Metabolic basis for the "rest" condition in fMRI: Comparison of eyes open vs. closed states reveals constancy of glucose metabolism across networks

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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: R-fMRI is a popular way to measure gray matter networks in the human brain as these networks are reliably observed across different subjects and scans. However the parameters defined as "resting" for R-fMRI scans remain quite variable. For example, subjects may lie with eyes closed or open. While studies have examined R-fMRI connectivity strength across these different "rest" conditions[1], no study has examined the rationale for choosing the "rest" condition based on metabolic demand across networks. Moreover, because R-fMRI derived networks use fluctuations of the spontaneous BOLD signal from an undefined baseline and which is removed in R-fMRI data analysis, the metabolic underpinnings of R-fMRI network variations between different brain states (e.g., normal vs. diseased) remain difficult to interpret. To begin to answer these questions, we compare glucose metabolism (CMR_{glc}) between eyes open and eyes closed and also across R-fMRI networks within each state.

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[2], here we applied different R-fMRI data analysis in conjunction with quantitative calibration of the PET data to reflect absolute 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[3]. 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. Three types of network definition were used. Definition 1: Using only the Brodmann regions of 37 previously reported networks. Definition 2: The same Brodmann regions, but using them as a seed to generate correlation-based R-fMRI networks. Per-subject and mean networks, at three different thresholds, were examined. Definition 3: Independent component analysis (ICA) of R-fMRI data[4] was used with components either within-group (e.g., only generated from eyes closed subjects) or across all subjects (22 subjects). Mean CMR_{glc} in all of these networks were calculated and for each type of network a 2D ANOVA was used to test for significance, with network as one variable and eyes open vs. eyes closed as the other variable.

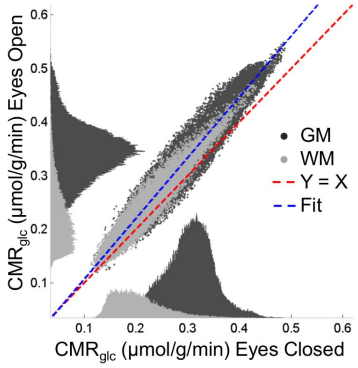

Figure 1. CMR_{glc} in eyes closed (horizontal) vs. eyes open (vertical) states, where gray and white matter (GM = dark gray, WM = light gray) histograms for each state are shown on each axis. The linear fit (blue) between the two states has a positive slope of 1.13 (R^2 = 0.93) vs. the line of identity (red), indicating a global CMR_{glc} increase in eyes open state.

RESULTS: Figure 1 shows a scatter plot of mean CMR_{glc} in the whole brain for the two states, depicting a global increase of ~13% in eyes open state vs. eyes closed state and where the CMR_{glc} shift was noticeable in both gray and white matter. Figure 2 shows CMR_{glc} at three thresholds using definition 2, individual networks and no nuisance signal regression (results were quite similar with nuisance signal regressions). For definition 1 (networks consisting only of Brodmann regions) and definition 2 (networks derived with correlation, using the same Brodmann regions as seeds), there was a significant increase in CMR_{glc} from the eyes closed state to the eyes open state, but no significant difference between R-fMRI networks or interaction between states and between networks (definition 1: $p \leq 2.4 \times 10^{-13}$, $p \geq 0.94$, $p \geq 0.99$, definition 2: $p \leq 5.8 \times 10^{-13}$, $p \geq 0.87$, $p \geq 0.99$, respectively). Using definition 3 (networks based on ICA) there was a significant difference between states and between networks, but without significant interactions ($p \leq 5.8 \times 10^{-8}$, $p \leq 3.4 \times 10^{-3}$, $p \geq 0.16$, respectively). However when components representing white matter, CSF, and noise were removed, results were similar to the other network definitions ($p \leq 1.1 \times 10^{-6}$, $p \geq 0.50$, $p \geq 0.99$, respectively).

DISCUSSION: Globally higher CMR_{glc} was observed in the eyes open state. Although there was a significant CMR_{glc} difference between the two states in both gray and white matter, there was no significant CMR_{glc} difference across gray matter networks in any given state. Although R-fMRI network analysis does not capture the metabolic state difference, R-fMRI networks were reliably detectable regardless of the state. While there were no significant differences between the R-fMRI networks observed across the two states, the smallest correlation based R-fMRI networks had greater CMR_{glc}, suggesting that nodes with a high density of connections have higher CMR_{glc} for a state.

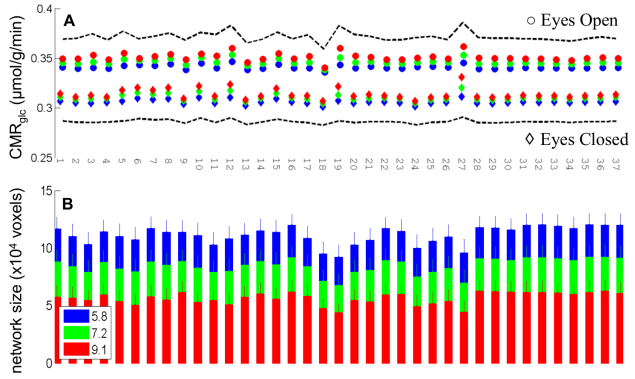

Figure 2. CMR_{glc} across 37 networks created using definition 1 (correlation with seed regions), per-individual networks and no nuisance signal regression. Variation of **(A)** CMR_{glc} across networks with eyes closed (diamond) vs. eyes open (circles) states and **(B)** sizes of networks, where blue ($Z \geq 5.8$), green ($Z \geq 7.2$), and red ($Z \geq 9.1$) indicate different R-fMRI thresholds and dashed line/errorbar is maximum SEM.

CONCLUSION: There is a global CMR_{glc} difference between eyes closed and open states. However, all R-fMRI networks were detected regardless of the state and CMR_{glc} was constant across networks within each particular state. This result suggests that the brain easily transitions between these networks and thus, in terms of metabolic demand, either "rest" condition can be chosen for R-fMRI studies.

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