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Connectomic Correlates of Cerebral Microhemorrhages in Mild Traumatic Brain Injury Victims with Neural and Cognitive Deficits

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Abstract : The clinical significance of cerebral microbleeds (CMBs) due to mild traumatic brain injury (mTBI) remains unclear. Here we use magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) and connectomic analysis to investigate the statistical association between mTBI-related CMBs, post-TBI changes to the human connectome and neurological/cognitive deficits. This study was undertaken in agreement with US federal law (45 CFR 46) and was approved by the Institutional Review Board (IRB) of the University of Southern California (USC). Two groups, one consisting of 26 (13 females) mTBI victims and another comprising 26 (13 females) healthy control (HC) volunteers were recruited through IRB-approved procedures. The acute Glasgow Coma Scale (GCS) score was available for each mTBI victim (mean $\mu = 13.2$; standard deviation $\sigma = 0.4$). Each HC volunteer was assigned a GCS of 15 to indicate the absence of head trauma at the time of enrollment in our study. Volunteers in the HC and mTBI groups were matched according to their sex and age (HC: $\mu = 67.2$ years, $\sigma = 5.62$ years; mTBI: $\mu = 66.8$ years, $\sigma = 5.93$ years). MRI [including T1- and T2-weighted volumes, gradient recalled echo (GRE)/susceptibility weighted imaging (SWI)] and gradient echo (GE) DWI volumes were acquired using the same MRI scanner type (Trio TIM, Siemens Corp.). Skull-stripping and eddy current correction were implemented. DWI volumes were processed in TrackVis (http://trackvis.org) and 3D Slicer (http://www.slicer.org). Tensors were fit to DWI data to perform DTI, and tractography streamlines were then reconstructed using deterministic tractography. A voxel classifier was used to identify image features as CMB candidates using Microbleed Anatomic Rating Scale (MARS) guidelines. For each peri-lesional DTI streamline bundle, the null hypothesis was formulated as the statement that there was no neurological or cognitive deficit associated with between-scan differences in the mean FA of DTI streamlines within each bundle. The statistical significance of each hypothesis test was calculated at the $\alpha = 0.05$ level, subject to the family-wise error rate (FWER) correction for multiple comparisons. Results: In HC volunteers, the along-track analysis failed to identify statistically significant differences in the mean FA of DTI streamline bundles. In the mTBI group, significant differences in the mean FA of peri-lesional streamline bundles were found in 21 out of 26 volunteers. In those volunteers where significant differences had been found, these differences were associated with an average of ~47% of all identified CMBs ($\sigma = 21\%$). In 12 out of the 21 volunteers exhibiting significant FA changes, cognitive functions (memory acquisition and retrieval, top-down control of attention, planning, judgment, cognitive aspects of decision-making) were found to have deteriorated over the six months following injury ($r = -0.32$, $p < 0.001$). Our preliminary results suggest that acute post-TBI CMBs may be associated with cognitive decline in some mTBI patients. Future research should attempt to identify mTBI patients at high risk for cognitive sequelae.

Keywords : traumatic brain injury, magnetic resonance imaging, diffusion tensor imaging, connectomics
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