# Enhancing endogenous CBV-weighted fMRI contrast at 9.4 T: a VASO study with slab-selective inversion-recovery

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**Introduction** The blood oxygenation level dependent (BOLD) contrast is inadequate for high-resolution functional mapping due to large signal contributions within and surrounding the large draining veins. A spin-echo (SE) sequence can reduce the signal from large veins but the spatial specificity is still inferior to CBV-weighted fMRI technique using contrast agent injection; the latter has been shown in animal models to be specific to the middle cortical layer where the neural activity is the highest [1,2]. An endogenous CBV-based technique, vascular space occupancy-dependent (VASO), has been proposed and applied in human fMRI [3]. However, its spatial specificity has yet to be examined at high spatial resolution, and its sensitivity at high magnetic field is low. In a preliminary study, we recently observed VASO-weighted functional contrast at 9.4 T using a slab-selective (SS) inversion recovery sequence, and found that the spatial characteristics, even with the presence of significant BOLD signal contamination, is similar to that of the CBV-weighted fMRI with contrast agent [4]. In this work, SS-VASO experiments were performed with very short TE to suppress the BOLD signal, and its temporal, spatial characteristics and the contrast to noise ratio (CNR) are compared with SE-BOLD.

**Materials and methods** All MRI experiments were performed on a 9.4 T/31 cm Varian MRI system. Cats were anesthetized and maintained under normal physiological conditions. An actively detuned two-coil system was used for the experiments: a Helmholtz coil for inversion and a surface coil for excitation and reception. The imaging parameters were: $2 \times 2$ cm$^2$ FOV, 2 mm slice thickness, and $64 \times 64$ matrix size. For the SS-VASO experiment, a 2-segmented inversion-recovery GE-EPI was used with TR = 2.5 s per segment, and TI/TE = 1.05 s/3.3 ms. The thickness of the inversion slab was 6 cm, slightly larger than the size of the animal's head. For SE-BOLD experiment, a 2-segmented double spin-echo EPI sequence was used with adiabatic full and half-passage pulses. TR = 2.5 s per segment, and TE = 40 ms. The binocular visual stimuli consisted of a high contrast drifting square wave grating. The stimulation paradigm was 10 control (50 s), 8 stimulation (40 s), and 20 control images. The SS-VASO and SE-BOLD experiments were interleaved, and ~25 data sets were averaged for each experiment to improve the signal to noise ratio (SNR). To detect the activation, student's *t*-test maps were calculated with a *t*-value threshold of 2.0 and minimal cluster size of 3 pixels. A ROI was drawn on the anatomical image at the middle of the cortex for temporal and CNR analysis. For the CNR calculation, the signal change between the stimulated state and the pre-stimulation control state is divided by the standard deviation of the control state.

**Results and discussions** A non-selective (NS) inversion recovery sequence is used for the original VASO (or referred as NS-VASO), the contrast of which relies on the difference in the $T_1$ of blood and tissue water. The steady state longitudinal magnetizations of the blood and tissue water at TI (before the excitation pulse) are: $M_{z,ss}=M_0\cdot[1-2\cdot\exp(-TI/T_1)+\exp(-TR/T_1)]$. VASO images are acquired at a TI when the magnetization of blood water is relaxing across zero. Because the blood and tissue nulling point is usually close, the remaining signal from the tissue is small when the blood signal is nulled. Currently, VASO studies are mostly performed at magnetic fields of 1.5 and 3 T. The detection of VASO signal at higher magnetic field is difficult because: (1) The stronger BOLD signal at higher field counteracts and reduces the sensitivity of the negative VASO signal. (2) The relative difference between the $T_1$ of blood and tissue water decreases at higher fields, reducing the VASO contrast. (3) The longer $T_1$ values of blood and tissue water at higher fields reduce the steady state signal for $TR<5T_1$. The dashed lines in Fig. 1 show the calculated baseline signal intensities (proportional to SNR) when the blood signal is nulled. The $T_1$ of blood (tissue) water used are 1.35, 1.63 and 2.2 s (1.0, 1.3 and 1.9 s) at 1.5, 3 and 9.4 T, respectively [5,6]. For a short TR of 2.5 s, the remaining tissue signal at 9.4 T is merely 3% of fully relaxed signal ($S_0$). Even if the BOLD contribution in the VASO signal were ignored, an estimation of the VASO CNR would be 15 to 20 times lower than the CNR of a SE-BOLD experiment at 9.4 T, assuming typical values for the functional CBV and $R_2$ changes [2].

The VASO contrast can be enhanced by using a slab-selective inversion pulse instead of the non-selective one [4]. For this method to work, the slab thickness has to be optimzied such that the fresh (uninverted) blood water spins from outside of the inversion slab flow to and fills the vasculature within the imaging slice only after each data acquisition but before the next inversion pulse. This optimal condition can be written as: $TI < t_{transit} < TR$, where $t_{transit}$ is the transit time of the fresh blood flow from the outside edge of the inversion slab to the imaging slice. Under this condition, The magnetization of blood water before each excitation pulse becomes $M_0\cdot[1-2\cdot\exp(-TI/T_1)]$, whereas the tissue magnetization is still $M_{z,ss}$. Thus, the contrast between the blood and tissue water is enhanced compared to the original VASO method. The solid lines in Fig. 1 show the calculated baseline signal intensity (or SNR) when the blood signals are nulled for the SS-VASO approach. Compared to the NS-VASO, the SNR increases with decreasing TR, more significantly for higher fields. The SNR of SS-VASO is ~12 times that of the NS-VASO at TR = 2.5 s, suggesting a ~ ½ -1 times CNR compared to SE-BOLD. This was confirmed in our SS-VASO experiments, where a TI of 1.05 s, shorter than the blood nulling point (~ 1.5 s), was chosen to better satisfy the optimal condition ($TI < t_{transit} < TR$). Nevetheless, the averaged CNR at the middle cortical ROI was found to be 1.14 and 2.34 for the SS-VASO and SE-BOLD, respectively. In the activation maps, the negatively activated pixels of the SS-VASO (Fig. 2A) appeared mostly at the middle of the visual cortex, similar to the CBV-weighted maps obtained using contrast agent methods [2], while the activation of SE-BOLD is much more diffusive. On average, the total number of activated pixels is 126 and 389 for the SS-VASO and SE-BOLD, respectively. Note also for the TR/TI used in our study, the CSF signal is nulled in the SS-VASO image (Fig. 2A). The time courses at the middle cortical ROI are shown in Fig. 2C, where a post-stimulus signal undershoot is observed for the SE-BOLD, while the SS-VASO signal returns to the baseline faster, similar to the observation of the original VASO [1].

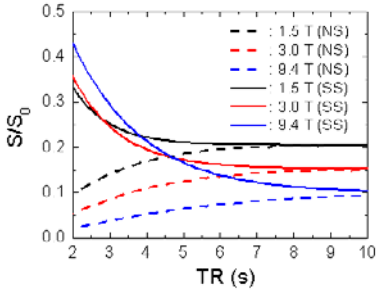


**Fig 1.** Normalized baseline signal intensity as a function of TR at corresponding blood nulling points for VASO methods with non-selective (dashed lines) and slab-selective (solid lines) inversions.

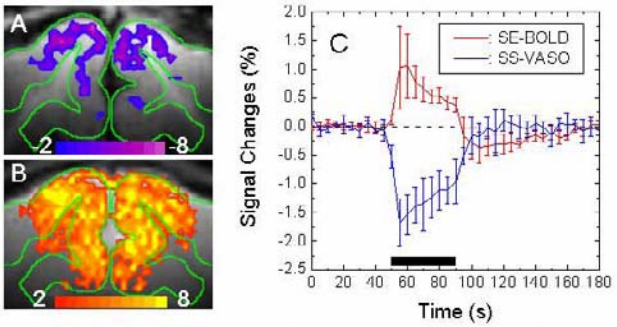


**Fig 2.** The student's *t*-test map of a representative animal for SS-VASO (A) and SE-BOLD (B). The green tours indicate the gray matter area of the visual cortex. (C) The averaged time courses (n=4) of SE-BOLD and SS-VASO signal changes from a middle cortical ROI.

Our results demonstrate that SS-VASO functional contrast can be obtained at 9.4 T. The source of the SS-VASO response is more complex than the original VASO. It is highly dependent on the slab thickness and the blood flow velocity, as well as the TR and TI values. It may also be influenced by CBF if the in-flow blood water did not fully replace the in-plane water. Nevertheless, this method shows a better special specificity than the SE-BOLD, with about half the CNR at 9.4 T. The CNR of SS-VASO is significantly enhanced compared to the original VASO, especially at short TRs and high fields. Therefore, it may be a useful tool for high resolution functional brain mapping in humans.

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**References:** [1] Lu H et al., *Magn Reson Med* 2004; 52:1060-1068. [2] Zhao F et al., *Neuroimage* 2006; 30:1149-1160. [3] Lu H et al., *Magn Reson Med* 2003; 50: 263-274. [4] Jin T and Kim S-G, *Proceedings of the 28th IEEE-EMBS conference*, p. 25-28. [5] Lu H et al., *Magn Reson Med* 2005; 53:808. [6] Tsekos NV et al., *Magn Reson Med* 1998 ; 39:564-573.