Functional CBV Contrast Revealed by Diffusion Weighted Stimulated-Echo Imaging

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Introduction:
BOLD based functional MRI is often limited in spatial specificity because of the vascular spread of the oxygenation based signal changes. Recent optical imaging and animal MRI studies have shown that changes in the cerebral blood volume (CBV) are more closely tied to the small vessel networks and thus more accurate in spatial localization of brain function[1-3]. These techniques, however, tend to be invasive or require the injection of contrast agents, limiting their practical use in human subjects. A non-invasive method of obtaining CBV contrast, based on a black-blood technique employing inversion recovery, has been reported recently[4-5]. A similar intra-vascular signal void has been shown by a diffusion weighting technique, in that the diffusion weighting gradients can be employed to dephase the intra-vascular moving proton pools and remove their signal contributions[6]. This effect can be achieved in large vessels with relatively small diffusion weighting gradients (low *b* factors), as demonstrated in earlier results[7]. Increasing the strength of the *b* factors would eliminate the signal from smaller vessels and, under optimal conditions and with sufficient *b* factor strength, the signal from all vessels can be removed. At this point, stimulus related signal changes are negative and likely due to local changes in cerebral blood volume (CBV), which accompany functional activation, and their effect on local diffusion[8-9]. However, positive BOLD signal changes, overlapping with the negative CBV related signal changes, present a confound to accurate measurement of functional CBV. In this study we apply a methodology to reduce the effect of BOLD signal changes. Instead of a typical gradient echo BOLD sequence with diffusion gradients, as previously used, here we employ a stimulated echo sequence. A stimulated echo, along with a relatively short effective TE and diffusion weighting, will help eliminate any BOLD contamination within the signal. We apply a series of *b* factors to a visual activation experiment and measure the dependent changes in both the positive and negative activation to estimate individual contributions from the BOLD and CBV mechanisms. It is hoped that this new non-invasive method for CBV imaging could be useful in human brain imaging to achieve more specific functional localization.

Methods:
Five subjects participated in this study after providing informed consent. Visual cortex activation was induced using periods of activation consisting of a flashing, rotating checkerboard and periods of rest consisting of only a fixation cross at the center of the visual field. The rest and activation conditions each lasted 30 seconds, alternating over a 3 min acquisition. The study was performed on a GE 3T Signa system. Isotropic diffusion weighting was used in a stimulated echo sequence with a single-shot spiral readout to acquire 5 slices parallel to the calcarine sulcus. In order to accommodate the diffusion gradients, the TR was set to 2 sec and the TE was set to minimal at 20 ms. The *b* factors used were 2, 100, 200, 300, 400, 500, and 900 s/mm^2. The raw data was smoothed temporally with a low-pass filter to reduce the effects of noise and respiration related fluctuations especially apparent at high *b* factors. For each *b* factor, activation maps displaying both positive and negative BOLD signal changes were determined using a multiple regression algorithm. The number of active voxels was determined by counting those voxels passing a threshold within a region-of-interest containing the visual cortex. The time courses of both positive and negative activations were also determined.

Results and Discussion:
All subjects still showed residual positive BOLD activation in the low *b* factor condition, which quickly diminished with the application of diffusion weighting gradients. However, the total amount of negative activation was not reduced as significantly as in the positive case. Representative activation maps with a threshold of z=|3.0| are overlaid onto an anatomical image for one subject in Figure 1 showing the extensive positive activation (red areas) at b=2 and the extent of negative activation (blue areas) at b=300. Figure 2 shows the average time course of negative activation across subjects. It can be seen that increasing *b* factor generally increases the relative negative change in signal, indicating a more coherent and better tuned response. Characterizing the signal dependence on the *b* factors would help determine optimal parameters such that peak sensitivity would occur predominantly in the capillary networks, thereby improving the spatial specificity.

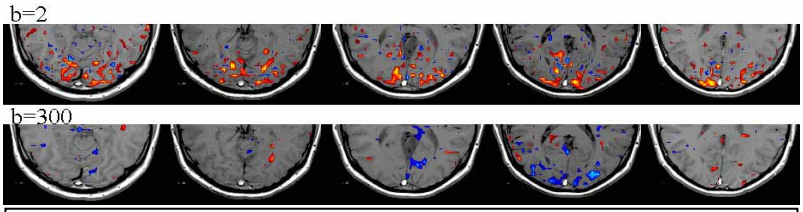

Fig. 1: Activation with threshold z=|3.0|, showing positive (red) and negative (blue) activations for a single subject at b=2 (top) and b=300 s/mm2 (bottom).

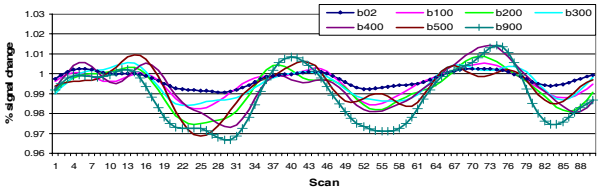

Fig 2: The negative signal response averaged across subjects for each b factor used.

Conclusions: We have shown that the use of a stimulated echo sequence with short TE can greatly reduce the positive BOLD signal influence to provide better determination of CBV related negative signal changes under progressive diffusion weighting. The methodology presented here would allow specific parameter optimization to reach peak sensitivity in the capillaries, and provide improved spatial co-localization of the functional activity to the neuronal activity.

References and Acknowledgment:
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