Resting-State Functional Connectivity Strength Depends on the Magnitude of Resting BOLD Fluctuations and Not Differences in CBF

A. L. Rack-Gomer[1,2], J. Liau[3], and T. T. Liu[1,2]
[1]Bioengineering, UC San Diego, La Jolla, CA, United States, [2]Center for Functional MRI, UC San Diego, La Jolla, CA, United States, [3]School of Medicine, UC San Diego, La Jolla, CA, United States

INTRODUCTION

Correlations between spontaneous fluctuations in the blood oxygenation level dependent (BOLD) signal are finding increasing use as measures of functional connectivity in the brain. Inter-subject differences in functional connectivity strength have shown promise in predicting cognitive performance and diagnosing disease [1,2]. However, the interpretation of functional connectivity differences is complicated by the BOLD signal's dependence on both neural and vascular factors. Prior work has shown that the task-related BOLD response amplitude is negatively correlated with baseline cerebral blood flow (CBF) across subjects and positively correlated with resting-state fluctuation amplitude (RSFA) within subjects, where RSFA and CBF are thought to be related to vascular responsiveness to neural activity [3,4]. We previously reported that resting-state functional connectivity strength was negatively correlated with baseline CBF across subjects, suggesting that vascular differences may contribute to functional connectivity differences [5]. The goal of this work was to assess the relationship between RSFA and functional connectivity strength, and between RSFA and measures of CBF (functional responses and baseline), across healthy subjects.

METHODS

Seventeen healthy subjects were scanned on a GE Signa 3T scanner. The scan protocol included a bilateral finger tapping block design, baseline CBF and calibration scans, and two five-minute resting BOLD scans. Data were collected over 6 oblique slices in the primary motor cortex (resolution = 3.75×3.75×6 mm). The finger tapping and CBF baseline scans were acquired with a PICORE QUIPSS II arterial spin labeling (ASL) sequence with dual echo spiral readout (TR = 2s, TI1/TI2 = 600/1500 ms, TE1/TE2 = 9.2/30 ms, FA = 90°). The two resting BOLD scans were acquired with spiral readout (TE = 30 ms, TR = 500 ms, FA = 45°). All images were coregistered in AFNI. Regions of interest were defined for the motor cortex from the intersection of the BOLD and CBF activation maps, obtained from a general linear model analysis of the dual echo finger tapping data. The task response amplitude was calculated as the average %ΔCBF in the motor cortex during finger tapping. Baseline CBF (ml/100g/min) was measured in the motor cortex from the ASL scans. Nuisance terms were regressed out of the resting BOLD data, including a linear trend, motion parameters, physiological noise terms, and the global signal from the frontal lobe region. The corrected time series were low-pass filtered (< 0.08Hz). RSFA values were calculated as the average standard deviation of the time courses, normalized by their means, in the motor cortex. Functional connectivity strength was computed as the mean correlation (r) of all time courses in the left motor cortex with those in the right motor cortex.

RESULTS AND DISCUSSION

We found that functional connectivity strength is significantly correlated with RSFA across subjects (Fig 1a). However, significant correlations were not found between mean r and baseline CBF (Fig 1b), or between RSFA and baseline CBF (Fig 1c). These findings suggest that inter-subject differences in functional connectivity are not due to differences in the baseline vascular state. We previously reported that functional connectivity strength and baseline CBF were negatively correlated, but this trend was not significant in the larger subject population presented here (previously N=9), and was further decreased by additional noise correction steps (removal of motion and global signal).

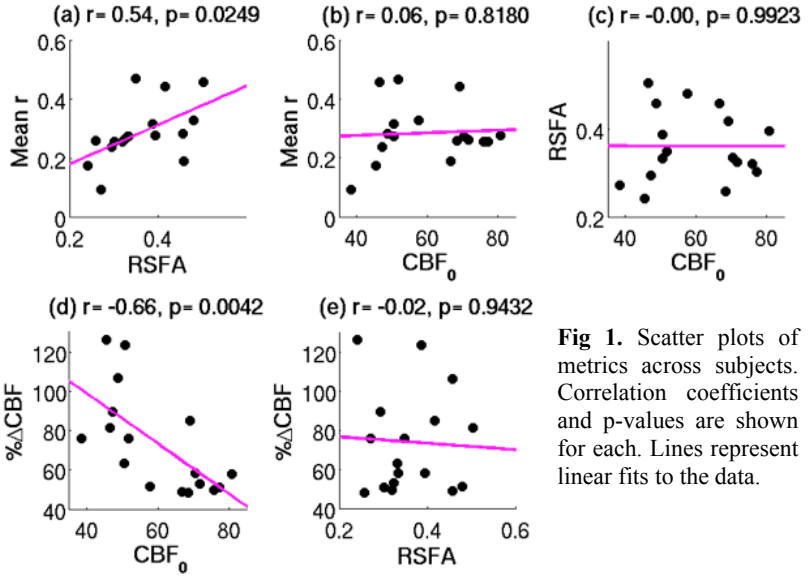

Fig 1. Scatter plots of metrics across subjects. Correlation coefficients and p-values are shown for each. Lines represent linear fits to the data.

While the task related CBF response amplitude (%ΔCBF) displays a strong inverse dependence on baseline CBF (Fig 1d), no relationship is present between %ΔCBF and RSFA (Fig 1e). These results suggest that RSFA does not reflect vascular sensitivity to neural activity across subjects. Prior work has shown that RSFA is correlated with vascular reactivity across voxels [4]. However, additional work has shown that the relationships between the BOLD response and physiological parameters across voxels differ from those found across subjects [3]. A preliminary study in the visual cortex found across subject correlations between RSFA and baseline vascular parameters such as CBF and venous oxygenation [6]. More work is necessary to determine if brain region or experimental differences influence these relationships.

The results presented here suggest that RSFA may serve as an accurate reflection of inter-subject differences in spontaneous neural activity and lend support to studies that have used RSFA to examine neural activity differences across resting conditions and disease state [7,8]. We find that inter-subject variability in functional connectivity strength is not related to vascular differences, but does exhibit a dependence on the magnitude of resting-state fluctuations. Because measures of correlation depend on both the strength of the underlying correlation and the signal-to-noise ratio (SNR) of the measure, it is possible that the relationship between functional connectivity strength and RSFA reflects inter-subject differences in SNR that are related to the size of the fluctuations. Further work is required to elucidate the factors that contribute to the relationship between RSFA and correlation strength.

REFERENCES

[1] Hampson et al. J Neurosci 26:13338-43, 2006 [2] Greicius et al. PNAS 101:4637-42, 2004. [3] Liau et al. ISMRM, p. 854, 2008. [4] Kannurpatti et al. Neuroimage 40:1567-1574, 2008. [5] Rack-Gomer et al. ISMRM, p. 1649, 2009. [6] Lu et al. ISMRM, p. 218, 2009. [7] Yan et al. PLoS One 4:e5743, 2009. [8] Zang et al. Brain Dev 29:83-91, 2007.