fMRI-derived functional connectivity density mapping as a biomarker of state changes as reflected by glucose metabolism

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TARGET AUDIENCE: Neuroscientists interested in the metabolic basis of resting-state fMRI (R-fMRI), clinicians interested in R-fMRI biomarkers for state changes.

PURPOSE: Resting-state fMRI is a popular way to measure networks in the human brain. However, a lack of understanding of its metabolic basis has made translation to clinical settings difficult. Herein, we search for resting state fMRI derived biomarkers of a state change where a global change in brain metabolism was observed.

METHODS: Simultaneous R-fMRI (TR=2s, 300 images) and fluorodeoxyglucose PET data were recorded in 11 subjects with eyes open and 11 different subjects with eyes closed. In either state no task or overt stimuli were presented. Although these R-fMRI and PET data that were previously reported[1], here we applied different R-fMRI data analysis in conjunction with quantitative calibration of the PET data to reflect absolute glucose metabolism (CMR_{glc}). A PET calibration factor was applied by comparison of the mean eyes closed PET data to another PET database from 13 subjects under the same condition for whom quantitative CMR_{glc} was available[2]. The current PET data were thus converted into absolute CMR_{glc} units of µmol/g/min. R-fMRI data were processed with standard R-fMRI processing techniques, both with and without regression of nuisance signals (including the "global" signal). Networks were generated using Brodmann regions of 37 previously reported networks as seeds to generate correlation-based resting state fMRI networks at 3 thresholds. As CMR_{glc} in the eyes open state was globally higher than in the eyes closed state (Figure 1A), several voxel-wise fMRI metrics were calculated to determine which had similar behavior. The first type of metric was functional connectivity density (FCD) based[3] that was calculated in terms of total connections, short-range connections (connections within 3mm of the voxel or less) and long range connections (connections at distance greater than 3mm). The second type of metric was variance-based, included standard variance, amplitude of low frequency fluctuations (ALFF), and the fractional ALFF (FALFF)[4].

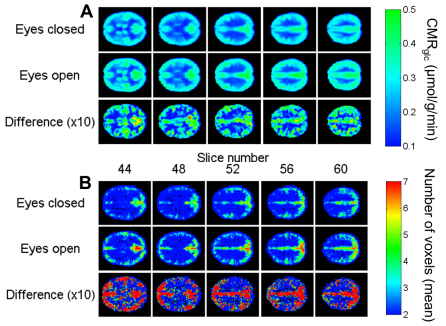

Figure 1. PET and R-fMRI from representative slices. (A) CMR_{glc} data shows significantly higher global rates in gray vs. white matter. (B) Local FCD shows global increase across gray vs. white matter. In each case, eyes closed (top), eyes open (middle), and their difference x10 (bottom).

RESULTS: All of the variance-based metrics (inc. ALFF and FALFF) had similar values depending on the threshold used to create the networks rather than eyes open or eyes closed. FCD at short-range connections (with no regression of nuisance signals), shown in Figures 1B and 2A, showed a difference between conditions that in some cases was less than the difference between thresholds. 2D ANOVA revealed a significant difference between eyes open and eyes closed but no significant difference between networks or network-state interaction ($p \leq 1.03 \times 10^{-5}$, $p \geq 0.99$, $p \geq 0.99$, respectively). However this difference was lost if nuisance signal regression was conducted prior to FCD, as shown in Figure 2C.

DISCUSSION: An FCD based metric produced the result most similar to the global state change observed with CMR_{glc} across the brain between the eyes open and eyes closed states. This result was lost if regression of nuisance signals (including the "global" signal) was done during R-fMRI data analysis. Thus FCD may have value as a biomarker of the global brain metabolism as it changes between states, but that part of this biomarker value seems linked to the regressed "nuisance" signal.

CONCLUSION: FCD based metrics may prove to be a good biomarker of global changes in brain metabolism in clinical settings for R-fMRI data, however there is an important caveat that nuisance signal regression may eliminate this.

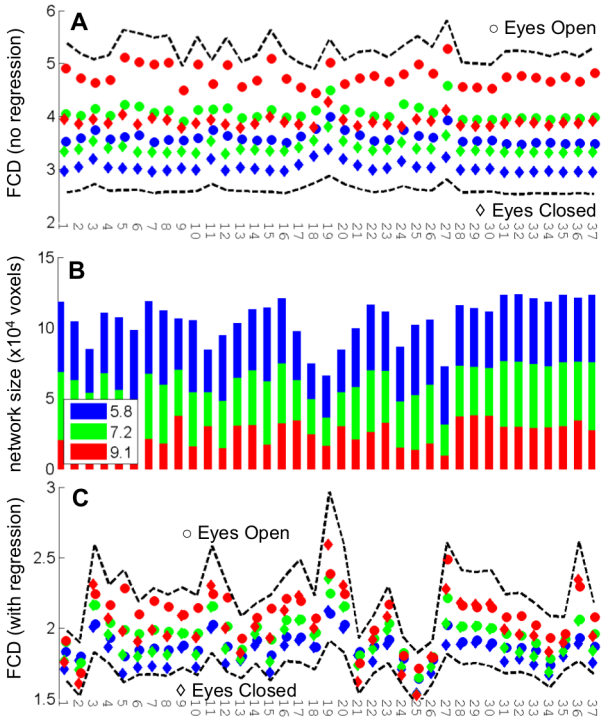

Figure 2. FCD analysis for 37 networks for eyes closed (diamond) vs. eyes open (circles) states. Variations of (A) FCD without global signal regression across networks, (B) sizes of networks in A and C, and (C) FCD with global signal regression across networks. In each case, blue ($Z \geq 5.8$), green ($Z \geq 7.2$), and red ($Z \geq 9.1$) indicate different R-fMRI thresholds and dashed line is maximum SEM per network.

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