An intra-subject investigation of the BOLD contrast mechanism in response to visual stimulation and breath hold at 1.5T, 3.0T and 7.0T: insight into the extravascular sensitivity, resolution-dependence and vascular origins of BOLD contrast

M. J. Donahue[1], H. Hoogduin[2], P. C. van Zijl[3,4], P. Jezzard[1], R. P. Bokkers[2], M. J. van Osch[5], J. J. Zwanenburg[2], P. Luyten[2], and J. Hendrikse[2]

[1]Clinical Neurology, The University of Oxford, Oxford, United Kingdom, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, United States, [4]FM Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, United States, [5]Leiden University Medical Center, Leiden, Netherlands

Introduction. Recent advances in multi-channel receiver coils, parallel imaging, and field inhomogeneity correction schemes have made 7.0T an increasingly useful field strength (B_0) for whole-brain functional neuroimaging [1-8]. SNR improvements at 7.0T have been systematically demonstrated [7], however an additional advantage of high-field is the shorter T_2* of venous blood (7.0T $T_{2,v}$*<5ms; 3.0T $T_{2,v}$*≈15-25ms; 1.5T $T_{2,v}$*≈90-100ms) relative to tissue T_2* (7.0T $T_{2,t}$*≈25-30ms; 3.0T $T_{2,t}$*≈35-45ms; 1.5T $T_{2,t}$*≈55-65ms) [9-12]. This important effect should desensitize BOLD contrast to intravascular (IV) effects at high field. While IV and extravascular (EV) BOLD effects have been quantified separately at high and low field [9,10,12], a systematic comparison of such effects at 1.5T, 3.0T and 7.0T in the *same* subjects, exploiting the recent methodological advancements at 7.0T, has not been performed. Here, we investigate BOLD contrast by performing gradient echo BOLD at 1.5T, 3.0T and 7.0T in sequence in the same subjects. The primary objective of this study was (1) to quantify IV/EV ΔR_2* at each B_0, with the hypothesis that the short $T_{2,v}$* at high field will lead to primarily EV BOLD effects at 7.0T. Additional objectives were (2) to compare total BOLD effects at high spatial resolution (HSR) and low spatial resolution (LSR) at each B_0 and (3) to measure total BOLD effects in response to neuronal (visual) vs. vascular (breath hold) reactivity at each B_0. Results should provide a useful reference for how, when controlling for inter-subject variation, BOLD contrast is influenced by B_0.

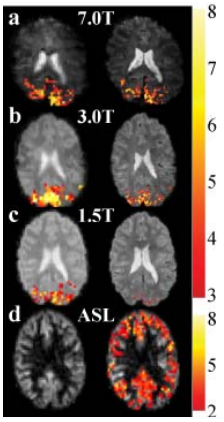

Fig 1. Act. (z) maps

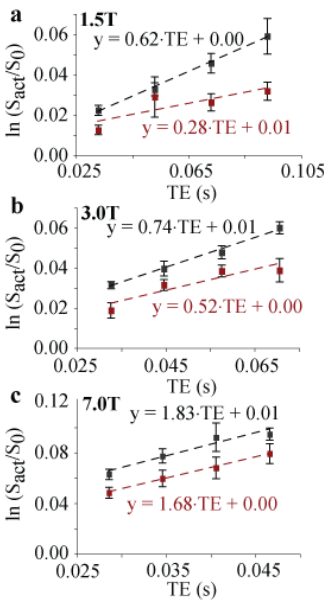

Fig 2. IV/EV Contributions

Methods. All subjects (n=7; age=24±6) provided informed, written consent and were scanned consecutively (randomized) at B_0=1.5T, 3.0T and 7.0T (Philips). Scan duration=1hr per scanner. Common BOLD scan parameters: FOV=220x220 mm^2, 25 slices, SENSE=2.0, TR=3200 ms. *IV/EV Comparison.* LSR (LSR=3.5x3.5x3.5 mm^3) BOLD visual fMRI was performed at four TEs, each with (b=100 s/mm^2) and without (b=0 s/mm^2) bipolar flow-dephasing gradients. LSR was chosen to allow for comparison between B_0 with adequate SNR. TE values were approximately centered on $T_{2,t}$* at each B_0: 33,53,73,93 ms (1.5T); 32.7,44.6,57.6,70.7 ms (3.0T) and 28.6,34.6,40.6,46.6 ms (7.0T). ΔR_2^* from total (tot) and extravascular (ext) BOLD effects were found by measuring signal during baseline (S_0) and visual stimulation (S_{act}) and fitting $\ln(S_{act}/S_0)$=-TE·ΔR_2* to b=0 s/mm^2 and b=100 s/mm^2 data, respectively. *HSR/LSR Comparison.* BOLD visual fMRI was performed at HSR=1.5x1.5x1.5 mm^3 at each B_0 with TE=53, 44.6 and 34.6 ms for 1.5T, 3.0T and 7.0T, respectively. Results were compared to LSR visual fMRI data above. *Visual vs. Breath Hold (BH) Comparison.* BOLD BH was performed at LSR at each B_0 with TEs equal to the HSR experiment. A pseudo-continuous ASL sequence (TR/TI=4000/1600 ms; SR=3.5x3.5x7 mm^3) with BH was performed at 3.0T for CBF estimation. *fMRI Paradigms.* Visual: 32/16s x 3 crosshair-fixation/blue-yellow flashing (8 Hz) checkerboard; BH: 32/16s x 3 normal breathing/exhale+BH. *Analysis.* Data were corrected for motion and baseline drift; voxels meeting activation criteria (z>3; SNR>33 (BOLD 3.0T,7.0T), SNR>13 (BOLD 1.5T) SNR>2 (ASL 3.0T), cluster>3) were analyzed. SNR thresholds were chosen after studying dependence of ΔS/S on thermal SNR [7]. For IV/EV analysis, only voxels meeting activation criteria in all TE scans were analyzed; for visual vs. BH comparison, identical voxels (at identical TE) were used.

Results and Discussion. Fig. 1 shows representative LSR (left) and HSR (right) activation maps for 7.0T (a), 3.0T (b) and 1.5T (c), and the ASL difference image and BH activation map (d). *IV/EV Findings.* BOLD ΔS/S for 1.5T (Fig. 2a), 3.0T (Fig. 2b) and 7.0T (Fig. 2c) without (black) and with (red) flow-dephasing gradients show a linear trend of $\ln(S_{act}/S_0)$ with TE. At 7.0T, the slopes with and without gradients were not statistically different (P=0.11); thus, BOLD effects at 7.0T are almost purely EV. ΔR_2* values are shown in Table 1 (left); EV fractions are found to be 45±13%, 70±11% and 92±19% at 1.5T, 3.0T and 7.0T, respectively. Subject-averaged time courses for 7.0T (Fig. 3a,b) and 1.5T (Fig. 3c,d), without (left) and with (right) flow-dephasing gradients reveal only small ΔS/S at 1.5T in the presence of gradients, reinforcing that BOLD has large IV contributions at 1.5T. $\Delta R_{2,ext}$* is expected to increase~B_0, however we find a larger increase at 7.0T, suggesting that at LSR, CSF contributions to gradient echo BOLD $\Delta R_{2,ext}$* may be substantial. *HSR/LSR Findings.* LSR $(\Delta S/S)_{tot}$ < HSR $(\Delta S/S)_{tot}$ at 1.5T and 3.0T, a trend that is reversed at 7.0T (Table 1). Given the IV/EV results at HSR, this is likely due to a different IV/EV ratio at LSR and different activated voxels at each SR. *Visual vs. BH Findings.* ASL breath-hold ΔS/S=65.3±9.3%; BOLD BH $(\Delta S/S)_{tot}$ and visual $(\Delta S/S)_{tot}$ at each B_0 (overlapping voxels at each B_0) are shown in Table 1. Visual LSR $(\Delta S/S)_{tot}$ is 2.0-2.5 times larger than BH LSR $(\Delta S/S)_{tot}$ at each B_0 (P<0.01), indicating that vascular and neuronal BOLD effects are unequal. The EV origin of the BOLD effect at 7.0T (Fig. 2c), combined with BH CBF changes, enables estimation of BOLD calibration "M" values at 7.0T [13-15]: M=12.3±1.6% and M=14.8±2.0% for β=1.0 and Grubb (α)=0.38 and 0.50 [13-16], respectively. However, it has recently been shown that $CMRO_2$ reduces during CO_2-administered hypercapnia experiments [17] and also that CBF/CBV relationships are unequal during visual and BH [18]. Therefore caution should be exercised when calibrating neuronal BOLD responses based on such measures. *Conclusion.* We performed a BOLD comparison between 1.5T, 3.0T and 7.0T in identical subjects (3hr window). The primary result of this study is that, (1) when accounting for inter-subject variability, EV BOLD effects are approximately 92%, 70% and 45% at 7.0T, 3.0T and 1.5T, respectively. Additional conclusions suggest that (2) $(\Delta S/S)_{tot}$ comparisons between B_0 should be made with caution due to different IV/EV contributions, and (3) BOLD BH reactivity is 2.0-2.5 times smaller than BOLD visual reactivity.

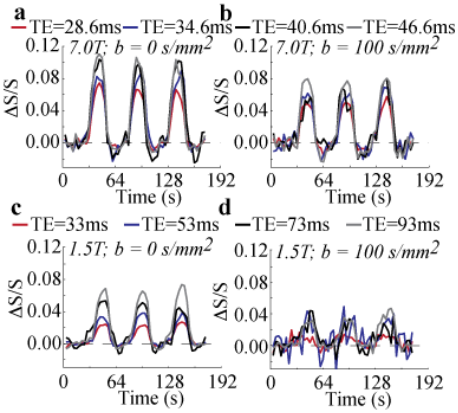

Fig 3. BOLD 7.0T (a,b) and 1.5T (c,d) courses

Table 1	$\Delta R_{2,tot}$* (s^{-1})	$\Delta R_{2,ext}$* (s^{-1})	$\Delta R_{2,ext}$*/$\Delta R_{2,tot}$*	HSR $(\Delta S/S)_{tot}$	LSR $(\Delta S/S)_{tot}$	LSR BH $(\Delta S/S)_{tot}$
1.5T	-0.62±0.10	-0.28±0.07	0.45±0.13	5.3±2.4%	3.3±0.9%	1.5±0.9%
3.0T	-0.74±0.05	-0.52±0.07	0.70±0.11	5.5±0.5%	4.0±1.0%	2.0±0.9%
7.0T	-1.83±0.26	-1.68±0.25	0.92±0.19	6.0±0.5%	8.0±1.6%	3.2±1.1%

References. [1]Adriany et al. MRM.2008;59. [2]Duyn et al. PNAS.2007;104. [3]Adriany et al. MRM.2005;53. [4]Speck et al. MAGMA.2008;21. [5]Wiggins et al. ISMRM.2008;#148. [6]Vaughn et al. ISMRM.2008;#152. [7]Triantafyllou et al. Neuroimage.2005;26. [8]Pfeurffer J et al. MRI.2004;22. [9]Duong et al. MRM. 2003.49. [10]Yacoub et al. MRM.49;2003. [11]Zhao et al. MRM.2007;58. [12]Lu et al. MRM.2005;53. [13]Ogawa et al. PNAS.1990;87. [14]Davis et al. PNAS.1998;95. [15]Chiarelli et al. MRM.2007;57. [16]van Zijl et al. Nature Medicine.1998;4. [17]Zappe et al. Cereb Cortex.2008;18. [18]Donahue et al. JCBFM. 2008;[E-pub]. **Funding.** Oxford NIHR Biomedical Research Centre, Netherlands Organization for Scientific Research, R01-EB004130, NIH- P41RR015241.