GABA Concentration Predicts the Strength of Functional Connectivity

Xi Chen*[1], Hong Gu*[1], and Yihong Yang[1]

[1]*Neuroimaging Research Branch, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, United States*

Introduction

Resting-state brain activity has been shown to predict task-induced brain activation and corresponding cognitive performance [1,2]. Meanwhile, it has been shown that GABA concentration in specific brain regions was negatively correlated with the amplitude of BOLD response elicited in the same regions [3,4]. However, the relationship among GABA level, resting-state brain activity and task-induced brain activation remains to be elucidated. In this study, we investigate 1) whether GABA concentration is related to functional connectivity strength; and 2) whether resting-state BOLD fluctuations act as a mediator in the prediction of task fMRI response from GABA concentration.

Methods

Subjects and Experiment Design. Sixteen healthy volunteers (8 male; age: 36±6.8) participated in the study. All subjects underwent a high-resolution anatomical scan, an 8 min eyes-closed resting fMRI scan, two resting MRS scans with a voxel in the calcarine fissure or right inferior parietal lobule (IPL; as a control site), and a 4.5 min block-design visual-task fMRI scan using a full-screen black-and-white checkerboard flashing at 3 Hz.

Data Acquisition. All MRI and MRS scans were acquired on a Siemens 3T Trio scanner using a 12-channel coil. The resting and task fMRI scans were acquired using a single-shot GE EPI sequence with the following acquisition parameters: TE/TR = 27/2000 ms; FA = 78º; FOV = 22×22 cm^2; 64×64 imaging matrix; slice thickness/gap = 4/0 mm; 39 slices). GABA-edited MR spectra were acquired from a 3×3.5×2.5 cm^3 volume using the MEGA-PRESS method [5], with TE/TR = 68/5000 ms and 96 averages. The anatomical scan was acquired with a T_1-weighted 3D MPRAGE sequence (256×192×208 imaging matrix; 1×1×1 mm^3 in-plane resolution; TI/TR/TE = 900/1900/3.51 ms; FA = 9º).

Data Processing and Analyses. Slice-timing correction, motion correction, spatial smoothing (FWHM = 6 mm), and quadratic detrending were performed for all fMRI data sets in AFNI. Before any calculation, the resting data was also band-pass filtered (0.01 – 0.1 Hz) and regressed out with the following uninteresting covariates: 1) six motion parameters; 2) whole-brain global average signals; 3) the first three principal components from the white matter and CSF voxel time courses ensembles respectively. For the visual task BOLD data, GLM models were constructed to obtain the visual stimulus-evoked activation maps; the six motion parameters were used as covariates. For each individual, a region of interest (ROI) in the primary visual cortex was generated based on the activation map. The activation map was thresholded ($p_{corrected}$<0.05) such that each ROI was about the 1.2% of the whole-brain volume (399 ± 40 voxels). Within the ROI, correlation coefficients (CC) between any voxels were calculated and averaged as a measurement of correlation strength of the resting BOLD fluctuations; the signal percentage change induced by the visual stimulus was averaged to evaluate the strength of stimulus-evoked BOLD responses. The MRS data were quantified using LCModel [6]. The GABA and creatine concentrations were obtained from the difference and off-resonance spectra respectively, using corresponding simulated basis sets.

Statistical Analyses. To investigate the interplay of the GABA concentration, resting BOLD fluctuations, and stimulus-induced BOLD signal change, regression analyses were performed among quantities of the functional connectivity strength (average CC of resing-state fMRI), ratio of GABA/total creatine (tCr), and brain activation amplitude (average BOLD signal change induced by visual stimulation). Mediation analyses using Sobel test were conducted to test whether the resting-state activity acted as a mediator in the prediction of task activation from GABA concentration.

Results

The regression analyses show significant negative correlation between the connectivity strength and GABA/tCr (R = -0.64, p<0.01, n=15) in primary visual cortex (Fig.1). Our analyses also confirm the negative correlation (R = -0.54, p<0.05, n=15) between the GABA concentration and BOLD amplitude in response to visual stimulation [4] and the positive correlation (R = 0.72, p<0.005, n=15) between the connectivity strength and individuals' task-evoked BOLD responses [2] (Fig.2 and 3). As a negative control, there is no correlation between the functional strength / evoked BOLD responseamplitude in the visual vortex and the GABA/tCr in the IPL (p>0.4). The mediation analysis using Sobel test shows that the GABA concentration – task activation relationship is mediated by the functional connectivity strength (p<0.05), while the GABA concentration does not show significant mediation effect on the connectivity strength - task activation prediction (p=0.60).

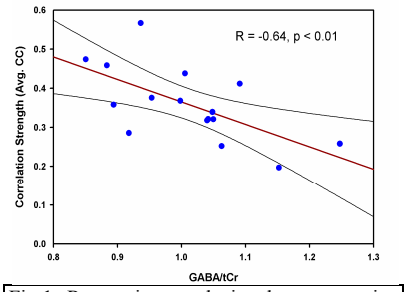

Fig.1 Regression analysis shows negative correlation between functional connectivity strength (indicated by average CC) and GABA/tCr.

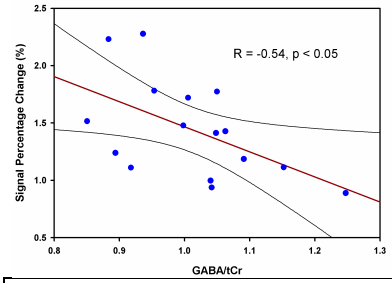

Fig.2 Regression analysis shows negative correlation between the amplitude of task-evoked BOLD response (indicated by average signal percentage change) and GABA/tCr.

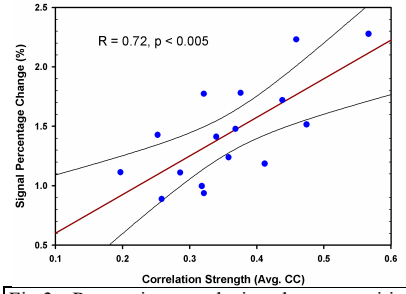

Fig.3 Regression analysis shows positive correlation between the amplitude of task-evoked BOLD response (indicated by average signal percentage change) and functional connectivity strength (indicated by average CC).

Discussion

In this study, we found that the spatiotemporal correlation strength of resting BOLD fluctuations is negatively correlated with resting GABA concentration in primary visual cortex, both of which can predict the amplitude of evoked BOLD responses to visual stimulus. The mediation analysis shows that the functional connectivity strength, acting as a mediator, has a significant unique effect in predicting the stimulus-evoked BOLD signal changes, and the effect of the GABA concentration on the fMRI BOLD responses reduces when the resting correlation strength was added into the prediction model.

It has been shown that suppression of $GABA_A$ receptor-mediated inhibition increases the spread of synchronized activity [7], as well as the cerebral oxygen consumption [8] in rats, which may lead to higher correlation strength. Findings in this study may help to understand the interplay of the neurotransmitter level, intrinsic brain activity and evoked brain activation.

References

1. Hampson et al, J. Neurosci. 2006;26:13338-43. 2. Liu et al., NeuroImage 2011;54:2278-86. 3. Northoff et al., Nat. Neurosci. 2007;10:1515-17. 4. Muthukumaraswamy et al., PNAS 2009;106:8356-61. 5. Mescher et al., NMR Biomed 1998; 11:266–272. 6. Provencher, MRM 1993;30:672-9. 7. Chagnac-amitai and Connors, J. Neurophysio. 1989;61:747-58. 8. Weiss et al., Int J Dev Neurosci. 2008;26:517-21.

*Contributed equally to this work.