Underestimation of functional connectivity with impaired cerebrovascular reserve : a working model of moyamoya disease

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Background:

Functional connectivity (FC) by blood-oxygenation-level-dependence (BOLD) functional MRI (fMRI) has general impacts on the studies of basic and clinical neurosciences. Networks or sub-networks, as identified by FC, have provided the infrastructures of functional integration, and the human connectome project (HCP) also implemented the resting-state BOLD-based fMRI with optimized protocols of fMRI without verification of cerebrovascular or hemodynamic response. But preserved cerebrovascular reserve (CVR) is essential for BOLD based on physiological mechanisms of cerebral blood flow, cerebral blood volume and tissue metabolism. In this study, the effects of CVR on FC by BOLD-based fMRI was tested using the working model of moyamoya disease which shows impairment CVR due to progressive luminal stenosis of major intracranial arteries. With preserved and normal motor function of 11 patients of moyamoya disease, under-estimation of FC between somatomotor (SM) cortices predicted by somatotopy (1) was verified with linearity relation to the impaired CO_2-CVR, as measured by parametric carbogen inhalation test.

Methods:

Eleven patients (4M, 8-51 years old), fulfilling diagnostic criteria of moyamoya disease by conventional cerebral digital subtraction angiogram (Suzuki stages I-III), were selected from the database of moyamoya disease with pre-surgical evaluation using parametric carbogen inhalation test with the following criteria as (1) no deficit of present motor function by neurological physical examination, (2) no history of motor dysfunction, (3) preserved corpus callosum, (4) limited head motion (less than 1 mm and 1 degree for translation and rotation, respectively, during fMRI studies) and (5) no intravenous anesthesia. One normal subject was recruited for comparison. The CO_2-CVR of BOLD fMRI was conducted using a 3T MR system (GE Discovery MR750 with an 8-channel head coil) and single-shot gradient echo EPI (echo planar images) [TR = 2000 msec, TE = 30 msec, acquisition matrix = 64×64×40, field of view (FOV) = 230*230 mm^2, slice thickness = 4 mm, and repetition number (NR) =360]. The T1-weighted anatomical images with 3D inversion recovery spoiled gradient echo were acquired by parameters as TR/TE/TI= 8.2/3.2/140 msec, acquisition matrix = 256×256×176, FOV = 230*230 mm^2, and slice thickness = 0.9 mm. In carbogen inhalation task, medical grade carbogens (1-5% CO_2) and air was delivered alternatively with five blocks of 2 minutes after 2 minutes baseline of air inhalation. Gas inhalation was obtained by a medical grade non-rebreathing mask with high flow rate (15 liters /minute) and a home-made automatic switching system. The end-tidal CO_2 ($etCO_2$) was recorded with PowerLab (ADInstruments, CO, USA).

The data analysis was performed using Group ICA of fMRI Toolbox (GIFT, Mind Research Network, NM, USA) and SPM8 (Wellcome Trust Center for Neuroimaging, London, UK). The standard preprocess of fMRI data was performed with SPM8 including slice timing, realignment, coregistration, normalization and smooth with the 8-mm kernel. For carbogen task, ICA components were extracted with GIFT and correlated with recorded end-tidal CO2. Carbogen response function (CRF) was derived from optimal ICA components with correlation coefficient (cc) > 0.3 and combination with weighting of cc values. Initial 2-min baseline (NR=60) provided the sessions of resting fMRI or FC analysis of left SM cortices as defined by somatotopy. One-sample t test of CRF and time courses derived from seeds of left SM cortices, including motion parameters as regressors, provided the maps of CO_2-CVR and FC, respectively. Scatter plots of Δt (t values from one sample t test) of FC and CO_2-CVR in bilateral SM cortices, defined by somatotopy of Brodmann's areas 4 and 6, was applied to show the linear regression between CO_2-CVR and FC.

Results:

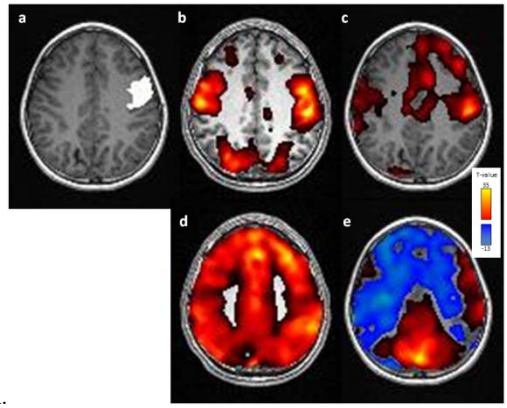
Impaired CO_2-CVR might involve somatomotor cortices in patients of moyamoya disease with change of FC as compared to a normal subject (Figure A). The contra-lateral (right) SM cortices showed significant reduction of functional connectivity as compared to the control groups after normalization to FC of left SM cortices ($p<0.004$, two-sample t test). Three patients were excluded due to normal CO_2-CVR or severe impairment of CO_2-CVR in bilateral SM. Normalized ΔFC and Δ CO_2-CVR showed prominent linearity by linear regression (Figure B, slope=-0.05, r=0.8).

Conclusion:

Impaired CVR was supposed to cause dissociation between functional integrity and functional connectivity due to regional variation of CVR. And reversed linearity between Δt of FC and Δt of CO_2-CVR suggested enhanced FC or neuroplasticity in moyamoya disease. Underestimated or aberrant FC should be considered with impaired CVR, and studies of FC in diseased states need evidence of preserved CVR.

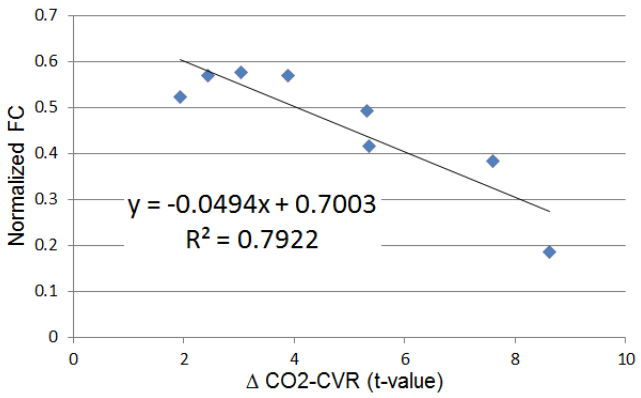
Reference:

(1) Biswal B et al., Mag. Reson. Med. 34 537, 1995.



A.

Figure A :
FC by the seeds of left somatomotor cortex (a, white area) was limited in a patient of moyamoya disease (c) as compared with a normal subject (b). The findings were consistent with CO_2-CVR of the normal subject and the patient (d and e, respectively).



B.

Figure B :
Linearity between Δ CO_2-CVR and normalized FC suggested enhanced FC or neuroplasticity in moyamoya disease.