The relationship between functional connectivity strength and cerebral blood flow

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Introduction

The human brain is a complex network, where separated modules interlinked through hubs providing efficient and economic communications [1,2]. Hubs have a privileged role in integrating specialized information. Graph-based network analysis of structural [3,4] and functional [5,6] connectivity data have identified a set of hubs located in precuneus/posterior cingulate and medial prefrontal cortex, which closely resemble the default mode network that consume relatively high metabolic energy [7]. This suggests a fundamental link between brain functional connectivity strength and metabolic demand. However, the direct evidence is missing. In this study, we investigated the relationship between functional hubs and cerebral blood flow (CBF) by analyzing resting-state BOLD and ASL imaging data collected on the same subjects.

Methods

Participants: Forty-eight healthy young adults (27.4±7.1 yrs, 25 females) participated in the study. All participants were screened to ensure no history of neurologic/psychiatric conditions or drug abuse. Informed consent was obtained from all subjects in accordance with the guidelines and approval of the Institutional Review Board of the Intramural Research Program of the National Institute on Drug Abuse.

Data acquisition: Scanning was performed on a 3.0 T Siemens Allegra MR Scanner. High-resolution anatomical images were acquired using a 3-D MPRAGE T1-weighted sequence with repetition time (TR) = 2500 ms, echo time (TE) = 4.38 ms, flip angle (FA) = 8° and 1.0 mm isotropic voxels. Resting-state fMRI BOLD images were acquired using a gradient-echo EPI sequence with TR = 2000 ms, TE = 27 ms, FA = 77°, thirty-nine 4-mm slices without interslice gap, field of view (FOV) = 220x220 mm^2 and an in-plane resolution of 3.44x3.44 mm^2. Resting-state ASL data were acquired using a pseudo continuous arterial spin labeling (pCASL) technique. Interleaved control and label images were acquired using a gradient echo EPI sequence with TR = 4500 ms, TE = 21 ms, FA = 90°, twenty 5-mm slices with 20% gap, FOV = 220x220 mm^2 and an in-plane resolution of 3.44x3.44 mm^2.

Data processing and analysis: Anatomical images were segmented using unified segmentation model developed in SPM8 [8]. The rigidly aligned gray matter (GM) and white matter (WM) images were further aligned using a nonlinear registration algorithm (DARTEL) [9]. A custom template was created based on the registration results and each individual's GM and WM images were transformed to the DARTEL template space, modulated by the determinant of the Jacobian of the transformation. Finally, images were transformed to Talairach space using AFNI and spatial smoothed (FWHM=6mm). Preprocessing steps for resting-state BOLD data included slice-timing correction, volume registration, linearly detrending, spatial normalization, temporal band-pass filtering (0.01-0.1Hz) and spatial smoothing (FWHM=6 mm). Several nuisance variables, including motion, WM, ventricles and whole brain average signal, were removed by multiple linear regression analysis. The time course of each voxel within the GM mask was extracted and correlated to the time course of every other voxel. Functional connectivity strength at a given voxel x_0 was computed as the average of functional connectivity between x_0 and all other voxels in the brain. Voxels with top 25% of functional connectivity strength were considered as functional hubs. Similarly, structural hubs were also detected based on structural connectivity computed as the correlation of GM volume across subjects. For resting-state ASL data, after slice-timing correction, volume registration and spatial smoothing (FWHM=6mm), CBF-weighted time series were created from the difference images between control and labeled images. Absolute CBF time series were calculated using one-compartment model and averaged together to get individual-level absolute CBF maps followed by spatial normalization. To quantitatively evaluate the interrelation between functional connectivity strength and CBF, we performed correlation analysis across voxels as well as across participants. For each participant, correlation analyses were carried out between functional connectivity strength and CBF values across voxels within the GM mask. Across-subject correlations were computed at each voxel within the GM mask between functional connectivity strength and CBF.

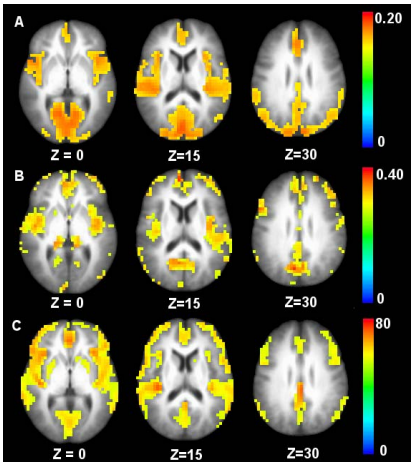

Fig 1. Spatial maps of functional connectivity hubs (A), structural connectivity hubs (B) and CBF hubs (C), where the regions with top 25% of the metrics.

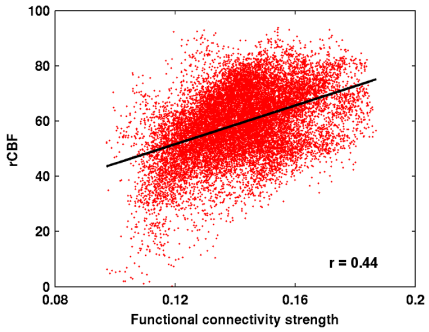

Fig 2. Scatter plot of functional connectivity strength against CBF across all voxels.

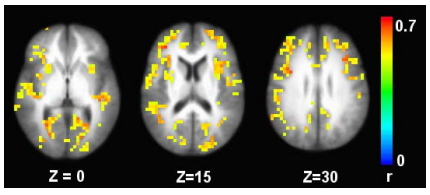

Fig 3. Map of significant correlations between functional connectivity strength and CBF statistics across subjects. The significant threshold was set at p = 0.05 combining with a minimum cluster size of 6080 mm^3.

Results

Functional connectivity hubs (Fig.1A) were identified in posterior cingulated (PCC)/precuneus, anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), bilateral temporal cortices, and visual cortices. Structural connectivity hubs (Fig.1B) distributed in PCC, ACC, mPFC, lateral prefrontal cortex (lPFC), and temporal cortices, overlapped with a number of regions of the functional hubs. The spatial pattern of brain regions with high CBF (Fig.1C) was also similar with the functional and structural hubs, predominately located in PCC, ACC, mPFC/lPFC, and temporal cortices. The voxelwise relationship between functional connectivity strength and CBF after averaging data from all subjects is shown in Fig.2, and strong correlation between the two indices across voxels ($r = 0.44$, $p < 0.00001$) is observed. This relationship (connectivity vs. CBF) is slightly weaker but remains significant after controlling for gray matter volume (GMV) in each voxel ($r = 0.40$, $p < 0.00001$) or structural connectivity strength ($r = 0.43$, $p < 0.00001$). Across-subject correlation analysis revealed a set of regions positive correlated between functional connectivity strength and CBF (Fig. 3). These regions include bilateral frontal cortices, temporal cortices, PCC/precuneus and cuneus.

Discussion

In the present study, we found that the functional hubs are located primarily in the default mode network and primary visual cortical regions, in accordance with previous functional [5,6] and structural studies [3,4]. The functional hubs largely overlap with the brain regions that have the highest CBF as observed in PET [7] and ASL [10] studies. These regions are in general consistent with previous DTI-based studies demonstrating high positive correlation between the centrality of structural hubs and regional CBF [3, 11]. The robust relationship between functional connectivity and CBF shown in the current study suggests an underlying metabolic energetic basis of functional connectivity hubs.

References

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