The influence of carbon dioxide on brain functional homotopy using resting-state fMRI

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Target Audience: Scientists and physicians who are interested in brain networks using resting state functional MRI (RS-fMRI) and its clinical applications.

Purpose: Homotopy is a fundamental characteristic of the intrinsic functional architecture of the human brain. Recently, such a high degree of interhemispheric synchrony can be estimated based on spontaneous activity by use of resting state fMRI (RS-fMRI) with blood oxygenation level dependent (BOLD) technique [1]. Regional homogeneity (Reho) is another brain characteristic signifying local brain tissue synchronization, which can be measured with RS-fMRI [2]. Carbon dioxide (CO_2) is a potent vasodilator and has been known to cause cerebral blood flow (CBF) and BOLD signal changes. In this study, we have evaluated how CO_2 breathing can influence brain functional homotopy and Reho in healthy brains in order to better understand physiologic respiratory noise of RS-fMRI data.

Materials and Methods: Fourteen healthy controls (8 male and 6 female, 27.6 ± 6.4 years old) participated in this hypercapnia study. Two 5-minute long RS-fMRI standard BOLD scans were performed at 3T MR with TR/TE=1500/25ms, FOV=220×220mm^2, matrix =64×64, number of slices=33, slice thickness=3mm, and 200 measurements. The first one was acquired under a normocapnia condition (breathing room air) and the second under a hypercapnia condition (breathing a mixture of 5% CO_2, 21% O_2, and 72% N_2). Enough time was given between the two functional runs in order to allow end tidal CO_2 ($EtCO_2$) level to reach equilibrium, which was monitored and recorded throughout the experiment on a MEDRAD system. In addition, a high resolution anatomical T1 image was acquired for image co-registration and segmentation. RS-fMRI data were processed using the Configurable Pipeline for the Analysis of Connectomes (C-PAC, fcp-indi.github.com) to generate voxel mirrored homotopic connectivity (VMHC) and Reho at normocapnia and hypercapnia conditions. The average across gray matter voxels within regions defined by the MNI structural atlas[3] was taken. Values were compared using a paired Student's t-test and a p value <0.05 was considered significant.

Results: The average $EtCO_2$ increased significantly from the normocapnia to hypercapnia condition (40.15 ± 2.63 to 47.39 ± 2.74 mmHg, $p<0.01$). A significant decrease in global gray matter VMHC (**Figure 1**) is seen under hypercapnia versus normocapnia conditions ($p<0.001$) at resting state, and also in the regions indicated in **Figure 2** except for thalamus, caudate, and cerebellum. A significant global gray matter decrease was also seen in Reho ($p<0.002$), predominantly in the frontal and parietal regions. However, was not as pronounced as changes seen in VMHC.

Discussion and Conclusion: Our observation of decreased brain homotopy (i.e. inter-hemispheric correlations) during CO_2 breathing is consistent with previous reports that elevated arterial CO_2 decreases brain connectivity, which may be secondary to general reduction in spontaneous neural activity or oxygen metabolic rate during hypercapnia [4]. The changes of Reho found only in frontal and parietal regions indicate that the local synchronization (between nearest neighboring neurons) was affected by blood flow and/or neuronal activity changes, but the change is much less diffuse compared with VMHC. This study has implications on RS-fMRI data analysis methodology in dealing with effects of varied cardiac and respiratory patterns that can potentially influence blood flow and CO_2 levels.

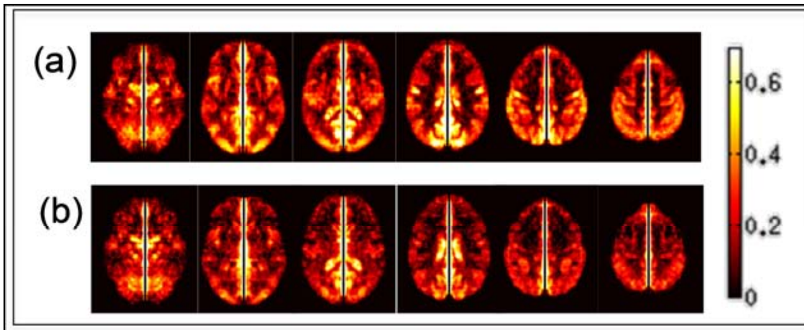

Fig 1. Average VMHC maps of fourteen subjects under (a) normocapnia and (b) hypercapnia conditions showed general reduction of VMHC, an index of inter-hemispheric functional connectivity. Color bar shows the range z values.

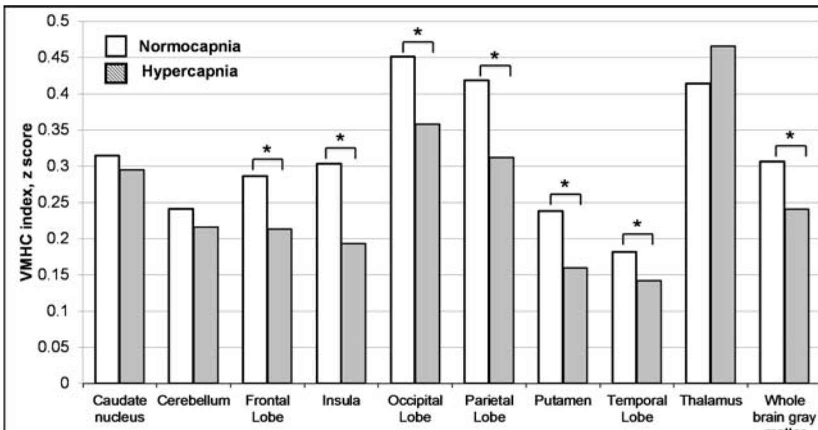

Fig 2. Average regional and whole brain gray matter VMHC index z score showed significant reduction under hypercapnia compared to normocapnia condition (*p<0.05) in regions marked with asterisk.

References: 1. Zuo et al, J Neurosci 2010;10:30-43. 2. Zang Y etal Neuroimage 2005;22:394-400. 3. Collins et al. Human Brain Mapping 1995; 3: 190-208. 4. Xu F, et al J Cereb Blood Flow Metab. 2011 Jan;31(1):58-67.

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