Influence of the choice of the impulse response function in statistical analysis of diffusion fMRI time series at high b-value

Emilie Vallée[1], Live Eikenes[2], Anders Kristoffersen[3], and Asta K Håberg[2,3]

[1]MI Lab, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway, [2]Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway, [3]MI Lab, Department of Medical Imaging, St. Olavs Hospital, Trondheim, Norway

Introduction Diffusion-weighted fMRI (DfMRI) at high b-value is a new method in functional MRI. DfMRI has been proposed as a method that detects true neuronal activity as changes in the grey matter diffusion properties due to neuronal swelling caused by the obligatory water influx concomitant to Na^+ influx during neuronal activation [1]. However the variations of the diffusion signal are quite difficult to measure due to the high level of noise present in the DfMRI data, and the origin of the diffusion signal remains uncertain. Indeed, the DfMRI signal has been attributed to both neuronal [1-3] and vascular [4-5] processes. In the current work, we assume that both the vascular process and the neuronal process are detectable with DfMRI. Two different response functions in the analysis of the DfMRI data are used to depict voxels that are more likely to be activated due to a vascular process from those that are more likely to be activated due to a neuronal process. The origin of the signal produced by each analysis method is investigated by specifically looking into the early phase of the signal.

Methods 24 healthy volunteers were scanned with a 3T Philips MRI scanner using a single shot spin-echo EPI sequence sensitized to diffusion at a b-value b=1800s/mm^2 (TR=935ms, TE=81ms, matrix size= 80x80 with 6 slices of 3mm thickness, FOV=220mmx220mm, diffusion gradients were applied in y-direction). In addition a gradient-echo (GE) BOLD sequence was acquired with the same settings. Visual stimulation was performed using flickering checkerboard (frequency, 8Hz). Three different duration of the visual stimulation were used: i) 4 cycles (7s stim./ 27-37s rest) (6 individuals), ii) 3 cycles (14s stim./30-45s rest) (12 individuals), iii) 3 cycles (21s stim./30-40s rest) (6 individuals). Duration of the rest periods was randomized to increase the signal-to-noise ratio (SNR) of the signal averaged over all cycles, trials and subjects. Because of the large difference in SNR between the BOLD and the DfMRI sequence, DfMRI sequences were repeated 10 times and BOLD sequences 2 times per volunteer. Diffusion data sets were analyzed in two different ways: a general linear model was applied using a response function modeling the diffusion process (DRF) introduced in ref. [2] and the vascular process (HRF) (double gamma function). A mean time course was extracted from each activation map and deconvolved. Furthermore, to verify whether or not the diffusion signal obtained can be attributed to a change of diffusion properties occurring in grey matter due to neuronal swelling, a DfMRI and a GE BOLD sequence were acquired while volunteers were resting for noise measurements. The mean SNR of each time series, defined as the mean of the signal divided by the standard deviation of the time series, and standard deviation (SD) maps were calculated.

Results The DfMRI time courses obtained using DRF in the analysis present an earlier (2-3s before the BOLD signal) and a steeper increase than the usual BOLD time course (fig.1). These results are in line with results from previous studies [1-3]. The deconvolved time courses have a time-to-peak of 2.5s (table.1), whereas the DfMRI time courses obtained using HRF are similar to the usual BOLD time course and the deconvolved time courses present a time-to-peak of 5.1s. The SNR of the DfMRI time series is 14 times smaller than for the BOLD time series, making the diffusion signal very difficult to detect. At b=1800 s/mm^2, the mean percentage of activation of the diffusion signal in the visual cortex is of the order of 1.8% whereas the standard deviation of the noise in the same area reaches 10.3% of signal change, completely overshadowing the diffusion signal (Table.1). Moreover, standard deviation maps across time of the diffusion images (fig. 2) show that noise in the visual cortex is stronger (higher standard deviation than in other areas, in white on the diffusion SD map) and consequently does not correspond to thermal noise (in grey on the diffusion SD map) only, but also to physiological noise and artefacts.

Discussion The diffusion signal detected using DRF in the analysis reflects a process that reaches its maximum in 2.5s, which is rather late to be directly related to a neuronal origin. This result does not correspond to the 0.5s time-to-peak hypothesized in [2], but is still in line with the 2-3s shift between the diffusion and the BOLD signal from the figures in [1-3]. Interestingly, DfMRI at b=1800s/mm^2 is also able to depict in the same proportions (116 activated voxels for the DRF and HRF analyzed data), a signal that lines up with the BOLD signal and that presents a deconvolved curve with a time-to-peak of 5.1s, which clearly reflects the vascular process and is in line with results from [4-5]. Nonetheless, the low SNR of the diffusion signal makes it quite difficult to detect. It requires therefore intense averaging. The noise in the visual cortex in DfMRI is not just thermal but also physiological and artefactual. In the case of DfMRI at b=1800s/mm^2, noise is temporally correlated in the visual cortex and does not meet the randomness property essential in averaging. Though we randomized rest periods for increasing robustness of averaging, the type of response function chosen for the analysis (DRF or HRF) directly influences which voxels were considered active. Averaging of correlated noise in a non-robust manner may have combined noise time series into a signal that may appear interesting. Our results suggest that the physiological noise and artefacts in the diffusion images may have caused the DfMRI curve obtained using DRF in the analysis. The DfMRI curve is probably the sum of the vascular signal (obtained using HRF in the analysis) and correlated noise. However, further investigations are required to confirm this assumption.

References: [1] Le Bihan D et al., PNAS 103(21):8263-8(2006) [2] Aso T et al., NeuroImage, 47(4):1487-95 (2009) [3] Khono S et al., J Cereb Blood Flow Metab, 29(6):1197-207 (2009) [4] Miller KL et al., PNAS 104(52):20967-72 (2007) [5] Autio JA et al., NeuroImage, 57(1):140-8, (2011)

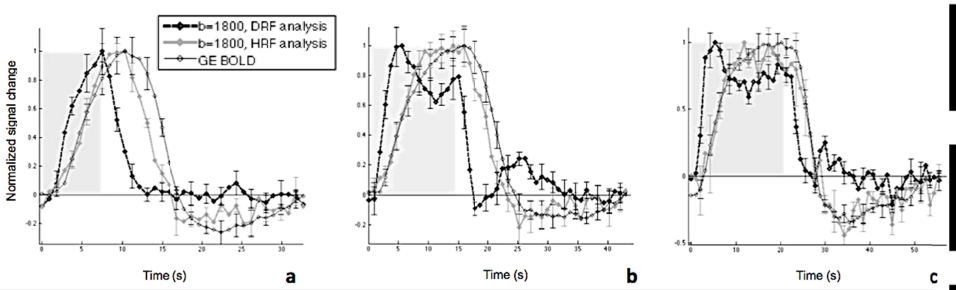

Fig.1 Normalized averaged time series of the diffusion signal analyzed with DRF and HRF response functions and normalized averaged GE BOLD time series for 7s (**a**), 14s (**b**) and 21s (**c**) stimulation.

	Time-to-peak (deconvolved curve)	Mean percentage of activation	SD of noise under resting state (in percentage of signal change)	Time series SNR	Number of activated voxels (p<0.05)
Diffusion b=1800, DRF analysis	2.5 ± 0.3s	1.9 ± 0.2%	10.3 ± 1.5%	9.8 ± 1.5	116±62 (of which 31 vox common to HRF analysis)
Diffusion b=1800, HRF analysis	5.1 ± 0.1s	1.7 ± 0.2%	10.3 ± 1.5%	9.8 ± 1.5	116±29 (of which 31 vox common to DRF analysis)
GE BOLD	5.5 ± 0.2s	2.5 ± 0.3%	0.7 ± 0.01%	140 ± 24	809±76

Table.1 Time-to-peak of the deconvolved time series and noise study of the DfMRI and GE BOLD signals in the visual cortex

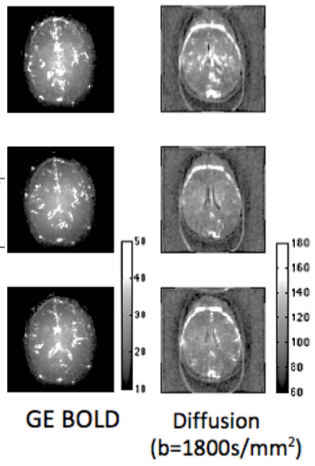

Fig.2 Maps of standard deviation across time of a GE BOLD and a DfMRI (b=1800 s/mm^2) data set.