International Journal of Psychophysiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Structural neuroimaging in sport-related concussion

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ARTICLE INFO

Keywords:
Computed tomography (CT)
Magnetic resonance imaging (MRI)
Sports-related concussion (SRC)
Mild traumatic brain injury (mTBI)
Quantitative neuroimaging
Diffusion tensor imaging

ABSTRACT

Structural neuroimaging of athletes who have sustained a sports-related concussion (SRC) can be viewed as either standard clinical imaging or with advanced neuroimaging methods that quantitatively assess brain structure. Negative findings from conventional computed tomography (CT) or magnetic resonance imaging (MRI) are the norm in SRC. Nonetheless, these conventional measures remain the first line of neuroimaging of the athlete as they do detect clinically significant pathologies, when present, such as hemorrhagic abnormalities in the form of hematomas, contusions and mircobleeds along with regions of focal encephalomalacia or other signal abnormalities, with CT best capable of detecting skull fractures. However, advanced neuroimaging techniques hold particular promise in detecting subtle neuropathology in the athlete which standard clinical neuroimaging cannot. To best understand what conventional as well as quantitative neuroimaging methods are detecting in SRC, this review begins by covering basic neuroanatomical principles associated with mild traumatic brain injury (mTBI) and the brain regions most vulnerable to injury from SRC, as these regions define where advanced neuroimaging methods most likely detect abnormalities. Advanced MRI techniques incorporate quantitative metrics that include volume, shape, thickness along with diffusion parameters that provide a more fine-grained analysis of brain structure. With advancements in image analysis, multiple quantitative neuroimaging metrics now can be utilized in assessing SRC. Such multimodality approaches are particularly relevant and important for assessing white matter and network integrity of the brain following injury, including SRC. This review focuses just on the structural side of neuroimaging in SRC, but these techniques also are being integrated with functional neuroimaging, where the combination of the two approaches may provide superior methods in assessing the pathological effects of SRC.

Standard clinical neuroimaging with computed tomography (CT) and magnetic resonance imaging (MRI) typically do not reveal abnormalities in sports-related concussion (SRC; see Bigler and Orrison, 2004).[1] In contrast, advanced magnetic resonance (MR)-based neuroimaging techniques have the potential to detect subtle neuropathological changes associated with SRC. The importance of detecting subtle pathology in SRC is critical to not only understanding the nature of the injury but potentially, will have widespread clinical import for managing SRC, return to play decision making and tracking an athlete's neurological and neuropsychiatric status over a lifetime. Current clinical decision making informed only with negative conventional neuroimaging and existing standards that rely on traditional approaches to neurocognitive and neurobehavioral assessments have fallen short of addressing the nature and degree of potential brain pathology associated with SRC. As recently shown by Tator et al. (2016), within a University-based concussion clinic, the median postconcussion syndrome (PCS) symptom duration in that clinical sample was seven months. The majority of the 221 individuals that participated in the Tator et al. investigation had sustained SRC or concussion associated with some recreational activity with almost 12% of this sample reporting PCS lasting beyond two years (see also Hiploylee et al., 2017). Of particular importance for the current review, the Tator et al. (2016) study excluded all patients with positive neuroimaging findings on conventional CT or MRI. As such traditional neuroimaging generally do not detect nor illuminate the role that subtle brain pathology may play in SRC, while advanced quantitative methods have that potential (Mitra et al., 2016; Sussman et al., 2017).

In the absence of any conventional neuroimaging finding, how does one understand the symptoms, problems and complaints of the athlete with SRC? Since the symptoms associated with PCS – headache, fatigue,

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[1] In this review the term 'head injury' merely refers to the athlete having sustained some kind of blow, impact and/or acceleration/deceleration to the head without necessarily implying brain injury. The term concussion is used interchangeably with mild traumatic brain injury (mTBI). Sports-related brain injury means that the athlete met clinical criteria for having sustained a TBI. Sports-related head injury in this review merely refers to some impact involving the head during a sports activity.

http://dx.doi.org/10.1016/j.ijpsycho.2017.09.006
Received 11 January 2017; Received in revised form 3 September 2017; Accepted 7 September 2017

visual disturbances, vertigo, sleep disruption, mood dysregulation, inefficient memory, problems with concentration, etc. – are all nondescript and nonspecific (Meyer and Arnett, 2015), such symptoms provide no ability to differentiate possible underlying brain pathology specific to SRC or that which may have predated the injury, as in the Tator et al. (2016) study 26.2% of the participants that met inclusion criteria had a diagnosable pre-injury neuropsychiatric disorder prior to sustaining a concussion. For some is PCS following SRC merely an extension of an existing disorder? Other than the fact that PCS symptom reporting occurred after some trauma involving the head, what biomarker is there that provides the clinician or researcher with any objective information about the brain injury or even that the brain was injured? Likewise, traditional neuropsychological approaches have no ability to detect actual brain pathology, only inferences about neural systems that may be affected (see Bigler, 2016b). As pointed out by Kontos et al. (2016) and Prince and Bruhns (2017), performance on the neuropsychological examination in someone following a concussion potentially will be influenced by a host of factors not necessarily related to a specific brain abnormality, since pain, mood dysregulation, poor sleep hygiene and a variety of other somatic factors may affect the individual who sustained a concussive brain injury (see also Silver, 2012). On the other hand, advanced neuroimaging analyses have that potential to specifically identify SRC-related neuropathology, which is the focus of this review. It needs be emphasized that most advanced neuroimaging methods have only been developed within the last decade, so none are ready for clinical implementation in the management of SRC as of this writing (see Broglio et al., 2017), conclusions that have been reinforced by other reviews (Dimou and Lagopoulos, 2014), meta-analyses (Tarnutzer et al., 2016) and consensus conferences on sport (Kamins et al., 2017; McCrea et al., 2017).

The foundation for this review is that understanding SRC depends, in part, on an informative understanding about relevant brain anatomy in conjunction with common features associated with acceleration/deceleration deformation of the brain within the cranial vault following impact. While each injury is unique to that individual, there are some shared injury dynamics and regions of interest (ROI) that are most common to SRC and brain injury. This will constitute the first part of this review. Next, this review will examine the structural neuroimaging findings, albeit infrequent, that may be visibly identifiable in conventional CT and/or MRI reflective of sports-related brain injuries, where CT is typically only performed in an acute setting as part of emergent medical decision making or to evaluate for suspect facial bone or skull fractures. Otherwise, MRI is the method of choice because of its superiority in detecting structural brain pathology associated with traumatic brain injury (TBI), including those from SRC (Ellis et al., 2016). Some examples of acute CT findings will be discussed, but the main focus will involve MR techniques. The standard clinical approach to interpreting a MRI scan involves the identification of a visible abnormality and how brain anatomy conforms to expected age and typical developed brains from healthy individuals, with no history of brain injury and/or neurological or neuropsychiatric disorder. However, not detected by just "looking" at the scan image, there are now a variety of advanced image analysis techniques that use various MR metrics to quantify the size, shape, thickness, volume, or diffusion properties of a given ROI that may reflect structural pathology associated with TBI. This review will not address functional neuroimaging findings in SRC, including MR spectroscopy, as this has recently been reviewed elsewhere (see Kamins et al., 2017; McCrea et al., 2017). Although referred to at times in this review, there will be no in depth coverage of the neuroimaging literature on chronic traumatic encephalopathy (Gangolli et al., 2017; Raji et al., 2016; Shetty et al., 2016) or recent post-mortem analyses of CTE findings in professional (Mez et al., 2017) or collegiate athletes (Mez et al., 2016) and the potential to image such abnormalities.

1. The meaning of "subtle" pathology in concussion

This review is focused on the structural side of brain imaging in SRC, where the neuroanatomical appearance and findings of brain structure are central in the identification of healthy brain parenchyma. However, in the living individual, the best that currently can be achieved is a macroscopic view of brain parenchyma. While investigators who use diffusion MR techniques, like diffusion tensor imaging (DTI) like to imply "microstructural" pathology, but with the macroscopic scale of contemporary neuroimaging being limited to acquisition parameters that typically assess tissue at the millimeter level, means that anything more molecular, must be inferred. Nonetheless, what does it mean if there is even a 1 mm × 1 mm × 1 mm voxel difference observed? First, neuroimaging analyses examining the entire brain typically would not consider a single, isolated 1 mm^3 voxel as a significant finding, if it were the only finding in all of the analyses. Commonly, a priori established neuroimaging cluster thresholds to be significant involve multiple voxels in a neuroimaging investigation prior to the actual study being conducted (Chumbley et al., 2010). Nonetheless, it is still instructive to consider what is present in a cubic millimeter of tissue. Based on the computational modelling of the mouse brain by Braitenberg (2001), Mills and Tamnes (2014) estimate that one cubic millimeter of gray matter is proportionally comprised of the following: 30% axons, 30% dendrites, 12% dendritic spines, 14% cell bodies and blood vessels, 9% glial cells and 5% extracellular space. Translating this into something more relevant in understanding concussion, Insel and Landis (2013) estimate that within a single cubic millimeter of cortical gray matter there are approximately 80,000 neurons and 4.5 million synapses. As demonstrated in cases of focal epilepsy, lesions that constitute no more than few millimeters of abnormal tissue, strategically placed, may be the source of widespread network disruption (Jackson et al., 2017). Additionally, modelling of small foci of abnormal electrophysiological activity can be very disruptive to otherwise healthy brain networks (Izhikevich and Edelman, 2008; Omidvarnia et al., 2017).

Furthermore, as reflected in the estimates by Mills and Tamnes any MR-defined abnormality detected at the macroscopic level is likely to influence multiple cellular and vascular components, so it is not just affecting neurons. In TBI, white matter is also differentially injured due to its elasticity and deformation characteristics that diverge from gray matter as well as the fact that some white matter tracts have many crossing fibers or bend at different points in their trajectory from origin to terminus (Schmidt et al., 2016; Wright et al., 2017). So where the lesion/abnormality is defined, regardless of its size, may have particular important for sequelae that may emerge. What this means in SRC is that the angle or angles in which the head is struck, or the direction of acceleration/deceleration injury creates unique shear-strain dynamics for each concussion and no uniform area that is consistently injured in every case.

2. Brain anatomy relevant to brain injury

Understanding the neuroanatomical outcomes that may accompany sport-related brain injuries, begins with understanding that TBI occurs as a result of brain deformation. As stated in the consensus definition from the 'International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health' TBI is defined as follows:

> TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force (Menon et al., 2010, p. 1637).

That the causal event inducing a TBI occurs as a result of an "external force" means that a threshold has to be surpassed to induce sufficient parenchymal deformation to induce brain injury, where tissue deforms beyond its tolerance to maintain physiological and structural integrity.