BOLD Functional Connectivity Analysis based on Intravascular-weighting and Parenchymal R2*

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TARGET AUDIENCE: Researchers interested in BOLD contrast mechanisms and improving BOLD sensitivity for detection of resting state networks.

PURPOSE: The purpose of this study is to apply multi-echo (ME) baseline blood oxygenation level-dependent (BOLD) imaging to detect and characterize functional networks and ultimately to use this information to improve the robustness and sensitivity of BOLD functional connectivity analyses. BOLD resting state studies are typically performed using a single-shot gradient echo (GRE) sequence acquired at a single echo time (TE). BOLD contrast-to-noise ratio (CNR) is maximized when TE ~ tissue T_2*; as venous T_2* < tissue T_2*, the contribution of intra-vascular (IV) signals to functional networks should vary with choice of TE, which is commonly in the range of 30-45 ms at 3T. Understanding the magnitude of this effect is fundamental to connectivity analyses, as similar to evoked BOLD responses, connectivity analyses performed on voxels that partially include draining veins may provide suboptimal or even false markers of hemodynamic and/or neuronal activity. While much work has focused on characterizing IV sensitivity of evoked BOLD responses at different field strengths, only limited quantitative information is available on how IV sensitivity contributes to resting state connectivity. Here, we acquire BOLD images at multiple TEs at baseline and apply common connectivity analyses at each TE and to calculated R_2* maps. Connectivity maps are compared at individual and group levels, and in relation to proximity to large vessels, to understand the extent to which TE influences IV sensitivity and robustness of resting state BOLD functional connectivity analyses.

METHODS: 12 volunteers (age= 67±7 yrs) provided, informed written consent in accordance with the local IRB. *Experiment.* BOLD: A 3T ME single-shot, GRE EPI sequence was used to quantify BOLD contrast (slices=35; spatial resolution=3x3x4 mm^3; TR/TE1/TE2/TE3 = 3000/14/42/70 ms; measurements=120). All TEs were acquired in one TR and therefore scan duration was identical to typical single-TE BOLD experiments. Phase-contrast angiography (PCA) was also performed in a subgroup of volunteers (n=8). *Analysis.* BOLD: Preprocessing steps included high frequency (f>0.1 Hz) noise removal, baseline drift correction, smoothing (FWHM=3 mm), and affine motion correction. BOLD data were registered to a 2 mm resolution MNI template. Baseline drift correction was performed in MATLAB using 3rd order polynomial fitting. Voxel-wise R_2* maps were calculated using a linear log fit to the ME fMRI data, and weighted[2] (wtd) maps were additionally calculated using the weights $w_i = (TE_i e^{-TE_i/T2^*}) / \sum(TE_i e^{-TE_i/T2^*})$ for i=14, 42 or 70 ms. Baseline synchrony was evaluated using multi-subject temporal concatenation of the time courses, independent component analysis (ICA) and dual regression[1] for the (i) three TEs separately, (ii) averaged (avg) and weighted (wtd) BOLD data, and (iii) R_2* maps. PCA data were registered to the same MNI template as above. An averaged map of vascular distribution was created to understand the extent to which connectivity maps overlapped with veins at each TE. The primary network of investigation in this study was the default mode network (DMN), which was identified from the ICA analysis. Group z-statistic maps and inter-subject spatial variance maps of functional connectivity, and DMN connectivity SNR (C_{SNR}=mean z-score/std. deviation in z-scores across all subjects) maps were compared across subjects.

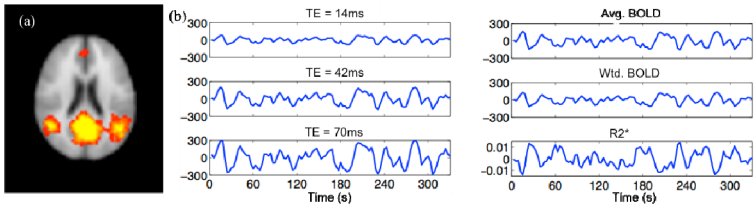

Figure 1: (a) *Common DMN mask obtained using dual regression.* ***(b)*** *Mean time course of the voxels in the common mask for all six analyses for one representative subject.*

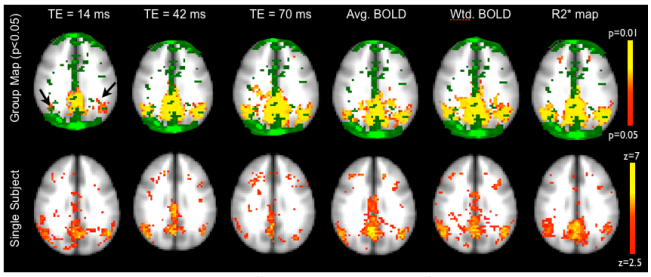

Figure 2: Top: *Group maps fo the DMN (n=12) for BOLD at TE = 14 ms, 42 ms, 72 ms, avg. BOLD data, wtd BOLD data and R2* data.* ***Bottom:*** *DMN identified for a single subject for each of the six analyses.*

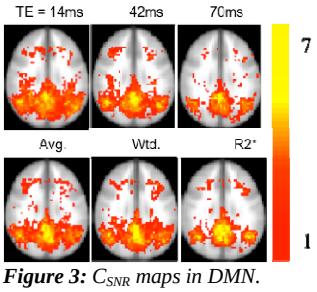

Figure 3: *C_{SNR} maps in DMN.*

RESULTS: Fig. 1a shows voxels common to all six analysis procedures. Fig. 1b depicts the time course for TE = 14 ms, 42 ms, 70 ms, avg. BOLD, weighted (wtd) BOLD, and R_2*. R_2* decreases with increased oxygenation, so the time course is inverted for the R_2* data compared to BOLD. The amplitudes of the temporal fluctuations in the avg and wtd BOLD data were not significantly different from the BOLD data at TE = 42 ms. The amplitude of the fluctuations at TE = 14 ms was 0.47 times those observed at TE = 42 ms. Fig. 2 shows large vessels obtained from the PCA data in green with the common BOLD map (n=12) for the different analyses procedures. DMN regions at TE = 14 ms co-localize most with large vessels as shown by the black arrows. The DMN map for a single subject shows robust connectivity in the R_2* data, analogous to the group map. Data in Fig. 3 demonstrate that R_2* maps provide a high inter-subject C_{SNR} more spatially specific to the DMN. 24% more voxels in the R_2* analysis had increased inter-subject C_{SNR}>2 compared to single-TE BOLD.

DISCUSSION: As anticipated, we observed that sensitivity of baseline BOLD contrast for functional networks depends on TE choice. BOLD data at short TEs suffers from IV contamination while longer TE data have higher comparative extravascular sensitivity but lower overall C_{SNR} and elevated susceptibility distortions. Optimization of BOLD contrast at rest is a challenge because the extent of R_2* fluctuations may be spatially dependent in the brain. However, we observed that the TE dependent-variability can be reduced when functional connectivity analyses are applied to quantitative R_2* maps, which can be obtained in the same time as single TE experiments performed at intermediate temporal resolution (TR=3000 ms). Finally, we observed that functional maps obtained from R_2* data co-localize less with large vessels.

CONCLUSION: Inter-subject variability in the DMN map obtained from R_2* maps was reduced when compared to BOLD data obtained at a typical TE = 42 ms or wtd BOLD data. R_2* maps from ME BOLD, acquired within the same time as single-TE BOLD, may therefore have a higher potential to distinguish differences between populations (e.g., diseased vs. healthy) with smaller sample sizes.

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