Differentiating sensitivity of post-stimulus undershoot under diffusion weighting: implication of signal origins

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Introduction: Functional MRI largely depends on measurements of positive BOLD responses to a stimulus. It is generally known that this BOLD response can be spatially diffuse, and not specific to the site of activation. Recent reports have indicated that the post-stimulus signal undershoot commonly observed as part of the BOLD hemodynamic response may provide means to improve spatial localization of neuronal activity relative to the positive BOLD response (1). However, current research is still under debate as to the source and nature of this undershoot, for instance whether it is due to metabolic or vascular changes (2,3,4). In this current report, we hope to add evidence to the characterization of the BOLD undershoot by examining the response to moderate diffusion weighting. It has been shown that this flow-sensitive diffusion weighting strategy can be used to produce differentiation between signal arising from intravascular and extravascular sources, and further, from large vessels and capillaries (5).

Methods: A total of six subjects were scanned after giving informed consent as approved by the Duke University Medical Center IRB. Scans were performed at 4T using a gradient echo spiral imaging sequence with FOV=24cm, TE=40ms, and a 128x128 imaging matrix. Three diffusion weighting b factors of 1, 63, and 125 s/mm^2 were applied in a ramped series such that within a 1.5 sec TR, a volume at each b-factor was acquired. Eight slices were acquired in a total of 210 volumes (70 at each b-factor) while the subject observed a visual stimulus consisting of a flashing, rotating checkerboard. The stimulus alternated with a control condition of simply a fixation cross. Each stimulus block lasted 45 seconds, and after an initial fixation period, the task and fixation pairs were repeated three times. A total of six runs were acquired for each subject. The runs were averaged, and a multiple linear regression was performed on data from each b-factor separately to determine areas of activation. The maps from each b-factor were examined and those voxels producing activation in all three maps were analyzed. Time courses of activation were determined from these voxels, and then the stimulus blocks were averaged to determine a shortened time course. Since each b-factor is acquired at a slightly different position in time, the time courses were shifted temporally to align properly. The initial fixation period provided a baseline to determine the percent change in signal, as well as a static measure of the apparent diffusion coefficient (ADC). Active voxels were separated into two groups: those which showed a significant change (reduction by > 20%) in the undershoot signal under diffusion weighting and those which did not. The BOLD signal in these groups was averaged and analyzed, as well as their respective static ADCs.

Results and Discussion: All subjects showed extensive BOLD activation at each b-factor, and the majority of voxels show post-stimulus undershoot with differentiation related to diffusion weighting. Figure 1a shows the average time course for voxels showing a reduction in BOLD undershoot as a result of the diffusion weighting. The time course in Fig 1b does not show significant change of the undershoot signal. Both time courses exhibit a reduction in the positive BOLD signal as a result of the diffusion weighting, corresponding with previous reports (5,6). The differentiating sensitivity of the positive BOLD response and post-stimulus undershoot under diffusion weighting is indicative of different vascular sources for these two signals. As such, the respective spatial regions corresponding to these two groups were identified. Figure 2 shows slices from a representative subject in which the blue overlay represent areas showing no change in undershoot (including those originally with no undershoot) and the red areas indicate a reduction of the undershoot. It can be seen that these two groups exhibit distinct spatial distributions, with the area showing no change in undershoot being more extensive. To further focus on the contributing sources of these signals, an analysis of the static ADC values was carried out. It was found that regions showing significant reduction of undershoot under diffusion weighting have higher ADC values, (2.0 x 10^{-3}), suggesting that they are more inclusive of intravascular signal from the large veins. The reduction of the positive BOLD response from these regions is also likely from the intravascular components of these large vessels. On the other hand, regions with unaffected undershoot have lower ADC values (1.3 x 10^{-3}), suggesting their extravascular and small vessel origins. The reduction in positive BOLD signal in this area is likely from the intravascular contribution of the vasculature (e.g. venules) that does not exhibit undershoot, thus not contributing to alter its response characteristics. As such, we conclude that diffusion weighting can differentiate the sources of the BOLD post-stimulus undershoot, and help determine the vascular origins and spatial distribution of the undershoot signal.

References: 1: Zhao et al, NeuroImage 34, 2007; 2: Buxton et al, MRM 39, 1998; 3: Lu et al, JCBFM, 24, 2004; 4: Yacoub et al, JCBFM 26, 2006; 5: Song et al, MRM 35, 1996; 6: Michelich et al, NMR Biomed 19, 2006. This study is, in part, supported by NIH grant (NS 50329).

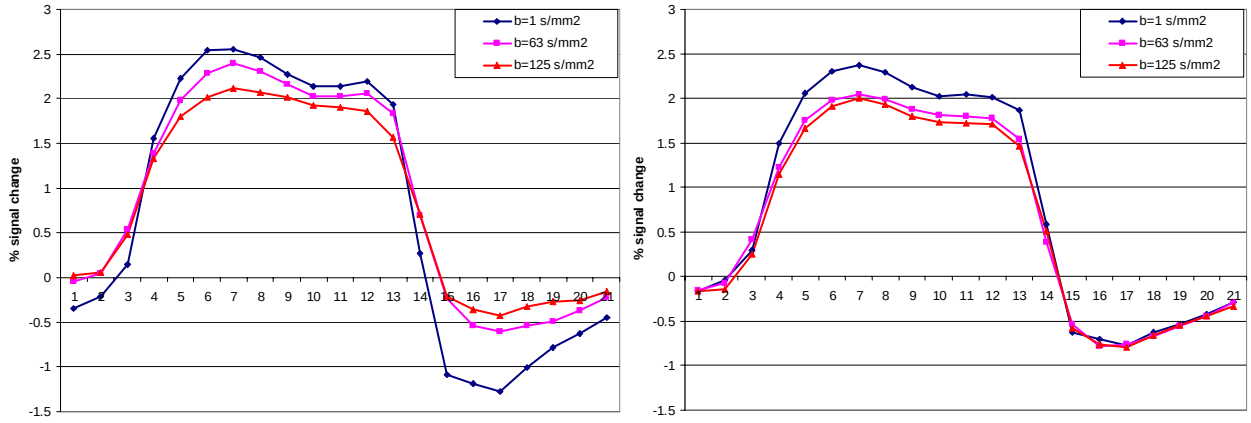

Figure 1: Time course of voxels showing A) reduced undershoot with increased diffusion weighting, and B) no affect on undershoot.

Figure 2: Blue areas represent no change in undershoot signal; red areas are those in which a reduction of undershoot occurs.