

Regionally specific association between reduced CVR and cortical thinning in the pediatric population with sickle cell disease

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Introduction: Sickle cell disease (SCD) is a genetic disorder that can not only jeopardize health, but also affect normal physiological and neurological development. For example, children suffering from SCD without any history of overt symptoms may still have cognitive deficits^[1], even with normal appearing conventional MRI^[2]. Computationally intensive analysis on high resolution MRI, however, have demonstrated grey matter thinning in children with SCD, suggesting a possible connection to decline in executive function^[3]. Cerebrovascular reactivity (CVR), defined as the percent change in cerebral blood flow in response to a vasoactive stimulus, is an MRI method for gauging vascular health in the brain and has recently shown potential in clinical assessment of pediatric SCD patients^[4]. This measure may also be associated with healthy brain development as regions of significantly reduced CVR have previously been spatially correlated to regions of cortical thinning^[5]. However, it is unknown whether the globally compromised CVR observed in children with SCD has a direct physiological impact of cortical integrity and could serve as a biomarker of cognitive decline. The purpose of this study was to assess if reduced CVR is associated with cortical thinning in children with SCD. We hypothesized that the severity of CVR impairment is strongly correlated to the degree of cortical thinning.

Methods: 10 SCD patients (8-18 years) and 15 healthy controls were imaged on a clinical 3T MRI scanner using a 32-channel head coil. CVR data was acquired using a blood-oxygen level dependent (BOLD) sequence during a computer-controlled administration of a vasoactive stimulus delivered in programmed cycles of low and increased levels of CO₂ through a rebreathing mask. The BOLD images were acquired with TR/TE = 2000/40ms, FOV = 220mm, matrix size = 64x64, slices = 25, slice thickness = 4.5mm, volumes = 240, time = 8 min. T1-weighted anatomical images were acquired using a 3D-MPRAGE sequence with TR/TE = 2300/2.96ms, FOV = 256mm, voxel size = 1.0x1.0x1.0mm, FA = 9°, PAT = 2, time = 5:03min. High resolution CVR maps were computed using FSL v4.1 by correlating the voxel-wise BOLD signal changes to the end-tidal CO₂ waveform, followed by coregistration to the anatomical space. The T1-weighted images were processed with standard corrections (linear registration into standardized space, RF inhomogeneity correction) through the CIVET pipeline^[6]. The T1 images were then converted into cortical thickness surface maps using the Constrained Laplacian Anatomical Segmentation using Proximities (CLASP) method^[7]. The CVR maps were also converted into surface maps based on the T1 cortical segmentation. Both surface maps were coregistered into the MNI pediatric MRI Atlas. The MATLAB based program SurfStat was used to perform T-tests on cortical thickness and CVR between the groups in order to identify significantly different regions^[8]. The SCD CVR and cortical thickness data were normalized to the regional average control values. Correlation analysis was performed on the normalized data for each significantly different region.

Result: From the whole brain cortical thickness group comparison analysis, the right cuneus ($P < 0.04$), the bilateral post central ($P < 0.001$) and the right inferior temporal gyrus ($P < 0.001$) was found to be significantly thinner in SCD compared to the controls. The regional correlation analysis on these areas showed strong correlation in the right post central gyrus ($r = 0.6210$), moderate to significant correlation in the left post central ($r = 0.4112$) and the right inferior temporal gyrus ($r = 0.4729$) and moderate correlation in the right cuneus ($r = 0.3377$).

Discussion: In this study, we have demonstrated a linear relation between the degree of cortical thinning and reduced CVR in specific regions of the brain within the pediatric SCD population. This finding can potentially indicate that certain cortical areas are increasingly susceptible to disruptions in normal blood flow regulation leading to poor maintenance of the structural integrity in these areas. Future objectives will include measures of cognitive ability, which will be correlated with CVR and cortical thickness data in order to investigate the relationship between cognitive deficits, CVR and cortical thinning.

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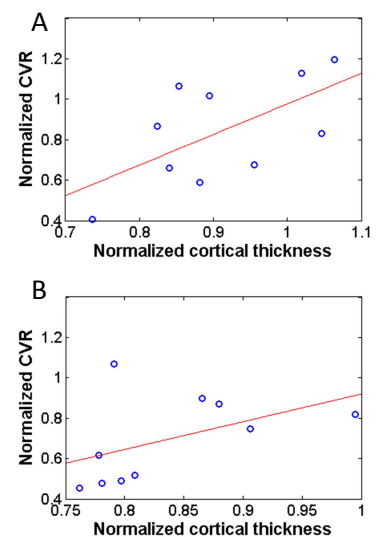


Fig. 1 Correlation between normalized CVR and cortical thickness for a) the right post central gyrus ($r = 0.6210$) and b) the right inferior temporal gyrus ($r = 0.4729$).