Whole-brain non-invasive hemodynamic imaging, enabled by a novel CBV-weighted single-shot 3D VASO-FLAIR GRASE sequence combined with CBF-weighted ASL and BOLD fMRI, identifies regional hemodynamic and metabolic discrepancies

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Introduction. Functional MRI (fMRI) is commonly performed using the blood-oxygenation-level-dependent (BOLD) technique, which is sensitive to composite changes in cerebral blood flow (CBF), cerebral blood volume (CBV), hematocrit (Hct) and the cerebral metabolic rate of oxygen ($CMRO_2$) [1,2]. By combining BOLD with additional fMRI methodologies such as CBF-weighted (CBFw) arterial spin labeling (ASL) [3] and CBV-weighted (CBVw) vascular-space-occupancy (VASO) [4], it should be possible to elucidate the relationship between BOLD, hemodynamics and metabolism [5]. Such a protocol would be of use in understanding the BOLD contrast mechanism as well as in clinical scenarios for identifying specific contributors to hemodynamic impairment. However, this multi-modal approach has been hindered by an inability to obtain reliable, non-invasive whole-brain CBF and CBV measures. The ASL contrast mechanism is now well-investigated [6] and reproducible whole-brain CBF measurements have been reported using single-shot 3D GRASE ASL [7]. VASO has been shown to be predominately sensitive to CBV when imaging at long TR [8], controlling for CSF effects [8,9], and using body coils for RF transmission. However, whole-brain VASO approaches have low SNR and less thorough blood nulling compared to single-slice approaches [9]. The purpose of this study was twofold. First, to assess the feasibility of performing whole-brain CBVw imaging using the 3D GRASE readout in conjunction with a VASO-FLAIR (simultaneous blood and CSF nulling) magnetization preparation. Second, to assess the sensitivity of a combined whole-brain BOLD, ASL and VASO-FLAIR approach for detecting CBF, CBV and metabolic adjustments in motor and visual cortex (MC, VC), where flow-metabolism coupling is different [10,11]; an ability to detect flow-metabolism differences between VC and MC in healthy volunteers should potentiate the clinical import of this approach for detecting pathology-induced regional flow-metabolism variations.

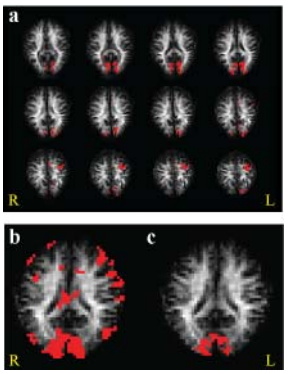

Figure 1. Activation Maps

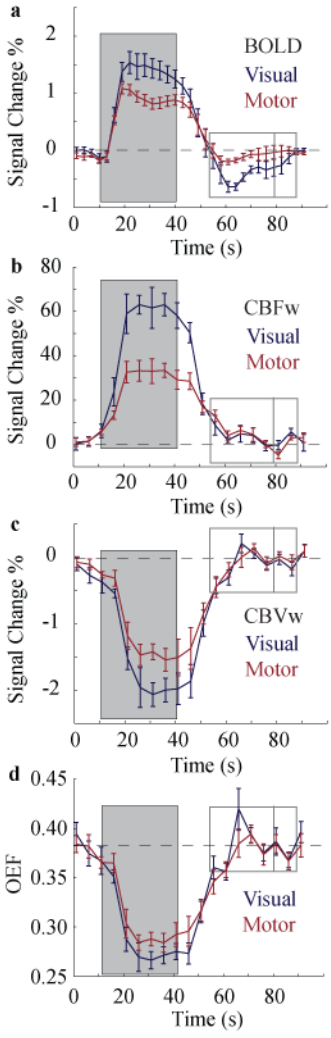

Figure 2. Time Courses

Methods. *Experiment.* All subjects (n=8; age=29±6yrs; right-handed) provided informed, written consent and were scanned on a 3T Siemens scanner sequentially with gradient echo BOLD EPI (TR/TE=3000/40ms), 3D GRASE ASL (pulsed ASL with background suppression; TR/TI/TE=2500/1600/40ms) and 3D GRASE VASO-FLAIR (TR/TI1TI2/TE=5000/2256/737/40ms). VASO-FLAIR was used to null blood and CSF simultaneously, thereby desensitizing CBV quantification to CSF partial volume effects [8]. The 3D GRASE readout (duration~504 ms; centric k-space ordering) allows for whole-brain imaging following a single excitation pulse. Common scan parameters: spatial resolution=3.8x3.8x3.8 mm^3, 22 slices, bandwidth=2004 Hz/pixel. *Functional paradigm:* 60/30s off/on flashing blue-yellow checkerboard (f=8 Hz) x 4. During visual stimulation, volunteers were instructed to move a joystick unilaterally (right hand; f=1 Hz). *Post-processing.* Data were corrected for motion, baseline drift and co-registered using FSL routines [12]. Time courses in voxels meeting activation criteria ($|z|>2.5$, cluster size>3) in BOLD, VASO-FLAIR and ASL were calculated. CBV was estimated from VASO-FLAIR data [8], which was then used in conjunction with BOLD to estimate Y_v and OEF changes ($Y_v=Y_a$-OEF$\cdot Y_a$) assuming baseline $Y_a=0.98$ and $Y_v=0.61$ [5]. Finally, $CMRO_2=$OEF$\cdot$CBF$\cdot Y_a\cdot$Hct was calculated under the assumption of constant arterial oxygen content ($Y_a\cdot$Hct).

Results and Discussion. A VASO-FLAIR activation map is shown in Fig. 1a; activation is largely localized to VC and left MC as expected for the tasks. Voxels meeting activation criteria in BOLD, VASO-FLAIR *and* ASL were found to have better localization to gray matter in the functional region than BOLD alone (Fig. 1b,c). Fig. 2 shows the BOLD (a), CBFw ASL (b), CBVw VASO-FLAIR (c) and OEF (d) courses for VC and MC. Note the consistently smaller magnitude signal changes in MC (BOLD: 0.9±0.1%; VASO-FLAIR: 1.4±0.1%; ASL: 32±2%) compared to VC (BOLD: 1.4±0.1%; VASO-FLAIR: 1.8±0.2%; ASL: 58±5%) which translates to a smaller OEF and $CMRO_2$ change in MC (OEF: -24±1%; $CMRO_2$: 5±2%) compared to VC (OEF: -29±3%; $CMRO_2$: 17±3%). $CMRO_2$:CBF ratios were 29±6% and 16±6% in VC and MC, respectively. The BOLD post-stimulus undershoot is larger in VC (VC: -0.63±0.06%; MC: -0.21±0.05%; P<0.05) and takes longer to return to baseline in VC (VC: 43±6s; MC: 36±4s; P<0.05), yet CBV returns to baseline at approximately the same time in both regions (MC: 21±4s; VC: 20±3s; P>0.05). *Technologic Findings.* First, since the 3D GRASE readout employs a single excitation RF pulse per TR, an identical TI is maintained in all slices of the 3D volume, thereby maintaining blood water nulling throughout the long echo-train. Second, the 3D GRASE readout is fundamentally a spin echo weighted sequence; since spin echo BOLD effects are approximately 1/3 of extravascular gradient echo BOLD effect at 3T, BOLD effects in 3D GRASE ASL and VASO-FLAIR sequences are expected to be small (<0.5%). Third, when identical bandwidth and spatial resolutions are employed, in-plane distortions are similar between EPI (BOLD) and 3D GRASE, thereby maintaining co-registration accuracy. *Physiologic Findings.* These data allow for whole-brain hemodynamic reactivity to be compared, which elucidates several important physiological effects. First, as has been shown [10,11], magnitude flow and metabolism changes are different between VC and MC *during stimulation*; $CMRO_2$:CBF coupling we report here are within error of literature values [11], however have been obtained without the use of contrast agents or capnic challenge. Thus, the combined whole-brain protocol identifies regional discrepancies in CBF and metabolism, which should be of use in clinical scenarios where hemodynamic relationships are impaired. Second, by comparing *post-stimulus* adjustments in Figs. 2a and 2c, it can be seen that the magnitude and duration of the BOLD undershoot is not due to CBV differences between regions, but to small metabolic differences (Fig. 2d). This is important in light of the on-going debate concerning the nature of the BOLD post-stimulus undershoot and neurotransmitter-mediated signaling effects [5,13]. Interestingly, the majority of studies relating elevated metabolism to the BOLD undershoot were conducted in VC [5,14,15], whereas many studies linking elevated CBV with the undershoot were conducted in MC [16,17] where metabolic increases may be smaller. *Conclusion.* By combining the VASO-FLAIR preparation with a 3D GRASE readout, we show that it is possible to obtain whole-brain CBVw images. The primary goal of this study, to generate a whole-brain imaging protocol for identifying different hemodynamic constituents of pathologic impairment, has been preliminarily tested by identifying known flow-metabolism variations in visual and motor cortex.

References. [1]Buxton et al. *Neuroimage*.2004;23. [2]van Zijl et al. *Nat Med*.1998;4. [3]Williams et al. *PNAS*.1992;89. [4]Lu et al. *MRM*.2003;50. [5]Lu et al. *JCBFM*.2004;24. [6]Petersen et al. *Br J Radiol*.2006;79. [7]Günther et al. *MRM*.2005;54. [8]Donahue et al. *MRM*.2006;56. [9]Scouten and Constable. *MRM*.2007;58. [10]Stefanovic et al. *Neuroimage*.2006;30. [11]Chiarelli et al. *MRM*.2007;57. [12]Jenkinson et al. *Neuroimage*.2002;17. [13]Attwell and Iadecola. *Trends Neurosci*.2002;25. [14]Donahue et al. *JCBFM*.2008;[E-pub]. [15]Frahm et al. *Neuroimage*.2008;40. [16]Mandeville et al. *MRM*.1998;39. [17]Mandeville et al. *JCBFM*.1999;19. **Funding**. The Dunhill Medical Trust and the Oxford NIHR Biomedical Research Centre.