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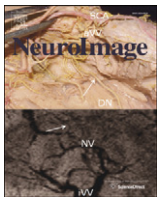

High *b*-value diffusion-weighted fMRI in a rat forepaw electrostimulation model at 7 T

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ABSTRACT

Spin-echo diffusion-weighted functional MRI (DW-fMRI) was performed on a rat forepaw electrostimulation model at 7 T. This small animal model used electric (rather than visual) stimulation and allowed DW-fMRI experiments to be performed over a broader range of acquisition parameters than previous work on humans and cats. Resting state experiments with injections of ultra-small superparamagnetic iron oxide (USPIO) were also used to investigate the effects of gradient coupling on the signal change. The experiments were performed over five *b*-values (0, 200, 800, 1400 and 2000 s/mm^2) and three echo-times (30, 60 and 90 ms). Alterations to the stimulation-induced response with respect to TE and *b*-value were evaluated in two intervals: the positive stimulus-correlated response (5–20 s after stimulus onset) and the post-stimulus undershoot (27–40 s). There was no strong dependence of the signal change on *b*-value for any of the intervals or TEs. Similarly, changes to the apparent transverse relaxation rate showed no clear dependence on *b*-value. In contrast to previous DW-fMRI studies, the simplest explanation for the observed data is a single-compartment signal model with the functional signal changes probably corresponding to extravascular SE-BOLD. Experiments with USPIO suggested that at 7 T and within the range of parameters used, the influence of gradient coupling may be sufficient to explain minor DW-fMRI signal changes.

Introduction

Over the past few years, diffusion-weighted functional MRI (DW-fMRI) has attracted attention as a technique that might provide information more directly correlated with the actual neural activity than standard blood oxygen-level dependent (BOLD) fMRI (Darquie et al., 2001; Le Bihan et al., 2006; Gangstead and Song, 2002; Song et al., 2002; Harshbarger and Song, 2006). When motion-probing gradients (MPGs) were applied during fMRI experiments, the amplitude and onset of the response were found to be dependent on the diffusion-weighting, as characterised by the *b*-value. Although there were differences in the experimental setup (through factors such as the type of animal, field strength and stimulus paradigm) and the imaging protocol (via imaging sequence and range of acquisition parameters), changes to the response amplitude in most previous DW-fMRI studies were roughly consistent with a signal decrease for *b*-values in the range 0–600 s/mm^2, followed by an increase for higher *b*-values up to 2400 s/mm^2 (Le Bihan et al., 2006; Miller et al., 2007; Jin et al., 2006b; Yacoub et al., 2008; Kershaw et al., 2009; Kuroiwa et al., 2009). For *b*-values 0–600 s/mm^2, the signal changes have been largely attributed to attenuation of the blood contribution (Jochimsen et al., 2004; Duong et al., 2003; Le Bihan et al., 1998; Callaghan, 1991).

To date, all explanations put forward for high *b*-value DW-fMRI signal changes have been based on some form of compartmentalisation of in vivo water signal. A common feature of these models is the assumption that the diffusion coefficient of each compartment remains unchanged by the application of the stimulus. That is, rather than invoking real changes to the diffusion properties of water, the signal changes are explained as a mixture of competing changes to compartmental volume fractions or transverse relaxation rates. In the paper of Le Bihan et al. (2006), it was proposed that the effects observed at high *b*-value are the result of extravascular (EV) water molecules transferring between slow- and fast-diffusion phases

Abbreviations: fMRI, functional magnetic resonance imaging; DW-fMRI, diffusion-weighted fMRI; BOLD, blood oxygen-level dependent; MPG, motion-probing gradient; ADC, apparent diffusion coefficient; IV, intravascular; EV, extravascular; CSF, cerebrospinal fluid; TE, echo-time; SE, spin echo; EPI, echo-planar imaging; ROI, region-of-interest; PSCR, positive stimulus-correlated response; PSU, post-stimulus undershoot; USPIO, ultra-small superparamagnetic iron-oxide.

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during stimulus-induced cell swelling. This model was later modified to include residual intravascular (IV) components and to take into account possible changes to the apparent transverse relaxation rate of tissue (Aso et al., 2009). Kershaw et al. (2009) also used an extravascular compartmentalisation into slow and fast diffusing water molecules, but in this case it was suggested that alteration of the DW-fMRI signal is due to distinct changes to the transverse relaxation rates of each compartment. Harshbarger and Song (2006) suggested an interpretation based on an IV–EV separation of signal that increasingly reflects cerebral-blood-volume-weighting at higher *b*-values. In a series of papers, Jin et al. put forward a picture dividing the signal into tissue, arterial blood, venous blood and cerebrospinal-fluid (CSF) compartments (Jin et al., 2006a,b; Jin and Kim, 2008). From their experiments on domestic cats at 9.4 T, they essentially argued that no new mechanism is required to explain changes to the apparent diffusion coefficient (ADC) during high *b*-value DW-fMRI because the observations could be attributed to changes in one or other of those compartments.

Another factor that has been mentioned as a possible source of DW-fMRI signal changes is the so-called "coupling" of the applied MPGs and internal field inhomogeneities (Jin and Kim, 2008; Miller et al., 2007; Yacoub et al., 2008; Pampel et al., 2010). It has long been known that the presence of subvoxel susceptibility variations can affect diffusion measurements (Stesjkal and Tanner, 1965; Zhong et al., 1991, 1998). It is also recognised that the BOLD effect, which is related to the diffusion of water molecules through the field gradients within and surrounding blood vessels, may be perturbed by the applied MPGs so that a significant dependence on *b*-value may be observable. However, simulations performed by Pampel et al. (2010) found that superposition of applied MPGs and blood-vessel-induced field gradients would most likely reduce, rather than increase, the fractional signal change with increasing *b*-value. It was therefore concluded that this mechanism is unlikely to be responsible for the DW-fMRI signal increases observed at high *b*-value, but may instead obscure other sources of signal change.

In principle, an explanation for DW-fMRI signal changes should apply to other stimulus types, brain-sensory systems and animal models. Previous high *b*-value DW-fMRI studies have been limited to visual stimulation on either humans or domestic cats. Visual stimulation is a reliable technique that elicits a physiological response that is detectable with fMRI. However, it is not yet known whether the signal changes observed with high *b*-value DW-fMRI also translate to other functional imaging models. Another constraint of previous work is the limited number of experiments that can be performed on human subjects, which restricts the range of imaging parameters that can be used in each study. Experiments on cats are less constrained by this problem, yet the range of parameters used in previous studies has been limited. Performing experiments over a broader range of TEs and *b*-values may help to distinguish between different interpretations.

A model widely used in functional MR imaging research is the rat forepaw electrostimulation model. The functional response in this small animal model has been extensively studied for the $b=0$ case (e.g. Keilholz et al. (2006); Kennan et al. (1998); Lee et al. (2002); Mandeville and Marota (1999)). However, even though there have been experiments with applied MPGs of up to 500 s/mm^2 at 9.4 T (Lee et al., 1999), there have been no high *b*-value studies. An advantage of the rat forepaw model is that longer experiments can be performed, allowing DW-fMRI signal changes to be investigated over a broader range of acquisition parameters. This model also uses electric stimulation to activate the somatosensory cortex, so that both the stimulus type and brain-sensory system differ from previous work. The present manuscript reports the results of spin-echo echo-planar imaging (SE-EPI) DW-fMRI experiments performed at 7 T with the rat forepaw electrostimulation model. The response was measured for *b*-values 0–2000 s/mm^2 and TEs 30–90 ms.

Theoretical background

The baseline signal from a multicompartmental system in slow exchange can be written as

$$S = \sum_i S_{oi} e^{-bD_i} e^{-\mathrm{TE}\,R_{2ai}}, \tag{1}$$

where D_i and R_{2ai} are the apparent diffusion coefficient and apparent transverse relaxation rate of compartment *i*, respectively. S_{oi} is an aggregation of quantities like the compartmental volume fraction and proton density, but is essentially the compartmental signal intensity when *b* and TE are zero. Following previous models of high *b*-value DW-fMRI signal changes in assuming that physiological changes during stimulation only affect the S_{oi} and R_{2ai}, it ensues that the fractional signal change is

$$\frac{\Delta S}{S} = \frac{\sum_i (S_{oi} + \Delta S_{oi}) e^{-bD_i}\ e^{-\mathrm{TE}(R_{2ai} + \Delta R_{2ai})}}{\sum_i S_{oi}\ e^{-bD_i}\ e^{-\mathrm{TE}\,R_{2ai}}} - 1. \tag{2}$$

For the special case of one compartment, the logarithmic fractional signal change

$$\ln\left(1 + \frac{\Delta S}{S}\right) = \ln\left(1 + \frac{\Delta S_o}{S_o}\right) - \mathrm{TE}\,\Delta R_{2a} \tag{3}$$

is linear in TE and independent of *b*-value. After some algebraic manipulation, the expression for two or more compartments is

$$\begin{aligned} \ln\left(1 + \frac{\Delta S}{S}\right) &= \ln\left(1 + \frac{\Delta S_{oj}}{S_{oj}}\right) - \mathrm{TE}\,\Delta R_{2aj} \\ &\quad + \ln\left(\frac{1 + \sum_{i\neq j} B_i(b,\mathrm{TE}) F_i(b,\mathrm{TE})}{1 + \sum_{i\neq j} B_i(b,\mathrm{TE})}\right), \\ B_i(b,\mathrm{TE}) &= \left(\frac{S_{oi}}{S_{oj}}\right) e^{-b(D_i - D_j) - \mathrm{TE}\left(R_{2ai} - R_{2aj}\right)}, \\ F_i(b,\mathrm{TE}) &= \left(\frac{1 + \Delta S_{oi}/S_{oi}}{1 + \Delta S_{oj}/S_{oj}}\right) e^{-\mathrm{TE}\left(\Delta R_{2ai} - \Delta R_{2aj}\right)}. \end{aligned} \tag{4}$$

Note that the last term on the right-hand side of Eq. (4) is a nonlinear function of *b*, TE and the compartmental parameters.

To fit experimental data to a nonlinear function it is usually necessary to use an iterative nonlinear fitting algorithm. It is well known that the success of this procedure depends on the quality of the data, as even small uncertainties in the data can lead to unreasonably large uncertainty in the parameter estimates, in particular for the rate constants. Instead of directly fitting the data to a multicompartmental model, an alternative strategy that has been used when interpreting DW-fMRI data is to select a range of physiologically relevant values for the parameters, simulate the expected signal changes with the model, and then compare the empirical measurements to the simulations (e.g. Duong et al.,2003; Jin et al.,2006a,b). However, that approach is based on specific models where the number of compartments is chosen a priori. In the procedure adopted for this work, no a priori selection of the model form is made. Rather, the simple signal model $S = S_o\, e^{-\,bADC} e^{-\,TER_{2a}}$ is used, from which it follows that

$$\ln\left(1 + \frac{\Delta S}{S}\right) = \ln\left(1 + \frac{\Delta S_o}{S_o}\right) - \mathrm{TE}\ \Delta R_{2a} - b\ \Delta ADC. \tag{5}$$

The similarity between this equation and Eq. (4) is immediate if a correspondence between ΔADC and the nonlinear term on the right-hand side of Eq. (4) is made. The advantages of Eq. (5) are that the fitting procedure is linear and the experimental results across a