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Simultaneous Multi-Slice Spectral-Spatial Excitations for Reduced Signal Loss Susceptibility Artifact in BOLD fMRI

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Abstract

Purpose—Simultaneous Multi-Slice (SMS) imaging can significantly increase image acquisition rates and improve temporal resolution and contrast in gradient-echo BOLD fMRI experiments. Through-plane signal loss due to B_0 inhomogeneities at air-tissue interfaces limit fMRI of structures near the nasal cavity and ear canals. This work implements spectral-spatial (SPSP) RF pulses for reduced through-plane signal loss across multiple simultaneously excited slices.

Theory and Methods—Multi-Band (MB) and Power Independent of Number of Slices (PINS) methods are combined with SPSP excitation for signal loss compensation in slice-accelerated human brain imaging. Nine simultaneous slices of 5 mm thickness and 20 mm apart were excited using standard MB RF pulses and the proposed SPSP-SMS pulses, yielding coverage of 36 slices in four shots with 350 ms volume TR. The pulses were compared in breath-hold fMRI at 3 T.

Results—The SPSP-SMS pulses recovered approximately 45% of voxels with signal loss in standard SMS images. Activation in areas of signal recovery increased by 26.4% using a 12.6 ms SPSP-MB pulse and 20.3% using a 12.1 ms SPSP-PINS pulse.

Conclusions—It is demonstrated that SPSP-SMS pulses can improve BOLD sensitivity in areas of signal loss across simultaneous multiple slices.

Keywords

Simultaneous multi-slice excitation; spectral-spatial excitation; susceptibility artifact correction; BOLD fMRI

Introduction

Simultaneous Multi-Slice (SMS) imaging methods have garnered interest within the MRI community because of the significant reduction in the time required to scan a volume. This is particularly useful in MRI experiments that benefit from higher temporal resolution and greater sampling power. In particular, it has been demonstrated that SMS methods can

increase Blood Oxygen Level Dependent (BOLD) functional MRI (fMRI) acquisition speeds by factors of four and greater (1–4). This translates into increased statistical power in the activation analysis (5) and a better ability to identify nuisance physiological signal components (6). The most common method of achieving SMS excitations is with a Multi-Band (MB) RF pulse, where the waveform of a single slice is phase modulated with multiple frequencies and then recombined linearly. Recently, Power Independent of Number of Slices (PINS) RF pulses were introduced as another approach to SMS excitation (7). PINS pulses require approximately factor N lower peak RF power to excite the same number of slices than its corresponding MB pulse. However, PINS pulses excite an infinite train of equidistant slices due to a small Field-of-Excitation (FOX).

Gradient-echo BOLD fMRI in the lower brain remains challenging due to susceptibility induced signal loss. The signal loss is particularly problematic in the through-plane direction in axial slices due to the proximity of inferior air cavities. There have been several methods proposed to mitigate the signal loss due to susceptibility effects. Among these are z-shim methods (8), thin slice averaging (9), shim coils (10), multi-echo sequences (11), parallel transmission (12), and tailored RF pulses (13). Methods that can achieve signal loss corrections in a single excitation are of particular importance in the fMRI context because they do not increase scan time. Spectral-spatial (SPSP) pulses have recently been shown to be capable of reducing the signal loss artifact in a single excitation (14–16). Such pulses are designed to have a SPSP excitation with a frequency dependent through-plane phase pattern, which is equal and opposite to that produced by the magnetic susceptibility at echo time T_E . By exciting with a pre-compensated phase, a phase-coherent signal at the center of k-space is created at T_E and thus recovers the majority of the original signal. Crucially, only off-resonance components will be corrected, meaning that the excitation is equivalent to that of a standard pulse in regions with little or no off resonance. Because of this, SPSP pulses can be used to simultaneously excite numerous slices compensated for signal loss across the entire volume of the brain.

Theory

Susceptibility Artifact Correction with Spectral-Spatial Pulses

Signal loss artifact arises from through-plane variations in the magnetic susceptibility at the interface between air and tissue. During the time between the excitation and the acquisition of the center of k-space, the excited spins will develop inhomogeneous phases that result in cancellations during data readout. This results in signal loss artifacts characterized by large signal voids in the images. It has previously been shown that SPSP pulses are capable of mitigating this signal loss by pre-compensating the slice with an equal and opposite frequency dependent through-plane phase. In these pulse designs the through-plane susceptibility gradient was modeled using a linear relationship $G_s(f) = \alpha f$ with value α measured to be on the order of $-1.0 \mu\text{T/m/Hz}$ in the typical human brain (17). At T_E the phase of a given spin will then be both z - and f -dependent: $\phi_s(z, f) = \gamma G_s(f) z T_E = \gamma \alpha f z T_E$.

An SPSP pulse can be designed using the small tip-angle approximation (18), where an excitation of duration T can be thought of as a time-symmetric analogue to acquisition and the resulting magnetization profile is the Fourier transform of the RF pulse $B(t)$:

$$M(z)e^{-\gamma\alpha f z T_E} = \int_0^T B(t)e^{-i(k_z(t)z + k_f(t)f)} dt. \quad [1]$$

Here, the corresponding excitation k-space trajectories differ only in that they are time-reversed: $k_z(t) = \gamma \int_t^T G_z(s) ds$ and $k_f(t) = T - t$, with gyromagnetic ratio γ and slice-select gradient G_z . Note that the excited slice magnetization $M(z)$ is pre-compensated for the frequency dependent through-plane susceptibility gradient. An SPSP pulse typically achieves spatial localization with slice-select sub-pulses consisting of a trapezoidal gradient and RF waveform $p(t)$, which is the inverse Fourier transform of $P(z)$, the desired slice profile along z that has slice thickness z_0 . An infinite number of distinct frequency bands are produced by repeating the sub-pulses H times per excitation (19). The resolution of the frequency bands will be proportional to $1/H$. The separation stop-band f_s between aliased frequency bands will be determined by $1/T_{\text{sub}}$ where T_{sub} is the time between each sub-pulse. One can either alternate the gradient polarity of each sub-pulse and put the gradient rewinder at the end or keep the gradient polarities the same and include a rewinder with each sub-pulse. The latter is known as the “fly-back” design and is less susceptible to timing errors due to eddy currents than its dual-polarity counterpart (20).

In this work a design approach is taken whereby the final RF pulse is obtained by the complex summation of J number of SPSP pulses that each produce the desired through-plane phase pre-compensation for the j^{th} frequency band centered at $J f$ (21) where f is the frequency sampling step size. Placing each pulse at the proper spectral position is done so by phase modulating $p(k_z(t))$ by $J f$. The through-plane phase pre-compensation for a given frequency band is introduced by shifting the center of the k-space of its waveform, which is equivalent to unbalancing the slice-select gradient thus creating a z -shim. The shift for a given T_E and f is $k = \gamma \alpha f T_E$. The final form of the SPSP pulse is obtained by summing over the frequency bands:

$$B_{\text{SPSP}}(t) = w(t) \sum_{j=-J/2+1/2}^{J/2-1/2} p_j(k_z(t) + j\Delta k) e^{i2\pi j\Delta f(T-t) + i\theta_j}. \quad [2]$$

Here $w(t)$ is a temporal weighting function applied to the entire pulse to smooth the spectral profile of each frequency band. Its Fourier transform is $W(f)$, the width of which will determine the passband f_p of the pulse. The term θ_j is an adjustable constant phase, which is set such that the bands have the same phase in regions where they overlap.

Evaluating Eq. [1], the magnetization profile of the SPSP pulse is:

$$M_{\text{SPSP}}(z, f) = P(z)W(f) * \sum_{j=-J/2+1/2}^{J/2-1/2} \delta(f - j\Delta f) e^{-i\gamma\alpha j\Delta f T_E z + i\theta_j}. \quad [3]$$

The magnetization will be comprised of a series of overlapping frequency bands each with a unique through-plane phase pre-compensation. Note that only the central frequency passband, which will have a net width of approximately $J f$, is being considered here.

Multi-Band SMS Excitation

SMS excitation is typically achieved using an MB RF pulse, a modulated single-slice waveform that produces N slices with separation Δz . For slices symmetric about the isocenter, this is written as:

$$B_{\text{MB}}(t) = p(k_z(t)) \sum_{n=-N/2+1/2}^{N/2-1/2} e^{2i\pi k_z(t)n\Delta z}. \quad [4]$$

The corresponding magnetization is:

$$M_{\text{MB}}(z) = P(z) * \sum_{n=-N/2+1/2}^{N/2-1/2} \delta(z - n\Delta z). \quad [5]$$

Since an MB pulse is just the linear superposition of N modulated waveforms, the peak RF voltage of an MB pulse will increase linearly with N and can restrict practical implementation of MB pulses due to hardware limitations. Furthermore peak power is proportional to the square of the peak voltage and therefore will increase by a factor of N^2 while the amount of Specific Absorption Rate (SAR) experienced by the subject follows the time integral of square of the voltage and thus increases with N .

PINS SMS Excitation

If peak RF power or SAR is a concern, the PINS technique, a series of non-selective pulses separated by gradient z-blips, is a useful alternative. The distinguishing characteristic of a PINS pulse is that these z-blips are designed such that the FOV is relatively small. In this manner, multiple slices are simultaneously excited with separation Δz being equal to the FOV. The number of effectively excited slices is not an independent variable and is determined by the dimension of the RF coil and the subject dimensions along the slice direction. From an excitation k-space perspective, a PINS pulse can be constructed by first selecting the appropriate area for the z-blip:

$$A_{\text{blip}} = \frac{2\pi}{\gamma \Delta z}. \quad [6]$$

This z-blip is repeated multiple times in order to create a k-space trajectory that can provide sufficient resolution along the slice-select direction. Interspersed between the z-blips are rectangular RF sub-pulses, which are weighted by $p(k_z(t))$ along the whole PINS pulse:

$$B_{\text{PINS}}(t) = p(k_z(t)) \text{rect}(t/t_0) \sum_{l=0}^L \delta(t - l(t_0 + t_{\text{blip}}) - t_0/2). \quad [7]$$

Here, L is the total number of z-blips and t_{blip} is the duration of each. The time t_0 between subsequent z-blips also corresponds to the length of an individual RF rectangular sub-pulse. The parameter t_0 can be adjusted to either minimize the overall pulse length or the required peak RF voltage. The magnetization generated by a PINS pulse is:

$$M_{\text{PINS}}(z) = P(z) * \sum_{n=-\infty}^{\infty} \delta(z - n\Delta z). \quad [8]$$

SPSP-SMS Pulse Designs

The SPSP-MB pulse is constructed from Eqs. [2] and [4]:

$$B_{\text{SPSP-MB}} = w(t) \sum_{j=-J/2+1/2}^{J/2-1/2} p(k_z(t) + j\Delta k) e^{i2\pi j\Delta f(T-t) + i\theta_j} \sum_{n=-N/2+1/2}^{N/2-1/2} e^{i2\pi k_z(t)n\Delta z}. \quad [9]$$

Likewise Eq. [10], the corresponding expression for the SPSP-PINS pulse, is formed by combining Eqs. [2] and [7] and repeating H number of times:

$$B_{\text{SPSP-PINS}}(t) = w(t) \sum_{j=-J/2+1/2}^{J/2-1/2} p(k_z(t) - j\Delta k) e^{i2\pi j\Delta f(T-t) + i\theta_j} \text{rect}(t/t_0) \sum_{h=0}^{H-1} \sum_{l=0}^L \delta(t - (l(t_0 + t_{\text{blip}}) + t_0/2 + hT_{\text{sub}}))$$

where T_{sub} is the duration of a single PINS sub-pulse, including any rewinding gradients.

Finally, the magnetization generated by these pulses can be written as:

$$M_{\text{SPSP-MB}} = [P(z)W(f)] ** \left[\sum_{n=-N/2+1/2}^{N/2-1/2} \delta(z - n\Delta z) \sum_{j=-J/2+1/2}^{J/2-1/2} \delta(f - j\Delta f) e^{-i\gamma\alpha j\Delta f T_E z + i\theta_j} \right] \quad [11]$$

and

$$M_{\text{SPSP-PINS}} = [P(z)W(f)] ** \left[\sum_{n=-\infty}^{\infty} \delta(z - n\Delta z) \sum_{j=-J/2+1/2}^{J/2-1/2} \delta(f - j\Delta f) e^{-i\gamma\alpha j\Delta f T_E z + i\theta_j} \right] \quad [12]$$

Methods

Pulse Design

Matlab (Mathworks, Natick, MA) was used to create fly-back SPSP-MB and SPSP-PINS pulses with $p(k_z(t)) = \text{sinc}(k_z(t))$ and peak slew rates of 150 mT/m, peak gradients of 30 mT/m, and a sampling resolution of 10 μs . In order to create a smooth phase pattern, $J = 5$

frequency bands were placed with $f = 60$ Hz. These values were chosen via visual inspection of the simulated SPSP profiles. A value of $T_E = 35$ ms was used to calculate the k-space shift k for $\alpha = -1.0$ mT/m/Hz. The SPSP-MB pulse consisted of six sub-pulses (2.14 ms each, $f_s \approx 470$ Hz) designed to excite $N = 9$ slices with thickness $z_0 = 5$ mm and separation $z = 20$ mm. A 10 mT/m excitation gradient was used during the application of the RF waveform while the peak gradient value was used for the fly-back portion of each sub-pulse. From a frequency perspective, this resulted in a separation of 8500 Hz between adjacent slices. The temporal weighting function $w(t)$ was chosen such that $f_p \approx 120$ Hz and had a Gaussian shape. The total pulse duration was 12.62 ms. The SPSP-PINS pulse was composed of four sub-pulses (3.06 ms each, $f_s \approx 325$ Hz) comprising ten 180 μ s z-blips interleaved with $t_0 = 60$ μ s rectangular RF pulses. In the case of PINS, the frequency separation between adjacent slices is determined directly by the inverse of the time interval between RF pulses, and in this case was 4170 Hz. In other respects it was comparable to the SPSP-MB pulse: $z = 20$ mm, $z_0 = 5$ mm, 10 mT/m excitation gradient, $f_p \approx 130$ Hz, and total duration $T = 12.06$ ms. The number of sub-pulses were chosen such that both pulses were approximately the same length. Figure 1 plots the real and imaginary RF components of the SPSP-MB (a) and SPSP-PINS (b) pulses described here, along with their respective slice-select gradients G_z . The magnetization profile $M(z, f)$ produced by the pulses was examined via Bloch equation simulations also ran in Matlab.

Human Brain Imaging

Images of the human brain were acquired in four normal adult subjects using a Siemens TIM Trio VB17 3T scanner (Siemens Healthcare, Erlangen, Germany) after informed consent approved by the University of Hawaii and Queens Medical Center joint Institutional Review Board. In each subject, four whole brain scans were acquired using 1) a single-slice sinc pulse, 2) a standard $N = 9$ MB (Standard-MB) pulse, 3) the $N = 9$ SPSP-MB pulse, and 4) the SPSP-PINS pulse. The MB parameter $N = 9$ was chosen such that these pulses would excite approximately the same slices as the PINS pulse. In all scans 36 slices were acquired such that the SMS acquisitions required four excitations per volume. For the SMS acquisitions, a blipped-CAIPI EPI sequence (4) was implemented (350 ms TR, 36 ms TE, 37° FA, 96×96 in-plane resolution, 240 mm FOV, 2.5×2.5×5 mm³ voxels, CAIPI shift FOV/3). Single-slice reference images were acquired for the calculation of slice-GRAPPA (22) kernels with kernel size 3×4, which were then used for the reconstruction of all SMS scans. A standard 2D EPI sequence with TR = 1400 ms and otherwise identical parameters was used for the single-slice acquisitions. The Siemens body transmission coil and 32-channel receiver coil were used for all scans.

The ability for the SPSP-SMS pulses to recover lost signal were quantitatively assessed by first determining the regions in the Standard-MB images that were below 10% of their normalized maximum intensities. These voids were taken to represent voxels where the SPSP pulses had the potential to have a meaningful effect. The SPSP-SMS pulse image voxels that both had magnitudes above their respective 10% thresholds and were located in the void regions were then counted, and the total percentages of the recovered voxels within the voids were calculated. Difference images were also calculated for qualitative purposes. Subtracting the normalized Standard-MB image volume from the two SPSP-SMS image

volumes created these difference maps. Three voxel by three voxel in-plane smoothing and windowing between 5% and 20% change, relative to the maximum image intensity, was performed on the difference images.

Functional MRI Experiments

Three five-minute long fMRI breath-hold experiments, consisting of a 20 s breathing/20 s breath-holding paradigm, were also performed for each subject using the same sequence parameters as above. Breath-holding fMRI creates a relatively large BOLD contrast throughout the whole brain and is useful for evaluating methodology. In addition to scanning with each of the two SPSP-SMS pulses, uncorrected control data with the same temporal resolution was acquired with the Standard-MB pulse. FSL (FMRIB, Oxford, UK) was employed to analyze the fMRI data with the FMRI Expert Analysis Tool (FEAT) (23–25) and the following preprocessing protocols: MCFLIRT motion correction (26, 27), BET brain extraction (28), 5 mm Full-Width-Half-Max spatial smoothing, and FILM pre-whitening (29). Each voxel time series was fit with a boxcar function convolved with the double-gamma hemodynamic response function. Motion parameters were also included in the model. The resulting activation maps were clustered with a Z-stat threshold of 2.3 and cluster P threshold of 0.05 (30).

Two Regions of Interest (ROIs) were used in the quantitative analysis of the effect of using SPSP-SMS pulses in fMRI experiments. The first, ROI-1, was determined directly by the voxels exhibiting significant recovery in the human brain imaging analysis above. ROI-2 was then defined as the remaining volume of the brain outside of ROI-1. Activation coverage in both ROIs was calculated by determining the percentage of their respective volumes that contained voxels with Z-stat greater than or equal to 2.3. The quantity of interest was the change in activation coverage when using SPSP-SMS versus Standard-MB pulses.

SPSP-MB Pulse Slice Thickness Comparison

In order to get an idea how SPSP-SMS pulses might translate to applications requiring thinner slices, a comparison of signal recovery as a function of slice thickness was performed for the SPSP-MB pulse design. Six pulses for $N = 7$ were constructed with slice thicknesses ranging from 2.5 to 5.0 mm in steps of 0.5 mm. A pulse was first designed for 2.5 mm with the following parameters: 180 mT/m peak slew rate, 30 mT/m peak gradient, $J = 5$, $f = 70$ Hz, $T_E = 36$ ms, $\alpha = -1.0$ mT/m/Hz, six 2.14 ms sub-pulses, $z = 20$ mm, 18.2 cm FOX, $f_s \approx 455$ Hz, and $f_p \approx 120$ Hz. The total length of the pulse was 12.9 ms. The remaining five pulses with increasing slice thicknesses were then constructed by decreasing the excitation gradient while keeping its duration constant. This was done such that they would have identical parameters other than the slice thickness. Four normal human subjects were scanned after informed consent using the blipped-CAIPI EPI sequence and reconstruction described above. A total of 28 slices were acquired in each subject. Signal recovery using the SPSP-MB pulses was calculated using the Human Brain Imaging analysis method previously described.

Results

Simulations

Figure 2 shows Bloch equation simulations ($FA = 90^\circ$) of the transverse magnetization and pre-phasing patterns for the SPSP-MB (A) and SPSP-PINS (B) pulses in the frequency range between -150 and $+150$ Hz across a 26 cm FOV_z on the left, with a single slice FOV_z on the right. Also shown is the on-resonance magnetization profile along z . The overall results are comparable for the two pulses. As expected, the SPSP-PINS pulse excites periodic slices across the entire FOV_z and the SPSP-MB pulse only produces $N = 9$ slices centered about isocenter. Both phase patterns are very good approximations of the target phase pattern (see Fig. 2 of Ref. (14)). Each slice excited by SPSP-PINS is identical in all aspects, regardless of its position relative to isocenter. The SPSP-MB however shows some small decrease in the maximum magnitude of the slices far from isocenter. This was due to a slight undersampling of the RF waveform using the $10\ \mu\text{s}$ dwell time, which was used instead of a smaller dwell time due to hardware limitations.

Human Brain Imaging

Figure 3 shows the brain volumes consisting of 36 slices acquired in a representative subject for each of the three SMS experiments using Standard-MB (A), SPSP-MB (B), and SPSP-PINS (C) pulses. Sets of the nine simultaneously excited slices correspond to each column in the figure. The Standard-MB slices contain regions that suffer from signal loss due to susceptibility variations in the vicinity of the nasal cavity and the ear canals. This is indicated by the dashed white line. The signal recovery due to the SPSP-SMS pulses can be observed in the corresponding areas in (B) and (C). Figure 4 shows the slices within the dashed white line in more detail for the Standard-MB, SPSP-MB, and SPSP-PINS experiments in (A), (B), and (C), respectively. The region below the 10% threshold in (A) is mapped by the black voxels in (D), and is where the efficacy of the SPSP-SMS pulses are evaluated. This same region is plotted in (E) and (F) where white indicates voxels which have been successfully recovered by SPSP-MB and SPSP-PINS, respectively. The quantitative analysis is derived from the number of black and white voxels, while the white voxels are also used to define ROI-1 in the fMRI section. Table 1 displays the signal recovery results for the SPSP-MB and SPSP-PINS pulses for the four subjects along with the average percent of recovered signal. The relative percent of the brain that comprises the recovery regions is also included. It is seen that both SPSP pulses reliably recover around 45% of the reduced signal, with SPSP-PINS slightly outperforming SPSP-MB by this metric.

On display in Figure 5 are the difference images derived from Fig. 3, used here for visualization purposes. The increases in intensity when using the SPSP-MB pulse as opposed to the Standard-MB pulse are seen in (A), while the equivalent comparison between the SPSP-PINS pulse and the Standard-MB pulse is shown in (B). From this it can be seen that some regions that did not exhibit voids in the Standard-MB volume still suffered from decreased signal and using an SPSP pulse could increase sensitivity in those areas. This is most evident in the sixth row, despite these slices being excluded from ROI-1 in the quantitative analysis. It is evident from Fig. 5 that both SPSP pulses perform similarly well

in recovering signal, with no obvious variations between their recovery patterns. Comparable results were observed for all subjects in the study, although there was significant variation between subjects with respect to the volume of voxels that suffered from signal loss. This is expected, as the signal loss artifact is largely dependent upon the anatomy of the individual subject. Although not shown here, there were no significant decreases in signal due to the use of an SPSP pulse.

Functional MRI Results

Figure 6 shows the breath-hold BOLD activation across the entire brain of Subjects One (top) and Four (bottom) using the Standard-MB (A, D), SPSP-MB (B, E), and SPSP-PINS (C, F) pulses. The solid blue lines encompass manually selected regions where the use of SPSP-SMS pulses resulted in significant increases in the number of activated voxels. Even with visual inspection alone it can be seen that the SPSP-SMS pulses significantly increase the activation coverage compared to the Standard-MB pulse, particularly in Subject One. It is noteworthy that these regions extend beyond the data-driven definition of ROI-1 (refer to Fig. 4). Examining Fig. 5 reveals that this is not completely unexpected, although neither Figs. 4 nor 5 alone would have predicted the broad scope of the region of recovery in Subject One. Relatively speaking, the SPSP-MB pulse data exhibited higher activation coverage in ROI-1 than the SPSP-PINS data.

Table 2 shows the changes in activation coverage for both SPSP-SMS pulses in both ROIs calculated for all subjects. On average, both SPSP-SMS pulses increased the coverage in ROI-1 with 26.4% for SPSP-MB and 20.3% for SPSP-PINS. The increase in fMRI sensitivity in ROI-1 was accompanied by slightly decreased sensitivity in ROI-2, 2.6% for the SPSP-MB pulse and 5.7% for the SPSP-PINS pulse, although two of the SPSP-MB pulse experiments did not see a significant decrease in ROI-2 sensitivity. Examples of both an increase (Subject One) and a decrease (Subject Four) can be seen in (B) and (E) of Fig. 6, respectively. The SPSP-PINS data showed a decrease in ROI-2 activation sensitivity consistently in all subjects.

SPSP-MB Pulse Slice Thickness Comparison

Figure 7 shows the comparison of signal recovery as a function of slice thickness for the $N = 7$ SPSP-MB pulses, with the Standard-MB images in the left column and the corrected SPSP-MB images in the right. Only the seven slices that showed signal loss and subsequent recovery are shown. From this figure it can be seen that the thinner slices show less through-plane signal loss compared to the thicker slices as expected. The degree of signal loss is roughly proportional to the slice thickness, in particular for the more superior slices with signal loss in the frontal brain. Using the signal recovery analysis described above, subject averaged percent signal recoveries of 39, 37, 40, 41, 37 and 44 for 2.5, 3, 3.5, 4, 4.5, and 5 mm slice thicknesses were found. Although the thinner slices did show decreased signal loss and subsequently less recovered pixels, the SPSP-MB pulse still provides approximately the same percent improvement for all slice thicknesses. It is therefore surmised that improvements in BOLD sensitivity similar to those reported here will be seen in experiments with thinner slices, with the main difference being that the region of interest will be smaller. It should be further noted that visual inspection indicates that for all

thicknesses the SPSP-MB image quality is comparable, indicating that using thicker slices is a viable option for fMRI experiments that were previously made impractical by the severity of the artifact.

Discussion and Conclusions

We have presented two alternative SPSP-SMS pulse methods for correcting susceptibility induced signal loss in SMS acquisitions. Both methods were shown to recover approximately 45% of the regions of signal dropout in volumes consisting of 36 $2.5 \times 2.5 \times 5$ mm³ resolution slices. We also investigated how such pulses perform in the context of breath-holding BOLD fMRI. It was shown that susceptibility artifact-corrected fMRI data could be acquired at a rate of approximately three volumes per second, enabling future fMRI studies of the frontal lobe and nearby regions with high temporal resolution. The ability for SPSP pulse methods to provide whole brain signal loss compensation with little time penalty is a major advantage over the gradient based z-shim methods. The increased length of the SPSP pulses compared to the Standard-MB pulse however may increase the minimum TE values. This could also limit the bandwidth or resolution of the readout scheme, as 96×96 was the highest matrix size attainable for the 2D EPI sequence used in this work. Larger matrix sizes could, however, be easily achieved by the use of in-plane under-sampling, at the expense of some slice acceleration so as to keep the total acceleration factor within the capabilities of the receiver array. It was also seen that SPSP pulses seem to be equally effective in recovering signal in thick slices as well as thinner ones.

Both pulses were demonstrated to be effective at recovering lost signal in the whole brain and were also demonstrated to significantly increase the number of activated voxels in regions corrupted by signal loss. This is the first known demonstration of the use of SPSP pulses (single-slice or multi-slice) for providing an increase in BOLD activation to our knowledge. Although an increase in activation was observed, both pulses experienced some small losses in fMRI sensitivity in the rest of the brain in some of the subjects. The cause of these losses is not known at this point but we speculate that the pulse may cause unwanted de-phasing in these regions possibly due to deviation from the linear approximation between susceptibility gradient and frequency. Separate experiments mapping the temporal signal-to-noise ratio of the three pulses (not shown) indicated that for the SPSP pulses there is no general loss in the quality of the signal with time compared to the Standard-MB pulse and show significant improvement in the areas of signal drop-out. These losses in BOLD sensitivity in ROI-2 however were not as localized as the gains in ROI-1 and therefore will be useful for studies that simultaneously look for activation of the frontal lobe and any other region in the brain. Furthermore, it should be reiterated that two of the four subjects experienced no statistically significant loss when using the SPSP-MB pulse.

In situations where peak RF pulse voltage and SAR are a concern, or where high flip-angles need to be achieved by the correcting SPSP pulse, SPSP-PINS pulses have a distinct advantage over SPSP-MB pulses. In this work the applied peak voltage on the Siemens scanner's body RF coil that achieved FA=37° was 222 V, 263 V, and 75 V for Standard-MB, SPSP-MB, and SPSP-PINS, respectively. Moreover, the system voltage limits of 458 V would not have allowed for Standard-MB excitations above 77° and SPSP-MB excitations

above 65° , while $FA=230^\circ$ could be achieved in practice with SPSP-PINS pulses, if so necessitated by the experiment. In general, PINS pulses are fundamentally constrained by the ratio of the slice separation to slice thickness and may be found to be rather constrictive in applications where this ratio needs to be large. A second drawback of the PINS design is that head and coil dimensions are needed to restrict the number of slices. This is more problematic for an axial excitation as proposed here for through-plane signal loss compensation. We did observe some additional slice aliasing artifact with the SPSP-PINS pulse compared to the SPSP-MB pulse. For the sake of simplicity, the SPSP-PINS pulse was reconstructed with the $N = 9$ single-slice reference images. It is possible that reconstruction with a larger number of reference slices will decrease the aliasing artifact, particularly from the neck regions, increasing the SPSP-PINS pulse performance to a level more on par with the SPSP-MB pulse. Doing this would not directly penalize the fMRI experiment, and the only consequences are the time needed to acquire any additional reference slices and the corresponding fractional increase in the time to run the reconstruction algorithm.

It is worthwhile to consider how the SPSP methods presented here might be applied at higher fields such as 7 T. One can expect approximately $7/3$ more signal dephasing in a slice at 7 T compared to that at 3 T because the variation in phase across a slice is linearly proportional to B_0 . Therefore to match performance at 3 T, the 7 T pulse parameters will need to be scaled by the same factor. For example, TE and sub-pulse length all need to be divided by $7/3$. Shorter sub-pulses contribute to a shorter total pulse length, which is advantageous for the addressing the issue of the decreased TE. The primary concern, however, is that shorter sub-pulses are now needed to excite a sufficient number of thinner simultaneous slices. This may be challenging due to hardware limitations including gradient peak and slew rate, RF sampling resolution, and peak B1 values. Likely a compromise with the other pulse performance parameters will be needed. The application of SPSP-SMS pulses to higher field will be addressed in future work.

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References

1. Larkman DJ, Hajnal JV, Herlihy AH, Coutts GA, Young IR, Ehnholm G. Use of multicoil arrays for separation of signal from multiple slices simultaneously excited. *J Magn Reson Imaging*. 2001; 13(2):313–317. [PubMed: 11169840]
2. Moeller S, Yacoub E, Olman CA, Auerbach E, Strupp J, Harel N, Ugurbil K. Multiband multislice GE-EPI at 7 tesla, with 16-fold acceleration using partial parallel imaging with application to high spatial and temporal whole-brain fMRI. *Magn Reson Med*. 2010; 63(5):1144–1153. [PubMed: 20432285]
3. Feinberg DA, Moeller S, Smith SM, Auerbach E, Ramanna S, Glasser MF, Miller KL, Ugurbil K, Yacoub E. Multiplexed echo planar imaging for sub-second whole brain FMRI and fast diffusion imaging. *PLoS One*. 2011; 5(12):e15710. [PubMed: 21187930]
4. Setsompop K, Gagoski BA, Polimeni JR, Witzel T, Wedeen VJ, Wald LL. Blipped-controlled aliasing in parallel imaging for simultaneous multislice echo planar imaging with reduced g-factor penalty. *Magn Reson Med*. 2012; 67(5):1210–1224. [PubMed: 21858868]
5. Feinberg DA, Yacoub E. The rapid development of high speed, resolution and precision in fMRI. *NeuroImage*. 2012; 62(2):720–725. [PubMed: 22281677]

6. Hu X, Le TH, Parrish T, Erhard P. Retrospective Estimation and Correction of Physiological Fluctuation in Functional MRI. *Magn Reson Med*. 1995; 34:201–212. [PubMed: 7476079]
7. Norris DG, Koopmans PJ, Boyacioglu R, Barth M. Power independent of number of slices radiofrequency pulses for low-power simultaneous multislice excitation. *Magn Reson Med*. 2011; 66(5):1234–1240. [PubMed: 22009706]
8. Frahm J, Merboldt K-D, Hanicke W. The Influence of the Slice-Selection Gradient on Functional MRI of Human Brain Activation. *J Magn Reson B*. 1994; 103:91–93. [PubMed: 8137075]
9. Merboldt K-D, Finsterbusch J, Frahm J. Reducing inhomogeneity artifacts in functional MRI of human brain activation-thin slices vs gradient compensation. *J Magn Reson*. 2000; 145:184–191. [PubMed: 10910686]
10. Wilson JL, Jezzard P. Utilization of an intra-oral diamagnetic passive shim in functional MRI of the inferior frontal cortex. *Magn Reson Med*. 2003; 50(5):1089–1094. [PubMed: 14587020]
11. Song AW. Single-Shot EPI with Signal Recovery from the Susceptibility-Induced Losses. *Magn Reson Med*. 2001; 46:407–411. [PubMed: 11477647]
12. Deng W, Yang C, Alagappan V, Wald LL, Boada FE, Stenger VA. Simultaneous z-shim method for reducing susceptibility artifacts with multiple transmitters. *Magn Reson Med*. 2009; 61(2): 255–259. [PubMed: 19165881]
13. Stenger VA, Boada FE, Noll DC. Three-dimensional tailored RF pulses for the reduction of susceptibility artifacts in T2*-weighted functional MRI. *Magn Reson Med*. 2000; 44:525–531. [PubMed: 11025507]
14. Yip CY, Yoon D, Olafsson V, Lee S, Grissom WA, Fessler JA, Noll DC. Spectral-spatial pulse design for through-plane phase precompensatory slice selection in T2*-weighted functional MRI. *Magn Reson Med*. 2009; 61(5):1137–1147. [PubMed: 19267346]
15. Yang C, Deng W, Alagappan V, Wald LL, Stenger VA. Four-dimensional spectral-spatial RF pulses for simultaneous correction of B1+ inhomogeneity and susceptibility artifacts in T2*-weighted MRI. *Magn Reson Med*. 2010; 64(1):1–8. [PubMed: 20577982]
16. Yang C, Deng W, Stenger VA. Simple analytical dual-band spectral-spatial RF pulses for B1+ and susceptibility artifact reduction in gradient echo MRI. *Magn Reson Med*. 2011; 65(2):370–376. [PubMed: 21264930]
17. Yang C, Poser BA, Deng W, Stenger VA. Spectral decomposition of susceptibility artifacts for spectral-spatial radiofrequency pulse design. *Magn Reson Med*. 2012; 64(6):1905–1910. [PubMed: 22334396]
18. Pauly J, Nishimura D, Macovski A. A K-Space Analysis of Small-Tip-Angle Excitation. *J Magn Reson*. 1989; 81(1):43–56.
19. Meyer CH, Pauly JM, Macovski A, Nishimura DG. Simultaneous spatial and spectral selective excitation. *Magn Reson Med*. 1990; 15(2):287–304. [PubMed: 2392053]
20. Block W, Pauly J, Kerr A, Nishimura D. Consistent fat suppression with compensated spectral-spatial pulses. *Magn Reson Med*. 1997; 38(2):198–206. [PubMed: 9256098]
21. Pauly, J.; Cunningham, C.; Daniel, B. Proceedings of the 11th Annual Meeting of ISMRM. Toronto, Canada: 2003. Independent dual-band spectral-spatial pulses; p. 966
22. Griswold MA, Jakob PM, Heidemann RM, Nittka M, Jellus V, Wang J, Kiefer B, Haase A. Generalized autocalibrating partially parallel acquisitions (GRAPPA). *Magn Reson Med*. 2002; 47(6):1202–1210. [PubMed: 12111967]
23. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. *Neuroimage*. 2012; 62(2):782–790. [PubMed: 21979382]
24. Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, Beckmann C, Jenkinson M, Smith SM. Bayesian analysis of neuroimaging data in FSL. *Neuroimage*. 2009; 45(Suppl 1):S173–S186. [PubMed: 19059349]
25. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens T, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004; 23(Suppl 1):S208. [PubMed: 15501092]
26. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001; 5(2):143–156. [PubMed: 11516708]

27. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002; 17(2):825–841. [PubMed: 12377157]
28. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp*. 2002; 17(3):143–155. [PubMed: 12391568]
29. Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage*. 2001; 14(6):1370–1386. [PubMed: 11707093]
30. Worsley K. Statistical analysis of activation images. *Functional MRI: an introduction to methods*. 2001; 14:251–270.

FIG 1.

Diagrams showing the real and imaginary RF waveforms and slice-select gradient of the SPSP-MB (A) and SPSP-PINS (B) pulses. The SPSP-MB pulse consists of six 2.14 ms MB sub-pulses and has a total duration of 12.62 ms. Four 3.06 ms PINS sub-pulses, each comprising ten G_z blips interleaved with eleven 60 μ s hard RF pulses, produce an SPSP-PINS pulse 12.06 ms long.

FIG 2.

Bloch equation simulations of the SPSP-MB (A) and SPSP-PINS (B) pulses. The magnitude (top) and phase (middle) of the transverse magnetization, as a function of z and f , are plotted for 26 cm FOV_z (left) and a single slice (right). The on-resonance profile of the magnitude along z is shown in the bottom panel. Compared to each other, the pulses produce very similar excitations.

FIG 3.

Human brain images acquired at 3 T using the Standard-MB (A), SPSP-MB (B), and SPSP-PINS (C) pulses. Each column of nine slices was excited and acquired simultaneously and then separated via slice-GRAPPA reconstruction. The images excited with the Standard-MB pulse show signal loss particularly noticeable in the slices that contain the orbital frontal and inferior temporal regions near the nasal cavity and ear canals, as indicated by the dashed lines.

FIG 4.

The three slice groups most affected by the susceptibility artifact are plotted for the Standard-MB (A), SPSP-MB (B), and SPSP-PINS (C) pulses, corresponding to the dashed box in Fig. 3. The effect of the SPSP pulses can be easily identified by visual inspection. The black region in (D) maps the voxels in (A) below 10% of the maximum image intensity. The SPSP-MB and SPSP-PINS pulses both affected recovery above 10% for a significant number of these voxels, indicated by white voxels in (E) and (F), respectively.

FIG 5.

Difference images created by subtracting the Standard-MB pulse image volume from the SPSP-MB (A) and SPSP-PINS (B) pulse image volumes provide an alternate perspective on the regions affected by the SPSP pulses. It can be seen that their effect extends into the sixth slice row, a fact not necessarily discernible from visual inspection of Figs. 3 or 4. Both SPSP-SMS pulses have very similar recover patterns.

FIG 6.

Comparison of the breath-hold BOLD fMRI activation data for the images excited with Standard-MB (A,D), SPSP-MB (B,E), and SPSP-PINS (C,F) pulses in Subject One (top) and Four (bottom). The manually defined blue lines designate areas where there is a noticeable increase in activation coverage when using the SPSP-SMS pulses. This figure indicates that the SPSP-SMS pulses can effectively recover lost BOLD activation signal in regions otherwise undetected in the Standard-MB pulse experiment. The first and last slice groups exhibited insignificant amount of activation and have been omitted.

FIG 7.

Comparison of signal recovery as a function of slice thickness for an $N = 7$ SPSP-MB pulse. Only the slices that showed signal loss and subsequent recovery are shown. Recovery is clearly visible even in the 2.5 mm thick slices. All of the slice thicknesses show comparable image quality.

Table 1

Percent of voxels less than 10% of the normalized maximum intensity in the Standard-MB pulse images that are recovered by the SPSP-SMS pulses. Also noted is the percent of voxels in the brain included in the recovery region.

Subject #	1	2	3	4	Weighted Average	
SPSP-MB	% Recovered	47.0	37.6	40.1	45.9	43.3
SPSP-PINS	% Recovered	52.1	46.8	40.1	51.8	48.8
% Voxels in Recovery Region	3.3	1.8	1.0	3.0	2.2	

Table 2

Change in the percent of each ROI that comprises activated voxels with Z value greater than 2.3 for the two SPSP-SMS pulses, as compared to the Standard-MB Pulse.

Subject #		1	2	3	4	Weighted Average
SPSP-MB	ROI-1	38.5	19.2	15.3	21.3	26.4
	ROI-2	3.4	0.7	-8.0	-6.6	-2.6
SPSP-PINS	ROI-1	28.0	14.9	12.2	18.0	20.3
	ROI-2	-3.6	-4.1	-6.2	-9.3	-5.7