Brain Network Dysfunction in Young Athletes with Persistent Post-Concussion Syndrome

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Target audience: Clinicians, Neuroscientists

Purpose:

Traumatic brain injury (TBI) is one of the leading causes of morbidity in the United States, with the highest incidence among young adults age 15-24 years. Approximately 75% of TBI patients have mild TBI (mTBI) and typically exhibit few or no abnormalities on conventional brain imaging but experience a broad spectrum of neuropsychological impairments related to attention, executive function and memory [1]. The majority of mTBI patients recover within a few months, but for up to 20% symptoms persist and lead to a devastating impact on interpersonal relationships and potentially to long-term disability. Yet despite the high prevalence of persistent post-concussion syndrome (PPCS), the pathophysiological basis of PPCS remains unknown. The poor sensitivity of conventional neuroimaging not only limits diagnosis but also prevents clinicians from identifying the subset of mTBI patients at risk of long-term neurological sequelae. Recently, the analysis of spontaneous fluctuations in resting brain activity has led to the concept of resting state networks, which can be characterized by temporal correlations in low frequency (<0.1 Hz) BOLD signal fluctuations across functionally related brain regions. In this resting state functional MRI (rs-fMRI) study, multiple resting state networks in the brains of mTBI patients with PPCS were compared with those from healthy control subjects to determine whether the functional connectivity within these networks differed significantly.

Methods:

MRI acquisition: Ten mTBI patients (17.6±1.6 years, 4 females) presenting with PPCS for at least 3 months post-injury and ten healthy volunteers (20.4±1.9 years, 6 females) were enrolled with written informed consent. MRI data were acquired on a Siemens TIM Trio 3T scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-channel head-only receive coil. Anatomical images were acquired using a 3D T1-weighted sequence (MPRAGE) at 1x1x1 mm^3 resolution and 176 sagittal slices. Functional images were acquired axially using a single-shot EPI sequence with TR/TE=3000/23 ms at 3x3x3mm^3 resolution and 35 slices. Data from 120 timepoints were analyzed.

MRI processing: Functional data were pre-processed using motion correction and in-plane smoothing. Functional and anatomical images were co-registered to the MNI-152 T1 template. Functional connectivity maps were obtained using a technique combining independent component analysis (ICA) and dual regression against a 20-component template (fCON 1000[2]). Motion parameters were regressed out using global signal regression. The following 5 networks were analyzed: default mode (DMN), executive control, temporo-parietal memory, attention and salience networks. Differences between groups in the ICA analysis were evaluated using a two sample t-test (SPM) with age and sex as covariates. The CONN toolbox[3] was also used to quantify local efficiency in these networks for all the subjects.

Neurocognitive tests: Controls and mTBI patients were administered a battery of neurocognitive test including the Hopkins Verbal Learning Test-Revised (HVLT-R, a measure of verbal learning and memory), the Digit Span (measure of verbal attention, executive function and working memory), the FAS/Animals (measure of initiation of behavior), Trail Making Test A and B (measure of straightforward visual tracking and of set shifting), Stroop Color (test of inhibitory control), and the Symbol Digit Modalities Test (measure of visual search, task persistence and processing speed).

Fig 1: Average across groups (Controls and mTBI patients) and differences between groups (Controls > mTBI) in 5 resting-state networks (p<0.01, Z-statistic>2.3). The brain regions showing significant differences between groups are listed for each network.

Results:

Mean Z-statistics of the functional connectivity independent components representing the DMN, executive control, temporo-parietal memory, attention and salience networks for the control and mTBI cohorts are shown in Figure 1. Statistical differences (p<0.01) between the two cohorts are shown, and the neuroanatomic regions affected within each network are listed. The most commonly affected brain regions in mTBI patients were the inferior and superior parietal lobules, one of which was affected in all of the networks except for the temporo-parietal memory network. The DMN also showed a large region of voxels with negative Z-statistics in the occipital cortex in mTBI patients compared to controls. In contrast, mTBI subjects showed regions with significantly less negative Z-statistics in the fornix and in the callosal body in the temporo-parietal memory network compared to the controls. Multiple neurocognitive tests show differences between controls and mTBI such as the HVLT-R, the FAS, the Digit Span and the Trail Making B. A statistically significant correlation between the local efficiency of the DMN network with the HVLT-R recognition score (R=0.57, p=0.01), and between the local efficiency of the executive control network and the FAS score (R=0.44, p=0.05) were found (Fig 2).

Conclusion:

This prospective rs-fMRI pilot study demonstrates that multiple resting brain networks are altered in young athletes with PPCS compared to healthy controls and that these network dysfunctions are correlated with neurocognitive tests. Our results suggest that the inferior and superior parietal lobules are functionally important grey matter nodes within multiple brain networks that are implicated in the pathogenesis of PPCS. The inferior parietal lobule (IPL) is concerned with language, mathematical operations, body language and has been involved interpretation of sensory information. The FAS test requires rapid production of words based on letter cues (words starting wi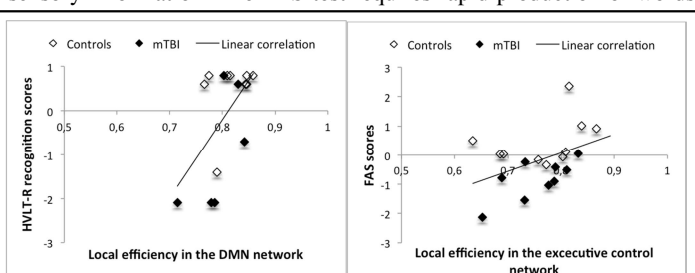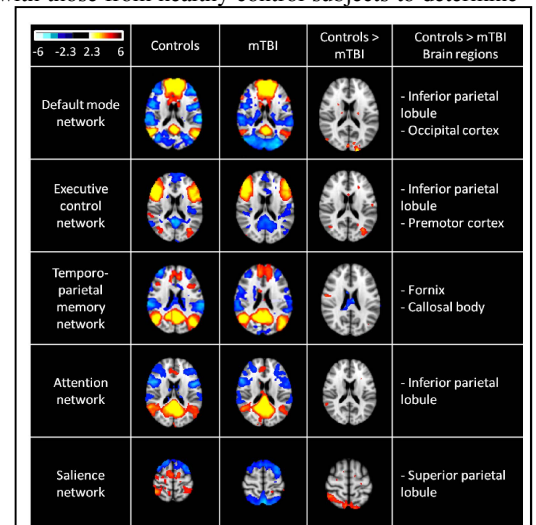th F, A, S), thus requiring a high level of attention. The significant correlation between this score with the local efficiency of the executive control network demonstrates the link between neurocognitive dysfunction and brain network alterations. These brain network alterations may provide a pathophysiological basis for the neurocognitive dysfunction experienced by young athletes after mTBI.

References: [1] Ropper, A.H., et al. Clinical practice. Concussion. N. Engl. J. Med. 2007. 356, 166–172. [2] Biswal, B.B., et al. Toward discovery science of human brain function. PNAS. 2010;107, 4734–4739 ; [3] Whitfield-Gabrieli, S., et al. Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012.

Fig 2 : Linear correlation between the neurocognitive tests (HVLT-R and FAS) and the local efficiency in the DMN and executive function networks