

Defense and Veterans Brain Injury Center

TBI Hot Topics Bulletin

SECOND QUARTER CY 2020



STAY INFORMED ABOUT TRAUMATIC BRAIN INJURY (TBI)

Are you a busy health care provider? Not enough time to keep up with research? Stay informed with the *TBI Hot Topics Bulletin*. We track the latest TBI scientific studies, advances, and discoveries most relevant to health care providers.

SCIENTIFIC STUDIES

The Late Contributions of Repetitive Head Impacts and TBI to Depression Symptoms and Cognition

Repetitive head impacts (RHI) are associated with long-term neuropsychiatric and cognitive disorders and have been linked to the development of neurodegenerative diseases. It is speculated that RHI may have a cumulative impact on brain health as well as increase the likelihood of recurrent TBI. However, because RHI and TBI are often associated, it is difficult to parse their contributions to any long-term consequences. Alosco et al. used the internet-based Brain Health Registry to obtain self-report data from 13,323 participants (mean age = 61.95, 72% female). In this sample, the authors identified those with RHI and TBI via a modified version of the Ohio State University TBI Identification Method (OSU TBI-ID). They designated whether participants had exposure to RHI (i.e., RHI+ or RHI-). They also categorized them based on TBI and loss of consciousness (LOC): those with a history of TBI and LOC (TBI+ with LOC), those with a history of TBI but without LOC (TBI+ without LOC), and those without a history of TBI (TBI-). Participants completed the Geriatric Depression Scale (GDS-15), the CogState Brief Battery (CBB), and the Lumos Labs NeuroCognitive Performance Tests (NCPT), all online. The authors used regression analyses to examine the independent and interaction effects of RHI and TBI on the cognitive and psychiatric variables. They found a dose-response pattern where participants with greater exposure to RHI and more severe TBIs had more symptoms of depression. Participants with RHI+/TBI+ with LOC also showed the most depressive symptoms and the greatest cognitive deficits.

Comment

The study indicates RHI and TBI may have negative synergistic effects on post-concussive symptoms. The literature on the neurological effects of RHI is inconsistent because not all those exposed to subconcussive impacts will develop neuropsychiatric or cognitive disorders. The number of events, their severity, and the age of injury may be key factors. However, if RHI is predictive of outcomes, knowing a patient's head injury history may prove useful in clinical management. Further research is needed to validate and expand these findings.

Alosco et al. (2020) *Neurology*, DOI: 10.1212/WNL.0000000000010040

Olfactory Sniffing Signals Consciousness in Unresponsive Patients with Brain Injuries

The hallmark of a severe brain injury is the loss of consciousness. Monitoring recovery has traditionally involved a patient's reaction to painful stimuli. However, this approach is confounded by reflexive movements, which are independent of consciousness. In this study, Arzi et al. used an olfactory indicator to differentiate between TBI patients in a minimally conscious state (MCS) and those experiencing unresponsive wakefulness syndrome (UWS), also known as a vegetative state. Their sample consisted of 31 brain-injured patients with MCS and 24 with UWS (16 of which transitioned to MCS later in the study). The authors employed a non-verbal, non-task-dependent measure known as the "sniff response" (i.e., air volume reduction). Each patient was exposed to a series of odorants by placing jars under the nose (5-sec duration). The jars contained substances soaked in cotton that produced pleasant smells (shampoo or roses), unpleasant smells (rotten fish or crayons), or no smell (i.e., an empty jar). Inhalation was measured using a nasal cannula linked to a spirometer.

The patients were exposed to 10 odorants per session in random order. A total of 146 sessions were administered over 10 weeks. Due to clinical demands, not all patients received the same number of sessions (mean = 3.4 sessions per patient). Patients were monitored by the Coma Recovery Scale-Revised (CRS-R) or Coma/Near Coma Scale (CNC). Their clinical progress was followed for five years. Subsequent analyses examined nasal inhalation in relation to group and clinical outcomes. Overall, the sniff response was significantly greater among MCS compared to UWS patients. However, the MCS group showed no significant difference between pleasant and unpleasant smells. The authors observed that all UWS patients with a positive sniff response eventually transitioned to a minimally conscious state (10 out of the 16). Thus, the sniff response showed 62.5% sensitivity and 100% specificity for change from UWS to MCS. The authors also found that patients exhibiting a sniff response shortly after injury were more likely to survive. Of the 24 patients who exhibited a sniff response, only 2 died within the five-year window. In contrast, 12 out of the 19 patients with no response died within two years.

Comment

To date, there are no biomarkers that signal a return to consciousness after a severe TBI. However, olfaction accesses primitive brain circuitry that may be linked to consciousness. The study indicates that the sniff response differentiates between MCS and UWS patients and may be prognostic of recovery. Further research is needed to validate these findings and explore their clinical utility.

Arzi et al. (2020) *Nature*, Epub 29 Apr. PMID: 32461641

Change in Balance Performance Predicts Neurocognitive Dysfunction and Symptom Endorsement in Concussed College Athletes

Balance dysfunction often follows TBI and is frequently associated with neurocognitive deficits. Balance metrics could be useful clinical indicators. However, a valid relationship with neurocognitive performance may be dependent on baseline testing. In this study, DaCosta et al. examined whether the magnitude of change in balance (i.e., post-injury – pre-injury baseline) is an indicator of neurocognitive deficits and self-reported symptoms post-TBI. The authors assessed 68 collegiate athletes with concussions (59 contact sport; nine non-contact sport). Most injuries occurred during play or practice, but nine individuals sustained concussions from non-sport activities (e.g., falls, motor vehicle accidents, and fights). All participants received balance testing pre-injury. After a concussion, they were referred for re-testing (within 24–48 hrs.). The assessments consisted of the Sports Concussion Assessment Tool (either SCAT-3 or SCAT-5), Immediate Post-concussion Assessment and Cognitive Testing (ImPACT), and the Modified Balance Error Scoring System (mBESS). Regression analyses showed that the magnitude of change derived from the mBESS predicted self-reported balance problems, as well as scores from all four cognitive domains of the ImPACT (verbal memory, visual memory, visual-motor speed, and reaction time). In contrast, the post-injury mBESS alone was not predictive of self-reported balance problems and only predicted three of the four composite scores (visual memory, visual-motor speed, and reaction time).

Comment

The study indicates that the magnitude of change in balance is a predictor of post-concussion symptoms and neurocognitive performance. Effective balance requires sensory and somatic systems that are often compromised by a head injury. The authors suggest that comparing baseline and injury data from the mBESS provides useful clinical information. This approach may be an effective triage tool for large groups of people (e.g., sports camps, military training, etc.). Further research is needed to study the influence of malingering, practice effects, and inter-rater reliability on balance assessments.

DaCosta et al. (2020) *Arch Clin Neuropsychol*, Epub 15 May. PMID: 32415967

Exosomal Neurofilament Light: A Prognostic Biomarker for Remote Symptoms after Mild Traumatic Brain Injury?

Detection of proteins in the blood (i.e., biomarkers) has emerged as a promising line of research in TBI diagnostics. Following a TBI, certain molecules cross the blood-brain barrier (BBB) and enter circulation. Research suggests that levels of these biomarkers may be related to the time since injury. The analysis of exosomes is especially promising, as these vesicles shield proteins from degradation, which extends their life in the bloodstream. Guedes et al. measured blood-based biomarkers in U.S. veterans and analyzed their levels in relation to mild TBI (mTBI), PTSD, depression, and post-concussive variables. The sample ($n = 195$) was drawn from the Chronic Effects of Neurotrauma Consortium Multicenter Observational Study (CENC). All participants were assessed for a history of mTBI (Ohio State University TBI-ID, Virginia Commonwealth University Retrospective Concussion Diagnostic Interview), post-concussive symptoms (Neurobehavioral Symptom Inventory: NSI), PTSD (PTSD Checklist Military Version: PCL-M), and depression (Patient Health Questionnaire Depression Scale: PHQ-9). Blood samples were analyzed for neurofilament light (NfL), interleukins (IL-6, IL-10), tumor necrosis factor (TNF- α), and vascular endothelial growth factor (VEGF). The authors found elevated exosomal and plasma NfL in participants with repetitive mTBIs. Regression analyses showed an association between elevated NfL and higher scores on the NSI, PCL-M, and PHQ-9. They also found NfL levels were positively correlated with the total number of mTBIs, years from the most recent injury, and years from the earliest injury.

Comment

The study provides further evidence that blood-based biomarkers are potential objective measures for the diagnosis and prognosis of mTBI. Many biomarkers degrade in circulation with time, limiting their clinical utility. In this study, the authors show the durability of NfL in both plasma and exosomes. Though their investigation involved patients with TBI, PTSD, and depression, they did not test whether NfL (or other biomarkers) can discriminate between them. If future studies show NfL can distinguish these conditions, it may prove a suitable biomarker for mTBI.

Guedes et al. (2020) *Neurology*, Epub 27 May. PMID: 32461282

Longitudinal Changes of Brain Microstructure and Function in Nonconcussed Female Rugby Players

A growing literature suggests subconcussive head impacts have a cumulative effect on brain health. Much of this evidence comes from diffusion tensor and resting-state imaging studies (i.e., DTI and rsMRI, respectively). Manning et al. examined the effects of subconcussive impacts on female athletes. For the contact group, they recruited varsity rugby players ($n = 73$). The non-contact group consisted of varsity swimmers and rowers ($n = 31$). The authors examined cross-sectional (contact vs non-contact) and longitudinal (in-season vs off-season) DTI and rsMRI measures in these groups. The rugby team's play was followed for five years. None of them reported concussions during this time, but many still experienced routine subconcussive hits. To substantiate this, a subset of the rugby players wore head-mounted accelerometers. The authors also recorded some practice sessions and analyzed the video for head impacts. The Sport Concussion Assessment Tool (SCAT) was used to monitor all participants' symptoms. The authors found that the DTI measure of fractional anisotropy (FA) was decreased in contact compared to non-contact athletes. There were also significant increases in mean, axial, and radial diffusivities (i.e., MD, AD, and RD, respectively). The authors observed greater hyperconnectivity in the default mode and visual networks for the contact athletes. Longitudinal analyses in the contact group showed changes in diffusion measures in the brain stem. Finally, contact athletes with a history of concussion showed a reduction in AD in the corpus callosum (genu and splenium).

Comment

This investigation contributes to the growing literature on subconcussive impacts and brain health. The authors show that changes in brain structure and function are sensitive to contact sports, even in the absence of concussion. They do not, however, connect these changes to neurocognitive and behavioral symptoms. The results still raise concerns regarding potential long-term effects from certain civilian and military activities (i.e., contact sports and blast exposure). Additional research is needed to replicate these findings, explore their duration, and identify any associated neurocognitive and behavioral effects.

Manning et al. (2020) *Neurology*, Epub 17 Jun. PMID: 32554762

Slow Blood-to-Brain Transport Underlies Enduring Barrier Dysfunction in American Football Players

Experimental evidence suggests that blood-brain-barrier dysfunction (BBBD) can follow TBI. This condition is associated with vulnerability to microbes, toxins, inflammation, and neural degeneration. Currently, there are no standardized clinical methods for assessing BBBD nor any in vivo data on microvascular permeability. Veksler et al. sought to validate a diagnostic approach to detect and track BBBD and microvascular pathology in cases of repetitive, mild TBI (mTBI). The authors scanned contact and non-contact sport athletes using a modified dynamic contrast-enhanced magnetic resonance imaging sequence (DCE-MRI). The sample consisted of 42 football players, 27 non-contact sport athletes, and 26 non-athletes. The authors used the NFL Sideline Concussion Assessment Tool to document previous head injuries, and the Standardized Assessment of Concussion (SAC) to assess symptoms. They also evaluated their method using the scans of 51 neurological patients (i.e., either ischemic stroke, brain tumor, or traumatic brain injury), and four rodent models (i.e., TBI: modified weight-drop and unilateral closed head impact; vascular injury: photothrombosis; and seizure: 4-aminopyridine perfusion). Cluster analysis showed that football players were three times more likely to display a pathological BBB compared to non-contact and non-athlete controls (27.4% versus 9.4%, respectively). For these comparisons, the authors used the normalized permeability index (NPI), which measures how much the BBB allows the passage of microscopic particles. A high NPI indicates a permissive barrier and potential pathology. Football players showed high NPI in several brain regions (white matter, midbrain peduncles, red nucleus, temporal cortex) and at various time points, suggesting BBBD can be chronic. Diffusion tensor imaging (DTI) showed a concurrent decrease in fractional anisotropy (FA) and an increase in mean diffusivity (MD) in tracts that correspond to the BBBD pathology (corpus callosum, cortical-spinal tract, thalamic radiations, inferior frontal occipital fasciculus). Approximately half (47.4%) of the football players had resolution of focal pathology at later time points. The authors further validated DCE-MRI in the neurological patients and rodent models. Using gadolinium contrast, they found evidence of a “fast leak,” which occurs within minutes at the site of the injury or tumor, and a “slow leak,” which progresses over time in the surrounding tissue. Gadolinium contrast accumulation corresponded with areas of high NPI in the animal models.

Comment

Using a novel DCE-MRI approach the authors were able to identify brain regions affected by BBBD, as well as show correlations between BBBD and compromised white matter. More research is needed to address this pathology and its clinical implications. While BBBD may be relevant, mTBI patients are typically not scanned if they lack symptoms. Accordingly, how and when to incorporate this technology into clinical management requires further consideration.

Veksler et al. (2020) *Brain*, Epub 28 May. PMID: 32464655

ABOUT

The *Bulletin* is a product of the Defense and Veterans Brain Injury Center (DVBIC) Research Division and provides a quarterly summary of TBI research relevant to health care providers. This issue covers research published April to June 2020.

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