Association between CVR impairment and cortical thinning in children with sickle cell disease

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Introduction: Sickle cell disease (SCD) is a genetic disorder resulting in the pathognomonic change of red blood cells into the sickle shape. This will result in hemolytic anemia as well as vasculopathies. In addition, children with SCD also suffer from long-term neurocognitive deficits.[1] One method to assess cerebrovascular health in SCD is cerebrovascular reactivity (CVR), which is measured as the percent change in cerebral blood flow in response to a vasoactive stimulus. This parameter can be acquired with MRI and has recently shown potential in clinical assessment of pediatric SCD patients.[2] Importantly, measures of CVR may also be relevant in assessing neurological impairment as compromised CVR may result in hypoperfusion of the brain, which leads to neuronal cell loss with subsequent decline in neurocognitive function. However, it is unknown whether the globally compromised CVR previously observed in children with SCD has a direct physiological impact on cortical integrity, and could potentially serve as a marker for neurocognitive decline. The aim of this study was to investigate whether 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: 42 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 CO_2 through a rebreathing mask. The BOLD images were acquired with TR/TE = 2000/40ms, FOV = 220mm, matrix size = 64×64, 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 = 1.0×1.0×1.0mm, 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 CO_2 waveform, followed by coregistration to the anatomical space. The T1-weighted images underwent registration into a standard space through the CIVET pipeline.[3] The T1 images were then converted into cortical thickness surface maps using the Constrained Laplacian Anatomical Segmentation using Proximities (CLASP) method.[4] The CVR maps were also converted into surface maps based on cortical averages using the segmentation boundaries. Both surface maps were then coregistered into the MNI152 Atlas. The MATLAB based program SurfStat[5] was used to perform unpaired Students t-tests on cortical thickness and CVR between the patients and controls in order to identify significantly different regions of interest based on the Brodmann atlas. The SCD CVR and cortical thickness data were normalized to the regional average control values. Correlation analysis was performed on the normalized data for every Brodmann area.

Result: From the whole brain cortical thickness group comparison analysis, the right BA 17 ($p < 0.04$), the bilateral BA 1-3 ($p < 0.001$) and the right BA 21 ($p < 0.001$) was found to be significantly thinner in the SCD patients compared to the controls. The regional correlation analysis on the Brodmann areas showed strong correlation in the bilateral BA 27 ($r = 0.6493$) and moderate to strong correlation in the right BA 1-3 ($r = 0.5664$). 17 other regions (BA 4, 5, 7, 23, 25, 26, 29, 32, 33, 34, 39, 40, 42, 43, 44, 45, 52) exhibited correlations with $r > 0.43$, most of which were localized in the right hemisphere.

Discussion: In this study, we have demonstrated a linear relation between the degree of cortical thinning and reduced CVR in 19 BA regions (1-3, 4, 5, 7, 23, 25, 26, 27, 29, 32, 33, 34, 39, 40, 42, 43, 44, 45, 52) within the pediatric SCD population. This finding potentially indicates 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. Approximate Bayesian computation will be utilized in future studies to determine the best model for correlation.

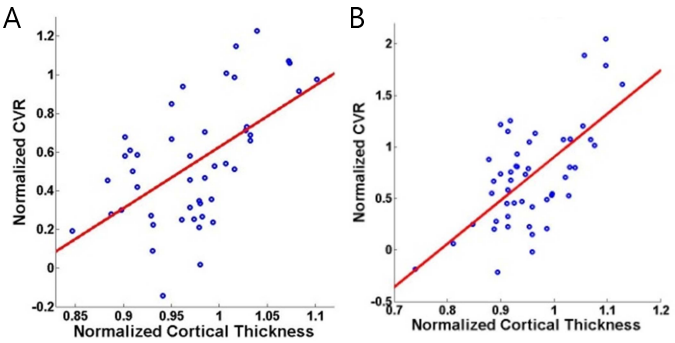

Fig. 1 Correlation between normalized CVR and cortical thickness for A) right BA27 ($r = 0.6493$) and B) right BA1-3 ($r = 0.5664$)

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