How vascular effects contribute to heavily diffusion-weighted fMRI signal

D. Le Bihan[1,2], T. Aso[1,2], S-I. Urayama[2], C. Poupon[1], N. Sawamoto[2], K. Aso[2], and H. Fukuyama[2]

[1]I²BM/DSV/CEA, NeuroSpin, Gif-sur-Yvette, France, [2]Human Brain Research Center, Kyoto University, Kyoto, Japan

INTRODUCTION - Using heavily diffusion-sensitized MRI a transient decrease in water diffusion has been reported in the activated visual cortex of human subjects[1]. The steep onset of the diffusion response and its temporal precedence relative to the BOLD fMRI response suggest a non-vascular origin. However, this assumption has been challenged by recent studies[2-3]. The purpose of this work is to provide a theoretical framework which resolves the controversy.

THEORY - The diffusion-sensitized fMRI (DfMRI) spin-echo signal in a voxel is the sum of the tissue and vascular compartment signals, where the vascular part consists of compartments of different size and nature (arteries, capillaries, veins). In addition to the relaxation and diffusion terms, due to blood flow the vascular signal is further attenuated by a pseudo-diffusion term, according to the IVIM model[4]:

$$S = F_t \cdot S_{0,tissue} \exp(-TE/T2'_t) \cdot \exp(-bADC) + \sum_i F_i S_{0,blood} \cdot \exp(-TE/T2'_{b,i}) \cdot \exp(-b[D_{b,i} + D_i^*]) \quad [1]$$

where b is the degree of diffusion sensitization, S is the MRI signal at a particular b-value, F_t is the pure tissue volume fraction, ADC is the tissue apparent diffusion coefficient. $T2'_t$ is the tissue apparent transverse relaxation time which includes intrinsic diffusion effects through the local field gradients induced by nearby vessels containing paramagnetic deoxyhemoglobin (deoxyHb)[5]. $S_{0,\ tissue/blood}$ is the tissue/blood signal contribution at (b=0, TE=0) which may include a T1 component if TR is ≈< T1. F_i, $T2'_{b,i}$ $D_{b,i}$ are the vascular volume fractions, apparent relaxation times and diffusion coefficients of each vascular compartment and D_i* the IVIM pseudo-relaxation coefficient. $\Sigma_i F_i$ represents the total blood volume fraction (<5%)[6] and $F_t + \Sigma_i F_i = 1$. Exchange effects between capillary blood and tissue during TE are assumed to be negligible[7].

At b=0 the spin-echo signal is reduced to $S = F_t S_{0,tissue} exp(-TE/T2'_t) + \Sigma_i F_i S_{0,blood} exp(-TE/T2'_{b,i})$ [2]

Upon activation S slightly increases mainly due to the lengthening in $T2'$ in blood and tissue caused by a reduction of the local differences in magnetic susceptibility between the tissue and the intravascular blood[7] which results from the decrease in intravascular deoxyHb (so-called BOLD effect). With refocused spin-echo sequences the increase in T2' is less than with gradient-echo sequences where additional susceptibility effects are present ($T2^*$)[5]. At 1.5T the spin-echo ($T2'_t$) tissue response contribution is estimated to be as low as 30% of the overall ($T2^*$) response[8] while obviously sharing the same temporal profile because both are driven by the deoxyHb content time-course. Effects of variations in So(T1) (in-flow) and the tissue volume fraction, F_t, (induced by a CBV increase) have been shown to be negligible[7].

For large b values the intravascular component is cancelled out: First, the intravascular signal is crushed because water diffusion in blood water is ~2.5 times greater than in brain tissue (~0.8 10^{-3} mm²/s). At b=1800 s/mm², this results into a ~10 fold attenuation of the blood signal compared to the tissue diffusion signal. Second, the IVIM effect induces a further signal reduction[7]. The observed (small) activation induced change, dS_{obs}/S_{obs}, in the diffusion-weighted signal then becomes:

$$dS_{obs}/S_{obs} \sim - b\ dADC + TE\ dT2'_t/T2'^2_t - ADC\ db \quad [3]$$

The overall diffusion-weighted signal response thus appears as the sum of a pure diffusion component, linked to the variations, $dADC$, of the tissue apparent diffusion coefficient, a residual relaxivity component, linked to variations, $dT2'_t$ in the tissue, induced by variations of the intravascular deoxyHb content and a term of modulation of the b value by local field inhomogeneities. Note, however, that the relationship of dS/S with the ADC and $T2'_t$ is in fact more complex: First, the diffusion term ($b\ dADC$) can be expanded taking into account the presence of a slow and a fast diffusion phase within the tissue[1,9]; second, variations with TE are not linear, as $T2'$ depends on TE and the ADC[5].

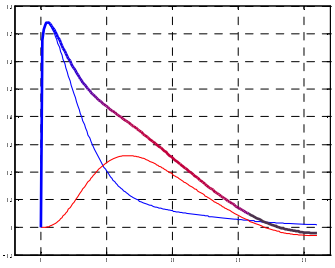

Figure 1: Impulsional response time course of the DfMRI signal extracted from the visual cortex of 13 subjects. Pale red: Relaxivity component, Pale blue: Diffusion component. Bold color: Total DfMRI response with color-encoding of the fractional contribution of each component.

RESULTS AND DISCUSSION – Upon neuronal activation the diffusion component is expected to increase with the b value ($dADC<0$), as shown experimentally[1], while the tissue relaxivity contribution increases with TE ($dT2'_t>0$). Both terms contribute to a positive DfMRI signal response, but to different degrees and with different time courses if mechanisms are different[1,9]. Experimental data obtained at 3T from 13 subjects[10] show that the residual relaxivity contribution represents about 25% of the overall DfMRI response at b=1800s/m² and TE=89ms, while the intrinsic diffusion component peaks 6s earlier than the relaxivity component (Fig.1). Interestingly, this model also well predicts a DfMRI response during pure vascular events, such as those induced by hypercapnia. This pure relaxivity response shares the time course of the vascular response, as reported[2]. Vascular effects may also contribute through the third (modulation) term of Eq. [3]. The local field gradients induced by paramagnetic deoxyHb in the vascular compartment produce cross-terms with the external gradient pulses used to measure diffusion and may modulate the DfMRI signal with the variations of the deoxyHb content. However, due to the geometry of the capillary network, the *decrease* in deoxyHb during neuronal activation leads to a local *increase* of the local b-value (db >0) [11-12] and, thus, to a *decrease* of the DfMRI signal, in opposition to the diffusion and T2' terms. With a conventional, monopolar gradient pulse (MPG) diffusion spin-echo sequence, those cross-terms effects could become significant, especially at ultra-high field, and potentially wipe out signal changes induced by true variations in water diffusion. This effect could partially explain the weak results obtained at 9.4T with a MPG sequence[3]. The model even predicts that a negative DfMRI response could be observed when USPIOs are added to the blood, further increasing the local field gradients[3]. This effect could, however, be suppressed by using a bipolar gradient pulse sequence to generate diffusion signals from 2 echoes or stimulated-echoes. This scheme can be designed to mitigate or cancel the effects of the local magnetic-susceptibility gradients[13], while allowing a reduction of T2' effects through shorter TEs.

In summary, during neuronal activation residual vascular effects only represent a fraction of the DfMRI signal. The diffusion component is expected to largely dominate at very large b values, such as b=1800 s/mm² before hemodynamic events take place. However, as the BOLD response has a slower response and return to baseline, the tissue relaxivity component dominates the DfMRI signal after the end of the activation window.

References: [1]Le Bihan D et al. PNAS 2006; 103: 8263; [2]Miller et al. PNAS 2007; 104: 20967; [3]Jin T et al. *Neuroimage.* 2008; 41: 801 ; [4]Le Bihan D et al. *Radiology* 1988; 168: 497; [5]Ogawa S et al. *Biophysical Journal* 1993; 64: 803 ; [6]Grubb RL, et al. *Stroke.* 1974; 5: 630; [7]Van Zijl PCM et al. *Nature Medicine* 1998; 4: 159; [8]Boxerman JL et al. *MRM* 1995; 34: 4; [9]Le Bihan D. *Phys.Med.Biol.* 2007; 52: R57; [10]Aso et al. ISMRM 2009 ; [11]Does MD et al. *MRM.* 1999; 41: 236; [12]Kiselev VG et al. *NeuroImage* 2004; 20: 1765 ; [13]Finsterbusch J. *J.Magn.Reson.* 2008; 193: 41.