# Alterations of brain connectivity in anemic subjects using fMRI under hypoxic and hyperoxic states

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## Introduction

Anemia is characterized by insuffcient hemoglobin (HgB) leading to low oxygen content[1]. Previously we found anemia is an independent predictor of white matter (WM) damage and cognitive dysfunction regardless of disease type in a study of clinically asymptomatic adults with hemoglobinopathies. We use a novel application of BrainSync[2] to compute a connectivity similarity index (CSI) of individual time-series data to an averaged reference. fMRI time-series data can be represented as points on the hypersphere, with geodesic distances between these points equal to the inverse cosine of the Pearson correlation between their time series. Aligning these hypersphere representations from subject to reference through an orthogonal transform (rotation and/or refection) retains an individual's connectivity profile while allowing direct comparison of their aligned time series at homologous locations across subjects. The geodesic distance between subject and reference is referred to as CSI. We test where CSI predicts the severity of anemia and whether it can predict psychomotor processing speed and WM volume (WMV). Also, we investigate whether inducing hypoxia and hyperoxia affects the brain's connectivity.



## Methods

MRI data, CBC and neuropsychological testing results were obtained from sickle cell anemic (age=22.6±9.1, F=10, M=21, HgB = 9.3±1.6), non-sickle anemic (age=23.9±8.4, F=9, M=12, HgB=11.4±2.4) and controls subjects (age=25.9±9.1, F=17, M=9, HgB=13.3±1.3). (Recruited with informed consent or assent; IRB: CHLA CCI#11-00083). 3D T1 (TE/TR=3.8ms/8.3ms; SENSE=2; resolution=1mm3) and fMRI (TE/TR=50ms/2000ms; flip angle=90° ; resolution=2.3x2.3x5mm) were acquired on a 3T Philips Achieva (v.3.2.1.; 8-channel head coil). Subjects were fitted with a rebreathing apparatus[1] and fMRI were acquired under conditions of room-air/resting (8mins), hypoxia (5mins) and hyperoxia (5mins). The following steps were repeated on all 3 datasets. T1 and fMRI data were preprocessed using BrainSuite (brainsuite.org, v.18a). BrainSync was used to synchronize each subject's time-series data to reference time-series, created using BrainSync Alignment[3] from 12 control subjects, and CSI was computed. 100,000 random permutations were run to create a null distribution of correlations at each point to determine the effect of HgB level on CSI (age/sex regressed) then corrected for multiple comparison (FDR). Significant voxels were retained ($p \leq 0.05$). Each subject's brain average CSI was computed and linearly correlated against HgB, processing speed and WMV.

## Results

Anemia had significant effect on CSI from fMRI (Fig 1&2) under room-air conditions (p=0.0045, r2=0.15), hypoxia (p=0.0001, r2=0.18), and hyperoxia (p<0.0001, r2=27). Global average CSI related to processing speed in all conditions except hypoxia (room-air: p=0.0004, r2=0.276; hypoxia: p=0.0602, r2=0.055; hyperoxia: p=0.0078, r2=0.109) and related to WMV in all conditions except hyperoxia (room-air: p=0.0062, r2=0.143; hypoxia: p=0.0049, r2=0.108; hyperoxia: p=0.0555, r2=0.052).

## Conclusion

Resting state global CSI was a powerful predictor of white matter volume and processing speed in a population at risk for white matter shrinkage and cognitive dysfunction and was correlated with anemia severity. Deliberate manipulations of brain oxygenation strengthened the association between CSI and hemoglobin but weakened its association with white matter volume and processing speed. These observations suggest that CSI reflects both functional connectivity and cerebrovascular hemodynamics, consistent with the indirect nature of the BOLD signal. Importantly, CSI, white matter volume, and processing speed varied only with the hemoglobin level, not the anemia subtype, suggesting impaired oxygen carrying capacity may be responsible for the morphological and functional changes. We propose that resting state global CSI may be a useful biomarker for white matter health in chronically anemic subjects.

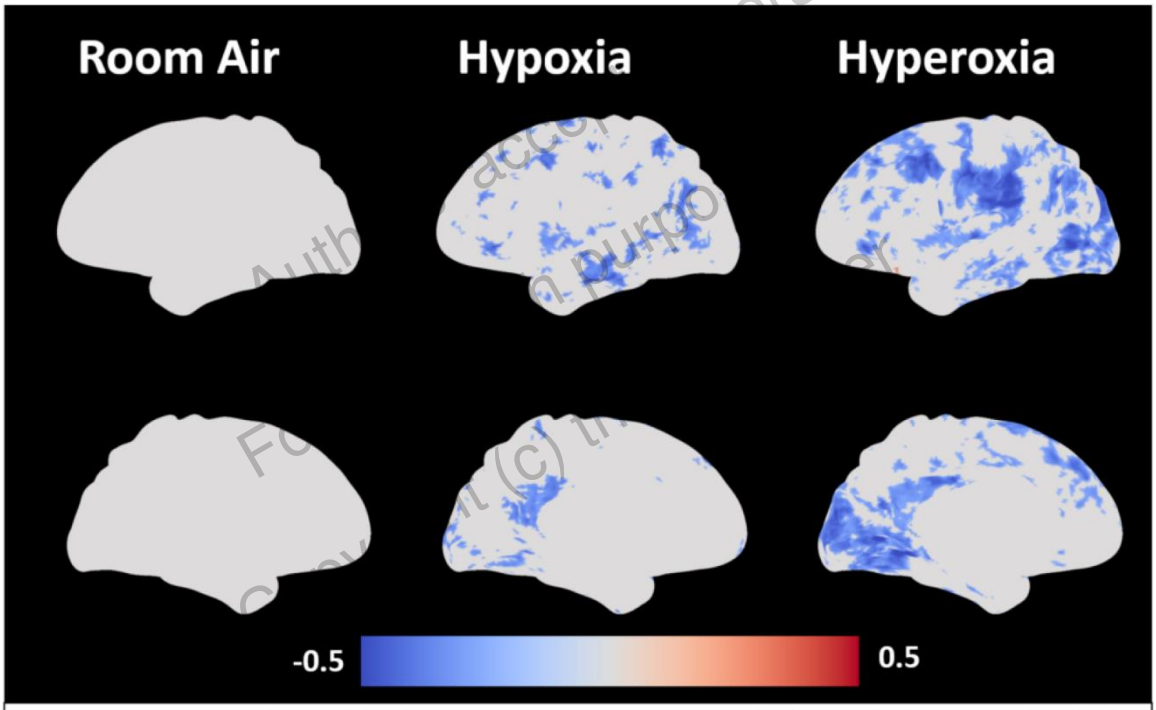


**Figure 1.** Main effect of hemoglobin level on connectivity similarity index (controlled for age and sex). The significant vertices on the brain surfaces are labelled by the correlation coefficient as shown in the colorbar. Results were generally symmetrical between the two hemispheres so only the left hemisphere is displayed. Under room-air, significant results were only found subcortically. The other conditions showed results diffusely throughout the brain except in the prefrontal cortex, possibly due to signal dropout. Largest clusters were found in the precuneus in both hypo- and hyperoxia and the somatosensory, motor and visual cortex under hyperoxia. Top row: lateral view and Bottom row: medial view of labeled Conte-69 surface.

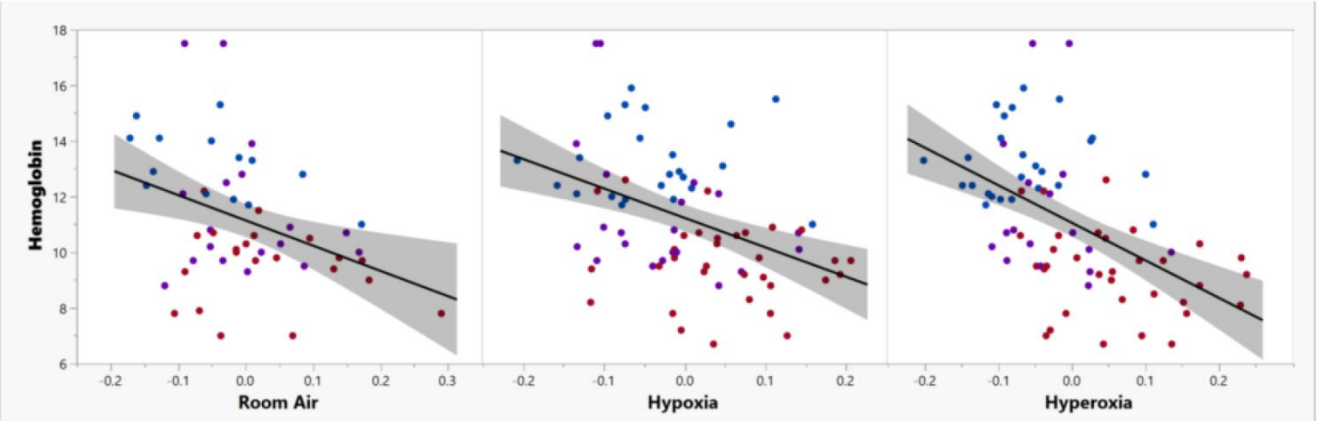


**Figure 2.** Scatterplots of correlation between hemoglobin level and average connectivity similarity index (age and sex regressed) of individual fMRI time-series to a reference template created from normal controls. Left to right: fMRI data collected under room-air, induced transient hypoxia and hyperoxia. Black line indicates the trend line and the shading is the 95% confidence region for the fitted line. Red: Sickle Cell Disease; Purple: non-sickle controls; Blue: normal controls.



## References

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