Time-course of ΔR_2 during visual stimulation and hypercapnia diffusion-weighted fMRI experiments

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Introduction: It has been suggested that heavily diffusion-weighted (DW) fMRI signal change originates from extravasular tissue and reflects neuronal activity via cell-swelling because the signal from flowing blood is significantly attenuated by heavy diffusion-weighting and the functional signal change preceded the signal change observed in GE-BOLD imaging [1]. However, it has also been suggested that there is a BOLD contribution to the signal change [2-4]. BOLD signal change is due to changes in the voxel-scale concentration of paramagnetic deoxyhaemoglobin during neural activation. This is usually interpreted as a change in transverse relaxation rate (ΔR_2). In this study, a sequence with two EPI aquisitions after pulsed-gradient spin-echo (PGSE) diffusion-weighting was constructed to allow us to estimate the transverse relaxation rate (R_2) at a particular b-value (Fig. 1). The sequence was applied to two DW fMRI experiments, visual stimulation (VS) and hypercapnia (HC), to compare ΔR_2 from experiments where neuronal activation is supposedly present (VS) and not present (HC).

Methods: The DW fMRI experiments were conducted on a whole-body 3T MRI system (Signa HDx, GE Healthcare). Eleven and 4 healthy volunteers participated in the VS and HC experiments, respectively. Images were acquired with b-values of 1, 200 or 1400 s/mm². In each experiment, the highest (1400 s/mm²) and lower b-values (1 or 200 s/mm²) were alternated every TR, which was 2000ms for VS and 1000ms for HC. The following imaging parameters were common for both VS and HC: $TE_1 = 71.3$ ms, $TE_2 = 129.2$ ms, 64 x 64 matrix, 3.75 x 3.75 x 5 mm³ voxel size, 4 slices. Stimulation of the visual cortex was performed with a black-and-white checkerboard alternating at 8 Hz (4 cycles of 40s activation and 80s rest). HC was induced by administering 5% CO_2 (2 cycles of 60s administration and 120s rest). After smoothing (3×3 spatial + 3(VS)- or 7(HC)-point temporal box filters), activated voxels were identified for both VS and HC with a pixel-by-pixel t-test analysis of the first-echo image sets. All voxels in the $b = 200$ and 1400 s/mm² data sets with t-value>4 were defined as activated. ROIs were manually selected from the activated pixels in the visual cortex for VS and from the whole cortex for HC. The average DW fMRI time-series in each ROI were collected and further averaged over subjects for both the first and second echoes. Each DW fMRI time-course was linearly interpolated to compensate for the different acquisition times of the $b = 1400$ and $b = 1$ or 200 s/mm² images. Assuming single-exponential decay between the first and second echoes, the transverse relaxation rate, R_2 was estimated with $R_2(t, b) = \ln(S_{TE1}(t, b) / S_{TE2}(t, b)) / (TE_2 - TE_1)$, where S_{TE1} and S_{TE2} are the DW fMRI signal intensities at time t and diffusion-weighting b. ΔR_2 was obtained by subtracting the baseline R_2. At each time point, significant differences for the % signal change ($\Delta S/S$) and ΔR_2 at different b-values were evaluated by standard analysis of variance (ANOVA) with Bonferroni–Dunn correction for multiple comparisons.

Results and Discussion: Similar to the results in a previous report [3], there was a significant increase in the VS induced $\Delta S/S$ from $b = 200$ and 1400 s/mm² (Fig. 2a). In contrast, the HC experiment found no significant difference between $\Delta S/S$ at different b-values (Fig. 2b). This result is inconsistent with earlier VS and HC DW fMRI observations made by Miller et al [2].

The changes in R_2 with time show a decrease during both VS and HC (Fig. 3, vertical scale reversed), reflecting shortening of R_2. ΔR_2 at $b = 1400$ s/mm² for VS has a larger reduction than $b = 1$ and 200 s/mm² during the latter part of the stimulation, indicating that BOLD signal changes during VS depend on the b-value. The larger decrease of ΔR_2 at $b = 1400$ s/mm² may reflect the relatively larger extravascular BOLD effect of slow water molecules near capillary-sized vessels, as hypothesised in [3].

On the other hand, ΔR_2 during HC has no obvious dependence on b-value (Fig. 3b). Under the assumption that during HC neuronal activation does not contribute to the BOLD signal, the VS result for $b = 1400$ s/mm² (Fig. 3a) suggests that R_2 changes at high b-value may demonstrate a higher sensitivity to neuronal activation than at lower b-values.

Regardless of b-value, ΔR_2 decreased in response to VS and thereafter increased. Qualitatively, the shape is similar to a typical BOLD response, but in reverse. In contrast, for VS $\Delta S/S$ follows a different pattern at each b-value as the post-stimulus undershoot is smaller for $b = 1400$ s/mm² and the signal change during VS is reduced for $b = 200$ s/mm² but increases again at $b = 1400$ s/mm² (Fig. 2a). The difference in the pattern of signal changes wrt b-value between $\Delta S/S$ and R_2 may indicate that DW fMRI signal change contains a contribution from another diffusion-related source as well as BOLD.

References: [1] Le Bihan *et al.*, PNAS 103(21):8263-8268 (2006). [2] Miller *et al.*, PNAS 104(52):20967-20972 (2007). [3] Kershaw *et al.*, NMR Biomed 22(7):770-778 (2009). [4] Aso *et al.*, Neuroimage 47(4):1487-1495(2009).
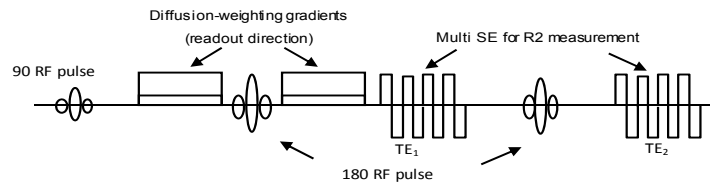
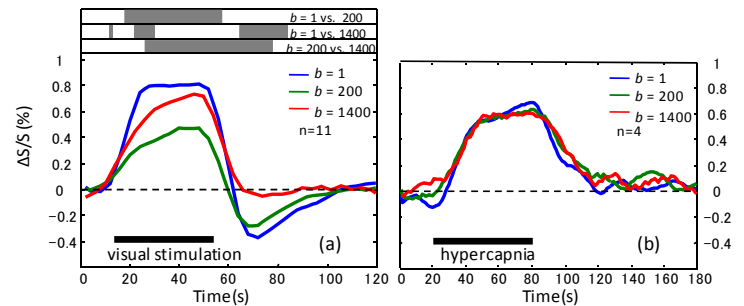Fig. 1. Diffusion-weighted multiple spin-echo EPI sequence

Fig. 2. DW fMRI time-courses for (a) VS and (b) HC from the first echo at TE = 71.3ms. Black bars indicate the duration of stimulation. Gray rectangles indicate times where there are significant differences between the responses at different b-values (p < 0.001).
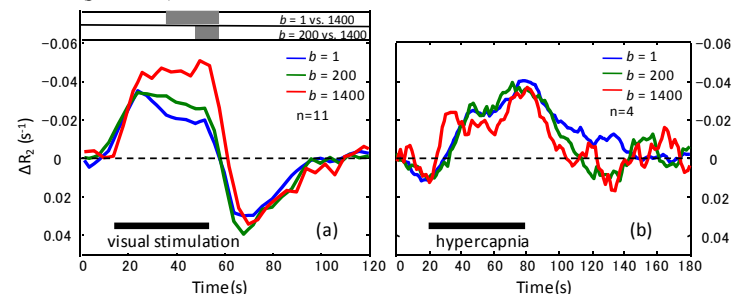

Fig. 3. ΔR_2 time-courses for (a) VS and (b) HC. The vertical axis is reversed for comparison with the shape of the DW fMRI time-courses. Gray rectangles indicate times where there are significant differences (p < 0.016).