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Simultaneous BOLD/perfusion measurement using dual-echo FAIR and UNFAIR: sequence comparison at 1.5T and 3.0T

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Abstract

Functional MRI (fMRI) studies designed for simultaneously measuring Blood Oxygenation Level Dependent (BOLD) and Cerebral Blood Flow (CBF) signal often employ the standard Flow Alternating Inversion Recovery (FAIR) technique. However, some sensitivity is lost in the BOLD data due to inherent T1 relaxation. We sought to minimize the preceding problem by employing a modified UN-inverted FAIR (UNFAIR) technique, which (in theory) should provide identical CBF signal as FAIR with minimal degradation of the BOLD signal. UNFAIR BOLD maps acquired from human subjects ($n = 8$) showed significantly higher mean z-score of ~17% ($p < 0.001$), and number of activated voxels at 1.5T. On the other hand, the corresponding FAIR perfusion maps were superior to the UNFAIR perfusion maps as reflected in a higher mean z-score of ~8% ($p = 0.013$), and number of activated voxels. The reduction in UNFAIR sensitivity for perfusion is attributed to increased motion sensitivity related to its higher background signal, and, T2 related losses from the use of an extra inversion pulse. Data acquired at 3.0T demonstrating similar trends are also presented.

Keywords: FAIR-UNFAIR; Simultaneous BOLD/CBF; 3.0T; FOCI pulses

1. Introduction

Blood Oxygenation Level Dependent (BOLD [1]) related changes during neuronal activity in normal brain are accompanied by increases in local Cerebral Blood Flow (CBF) [2–4]. Recent studies have shown that the simultaneous measurement of BOLD and CBF offers the possibility of separating these phenomena and of estimating changes in cerebral oxygen consumption [2,4]. This has stimulated the development of methods to non-invasively measure these two parameters. Related studies to date have largely employed the Flow-Alternating Inversion-Recovery (IR) FAIR method [5,6]. This approach uses the perfusion weighted image series obtained by subtracting consecutive selective and non-selective IR pairs, while the BOLD response is calculated from the non-selective IR image series. One limitation of this approach is that the calculated BOLD response from FAIR experiments compared to standard gradient-echo techniques is relatively poor. This poor performance is caused by the dependence of the BOLD signal on the background magnetization, which for FAIR, is exponentially attenuated by T1 relaxation processes inherent of the technique. Although T1 effects can be minimized by using longer inversion times, this approach undesirably decreases the temporal resolution with potential degradation in perfusion sensitivity.

In theory, background signal loss in FAIR can be minimized by preceding the FAIR inversion pulse with a non-selective inversion as originally proposed by Helpern *et al* in the UNFAIR technique [7,8]. *In theory*, both FAIR and UNFAIR should provide identical perfusion performance [8]. For the BOLD performance, however, a substantially better signal response is expected with UNFAIR due to its significantly higher background. Whilst recent studies have concentrated on assessing the performance of UNFAIR with respect to perfusion, the potential advantage of this technique over FAIR for simultaneous BOLD and perfusion measurements has not been assessed although it has been

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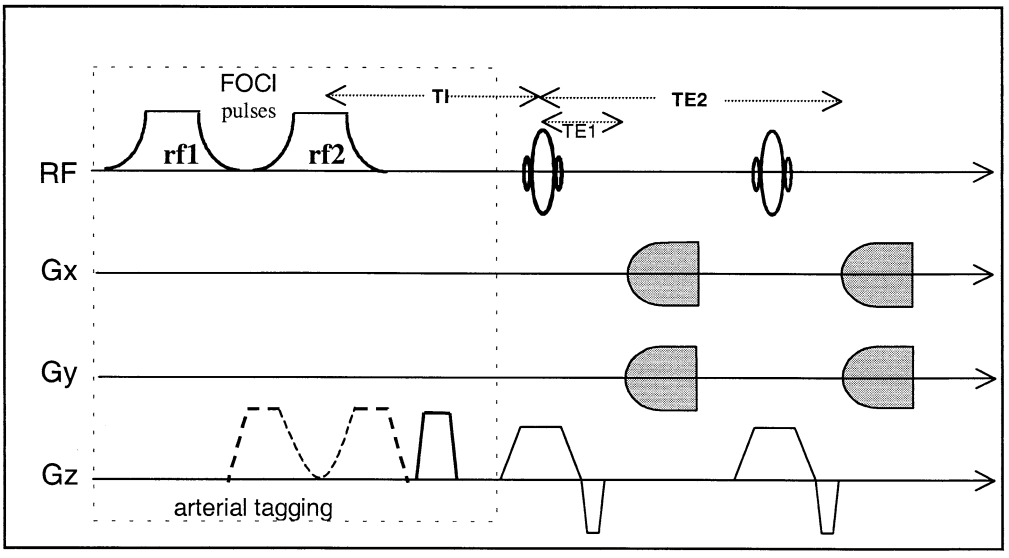

Fig. 1. Schematic representation of the modified FAIR and UNFAIR sequence for simultaneous BOLD and Perfusion measurement. Perfusion signal optimization was achieved by using highly selective FOCI inversions at short TE = 7 ms (echo 1). For optimal BOLD contrast, a second signal (echo 2) was acquired at longer TE of 35 ms. FOCI RF pulses were implemented for optimal perfusion sensitivity.

alluded to in recent studies [8]. Furthermore, most studies to date designed to simultaneously measure perfusion and BOLD have relied on single-echo based techniques [2–4]. The single-echo approach is sub-optimal as the selected echo usually favors either the BOLD or the perfusion signal. For example, selecting the shortest echo time possible will optimize the perfusion signal to noise (SNR) but degrades the BOLD performance. On the other hand, employing long echo times optimizes BOLD performance, this increase reduces perfusion signal and increases the risk of BOLD contamination in the perfusion data. The goal of this study was therefore two-fold: i) to assess the feasibility of both the FAIR and UNFAIR techniques for simultaneous multislice measurement of BOLD and perfusion, and ii) to compare the performances of both sequences. Results obtained from human subjects are presented for both 1.5T and 3.0T systems, otherwise using identical manufacturer scanner hardware.

2. Methods

2.1. BOLD/PERFUSION Sequence

A schematic diagram of the modified FAIR and UNFAIR sequences for simultaneous BOLD and perfusion measurements is shown in Fig. 1. The sequence consists of two main sections: i) an inversion and ii) a double-echo readout section. For improved perfusion sensitivity, we replaced the widely used conventional hyperbolic secant (HS) [9] inversion RF a highly spatially selective C-FOCI inversion pulse [10–12]. The pulse length, bandwidth, μ, and scaling factor for the pulse were 16.38 ms, 2.6 KHz, 7, and 10.5, respectively. Readout RF pulse was 5 lobe sinc-function with a bandwidth of 3 KHz. Additional perfusion sensitivity was achieved by implementing short (22 ms) trapezoidal spiral waveforms for rapid readout of the first echo that was used to calculate the perfusion images. The latter substantially minimizes the amount of T2* weighting (hence the BOLD weighting) in the perfusion data. The details on the design and implementation of this pulse have been extensively described elsewhere [12]. For optimum BOLD performance, a second readout with longer variable TE was implemented to enhance T2* weighting and BOLD signal (Fig. 1).

For BOLD and perfusion measurements with UNFAIR, both inversion RF pulses (rf1 and rf2) are switched on. The amplitude of the selective inversion gradient is alternated between ‘OFF’ and ‘ON’ for the non-selective (BOLD acquisitions) and selective flow-weighted acquisitions. For FAIR based acquisitions, only one inversion RF (rf1) is used, and the amplitude of the selective inversion gradient alternated between zero and its desired value for non flow- and flow-weighted acquisitions. The desired gradient value is determined by the width of the slab in the selective inversion FAIR experiment.

2.2. Experimental

Studies were performed on 1.5T and 3.0T MR systems (General Electric, Milwaukee, WI) using a quadrature head coil transceiver. Both systems are equipped with shielded gradients, and capable of 40mT/m with a slew rate of 120T/m/s although only around 50% of the maximum value

was used. All clinical studies were performed as part of an approved Intramural Review Board Protocol at the National Institutes of Health.

The UNFAIR/FAIR hybrid sequence was used to simultaneously acquire multi-slice BOLD/perfusion images (five axial slices) from normal human brain (age range 23–30 yrs) at 1.5T (n = 8) and 3.0T (n = 5). Slice thickness was 5 mm. Since the total imaging volume was 25 mm (i.e. 5slices*5 mm), an inversion width of the same size should (ideally) be utilized for the selective inversion RF pulse in order to minimize the transit time of blood to the imaging volume. However, setting the inversion width equal to the imaging slab width causes interaction between the pulses and results in contamination from static tissue. Based on previous calibration experiments [12], we used selective inversion width of 50 mm for perfusion-weighted acquisitions. For non-perfusion weighted acquisitions, the FOCI gradient amplitude was basically set to zero. Mild bipolar gradients ($b \sim 3$ s/mm^2) were applied within the TE interval to selectively reduce vascular contributions in the perfusion images. Structural high-resolution spin-echo T1 weighted images (for overlaying fMRI maps) were acquired at the same spatial location as the functional images. Parameters were 256 × 256 matrix, TE 16 ms, TR 600 ms, FOV 24 cm, NEX 2, slice thickness 5 mm.

Functional MRI experiments with primary sensorimotor cortex stimulation were performed with the FAIR and UNFAIR techniques at 1.5T and 3.0T. For both sequences, we performed 80 interleaved selective and non-selective repetitions over a period of four minutes. Subjects were asked to perform a sequential finger-tapping task, cued by a visual stimulus projected onto a screen and paced at 1 Hz. All subject were strongly right handed and all performed the task with the dominant hand. The experimental paradigm consisted of four repetitive cycles (ON-OFF) during which the subjects switched between rest and finger tapping every 30 seconds. Total scan time for each run was 4 minutes. Specific timing parameters included: relaxation (recovery) delay = 1.45 s, TI = 1.3 s, TE1/TE2 = 7/35 ms, FOV = 24 cm, matrix = 64 × 64.

2.3. Data analysis

BOLD and perfusion fMRI data were analyzed off-line on a Sun Sparc workstation using the Medx fMRI software (Sensor Systems, VA), and using programs written in-house in the IDL programming language (Research Systems, Boulder, CO). Each FAIR/UNFAIR series (total of 80 repetitions) yielded 40 selective/non-selective short-TE (7 ms) and long-TE (35 ms) images. To obtain perfusion data, the non-selective short TE acquisitions were subtracted from the selective (flow-weighted) short-TE image in the time series (*vice-versa for UNFAIR*). The resultant time-series of perfusion-weighted images were used to compute statistical activation maps. For BOLD maps, we used the non-selective long-TE raw images from each time series as they contain minimal perfusion contamination.

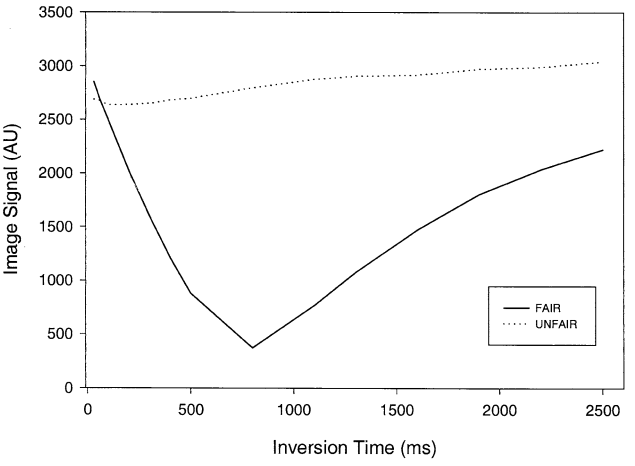

Fig. 2. Variation of raw FAIR and UNFAIR raw image signal (in absolute mode) from normal human brain as a function of TI. The value at TI = 0 correspond to the raw signal immediately following inversion. The absolute signal for FAIR with just one inversion RF initially decreases as the magnetization recovers towards zero, and then gradually increases past the null point. UNFAIR with two back-to-back inversions ensures the initially inverted magnetization is immediately restored almost to its equilibrium state. Slight increase with TI is due to saturation effects since TR < 5*T1. These plots clearly demonstrate the far superior raw signal inherent in the UNFAIR technique, which enhances its BOLD performance.

Image registration in MEDx was performed using the Automated Image Registration program, which sought to minimize the sampling coefficient of variation of ratios of voxel values between the first raw image and each successive raw image. Data sets were chosen for their high quality as demonstrated by single subject motion plots; a graph representing the X, Y, Z displacement of the center of intensity from each timepoint, so giving an estimate for head motion, was evaluated for all the timeseries; only data with a head motion estimate less than 0.5 mm were included in further analysis. Voxel signal intensities were globally normalized to account for variability in image-by-image intensity and then detrended in a polynomial first order fashion. The fMRI time series were analyzed on a pixel-by-pixel basis using statistical *Student t*-test for significance. After correction for multiple comparisons, the use of a threshold Z score > 2.8 (>3.5 for BOLD maps) guaranteed a significance level for $P < 0.002$ (<0.0002 for BOLD maps) in the perfusion activation maps at both fields. Statistical z-maps were overlaid onto co-registered high-resolution T1 weighted images. Based on anatomical landmarks, specific ROIs were drawn on the T1 images, encompassing premotor and sensorimotor cortices of the dominant (left) hemisphere; only activated voxels within the ROIs were considered for further analysis, which included: i) mean number of activated voxels, ii) mean z-score values and the mean time course of those voxels, percent CBF and percent BOLD signal changes.

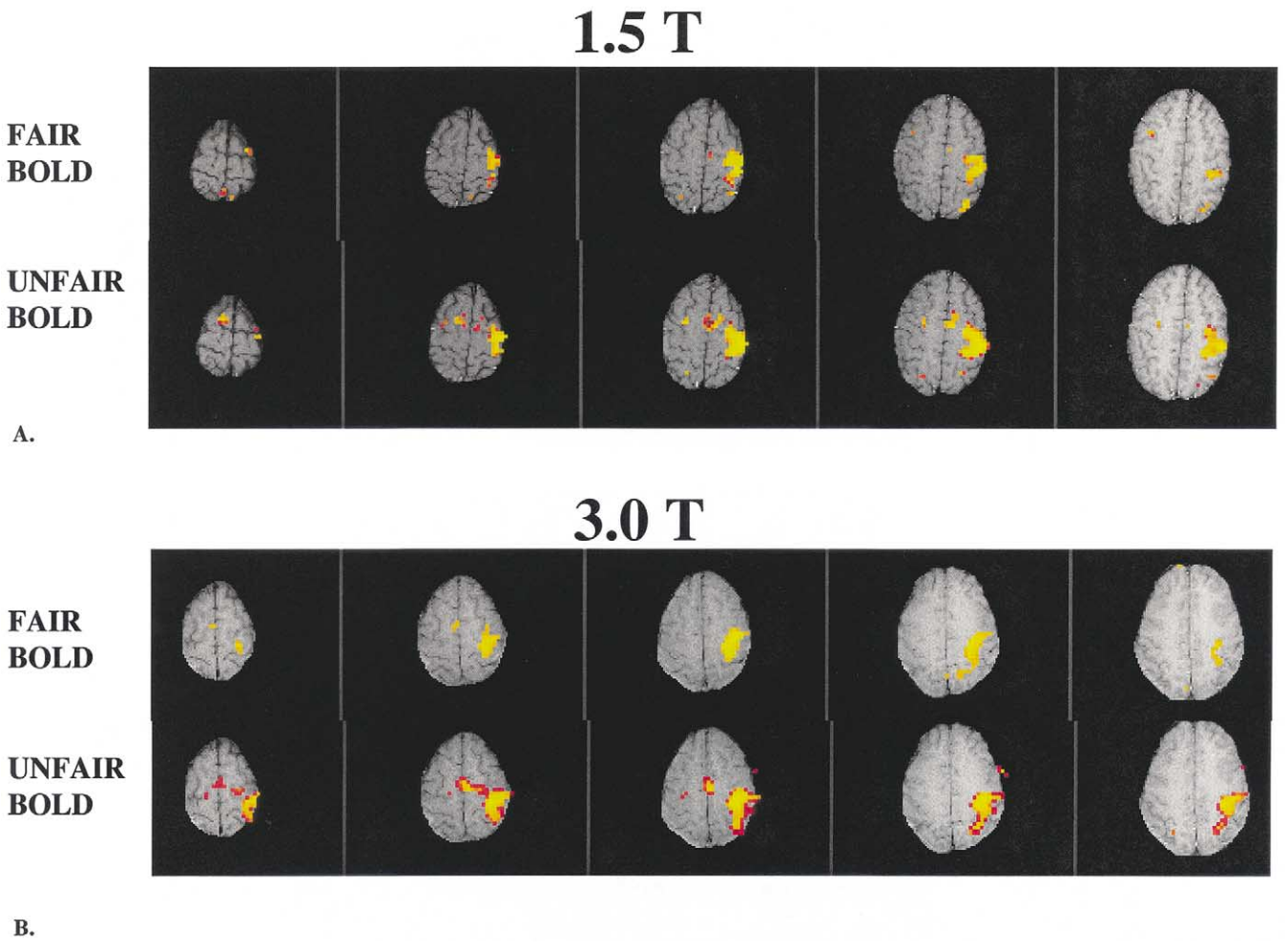

Fig. 3. (A) FAIR and (B) UNFAIR BOLD activation maps overlaid on high-resolution T1W images from a subject obtained at 1.5T and 3.0T are shown. The size of the activated region is significantly larger for the UNFAIR BOLD acquisition at both fields.

3. Results

A comparison of the relative background signal intensities for FAIR and UNFAIR is shown in Fig. 2: FAIR and UNFAIR raw background signal (in absolute mode) obtained from gray matter in one subject is plotted versus TI. Because the FAIR technique incorporates just one inversion tagging pulse, the initially inverted signal (at TI = 0ms) can be seen to decrease as it recovers towards the null point, following which the signal continues to increase. UNFAIR on the other hand incorporates two back-to-back inversion tagging pulses resulting in 360° flip of the magnetization at TI ~ 0ms. As shown in Fig. 2 this flip results in a significantly higher UNFAIR background signal for the entire TI range.

Typical FAIR and UNFAIR BOLD activation maps obtained from single subjects at 1.5T and at 3.0T are shown in Fig. 3A–B. The maps were overlaid on high resolution T1 weighted images for display. The corresponding perfusion activation maps obtained with each technique are shown in Fig. 4A–B. The mean number (±SD) of BOLD related activated voxels using UNFAIR at 1.5T was 136 ± 59 (231 ± 43 at 3.0T). The corresponding data obtained during the same experimental setting with the FAIR technique were 77 ± 48 (192 ± 97 at 3.0T). The latter data is plotted in Fig. 5A and clearly shows significantly better BOLD performance for UNFAIR. The superior UNFAIR BOLD performance is further reflected by significantly higher mean z-scores (5.22 ± 0.53 at 1.5 T; 5.6 ± 0.49 at 3.0 T) at both fields (see Fig. 5B), when compared to FAIR (4.48 ± 0.3 at 1.5 T; 5.13 ± 0.6 at 3.0 T). For CBF, the UNFAIR technique showed a reduction in performance compared to FAIR. In this case, the mean number of perfusion-related activated voxels for FAIR (53 ± 38 at 1.5T; 195 ± 68 at 3.0T) was higher (see Fig. 5C) than UNFAIR (36 ± 31 at 1.5T; 127 ± 85 at 3.0T). As shown in Fig. 5D, these improved performance of FAIR-CBF was again reflected in higher mean z-scores (3.75 ± 0.45 at 1.5 T; 4.7 ± 0.39 at 3.0 T) compared to UNFAIR-CBF (3.46 ± 0.54 at 1.5 T; 4.16 ± 0.44 at 3.0 T). Compared to FAIR, the preceding z-scores at 1.5T pertain to approximately 17% (~10% at 3.0T) increase in BOLD performance for UN-

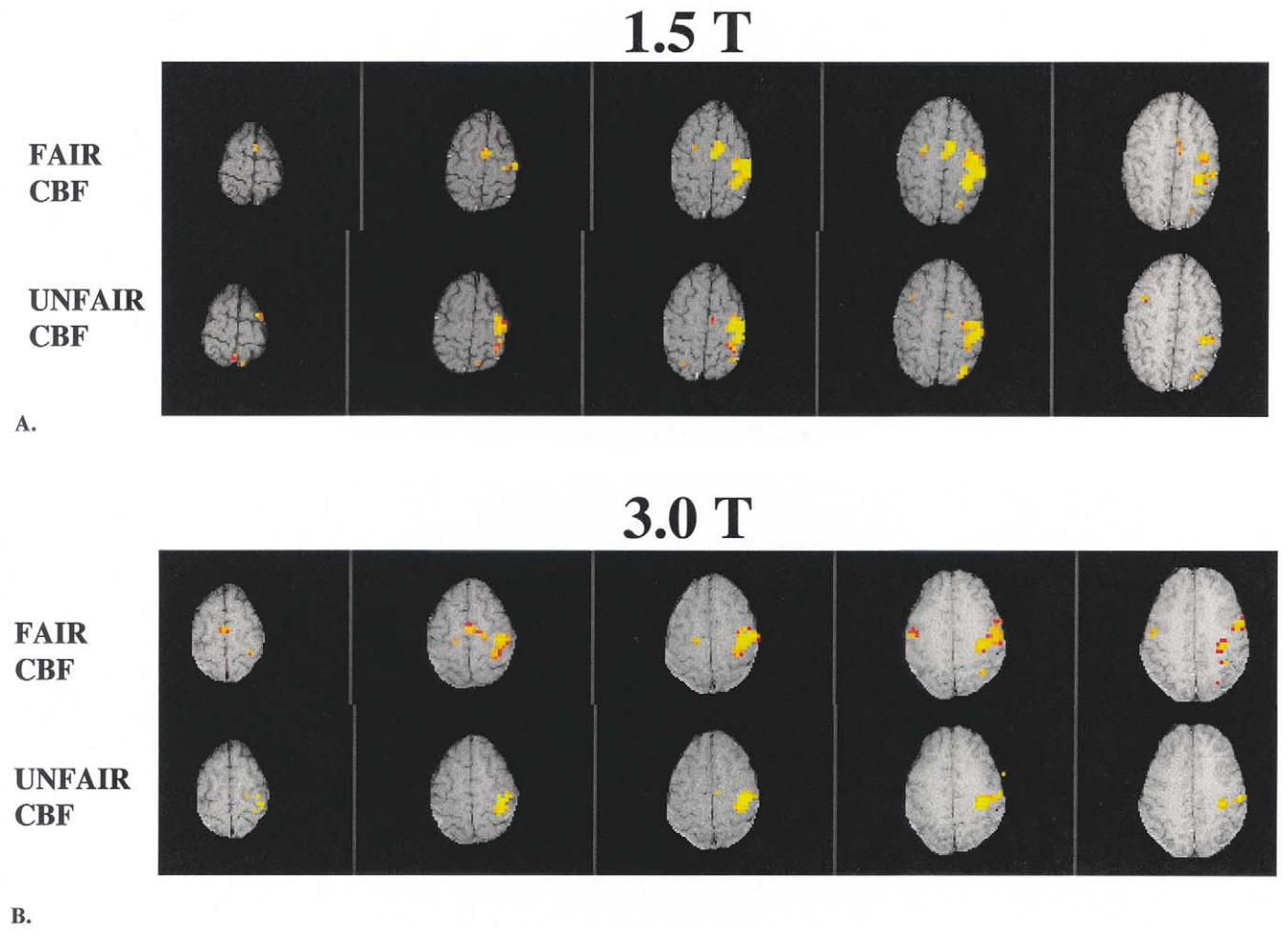

Fig. 4. (A) FAIR and (B) UNFAIR corresponding perfusion activation maps at 1.5T and 3.0T are shown. A greater extent of the activation blobs is clearly evident in the FAIR images. Results are obtained from subjects in the same experimental session.

FAIR and a corresponding reduction of about −8% (about −12% at 3.0T) for the perfusion values.

4. Discussion

This study focused on the evaluation and comparison of two methods: FAIR and UNFAIR for simultaneous measurement of BOLD and perfusion. During the task condition, brain activation in the primary sensorimotor cortex was observed in all subjects and extended through a number of slices. As shown in Figs. 3 and 4, the activation pattern for both techniques corresponded well with the expected brain activation in the hand area. This observation was true for all volunteers studied at both field strengths. However, slight differences in spatial location between BOLD and perfusion images are clearly evident in both FAIR and UNFAIR techniques. In fact, BOLD images display larger activation clusters, mostly in the region of cerebral sulci. In addition, activation of the supplementary motor cortex was clearly depicted in five subjects. The UNFAIR technique clearly manifested superior BOLD performance at both 1.5T and 3.0T in all volunteers. This improved performance was expected in view of its superior background signal as demonstrated in Fig. 2. Utilizing two back-to-back inversion pulses ensures higher UNFAIR background signal that improves the BOLD performance. FAIR on the other hand utilizes an inversion-recovery based approach. The resultant T1 relaxation inherent to this method substantially attenuates the background magnetization and thereby compromises the BOLD performance. Improvement in the FAIR-BOLD can be obtained by increasing the TI between the inversion and readout pulse to allow further recovery of the magnetization. In practice, this approach is usually avoided due to degradation of temporal resolution.

The perfusion-based activation maps reveal better performance for FAIR as reflected in higher z-scores and greater extent of activation. The extent of perfusion activation is of course dependent on the baseline perfusion SNR. In theory, both techniques should manifest identical perfusion sensitivity for the same sequence parameters as applied in this comparative study. However, our current implemen-

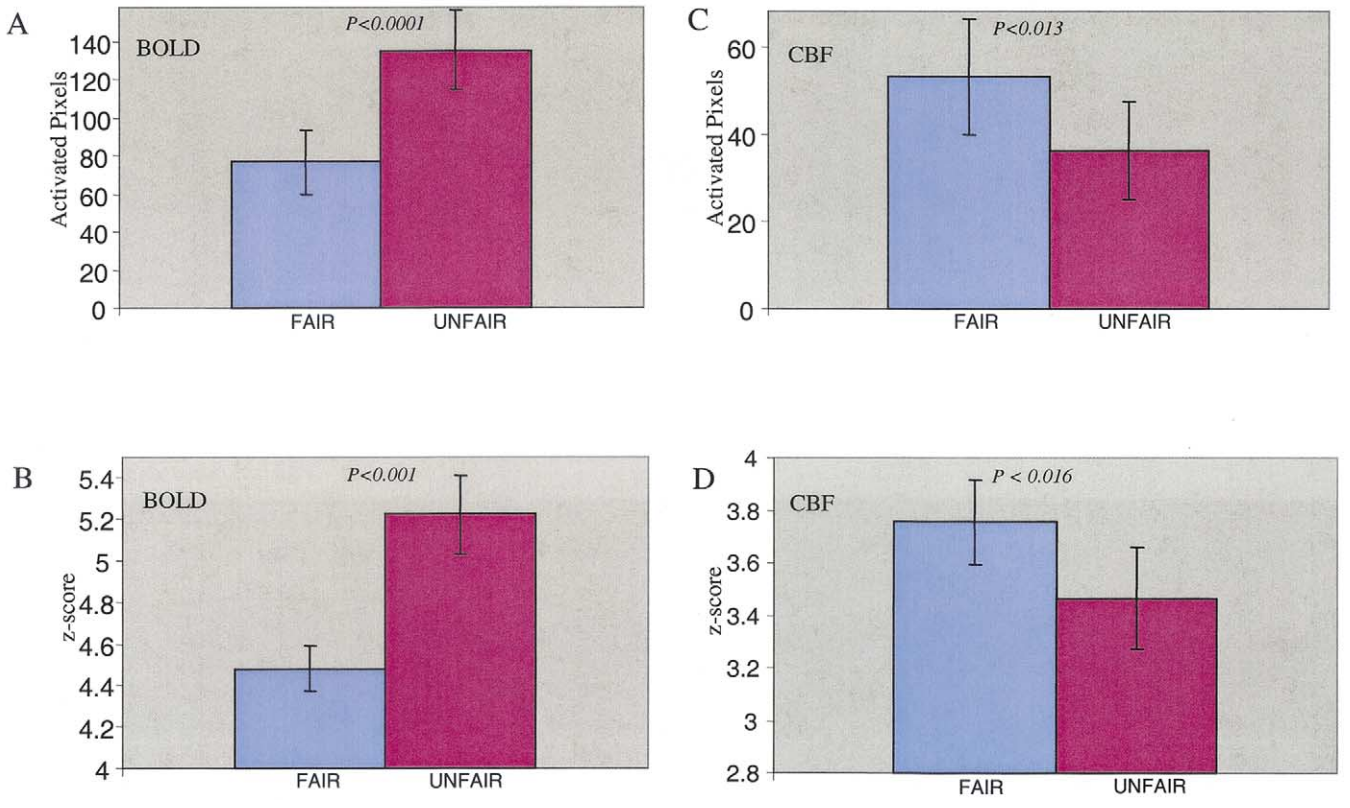

Fig. 5. (A) Mean number of BOLD activated pixels obtained for both techniques at 1.5T. (B) Comparison of the average z-score for the FAIR and UNFAIR BOLD. (C) Comparison of the mean number of activated perfusion pixels obtained with the FAIR and UNFAIR at 1.5T. (D) Plot of average z-score obtained with both techniques. Results are based on data collected at 1.5T.

tation of FAIR has consistently yielded a slightly higher CBF signal-to-noise ratio than UNFAIR. An analysis of signal from gray matter revealed the FAIR perfusion signal to be ~4% better at 1.5T than UNFAIR, and by ~7% at 3.0T. These differences may be partly explained by additional T2 losses suffered in UNFAIR due to the presence of an additional inversion pulse [13]. Further evidence of the latter effect stems from higher perfusion losses at 3.0T where T2 values are shorter. We used relatively long FOCI pulses (16.24 ms) to allow reduced radio frequency (RF) bandwidths in order to retain their excellent profiles while circumventing RF power deposition problems with the UNFAIR technique at higher fields (≥3.0T). However, minimizing of the signal losses suffered from the extra inversion RF in UNFAIR would partly reduce T2 dependent CBF losses. If indeed the T2 dependent losses are found to significantly contributing to the reduced UNFAIR CBF SNR, then these losses can be further minimized by using shorter FOCI RF pulses with higher bandwidths. Alternatively, even shorter pulses length combination might entail implementing a very short (~100 us) rectangular non-selective pulse in conjunction with one FOCI selective inversion pulse. These effects are currently being investigated and will be reported in future communications.

Additional UNFAIR perfusion related losses might arise due to its higher background signal, which increases the potential for larger subtraction errors in the presence of motion. The latter effects have recently been well demonstrated in separate communications by Frank *et al* [14], and Duyn *et al*. [15].

As already mentioned, the FAIR BOLD performance can be improved by using a longer inversion delay (TI) to allow further growth of the static magnetization. However, this approach poses two potential problems: lengthening the TI will increase TR which reduces the temporal resolution; secondly, longer than optimal TI (~1.5s at 1.5T) will attenuate the perfusion signal. Based on the preceding remarks, it is fair to state that there is not much room for improving the FAIR related BOLD performance. Nonetheless, selection of either of these methods for the simultaneous BOLD/CBF measurement will depend on the specific experimental goals and available hardware resources. Our TI selection of ~1.3s in this study represents a compromise designed to provide reasonable temporal resolution while yielding acceptable BOLD and perfusion SNR.

Our results suggest that FAIR is suitable for studies for which CBF measurement is the primary goal. For higher sensitivity BOLD mapping, the UNFAIR technique provides superior performance with a loss in perfusion sensitivity that is significantly less than the FAIR related BOLD loss. In addition, other considerations may have to be taken into account, e.g. RF power deposition for FAIR is about

40% lower at 3.0T indicating that this method may therefore be more appropriate for higher fields (>3.0T). In addition, one can take advantage of the T1 attenuation effects inherent to FAIR to reduce the background signal from both tissue and cerebrospinal fluid (CSF). This attenuation can potentially minimize CSF contamination [3] and reduce motion-induced background noise [14,15]. Both techniques are limited to restricted coverage of the brain, mostly because of physiological reasons related to the blood transit time through the image.

5. Concluding remarks

We have presented FAIR and UNFAIR sequences comparison for the simultaneous multislice measurement of BOLD and perfusion by incorporating a dual-echo spiral-based acquisition scheme, and FOCI inversions for efficient spin-tagging. The feasibility of both techniques was demonstrated and compared at two clinically relevant field strengths in human brain. Our current data reveals that FAIR provides better perfusion maps than UNFAIR. However, the corresponding BOLD performance is compromised by its inherently lower background tissue signal. The dual-echo UNFAIR sequence on the other hand provides excellent BOLD performance with a comparatively small reduction in perfusion signal. It is technically feasible to improve the performance of both techniques, particularly the UNFAIR method, by reducing the overall length of the inversion pre-pulses. In essence, each technique has its own advantages and disadvantages and method selection should be dictated by experimental circumstances.

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