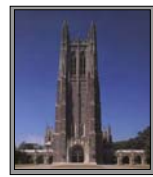




# Compartmental Selectivity of Diffusion Weighted BOLD fMRI at 4T

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## 1 INTRODUCTION

Conventional blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) techniques provide a non-invasive tool to monitor brain activity through the vascular response to changes in neuronal activity. While these techniques provide valuable tools to clinicians and researchers, contributions from large vessels distant from the site of neuronal activity limit the specificity of conventional gradient-echo BOLD imaging. A number of approaches have been introduced to reduce the contribution of large vessels in BOLD fMRI. Low levels of diffusion weighting (DW) have been used to suppress intravascular contributions to BOLD contrast [1,2]. Spin-echo acquisition has been used to selectively suppress the BOLD signal from the area surrounding large vessels. Imaging at higher field strengths can also help to suppress vascular contributions due to the shortened  $T_2^*$  of blood. The goal of this research was to systematically investigate the combined effect of these approaches to BOLD small vessel localization through an analysis of compartmental selectivity for the purposes of protocol design and development of new functional imaging methods.

## 2 METHODS

### Stimuli and Experimental Design

- Nineteen 20 second blocks alternated between a fixation cross and an 8 Hz reversing black and white radial checkerboard. Each acquisition began and ended with a fixation block.
- Data for all exams were acquired from the same healthy subject recruited under an IRB approved protocol.

### Imaging Parameters

- 4T MR imaging system with 40 mT/m, 150 T/m/s gradients. (GE Healthcare, Milwaukee, WI)

#### Experiment A: Gradient Echo – High DW

- Diffusion weighted single-shot gradient-echo spiral imaging
- 64 x 64, TR = 1 s, TE = 68.6 ms, Flip Angle = 68°, FOV = 24 cm, 380 temporal volumes
- 7 Coronal slices (5 mm thick with 5 mm spacing between slices)
- Diffusion weightings: 0, 102, 202, 302, 402, 502, 602, 702, 1570 sec/mm<sup>2</sup>
- Diffusion direction: All three axes simultaneously
- Volume transmit/receive head coil (Nova Medical, Wakefield, MA)

#### Common Parameters for Spin Echo Acquisitions:

- Diffusion weighted single-shot spin-echo spiral imaging
- 64 x 64, TR = 1 s, FOV = 24 cm, 380 temporal volumes
- 6 Coronal slices (5 mm thick with 5 mm spacing between slices)
- Volume transmit head coil and four-channel visual array receive coil (Nova Medical)

#### Experiment B: Spin Echo – High DW

- Diffusion weightings: 0, 79, 158, 237, 316, 394, 473, 552, 1238 sec/mm<sup>2</sup>, TE = 69.6 ms
- Diffusion direction: All three axes simultaneously

#### Experiment C: Spin Echo – Medium DW, one direction

- Diffusion weightings: 0, 26, 51, 76, 101, 126, 150, 175, 200 sec/mm<sup>2</sup>, TE = 41.7 ms
- Diffusion direction: All three axes simultaneously

#### Experiment D: Spin Echo – Medium DW, Approx. isotropic, flow-moment nulled

- Diffusion weightings: 0, 25, 50, 75, 99, 124, 149, 174, 199 sec/mm<sup>2</sup>, TE = 87.5 ms
- Diffusion direction: Approximately isotropic, flow-moment nulled

#### Experiment E: Spin Echo – Low DW

- Diffusion weightings: 0, 7, 14, 21, 28, 35, 42, 49, 56 sec/mm<sup>2</sup>, TE = 55.5 ms
- Diffusion direction: Isotropic, flow-moment nulled

### Data Processing

Data were analyzed using custom software in MATLAB (Mathworks, Natick, MA). Student's  $t$ -tests were performed between the signals measured during the fixation and checkerboard blocks, assuming a six second hemodynamic delay, to generate functional maps for each diffusion weighting. Data ten seconds prior to and 29 seconds after stimulus onset were averaged to generate a mean time course for each diffusion weighting. An ROI was drawn on the non-diffusion weighted functional maps to include active voxels ( $t > 10$  for gradient-echo,  $t > 5$  for spin-echo) within the occipital lobe for the spin-echo and gradient-echo data. An ROI averaged time course was then calculated from the mean epoch for each diffusion weighting as shown in Figures 1-5. Another ROI was drawn to include only voxels in the occipital lobe that were active ( $t > 3.6$ ) at all diffusion weighting. The ROI averaged time course for this ROI is shown in Figure 6.

## 3 RESULTS

As shown in Figure 1, the percent signal change during activation was highest with no diffusion weighting and was attenuated to a consistent value for all levels of diffusion weighting applied. Figure 2 shows a similar behavior with the spin-echo data, however, the overall magnitudes of the responses are smaller.

Additional investigation of moderate diffusion weightings shown in Figure 3 revealed that diffusion weightings of 25 sec/mm<sup>2</sup> and higher achieved consistent percent signal changes. Isotropic flow-moment nulled diffusion weighting yielded the same pattern in Figures 4 and 5. Figure 6 shows the mean signal time course for only those voxels which were active at all diffusion weightings. The 7 sec/mm<sup>2</sup> time course shows a larger percent signal change than the higher diffusion weightings.

## 4 DISCUSSION

Initial investigation of the response of the BOLD signal to a range of diffusion weightings revealed that increasing the diffusion weighting beyond a moderate level, perhaps even as low as 80 sec/mm<sup>2</sup>, has no effect on the magnitude of the activation observed. These results were consistent between spin-echo and gradient-echo acquisitions. Based on these initial findings, three additional spin-echo experiments were performed to study diffusion weightings less than 200 sec/mm<sup>2</sup> to help identify the minimum diffusion weighting necessary to suppress large vessel intravascular contributions. Results from diffusion weighting incremented from 0 to 200 sec/mm<sup>2</sup> (Figure 3), show that the activation was attenuated to a fixed level for diffusion weighting as low as 25 sec/mm<sup>2</sup>.

The first three experiments used diffusion weighting on all three axes simultaneously to minimize the echo time. This scheme generates a large flow moment, therefore data were collected using approximately isotropic, flow-moment nulled diffusion weighting to exclude this as a potential source of the effect. Figure 4 shows that the effect remained with the new diffusion weighting scheme.

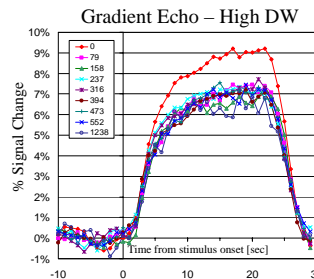


Figure 1: Experiment A mean signal time course in  $b=0$  active voxels for each DW

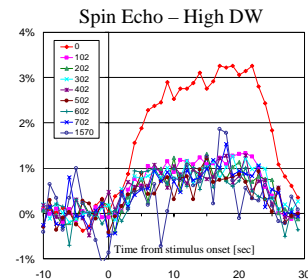


Figure 2: Experiment B mean signal time course in  $b=0$  active voxels for each DW

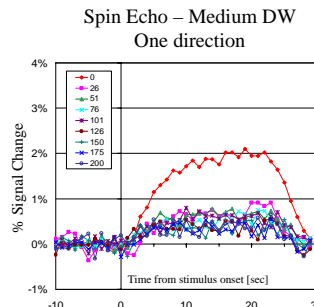


Figure 3: Experiment C mean signal time course in  $b=0$  active voxels for each DW

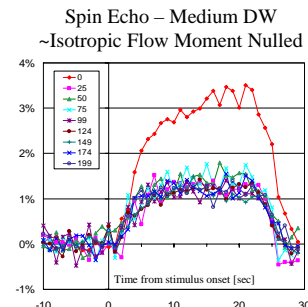


Figure 4: Experiment D mean signal time course in  $b=0$  active voxels for each DW

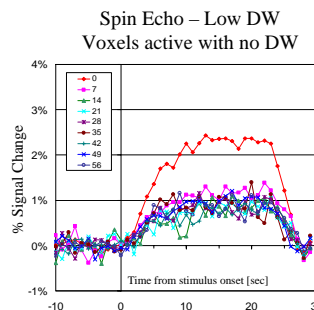


Figure 5: Experiment E mean signal time course in  $b=0$  active voxels for each DW

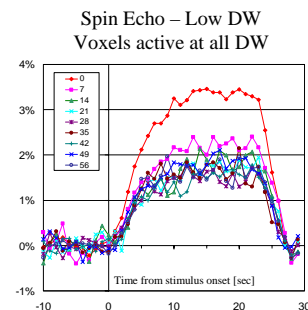


Figure 6: Experiment E mean signal time course in voxels active at all DW for each DW

An experiment was then conducted to finely sample very low  $b$ -values. As seen in Figure 5, there is significant attenuation even at 7 sec/mm<sup>2</sup>. Data were also analyzed to include only those voxels which were active ( $t < 3.6$ ) at all diffusion weightings to prevent a bias towards any particular diffusion weighting. The results in Figure 6 suggest that diffusion weightings greater than 14 sec/mm<sup>2</sup> do not further attenuate the magnitude of the activation. Diffusion weighting decreases the SNR of the data thus reducing the detectability of the activation. Therefore using the minimum diffusion weighting necessary to achieve the desired proton mobility effect will maximize functional sensitivity.

To better understand the effects of the methods employed in this experiment on the signal contributions from various proton pools within the brain, we propose considering the brain from the perspective of four different proton pools: large vessel intravascular (IVL), small vessel intravascular (IVS), extravascular near large vessels (EVL) and extravascular near small vessels (EVS). For functional localization, we are most interested in the small vessel signals (IVS & EVS) since this signal will be closest to the source of neuronal activity. The large vessel signal (IVL & EVL) will likely contain signal from a larger area of cortex and be displaced from the actual area of neuronal activity thus reducing the specificity and accuracy of the functional activation maps.

The shortened  $T_2^*$  of blood at higher field strengths attenuates the intravascular signal raising the possibility that diffusion weighting is unnecessary. However, the observed reduction in the magnitude of the activation resulting from diffusion weighting demonstrates that some residual intravascular signal remains even at 4T, confirming the value of diffusion weighting strategies.

While diffusion weighting can be used to suppress the IVL signal, the EVL signal will remain in gradient-echo acquisitions, even with very strong diffusion gradients (Figure 1). Spin-echo acquisition can be used to refocus the field inhomogeneities near large vessels but not small vessels thus suppressing the EVL signal. The large difference in the diffusion-weighted signal between spin-echo and gradient-echo acquisitions (~1.5% vs. 7%) demonstrates the significance of the EVL effect present in gradient-echo imaging.

Through the application of diffusion-weighting gradients in spin-echo acquisition, we can suppress the signal from IVL, IVS, and EVL. The cost of this approach, however, is reduced BOLD sensitivity as the desired IVS is suppressed leaving only the EVS signal component. The small size of remaining signal (Figures 2-6) demonstrates the need to minimize diffusion weighting to maximize detectability. Contrast mechanisms that preserve both IVS and EVS may give better detectability without sacrificing specificity. Future research into alternate contrast mechanisms, such as very low diffusion weighting or ADC contrast may yield a contrast mechanism that is selectively sensitive to the signal in and around small vessels.

### ACKNOWLEDGEMENTS & REFERENCES

- Duke University Program in Neural Analysis (<http://www.duke.edu/~ch/ProgNeu/index.htm>) – CRM
- Duke-UNC Brain Imaging and Analysis Center (<http://www.biacc.duke.edu>)
- Duke Center for Advanced MR Development (<http://camrd4.mc.duke.edu>)
- The spiral pulse sequence used in this experiment is based on a sequence developed by Gary Glover, Ph.D. at Stanford University.
- [1] Song, AW, et al., *Mag Res Med*, 35, 1996. [2] Weingarten CAP, et al., *NMR in Biomed*, 11, 1998.