 2–3 times the functional contrast of BOLD fMRI in a single frequency measurement, and more than 4 times the functional contrast when multiple measurements are combined.

Thus far we have considered the magnetization to consist of two discrete pools of spins with shifted resonance frequencies. A more realistic model of BOSS contrast would consider a spectrum of resonance frequencies as described by Schefler et al. (16). This spectrum is usually modeled as a summation of Lorentzian distributions centered at the deoxyhemoglobin and water frequencies (23). Increasing the concentration of deoxyhemoglobin within a voxel causes this spectrum to broaden (24, 25). The signal measured in SSFP imaging is the integral of the spectrum multiplied by the SSFP off-resonance profile (16). Since BOSS fMRI inverts a fraction of the spectrum, small changes in the size of this fraction can be detected as a change in the signal magnitude. While such a model of BOSS signal dynamics is more complete, the simpler description above is generally sufficient.

**Image Quality**

BOSS and BOLD imaging differ significantly in terms of image quality. With conventional BOLD imaging, a long TE is required for the $T_2^*$ contrast to evolve, resulting in lost signal due to dephasing and relaxation (12, 26). In addition, the long readouts used in BOLD produce image distortion (in EPI) or blurring (in spiral imaging) due to off-resonance and susceptibility boundaries (9–11, 26, 27). These effects couple BOLD contrast to image degradation. In comparison, BOSS functional contrast is inherent to the steady-state signal, allowing independent optimization of the image acquisition to achieve high SNR and minimize image artifacts. At TE = TR/2, the BOSS signal is similar to a spin echo in that it has no $T_2^*$ effects, and therefore has no signal dropout (22, 28). In addition, because SSFP is a fast imaging technique, shorter multishot readouts are used. These readouts essentially eliminate image distortion. Overall, BOSS fMRI is expected to exhibit significantly improved image quality over BOLD imaging.

Figure 5 compares BOLD and BOSS image quality for the same coverage (16-cm FOV, $128 \times 128$) and frame rate (1 s). These phantom images were acquired at 1.5 T with typical fMRI protocols for EPI-BOLD ($\alpha = 70^\circ$, TR = 1000 ms, TE = 50 ms) and 2DFT-BOSS ($\alpha = 5^\circ$, TR = 7.8 ms). The EPI-BOLD images exhibit significant warping and ghosting, while the BOSS images have no such artifacts. In addition, the EPI-BOLD images appear to have lower resolution than the BOSS images (insets of Fig. 5) even though the k-space coverage is the same. The blurring of the EPI image is due to $T_2^*$ decay over the single-shot readout (12).

The balanced-SSFP images shown in Fig. 3 exhibit signal intensity variations due to spatial drift in the magnetic field (this effect can also be seen at the bottom of the SSFP phantom image in Fig. 5). This signal attenuation is quite different from BOLD signal dropout near regions of susceptibility changes (such as the sinus cavities). While BOLD signal dropouts are unrecoverable, the specific spatial pattern of BOSS magnitude variations is dictated by the choice of transmit frequency. In the BOSS fMRI experiments presented above, the center frequency was chosen to achieve high signal (and therefore functional contrast) in the occipital lobe. High signal can easily be achieved in other brain areas by shifting the transmit frequency.

It should be possible to achieve complete coverage in BOSS imaging by combining careful shimming with acquisition at multiple transmit frequencies. Linear combination of multifrequency acquisitions has been used previously to achieve high-quality anatomical images with balanced SSFP (29). Whereas susceptibility boundaries introduce unrecoverable signal loss in BOLD imaging, they simply represent steep off-resonance gradients for BOSS imaging. As with other sources of off-resonance, regions of high susceptibility can be addressed in BOSS using multifrequency measurements.

**SNR**

Another advantage of BOSS fMRI is the high SNR of balanced SSFP. The SNR efficiency ($\eta$) of a pulse sequence depends on the (normalized) signal magnitude $|M_{eq}|/M_0$ and the duty cycle (the readout time $T_{read}$ divided by the imaging time $T_{im}$) (30):

$$\eta \propto \frac{T_{read}}{T_{im}} \frac{|M_{eq}|}{M_0}.$$  \[1\]

Balanced-SSFP imaging generally has high SNR efficiency because a large fraction of the total imaging time can be spent collecting data. The duty cycle in anatomical SSFP imaging tends to be limited by the need for a short TR, which dictates short readouts. BOSS fMRI can obtain a particularly high readout duty cycle because the TR can be longer than it is in most balanced-SSFP sequences (10–20 ms, as discussed below), which allows the majority of each TR to be dedicated to acquisition. In contrast, the long-TE GRE sequences used in BOLD fMRI have fairly low SNR.
The signal $M_{xy}$ is expressed as a fraction of $M_0$ ($T_1 = 880$ ms, $T_2 = 80$ ms, $T_2' = 60$ ms). The BOLD magnetization is calculated at the Ernst angle, and the BOSS magnetization is taken as the peak magnitude in Fig. 2. In 1 s, each method could acquire 12 slices with a 64 x 64 matrix. In BOSS: 3D interleaved EPI, ETL = 8, $\alpha = 5^\circ$, TR/TE = 10 ms/5 ms, 16 ms samples, $T_{\text{read}} = 12 \times 64^2 \times 16$ $\mu$s = 820 ms. In BOLD: multi-slice, single-shot EPI, $T_{\text{read}} = 32$ ms, $\alpha = 65^\circ$, TR/TE = 1000 ms/60 ms. BOSS is 3 times more SNR efficient than BOLD.

There are two reasons for this. First, a significant portion of the signal must decay in order for BOLD contrast to develop. Second, BOLD IMRI requires long TRs (0.5–2 s) to allow $T_1$ recovery, and only a small fraction of this time can be dedicated to data acquisition. These factors lead to higher SNR efficiency $\eta$ for BOSS IMRI.

Table 1 compares the SNRs of BOSS and BOLD for a standard IMRI experiment at 1.5 T with the same volume coverage (12 slices with a 64 x 64 matrix) and frame rate (1 s). In BOSS, multiple slices would be acquired using a 3D acquisition (which does not disrupt the steady state, unlike 2D multislice), allowing a high duty cycle in which the entire magnetization contributes signal every TR. GRE-BOLD sequences do not gain much from 3D acquisitions, due to incomplete $T_1$ recovery between RF pulses (31,32), so BOLD data are usually collected using multislice acquisitions. Since each slice is excited and read out separately in GRE-BOLD, the readout time used in the SNR analysis is the time required to read out a single slice. In the comparison in Table 1, BOSS IMRI has roughly three times the SNR efficiency of BOLD IMRI. This gain depends on the duty cycle of the BOSS readout, and ranges from a factor of 2 for a 40% duty cycle to a factor of 3 for a 90% duty cycle.

CNR

In this section we consider the functional CNR of BOSS and possible optimizations of sequence parameters based on CNR. The CNR of BOSS has a strong dependence on resonance frequency that is not found in most sequences. Assuming an activation-induced frequency shift $\Delta f$, the functional contrast at a given off-resonance frequency $f$ is:

$$\text{Contrast}(f) = \frac{|M_{xy}(f - \frac{\Delta f}{2}) - M_{xy}(f + \frac{\Delta f}{2})|}{M_0}$$ \[2\]

where normalization by $M_0$ expresses the contrast as a fraction of the total possible signal. For a given imaging setup, the thermal noise ($\sigma$) is independent of resonance frequency, allowing direct comparison of the CNR at different frequencies based on Eq. [2]:

$$\text{CNR}(f) = \frac{\text{Contrast}(f)}{\sigma} \times \text{Contrast}(f).$$ \[3\]

In other words, the proportionality in Eq. [3] results from the fact that $\sigma$ is a constant for a given experimental setup. The calculations presented here express CNR as a fraction of the total signal, as suggested by Eq. [2].

Figure 6 plots BOSS CNR over a band of off-resonance frequencies for several choices of TR and flip angle, assuming an activation-induced frequency shift of 5 Hz (8,16). For most choices of flip angle and TR, functional contrast peaks on-resonance where the phase transition has the greatest slope. For the approximate parameters used in this study (upper left-hand panel in Fig. 6), BOSS exhibits a strong functional CNR over a band of frequencies near-resonance, outside of which the functional CNR is considerably reduced and largely independent of resonance frequency.

The plots in Fig. 6 suggest that the flip angle can be optimized for a given TR based on CNR. One obvious criterion for optimization would be peak CNR. The profiles depicted along the diagonal of Fig. 6 represent the flip angle with the greatest peak CNR for the given TR. As the TR is lengthened, the flip angle with the greatest peak CNR increases. As indicated by the solid gray lines, this increase essentially maintains the magnitude profile from Fig. 2b.

This type of optimization can provide significant gains in peak CNR. For example, Fig. 7 demonstrates the potential gain in peak CNR that can be obtained for the TR used by Scheffler et al. (16). Figure 7b represents the functional CNR used in their study, and the dashed line indicates their placement of the transmit frequency (chosen as a region of high slope in the balanced-SSFP magnitude profile). The functional CNR of this imaging setup can be increased in two ways. First, the functional CNR for the same flip angle ($\alpha = 50^\circ$) can be increased by setting the transmit frequency to gather data at the CNR peak (i.e., by

FIG. 6. BOSS functional CNR for several flip angles ($\alpha = 4^\circ$, $10^\circ$, or $15^\circ$) and TRs (TR = 10, 20, or 40 ms). The gray lines show the balanced-SSFP signal profile (solid = magnitude, dashed = phase) and the black lines represent BOSS functional CNR (Eq. [3]). CNR calculations assume an activation-induced frequency shift of 5 Hz. The plots along the diagonal have the highest peak CNR for the given TR. As the TR increases, the flip angle with highest peak CNR also increases.
sliding the dashed line in Fig. 7b to 6 Hz off-resonance. Second, decreasing the flip angle to $\alpha = 15^\circ$ increases the signal magnitude near-resonance, further increasing the peak functional CNR (as shown by the dashed line in Fig. 7a). As can be seen by comparing the dashed lines in Fig. 7a and b, the proper choice of flip angle and transmit frequency could roughly triple the functional CNR.

A second possible criterion for optimizing the flip angle is signal stability. Most of the profiles in Fig. 6 have a fairly sharp peak in CNR, which could be problematic in the presence of fluctuations in voxel resonance frequency. A flatter CNR profile (at the expense of peak CNR) may be preferable to maintain signal stability. For example, the profile obtained with $TR = 40$ ms and $\alpha = 4^\circ$ (lower left-hand panel in Fig. 6) would be more immune to small drifts in the resonance frequency, since the CNR plateaus near resonance. This trade-off of peak CNR for signal stability offers an additional design parameter in BOSS experiments that is not present in BOLD fMRI.

In general, the ability to optimize BOSS parameters based on CNR increases flexibility in the design of fMRI experiments. For example, measurements of physiological fluctuations may favor a more peaked CNR, whereas activation experiments would benefit from a more stable signal to reduce sensitivity to physiological noise. The latter optimization may improve the functional CNR over that found in our data.

Balanced-SSFP Phase Transition

BOSS functional contrast is based on the abrupt phase transition that balanced-SSFP sequences exhibit near-resonance. This phase change is an unusual effect that warrants discussion.

First, we consider the source of the SSFP phase profile. Species in the flat portions of the phase profile at $TE = TR/2$ form a steady state in which off-resonance precession during the TR is canceled by the RF tip between TRs. Assuming the RF tip is about the imaginary axis (as is used in our simulations), spins that precess clockwise form a spin echo on the positive imaginary axis halfway through the TR (Fig. 8a) (22). Similarly, spins that precess counterclockwise form a similar echo on the negative imaginary axis (Fig. 8c). However, spins in the phase transition form a very different steady state. These spins are near-resonance, and therefore precess very little over a TR. For these species, relaxation is the dominant effect during the TR, so the RF tip primarily serves to cancel relaxation (Fig. 8b). Because the RF pulse tips along the imaginary axis, this steady state is formed along the real axis. A given off-resonance frequency forms a steady state that reflects the relative magnitude of relaxation and precession effects during a TR. These steady states lead to the phase profile shown in Fig. 2.

In order for BOSS fMRI to be a reliable method for detecting activation, it is critical that the SSFP phase profile be robust across a range of likely imaging conditions. In particular, we desire a stable transition region, since the transition is the source of functional contrast. The effects of various acquisition and physiological parameters on the phase profile are shown in Fig. 9. The most important characteristic of the phase profile is that the transition region depends only on $T_2$, and is unaffected by flip angle, TR, $TE$, or $T_1$. The width of the phase transition increases for decreasing $T_2$. However, this effect is minor for the relaxation times likely to be encountered in brain imaging. Lengthening the TR pushes the phase transitions closer together while preserving the absolute bandwidth over which the transition occurs. Use of $TE = TR/2$ changes the
The phase profile outside of the transition region (reflecting the formation of spin echoes halfway through the TR (22)). Spins in the phase transition, which are near-resonance, precess very little during each TR and their phase is essentially unaffected by the choice of TE. The phase profile is completely independent of flip angle and T₁. The fairly simple dependence of the phase profile on tissue and pulse sequence parameters indicates that BOSS contrast should be robust under a wide range of imaging conditions.

BOSS Imaging Parameters

BOSS imaging diverges from both BOLD fMRI and balanced SSFP in the choice of optimal imaging parameters. Unlike BOLD fMRI, the functional contrast is independent of TE because the phase transition is preserved throughout the TR. The formation of spin echoes at TR/2 makes this a good choice of TE since image artifacts will be minimal. However, shifted TEs simply introduce a slight gradient in the off-resonance signal phase, as shown in Fig. 9c. This lack of dependence on TE is different from BOLD fMRI, where the TE must be long to allow functional contrast to evolve. BOSS contrast allows flexibility in the choice of TE, and therefore in the readout trajectory.

BOSS fMRI also has several important differences from traditional SSFP imaging. As discussed above, the functional CNR of BOSS can be used to optimize the flip angle for a given TR. Additionally, the TR has a very different impact in BOSS imaging as compared to standard SSFP imaging. In balanced-SSFP imaging (using high flip angles), the TR is usually minimized to increase the distance between the signal magnitude nulls (shown in Fig. 2a). With sufficient shimming, this allows the object to be placed within the high-signal portion of the off-resonance profile, avoiding the characteristic “banding artifacts” caused by the magnitude nulls. In BOSS fMRI, activation can only be detected near the phase transition, meaning that only this portion of the off-resonance profile is useful. Increasing the TR pushes the phase transitions closer without affecting the transition width (see Fig. 9b), making BOSS contrast compatible (and perhaps superior with) long TRs. The ability to image with long TRs and small flip angles should be advantageous in high-field scanners where conventional balanced-SSFP methods are limited.

CONCLUSIONS

We have presented a new method for fMRI that directly detects dynamic changes in the deoxyhemoglobin concentration using a BOSS signal. This steady state inverts the frequency-shifted deoxyhemoglobin signal relative to the water signal, so that changes in the deoxyhemoglobin concentration during activation cause a signal modulation. BOSS imaging requires careful placement of the center frequency relative to the water and deoxyhemoglobin resonance frequencies, which can be achieved with careful shimming and acquisition at a small number of transmit frequencies. Additionally, BOSS may be more sensitive to physiological fluctuations than BOLD imaging. The BOSS fMRI method has several advantages over traditional BOLD fMRI. First, BOSS has fewer image artifacts because signal is acquired at a spin echo with short, multishot readouts. Second, BOSS data has higher SNR than BOLD due to the large fraction of imaging time that is dedicated to data acquisition. Third, BOSS functional contrast is greater than is usually seen in BOLD imaging because the BOSS signal change is produced by a signal inversion rather than an attenuation. These advantages make BOSS fMRI a powerful alternative for functional neuroimaging.

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