An Alternative Interpretation for Stimulus-Related Signal Changes in Diffusion-Weighted fMRI

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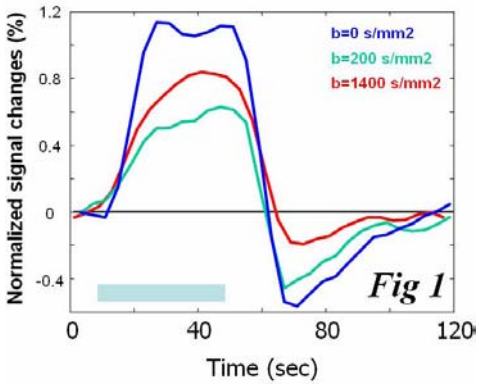
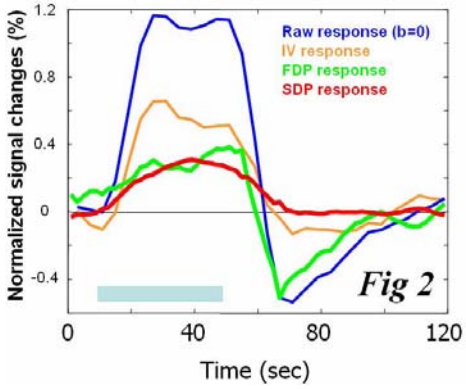
Introduction: The application of diffusion-weighting (DW) during a standard functional MRI visual-activation study has been reported to reveal a transient change in the apparent diffusion coefficient (ADC) [1]. It was suggested that the ADC change might reflect variations in cortical cell geometry induced by the stimulus. More recently, the change in ADC has been reinterpreted in terms of a two-phase functional diffusion model (2PFDM) [2], where water is said to exchange slowly between a slow-diffusion phase (SDP) and a fast-diffusion phase (FDP). Within this model the fMRI signal change is understood as an expansion (contraction) of the SDP (FDP) during the application of a stimulus rather than as a change in the rates of diffusion. From this model it was postulated that the expansion-contraction of the two water-phases is intimately related to neuronal swelling during activation, and hence measuring changes in the SDP expansion coefficient may provide a more direct method of observing neuronal activity. While this interpretation appears enticing, it ignores the possibility that the transverse relaxation rates of the two phases may be independently altered by an external stimulus. The aim of the present work is to propose an alternative interpretation and model for the stimulus-induced signal-change in DW fMRI.

Theory: It is well-known that the signal originating from brain during fMRI experiments may be broken down into intravascular (IV) and extravascular (EV) contributions like so: $S(t,b)=S_{IV}(t,b)+S_{EV}(t,b)$, and that the IV signal is often removed by the application of mild DW (b~50-250 s/mm2). It is proposed here that when DW is applied, the EV signal in SE-BOLD fMRI may be further decomposed into contributions from two compartments with distinct diffusion coefficients: $S_{EV}(t,b) = S_{FDP}(t)\exp(-b\,D_f)+S_{SDP}(t)\exp(-b\,D_s)$. Notice that the diffusion coefficients do not vary with time and the time-dependence of the EV signal is entirely contained in $S_{FDP}(t)$ and $S_{FDP}(t)$, reflecting the probable independence of the transverse relaxation of the two EV compartments. It is also assumed that D_f and D_s are much less than the apparent diffusion coefficient of the IV compartment.





Methods: A visual stimulation study was conducted on 8 healthy volunteers (7 males and 1 female, age 20 to 31 years). All participants gave their informed written consent and the study was approved by the Institutional Ethics Committee.

DW MRI was performed on a whole-body 3T MRI system (Excite HD, GE Medical Systems) equipped with an actively shielded whole-body magnetic field gradient (40 mT/m). DW images were obtained with a spin-echo echo-planar-imaging (EPI) sequence sensitized to diffusion by the addition of gradient pulses on either side of the refocussing RF-pulse. Two studies were performed on each subject with the DW alternating as either b=1400, 0, 1400, 0,… s/mm^2 or b=1400, 200, 1400, 200,… s/mm^2 to minimise the effects of motion during acquisition; b=1400 s/mm^2 was used in both runs to improve the signal-to-noise of heavily DW images. TE was 71.2 ms (the minimum value allowing a DW of 1400 s/mm^2), TR was 2 s for a total of 250 repetitions, FOV was 240 mm, slice thickness 4 mm (gap = 2 mm), and matrix size 64 x 64. Two axial slices were chosen. The activation task consisted of a set of 4 cycles of 40 s of an alternating black-and-white flickering checkerboard (8 Hz) followed by 80 s of rest. After smoothing (3x3x3 box filter), points were selected from the mid-stimulus (~20-40s after onset) and baseline (~100-120s after onset) parts of the time-course and a Student t test was used to identify activated pixels. Pixels with $t \geq 4$ for both the b=200s/mm^2 and b=1400 s/mm^2 images were selected as activated. Raw time-courses were decomposed into IV, FDP and SDP contributions by a linear fit to the data. In the fitting procedure it was assumed that at each time point t_n, $S(t_n,b) = S_{IV}(t_n,b) + S_{FDP}(t_n)\exp(-b\,D_f) + S_{SDP}(t_n)\exp(-b\,D_s)$ describes the signal across DWs, with D_s and D_f taken from the literature [3]. Another important assumption was that $S_{IV}(t_n,b)$ is negligible for b=200 and 1400 s/mm^2.

Results: Across the 8 subjects, a total of 308 pixels in the visual cortex passed the criteria for activation. The mean fractional SE-BOLD responses for the b=0, 200 and 1400 s/mm^2 images are shown together in Fig 1. The light-blue bar denotes the period during which the stimulus was applied. In Fig 2 the stimulus-induced signal changes have been decomposed into IV, SDP and FDP contributions normalised by and displayed in comparison to the observed response for b=0. An intriguing feature is that the SDP time-course has no post-stimulus undershoot, suggesting that the large EV undershoot originates from the FDP alone. At the same time, the SDP contribution shows a positive deflection that is highly correlated with the stimulation, implying that it closely reflects the neural response without contamination by confounding factors such as the undershoot.

Discussion: Repeating fMRI experiments at different DWs enables the decomposition of the stimulus-induced signal changes into IV and EV parts. Hence, the true EV response (ie unretarded by DW) can always be extracted. It is not yet clear what information the further decomposition of the EV contribution into FDP and SDP responses provides because the physical nature of these two compartments is still obscure. The SDP and FDP time-courses may be a mix of expansion-related and BOLD effects. However, there is a very close association between tissue diffusion and BOLD signals; in fact, the BOLD effect is observed because of molecular diffusion through the field gradients in tissue near cortical vessels. This implies that the size of the BOLD signal change is correlated with the rate of diffusion and so the BOLD contribution to the SDP response should be substantially smaller than that for the FDP. Therefore, as the SDP and FDP responses are of similar magnitudes, it is possible that the SDP time-course may be dominated by cell expansion- rather than BOLD-related changes.

References: [1] Darquie et al, PNAS 98(16):9391-9395 (2001); [2] Le Bihan et al, PNAS 103(21):8263-8268 (2006); [3] Brugiere et al, Am J Neuroradiol 25:692-698 (2004).