Can resting state fMRI be used to map cerebrovascular reactivity?

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TARGETED AUDIENCE: Physicians and researchers interested in mapping cerebral vascular function.

PURPOSE: Cerebrovascular reactivity (CVR), a specific measure of the cerebral blood vessels' dilatory function, is an important marker of brain's vascular health (1). During the past few years, CVR mapping has been shown to provide valuable information for the diagnosis and treatment evaluation in patients with cerebrovascular diseases (2,3). Currently, CVR mapping using hypercapnia gas inhalation is the main workhorse for clinical research studies and examination of chronic (e.g., stenosis) patients. However, when it comes to examining acute patients (e.g., acute stoke, traumatic brain injury), the inherent need of gas inhalation and the associated apparatus setup may present a practical obstacle in terms of clinical workflow. Therefore, in the present work, we aim to explore an alternative approach that does not require gas inhalation but utilizes the natural variation in respiration over time. Global, non-region-specific fluctuation in BOLD MRI signal is well known in the functional connectivity MRI (fcMRI) literature (4,5). It is attributed to respiratory and/or cardiovascular fluctuations (6,7), and is (rightfully) considered as a nuisance signal in fcMRI, which is usually discarded in pre-processing (8). We hypothesize that global BOLD signal from the brain which reflects spontaneous CO2 fluctuation, can serve as a reliable regressor for CVR estimation from the resting state BOLD data. We conducted three studies to test this hypothesis. First, a feasibility and reproducibility study was performed to evaluate the reliability of the "resting CVR map" generated by this new approach. Second, we validated the resting CVR map with conventional CVR map obtained with hypercapnia inhalation in healthy volunteers. Finally, we tested the utility of this new approach in detecting abnormal CVR in a group of patients with Moyamoya disease, a stenotic cerebrovascular disease. Our results suggested that using global BOLD signal from resting state BOLD MRI might be a reliable surrogate of CVR mapping in clinical settings when hypercapnia inhalation is not feasible.

METHODS: *Study 1: Feasibility and reproducibility.* This study was done by using resting state data collected in our previous study (9). 10 healthy subjects (28±7 yrs., 6 males) underwent a 35-minute session consisting of 7 resting state BOLD scans of 5 minutes each (single-shot gradient-echo EPI, TR/TE=1000/25ms, Field-of-view (FOV) 220×220mm^2, voxel size 3.4×3.4×5mm^3, 21 axial slices). The resting images were motion-corrected, smoothed, and detrended. Next, whole-brain-averaged gray matter BOLD time course in a scan was used as the independent variable and individual voxel's time course is used as the dependent variable. The linear regression analysis yields a resting CVR map in the unit of %BOLD signal change. The resting CVR maps were obtained for each subject and each run.

Study 2: Validation with CO2-inhalation-derived CVR. 6 healthy subjects (25±5 yrs., 3 males) underwent a 5min resting state BOLD scan followed by a 7 min hypercapnia BOLD scan. The imaging parameters were identical between the two scans: TR/TE=2000/25ms, Field-of-view (FOV) 220×220mm^2, voxel size 3.4×3.4×5mm^3, 43 axial slices. During the hypercapnia scan, subjects breathed room-air and 5% CO2 (mixed with 21% O2 and 74% N2) in an interleaved fashion (switching every 1 min) while BOLD EPI images were acquired continuously. End-tidal CO2 was recorded throughout the breathing task and a regression analysis between this signal and the MRI time course yielded the CVR map in the unit of %BOLD/mmHg (10). The resting CVR maps were obtained for each subject following the same processing as in study 1.

Study 3: Evaluation of Moyamoya patients. 5 patients with Moyamoya Disease (2 males, age range 24-48 yrs) were recruited. 2/1/2 patients had right/left/bilateral supraclinoid ICA stenosis, respectively. Each patient underwent a 9min BOLD scan with gas inhalation as well as a 9min resting state BOLD scan. CVR and resting CVR maps were obtained for each patient. Note that for the resting state data, averaged signal in the occipital lobes was used as the global regressor, as the posterior cerebral circulation was seen to be angiographically preserved in these patients.

RESULTS and DISCUSSION: *Study 1:* Figure 1 shows the test-retest results of the resting state fluctuation map in 5 subjects. Visual inspection found that the resulted maps showed good gray/white matter contrast, and the maps are consistent across difference scans. *Study 2:* Figure 2 shows the resting CVR map and CO2-inhalation CVR map averaged over six healthy subjects. Figure 2a and b are the same images displayed with different colormaps and contrast settings. It can be seen that resting CVR map and CO2-CVR map have virtually identical image contrast (note: their absolute value is different in that one represents total BOLD signal change and the other is BOLD signal change per mmHg CO2 change). This is confirmed by quantitative analysis of their scatter plot (Fig. 2c), showing a strong correlation (r=0.85) and an intercept of nearly 0. Interestingly, the appearance of "negative" voxels is also spatially matched, as can be seen in the green voxels in Fig. 2b (arrows) and the circled area in the scatter plot in Fig. 2c. These negative voxels are known to be caused by CSF volume change in the ventricles during vasodilation, suggesting that the resting CVR map is of similar physiological origin as CO2-CVR. *Study 3:* Figure 3 shows the CO2-inhalation-derived CVR maps and resting CVR maps of all five Moyamoya patients. Reduced CVR was observed in the diseases territories in all patients. The resting CVR maps were found to reveal a similar deficit pattern as the CO2-CVR maps. This result further demonstrated that vessel reactivity to spontaneous CO2 fluctuation is a major signal mechanism underlying the resting CVR map. It also suggests that using a global regressor in resting state BOLD scan could provide useful information about vascular dysfunction in clinical patients.

CONCLUSION: We proposed a new method to map cerebrovascular function without gas inhalation. Our results showed that the resting CVR generated by this method is reproducible, and of similar physiological origin as CO2-inhalation-derived CVR. This method might be a potential surrogate for detecting deficits in vascular reserve when CVR mapping with gas inhalation is not feasible in certain patient populations.

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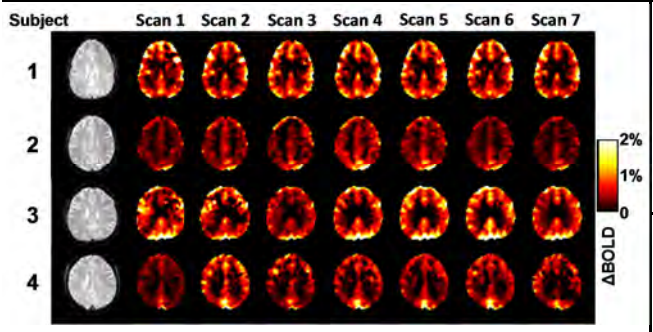

Fig. 1: Test-retest reproducibility of the resting CVR map generated from the linear regression analysis by using global gray matter BOLD signal as regressor. Four subjects are shown.

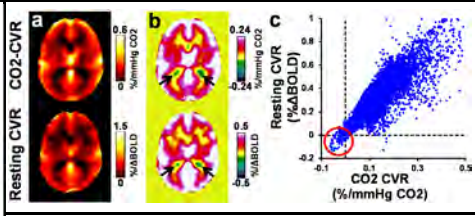

Fig.2: Comparison between resting CVR map and CO2-inhalation-derived CVR (N=6). (a) The maps displayed with normal range. (b) The same maps displayed with negative values in cold color (arrows). (c) Voxel-by-voxel scatter plot between the two maps.

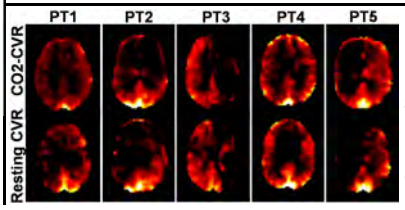

Fig. 3: Comparison between resting CVR map and CO2-inhalation-derived CVR in Moyamoya patients. (Top) CO2-CVR maps show pronounced deficits in the ACA/MCA perfusion territories of the patients. (Bottom) Resting CVR maps demonstrate a similar deficit pattern to CO2-CVR.