Understanding the Intra- and Extravascular contributions to the BOLD effect through simulations

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INTRODUCTION

Although functional magnetic resonance imaging based on blood oxygenation level dependent (BOLD) contrast has become a widely used tool in neuroscience, the physiological changes that underpin the BOLD effect are still not completely understood. In particular the relationship between the changes in blood oxygenation (ΔY) and cerebral blood volume (CBV), occurring in active brain tissue, and the variation in signal intensity of T_2^*-weighted images is not fully characterised. In probing this relationship, it has generally been assumed that the brain vasculature can be represented as an arrangement of randomly oriented infinite cylinders (IC) of varying size (1, 2) – a model which it has recently been shown produces similar susceptibility-related signal changes to those generated by a more realistic model of the vasculature (RV) (3). Here we describe simulations based on a finite difference method (3), which have been used to characterise the dependence of relaxation rate, R_2*, on blood volume and oxygenation, for signal from both extra- and intra-vascular compartments. Both models (IC and RV) were considered.

METHODS

The simulations spanned two different ranges of intra-/extra-vascular susceptibility difference, χ, reflecting: (i) BOLD contrast at 3 T (oxygenation fraction of the blood varied from 0.5 to 0.8); (ii) exogeneous contrast agents (1 to 4 mM MION- at 3T)(4), which could also be considered representative of BOLD effects at high field (> 9T). Blood volume fraction, V, and vessel sizes were also varied, potentially allowing the overall behaviour of the relaxation processes to be parameterised.

Intra and extravascular compartments were studied separately. **(a)** The extravascular signal was assumed to be characterised by a mono exponential decay, $\exp(-R_2^*TE)$. The relaxation rate obtained was parameterised as $\alpha V^\beta \chi^\gamma$, where V is measured as a percentage and χ is measured in ppm . **(b)** The intravascular decay was characterised by a term resulting from the distribution of cylinder orientations (1) multiplied by an exponential decay due to dephasing resulting from field inhomogeneities generated by neighbouring vessels (this term is not calculable with the IC model).

RESULTS AND DISCUSSION

Figure 1 shows the parameters that best fit the calculated R_2^* values for the extra-vascular signal as a function of the vessel diameter showing a significant difference for simulations carried out with χ-values typical of BOLD and exogeneous contrast at 3T. The haemodynamic response can be represented as a path on the χ-V surface over which ΔR_2^* varies. Figure 2a shows a typical path (black line) calculated using the ballon model (5) with relaxation rate coded in color (blue contour lines for lower fields and red contour lines for higher fields). Figure 2b shows the shape of the corresponding BOLD signal variation with time for the two different regimes. As would be expected from experiment, the initial dip is more visible at the higher field, not only due to the increased contrast due to the greater field strength, but also as a result of the different R_2^* dependencies on the oxygen and volume changes.

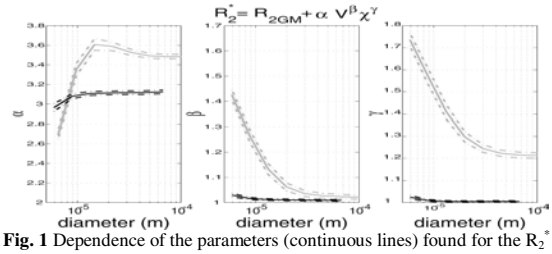

Fig. 1 Dependence of the parameters (continuous lines) found for the R_2^* fit for extravascular signal at 3T due to the RV model (grey-endogeneous contrast; black-exogeneous contrast) as a function of the average vessel diameter.

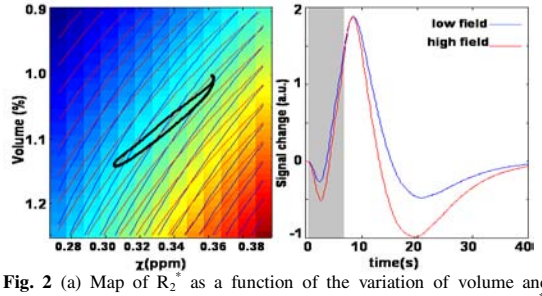

Fig. 2 (a) Map of R_2^* as a function of the variation of volume and susceptibility, blue and red coutour lines stand for the 3T and 9T iso-R_2^*. The black line is the trajectory in this space calculated using the balloon model, as presented in reference (5) (the parameters used, in ms, were: $\delta_f = 2$; $\delta_m = 6$; $\tau_h = 1.3$; $\tau_{MTT} = 4$; $f_1 = m_1$; $\tau = 20$; $\tau^+ = 10$) (b) shows the shape of the BOLD R_2^* response in arbitrary units in order to enhance the difference between the two different field strengths.

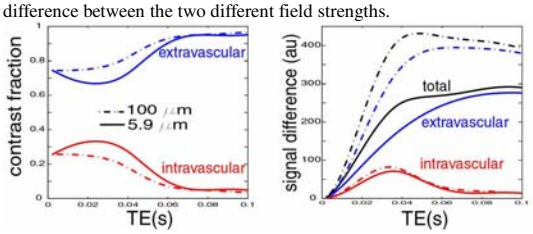

Fig. 3 (a) Relative contribution to the total contrast in a voxel with V=1.29% for a change of χ from 0.36 to 0.18ppm is shown as a function of echo time for extravascular (blue) and intra vascular (red) contributions. (b) The echo time dependence of the signal difference (black), extra-vascular (blue) and intra vascular (red). Dashed lines represent the case of average vessel diameter of 100μm, continuous lines represent average vessel diameter of 5.9μm.

Figure 3 shows that at different echo times different relative intra/extra-vascular contributions to the BOLD signal arise. At echo times varying from 0 ms to 40 ms, the intravascular contribution to contrast is over-represented (over 10 times greater than its volume fraction). The relative intravascular contribution increases for smaller vessels where diffusion plays a greater role.

Once analysis **(a)** and **(b)** had been carried out, it was possible to write the signal intensity following a GE sequence at 3T as a function V and χ,

$$Signal(t,V,\Delta\chi) = M_{0,GM}\,\tfrac{100-V}{100}\,e^{-R2^*,GM}\,\exp(-2.73V^{1.1}\chi^{1.3}t) + M_{0,V}\,\tfrac{V}{100}\,I(t)e^{-R2^*,Blood(\chi)}\exp(-3.5V^{1}\chi^{1.2}t)\exp(40V^{-0.4}\chi^{1.2}t)$$

where the first term represents a physiologically (appropriate weighting of the various vessel length scales) sensible average extravascular contribution to the signal, whilst the second term represents the intravascular contribution. The latter term has various contributions: (i)*I(t)* refers to the isotropically oriented vessels; (ii) the second term refers to the the unaccounted effect of relaxation due to diffusion around red blood cells (this was not simulated because such dependence can be measured *in vitro* with much more reliability); (iii) the third tem refers to static dephasing that should be the same as for gray matter at the static regime (Fig. 1 at large length scales) because the intravascular frequency shift distribution of the RV model was found to be well described by a convolution of extravascular frequency distribution of the RV model and that expected from isotropically oriented cylinders; (iv) the last term is an averaged effect through different length scales due to diffusion in the complex distribution of field shift, this relaxation value is positive because the diffusivity along the vessels, actually delays the process of dephasing described earlier as I(t);

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