Acetazolamide blocks increase in fc-fMRI global signal in hypoxia, while increasing Default Mode Network correlations

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Target Audience: People interested in BOLD functional connectivity and the physiology of cerebral hypoxia

Purpose: Sustained high altitude hypoxia alters cerebral physiology, with significant increases in $CMRO_2$, CBF, and OEF [1]. In susceptible individuals this is accompanied by symptoms of acute mountain sickness (headache with sleep, cognitive and gastrointestinal disturbance). Treatment with Acetazolamide (AZ), a carbonic anhydrase inhibitor, provides symptomatic relief and mitigates some of the CBF and $CMRO_2$ changes. Resting-state BOLD signal fluctuations are thought to be associated with the underlying spontaneous neuronal activity and regional synchrony that contributes to the high metabolic demand of cerebral tissue [2]. We investigated if the cerebral changes during hypoxia are accompanied by a change in the spontaneous BOLD activity, and whether this may be influenced by Acetazolamide treatment.

Methods: Resting-state fMRI data were acquired in five healthy subjects during normoxia and following 2-days sustained hypoxic hypoxia at 3800m under two conditions: Once with no acetazolamide treatment (n=5) and once while receiving Acetazolamide prophylaxis of 500mg/d (n=4). 5 minutes EPI fMRI data were acquired at 3T (GE MR750) (166 reps, 30 slices, 3.4x3.4x5mm^3, 64x64 matrix, TR=1.8s, TE=30ms). Data were corrected for motion and physiological noise, yielding a timeseries of percent BOLD change for each voxel. To examine the connectivity in the Default Mode Network (DMN), a voxel-wise correlation map with a seed ROI in posterior cingulated cortex (PCC) was calculated for each state (normoxia, hypoxia, hypoxia+AZ) [3]. The map of correlation coefficients, r, for each subject was converted to a z-score and averaged across all 5 subjects. To quantify changes in connectivity within the DMN, we measured the mean correlation between each of 6 regions in the DMN. This was converted to z-score and averaged across the 5 subjects. To quantify global change in BOLD activity, the global signal amplitude (GS amplitude) was measured by averaging all the percent change time series across all brain voxels and then calculating the standard deviation [3].

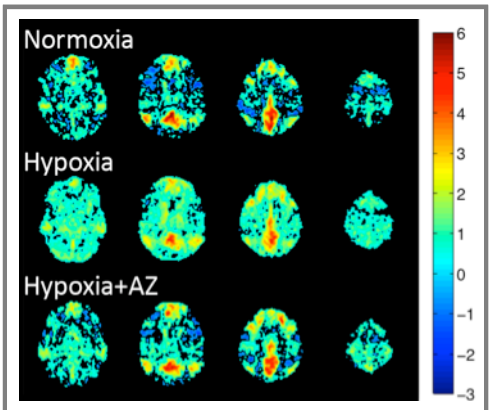

Fig 1. Average z score maps for 5 subjects (seed ROI in PCC) in Normoxia, Hypoxia, and Hypoxia + acetazolamide

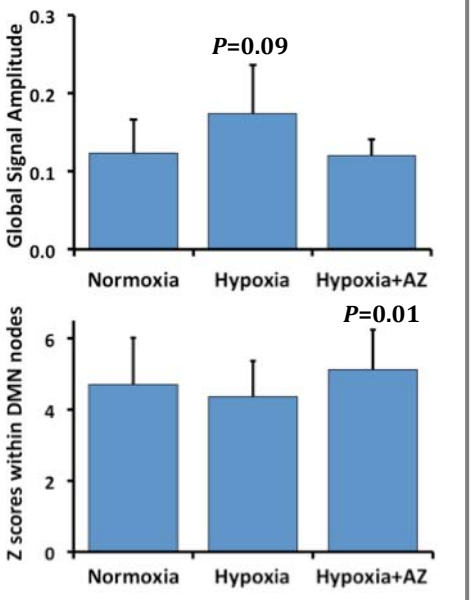

Fig 2. (TOP) change in Global Signal Amplitude, and (BOTTOM) change in connectivity within DMN in Normoxia, Hypoxia, and Hypoxia + acetazolamide

Results: Correlations with PCC are shown in Fig 1. Relative to normoxia, there is increased overall connectivity during hypoxia, which is not present with Acetazolamide. This was also seen as an increase in the global signal amplitude during hypoxia (Fig 2 top). Acetazolamide treatment trended towards preventing this rise in GS amplitude (P=0.09). In contrast, the connectivity within the DMN did not increase during hypoxia (Fig 2 - bottom), but increased significantly with acetazolamide (P= 0.01 relative to normoxia)

Discussion: BOLD functional connectivity increases during global hypoxia, with an increase in the global signal amplitude. Despite the same hypoxia stimulus, this effect is mitigated with acetazolamide. Previous studies have observed reduced global connectivity during hypercapnia, thus the hypocapnia that accompanies hypoxic hypoxia may be driving the increases in global connectivity seen here [4-6]. However $ETCO_2$ remains low even with acetazolamide treatment, thus low CO_2 is not the sole contributor. The impact of altered CBF, $CMRO_2$, or neural activity also needs to be considered as modulators of functional connectivity during hypoxia.

Reference: [1] Smith et al. JAP 2012 [epub] [2]. Raichle et al. 2007. *Nature*: 8: 700-710. [3] Wong et al. 2012. *Neuroimage*: 63: 356-364. [4] Biswal et al. 1996 *J.CBF & Metabolism*. [5] Xu et al. 2011. *J.CBF & Metabolism*. 31. 58-67. 17. 301-308 [6] Wey et al. 2012. *ISMRM*: 2114.
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