

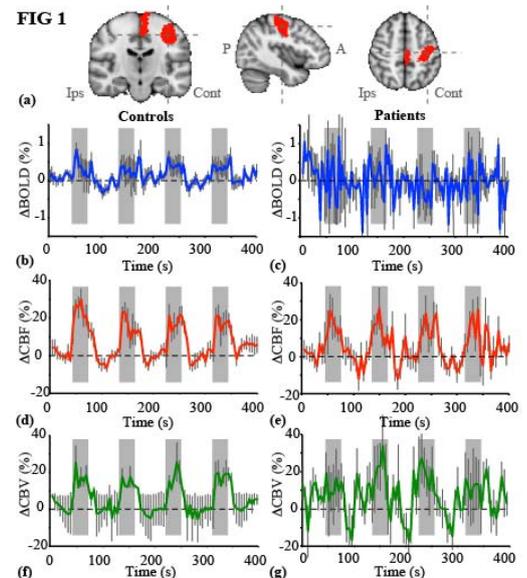
# BOLD, CBF, and CBV fMRI measurements in chronic stroke patients reveal details of altered neurovascular coupling

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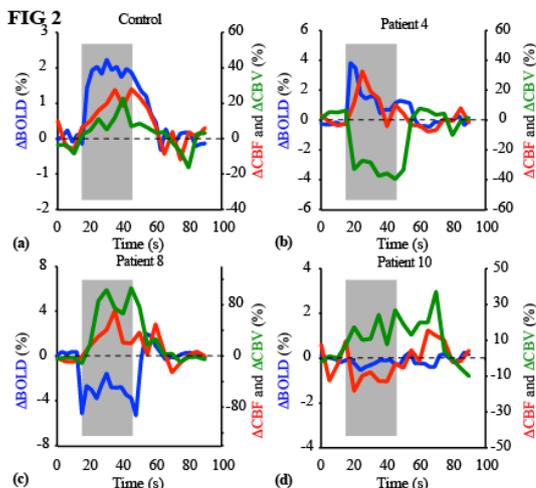
**Introduction.** The overall aim of this work is to apply a multi-modal, noninvasive functional MRI (fMRI) approach to better quantify hemodynamic compensation mechanisms during stroke recovery. More specifically, evaluation of cortical reorganization in chronic stroke patients requires methods to accurately localize regions of neuronally-associated hemodynamic changes. Blood oxygenation level-dependent (BOLD) fMRI is widely used in human brain mapping, but the sensitivity of this method depends on the relationship between changes in the cerebral metabolic rate of oxygen consumption (CMRO<sub>2</sub>), cerebral blood flow (CBF), and volume (CBV), which may be altered regionally in chronic stroke. Importantly, application of BOLD fMRI as a sole marker of brain function may provide paradoxical information following stroke, as discrepant relationships between CBF/CBV and CMRO<sub>2</sub> in stroke patients may elicit unusual, or absent, BOLD responses. Alternative methods, such as CBF-weighted (CBFw) arterial spin labeling (ASL) and CBV-weighted (CBVw) vascular space occupancy (VASO) have been proposed as noninvasive methods for measuring specific hemodynamic contributors to BOLD contrast [1,2]. These approaches have been applied in various physiology studies [3-5], however have not yet been applied collectively in patients with chronic stroke to understand altered neurovascular coupling phenomena. The aim of this study was to quantitatively evaluate the extent of, and variability in, neurovascular coupling in chronic stroke patients using BOLD, but additionally with more novel, multi-slice CBFw ASL and CBVw VASO fMRI techniques. The hypothesis to be investigated was that owing to relative uncoupling between CBF, CBV and CMRO<sub>2</sub> in patients with chronic cerebrovascular disease, BOLD data alone may yield ambiguous information in many patients, yet greater clarity can be evinced when BOLD contrast is supplemented with independent CBF and CBV measurements.

**Methods: Experiment.** Chronic stroke patients (n=11; 7 MCA and 1 each with ACA, PCA, intracerebral and subcortical stroke) with motor impairment and age-matched controls (n=11) provided informed, written consent and were scanned at 3T (Siemens) while performing four sets (60/30s off/on) of unilateral motor tasks using a custom-built joystick designed to isolate wrist extension-flexion movement of the stroke-affected hand. Volunteers were supervised and rehearsed joystick movement prior to scanning; in the scanner, a visual and laterally moving ( $f=1$  Hz) asterisk was used in an effort to pace the volunteers' joystick movement frequency. The order of BOLD, ASL and VASO scans were randomized between patients with the following scan parameters. **CBFw ASL:** Flow Alternating Inversion Recovery (FAIR) labeling with 3D GRadient And Spin Echo (GRASE) readout [6]; background suppression; TR/TI=2500/1600. **CBVw VASO:** VASO with simultaneous CSF nulling (VASO-FLAIR) [7] and 3D GRASE readout; TR/TI1/TI2=5000/2256/737 ms. **BOLD:** TE=40/TR=3000 ms; 2D echo planar imaging readout. All scans included 22 slices and possessed a matched spatial resolution of 3.8x3.8x3.8 mm<sup>3</sup>. **Analysis.** Data were corrected for motion, baseline drift and co-registered to standard space (MNI; 2 mm) and affected hemispheres were oriented as radiological left (contralateral to stroked vessel). An anatomical region of interest (FIG 1a, ROI) encompassing motor cortex contralateral to the moved hand (affected hand for patients) was used for signal change calculations. Within the same ROI, the BOLD, CBFw and CBVw reactivity was separately calculated for healthy subjects and patients.

**Results:** All three fMRI modalities showed significant changes within the ROI for healthy subjects (FIG 1b,d,f;  $P<0.0001$ ). Gray bars denote periods of joystick movement. Signal changes corresponded to a relative increase in BOLD=0.3±0.1%, CBF=20±4%, CBV=16±5%, and estimated CMRO<sub>2</sub>=0.7%. In stroke patients, BOLD fMRI yielded no significant changes on average (FIG 1c; BOLD=0.1±0.4%;  $P>0.05$ ), despite significant changes in CBF=15±7% (FIG 1e;  $p=0.0003$ ), CBV=14±9% (FIG 1g;  $p=0.001$ ) and an estimated change in CMRO<sub>2</sub>=1.8%. Closer inspection of individual volunteer data revealed additional information regarding impairment. For instance, FIG 2 shows representative control reactivity (a), and positive (b), negative (c) and absent (d) BOLD changes in separate patients. The BOLD dynamics are approximately consistent with the corresponding changes in CBF and CBV (FIG 2a, normal neurovascular coupling; FIG 2b, vascular steal; FIG 2c, CBV autoregulation; FIG 2d, common absence of reactivity). Motor Fugl-Meyer scores were comparable between patients with a positive BOLD response and those with absent or negative BOLD responses (mean=55.3 vs. 50.6).



**FIG 1.** (a) Mask used for signal change calculations. (b-f) Control (left) and patient (right) fMRI timecourses. Note the relative absence of BOLD changes, on average, in patients, yet more robust CBF and CBV changes.



**FIG 2.** Example control reactivity (a), and positive (b), negative (c) and absent (d) BOLD changes in separate patients, with corresponding CBF and CBV responses.

**Discussion.** These results demonstrate that in chronic stroke, motor activity can lead to measurable changes in CBF and CBV in the expected cortical areas despite an absent BOLD-fMRI response. BOLD fMRI may therefore be of limited value as a surrogate measure of cortical activation patterns in the course of rehabilitation among chronic stroke survivors that have persisting neurovascular dysfunction. These results highlight the value of ASL- or VASO-based fMRI in interpreting post-stroke functional reorganization. In healthy subjects, the change in BOLD signal during functional hyperemia largely relies on a decrease in oxygen extraction fraction, and thus a decrease in the amount of paramagnetic deoxygenated hemoglobin. In stroke patients, however, baseline CBF and CBV and impaired vascular reserve may alter these hemodynamic relationships. Atherosclerosis, which underlies approximately 25% of all ischemic strokes, likely decreases both resting CBF and vascular reserve capacity, while increasing resting CBV. As a consequence of these changes in hemodynamics, neuronal activity is not necessarily coupled to an increase in regional CBF and CBV as in healthy subjects. Importantly, while average trends across patients may not reach levels of significance, partly attributable to varying degrees of impairment and variability in task performance, clear trends on an individual subject basis may be apparent, thereby suggesting that such multi-modal imaging may be useful for understanding stages of impairment. Owing to the large and frequently unknown variability in neurovascular coupling that exists in chronic stroke, multi-modal fMRI approaches may be better suited than more commonly used BOLD fMRI for interrogating cortical reorganization.

**References.** [1] Williams DS et al. PNAS. 1992. [2] Lu H et al. MRM. 2003. [3] Poser B et al. HBM. 2011. [4] Hua J et al. NMR Biomed. 2011. [5] Ances BM et al. HBM. 2009. [6] Gunther M et al. MRM. 2005. [7] Donahue MJ et al. MRM. 2006.