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# An integrative model for neuronal activity-induced signal changes for gradient and spin echo functional imaging

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ABSTRACT

Gradient and spin echo (GRE and SE, respectively) weighted magnetic resonance images report on neuronal activity via changes in deoxygenated hemoglobin content and cerebral blood volume induced by alterations in neuronal activity. Hence, vasculature plays a critical role in these functional signals. However, how the different blood vessels (e.g. arteries, arterioles, capillaries, venules and veins) quantitatively contribute to the functional MRI (fMRI) signals at each field strength, and consequently, how spatially specific these MRI signals are remain a source of discussion. In this study, we utilize an integrative model of the fMRI signals up to 16.4 T, exploiting the increasing body of published information on relevant physiological parameters. Through simulations, extra- and intravascular functional signal contributions were determined as a function of field strength, echo time (TE) and MRI sequence used. The model predicted previously reported effects, such as feasibility of optimization of SE but not the GRE approach to yield larger micro-vascular compared to macro-vascular weighting. In addition, however, micro-vascular effects were found to peak with increasing magnetic fields even in the SE approach, and further increases in magnetic fields imparted no additional benefits besides beyond the inherent signal-to-noise (SNR) gains. Furthermore, for SE, using a TE larger than the tissue $T_2$ enhances micro-vasculature signal relatively, though compromising SNR for spatial specificity. In addition, the intravascular SE MRI signals do not fully disappear even at high field strength as arteriolar and capillary contributions persist. The model, and the physiological considerations presented here can also be applied in contrast agent experiments and to other models, such as calibrated BOLD approach and vessel size imaging.



## Introduction

Functional magnetic resonance imaging (fMRI) (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992) is currently the most popular imaging technique employed for studying brain function non-invasively. The development of fMRI was fueled by the observation of the blood oxygenation level-dependent (BOLD) effect (Ogawa et al., 1990). Underlying this effect are changes in deoxygenated hemoglobin (deoxy-Hb) content resulting from changes in cerebral blood volume (CBV), cerebral blood flow (CBF), and oxygen metabolism following sensory stimulation or cognitive tasks (e.g. Buxton, 2002; van Zijl et al., 1998 and references therein) (see Glossary). Such physiological changes are detectable with MRI because the MR signal is sensitive to microscopic magnetic field gradients. Deoxy-Hb, which is paramagnetic, alters the magnetic susceptibility of blood and creates magnetic field gradients in and around deoxy-Hb containing blood vessels (Ogawa et al., 1990, 1993; Spees et al., 2001; Thulborn et al., 1982; Weisskoff et al., 1993; Yablonskiy and Haacke, 1994). Functional signals from the brain are encoded simply by a $T_2^*$ or $T_2$-weighted gradient recalled echo (GRE) and spin echo (SE) images, respectively. Such images form the basis of the BOLD contrast. However, they also contain neuronal-activity coupled signal alterations originating from mechanisms beyond the BOLD effect.

MRI signals in GRE and SE fMRI arise from intravascular (IV) and extra-vascular (EV) water protons, both of which are dependent on the blood vessel volume and oxygenation as well as on MRI pulse sequence employed. Several imaging parameters, such as echo time (TE), read-out duration, diffusion weighting and field strength, can be selected in order to improve spatial specificity of MRI signals with respect to neuronal activity. The MRI sequence of choice is GRE sequence because it is easy to implement and because of its high Contrast-to-Noise-Ratio (CNR). However, it is generally believed that a single-refocused SE sequence at high but not low magnetic fields yields MRI signals that are spatially more specific because the venous IV signals are diminished at high fields (e.g. Duong et al., 2003; Ugurbil et al., 2003) and the remaining EV signals around large blood vessels are partly re-focused by the additional 180° radio-frequency (RF) pulse employed (Boxerman et

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al., 1995a,b; Gilles et al., 1995; Kiselev and Posse, 1999; Kjolby et al., 2006; Weisskoff et al., 1992, 1994; Yablonskiy and Haacke, 1994).

Ideally, fMRI signals should be co-localized with neuronal activity. However, the spatial and physiological specificity of GRE and SE fMRI signals is a complex issue (for a review see Harel et al. (2006b)). Spatial miss-localization can occur due to changes in blood oxygenation and volume in remote draining veins (Frahm et al., 1994; Haacke et al., 1994; Hoogenraad et al., 1999; Kim et al., 1994; Lai et al., 1993; Menon et al., 1993; Oja et al., 1999; Turner, 2002) and due to the different point-spread functions of fMRI signal contributions (Engel et al., 1997; Parkes et al., 2005; Shmuel et al., 2007; Yacoub et al., 2005) as a function of vessel size.

Recently, fMRI at 4.7 T, 7 T and 9.4 T has been used to experimentally investigate the laminar distribution of the BOLD signal in cats and non-human primates in order to test the spatial specificity and the ability of fMRI to resolve functional units (Goense and Logothetis, 2006; Goense et al., 2007; Harel et al., 2006a; Zhao et al., 2004, 2006). The rationale behind this approach is that the neuronal activity and the accompanying hemodynamic changes are not expected to be evenly distributed over the cortical layers. The largest local field potential (LFP), oxidative metabolism changes, neurotransmitter release, and also capillary density are found in layer IV of the cortex (Weber et al., 2008 and references therein). The GRE fMRI signal correlates well with LFP (Logothetis et al., 2001) and, therefore, for sensory stimulation, the fMRI signal should also be highest in this layer. The common finding of these various laminar distribution studies was that GRE fMRI signals, even at high magnetic field strength, peaks at the surface vessels, whereas the fMRI signals obtained using SE peaks also in laminar layer IV (with similar magnitude as surface vessels), demonstrating higher spatial specificity in the later. In one of these studies (Harel et al., 2006a), fMRI was combined with histology, showing an excellent correspondence of cytoarchitecture and the distribution of SE fMRI signal amplitudes.

Other popular test cases to assess the functional specificity of fMRI signals are the detection of ocular dominance columns (ODC) and of orientation columns (OC) in animals and humans. In most mammals, neurons in the primary visual areas preferentially responding to the stimulation of one eye are spatially clustered in ODCs or to one orientation in OCs, respectively. ODCs and OCs have been identified first using the invasive techniques of electrophysiology and optical imaging, and more recently using fMRI non-invasively in animal models (Duong et al., 2001; Moon et al., 2007 and references therein) and in humans (Moon et al., 2007; Yacoub et al., 2007, 2008 and references therein); in the human ODC study, it has also been shown that SE is more specific for such high resolution mapping compared to GRE (Yacoub et al., 2007).

The argument put forward to explain these findings derives from the magnetic field dependence of the venous intravascular contribution and Monte-Carlo simulations of extra-vascular contributions to the BOLD signal. The latter have revealed that, for the same susceptibility value, SE is most sensitive to small vessels (e.g. capillaries) and GRE to large vessels (e.g. draining surface veins) (Boxerman et al., 1995a,b; Gilles et al., 1995; Kiselev and Posse, 1999; Kjolby et al., 2006; Weisskoff et al., 1992, 1994; Yablonskiy and Haacke, 1994). Several fMRI techniques, e.g. the calibrated BOLD approach (Davis et al., 1998) and vessel size imaging (Kiselev et al., 2005), rely on the findings of these simulations.

However, there are several complications that are not fully and/or quantitatively accounted for in these studies. First, the IV contribution to the BOLD signal can be substantial (Obata et al., 2004; van Zijl et al., 1998). This is true especially at low field strengths, where the IV BOLD signal can be as large or larger than the EV BOLD signal (Boxerman et al., 1995a; Jochimsen et al., 2004; Norris et al., 2002; Song et al., 1996). (Note that the notions 'low' and 'high' field strengths are not labeling the field strengths in absolute but in relative terms. In this study, 'low field' labels 1.5 T and 3 T and 'high fields' 7 T and larger.) While largely absent from veins at very high magnetic fields due to the very short $T_2$ of deoxygenated blood (e.g. Duong et al., 2003 and references therein), IV contributions are conceivable from arterioles where oxygen extraction is low but not zero, and from capillaries close to their arterial ends where the deoxygenation levels are lower and hence $T_2$ values are longer (Silvennoinen et al., 2003). Second, for modeling purposes, it is assumed that blood vessels are randomly oriented relative to the external magnetic field which is not necessarily true for surface vessels and cortex-penetrating arteries and veins. Finally, vascular compartments (arteries, arterioles, capillaries, venules, veins) differ in blood oxygenation (Vovenko, 1999) and volume (Weber et al., 2008) and, following functional activation, change their oxygenation values by a different amount. Consequently, the respective relaxation rate changes have to be compared at different susceptibility values. While the arterial and arteriolar effects may be negligible at low magnetic fields, they can become significant at high magnetic fields because the frequency shift across the luminal boundaries of the blood vessels is proportional to the product of the fractional deoxygenation and the static magnetic field magnitude.

In the present study, through simulations, we quantitatively assess the various GRE and SE based fMRI signal contributions and their spatial distribution by using an integrative model for these fMRI signals. The study comprises Monte-Carlo simulations of the extra-vascular BOLD effect, as before, but in addition, incorporation of blood relaxation properties and physiological alterations that accompany neuronal activity changes in a generalized derivation of function-induced signal changes in GRE and SE fMRI. Consequently, GRE and SE fMRI signal changes include the BOLD effect, but also mechanisms that are independent of blood oxygenation changes. Analytical formulae are provided for: a) intrinsic IV and EV relaxation rates (with no deoxy-Hb) derived from published experimental data; b) deoxy-Hb dependence, derived from Monte-Carlo simulations for the EV BOLD signal and for IV BOLD signal from experimental values, and c) contributions of all vascular components from arteries to veins. The model is similar to other previously proposed models (e.g. Buxton et al., 2004; He and Yablonskiy, 2007; Hoogenraad et al., 2001; Lu et al., 2004; van Zijl et al., 1998), but is more comprehensive as it is valid for magnetic field strengths from 1.5 T up to 16.4 T for both GRE and SE. The latter is significant because, as is demonstrated in this study, earlier BOLD modeling results based on simulations covering a smaller range of magnetic fields and/or higher susceptibility differences across blood vessel boundaries cannot be necessarily generalized for higher fields and/or susceptibility gradients, especially for the SE fMRI signals.

We illustrate results obtained with this model for both hyperoxia (i.e. oxygenation change with no CBV change) and functional stimulation. They indicate, most notably, that for SE: a) the IV BOLD signal does not fully disappear for high field strengths but rather shifts to blood vessels with high blood oxygenation; b) diffusion weighting at low field strengths would increase micro-vasculature weighting; c) using a TE larger than the $T_2$ of tissue also enhances micro-vasculature weighting, although it compromises signal-to-noise ratio in order to gain spatial specificity; d) there is a limit to the magnetic field increases resulting in attaining an improved micro-vasculature weighting; and e) for a hyperoxia experiment, higher micro-vasculature weighting is obtained than for a functional activation experiment. For GRE, there is no field strength at which the BOLD signal in the micro-vasculature is larger than in the macro-vasculature. These results have consequences for assessing spatial specificity of fMRI and for the exact formulation of some standard fMRI techniques currently relying solely on theoretical estimates of EV BOLD signals, e.g. calibrated BOLD signal (Davis et al., 1998) and vessel size imaging (Kiselev et al., 2005).

## Theory

Transverse magnetization of nuclear spins decays to zero by processes such as dipole–dipole coupling that is irreversible under a refocusing transformation, as well as dephasing induced by large-scale magnetic field inhomogeneities that is reversible under refocusing. The signal decay is typically characterized by an exponential decay time