Calibration of BOLD fMRI motor activation maps using BOLD breath hold cerebrovascular reactivity mapping for effective compensation of brain tumor-related neurovascular uncoupling

Shruti Agarwal[1], Raag Airan[1], Sachin K. Gujar[1], Haris I. Sair[1], and Jay J. Pillai[1]

[1]*Division of Neuroradiology, Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States*

Introduction: The coupling between neuronal activity and the hemodynamic changes occurring in the adjacent vasculature is often disrupted in patients with brain tumors, resulting in false negative BOLD fMRI activation that can lead to inadvertent eloquent cortical resection and resultant postsurgical permanent disability [1]. This phenomenon of neurovascular uncoupling (NVU) is an under-recognized but critical limitation of clinical BOLD fMRI. Recent studies have shown that cerebrovascular reactivity (CVR) mapping using a breath hold (BH) task can detect NVU potential in patients with primary gliomas [2, 3]. In this study we propose a novel BH CVR-based NVU compensation algorithm based on initial work by Thomason et al., 2007[4]. We will demonstrate application of this algorithm for compensation of NVU at single subject level for motor activation.

Materials and Methods: Four patients with perirolandic low grade gliomas referred for presurgical motor mapping with BOLD fMRI were included in this study, approved by our IRB. Imaging was performed on a 3.0 T Siemens Trio MRI with a 12-channel head matrix coil utilizing 3D T1 MPRAGE (TR=2300 ms, TI= 900 ms, TE= 3.5 ms, 9° FA, 24-cm FOV, 256x 256x176 matrix, slice thickness 1 mm) and 2D gradient echo EPI T2* weighted BOLD sequences (TR= 2000 ms, TE=30 ms, 90° FA, 24-cm FOV, 64x64x33 matrix, 4 mm slice thickness 4 mm with 1 mm interslice gap).The motor task used was a vertical tongue movement task (3 minutes long with 30 seconds blocks of rest alternating with 30 seconds blocks of motion). A 4 minute 20 seconds duration BH task (40 seconds block of normal breathing (NB) alternating with 16 seconds block of BH repeated 4 times with a final 20 seconds block of NB) for CVR mapping. Z-score maps for the motor and BH tasks were obtained from the generalized linear model (GLM) analysis using AFNI software (reflecting motor activation vs. rest and hypercapnia condition vs. baseline, respectively). Motor activation maps were further analyzed using Amplitude Measured as a Percentage of Local Excitation (AMPLE) thresholding of 60% (i.e., only voxels with Z scores above 60% of a local cluster Z score maximum were considered "active") [5]. An ipsilesional (IL) region of interest (ROI) including the lesion and adjacent cortex up to two gyri away from the lesion margins was manually delineated. Each ROI was mirrored in the contralesional hemisphere (CL). Voxels whose expected IL activation was reduced or absent due to reduced CVR were identified using the following algorithm: Z-score plot (**Figure 1**) was created for both IL & CL ROIs by rearranging the voxels in ascending order of their Z-scores in the CVR map. Voxels having Z-scores above the Z-score at the intersection point of the IL and CL curves (point A) were considered to represent normal cortical CVR (i.e. not affected by NVU) in IL ROI and were thus excluded. The mean Z-score ($\boldsymbol{Z_m}$) of the remaining voxels was calculated (point B). Voxels with Z-scores (***Zcvr***) in the range of 50 to 150% of $\boldsymbol{Z_m}$ and having sub-threshold activation in motor task activation map were considered to have falsely reduced activation due to NVU and were subsequently calibrated using the following equation:

$$Zmotor_{calib} = Zmotor_{meas}\left(1 - x + x\frac{\bar{Zcvr}_{CL}}{Zcvr}\right)$$

$$x = \begin{cases} 1 & if \;\; Zmotor_{meas} < Zmotor_{thr} \;\; AND \;\; 0.5Z_m < Zcvr < 1.5Z_m \\ 0 & elsewhere \end{cases}$$

where $\boldsymbol{Zmotor_{calib}}$ = CVR calibrated Z-score; $\boldsymbol{Zmotor_{meas}}$= standard Z-score; $\boldsymbol{\bar{Zcvr}_{CL}}$ = average CVR Z-score in CL ROI; $\boldsymbol{Zmotor_{thr}}$= threshold used in generating motor activation map

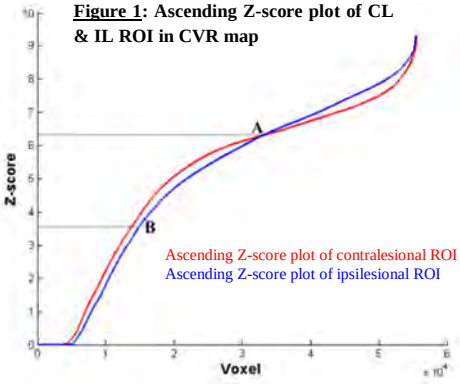

Figure 1: Ascending Z-score plot of CL & IL ROI in CVR map

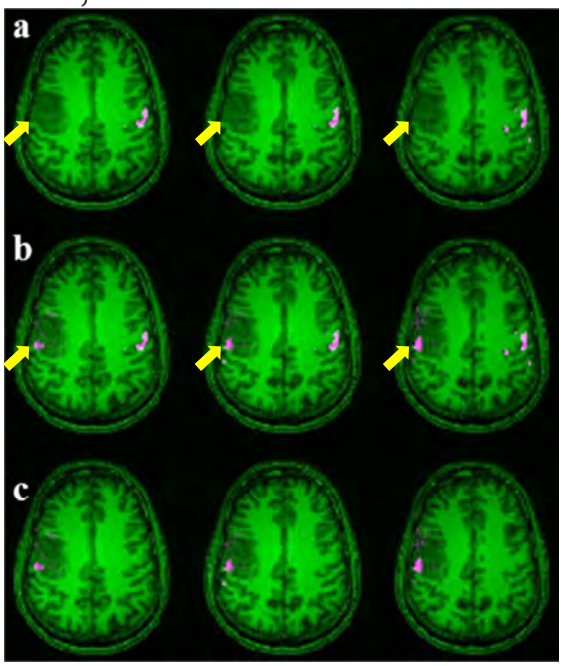

Figure 2: The top row shows a BOLD activation map (Z-score>4.3) obtained during a vertical tongue movement task in one patient. Arrow points to the NVU affected right primary motor cortex (PMC). The middle row displays the breath hold CVR-calibrated map with arrow pointing to the newly detected activation in the PMC. The last row shows a difference map between post (b) and pre (a) calibration.

Results: **Figure 2** shows an example of standard non-calibrated thresholded Z-score map, the CVR-calibrated motor map and difference map in one patient. In all four patients reduced CVR was present in the IL ROI, and after CVR normalization in the IL ROI the increase in number of active voxels in the post-calibrated maps compared to the number of active voxels in the non-calibrated maps was statistically significant (p=0.02 using paired t-test).

Discussion and Conclusions: In this preliminary study we demonstrate the feasibility of minimization of false negative motor task-based activation through use of a novel BH CVR-based calibration method to effectively compensate for NVU.

References: **1)** Holodny *et al.* AJNR 2000; 21:1415-1422. **2)** Pillai and Zacà. TCRT 2012; 11(4):361-74. **3)** Zaca et al. JMRI 2014; 40(3):383-90. **4)** Thomason *et al.*, Hum Brain Map 2007 28(1):59-68. **5)** Voyvodic *et al.*,JMRI 2009; 29(4):751-9.