Direct Non-invasive MRI Measurement of the Absolute CBV-CBF Relationship during Sensory-Motor and Auditory Stimulation in Normal Humans

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Introduction: BOLD fMRI is a powerful noninvasive approach for studying brain function, however, physiological interpretation of the signal is limited since it reflects a combination of changes in CBV, CBF, blood oxygenation and metabolism (1-4). While methods exist for non-invasive absolute CBF quantification, CBV measurement has been invasive and difficult especially in human subjects. Most calibrated fMRI studies typically assume $CBV=0.88CBF^{0.38}$ based on the absolute CBV-CBF relationship obtained in monkey brains under hypo/hypercapnia using PET (5). This practice is controversial since this relation may vary across brain regions, functional challenges, and species, as demonstrated by published power parameters ranging from 0.18-0.64 in steady-state across species, stimuli, modalities, relative and absolute contributions of whole/partial blood compartments (6-16). This study presents MRI validation of the absolute CBV-CBF relationship in humans.

Methods: Fifteen normal volunteers participated in this IRB-approved study. Absolute CBV was quantified non-invasively using a method based on acquisitions with varying extents of blood nulling at rest and activation, and fitting of signal changes to a three-compartment biophysical model (17-19); all volunteers were imaged with a recently developed extension of this method which enables whole-brain multi-slice imaging through a rotating slice acquisition and maintenance of steady state throughout varying inversion and recovery durations (19). Absolute CBF was quantified in thirteen volunteers using Q2TIPS PASL (20). Data was acquired at 3T (Tim Trio, Siemens, Erlangen, Germany) using a 32 channel head coil. High-resolution 3D, and 2D T1w images at same slice locations as CBV and CBF were used for registration. Sensory-motor (SM) stimulation consisted of bilateral finger-to-thumb apposition during an auditory (AU) stimulus, which also served as a metronome at 2Hz frequency. Sounds at 0.5kHz, 2kHz, 8kHz, and white noise were binaurally applied in a random order with equal weighting on tones versus noise (duty cycle 80%). CBV and CBF were acquired during stimulation (4 OFF/ON cycles, 78s each, 10Hz) consecutively with 20 transverse slices covering the whole brain and: 192x256mm FOV, 4x4x4mm, GE EPI, CBV parameters: TE/TS/TR:11ms/1.2s/3s, 60 TIs:400-1158ms, 2 averages. CBF parameters were TE/TI1/TR/sliceTR:20ms/1.4s/3s/52.3ms, 10cm adiabatic inversion 2cm inferior/superior, and bipolar gradient of 5cm/sec; PD with CBF parameters except TR/TI/TD=8s/6.05s/0. GM CBV data was calculated in MNI space allowing 18sec of each stimulus transition for settling of the hemodynamic response and averaging over blocks. CBV and CBF data was motion and drift corrected, and smoothed with an 8mm Gaussian kernel. CBF data was processed in each subjects' space, then registered to MNI space. CBF was calculated from the difference between interleaved labeled and control image pairs, averaged over multiple acquisitions. BOLD t-statistics were generated from the average of labeled and unlabeled CBF acquisitions. SM and AU activation masks were defined based on task-induced BOLD activation ($P<0.001$), separated from each other using Brodmann areas, and voxels with CBV>30 mL/100 g were excluded as vessels. Median CBV and CBF values were obtained for each ROI, resulting in one data point for each volunteer at baseline and activation. The CBV-CBF relationship was estimated by least squares fitting weighted by the inverse standard deviations of CBV and CBF, to a power function ($V = a F^{b}$) as well as a linear function ($V = c + F d$).

Results and Discussion: CBV and CBF increased bilaterally upon stimulation (Fig 1). SM CBF increased from 43.3±12.9 to 58±15.7 mL/min/100 mL by 35.7%, in good agreement with PET (baseline 42.5±10.1 (21), increase from 43.4 to 54.39 mL/min/100 mL (22)); PASL (increases of 25±6% at 1.73Hz, 47±5% at 3.46Hz (15)); as well as bolus tracking and FAIR (increases of 35.1±8.6% and 36.3±8.2% (23)). AU CBF increased from 54±8.3 to 59.2±8 mL/min/100 mL by 10.2%, in good agreement with reported baseline cortical GM CBF values of 52.8 ± 11.8 (10), 55 ml/100 ml/min (24), and 64±20 mL/min/100 mL using PET (12); 50±13 ml/100 ml/min using dynamic CT (25); and CBF increase of 10.8% using MRI (26). Baseline CBV increased from 6.8 ± 1.3 to 8.7 ± 1.5 mL/100 mL by 29.9% in the SM area; and from 6.7 ± 1.9 to 8.3 ± 1.8 mL/100 mL (by 29.4%) in the AU area, in comparison to a 19.4±2.7% increase during bilateral finger tapping using bolus tracking MRI (23). iVASO methods reported resting GM arterial CBVs of 2.04±0.27, 0.76±0.17ml/100 ml (22); and 1.6ml/100ml (23). With 21% arterial contribution (27,4), our results for baseline CBV in the SM and AU areas correspond to CBVa of 1.43 and 1.41 mL/100 mL, respectively, both well within the range of iVASO results. CBV was reported as 5.5+/-0.2 in GM and only 1.4+/-0.1 mL blood/100mL in WM using contrast-enhancement and VASO (28), consistent with observation of higher CBV values upon exclusion of WM voxels.

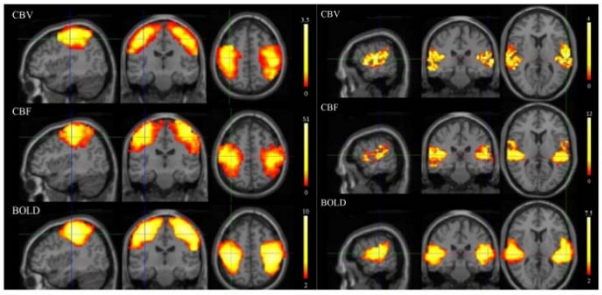

Figure 1: Increase in CBV, increase in CBF and BOLD t-statistics within SM (left) and AU (right) cortex with stimulation; composite over all volunteers.

CBV vs. CBF is shown in Figure 2 for both regions. Fitting the CBV-CBV relationship to a power function resulted in the expression $V = 1.51 F^{0.42}$ in the SM area and $V = 1.48 F^{0.40}$ in the AU area, in close agreement with each other, and in good agreement with Grubb's exponent of 0.38 in the original expression $V = 0.88 F^{0.38}$ (5). Power and linear fits overlap completely at intermediate CBV and CBF. The power relationship between absolute CBV and CBF has not previously been reported in either of these regions to the best of our knowledge. Smaller power exponents of 0.18 (hypocapnia (16)) and 0.31 (bilateral sequential finger-to-thumb apposition at 1.73Hz and 3.46Hz (15)) were reported using VERVE. These exponents reflect the relationship between relative changes in CBF and the venous contribution to CBV preventing a direct comparison; however, smaller values are consistent with an expected 36% to 46% venous contribution to CBV (4, 8). Our observations are also consistent with reports of CBV values consistently exceeding those estimated using Grubb's original relationship during bilateral finger tapping, during bolus tracking MRI (23). An exponent of 0.29 was found from absolute CBV vs. CBF in humans under hypo and hypercapnia with PET (10), in good overall agreement to our observations considering different modalities, stimuli, and methodologies.

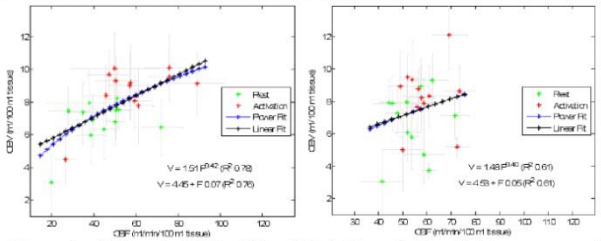

Figure 2: CBF and CBV within SM (left) and AU (right) cortex, and resulting power (blue) and linear (black) fits to resting (green) and activation (red) data for all volunteers. Error bars: one standard deviation.

Conclusion:
Direct non-invasive whole-brain MRI measurement of the absolute CBV-CBF relationship was presented in normal subjects during AU and SM stimulation, providing the first MRI validation of Grubb's relationship in humans using absolute measurements in these regions. The results were within physiologically expected ranges. Improved characterization of the CBV-CBF relationship in humans under various metabolic or functional challenges holds great potential for fMRI calibration; can form a solid basis for understanding of fMRI signal mechanisms and the relationship between neuronal activity, hemodynamic changes and metabolism leading to the BOLD effect, with further potential clinical utility in evaluating alterations of vascular state, characterizing damage, identifying disease and monitoring treatments or drug effects. Regional variations under a range of physiological states should also be considered in the interpretation of results.

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