# Swelling of slow water diffusion pool precedes hemodynamic response during activation of human visual cortex

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## Introduction

A transient decrease of the apparent diffusion coefficient (ADC) has been reported during activation of human visual cortex (1). This small effect has been tentatively ascribed to cell swelling, offering an exciting alternative to BOLD fMRI. Our aim was to further investigate its temporal relationship with cortical activation.

## Materials & Methods

The study was performed on 6 volunteers using a 3T MRI scanner equipped with a 8-channel phased-array coil. To eliminate diffusion signal contamination by BOLD induced susceptibility effects (2) a twice refocused spin-echo EPI sequence sensitized to diffusion by an interleaved pair of bipolar gradient pulses was chosen (3). Acquisition parameters were: voxel size=$3.8^3$mm$^3$, GRAPPA encoding (g=2), TE=87ms/TR=1s. Visual stimulation was obtained from a flickering dartboard during 3 epochs of 20 (or 16) seconds separated by a 20 second interval. The acquisition was repeated with 4 b values in random order (b=600, 1200, 1800 and 2400 s/mm$^2$). BOLD fMRI images were acquired for comparison using a GE EPI sequence with the same parameters (except TE=30ms). A set of 18 diffusion-sensitized images was also acquired in a resting condition with b values ranging from 0 to 3400 s/mm$^2$ with 200 s/mm$^2$ increments to perform a diffusion compartment analysis (4). Activation maps were calculated individually for each subject from the b=2400 s/mm$^2$ diffusion-sensitized data set using SPM software and a volume of interest (VOI) centered on calcarine fissures was defined from the voxels classified as activated (0.001 threshold). This VOI was then used subsequently for analyzing all data for each subject. The VOI averaged, baseline drift corrected signal time course for each b value was folded into a single [activation-rest] epoch by averaging the 3 subsequent epochs of the paradigm. The signal change time course, [dS/S](t), was defined as S(t)/S(baseline)-1. Using a diffusion biexponential model (4) the [dS/S](t) time course for each b value was converted into a slow diffusion pool swelling, $[df_{slow}/df_{slow}](t)$, time course according to:

$$df_{slow}/f_{slow} = [f_{slow}\exp(-bD_{slow}) + (1-f_{slow})\exp(-b\,D_{fast})]/\{f_{slow}[\exp(-bD_{slow}) - \exp(-b\,D_{fast})]\}dS/S \quad [1]$$

where $f_{slow}$ and $D_{slow/fast}$ are the volume fraction and the diffusion coefficient of the slow/fast water diffusion pool at rest. Since $df_{slow}/df_{slow}$ is a physiological parameter which does not depend on the b value (4), the $[df_{slow}/df_{slow}](t)$ time courses were averaged over the 4 b values and plotted for the VOI of each subject. The VOI averaged, baseline drift corrected raw BOLD signal was also expressed as a relative change to baseline, $[dS_{BOLD}/S_{BOLD}](t)$ and normalized to the amplitude of the diffusion-derived swelling response for temporal comparison. The time lag during the activation epoch between the $[df_{slow}/df_{slow}](t)$ and the $[dS_{BOLD}/S_{BOLD}](t)$ time courses was determined by minimizing a chi-square, $X^2(\Delta t)$, between the diffusion time course and the BOLD time course shifted by $\Delta t$ interval.

## Results

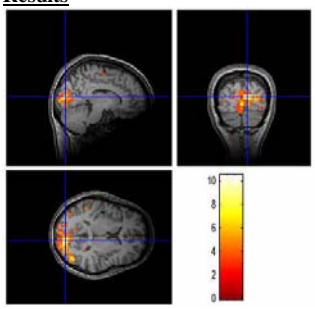


**Fig.1:** SPM activation map from a b=2400 s/mm$^2$ diffusion-sensitized data set showing areas of increased signal (decreased diffusion).

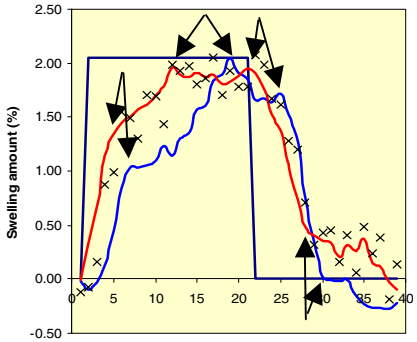



**Fig.2:** Diffusion-derived swelling (red) and normalized BOLD (blue) time courses for subject CH... Arrows: landmarks of interest showing the time lag between swelling and BOLD. Dark blue: activation paradigm.

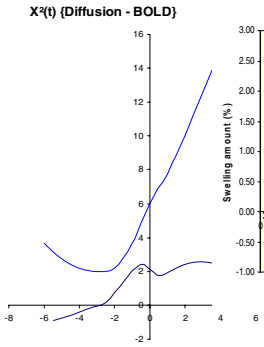



**Fig.3** Plot of $X^2(\Delta t)$ against $\Delta t$ between diffusion and time-shifted BOLD (blue) time courses, and $\Delta t$ derivative (black) to peak up minimum.

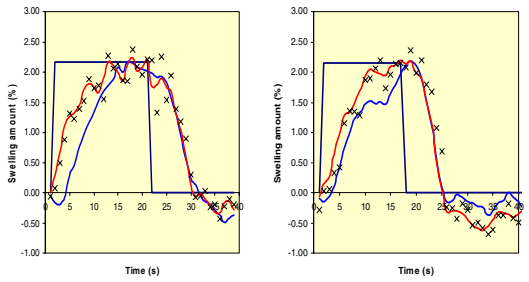


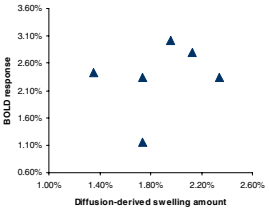

**Fig.4:** Diffusion-derived swelling (red) and normalized BOLD (blue) time courses of subjects YA... and NA...

Results were remarkably consistent across our 6 subjects (Table 1). Activation of visual cortex was well defined (Fig.1). The BOLD fMRI time courses showed usual patterns, including initial dip and post-stimulus undershoot (Fig.2, 4). The diffusion-derived swelling time courses showed no initial dip, but a post-stimulus undershoot was present in most cases. The diffusion-derived and the normalized BOLD time courses were strikingly similar in shape, but the BOLD time course always lagged behind the diffusion-derived time course during the activation period, qualitatively, as seen from accidental landmarks occasionally present on both time profiles, and quantitatively, as shown from the $X^2$ between the diffusion-derived swelling and the time-shifted BOLD time courses (Fig.3), with an average of 2.4±0.7s. Interestingly, the amplitude of the BOLD response (before normalization) was not correlated with the amount of swelling (cc=0.26) (Fig.5).

| Subject | VOI size (voxels) | Diffusion advance | Swelling | BOLD response |
|---|---|---|---|---|
| TA… | 72 | -1.9 s | 1.7% | 2.3% |
| NA… | 127 | -2.2 s | 2.1% | 2.8% |
| HI… | 127 | -2.2 s | 1.4% | 2.4% |
| BA… | 90 | -1.9 s | 2.3% | 2.3% |
| YA… | 148 | -3.2 s | 2.0% | 3.0% |
| CH… | 175 | -3.2 s | 1.7% | 1.2% |
| **Average** | **123** | **-2.4 ± 0.7 s** | **1.9± 0.4%** | **2.3± 0.6%** |

**Table 1**: Results from all subjects.

**Fig.5:** Correlation plot between amount of swelling and amplitud of BOLD response (before normalization).




## Discussion and conclusion

Consistent diffusion-derived activation time courses could be obtained. Using a diffusion biexponential model the diffusion signal time course could be converted into the swelling amount of a slow diffusion pool (4), a physiological parameter which could potentially be compared across subjects or according to stimulation conditions. Further studies will be, of course, necessary to assign this slow diffusion pool to cortical neurons and/or glial cells and to explain the origin of the swelling through the flux of ion/water across membranes, as the nature of the slow diffusion compartment remains a subject of investigation. However, the present study strongly suggests that a vascular origin of the diffusion-derived activation is not likely, as 1/the diffusion-derived (swelling) response precedes the BOLD-derived (hemodynamic) response by more than 2s; 2/the amount of swelling does not correlate with the amplitude of the BOLD response. Diffusion-sensitized MRI, especially at high b-value and high field, appears as a very promising new approach for fMRI, as it might provide a quantitative access to an early and direct physiological surrogate of cortical activation.

## References

1.Darquie et al. (2001) PNAS 98, 9391-9395; 2.Kennan et al (1995) in Diffusion and Perfusion MRI, Raven Press, p.110-121; 3.Reese et al. (2003) MRM 49, 177-182; 4.Le Bihan et al. (2006) ISMRM.