Detecting Alterations in Brain Connectivity in Anemic Subjects Using fMRI Under Hypoxic and Hyperoxic Conditions.

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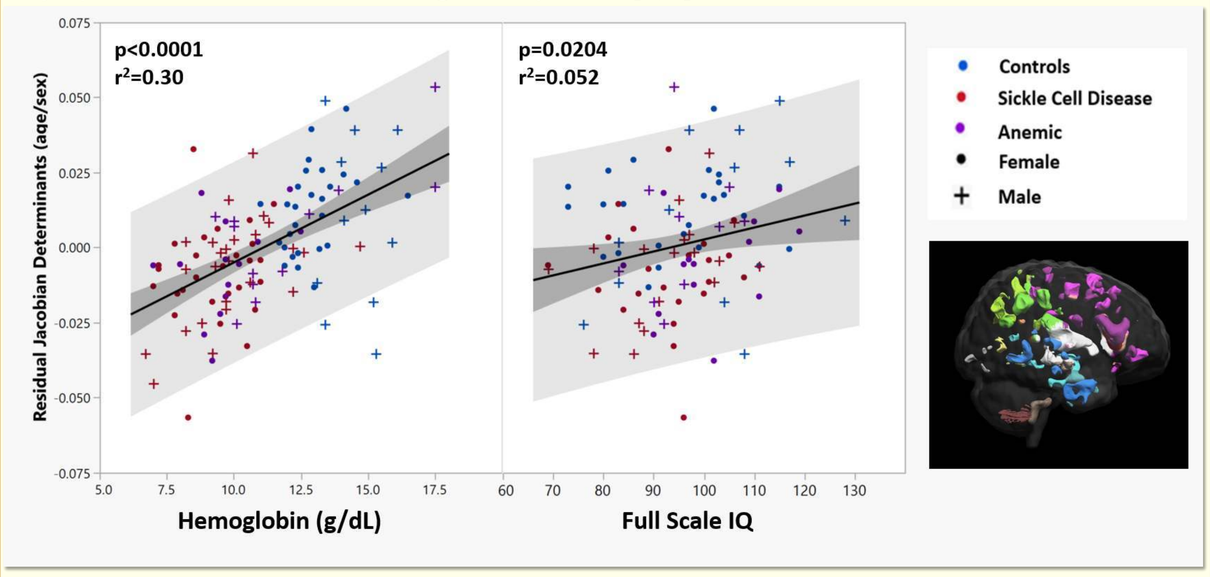
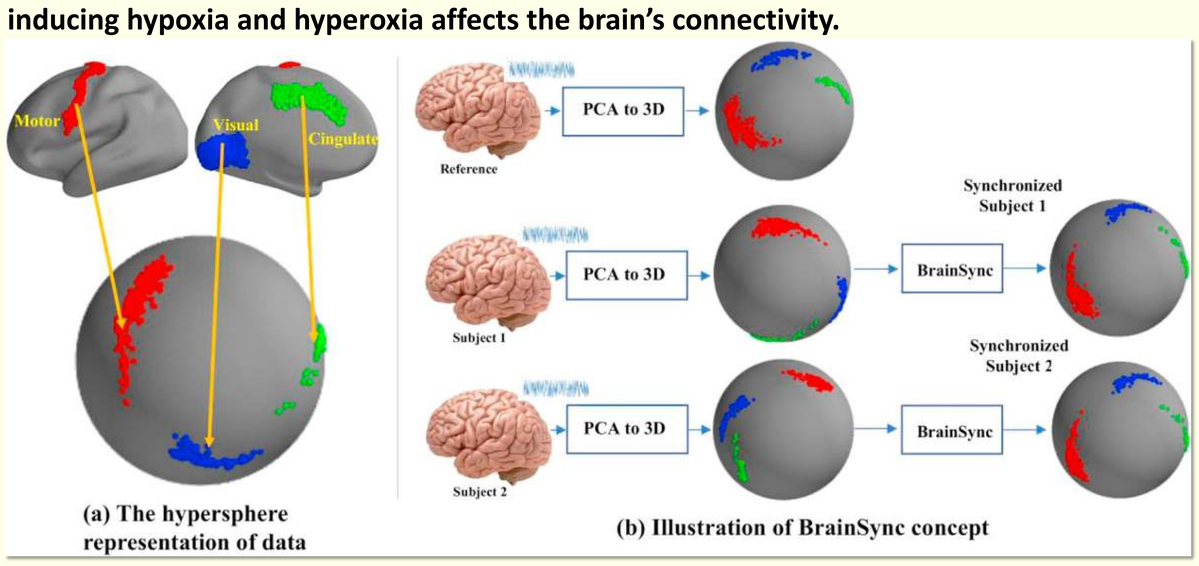
Introduction

Anemia is characterized by insufficient hemoglobin (HgB) leading to low oxygen content[2]. 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[3,4].



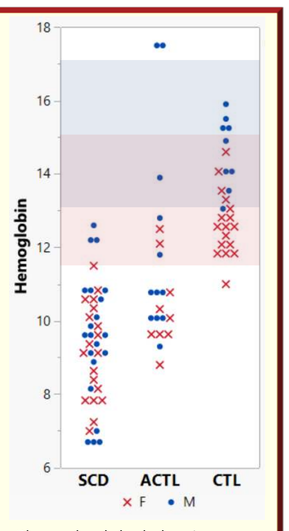
We use a novel application of BrainSync [5] to compute a connectivity dissimilarity index (CDI) of individual time-series data to an averaged reference. fMRI time-series data can be represented as points on the hypersphere, with geodesic distances between these points equal to the inverse cosine of the Pearson correlation between their time series. Aligning these hypersphere representations from subject to reference through an orthogonal transform (rotation and/or reflection) 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 CDI.
We test where CDI 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.



Adapted from [5] Joshi et. al. 2018, Neuroimage

Data Acquisition & Subjects

MRI data, complete blood count and neuropsychological scores were obtained from sickle cell disease (age=22.6±9.2, F=19, M=21, HgB = 9.3±1.6), non-sickle anemic (age=23.9±9.1, F=17, M=9, HgB=11.4±2.4) and controls subjects (age=25.9±9.1, F=9,M=12, 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 [2] and fMRI were acquired under conditions of room-air/resting (8mins), hypoxia (5mins) and hyperoxia (5mins). Exclusion criteria included pregnancy, previous overt stroke, acute chest, or pain crisis hospitalization within one month.



Blue and red shaded regions indicate normal range hemoglobin for males and females respectively

Data Analysis

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 [1] from 12 control subjects, and CDI 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 CDI (age/sex regressed) then corrected for multiple comparison (FDR). Significant voxels were retained (p≤0.05). Each subject's brain average CSI was computed and linearly correlated against HgB, processing speed and WMV as described in [3,4].

neuroimage.usc.edu/~choisoyo brainsuite.org

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Results:

Anemia had a significant effect on CDI from fMRI measured under all four conditions. (Figure 1) The results were generally symmetrical between the two hemispheres. Under room-air, significant relationships were only found subcortically. In the other 3 conditions, results were found diffusely throughout the brain except in the prefrontal cortex which we suspect is due to signal dropout. Largest clusters were found in the precuneus, somatosensory and motor cortices along with the visual cortex.

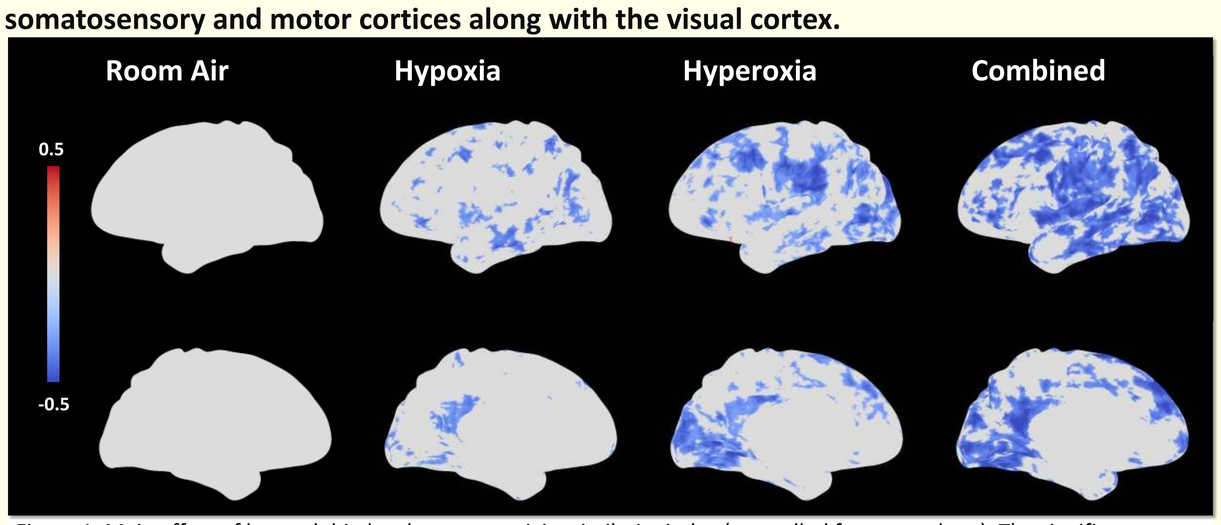

Figure 1: Main effect of hemoglobin level on connectivity similarity index (controlled for age and sex). The significant vertices on the brain surface are labelled by the correlation coefficient as shown in the colorbar. Top row: lateral view and Bottom row: medial view of labeled Conte69 surface.

Anemia had significant effect on the global average CDI from fMRI under all conditions. Strongest correlations were detected under hyperoxia and the weakest under room-air conditions. We note that we see overlap between sickle and non-sickle anemic patients (Figure 2) showing that the severity of anemia rather than the type of anemia was the important determinant of connectivity.

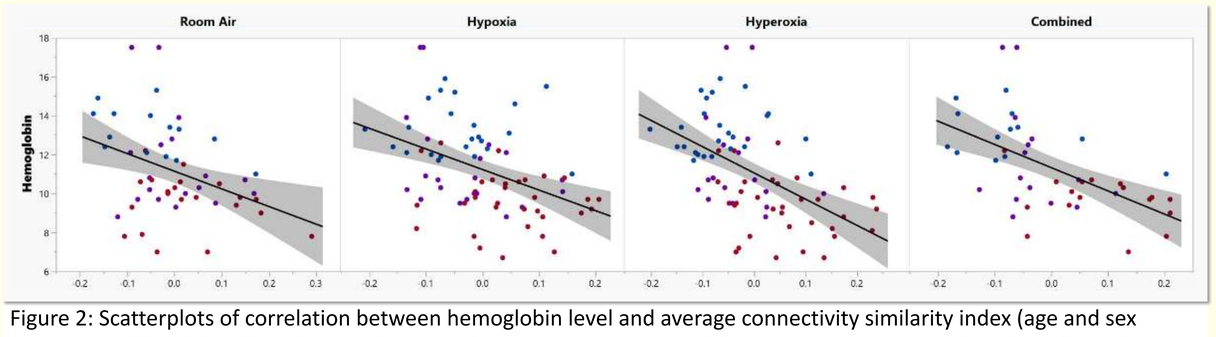

Figure 2: Scatterplots of correlation between hemoglobin level and average connectivity similarity index (age and sex regressed) of individual fMRI time-series to a reference template created from normal controls. Left to right: fMRI data collected under room-air, induced transient hypoxia and hyperoxia. 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.

Global average CSI related to Perceptual Reasoning in all conditions and white matter volume, except hyperoxia, of which room-air had the strongest interaction.

	Room-Air	Hypoxia	Hyperoxia	Combined
Age	NS	NS	NS	NS
Sex	NS	NS	NS	NS
Hemoglobin	0.013 (0.15)	<0.001 (0.15)	<0.001 (0.28)	0.001 (0.27)
White Matter Volume	0.0062 (0.14)	0.0049 (0.11)	NS	0.024 (0.12)
FSIQ	0.005 (0.18)	NS	NS	0.028 (0.13)
Verbal Comprehension	NS	NS	NS	NS
*Vocabulary	NS	NS	NS	NS
*Similarities	NS	NS	NS	NS
Perceptual Reasoning	<0.001 (0.26)	0.046 (0.06)	0.008 (0.11)	0.003 (0.22)
*Block Design	0.004 (0.18)	0.023 (0.08)	0.005 (0.12)	0.009 (0.18)
*Matrix Reasoning	0.004 (0.19)	NS	NS	0.021 (0.15)

Table 1: Predictors of global Connectivity Dissimilarity Index. Simple linear regression between global CDI and select measures. p-value(r^2) of significant ($p \le 0.05$) observed relationships are shown, otherwise marked as "NS" for non-significant.

Discussion

Resting state global CDI 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 CDI reflects both functional connectivity and cerebrovascular hemodynamics, consistent with the indirect nature of the BOLD signal. Importantly, CDI, 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 CDI may be a useful biomarker for white matter health in chronically anemic subjects.

References
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