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POSTER ABSTRACTS

113.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

Localization of Silent Cerebral Infarcts in Children with Sickle Cell Disease Impacts Structural Disconnection

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Silent cerebral infarcts (SCIs) occur in 40% of children with sickle cell disease (SCD) by 18 years of age and are associated with cognitive dysfunction. SCIs localize to the border zone of the brain, but the significance of this localization is unclear. In adults with stroke, an infarct's disruption of white matter (WM) tracts, or structural disconnection, is more strongly associated with the functional impact of the infarct than the size of the lesion. We aim to define the WM tracts disconnected by SCIs and the relationship between structural disconnection and functional connectivity (FC) in SCD. Simulated and real-world data were used to test the hypothesis that specific WM tracts are vulnerable to disconnection if an infarct occurs in the region at highest risk for SCIs, and that FC will decrease with increased structural disconnection in SCD.

Utilizing data from the Silent Infarct Transfusion (SITT) trial, the regions at greatest risk for SCIs were defined (risk region, PMID 30061156). A simulated dataset comprised of 1000 infarcts within the risk region and 1000 infarcts within the white matter outside of the risk region was created. The real-world dataset was comprised of 44 participants with SCD and SCIs (median age 13.0 [11.0, 15.8] years, 29 female/15 male). The Human Connectome Project (HCP) 842 atlas contains thousands of streamlines comprising 28 WM tracts (excluding brainstem and cerebellar tracts). The Lesion Connectivity Toolbox defined streamlines within the HCP 842 atlas that intersected with each individual lesion, permitting quantification of two measures of structural disconnection: tract-wise disconnection (the percentage of streamlines within each tract that intersect a lesion) and global disconnection (the average percentage of streamlines connecting each pair of gray matter (GM) parcels in the FC parcellation (PMID 25316338)). Tract density images (TDi) illustrate the number of streamlines impacted by a lesion within each voxel of the brain permitting computation of total lesion impact as the volume of the TDi image associated with each lesion. Resting state functional connectivity MRI was obtained in 27 of the real-world participants for computation of whole brain modularity as a metric of global FC.

The WM tracts with the highest mean tract-wise disconnection due to lesions within the risk region were the posterior and mid-anterior corpus callosum, superior longitudinal fasciculus, frontal aslant tract, and middle longitudinal fasciculus while the inferior frontal occipital fasciclus, anterior commissure, inferior longitudinal fasciculus, posterior corpus callosum, and arculate fasciculus were most impacted by lesions outside of the risk region. Numerous tracts showed a significant difference in tract-wise disconnection resulting from lesions in the risk region vs. lesions outside the risk region. The tracts impacted due to real-world lesions were similar to tracts impacted from lesions within the risk region (Table 1). Despite lesioned volume being equivalent ($p = 0.31$) for simulated data within and outside the risk region, the average volume of lesion impact as measured by volume of the TDi image was significantly larger for lesions occurring inside the risk region ($p < 0.001$; Fig 1). In the real-world dataset, whole brain modularity, a metric of global FC, decreased as global structural disconnection increased ($r = -0.49$, $p = 0.009$)

Using simulated data that was validated with a real-world dataset, specific WM tracts vulnerable to SCIs were identified. Previous work on cerebral hemodynamics in SCD elucidated the mechanism of injury in the border zone, and these results demonstrate the significance of the localization of this injury to the border zone. SCIs have a far-reaching effect as lesions in the risk region within the border zone were associated with a greater volume of structural disconnection compared to lesions of the same size distributed outside the risk region. These results suggest that the regions in which the SCIs localize represent "high impact" areas of the brain, where a lesion of a given volume may intersect a large number of streamlines. Further, given the correlation between global structural disconnection and whole brain modularity, these data link structural disconnection with function of the brain, suggesting these "high impact" regions may also play a key role in mediating communication between functionally connected GM regions.

Disclosures Mirro: *Nous Imaging:* Current holder of *stock options* in a privately-held company, Patents & Royalties. **Binkley:** *OpenCell Technologies:* Current Employment. **DeBaun:** *Global Blood Therapeutics:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Vertex/CRISPR:* Membership on an entity's Board of Directors or advisory committees; *Novartis Pharmaceuticals Corporation:* Other: Study steering committee member; *FORMA:* Consultancy. **Fields:** *ProClara Biosciences:* Current equity holder in private company; *Global Blood Therapeutics:* Consultancy.

Table 1. Structural Disconnection

Tract	Mean Tract Disconnection (%) Risk Region	Mean Tract Disconnection (%) Outside Risk	Mean Tract Disconnection (%) Real World	p-value Risk vs. Outside Risk	p-value Risk vs. Real World
CCPosterior	3.386	2.139	4.911	0.001*	0.248
CCMidAnterior	3.206	1.041	5.084	0.001*	0.126
SLF	2.747	0.635	6.329	0.001*	0.001*
FAT	2.681	0.626	5.206	0.001*	0.010*
MdLF	2.491	0.938	5.242	0.001*	0.052
FPT	2.436	1.375	3.276	0.001*	0.299
CCCentral	2.404	0.893	2.785	0.001*	0.733
EMC	2.261	1.158	4.223	0.001*	0.075
CCMidPosterior	2.132	1.026	3.693	0.001*	0.119
CS	1.224	0.577	1.945	0.001*	0.034
CT	1.175	0.623	1.748	0.001*	0.073
AR	0.974	0.563	2.102	0.028*	0.140
IFOF	0.917	2.515	4.368	0.001*	0.001*
OR	0.751	1.379	3.066	0.006*	0.001*
U	0.729	0.521	1.641	0.001*	0.001*
C	0.653	1.476	1.292	0.001*	0.099
AC	0.328	2.302	2.229	0.001*	0.001*
ILF	0.32	2.152	1.204	0.001*	0.007*
UF	0.012	0.513	0.136	0.001*	0.001*

*Statistically significant after correction for multiple comparisons with the Benjamini-Hochberg procedure.
Only the tracts with significant differences in tract-wise disconnection resulting from lesions in the risk region vs. lesions outside the risk region are shown in this table. CC (corpus callosum), SLF (superior longitudinal fasciculus), FAT (frontal aslant tract), MdLF (middle longitudinal fasciculus), FPT (frontopontine tract), EMC (extreme capsule), CS (corticostriatal pathway), CT (corticothalamic pathway), AR (acoustic radiation), IFOF (inferior frontal occipital fasciculus), OR (optic radiation), U (U-fibers), C (cingulum), AC (anterior commissure), ILF (inferior longitudinal fasciculus), UF (uncinate fasciculus).

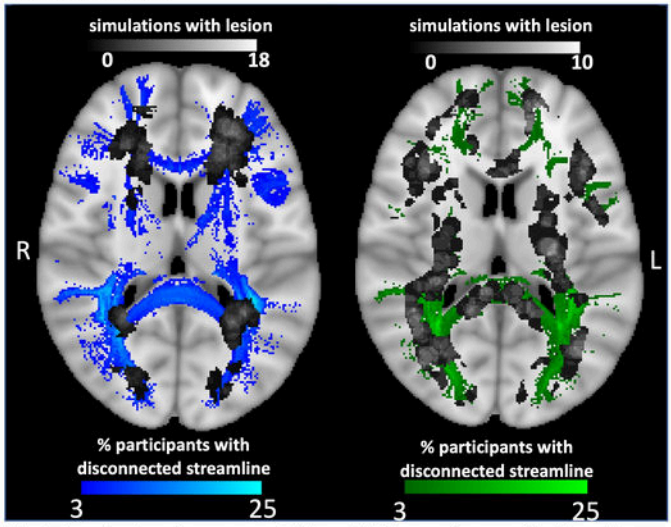

Fig 1. Lesion heatmaps overlaid on TDi impact maps for the risk region (left, blue) and outside of the risk region (right, green). Despite lesioned volume being equivalent between cohorts ($p = 0.31$), the average volume of lesion impact on structural disconnection was significantly larger for lesions occurring inside of the risk region ($p < 0.001$).

Figure 1

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