Published in final edited form as:

NMR Biomed. 2015 February ; 28(2): 264–271. doi:10.1002/nbm.3250.

Measurement of Parenchymal Extravascular R_2^* and Tissue Oxygen Extraction Fraction Using Multi-echo VASO MRI at 7 Tesla

Ying Cheng^{1,2}, Peter C. M. van Zijl^{1,3}, and Jun Hua^{1,3,*}

¹F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD USA

²Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD USA

³The Russell H. Morgan Department of Radiology and Radiological Science, Division of MR Research, The Johns Hopkins University School of Medicine, Baltimore, MD USA

Abstract

Parenchymal extravascular R_2^* is an important parameter for quantitative blood-oxygenation-level-dependent (BOLD) studies. Total and intravascular R_2^* values and changes in R_2^* values during functional stimulations have been reported in a number of studies. The purpose of this study was to measure absolute extravascular R_2^* values in human visual cortex and estimate the intra- and extravascular contributions in the BOLD effect at 7T. Vascular-space-occupancy (VASO) MRI was employed to separate out the extravascular tissue signal. Multi-echo VASO and BOLD fMRI with visual stimulation were performed at 7T for R_2^* measurement at a spatial resolution of $2.5 \times 2.5 \times 2.5 \text{ mm}^3$ in healthy volunteers ($n = 6$). The ratio of changes in extravascular and total R_2^* (R_2^*) was used to estimate the extravascular fraction of the BOLD effect. Extravascular R_2^* were found to be $44.66 \pm 1.55 \text{ s}^{-1}$ and $43.38 \pm 1.51 \text{ s}^{-1}$ (mean $\pm$ SEM, $n = 6$) at rest and activation, respectively, in human visual cortex at 7T. The extravascular BOLD fraction was estimated to be $91 \pm 3\%$. Parenchymal oxygen extraction fraction (OEF) during activation was estimated to be 0.24 ± 0.01 based on the R_2^* measurements, indicating an approximately 37% decrease compared to OEF at rest.

Keywords

BOLD; VASO; fMRI; extravascular; R_2^* ; high field; CBV; OEF

Introduction

Parenchymal extravascular R_2^* is an important parameter for quantitative blood-oxygenation-level-dependent (BOLD) studies. It is well known that the BOLD effect

*Corresponding Author: Jun Hua, Ph.D. Johns Hopkins University School of Medicine, Department of Radiology; Kennedy Krieger Institute, F.M. Kirby Research Center for Functional Brain Imaging 707 N Broadway, Baltimore, MD, 21205 jhua@mri.jhu.edu Tel: 443-923-9551 Fax: 443-923-9505.

increases with field strength, and the BOLD signal from extravascular tissue becomes more dominant at higher field, as the intravascular BOLD signal contribution is significantly reduced due to the faster R_2^* decay of venous blood [1-9]. The relative contribution of the extravascular BOLD effect can be estimated using the ratio of extravascular and total R_2^* changes during neuronal activation. Furthermore, R_2^* changes can also be used to estimate changes in physiological parameters such as venous oxygenation (Y_v) and tissue oxygen extraction fraction (OEF) during brain activation.

Total and intravascular R_2^* values at various field strengths have been reported in a number of studies in animals and humans [2, 7-22]. However, reports on extravascular R_2^* values remain scarce in the literature (Table 1), as it is not trivial to measure mainly due to the difficulty to separate out the extravascular and intravascular signals in parenchyma. Duong et al. [1] used diffusion gradients to suppress the intravascular BOLD signal in order to investigate the microvascular contribution in the BOLD effects at 4T and 7T. Van der Zwaag et al. [8] excluded the intravascular BOLD effects in large veins using high resolution anatomical scans and reported R_2^* values in human motor cortex at 1.5, 3 and 7T at a spatial resolution of $1 \times 1 \times 3 \text{ mm}^3$. Lu et al. [22] determined parenchymal extravascular R_2^* values at 1.5T and 3T using multi-echo vascular-space-occupancy (VASO) MRI, which eliminates the intravascular signal based on different T_1 relaxation times of blood and tissue [23]. Donahue et al. [13] employed bipolar crushing gradients to suppress fast flowing blood signal (intravascular), and measured extravascular R_2^* change (ΔR_2^*) during visual stimulation in human brain at 1.5T, 3T and 7T. To date, however, the combined BOLD/VASO method for determination of parenchymal extravascular R_2^* values [22] has not yet been used in human brain at 7T.

In this study, we applied multi-echo BOLD and VASO fMRI with visual stimulation to measure total and extravascular R_2^* values in the visual cortex in human brain at 7T. By comparing total and extravascular R_2^* during visual stimulation, the intra- and extravascular parenchymal contributions to the BOLD signal at 7T could be assessed. Y_v and OEF changes during activation were estimated from the R_2^* measurements.

Methods

The protocol was approved by the Internal Review Board of the Johns Hopkins University. Seven healthy subjects gave informed written consent before participating this study. From these, only six were included in the final report due to the fact that the relative extravascular R_2^* from subject 7 was more than two standard deviations larger than the averaged value from the other six subjects. Experiments were performed on a 7T human MRI scanner (Philips Healthcare, Best, The Netherlands), using a quadrature transmit head coil (10 inch or 25.4 cm in foot-head coverage) and a 32-channel phased array receive coil (Nova Medical, Wilmington, MA, USA). A single slice was carefully placed to cover the calcarine fissure. Three pseudo-randomized fMRI scans including two VASO (repetition time or TR = 4 s, inversion time or TI = 1293 ms) and one BOLD (TR = 2 s) scans were performed on each participant with visual stimulation (yellow/blue flashing checkerboard, 40s off 24s on, 4 blocks, 1 extra off period in the end). The blood nulling TI in VASO was calculated using blood $T_1 = 2212$ ms, measured from bovine blood with 79% oxygenation and Hematocrit

(Hct) = 0.43 at 7T [24]. The spatially nonselective inversion pulse in VASO was optimized for 7T in previous work (hyperbolic secant adiabatic pulse, duration = 20 ms, peak B1 = 15 μ T, bandwidth = 1050Hz, >95% inversion at half of the maximum B1 in phantom and brain) [25, 26]. A magnetization reset module (90° RF pulse followed by spoiler gradients) [27] was applied immediately after the readout in both VASO and BOLD scans to suppress inflow effects from non-inverted spins. For both BOLD and VASO fMRI, single-shot gradient echo (GE) echo-planar-imaging (EPI) readout was used with four echoes acquired at TE = 9, 27, 45 and 63 ms. Common imaging parameters included: flip angle (FA) = 67° (Ernst angle for BOLD scan based on a grey matter T1 of 2132 ms [28]), field of view (FOV) = 192×192mm², spatial resolution = 2.5×2.5×2.5 mm³, parallel imaging (SENSE) acceleration factor = 4, partial Fourier fraction = 0.6. Second-order shimming was applied in both BOLD and VASO scans, for which a water line width of <60Hz was achieved in all scans.

All fMRI images were corrected for motion and baseline drift using Statistical Parametric Mapping (SPM8, University College London, UK) and Matlab R2009b (Mathworks, Natick, MA, USA). BOLD and VASO images at different TEs were co-registered. The two VASO scans were averaged to improve signal-to-noise ratio (SNR) [22]. VASO images from all four echoes were used to extrapolate to an effective TE of 0 ms to minimize BOLD contamination. A general linear model (GLM) was used to detect activated voxels in VASO (TE = 0 ms) and BOLD (TE = 27 ms, second echo) scans. Temporal SNR (tSNR) was calculated as the voxel-wised average signal divided by standard deviation along the time course during the rest periods (excluding the data acquired during 20 s at the start of each rest period). The criteria for activation were t-score > 1.5 (BOLD), t-score > 1 (VASO), adjusted p-value < 0.05, cluster size > 4 and tSNR > 20 [29]. Only voxels activated in both modalities were used for R₂^{*} calculation so that voxels containing large vessels are excluded and signals are predominantly localized in the parenchyma [23, 29, 30]. Signal intensities (S) at the four echo times were numerically fitted as a function of TE (S =

S₀·exp(-TE·R₂^{*})) to obtain S₀ and R₂^{*} values on a voxel-wise basis.

Using the calculated R₂^{*} values, Y_v and parenchymal OEF can be quantified using the equations for the static dephasing regime described in [22, 31, 32]:

$$\Delta R_{2t}^{\dagger} \approx x_v \cdot \omega_0 \cdot \frac{4\pi}{3} \Delta \chi_{deoxy} \cdot Hct \cdot \left\{ CBV^{act} \left(1 - Y_v^{act} \right) - CBV^{rest} \left(1 - Y_v^{rest} \right) \right\} \quad [1]$$

where R_{2t}^{*} = R_{2t, act}^{*} - R_{2t, rest}^{*} (t denotes extravascular tissue), x_v = 0.7 is the venous fraction of cerebral blood volume (CBV) including capillaries [22], “act” and “rest” denote values during activation and rest, respectively. The reported susceptibility difference between fully oxygenated and deoxygenated blood (χ_{deoxy}) varies from 0.18 ppm to more than 0.3ppm in the literature [32-36]. Here, we adopted a value of 0.27 ppm from most recent studies [34, 35]. Other parameters assumed were: microvascular hematocrit (Hct) = 0.356 [37] and CBV^{rest} = 0.052ml blood/ml tissue [29]. CBV^{act} can be calculated from the VASO signal change [23]. By assuming Y_v^{rest} = 0.61, Y_v^{act} can be calculated from Eq. [1], and OEF can be quantified using [38]:

$$1 - Y_v = 1 - Y_a + OEF \cdot Y_a \quad [2]$$

where the arterial oxygenation (Y_a) was taken to be 0.98, corresponding to a resting state OEF of 0.38.

Results

Figs. 1a-b show representative activation maps (thresholded) superimposed on BOLD and VASO images from one subject. The VASO signal changes displayed are those found when extrapolating to TE = 0 ms. Figs. 1c-d show the corresponding t-score maps. Note that the t-scores for activated voxels in VASO (negative signal change upon activation) were positive as well, because the contrast itself was reversed when performing GLM analysis. The peak activated voxels were well localized in the visual cortex. For the purpose of this study, activations that were clearly outside the visual regions were excluded in the analysis. Figs. 1e-f show the time courses of fractional signal changes averaged over activated voxels in the BOLD and VASO scans, respectively. As expected, negative signal changes in VASO were observed upon neuronal activation because the concomitant vasodilatation results in tissue signal reduction at TE = 0ms [23].

Typical BOLD and VASO images at all four echo times are shown in Figs. 2a-b. As second order shimming was applied, and a single slice was acquired in the occipital lobe (which has a relatively homogeneous B0 field), the distortion found in these images was small. In addition, images at different TEs were co-registered before further analysis. The average tSNR (n = 6) of images at the longest echo time (TE = 63ms) were 16.0 ± 1.9 and 12.8 ± 1.7 for BOLD and VASO, respectively, which is considered sufficient for robust R_2^* fitting. (Please note that the tSNR threshold of 20 mentioned in Methods was only applied on the extrapolated (TE = 0 ms) VASO images and BOLD images at the second echo time during functional analysis. Here, the tSNR of images at the longest TE shows that it is sufficient for R_2^* fitting.) Figs. 2c-d show the averaged result (n = 6) of TE-dependence curves of relative and absolute signal changes for both BOLD and VASO fMRI. Only the commonly activated voxels in both modalities were selected. The absolute BOLD signal change (Fig. 2d) was the largest at the second echo time (TE = 27 ms), consistent with the notion that the optimal TE for BOLD contrast should be around tissue T_2^* [39]. The well-known linear relationship between $\Delta S/S$ and TE in BOLD and VASO was fitted (Fig. 2c). The VASO signal change is negative for very short TE, but reverses sign at longer TEs. This is expected as the extravascular BOLD effects (positive) become quite large at longer TE, which counteract the negative VASO signals. This also stresses the importance of extrapolating to TE = 0 or using a readout with very short TE [25] for VASO fMRI at 7T.

The fitted total and extravascular R_2^* values during rest and activation in six subjects are summarized in Table 2. Only the voxels that were activated in both BOLD and VASO scans were included. The ratio of extravascular R_2^* to total R_2^* was $91 \pm 3\%$ (n = 6, mean $\pm$ SEM). Figs. 3a-b show the R_2^* time courses from one subject.

CBV increased by $35.8 \pm 3.2\%$ (n = 6, mean $\pm$ SEM) during visual stimulation, calculated from a $-1.94 \pm 0.17\%$ (n = 6, mean $\pm$ SEM) VASO signal change using the extrapolated

VASO images at TE = 0 ms and assuming a baseline CBV value of 0.052ml blood/ml tissue[29]. Using Eqs. [1,2], Y_v^{act} and OEF during activation were quantified to be 0.75 ± 0.01 and 0.24 ± 0.01 ($n = 6$, mean $\pm$ SEM), respectively, indicating an approximately 37% OEF decrease during visual stimulation.

Discussion

In this study, we applied multi-echo VASO fMRI to remove the intravascular signal and measured the extravascular (tissue) R_2^* values in human visual cortex at 7T. Table 1 compares these data with the total and extravascular parenchymal R_2^* values reported at various field strengths (1.5T, 3T and 7T) in the literature. The R_2^* values measured here are in good agreement with the Donahue study [13], but differ considerably from the ones reported in the van der Zwaag study [8]. One plausible explanation may be that both the Donahue and current studies were conducted in the visual cortex with comparable spatial resolution, whereas the van der Zwaag study measured R_2^* values in the motor cortex with a much finer spatial resolution ($1 \times 1 \times 3 \text{ mm}^3$). As expected, both total and extravascular R_2^* increase with field strength. The absolute and relative R_2^* changes (R_2^* and R_2^*/R_2^*) during activation also increase with the field, indicating better sensitivity for BOLD fMRI as predicted. Extravascular R_2^* shows a linear trend with field strength ($R_2^* = -0.196 \cdot B_0 + 0.114$, correlation coefficient = 0.99, p-value = 0.09), consistent with the theoretical calculations for extravascular BOLD effects in the static dephasing regime model proposed by Yablonskiy and Haacke [32]. The relative contribution from the extravascular component in the total BOLD contrast becomes larger at higher field, as indicated by the larger ratio of extravascular R_2^* to total R_2^* . Our results showed that the BOLD effect is dominated by the extravascular component (91%) at 7T, in line with the results from Duong et al.[1] and Donahue et al.[13] that used crushing gradients to suppress the intravascular signal. These experimental results are consistent with the theoretical calculations that the intravascular BOLD signal will be significantly reduced relative to the extravascular signal at higher field due to the faster R_2^* decay of venous blood [1-9]. It is important to mention that the intravascular effects are actually larger than extravascular at short TE [7, 17, 21]. However, when using typical TEs for BOLD fMRI (which are usually comparable to GM T2*), the relative contribution from the intravascular venous compartment to the overall parenchymal effect is small.

When assuming resting OEF and CBV values from the literature, multi-echo VASO fMRI also allows the measurement of changes in physiological parameters such as Y_v and OEF in the parenchyma during neuronal activation. OEF reduction upon visual stimulation measured here at 7T agrees reasonably well with previously reported values: 33% [40, 41], 39% [22], 53% [33] at 1.5T and 45% [22] at 3T. A number of neurophysiology studies suggest that the vasodilation during functional stimulation occurs predominantly in arterioles and capillaries that are very close to the active neural tissue [42], indicating an improved spatial specificity for CBV weighted VASO fMRI, as demonstrated by several animal and human fMRI studies [23, 29, 30]. Therefore the OEF changes measured here were expected to be predominantly localized in the parenchyma by taking overlapping voxels activated in both BOLD and VASO scans, while some previous measurements were made mainly in the draining veins [33, 40, 41, 43-46].

In this 7T study, a blood T1 of 2212 ms was used to calculate the blood nulling time (TI) in VASO fMRI, which was measured from 79% oxygenation bovine blood (Hct = 0.43) at 7T[24]. Although this is within typical physiological range in normal human brains, it is known that blood T1 is sensitive to hematocrit and, to a lesser extent, to oxygenation [47-49]. This may affect the quantification of extravascular R_2^* values and relative CBV changes during functional activation. The oxygenation level of 79% corresponds mostly to an estimated average of the blood in capillaries and venules [38, 50]. As only voxels activated from both the BOLD and VASO scans were used in the calculations, blood signals in veins should be largely excluded (if blood in veins is not completely nulled in VASO scans, it would reduce or cancel out the negative VASO changes during activation, thus be excluded in the voxel selection). Therefore, only incompletely nulled blood in arteries and arterioles is most likely to affect the extravascular R_2^* quantification. However, since the R_2^* values are comparable in arterial blood (about 40 s^{-1} , unpublished data, experimental setup same as in [49]) and in extravascular tissue (Table 2) at 7T, this should not result in major biases in the extravascular R_2^* estimation. Gu et al.[51] showed that the VASO signal change ($\Delta S/S$, thus ΔCBV) during visual stimulation plateaus over a range of about 150 ms around the theoretical blood nulling TI. Donahue et al.[52] also demonstrated that at typical spatial resolution for fMRI (around 3mm) and at relatively long TRs (>4s), the variation of blood T1 over a range of 100 ms has very limited influence on VASO signal change and CBV estimation. It is therefore reasonable to expect that the blood T1 variation over typical physiological ranges in normal human brains should not have substantial effects on the CBV estimation here. Moreover, the relative difference of T1 values decreases with field strength[28, 30], which should further reduce the potential biases in R_2^* and CBV estimation resulted from blood T1 variations.

The contribution from physiological noises in fMRI signals has been shown to increase with field strength and voxel size [53]. In order to check this for our study, we measured the coefficients of variation for the R_2^* values (Total R_2^* : 0.073; Extravascular R_2^* : 0.085), which were found to be comparable to those reported at 3T (Total R_2^* : 0.076; Extravascular R_2^* : 0.063) and 1.5T (Total R_2^* : 0.077; Extravascular R_2^* : 0.079) in a previous study adopting similar methodology [22]. However, a larger voxel size was used in that study ($2 \times 2 \times 5 = 20 \text{ mm}^3$ versus $2.5 \times 2.5 \times 2.5 = 15.625 \text{ mm}^3$ here). From this we conclude that the noise contribution in the R_2^* measurements at 7T would be larger than 3T and 1.5T if the same voxel size were used. We also noticed that the total R_2^* values measured in subjects 4 and 6 were slightly lower than the corresponding extravascular R_2^* values (total R_2^* is expected to be higher than extravascular R_2^* due to additional blood contributions), although the difference was within noise range. This also occurred for one subject reported in previous 3T data but not 1.5T [22]. We attribute this to the many possible contributions to R_2^* , making it difficult to measure this parameter with great accuracy. More repeats and averaging may be necessary for robust R_2^* measurement on a single-subject level.

A potential source of errors when estimating Y_v^{act} and OEF using Eqns. 1 and 2 comes from the literature values assumed for the model parameters. While this has been investigated in previous works [54-56], here again we performed an error analysis by estimating OEF using parameter values (assumed in Methods) over the normal physiological range: baseline CBV from 0.045 to 0.055 ml/ml, microvascular Hct from 0.38 to 0.46 and χ_{deoxy} from 0.20 to

0.27 ppm. Less than 8% estimated OEF differences were found between the two ends of both Hct and χ_{deoxy} ranges, whereas about 14% difference were observed when varying baseline CBV values. The assumed CBV^{rest} value of 0.052ml/ml in this study is approximated [29] based on the reported 0.048 - 0.055 ml/ml range in the literature [57-61]. Although this error analysis shows that the estimated OEF values in this study are only moderately affected by these assumptions, the measurement of these physiological parameters in each participant would certainly improve the accuracy for OEF quantification.

Conclusions

Total and extravascular R_2^* values in the parenchyma in human visual cortex were measured using multi-echo VASO and BOLD fMRI with visual stimulation at 7T. The parenchymal extra-vascular R_2^* value was $44.66 \pm 1.55 \text{ s}^{-1}$ at rest, and the ratio of extravascular R_2^* to total R_2^* was $91 \pm 3\%$ at 7T, confirming a predominant contribution from the extravascular component of the BOLD effect. A 37% decrease in parenchymal OEF during stimulation was estimated based on these measurements, consistent with values reported at lower field strengths.

Acknowledgments

The authors thank Mr. Joseph S. Gillen, Ms. Terri Lee Brawner, Ms. Kathleen A. Kahl, and Ms. Ivana Kusevic for experimental assistance. This project was supported by the National Center for Research Resources and the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health through resource grant P41 EB015909. Equipment used in the study was manufactured by Philips. Dr. van Zijl is a paid lecturer for Philips Healthcare. Dr. van Zijl is the inventor of technology that is licensed to Philips. This arrangement has been approved by Johns Hopkins University in accordance with its conflict of interest policies.

Abbreviations

BOLD	blood oxygenation level dependent
VASO	vascular space occupancy
CBV	cerebral blood volume
OEF	oxygen extraction fraction
fMRI	functional MRI
GE	gradient echo
EPI	echo planar imaging
SENSE	sensitivity encoding
SNR	signal-to-noise ratio
GLM	general linear model

References

1. Duong TQ, Yacoub E, Adriany G, Hu X, Ugurbil K, Kim SG. Microvascular BOLD contribution at 4 and 7 T in the human brain: gradient-echo and spin-echo fMRI with suppression of blood effects. *Magn Reson Med*. 2003; 49(6):1019–27. [PubMed: 12768579]

2. Gati JS, Menon RS, Ugurbil K, Rutt BK. Experimental determination of the BOLD field strength dependence in vessels and tissue. *Magn Reson Med*. 1997; 38(2):296–302. [PubMed: 9256111]
3. Ogawa S, Menon RS, Tank DW, Kim SG, Merkle H, Ellermann JM, Ugurbil K. Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophys J*. 1993; 64(3):803–12. [PubMed: 8386018]
4. Song AW, Wong EC, Tan SG, Hyde JS. Diffusion weighted fMRI at 1.5 T. *Magn Reson Med*. 1996; 35(2):155–8. [PubMed: 8622577]
5. Ugurbil K, Hu X, Chen W, Zhu XH, Kim SG, Georgopoulos A. Functional mapping in the human brain using high magnetic fields. *Philos Trans R Soc Lond B Biol Sci*. 1999; 354(1387):1195–213. [PubMed: 10466146]
6. Ugurbil K, Toth L, Kim DS. How accurate is magnetic resonance imaging of brain function? *Trends Neurosci*. 2003; 26(2):108–14. [PubMed: 12536134]
7. Uludag K, Muller-Bierl B, Ugurbil K. An integrative model for neuronal activity-induced signal changes for gradient and spin echo functional imaging. *Neuroimage*. 2009; 48(1):150–65. [PubMed: 19481163]
8. van der Zwaag W, Francis S, Head K, Peters A, Gowland P, Morris P, Bowtell R. fMRI at 1.5, 3 and 7 T: characterising BOLD signal changes. *Neuroimage*. 2009; 47(4):1425–34. [PubMed: 19446641]
9. Yacoub E, Shmuel A, Pfeuffer J, Van De Moortele PF, Adriany G, Andersen P, Vaughan JT, Merkle H, Ugurbil K, Hu X. Imaging brain function in humans at 7 Tesla. *Magn Reson Med*. 2001; 45(4):588–94. [PubMed: 11283986]
10. Chen NK, Oshio K, Panych LP, Rybicki FJ, Mulkern RV. Spatially selective T2 and T2 * measurement with line-scan echo-planar spectroscopic imaging. *J Magn Reson*. 2004; 171(1):90–6. [PubMed: 15504686]
11. Chien D, Levin DL, Anderson CM. MR gradient echo imaging of intravascular blood oxygenation: T2* determination in the presence of flow. *Magn Reson Med*. 1994; 32(4):540–5. [PubMed: 7997123]
12. Deistung A, Rauscher A, Sedlacik J, Stadler J, Witoszynskij S, Reichenbach JR. Susceptibility weighted imaging at ultra high magnetic field strengths: theoretical considerations and experimental results. *Magn Reson Med*. 2008; 60(5):1155–68. [PubMed: 18956467]
13. Donahue MJ, Hoogduin H, van Zijl PC, Jezzard P, Luijten PR, Hendrikse J. Blood oxygenation level-dependent (BOLD) total and extravascular signal changes and DeltaR2* in human visual cortex at 1.5, 3.0 and 7.0 T. *NMR Biomed*. 2011; 24(1):25–34. [PubMed: 21259367]
14. Lee SP, Silva AC, Ugurbil K, Kim SG. Diffusion-weighted spin-echo fMRI at 9.4 T: microvascular/tissue contribution to BOLD signal changes. *Magn Reson Med*. 1999; 42(5):919–28. [PubMed: 10542351]
15. Li D, Wang Y, Waight DJ. Blood oxygen saturation assessment in vivo using T2* estimation. *Magn Reson Med*. 1998; 39(5):685–90. [PubMed: 9581597]
16. Li TQ, van Gelderen P, Merkle H, Talagala L, Koretsky AP, Duyn J. Extensive heterogeneity in white matter intensity in high-resolution T2*-weighted MRI of the human brain at 7.0 T. *Neuroimage*. 2006; 32(3):1032–40. [PubMed: 16854600]
17. Silvennoinen MJ, Clingman CS, Golay X, Kauppinen RA, van Zijl PC. Comparison of the dependence of blood R2 and R2* on oxygen saturation at 1.5 and 4.7 Tesla. *Magn Reson Med*. 2003; 49(1):47–60. [PubMed: 12509819]
18. Wright GA, Hu BS, Macovski A. 1991 I.I. Rabi Award. Estimating oxygen saturation of blood in vivo with MR imaging at 1.5 T. *J Magn Reson Imaging*. 1991; 1(3):275–83. [PubMed: 1802140]
19. Yacoub E, Van De Moortele PF, Shmuel A, Ugurbil K. Signal and noise characteristics of Hahn SE and GE BOLD fMRI at 7 T in humans. *Neuroimage*. 2005; 24(3):738–50. [PubMed: 15652309]
20. Zhao F, Wang P, Kim SG. Cortical depth-dependent gradient-echo and spin-echo BOLD fMRI at 9.4T. *Magn Reson Med*. 2004; 51(3):518–24. [PubMed: 15004793]

21. Zhao JM, Clingman CS, Narvainen MJ, Kauppinen RA, van Zijl PC. Oxygenation and hematocrit dependence of transverse relaxation rates of blood at 3T. *Magn Reson Med.* 2007; 58(3):592–7. [PubMed: 17763354]
22. Lu H, van Zijl PC. Experimental measurement of extravascular parenchymal BOLD effects and tissue oxygen extraction fractions using multi-echo VASO fMRI at 1.5 and 3.0 T. *Magn Reson Med.* 2005; 53(4):808–16. [PubMed: 15799063]
23. Lu H, Golay X, Pekar JJ, Van Zijl PC. Functional magnetic resonance imaging based on changes in vascular space occupancy. *Magn Reson Med.* 2003; 50(2):263–74. [PubMed: 12876702]
24. Dobre MC, Ugurbil K, Marjanska M. Determination of blood longitudinal relaxation time (T1) at high magnetic field strengths. *Magn Reson Imaging.* 2007; 25(5):733–5. [PubMed: 17540286]
25. Hua J, Jones CK, Qin Q, van Zijl PC. Implementation of vascular-space-occupancy MRI at 7T. *Magn Reson Med.* 2013; 69(4):1003–13. [PubMed: 22585570]
26. Visser F, Zwanenburg JJ, Hoogduin JM, Luijten PR. High-resolution magnetization-prepared 3D-FLAIR imaging at 7.0 Tesla. *Magn Reson Med.* 2010; 64(1):194–202. [PubMed: 20572143]
27. Lu, H. Magnetization “reset” for non-steady-state blood spins in Vascular-Space-Occupancy (VASO) fMRI. Proc 16th Annual Meeting ISMRM; Toronto, Canada. 2008; p. 406
28. Rooney WD, Johnson G, Li X, Cohen ER, Kim SG, Ugurbil K, Springer CS Jr. Magnetic field and tissue dependencies of human brain longitudinal 1H2O relaxation in vivo. *Magn Reson Med.* 2007; 57(2):308–18. [PubMed: 17260370]
29. Donahue MJ, Lu H, Jones CK, Edden RA, Pekar JJ, van Zijl PC. Theoretical and experimental investigation of the VASO contrast mechanism. *Magn Reson Med.* 2006; 56(6):1261–73. [PubMed: 17075857]
30. Jin T, Kim SG. Improved cortical-layer specificity of vascular space occupancy fMRI with slab inversion relative to spin-echo BOLD at 9.4 T. *Neuroimage.* 2008; 40(1):59–67. [PubMed: 18249010]
31. Yablonskiy DA, Ackerman JJ, Raichle ME. Coupling between changes in human brain temperature and oxidative metabolism during prolonged visual stimulation. *Proc Natl Acad Sci U S A.* 2000; 97(13):7603–8. [PubMed: 10861022]
32. Yablonskiy DA, Haacke EM. Theory of NMR signal behavior in magnetically inhomogeneous tissues: the static dephasing regime. *Magn Reson Med.* 1994; 32(6):749–63. [PubMed: 7869897]
33. Golay X, Silvennoinen MJ, Zhou J, Clingman CS, Kauppinen RA, Pekar JJ, van Zijl PC. Measurement of tissue oxygen extraction ratios from venous blood T(2): increased precision and validation of principle. *Magn Reson Med.* 2001; 46(2):282–91. [PubMed: 11477631]
34. Jain V, Abdulmalik O, Probert KJ, Wehrli FW. Investigating the magnetic susceptibility properties of fresh human blood for noninvasive oxygen saturation quantification. *Magn Reson Med.* 2012; 68(3):863–7. [PubMed: 22162033]
35. Spees WM, Yablonskiy DA, Oswood MC, Ackerman JJ. Water proton MR properties of human blood at 1.5 Tesla: magnetic susceptibility, T(1), T(2), T*(2), and non-Lorentzian signal behavior. *Magn Reson Med.* 2001; 45(4):533–42. [PubMed: 11283978]
36. Weisskoff RM, Kiihne S. MRI susceptometry: image-based measurement of absolute susceptibility of MR contrast agents and human blood. *Magn Reson Med.* 1992; 24(2):375–83. [PubMed: 1569876]
37. Kuhl DE, Alavi A, Hoffman EJ, Phelps ME, Zimmerman RA, Obrist WD, Bruce DA, Greenberg JH, Uzzell B. Local cerebral blood volume in head-injured patients. Determination by emission computed tomography of 99mTc-labeled red cells. *J Neurosurg.* 1980; 52(3):309–20. [PubMed: 7359185]
38. van Zijl PC, Eleff SM, Ulatowski JA, Oja JM, Ulug AM, Traystman RJ, Kauppinen RA. Quantitative assessment of blood flow, blood volume and blood oxygenation effects in functional magnetic resonance imaging. *Nat Med.* 1998; 4(2):159–67. [PubMed: 9461188]
39. Ugurbil K, Garwood M, Ellermann J, Hendrich K, Hinke R, Hu X, Kim SG, Menon R, Merkle H, Ogawa S, et al. Imaging at high magnetic fields: initial experiences at 4 T. *Magn Reson Q.* 1993; 9(4):259–77. [PubMed: 8274375]
40. Haacke EM, Lai S, Reichenbach JR, Kuppusamy K, Hoogenraad FG, Takeichi H, Lin W. In vivo measurement of blood oxygen saturation using magnetic resonance imaging: a direct validation of

- the blood oxygen level-dependent concept in functional brain imaging. *Hum Brain Mapp.* 1997; 5(5):341–6. [PubMed: 20408238]
41. Oja JM, Gillen JS, Kauppinen RA, Kraut M, van Zijl PC. Determination of oxygen extraction ratios by magnetic resonance imaging. *J Cereb Blood Flow Metab.* 1999; 19(12):1289–95. [PubMed: 10598932]
 42. Koehler RC, Roman RJ, Harder DR. Astrocytes and the regulation of cerebral blood flow. *Trends Neurosci.* 2009; 32(3):160–9. [PubMed: 19162338]
 43. Lu H, Ge Y. Quantitative evaluation of oxygenation in venous vessels using T2-Relaxation-Under-Spin-Tagging MRI. *Magn Reson Med.* 2008; 60(2):357–63. [PubMed: 18666116]
 44. Lu H, Xu F, Grgac K, Liu P, Qin Q, van Zijl P. Calibration and validation of TRUST MRI for the estimation of cerebral blood oxygenation. *Magn Reson Med.* 2012; 67(1):42–9. [PubMed: 21590721]
 45. Qin Q, Grgac K, van Zijl PC. Determination of whole-brain oxygen extraction fractions by fast measurement of blood T(2) in the jugular vein. *Magn Reson Med.* 2011; 65(2):471–9. [PubMed: 21264936]
 46. Xu F, Ge Y, Lu H. Noninvasive quantification of whole-brain cerebral metabolic rate of oxygen (CMRO₂) by MRI. *Magn Reson Med.* 2009; 62(1):141–8. [PubMed: 19353674]
 47. Blockley NP, Jiang L, Gardener AG, Ludman CN, Francis ST, Gowland PA. Field strength dependence of R1 and R2* relaxivities of human whole blood to ProHance, Vasovist, and deoxyhemoglobin. *Magn Reson Med.* 2008; 60(6):1313–20. [PubMed: 19030165]
 48. Lu H, Clingman C, Golay X, van Zijl PC. Determining the longitudinal relaxation time (T1) of blood at 3.0 Tesla. *Magn Reson Med.* 2004; 52(3):679–82. [PubMed: 15334591]
 49. Grgac K, van Zijl PC, Qin Q. Hematocrit and oxygenation dependence of blood (1)H₂O T1 at 7 tesla. *Magn Reson Med.* 2013; 70(4):1153–9. [PubMed: 23169066]
 50. Sharan M, Jones MD Jr, Koehler RC, Traystman RJ, Popel AS. A compartmental model for oxygen transport in brain microcirculation. *Ann Biomed Eng.* 1989; 17(1):13–38. [PubMed: 2919811]
 51. Gu H, Lu H, Ye FQ, Stein EA, Yang Y. Noninvasive quantification of cerebral blood volume in humans during functional activation. *Neuroimage.* 2006; 30(2):377–87. [PubMed: 16278086]
 52. Donahue, MJ.; Piechnik, SK.; Tijssen, R.; Gallichan, D.; Miller, KL.; Jezzard, P. A theoretical and experimental investigation of vascular-space-occupancy (VASO) blood nulling times: influence of hematocrit and oxygenation on null times and CBV quantification.. *Proc 17th Annual Meeting ISMRM; Hawaii, USA.* 2009; p. 1576
 53. Triantafyllou C, Hoge RD, Krueger G, Wiggins CJ, Potthast A, Wiggins GC, Wald LL. Comparison of physiological noise at 1.5 T, 3 T and 7 T and optimization of fMRI acquisition parameters. *Neuroimage.* 2005; 26(1):243–50. [PubMed: 15862224]
 54. Lu H, Golay X, Pekar JJ, Van Zijl PC. Sustained poststimulus elevation in cerebral oxygen utilization after vascular recovery. *J Cereb Blood Flow Metab.* 2004; 24(7):764–70. [PubMed: 15241184]
 55. Donahue MJ, Blicher JU, Ostergaard L, Feinberg DA, MacIntosh BJ, Miller KL, Gunther M, Jezzard P. Cerebral blood flow, blood volume, and oxygen metabolism dynamics in human visual and motor cortex as measured by whole-brain multi-modal magnetic resonance imaging. *J Cereb Blood Flow Metab.* 2009; 29(11):1856–66. [PubMed: 19654592]
 56. Hua J, Stevens RD, Huang AJ, Pekar JJ, van Zijl PC. Physiological origin for the BOLD poststimulus undershoot in human brain: vascular compliance versus oxygen metabolism. *J Cereb Blood Flow Metab.* 2011; 31(7):1599–611. [PubMed: 21468090]
 57. Brooks DJ, Beaney RP, Leenders KL, Marshall J, Thomas DJ, Jones T. Regional cerebral oxygen utilization, blood flow, and blood volume in benign intracranial hypertension studied by positron emission tomography. *Neurology.* 1985; 35(7):1030–4. [PubMed: 3874372]
 58. Grandin CB, Bol A, Smith AM, Michel C, Cosnard G. Absolute CBF and CBV measurements by MRI bolus tracking before and after acetazolamide challenge: repeatability and comparison with PET in humans. *Neuroimage.* 2005; 26(2):525–35. [PubMed: 15907309]

59. Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJ, Gibbs JM, Wise RJ, Hatazawa J, Herold S, et al. Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain*. 1990; 113(Pt 1):27–47. [PubMed: 2302536]
60. Lu H, Law M, Johnson G, Ge Y, van Zijl PC, Helpert JA. Novel approach to the measurement of absolute cerebral blood volume using vascular-space-occupancy magnetic resonance imaging. *Magn Reson Med*. 2005; 54(6):1403–11. [PubMed: 16254955]
61. Rostrup E, Knudsen GM, Law I, Holm S, Larsson HB, Paulson OB. The relationship between cerebral blood flow and volume in humans. *Neuroimage*. 2005; 24(1):1–11. [PubMed: 15588591]

Figure 1.

Representative BOLD (TE = 27 ms) and VASO (extrapolated TE = 0 ms) fMRI results from one subject. a-b: Activation maps (thresholded) superimposed on BOLD and VASO images. c-d: Corresponding t-score maps. As the contrast in VASO and BOLD scans were reversed when performing GLM analysis, the t-scores for activated voxels in both scans were positive. e-f: Corresponding time courses of fractional signal changes from BOLD and VASO activation maps. The horizontal bars indicate the periods of visual stimulation. The

blue and red points were used to calculate signals during rest and activation, respectively. Error bars show standard error over the included voxels within this subject.

Figure 2. Typical BOLD (a) and VASO (b) images at all four echoes (same scale). Group average (n = 6) relative (c, S/S) and absolute (d, arbitrary unit) fMRI signal changes versus TE in voxels that are both activated in BOLD (TE=27ms) and VASO (TE=0) methods. Error bars represent inter-subject variation. Lines in (c): results from linear fitting.

Figure 3.

Representative time courses of total (a) and extravascular (b) parenchymal R_2^* averaged over voxels activated in both BOLD (TE=27ms) and VASO (TE=0) scans from one subject. R_2^* values were fitted from data acquired at all four TEs. The horizontal bars indicate the periods of visual stimulation. Error bars show inter-voxel standard errors within the subject. The dash-dot lines depict average R_2^* values at baseline.

Table 1Comparison of extravascular and total parenchymal R_2^* values at 1.5T, 3T and 7T.

		Resolution (mm ³)	Extravas. $R_{2,\text{rest}}^*$ (s ⁻¹)	Extravas. R_2^* (s ⁻¹) ^a	Total $R_{2,\text{rest}}^*$ (s ⁻¹)	Total R_2^* (s ⁻¹)	Extravas. R_2^* fraction (%) ^b
1.5 T	Ref. [22]	2×2×2	16.14±0.64	-0.25±0.02	16.78±0.65	-0.57±0.10	47±7
	Ref. [13]	3.5×3.5×3.5	---	-0.28±0.07	---	-0.61±0.10	45±13
	Ref. [8]	1×1×3	---	---	11.6±0.3	-0.51±0.06	---
3.0 T	Ref. [22]	2×2×2	21.15±0.66	-0.38±0.05	22.06±0.84	-0.58±0.09	67±6
	Ref. [13]	3.5×3.5×3.5	---	-0.52±0.07	---	-0.74±0.05	70±11
	Ref. [8]	1×1×3	---	---	18.1±0.4	-0.98±0.08	---
7.0 T	Ref. [13]	3.5×3.5×3.5	---	-1.25±0.11	---	-1.37±0.34	91±11
	Ref. [8]	1×1×3	---	---	30.8±1.0	-2.55±0.22	---
	This study	2.5×2.5×2.5	44.66±1.55	-1.27±0.14	45.05±1.34	-1.40±0.16	91±3

mean ± standard error (SEM)

^a $R_2^* = R_{2,\text{act}}^* - R_{2,\text{rest}}^*$.^b Extravas. R_2^* fraction = $100 \times (\text{Extravas. } R_2^* / \text{Total } R_2^*) \%$.

Table 2

Extravascular and total BOLD effects measured in gray matter parenchyma at 7T.

	Extravas. $R_{2,\text{rest}}^*$ (s^{-1})	Extravas. $R_{2,\text{act}}^*$ (s^{-1})	Extravas. R_2^* (s^{-1}) ^a	Total $R_{2,\text{rest}}^*$ (s^{-1})	Total $R_{2,\text{act}}^*$ (s^{-1})	Total R_2^* (s^{-1})	Extravas. R_2^* fraction (%) ^b
Subject 1	40.38	39.08	-1.30	42.68	41.10	-1.57	83
Subject 2	46.61	45.16	-1.37	47.16	45.78	-1.45	95
Subject 3	40.46	39.73	-0.74	40.56	39.75	-0.81	91
Subject 4	45.18	43.89	-1.29	44.72	43.21	-1.51	86
Subject 5	45.02	43.26	-1.77	45.22	43.26	-1.96	90
Subject 6	50.34	49.17	-1.17	49.94	48.81	-1.13	103
Mean	44.66	43.38	-1.27	45.05	43.65	-1.40	91
SEM	1.55	1.51	0.14	1.34	1.33	0.16	3

SEM: inter-subject standard error.

^a $R_2^* = R_{2,\text{act}}^* - R_{2,\text{rest}}^*$.^b Extravas. R_2^* fraction = $100 \times (\text{Extravas. } R_2^* / \text{Total } R_2^*) \%$.