Assessment of hemodynamic effects in functional diffusion-weighted MRI

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Introduction: Recently, diffusion-weighted MRI methods to detect stimulus induced neuronal activation have been proposed.[1,2] These techniques are expected to be less susceptible to hemodynamic changes. Though efforts are underway to understand the physiological origins of the observed diffusion changes in the brain[3], there have been indications that in studies focusing on gray matter (GM), it would be hard to separate vascular and extra-vascular changes, even at high b-values (2400s/mm^2)[4]. But, given that vasculature is less pronounced in white matter (WM), and that WM is more directionally organized, diffusion related protocols may be gainfully employed there. One such functional DTI (fDTI) study in WM has been reported[2]. But, there is little known about the possible vascular effects in WM on such fDTI measurements. This study aimed at testing the possible vascular contributions in fDTI in WM and GM with relatively high b-value and with differing diffusion-weighting directions. This is important in order to distinguish hemodynamic responses from possible extra-vascular responses to stimuli. We chose carbogen (5%CO_2+ 95%O_2) challenge, which induces vasodilation without neuronal alterations, as a paradigm to test the influence of hemodynamic changes on diffusion measurements.

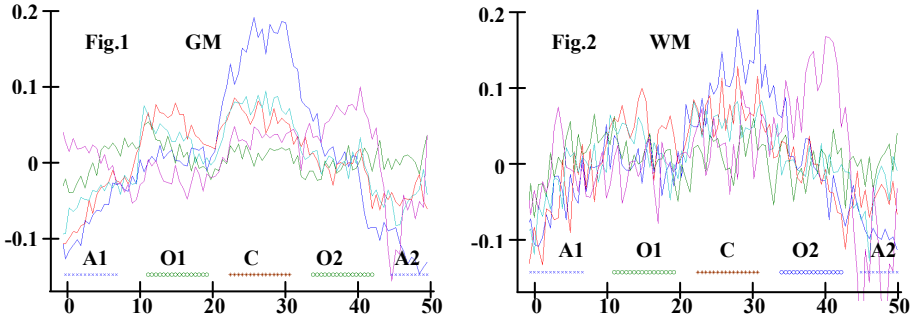
Methods: Adult male Sprague-Dawley rats (N=5) were anesthetized by mechanical ventilation with 1-2% isoflurane in air/O_2 (2:1) and were subjected to a carbogen challenge, wherein the respiratory setting was changed in the format Air->100% O_2->Carbogen->100% O_2->Air respectively, in that order. Each respiratory condition persisted for 10min. During the scan, anesthesia was maintained at 1% isoflurane and Pancoronium bromide, 1.0mg/kg/h, was administered i.v., to minimize motion. DTI data was collected with b=1750s/mm^2 (4 Shot Multi-slice EPI, TR:1s, TE:35ms, FOV:32x32x17mm *k*-matrix:64x64x17, Averages:1, δ=10ms, Δ=16.2ms, Gdiff=21G/cm, half sine shaped lobes). Diffusion weighting (DW) was performed in 6 electrostatic point-set directions[5]. It was periodically varied, with a period of 8 sets (b=0 s/mm^2 at the start and in the middle). In total, 752 3-d DW datasets were obtained during the experiment, which spanned about 50min.

Analysis: No motion correction had to be performed on the data. The complex data were phased, boosting the SNR, and letting the noise distribution remain Gaussian. WM and GM masks were prepared for each subject by thresholding Fractional Anisotropy (FA) calculated from the average diffusion tensor dataset. Voxels with FA>0.6 were grouped as WM and voxels with FA<0.2 were grouped as GM. A mask of noise only voxels was also prepared for each subject. Data from different DW directions were separated and non DW data were discarded from further analysis. The time series in each DW direction was de-trended voxelwise to correct for linear signal drifts. Since relative changes in signal values during different respiration conditions were of interest, but not those changes that had structural origins, the time series in each DW direction were normalized voxelwise by subtracting the mean value. Also, to normalize for variations across animals, each time series was divided by the noise standard deviation (σ) estimated from noise-only voxels. A single σ was used for all DW datasets, and across tissue types in each animal.

Results: Fig.1 and 2 show the mean waveforms obtained from GM and WM normalized data of different animals averaged across all DW directions. We observed that vascular changes induced by carbogen challenge apparently do persist in GM and WM at b=1750s/mm^2. To test the significance of these changes, the normalized data were partitioned into 5 time periods of 8min each where the respiratory settings were held constant (indicated in Figs.1 and 2 as A1, O1, C, O2 and A2. Notations: A:Air, O:Oxygen C:Carbogen). For every voxel, for every DW direction, data in this period were averaged. Thus, data changes at each voxel could be summarized with 30 values (5 respiratory conditions under 6 DW directions). Every value in the statistics table could thus be associated with a tissue type (tt), respiratory condition (resp), diffusion direction (dir), voxel number (vox). Since we were only interested in the carbogen challenge, we present results comparing signal changes between O1 and C only. However, the conclusions were found to be the same even if we included the other respiratory conditions. First, two-way ANOVA was performed by pooling data from all DW directions and we looked for changes in mean signal values with changing respiration condition. Results from this analysis are shown in Fig.3 and indicate that there were robust changes in mean values. Paired t-test between oxygen and carbogen pools in WM also showed significance with p<0.001. But, these analyses do not account for the repeated nature of the measurements, and the presence of an additional factor, namely diffusion direction. To address these, we performed a repeated ANOVA (ezANOVA, in R) with multiple factors (dir and resp were within voxel factors and tt was the between voxel factor). Results (summarized in Table.1) again showed that factor resp, which is of primary interest, turned out to be very significant, meaning that with changing respiration condition, the mean signal values differed in a robust manner between oxygen and carbogen, suggesting that even at b=1750s/mm^2, signal changes persist in WM. We also confirmed that group balancing (GM voxels=17561 WM voxels=1656) was not an issue. Apart from significant changes due to respiration, the test also found significant differences among tissue types. Fig.4 summarizes the interaction among all factors along with Fisher's Least Significant Difference bounds. The fact that we observe similar signal changes in different DW directions in both tissue types, though less pronounced in WM, may indicate a common underlying physiological mechanism.

Discussion: This study demonstrates that hemodynamic changes can significantly contribute to diffusion weighted signal, even at high b-values, in GM as well as WM. Our findings further underscore the complications of interpreting 'functional' DW MRI data and emphasize the need to carefully differentiate between neuronal and vascular effects

References: 1) Le Bihan et al., PNAS 103 (21), pp8263-8268, 2006 2) Mandl et al., Plos One, 3 (11), e3631, 2008. 3) Le Bihan, Phys.Med.Biol, 52(2007) R57-R90 4) Miller et al., PNAS 104 (52), pp20967-20972, 2007. 5) Cook et. al., JMRI 25:1051-1058 (2007)



Signal changes, averaged over all normalized DW time courses. X-axis, Time (min).

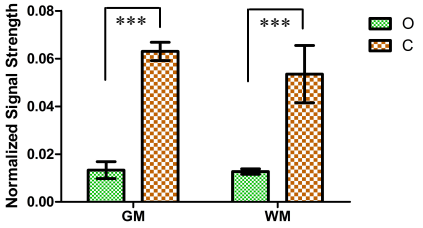


Fig.3 Two way ANOVA results by combining DW directions with 95% confidence intervals (*=p<0.001)**

Effect	F	p (*=p<0.05)
tt	6.37	0.01*
dir	2.04	0.07
tt:dir	1.08	0.37
resp	1532.39	0.00*
tt:resp	4.01	0.05*
dir:resp	25.58	0.00*
tt:dir:resp	0.29	0.92

Table.1. ANOVA Results for Fig. 4

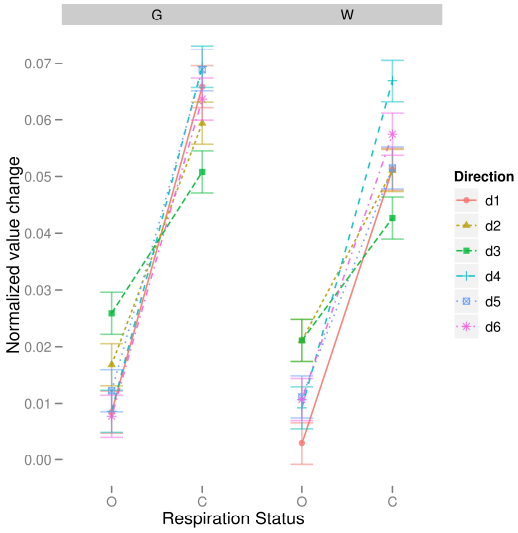


Fig.4 Signal variations between respiratory conditions and across tissue types with Fisher's Least Significant Difference error bars (G:GM, W:WM)