Potential TBI Biomarkers and Therapeutics

White Matter Disintegrity Following Mild Traumatic Brain Injury May Explain Abnormalities in Cognition, Emotion, and Sleep

Researchers from the McLean Hospital (Boston, MA), through a series of cross-sectional studies, aimed to determine whether measures of damage to neuronal pathways following mild traumatic brain injury (mTBI) would explain abnormalities in functional connectivity of the brain, cognition, and emotion and whether these measures could serve as biomarkers of mTBI.

The studies included individuals that had sustained a mTBI and healthy adults. Participants underwent magnetic resonance imaging (MRI) or diffusion tensor imaging (DTI) scans to assess changes in brain structures and functional connectivity. Attention, sleep, and emotion (aggression and depression) were also assessed. Examination of structural changes revealed a thickening of the cortex and a decrease in cortical surface area in mTBI patients during the acute/subacute phase of injury, followed by an increase in cortical thickness in specific regions of the brain in the chronic phase when compared to healthy controls (Figure 1; *Bajaj et al., 2018*). Increases in cortical thickness in certain brain areas were associated with decreases in the ability to pay attention.

Studies investigating the relationship between emotion, sleep, and the integrity of specific neuronal pathways showed that self-reported poor sleep quality and depressive symptoms following mTBI were correlated with reduced integrity of neuronal pathways in multiple areas of the brain involved in sleep-wake cycle and emotion regulation, information processing, cognitive control, attention, and executive function (Figure 2; *Raikes et al., 2018*). Furthermore, elevated aggression has been noted in adults with chronic mTBI. High levels of aggression were associated with changes in a neuronal pathway that connects the two sides of the brain (Figure 3; *Dailey et al., 2018*). Imaging also revealed that increased connection between neurons involved in recognizing emotions was associated with higher aggression in individuals with mTBI, but not in healthy controls (Figure 4; *Dailey et al., 2018*).

Taken together, these studies demonstrate the potential of observed changes in the anatomy of the brain which could potentially serve as injury markers to assist in predicting those at risk for prolonged symptoms and protracted recovery.

This effort was managed by CDMRP with support and program oversight by CCCRP/JPC-6.

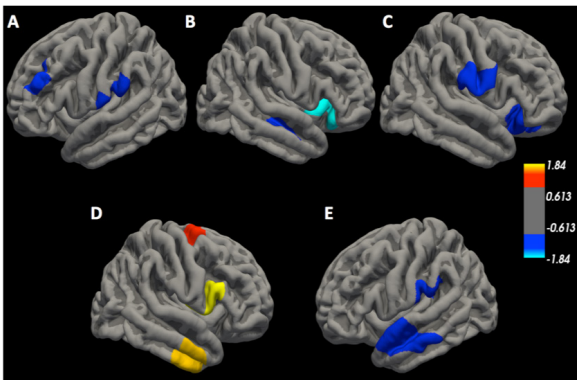

FIGURE 1: Compared to healthy controls, we observed thicker cortex within the left hemisphere in mTBI individuals following 3-6 months post mTBI (A), thicker cortex within the right hemisphere in mTBI individuals following 0-3 months post-mTBI (B), and 3-6 months post mTBI (C). However, compared to healthy controls, mTBI individuals had lesser cortical surface area following 3-6 months post mTBI (D). Lastly, cortical surface area was greater following 6-18 months post mTBI compared to 3-6 months post mTBI (D). (*Bajaj, et al., 2018, Human Brain Mapping, 39, 1886-1897*).

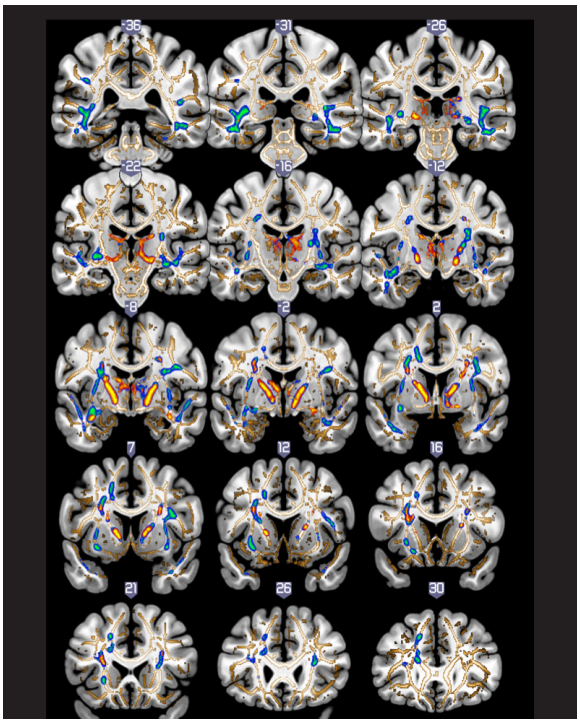

FIGURE 2: Whole-brain tract-based spatial statistics correlations with Pittsburgh Sleep Quality Index scores for the mTBI participants overlaid on the average FA skeleton (gold). Significant positive (Radial Diffusivity (RD) = green voxels) and negative (Fractional Anisotropy (FA) = yellow voxels) correlations were observed. Surrounding voxels are filled (FA = red; RD = blue) for visualization purposes. Images are in neurologic orientation (left is left and right is right) and MNI152 space (*Raikes, et al., 2018, Frontiers in Neurology, 9, 468*).

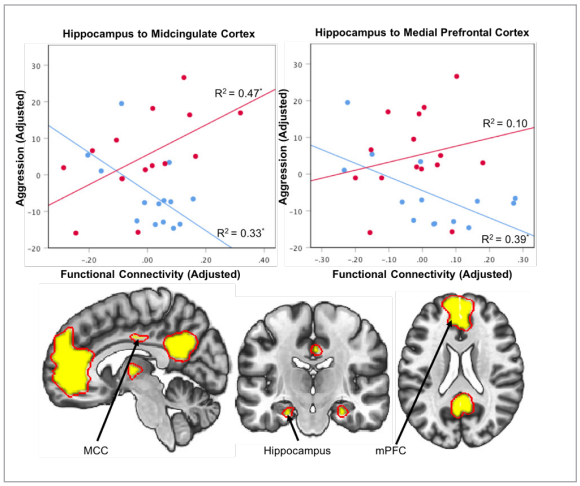

FIGURE 3: Significant group differences in ROI-to-ROI connectivity associated with aggression was found from the hippocampus to midcingulate cortex (MCC) and hippocampus to the medial prefrontal cortex (mPFC) (*Dailey, et al., 2018, NeuroReport, 29, 1413-1417*).

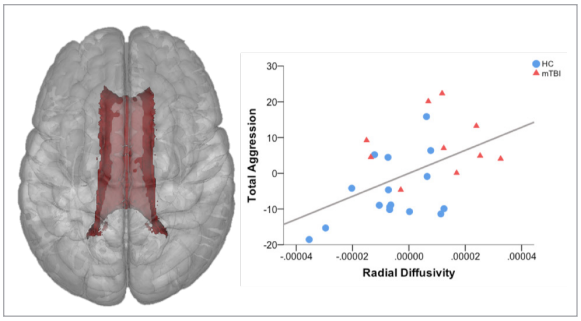

FIGURE 4: Corpus callosum shown in red overlaid on a standard brain. The scatterplot shows a significant association between a measure of poor white matter integrity (*i.e.*, radial diffusivity) of the corpus callosum and greater aggression, particularly among those with mild traumatic brain injury (mTBI)(*et al., 2018, Frontiers in Behavioral Neuroscience, 12, 118*).

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