Functional connectivity assessment using R2* resting-state functional MRI

Venkata Veerendra Nadh Chebrolu[1], Suresh Joel[1], Brice Fernandez[2], Ek Tsoon Tan[3], Luca Marinelli[3], Dattesh Shanbhag[1], Radhika Madhavan[1], Rachel Connett[4], Ajit Shankaranarayanan[4], and John Schenck[5]

[1]*Medical Image Analysis Lab, GE Global Research, Bangalore, Karnataka, India,* [2]*GE Healthcare, Muenchen, Germany,* [3]*MRI Laboratory, GE Global Research, NY, United States,* [4]*GE Healthcare, CA, United States,* [5]*MRI Technologies & Systems, GE Global Research, NY, United States*

Target Audience: Physicists and radiologists interested in R_2^* based resting-state functional MRI (rs-fMRI).

Purpose: In recent years, resting-state functional connectivity (rs-FC) has been widely used to image brain function. rs-FC is measured by correlation of blood oxygen level dependent (BOLD) MRI signal time-courses. BOLD signal has contributions from cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral metabolic oxygen rate ($CMRO_2$). The initial magnetization (M) is associated with CBF and CBV. Transverse relaxation rate (R_2^*) is associated with $CMRO_2$, which is related more specifically with neuronal activity than CBF and CBV [1]. Previously, R_2^* was used to improve the specificity of multi-echo BOLD rs-fMRI [2, 3]. In this work, we estimate functional connectivity using R_2^* time-courses and compare the results with conventional BOLD rs-fMRI. Figure 1 lists the possible changes in M and R_2^* and the corresponding changes in BOLD. Typically when R_2^* change is present, there would be corresponding change in BOLD. However, concomitant increases in R_2^* and CBV (or CBF) may not by accompanied by significant changes in BOLD signal. We hypothesize that connectivity estimated using R_2^* may be more sensitive than BOLD rs-fMRI in cases when BOLD effects from changes in R_2^* are compensated by changes in M. Further, we propose that R_2^* based connectivity would be less sensitive to vascular effects than BOLD rs-fMRI.

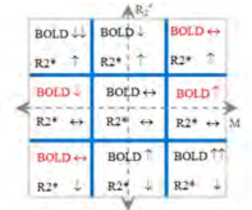

Figure 1: List of possible changes in M and R2 and the corresponding changes in BOLD.*

Methods: Five healthy subjects were imaged with multi-echo echo planar imaging (EPI) on GE 3T Signa HDxt (n=3) and Discovery MR750 (n=2) scanners using an 8 channel brain coil under institutional guidelines. The EPI acquisition had the following parameters: TR 2s, first echo-time (TE_1) of 12.3ms and echo-spacing (ΔTE) of 13ms for four echo EPI and TE_1 18ms and ΔTE 23ms for dual echo EPI, ASSET factor 2.0, BW=+/-250 kHz, 30 slices per TR, image matrix of 64×64 (4mm×4mm in-plane resolution) with slice thickness 4mm and at total of 300 time-points for rs-fMRI. A 1mm isotropic resolution T_1-weighted MRI was also obtained and was registered to MNI atlas. BOLD rs-fMRI was performed with echo-time of 38.2ms. R_2^* was estimated from the natural logarithm of multi-echo data using least-squares estimation. The preprocessing of BOLD and R_2^* time-courses included motion correction, registration to MNI atlas, physiological nuisance removal using COMPCOR [4], spatial smoothing using a 6 mm FWHM Gaussian filter and temporal band-pass filtering with 0.01 to 0.1 Hz zero-phase Butterworth band-pass filter. Thirteen 6-mm radius spherical regions were drawn around seed points associated with functional networks obtained from previously published work [5]. The mean time course for each seed region was computed. For every voxel, the Pearson correlation coefficient between the voxel and the seed time course was computed to create the FC map. Correlation coefficient was converted to z-score using Fisher transform.

Results and Discussion: Seed based functional connectivity of both BOLD and R_2^* produced expected typical functional networks. Five networks obtained from one subject using simultaneous acquisition of BOLD and R_2^* are shown in Figure 2. Joint histograms of the FC maps from BOLD and R_2^* rs-fMRI demonstrate nine possible scenarios (separated by dashed white lines, Figure 3). Though networks extracted from both methods were similar, there were differences with some networks showing larger connectivity extent on BOLD (e.g. DAS, red arrows) and other networks showing larger connectivity extent on R_2^* rs-fMRI (primary visual network, green arrows). Connectivity only seen on BOLD may arise due to non-$CMRO_2$ changes. This cannot be explained by the typical lower sensitivity of R_2^* rs-fMRI, which was overcome with optimal echo combinations to obtain sensitivity comparable to BOLD (Contrast-to-noise-ratio analysis to determine the optimal echo-times for multi-echo R_2^* fMRI has been submitted separately). Connectivity observed in R_2^* and not in BOLD rs-fMRI, may arise due to compensation of $CMRO_2$ effects by vascular changes in BOLD.

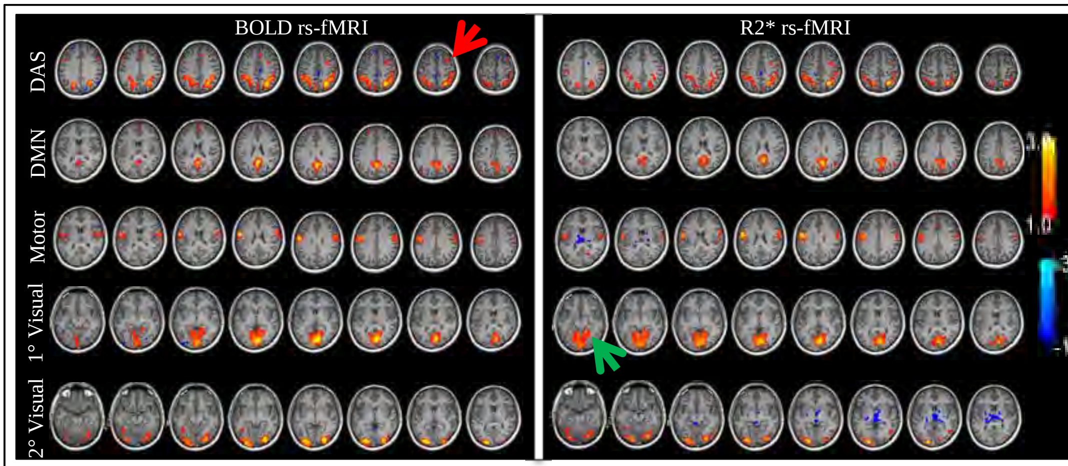

Figure 2: Functional connectivity (FC) of one subject derived from BOLD (left) and R2 (right) rs-fMRI using the same multi-echo acquisition (four echo acquisition). The color bars show the range of FC z-score overlaid on the T1-weighted MRI (MNI atlas space). DAS: Dorsal Attention System; DMN: Default Mode Network; Motor: Ventral Motor; 1º Visual: Primary Visual Network; 2º Visual: Secondary Visual Network.*

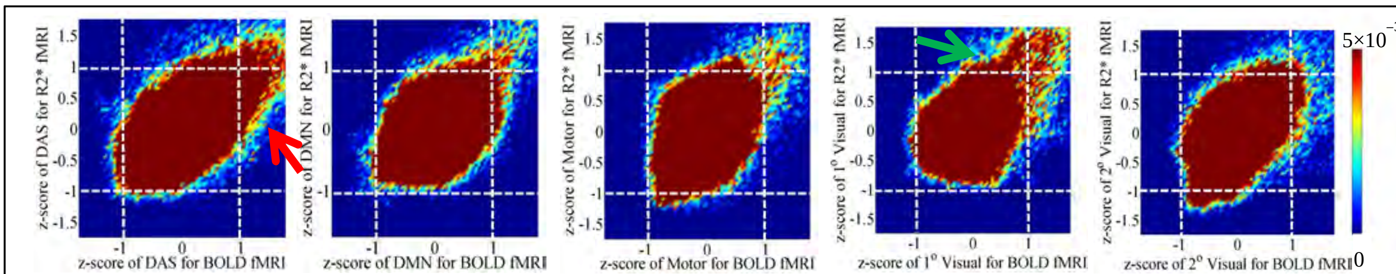

Figure 3: Joint 2D histogram of the z-scores for BOLD and R2 functional connectivity maps for the networks shown in Figure 2. Color bar shows % counts.*

Conclusion: R_2^* rs-fMRI based functional connectivity may provide additional sensitivity and specificity to $CMRO_2$ changes compared to BOLD rs-fMRI. Future work will analyze the reproducibility of the connectivity estimated from R_2^* rs-fMRI in larger cohorts.

References: [1] Hyder F, et al. (2013), ISBN: 978-1-4398-5265-1 Taylor & Francis, pp 99-124 1: 99-124. [2] Kundu P, et al (2012), NeuroImage 60: 1759-1770. [3] Kundu P, et al (2014) NeuroImage 102P2: 861-874. [4] Behzadi Y, et al (2007), NeuroImage 37: 90-101. [5] De Luca M, et al (2006), NeuroImage 29: 1359-1367.