Signal Source in Heavily Diffusion-Weighted functional MRI

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Introduction:

It has been suggested that heavily diffusion-weighted (DW) functional MRI (fMRI) signal changes originate from water in a slow diffusion phase and reflect neuronal activity via cell-swelling [1]. However, several investigations comparing signal changes during visual stimulation and hypercapnia have not arrived at any conclusive agreement on the signal source [2-4]. The role of the BOLD effect in heavily DW fMRI is also still unclear. In this study, we measured the transverse relaxation rate at different *b*-values and estimated the contribution of BOLD to DW fMRI.

Methods:

DW fMRI during visual stimulation was conducted on a whole-body 3T MRI system (Excite HD, GE Medical Systems). Images were acquired with a multiple spin-echo echo-planar-imaging sequence after pulsed-gradient spin-echo (PGSE) diffusion-weighting (b = 0, 200 and 1400 s/mm^2) (Fig.1). Six healthy volunteers were scanned with the following imaging parameters: TR = 2000ms, TE_1 = 71.3 ms, TE_2 = 109.2 or/and 129.2 ms, 64 x 64 matrix, 3.75 x 3.75 x 5 mm^3 pixel size, 4 slices. Visual stimulation was provided by a black-and-white checkerboard alternating at 8 Hz (4 cycles of 40s activation and 80s rest each). In each experiment, the higher (b = 1400 s/mm^2) and lower diffusion weightings (b = 0 or 200 s/mm^2) were alternated every TR. Activated voxels were identified by a pixel-by-pixel t-test analysis for both the first and second echo image sets. The time-series from activated voxels common to both image sets were collected and averaged to make the final DW fMRI time-courses. Transverse relaxation rate, R_2, time-courses were estimated from R_2 (t, b) = ln(S_{TE1}(t, b) / S_{TE2}(t, b)) / (TE_2 - TE_1), where S_{TE1} and S_{TE2} are the DW fMRI signal intensities for the first and second echoes, respectively, at time t and diffusion-weighting b.

Results and Discussion:

Figure 2 shows the DW fMRI signal change at TE = 71.2ms. The post-stimulus undershoot (PSU), which is a typical characteristic of the BOLD response, can be seen in the b = 0 and 200 time-courses but not for b = 1400 s/mm^2. The positive stimulus-correlated response (PSCR) is reduced for b = 200 s/mm^2, probably because of the significantly reduced intravascular contribution, but increases again at b=1400 s/mm^2. These results are consistent with previous studies [4, 5]. A similar PSCR and PSU pattern was also found in the DW fMRI time-courses at TE_2 = 109.2 or 129.2ms.

Figure 3 presents the baseline values of R_2 for all subjects. The means ± std were 16.3 ± 0.6 s^{-1}, 16.8 ± 0.6 s^{-1}, and 17.6 ± 0.7 s^{-1} for b = 0, 200, and 1400 s/mm^2, respectively. Using a paired t test, significant differences were found between the baseline R_2s at different b-values ($p<0.0001$), indicating that the baseline R_2 itself is b-value dependent. Since the signal from faster diffusing molecules would be more attenuated by diffusion weighting, this result suggests that slower moving molecules have a larger baseline R_2.

Figure 4 contains the stimulus-induced changes in R_2 (ΔR_2) plotted with the baseline R_2 subtracted. The changes in R_2 with time show a decrease during, and an increase after the visual stimulation, corresponding to the PSCR and PSU pattern in a typical BOLD time-course. ΔR_2 is consistent across b-values, suggesting that the BOLD effect is independent of the diffusion-weighting. Although the DW fMRI signal acquired by the PGSE sequence may be influenced by a cross-term/interaction between the motion-probing gradients and the BOLD induced field gradients [6], this effect may not be too strong for the signal at b=1400 because PSU is significantly reduced in the raw data despite the increase in ΔR_2 after the stimulation. If this effect were remarkable, a distinct PSU would show in the signal.

Conclusion:

As the ΔR_2 time-courses are independent of the b-value (Fig.4) and are quite different in shape from the raw signal changes for b = 1400 s/mm^2 (Fig.2), which has no PSU, the BOLD effect may not be the main contributor to heavily diffusion-weighted fMRI signal changes.

References:

[1] Le Bihan *et al*, PNAS 103(21):8263-8268 (2006).[2] Miller *et al*, PNAS 104(52):20967-20972 (2007).[3] Urayama *et al*, Proc. ISMRM 403 (2008). [4] Kuroiwa *et al*, Proc. ISMRM 2388 (2008). [5] Kershaw *et al*, Proc. ISMRM 25 (2007). [6] Hong *et al*, JMR 99:561-570 (1992).

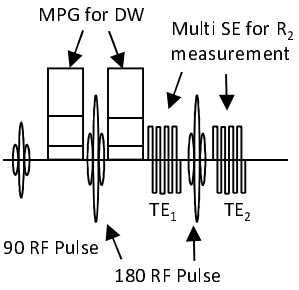

Fig.1 Diffusion-weighted multiple spin-echo EPI sequence

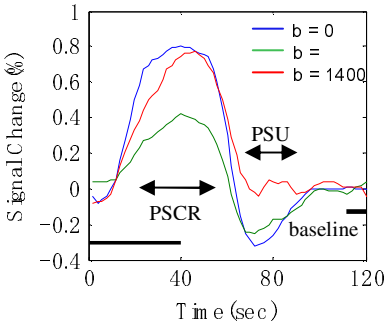

Fig.2 DW fMRI time-course at TE = 71.2ms. The horizontal line indicates the visual stimulation period.

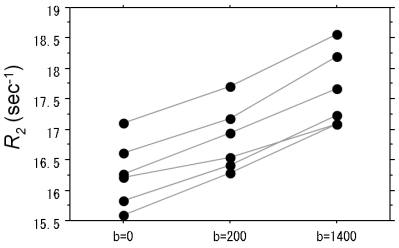

Fig.3 Baseline values of R_2 for all six subjects

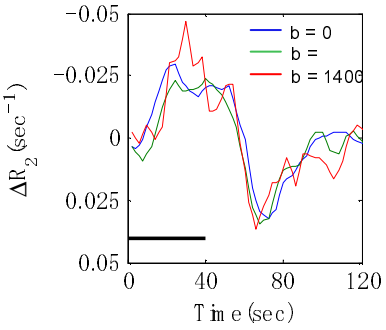

Fig.4 Changes in R_2 with respect to the baseline R_2. The vertical axis is reversed for comparison with the shape of the DW fMRI time-courses in Fig.2