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Reduced susceptibility effects in perfusion fMRI with single-shot spin-echo EPI acquisitions at 1.5 Tesla

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Abstract

Arterial spin labeling (ASL) perfusion contrast is not based on susceptibility effects and can therefore be used to study brain function in regions of high static inhomogeneity. As a proof of concept, single-shot spin-echo echo-planar imaging (EPI) acquisition was carried out with a multislice continuous ASL (CASL) method at 1.5T. A bilateral finger tapping paradigm was used in the presence of an exogenously induced susceptibility artifact over left motor cortex. The spin-echo CASL technique was compared with a regular gradient-echo EPI sequence with the same slice thickness, as well as other imaging methods using thin slices and spin-echo acquisitions. The results demonstrate improved functional sensitivity and efficiency of the spin-echo CASL approach as compared with gradient-echo EPI techniques, and a trend of improved sensitivity as compared with spin-echo EPI approach in the brain regions affected by the susceptibility artifact. ASL images, either with or without subtraction of the control, provide a robust alternative to blood oxygenation level dependant (BOLD) methods for activation imaging in regions of high static field inhomogeneity.

Keywords: Arterial spin label; Susceptibility artifacts; Spin-echo EPI; Perfusion fMRI

1. Introduction

Arterial spin labeling (ASL) perfusion imaging is an emerging methodology for visualizing regional brain function both at rest and during activation [1,2]. While clinical applications have demonstrated that ASL techniques are capable of providing reliable cerebral blood flow (CBF) measurements in various cerebrovascular and psychiatric disorders [3], recent evidence also suggests that ASL contrast may have certain advantages over blood oxygenation level dependant (BOLD) contrast in functional magnetic resonance imaging (fMRI) studies, including improved sensitivity at low task frequencies, reduced intersubject variability [4,5], and better spatial resolution [6,7]. One appealing feature of the ASL contrast is that it is not based on susceptibility effects and could be used to study brain function in regions of high static field inhomogeneity at tissue-air and tissue-bone interfaces. ASL contrast, therefore, may provide an alternative and complementary approach to optimized BOLD techniques with reduced sensitivity to macroscopic susceptibility effects such as Z-shimming [8-10], thin slices [11] and tailored RF pulse [12] etc. By far, most existing ASL perfusion methods have used fast gradient-echo techniques like echo-planar imaging (EPI) and SPIRAL for image acquisition because of the speed. As an inevitable consequence, susceptibility contrast has still been manifested in the resulting perfusion images.

Susceptibility-resistant techniques especially spin-echo approaches would be highly preferable for ASL perfusion fMRI. One practical challenge for pursuing this direction is that spin-echo methods generally take longer imaging time than gradient-echo methods, leading to a penalty in imaging coverage. Several research groups have used single-shot spin-echo sequences with repeated RF-refocusing (HASTE, RARE, GRASE) [13-15] for perfusion imaging, all of which lack multi-slice capability because of the long acqui-

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sition echo-train (on the order of a few hundred milliseconds). While 3-dimensional volume perfusion imaging with spin-echo approaches have become available recently [16], the relatively low temporal resolution (on the order of a few minutes per sample) restricts their potential use in functional studies.

We propose to use spin-echo EPI (or SPIRAL) acquisitions in perfusion fMRI to reduce and minimize the susceptibility artifact while preserving the imaging speed and coverage. A primary issue that needs to be addressed using this approach is that real T2 weighted signal only occurs exactly at the spin-echo center, while susceptibility effects (including off-resonance artifacts and intra-voxel dephasing) can still take place on the side-lobes of the spin-echo during the relatively long acquisition window [17,18]. The off-resonance artifact, which primarily manifests as geometric distortion, can be effectively corrected using the field map [19], and the effect of intra-voxel dephasing is minimized by shortening the acquisition window as well as adjusting the voxel size. In the present study, we provide a proof-of-concept demonstration that single-shot spin-echo EPI in combination with a multislice continuous ASL (CASL) technique can detect motor cortex activation in the presence of static susceptibility artifacts at 1.5T, and the results are compared with a routine gradient-echo EPI technique as well as other BOLD imaging methods using thin slices and spin-echo acquisitions.

2. Methods

2.1. MR imaging

Imaging was performed on a 1.5T whole-body scanner (GE Medical Systems, Milwaukee, WI) with the standard clinical quadrature head coil provided by the manufacturer. CASL was performed with a 0.25 G/cm gradient and 35 mG RF irradiation applied 8 cm beneath the center of the acquired slices. Interleaved images with (labeled) and without (control) labeling were acquired using a single-shot spin-echo blipped EPI sequence. Controlling for off-resonance artifacts was effected by applying an amplitude modulated version of the labeling pulse [20]. A post-labeling delay of 800 ms was inserted between the end of the labeling pulse (with a duration about 1600 ms) and image acquisition to reduce the transit time related artifacts [21]. Acquisition parameters were: FOV = 24 cm × 16 cm, 64 × 40 matrix, TR/TE = 3000/38 ms, bandwidth 100 kHz, flip angle = 90°, slice thickness 6 mm, inter-slice space 2 mm. 6 axial slices were acquired from inferior to superior in an interleaved order to cover the motor cortex, and each slice acquisition took about 70 ms. For BOLD imaging, a gradient echo EPI sequence was carried out using either the same slice thickness as the CASL sequence (6 slices of 6 mm with 2 mm interslice space), or reduced slice thickness (12 slices of 3 mm with 1 mm interslice space). Imaging with thin slices is effective in reducing the macroscopic susceptibility effect [11] and the 3 mm slice thickness in the present study was chosen to be compatible with the in- plane resolution. In addition, a single-shot spin-echo EPI sequence was carried out using the same slice thickness as the CASL sequence, which is sensitivity to microscopic BOLD effect [22]. In all the gradient-echo and spin-echo EPI methods, the FOV and matrix size were the same as the CASL sequence. Other acquisition parameters were: TR/TE = 2000/50 ms, flip angle = 90°, bandwidth 62.5kHz. Due to technical reason, this bandwidth could not be made the same as in the spin-echo CASL scan, which could cause about 10% signal-to-noise ratio (SNR) gain but slightly more signal dephasing in the BOLD scans. A chemical shift imaging (CSI) reference scan was performed prior to the gradient-echo and spin echo EPI scans as well as the CASL scans respectively, to acquire the field map information to correct for geometric distortion during offline image reconstruction. A routine T_1-weighted spin-echo sequence (TR/TE = 400/16 ms, 256 × 192, 35 slices, 5 mm thick) was used to acquire high resolution anatomic images.

Functional MRI experiments with sensorimotor cortex stimulation were carried out on 5 right-handed healthy subjects (24-33yrs, one male, mean 27.6yrs). Written informed consent was obtained prior to all human studies according to an Institutional Review Board approval. Functional scans using 4 different techniques were performed on each subject respectively, i.e., perfusion scan with CASL method, gradient-echo EPI scan, gradient-echo EPI scan with thin slices and spin-echo EPI scan. The 3 latter scans were primarily based on the BOLD contrast, hereafter referred as BOLD scans. The order of the 4 scans was counterbalanced across subjects. 360 and 180 acquisitions were performed during the perfusion and each of the BOLD scans respectively. Since perfusion images were generated by pair-wise subtraction, this resulted in the same sample points (180) in each of the perfusion and BOLD scans. The total scan time was 18 min for CASL and 6 min for each BOLD scan. The activation paradigm consisted of resting periods alternating with activation epochs of self-paced bilateral finger tapping every 1 min indicated by visually presented cues. During functional scans, susceptibility artifacts were produced by placing a small piece of metal close to the left temporal side of the subject's head.

2.2. Data Processing

Data were reconstructed offline, geometric distortion was corrected using the field map acquired from the CSI reference scan [19]. Images were then realigned using a six parameter, rigid-body, least squares realignment routine and smoothed using a 3D 6 mm FWHM Gaussian kernel. For perfusion, the series of labeled images were shifted in time by one TR using linear interpolation (average of the two adjacent label images), followed by pair-wise subtraction between the time-matched control and labeled images to

produce the time series of 180 perfusion-weighted images. For BOLD imaging with thin slices, the 12 3-mm slices were pair-wise added (1 + 2, 3 + 4, ..., 11 + 12) to obtain the same imaging coverage and SNR as the gradient-echo EPI sequence using 6slices of 6 mm thickness [11].

6 data sets of image series (180 images each) were analyzed using the VoxBo software package (http://www.voxbo.org), i.e., the gradient-echo EPI scan, gradient-echo EPI scan with thin slices, spin-echo EPI scan, perfusion-weighted image series plus the raw labeled and control image series acquired using the CASL sequence. Voxel-wise analysis of the functional data were conducted to identify voxels with a significant response to the motor cortex stimulation in each data set based on the modified general linear model [23]. *t* test was used to evaluate the significance of the variance in the data explained by the model. In all the data sets analyzed except for the perfusion image series, substantial temporal autocorrelation was observed as greater power in the low frequency range of the corresponding power spectrum. To account for the temporal autocorrelation in these data sets, the time-domain representation of the 1/frequency (1/*f*) function, derived from curve fitting of the average individual power spectrum, was placed within the K matrix [23,24] along with a "notch" filter designed to remove noise confounds irrelevant to the task frequency range, and a smoothing kernel representing the standard hemodynamic function [25].

The perfusion data were found not to have any substantial temporal autocorrelation from the power spectrum. Therefore, the analysis of these data were able to assume independence in time without the need for modeling of intrinsic temporal autocorrelation, "notch" filtering, or temporal smoothing. In addition to the above 6 data sets, the first 60 perfusion-weighted images (6 min scan) were also analyzed using VoxBo. This was done to compare the efficiency of functional imaging with BOLD and perfusion contrast based on an identical data acquisition time.

A region-of-interest (ROI) of somatosensory motor cortex related to hand movement was defined upon the anatomic images based on the "precentral knob" landmark structure [26] for each subject on the left and right hemisphere respectively, and a control ROI of prefrontal lobe which has no documented relationship with sensorimotor function was also defined individually. Functional SNR was then measured as the mean t value within the hand motor ROI in the left or right hemisphere divided by the standard deviation (SD) of the t values in the control ROI for each of the 7 data sets in each subject. The individual t-maps were superposed upon anatomic images and then thresholded at a Bonferroni corrected (based on all the voxels inside the brain in the 6 slices) two-tail $\alpha = 0.05$ for display. The functional SNRs measured in each of the data sets were entered into repeated-measures ANOVA using the SPSS software package to assess effects of imaging methods and brain hemisphere.

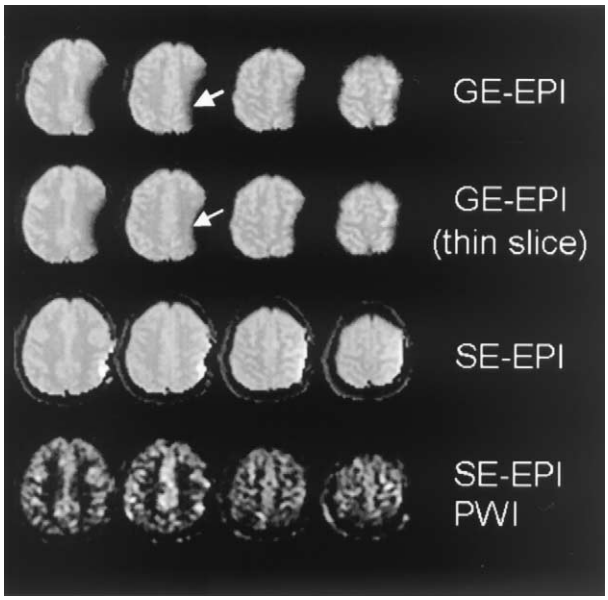

Fig. 1. A representative individual raw data set of gradient-echo and spin-echo EPI images along with the perfusion-weighted images (PWI) produced by averaging the whole time series of CASL difference images, 4 slices through the motor cortex are shown. The thick and thin arrows indicate the susceptibility artifacts in the gradient-echo EPI images with thick (6 mm) and thin (3 mm) slices respectively, and the thin slices are pair-wise added to obtain equal signal-to-noise ratio as the thick slices.

3. Results

A representative data set of raw images acquired using the gradient-echo and spin-echo EPI sequences in one subject are displayed in Fig. 1. Four axial slices through the motor cortex are shown. It can be clearly seen that the intentionally produced susceptibility artifact disrupts a large portion of the left cortex in the gradient-echo EPI images (thick arrow). While gradient-echo EPI images acquired using thin slices show partially recovered signal in the affected left motor cortex (thin arrow), the signal drop-out caused by susceptibility artifact is nearly fully recovered in the raw spin-echo EPI images. The bright rim at the left edge of the cortex in the spin-echo EPI images probably arises from residual geometric distortion of signal compression even after field map correction. In the perfusion-weighted images (PWI) produced by averaging the time series of CASL difference images, this hyperintensity is hardly visible due to the pair-wise subtraction.

Fig. 2 displays a representative individual data set of functional activation images. The activation map of the gradient-echo EPI scan shows large defects in the left sensorimotor area, whereas the gradient-echo EPI scan using thin slices shows improved sensitivity to sensorimotor stimulation in the presence of field inhomogeneity, as indicated by partially recovered activation in the left motor cortex (thin arrow). In the activation maps generated using CASL approach, both the perfusion and the raw labeled image series acquired using 18 min scan show robust activation in the left motor cortex (thick arrow). Note the raw labeled

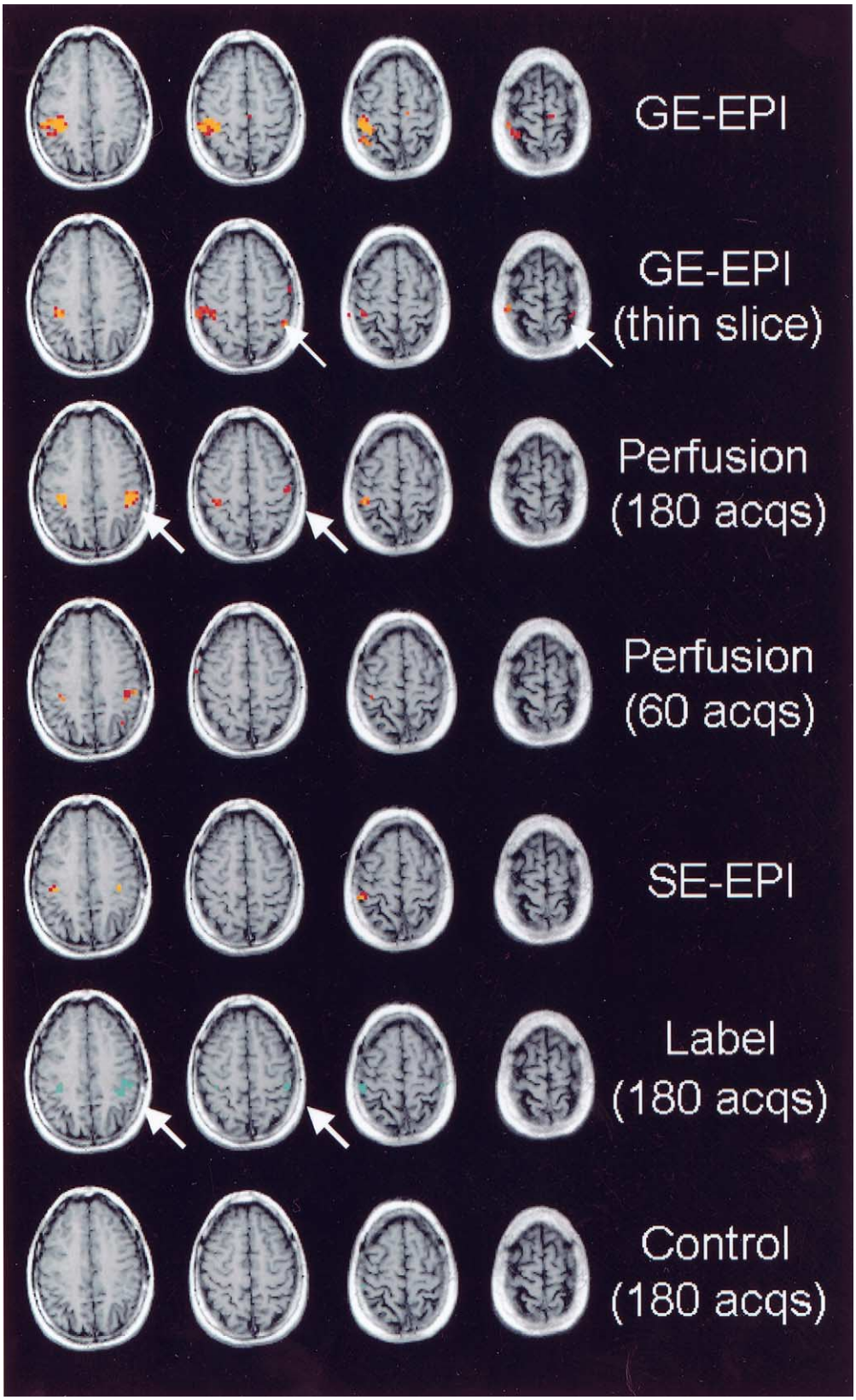

Fig. 2. A representative individual data set of functional images produced by the gradient-echo (GE) EPI data, GE-EPI data with thin slices, perfusion data of 18 min scan, perfusion data of 6 min scan, spin-echo (SE) EPI data, the labeled and control acquisitions of the 18 min CASL data, respectively. The t-maps are superposed upon anatomic images and thresholded at a Bonferroni corrected $\alpha = 0.05$, the color scale of red to yellow represents positive activation and dark blue to bright blue represents negative activation. The thin and thick arrows indicate the recovered activation in the left motor cortex detected in the GE-EPI data with thin slices and perfusion data respectively.

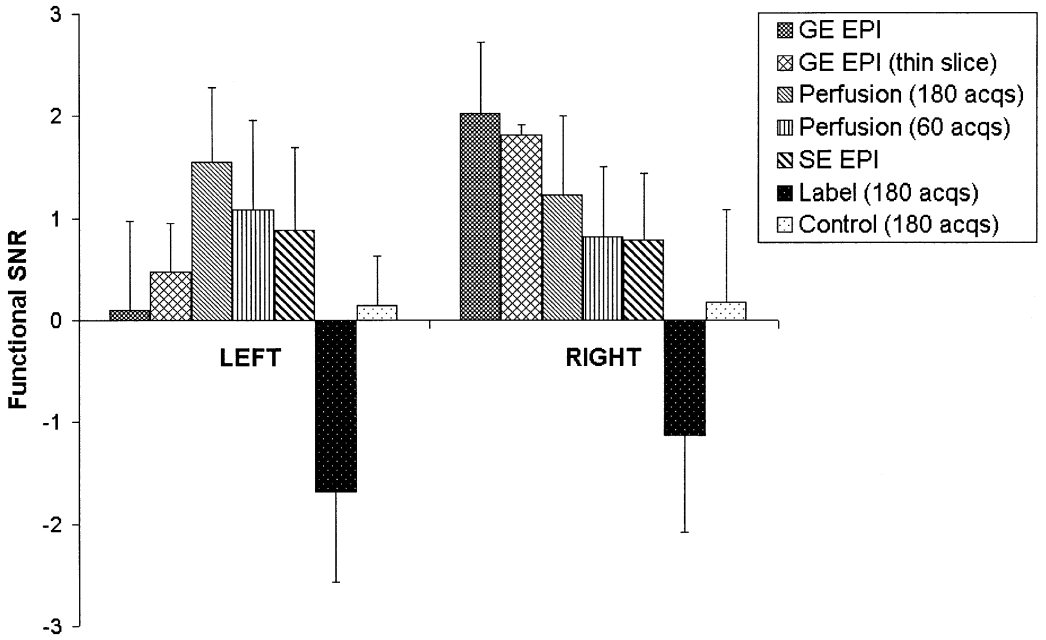

Fig. 3. Mean functional SNR values averaged across 5 subjects measured in each of the data sets respectively. The error bars indicate the corresponding standard deviation.

acquisitions produce significantly decreased signal in response to motor cortex stimulation, primarily because of increased inflow of inverted arterial blood water during activation. Both the perfusion data from the 6 min scan and the spin-echo EPI scan yield similar pattern of activation but at a relatively low level of statistical significance as compared to the perfusion or labeled data from the 18 min scan. In the right hemisphere, which is not affected by the susceptibility artifact, the BOLD data acquired by gradient-echo EPI scans using both 6 mm and 3 mm slice thickness show greater activation than the perfusion data as well as the spin-echo EPI data, in good agreement with previous finding that BOLD contrast has superior functional sensitivity than perfusion contrast over short time periods [4,5]. The observation of greater activation in the gradient-echo BOLD data as compared with spin-echo BOLD data in the right motor cortex is also consistent with previous study performed in the absence of susceptibility artifact [22]. In addition, the control acquisitions of the CASL scan show little activation above threshold.

These empirical observations are further supported by measured values of functional SNR illustrated in the column plot of Fig. 3. Statistical analysis using repeated-measures ANOVA was carried out to compare the perfusion and labeled data (absolute value) with gradient-echo EPI, gradient-echo EPI with thin slices and spin-echo EPI data respectively. As can be clearly seen in Fig. 3, both the perfusion and labeled data yield improved functional SNR compared with the BOLD data acquired using gradient-echo EPI methods in the left motor cortex, while gradient-echo BOLD data provide the greatest functional SNR in the unaffected right motor cortex. This leads to significant effects of imaging methods $\times$ brain hemisphere interaction (Perfusion (180 acqs) vs. GE-EPI, $F(1,4) = 11.33$, $p = 0.028$; Perfusion (180 acqs) vs. GE-EPI (thin slice), $F = 7.98$, $p = 0.048$; Perfusion (60 acqs) vs. GE-EPI, $F = 9.36$, $p = 0.038$; Perfusion (60 acqs) vs. GE-EPI (thin- slice), $F = 8.73$, $p = 0.042$; Labeled (180 acqs) vs. GE-EPI, $F = 37.85$, $p = 0.004$; Labeled (180 acqs) vs. GE-EPI (thin slice), $F = 20.54$, $p = 0.011$). Although perfusion experiments require more time to get the same number of sample points as in BOLD data, the current results suggest that perfusion contrast acquired with single-shot spin-echo EPI has superior functional sensitivity as well as efficiency as compared to gradient-echo BOLD contrast in the presence of susceptibility artifacts. Fig. 3 also indicates improved sensitivity in the left motor cortex by using thin slice (3 mm) versus thick slice (6 mm) gradient-echo EPI scans, resulting in a trend in the effect of imaging methods $\times$ brain hemisphere interaction ($F(1,4)$ 61 2.27, $p = 0.206$). When the functional SNRs measured in the perfusion and labeled data (absolute value) are compared with those measured in the spin-echo EPI scans, the perfusion and labeled data of 18 min scan show improved functional sensitivity, resulting in a trend in the main effect of imaging method (Perfusion vs. SE-EPI, $F(1,4) = 3.27$, $p = 0.145$; Labeled vs. SE-EPI, $F = 1.77$, $p = 0.254$). However, no trend of difference is found between the functional SNRs of the perfusion data acquired using 6 min scan and the spin-echo EPI data, suggesting no improvement in imaging efficiency of the current CASL approach as opposed to direct spin-echo EPI methods. Spin-echo EPI scans also show increased sensitivity compared to gradient- echo EPI scans in the left motor cortex, and the imaging methods $\times$ brain hemisphere interaction reaches

significance (SE-EPI vs. GE-EPI, $F(1,4) = 20.77$, $p = 0.010$; SE-EPI vs. GE-EPI (thin slice), $F = 36.08$, $p = 0.004$). In addition, the perfusion and labeled acquisitions of 18 min scan show similar absolute level of functional SNR, with a general trend for greater activation in the left motor area than in the right which is consistent with the handedness of the subjects (5 right-handed).

4. Discussions

The results presented above demonstrate that ASL perfusion images, either with or without subtraction of the control, can be used for activation imaging in regions of high static field inhomogeneity. While the perfusion images generated by pair-wise subtraction generally have relatively low temporal resolution and are suitable for studies of slow variation in brain activity, the labeled acquisition seems to provide an alternative approach for dynamic imaging of brain function in regions of high static susceptibility. Theoretically, the sensitivity of the labeled acquisition should be a factor of square root 2 higher compared with the ASL contrast by skipping the pair-wise subtraction, and this gain in sensitivity could be further increased because the temporal resolution can be doubled. However, this contrast would suffer greater motion artifacts and baseline drift effects as in general BOLD approaches, and it cannot provide absolute CBF quantification. In the present experiments, the labeled acquisitions yield similar level of functional activation as compared to the perfusion data, probably due to the counteracting effect between the inverted inflowing arterial blood and the positive BOLD signal of the spin-echo EPI acquisitions during activation. All together, the labeled and perfusion acquisitions have the potential to provide imaging methodologies in the presence of static susceptibility effects, which may be able to meet a wide spectrum of experimental designs at both short and long time scales even including event-related designs [27,28].

Our data suggest improved functional sensitivity and efficiency of perfusion fMRI as compared with gradient-echo BOLD techniques including thin slices methods in the presence of static field inhomogeneity. However, improved functional sensitivity can also be obtained using alternative gradient-echo BOLD methods with reduced sensitivity to static susceptibility effects, especially those introduced recently such as single-shot Z- shimming [10], reversed SPIRAL [29] etc. which cause no penalty in the temporal resolution of BOLD fMRI. Spin-echo BOLD methods also provide an attractive approach for imaging in brain regions with large static field inhomogeneity especially at high magnetic field [30]. These methods are sensitive to the BOLD contrast at microscopic (capillary) level and are expected to provide more precise spatial localization compared to gradient-echo methods [22]. Our results displaying similar activation patterns in the spin-echo EPI and CASL perfusion data basically support this point of view. For imaging studies of relatively slow effects on brain function, the ASL perfusion contrast would still be advantageous because of its stable noise characteristic over the entire frequency spectrum. As stated, the spin-echo EPI image series have substantial temporal autocorrelation and its power for detecting activation over relatively long time periods is confounded by the low frequency noise as in gradient-echo BOLD data.

Another interesting observation in the current experiment is that the control acquisitions of the CASL scan display little activation (Fig. 2&3) in response to motor cortex stimulation. Since the control acquisitions are theoretically identical to the spin-echo EPI scan except for a longer TR, similar activation patterns are expected to be observed in these two data sets. The reason for the lack of activation in the control acquisitions is not well understood. Inflow effects are less likely since spin-echo methods are much less sensitive to inflow effects than gradient-echo methods [22]. Another explanation might be the control pulse which is an amplitude modulated version of the labeling pulse still has some effects of inverting the arterial blood, which may to certain extent counterbalance the BOLD effects. This speculation is supported by the previously determined efficiency of about 70% for the amplitude modified CASL approach [20].

5. Conclusion

Single-shot spin-echo EPI in combination with multislice CASL at 1.5T has been demonstrated to successfully detect motor cortex activation in the presence of exogenously induced susceptibility artifact. ASL perfusion fMRI with spin-echo acquisitions provides a practical approach for imaging brain function in regions of high static inhomogeneity.

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