Hypercapnia effects on spontaneous low frequency fluctuations using RS-fMRI

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Target Audience: Research scientists and clinicians who are interested in resting-state functional MRI (RS-MRI) and methodology.

Purpose: Resting state functional MRI (RS-fMRI) is a robust technique to assess functional connectivity using blood oxygenation level dependent (BOLD) technique to analyze spontaneous low frequency fluctuations (LFF) of the human brain. Default mode network (DMN) is the most well-established resting state network [1] of multiple brain regions that are active when brain is at wakeful rest, but deactivated during task settings. Since the levels of arterial CO_2 (vasodilator) have been shown to have an effect on cerebral blood flow (CBF) and BOLD signals, we evaluated the influence of CO_2 on both the amplitude and correlations of LFF of DMN in healthy brains. A resting brain under hypercapnia (i.e. breathing 5% CO_2) would help us better understand the resting state networks associated with blood flow changes and also functional connectivity variations due to physiologic cardiac (e.g. flow changes) and respiratory (CO_2 changes) noises in 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 BOLD scans were performed at 3T MR with the following parameters: TR/TE=1500/25ms, FOV=220×220mm^2, matrix =64×64, number of slices=33, slice thickness=3mm, and number of image volumes=200. During both functional scans, subjects were instructed to fixate on a crosshair. 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 74% N_2). Enough time was given between the two functional runs in order to allow $EtCO_2$ 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-based amplitude of fractional low frequency fluctuations (fALFF) maps as well as connectivity maps within DMN at normocapnia and hypercapnia conditions. The default mode network was defined on the average connectivity map of the normocapnia condition. The average of voxels within this mask was calculated on the fALFF and connectivity maps. Results 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 average DMN connectivity (within network) from the normocapnia to hypercapnia condition is observed (p<0.001), as well as a reduced cluster volume (voxel number: 15,783 vs. 8,770) (**Figure 1**). A significant correlation was seen between the decrease in average DMN connectivity and the increase in $EtCO_2$ (p=0.002) (**Figure 2**). Average fALFF values within DMN regions also decreased significantly (p<0.001) during hypercapnia (**Figure 3**).

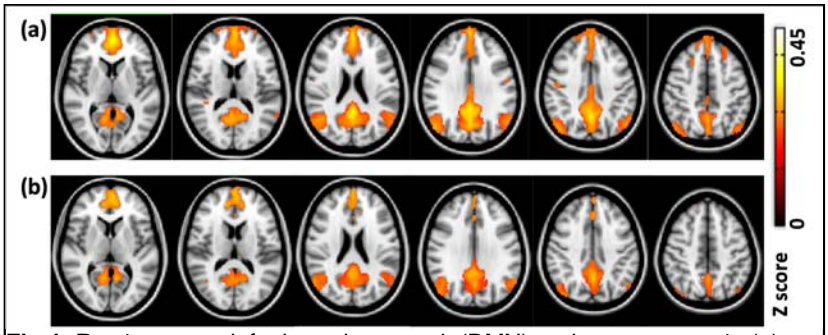

Fig 1. Resting state default-mode network (DMN) under normocapnia (a) and hypercapnia (b) conditions with seed placed in medial prefrontal cortex. There is significant decrease of both connectivity strength and cluster size of DMN under hypercapnia compared to normocapnia.

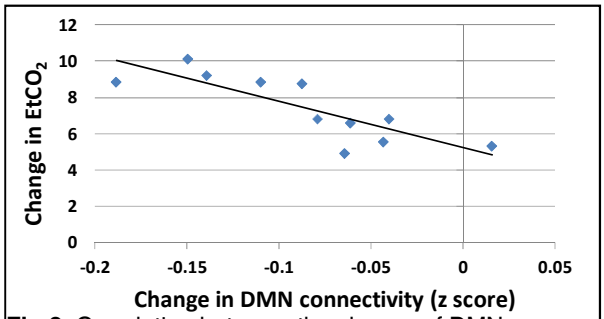

Fig 2. Correlation between the change of DMN connectivity and the change of EtCO2 in healthy brains between hypercapnia and normocapnia conditions showing significantly inverse correlation (r=-0.83, P=0.002).

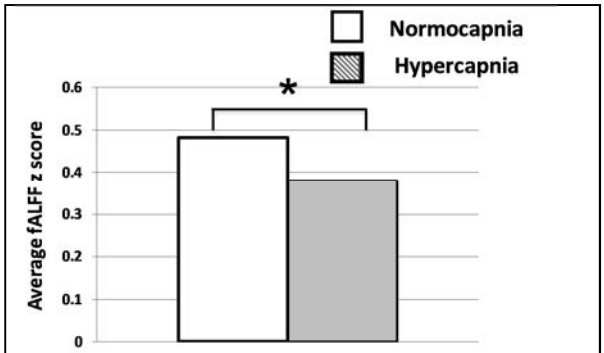

Fig 3. Comparison of fALFF of DMN regions (as defined by normocapnia DMN mask) showed significant decrease of averaged fALFF during CO_2 breathing (P<0.001).

Discussion and Conclusion: Our data showed that the correlation strength and the cluster size of the distributed regions within DMN were decreased in resting brains under hypercapnia; however, the intrinsic correlations of DMN remain. The decreased fALFF during hypercapnia may be associated with mild suppression of oxygen metabolic rate [4] and spontaneous neuronal activity.

References: 1. Buckner RL et al Ann. N.Y. Acad. Sci 2008; 1124:1-38. 2. Zuo XN et al Neuroimage 2010;49:1432-45; 3. Xu F et al Proc Intl Soc Mag Reson Med, 2009; 17; p215. 4. Xu F, et al J Cereb Blood Flow Metab. 2011 Jan;31(1):58-67.