The Anemic Brain: Hemoglobin Level Predicts Brain Volume in Watershed Areas and Cognitive Function

Soyoung Choi[1,2,3], Sharon H. O'Neil[4,5], Anand A Joshi[2], Adam M Bush[3,6], Matt Borzage[3,6], Julie Coloigner[3], Thomas D Coates[3,7], John C Wood[3,7], Richard M Leahy[1,2]

[1]Neuroscience Graduate Program, University of Southern California, Los Angeles CA
[2]Signal and Image Processing Institute, University of Southern California, Los Angeles CA
[3]Department of Pediatrics and Radiology, Children's Hospital Los Angeles USC, Los Angeles, CA
[4]Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA
[5]Division of Neurology and The Saban Research Institute, Children's Hospital Los Angeles, Los Angeles CA
[6]Biomedical Engineering, University of Southern California, Los Angeles, CA
[7]Division of Hematology, Oncology and Blood and Marrow Transplantation, Children's Hospital Los Angeles, Los Angeles CA

Introduction

Sickle cell disease (SCD) is a life-threatening genetic disease whose patients suffer from chronic anemia, hemolysis, vascular damage, stroke and impaired cerebral blood flow that lead to early and cumulative neurological insults [2,5]. We previously reported white matter (WM) volume loss in asymptomatic SCD patients [3,4] and found that anemia, rather than the type of anemia, was a strong predictor of WM volume loss in both SCD patients and control subjects [4]. This study aims to identify brain regions that are susceptible to injury due to anemia in a population comprised of SCD patients, beta-thalassemia anemic patients, and racially matched controls. Additionally, we aim to identify the neurocognitive effects that may result from injury in these vulnerable areas.

Data Acquisition & Subjects

MRI data were acquired on 82 subjects (Table 1) on a 3T Philips Achieva (v.3.2.1) using an 8-channel head coil. 3D T1-weighted images (TE =3.8ms TR =8.3ms; resolution = $1mm^3$). Complete blood counts were collected and a neuropsychological battery was completed by all subjects.

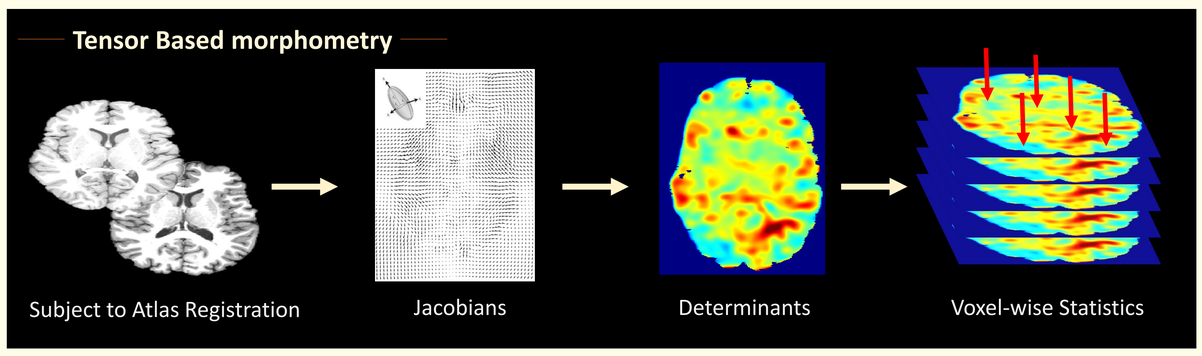
	SCD	ACTL	CTL	Total
N	32	15	35	82
Age	23.4 ± 9.8	23.8 ± 6.6	28.6 ± 12.4	25.7 ± 10.7
Male:Female	13:19	7:8	10:25	30:52
Hemoglobin	9.4 ± 1.4	11.5 ± 2.7	13.5 ± 1.4	11.5 ± 2.5

Table 1. SCD: sickle cell disease; ACTL: non-sickle anemia; CLT: control

Exclusion criteria included pregnancy, previous overt stroke, acute chest, or pain crisis hospitalization within one month. 6 subjects were excluded for bad scans due to excessive motion or scanner artifacts.

Data Analysis

T1-weighted images were processed using BrainSuite (brainsuite.org) in a semi-automated fashion to extract the brain and register to an atlas. Tensor-based morphometry was performed to calculate Jacobian determinants on the atlas for each subject which quantifies voxel-wise differences in brain volume relative to the atlas.



ANOVA was performed at each voxel to determine the main effect of hemoglobin level on Jacobian determinants when controlling for age (log transformed) and sex. Clusters <1000 contiguous significant voxels were thresholded out and average Jacobian determinants were calculated for each subject in these regions. Pearson's correlations were performed between residual average Jacobian determinants (age and sex regressed) with neuropsychological scores. Pearson's correlations were performed again for males and females separately.

Discussion

Chronic anemia was found to predict lower brain volume throughout the brain especially WM tissue of watershed and middle cerebral arterial territories but seems to spare the prefrontal and visual cortex (Fig.1). Anemic patients raise their cerebral blood flow to maintain oxygen delivery at rest. This would then lower their cerebral vascular reserve which leaves them more vulnerable to hypoxic damage and stroke, especially in WM tissue of watershed regions [1]. The effects of anemia on brain volume were found globally (Fig.1). Many of these clusters were found along major long-range WM fiber pathways which relay information to multimodal cortices responsible for higher cognitive function. These regional brain volumes that were vulnerable to anemia showed significant positive correlation with a range of neuropsychological measures. Anemia affected brain volume similarly in men and women but sex differences were detected in anemia's relation to cognitive performance.

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This work was supported by NHLBI (1U01-HL-117718-01), NCRR (5UL1 TR000130-05), NIH (R01 NS074980), and NIH T32 (MH 111360-1 A1). Philips Healthcare provided support for protocol development and applications engineering on a support-in-kind basis.
All patients were recruited with informed consent or assent; the study was approved by the Institutional Review Board at Children's Hospital Los Angeles (CCI#11-00083).

Results:

Results showing regions in which anemia has an effect ($p<0.05$, uncorrected) on Jacobian determinants (controlled for sex and age) are seen diffusely throughout the brain. The number of voxels is larger in the right than the left hemisphere (Fig.1). These regions do not survive FDR correction for multiple corrections.

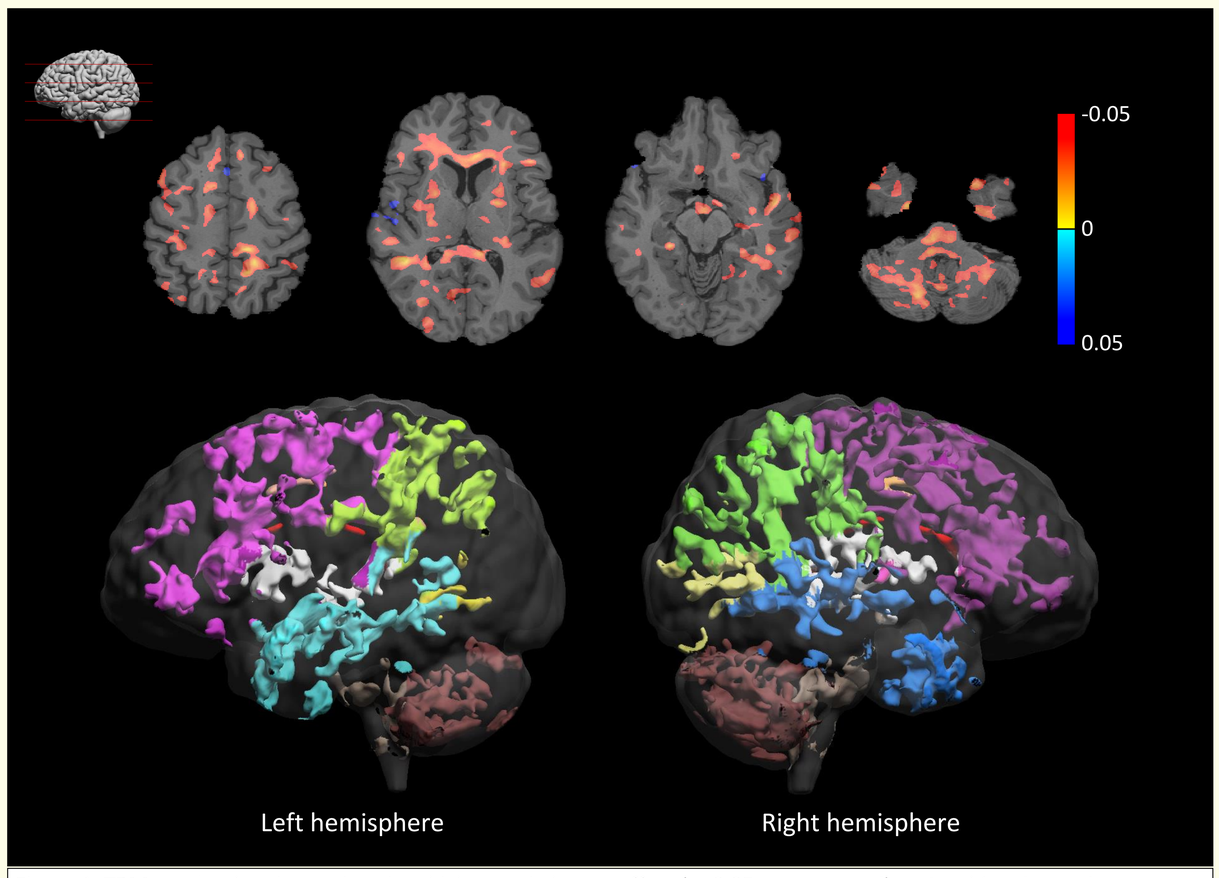

Figure 1. TBM results showing regions in which anemia has an effect ($p<0.05$, uncorrected) on Jacobian determinants (controlled for age and sex). Top row: Volumetric overlay of atlas template with p-values where red indicate a positive correlation and blue indicate a negative correlation as indicated by the colorbar. 3D-rendering of left (bottom left) and right (bottom right) hemisphere significant voxels colored by region for easy visualization (pink: frontal lobe; green: parietal; blue: temporal; yellow: occipital; white: deep WM and subcortex; brown: brainstem and cerebellum).

Hemoglobin, Wechsler Full Scale Intelligence Quotient (FSIQ), Rey-O Copy, and Digit Span, had significant ($p<0.05$) positive correlations to average Jacobian determinants. Coding score and Trail-Making Test had trending but non-significant positive correlations (Fig.2). Hemoglobin and FSIQ's relationship to average Jacobian determinants survive Bonferroni correction.

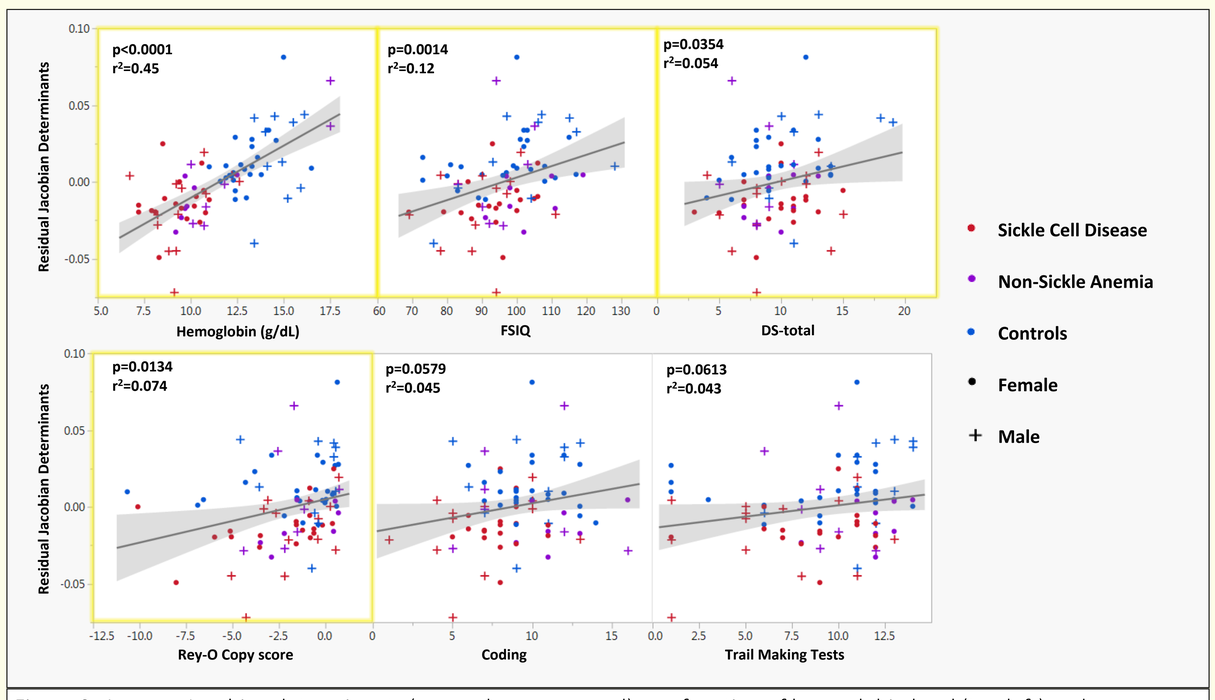

Figure 2: Average Jacobian determinants (age and sex regressed) as a function of hemoglobin level (top left) and neuropsychological test scores. Solid line shows the linear regression of the data and shaded area delimits the 95% confidence interval. Significant correlations ($p<0.05$) are highlighted in yellow. Points in scattergrams are labeled by color for disease state and symbols for sex. (FSIQ: Wechsler Full Scale Intelligence Quotient; DS-total: Digit Span)

Males had significant correlations between average Jacobian determinants and hemoglobin levels ($p<0.0001$; $r^2=0.045$), FSIQ ($p=0.0073$; $r^2=0.23$) and Trail-Making Test ($p=0.0321$; $r^2=0.15$) and females in hemoglobin levels ($p<0.0001$; $r^2=0.46$) and Rey-O Copy ($p=0.0409$; $r^2=0.081$).

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