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Gas-free calibrated fMRI with a correction for vessel-size sensitivity

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ABSTRACT

Calibrated functional magnetic resonance imaging (fMRI) is a method to independently measure the metabolic and hemodynamic contributions to the blood oxygenation level dependent (BOLD) signal. This technique typically requires the use of a respiratory challenge, such as hypercapnia or hyperoxia, to estimate the calibration constant, *M*. There has been a recent push to eliminate the gas challenge from the calibration procedure using asymmetric spin echo (ASE) based techniques. This study uses simulations to better understand spin echo (SE) and ASE signals, analytical modelling to characterize the signal evolution, and in vivo imaging to validate the modelling. Using simulations, it is shown how ASE imaging generally underestimates *M* and how this depends on several parameters of the acquisition, including echo time and ASE offset, as well as the vessel size. This underestimation is the result of imperfect SE refocusing due to diffusion of water through the extravascular environment surrounding the microvasculature. By empirically characterizing this SE attenuation as an exponential decay that increases with echo time, we have proposed a quadratic ASE biophysical signal model. This model allows for the characterization and compensation of the SE attenuation if SE and ASE signals are acquired at multiple echo times. This was tested in healthy subjects and was found to significantly increase the estimates of *M* across grey matter. These findings show promise for improved gas-free calibration and can be extended to other relaxation-based imaging studies of brain physiology.

Introduction

Calibrated functional magnetic resonance imaging (fMRI) was developed to disentangle the hemodynamic and metabolic contributions to the blood oxygenation level dependent (BOLD) signal using simultaneous measurements of the gradient echo BOLD signal and cerebral blood flow (CBF) (Davis et al., 1998; Hoge et al., 1999). A calibration experiment is run to estimate the calibration constant, *M*, and is most commonly performed using a respiratory challenge where subjects inhale a gas mixture with additional carbon dioxide and/or oxygen to elicit changes in the BOLD signal and CBF or arterial oxygen tension (Bulte et al., 2012; Chiarelli et al., 2007; Davis et al., 1998; Gauthier and Hoge, 2012). The use of hypercapnia, the state of elevated CO_2 in blood, suffers from multiple limitations: it may violate the assumption of isometabolism on which standard calibration models depend (Bulte et al., 2009; Chen and Pike, 2010a; Hall et al., 2011; Xu et al., 2011), and it typically measures perfusion changes using time-resolved arterial spin labelling (ASL), an imaging technique with a low signal-to-noise ratio. Similarly, the use of hyperoxia, the state of elevated O_2 in blood, requires either the additional measurement of the oxygen extraction fraction and the concentration of hemoglobin in blood or the assumption of those two parameters (Chiarelli et al., 2007; Mark et al., 2011) that can lead to bias (Blockley et al., 2012). Hyperoxia may also produce concomitant decreases in CBF if blood CO_2 is not controlled (Bulte et al., 2007; Croal et al., 2015). In general, gas challenges require additional apparatus and increased subject tolerance and preparation, thus, a gas-free alternative would greatly improve the appeal of calibrated fMRI.

To date, a limited number of studies have examined gas-free calibration of the BOLD signal by substituting the gas challenge with a measurement of R_2' at rest, the reversible component of the transverse

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relaxation rate (Blockley et al., 2015; Fujita et al., 2006; Kida et al., 2000; Shu et al., 2015). Under the assumption that the primary difference between the apparent and the irreversible relaxation rates (R_2* and R_2, respectively) in a voxel is from the field inhomogeneities generated by deoxyhemoglobin (deoxyHb) (Blockley et al., 2012; Fujita et al., 2006), R_2' is the favoured candidate for gas-free calibration due to its intimate relationship with baseline blood oxygen saturation and the deoxygenated cerebral blood volume (CBV) (Yablonskiy and Haacke, 1994). However, as in most areas of MR relaxometry, the apparent values of R_2' are highly dependent on the measurement technique and may produce different values due to multi-exponential decay, imperfect spin echo refocusing, and other acquisition related factors (Ni et al., 2014). Blockley et al. (2015) recently proposed a calibration technique that is insensitive to multi-exponential decay and intrinsic tissue T_2 differences based on using spin echo (SE) and asymmetric spin echo (ASE) imaging. When compared against traditional hypercapnic calibration, their ASE calibration underestimated M across grey matter (GM) and the visual cortex, on average. This underestimation was postulated to arise from incomplete spin echo refocusing of spins diffusing in the extravascular space. This effect is the same source of contrast in SE BOLD imaging, and is known to be vessel-size and field strength dependent (Boxerman et al., 1995).

In addition to imperfect SE refocusing, several other sources may confound the observed R_2' values. Macroscopic field inhomogeneities, which are prominent around air-tissue interfaces, lead to dramatic geometric distortions and signal intensity distortions in echo planar imaging (EPI). The intensity distortions tend to increase R_2' and these effects can be mitigated by a range of acquisition-related methods (Blockley and Stone, 2016). Cerebrospinal fluid (CSF) has recently been shown to significantly increase measured R_2' in grey matter (Simon et al., 2016; Stone and Blockley, 2016). This is postulated to arise from a chemical shift between CSF and parenchyma, resulting in enhanced signal dephasing in tissue voxels with partial voluming with CSF (He and Yablonskiy, 2007). By adding a fluid attenuated inversion recovery (FLAIR) preparation to the imaging sequence, the CSF signal can be eliminated and the R_2' of neighbouring parenchymal voxels tends to decrease. Unlike field inhomogeneities and CSF, which can be prospectively and retrospectively managed, additional non-deoxyHb sources of tissue magnetic susceptibility, such as iron depositions and myelin, will alter R_2' in a less predictable manner (they can increase or decrease R_2', depending on their susceptibility and relative concentration). Kida et al. (2000) found that these other sources of susceptibility have negligible contributions to the observed R_2 and R_2* (and hence R_2') at 7 T in rats. In this study, which was performed at a field strength of 3 T, we do not consider these other sources, consistent with earlier work (Blockley et al., 2015; Fujita et al., 2003).

The purpose of this study was to determine how incomplete refocusing of SE and ASE signals affects the estimation of R_2' and how it can be accounted for to obtain a more accurate estimate of M. Simulations were used to determine the vessel-size dependence of the R_2' underestimation and to develop a strategy to retrospectively correct for it. This strategy was tested in vivo, taking precautions to avoid confounds from macroscopic field inhomogeneities and CSF partial volume. These ASE-based M calculations were compared against hypercapnic calibration in the same subjects.

Theory

Calibrated fMRI with asymmetric spin echo imaging

The standard calibrated fMRI model that relates changes in the cerebral metabolic rate of oxygen ($CMRO_2$) and CBF to changes in the gradient echo (GE) BOLD signal is (Davis et al., 1998)

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1 - \left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\left(\frac{CMRO_2}{CMRO_{2|0}}\right)^{\beta}\right), \quad (1)$$

where the subscript '0' refers to a value at baseline and $\Delta BOLD = BOLD - BOLD_0$. α is the Grubb constant and accounts for coupling between CBV and CBF arising from an empirical power law relation between the two (Grubb et al., 1974). β describes the non-linear dependence of the change in R_2* on the susceptibility offset of blood relative to tissue (Berman and Pike, 2016; Boxerman et al., 1995). M is proportional to the resting concentration of deoxyHb in blood and it can be considered the maximum fractional increase in the GE BOLD signal, which would theoretically occur upon removal of all deoxyHb in blood (i.e., venous oxygen saturation → 100%) (Gauthier et al., 2011; Hoge et al., 1999; Krieger et al., 2014). M is estimated with hypercapnia (M_{HC}) by measuring changes in CBF and the BOLD signal using

$$M_{HC} = \frac{\Delta BOLD}{BOLD_0}\Big/ 1 - \left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}. \quad (2)$$

Rather than perturb the oxygen saturation (SO_2) like a gas-based calibration would, a spin echo image perturbs the spins of the system such that, *in the absence of diffusion*, the SE will refocus all the spin dephasing induced by deoxyHb present in blood vessels and will, therefore, be equal to the maximum possible GE BOLD signal. To then estimate R_2', one can acquire another image with R_2*-weighting, since $R_2^* = R_2 + R_2'$. Acquiring an ASE image is appropriate for this because it will have the same slice profile as the SE image. Example SE and ASE sequences and their transverse signal decays are displayed in Fig. 1. If the spin echo in the ASE image is shifted earlier by a time τ, the signal can be described by

$$S_{ASE}(TE, \tau) = S_0 e^{-R_2 \cdot TE} e^{-R_2' \tau}, \quad (3)$$

where TE is the echo time, τ is the ASE offset, and S_0 is the signal at TE = 0. In the convention used here, $\tau > 0$ corresponds to TE occurring a time τ *after* the SE occurs. Eq. (3) assumes $\tau > 0$ but in the case of $\tau < 0$, τ should be replaced by $|\tau|$. The SE signal, S_{SE}, is also described by Eq. (3) but with $\tau = 0$. If τ is chosen to be the same as the echo time used for functional imaging, then M from ASE imaging (M_{ASE}) can be estimated from the ratio of an SE and ASE image, both acquired at time TE (Blockley et al., 2015):

$$M_{ASE} = \ln(S_{SE}/S_{ASE}) = R_2' \tau. \quad (4)$$

Quadratic spin echo attenuation

The model of gas-free calibration described above by Eq. (4) applies in the absence of diffusion, where the 180° pulse will perfectly refocus

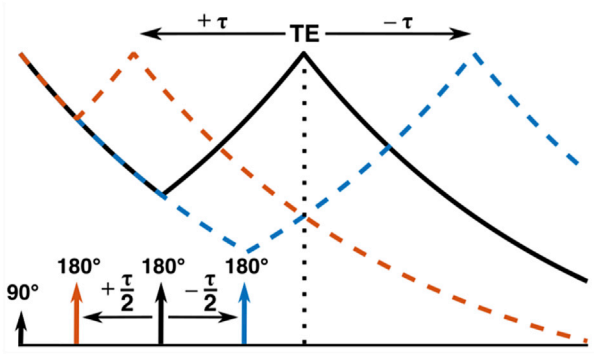

Fig. 1. A schematic of the SE and ASE pulse sequences and their transverse signal decay. All three sequences share the same 90° excitation pulse and sample the signal at the same echo time (TE, dotted vertical line). The black curve represents the pure SE sequence signal decay. The dashed orange curve represents the ASE sequence signal decay when the ASE offset is +τ. The dashed blue curve represents the ASE sequence signal decay when the ASE offset is –τ. The three signals have no T_2 decay, no diffusion effects, and only show R_2'-related decay and refocusing. The two ASE signals are equal at TE.