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Technical Note

Three-dimensional acquisition of cerebral blood volume and flow responses during functional stimulation in a single scan

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ABSTRACT

In addition to the BOLD scan, quantitative functional MRI studies require measurement of both cerebral blood volume (CBV) and flow (CBF) dynamics. The ability to detect CBV and CBF responses in a single additional scan would shorten the total scan time and reduce temporal variations. Several approaches for simultaneous CBV and CBF measurement during functional MRI experiments have been proposed in two-dimensional (2D) mode covering one to three slices in one repetition time (TR). Here, we extended the principles from previous work and present a three-dimensional (3D) whole-brain MRI approach that combines the vascular-space-occupancy (VASO) and flow-sensitive alternating inversion recovery (FAIR) arterial spin labeling (ASL) techniques, allowing the measurement of CBV and CBF dynamics, respectively, in a single scan. 3D acquisitions are complicated for such a scan combination as the time to null blood signal during a steady state needs to be known. We estimated this using Bloch simulations and demonstrate that the resulting 3D acquisition can detect activation patterns and relative signal changes of quality comparable to that of the original separate scans. The same was found for temporal signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR). This approach provides improved acquisition efficiency when both CBV and CBF responses need to be monitored during a functional task.

Introduction

Cerebral blood volume (CBV) and cerebral blood flow (CBF) are two fundamental parameters in brain physiology. For instance, CBV and CBF responses during functional stimulation are required to quantify cerebral metabolic rate of oxygen ($CMRO_2$) dynamics in most quantitative blood-oxygenation-level-dependent (BOLD) approaches, such as the calibrated BOLD approach (Blockley et al., 2013; Davis et al., 1998; Hoge et al., 1999; Lin et al., 2008, 2009, 2011) and other models (Donahue et al., 2009a; Hua et al., 2011c; Huber et al., 2013; Lin et al., 2008, 2009, 2011; Lu et al., 2004b; Uh et al., 2011). In the calibrated BOLD method, $CMRO_2$ change is estimated from BOLD and CBF changes measured during separate vascular and neuronal tasks, where the vascular stimulation is used as the calibration condition for BOLD signals. A different BOLD model proposed by Lu and van Zijl (Lu et al., 2004b), and later used and refined by others, estimates $CMRO_2$ change from separately measured BOLD, CBF and CBV responses during neuronal tasks (no vascular task is involved in this model). Accurate information about CBF and CBV dynamics is critical in both models. In the calibrated BOLD method, the CBV change is often derived from the measured CBF change using Grubbs equation with a constant exponent (Grubb et al., 1974), which is commonly assumed to be identical in vascular and neuronal tasks. However, recent studies have shown that this power-law relationship between CBF and CBV can vary substantially under different conditions (Blockley et al., 2009; Chen and Pike, 2009; Donahue et al., 2009d; Hua et al., 2010, 2011c; Ito et al., 2001; Lin et al., 2008; Rostrup et al., 2005). (Lin et al., 2008) demonstrated that using dynamic CBV measurements improves the accuracy for estimating $CMRO_2$ changes during functional stimulations, as compared with calculating CBV changes from CBF measurements and the Grubb's equation with an assumed constant. Therefore, it is important to measure both CBV and CBF dynamics to capture microvascular status alterations during functional stimulations.

The ability to detect CBV and CBF responses in one single scan is desirable as it will not only shorten total scan duration, but also reduce temporal variation due to factors such as subject motion, task performance, and physiologic changes between scans. The arterial spin labeling (ASL) technique can be used to measure CBF and CBV changes in the same scan by acquiring images at multiple post-labeling delays (Alsop et al., 2014; Brookes et al., 2007; Donahue et al., 2006b; Francis et al., 2008). However, the scan time of this method is relatively long

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compared to the typical temporal resolution in functional studies. A number of MRI methods have been developed to measure CBV or CBF *separately*. For instance, CBV and CBF changes can be *separately* measured with vascular-space-occupancy (VASO) MRI (Lu et al., 2003) and flow-sensitive alternating inversion recovery (FAIR) arterial spin labeling (ASL) MRI (Kim, 1995; Kwong et al., 1995), respectively. Based on the T1 difference between blood and brain tissue, VASO MRI employs a spatially nonselective inversion pulse to invert both blood and tissue signals and acquires MR images at the time when blood signal recovers to zero (nulled), which can be used to calculate CBV changes (Lu et al., 2003). In FAIR ASL, an inversion pulse with and without spatially selective gradient is applied to produce the tagged and control images, respectively, from which CBF maps can be deduced (Kim, 1995; Kwong et al., 1995). Thus, a common feature in the pulse sequences of both methods is that an inversion pulse is exploited to perturb the blood water spins before image acquisition. The major difference, on the other hand, is that VASO images are always acquired at the blood nulling inversion time (TI), while FAIR ASL images need to be acquired at a much longer post-labeling delay (TI $\approx$ 1.5–2 s) (Alsop and Detre, 1996; Donahue et al., 2006a; Silva et al., 1997; Ye et al., 1997) to allow water exchange in the capillary bed to take place. Therefore, it is possible to combine VASO and FAIR MRI to share the same inversion pulse and acquire CBV and CBF weighted images at two different TIs in a single scan. Based on this principle (Yang et al., 2004), previously devised an elegant technique for concurrent measurement of CBV, CBF and BOLD responses during functional stimulation. This method has recently been implemented on a 7 T human MRI scanner by (Krieger et al., 2013). Another method for simultaneous measurement of CBV and CBF is the double-echo FAIR (DEFAIR) approach proposed by (Thomas et al., 2001), in which CBF is measured with FAIR ASL and CBV is determined based on the different T_2 values calculated from the double echoes in the intra- and extravascular compartments. Both techniques were implemented in two-dimensional (2D) mode to acquire a single slice (Lin et al., 2008, 2009, 2011; Yang et al., 2004) or three slices (Gu et al., 2005) in one repetition time (TR).

Here, we propose a 3D MRI approach to measure CBV and CBF responses during functional stimulation in one single scan. It exploits the same principle as (Yang et al., 2004), which combines VASO and FAIR MRI with a common inversion pulse. A single-shot 3D fast gradient echo (GRE, also known as turbo field echo, TFE or TurboFLASH) sequence was used for image acquisition at two TIs. In addition, the magnetization pathways were simulated. The 3D VASO–FAIR sequence was implemented on a 3 T human MRI scanner, and functional experiments with visual stimulation were performed on healthy volunteers to compare the data of the combined sequence and original separate scans in order to validate the accuracy of the combined scan.

Materials and methods

Pulse sequence and simulations

Fig. 1 illustrates the combined 3D VASO–FAIR pulse sequence. Similar to the FAIR sequence, interleaving slab-selective (SS) and non-selective (NS) inversion preparation was employed. In each of the SS and NS scans, two image acquisition modules are deployed after the inversion at different TIs: TI_1 (blood nulling) and TI_2. CBV-weighted VASO images are obtained at TI_1 after NS inversion when the blood signal is nulled, and FAIR images are collected at a later time TI_2 in both SS and NS scans. These two FAIR components are combined later to obtain the CBF-weighted signals. A single-shot 3D fast GRE sequence with centric (low-high) phase encoding profile was employed in all imaging modules. This readout has recently been used in VASO MRI, which showed minimal geometrical distortion and signal dropouts, low power deposition due to small flip angles, and negligible T_2^* contamination in VASO fMRI because of the very short echo time (TE) used (Hua et al., 2013a).

A magnetization transfer (MT) prepulse was applied immediately before the inversion pulses to prepare a smaller tissue magnetization, thus expediting the inversion recovery process so that the detectable tissue signals, and thus their signal-to-noise ratios (SNRs) are enhanced (Hua et al., 2009a, 2013a). When using moderate irradiation power and durations, and a frequency offset sufficiently far away from water resonance (40 ppm or more), the MT prepulse has been shown to have negligible effect on blood signal so that the same blood nulling TI can be used for VASO (Balaban et al., 1991; Hua et al., 2009a, 2013a; Wolff and Balaban, 1989).

A spatially nonselective saturation (90° RF pulse followed by spoiler gradients) was deployed immediately after the second imaging module to set all residual magnetizations (blood and tissue) to zero. The purpose for this post-saturation module is two-fold. First, it suppresses the inflow effect due to non-steady-state blood spins in VASO MRI by establishing a steady state for all blood spins entering the RF transmit coil after the first repetition time (TR) (Hua et al., 2013a; Lu, 2008; Wu et al., 2007a). Second, it ensures that blood spins in and outside

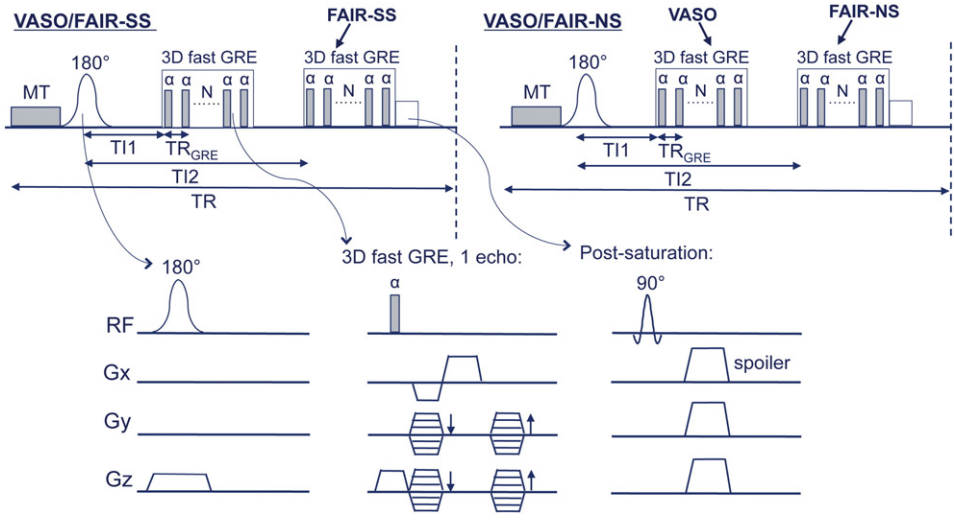

Fig. 1. Pulse sequence of the combined 3D VASO–FAIR approach. A pair of interleaving slice-selective (SS) and nonselective (NS) scans are shown. A magnetization transfer (MT) prepulse is added before the adiabatic FOCI inversion pulses. The imaging module used here is a 3D fast GRE readout for both VASO and FAIR ASL images, in which VASO signal is acquired at blood nulling time TI_1 and ASL signal at time TI_2. A post-saturation module comprising a non-selective 90° saturation pulse and spoiler gradients is applied immediately after the FAIR ASL readout.