THE EFFECT OF HYPERCAPNIA ON RESTING STATE FMRI

J. Uh[1], F. Xu[1], U. Yezhuvath[1], Y. Cheng[1], H. Gu[2], Y. Yang[2], and H. Lu[1]

[1]Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States, [2]Neuroimaging Research Branch, National Institute on Drug Abuse, National Institute of Health, Baltimore, Maryland, United States

INTRODUCTION: Resting state fMRI (RS-fMRI) is a topic of growing interest because it provides an opportunity to study spontaneous neural activity at rest (1,2). However, the nature of resting state network (RSN) is not yet clear. In particular, it would be of great interest to show that RSN indeed changes when the resting brain activity is altered. Hypercapnia (HC) challenge provides an excellent model condition for this purpose because 1) electroneurophysiology studies in animals have shown that mild HC reduces neural activity at rest (3); 2) HC is a non-invasive maneuver and can be easily administered in humans. In this work, we performed RS-fMRI at normocapnia (NC) and HC conditions to investigate the effect of HC on RSN. For comparison, we also studied visual-evoked BOLD signals during NC and HC conditions. In order to conduct a quantitative comparison of the signal amplitude of RS-fMRI, we propose an index to quantify the "magnitude of resting state connectivity" that is equivalent to BOLD percentage signal in conventional fMRI.

METHODS: Ten healthy subjects (age 27.4±6.7years, 5 males) were studied on a 3T system (Philips Achieva) after consent was obtained. RS-fMRI scan was performed while the subjects maintain fixation on a crosshair. For the visual-task fMRI, a fixation of 39s was followed by three cycles of checkerboard stimulation (21s, 5Hz) and crosshair (39s). The imaging parameters were: FOV=220x220mm^2, matrix size =64×64, number of slices=33, slice thickness=3mm (gap 1mm), TR/TE=1500ms/25ms, and number of image volumes=200(RS-fMRI), 146(task fMRI). To ensure HC indeed caused the expected vascular changes, we measured the brain venous oxygenation using a recently developed TRUST MRI technique (4). All three scans were performed at both NC and HC conditions. A minimum time of 2 min was waited in transition between NC/HC conditions. A mouthpiece and a nose clip were mounted to the subjects throughout the entire scan time (~40min) to control breathing air type. The breathing air was either room air (NC condition) or 5% CO_2 from a large air bag (HC condition). End-tidal CO_2 was monitored and recorded throughout the experiment.

The RS-fMRI data were analyzed by AFNI (NIMH Scientific and Statistical Computing Core) to identify RSN. The image volumes were first coregistered, and linear trend was removed. It was followed by Talairach transformation, smoothing with 6mm FWHM, and low-pass filtering (cut off frequency=0.1Hz). Two cubic ROIs (size=0.73cm^3 for each) at the left and right posterior cingulate cortex were used as seed voxels. The correlation between the time course of each voxel and the seed was calculated for each subject. Then, a group analysis was performed to identify voxels significantly correlated with the seed (threshold: p<0.01, cluster>2.7cm^3). For quantitative analysis, we define the magnitude of connectivity, M_c, as a measure analogous to %BOLD change in conventional fMRI. The M_c was calculated for each subject by a linear regression between the time courses of the seed ROI, x, and a target ROI, y: $y' = M_C\, x'$, where $x' = [x - \text{mean}(x)]/\text{norm}(x-\text{mean}(x))$; $y' = [y - \text{mean}(y)]/\text{mean}(y)$; and "norm" indicates the norm of a vector and can be either a 2-norm or 1-norm. The definitions of x' and y' ensure that M_c is not sensitive to the amplitude of the seed, but reflects that of the target. The target ROI was selected to be the voxels showing significant correlation with both of NC and HC in the group analysis (see Fig. 1). For visual task BOLD fMRI, general linear regression analysis was performed and the signal changes were calculated from voxels activated in both NC and HC visual scans (Fig. 2).

RESULTS and DISCUSSION: End-tidal CO_2 and cerebral venous oxygenation at NC were 40.1±2.6 (mean±std) mmHg and 58.1±8.6 %, respectively. HC challenges resulted in an end-tidal CO_2 increase of 8.2±1.6 mmHg and a venous oxygenation increase of 28.0±16.0%. Figure 1 shows the default resting state network at NC and HC identified by the group analysis (N=10). The network at NC (Fig. 1a) clearly illustrates the connectivity of posterior cingulate cortex to the bilateral parietotemporal regions (size = 62.7 cm^3) and the medial frontal cortex (size=37.0 cm^3). At HC (Fig. 1b), the connected cluster sizes were dramatically reduced to 14.0 cm^3 and 2.7 cm^3, respectively, corresponding to 78% reduction for the parietotemporal clusters and 93% for the frontal cluster. The magnitude of connectivity also shows significant reduction due to hypercapnia: M_c=0.39±0.07 (mean±SEM) for NC, M_c=0.27±0.06 for HC (paired t-test, p = 0.0027), and the percentage reduction of M_c was 33.4±6.7%. The size of visual-evoked fMRI activation also reduced from 145±16 cm^3 (NC) to 122±11 cm^3 (HC), a decrease of 33.4%. The %BOLD change in visual cortex shows 1.73±0.07% and 1.19±0.10% for NC and HC, respectively (Fig. 2). This corresponds to 29.3±7.5% reduction of %BOLD change due to HC.

In summary, we found that resting state network as determined by BOLD fMRI shows a reduction in both cluster size and signal amplitude due to HC challenge, consistent with findings in electroneurophysiology in animals. We also found a similar reduction of visual-evoked fMRI signal in the same subjects. However, as pointed out previously (5,6), reduced visual fMRI signal may be partly attributed to higher basal CBF and venous oxygenation, which effectively causes a "ceiling" effect because venous oxygenation does not have much room to go further up. Conceivably, these vascular effects may have also contributed to the reduction of RSN observed in this study. Thus, caution should be used in interpreting BOLD RSN changes, especially when vascular physiology has also changed (e.g. sleeping, sedation, aging).

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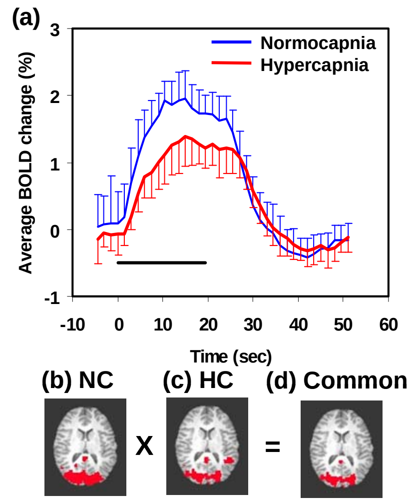

Fig. 2: %BOLD change by visual stimulation (a) for the common visual cortex (d) identified from NC (b) and HC (c). Threshold of p < 10^{-4} and cluster size > 40 cm^3 is used.
The black line in (a) indicates the duration of visual stimulation.

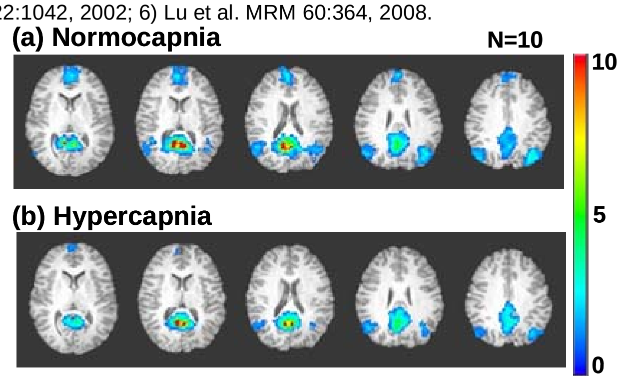

Fig. 1: Resting state network identified at normo- and 5% CO2 hypercapnia conditions by resting-state fMRI. Color bar indicates T-statistic value.
Threshold of p<0.01 and cluster size > 2.7 cm^3 is used.

	Normo-capnia	Hyper-capnia	% difference
End-tidal CO_2 (mmHg)	40.1	48.3	20.4
%Venous oxygenation	58.1	74.3	28.0
Magnitude of connectivity (%)	0.39	0.27	-33.4
%BOLD change	1.73	1.19	-29.3

Table 1: Measurements at normo- and hypercapnia