Not TRAUMATIC BRAIN INJURY

"Concussion" is not a true diagnosis, but soon could be

Douglas H. Smith[1,†] and William Stewart[1,2,3]

[1]Center for Brain Injury and Repair and Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA, USA
[2]Department of Neuropathology, Queen Elizabeth University Hospital, Glasgow, UK
[3]Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK

[†]email: smithdou@pennmedicine.upenn.edu

In current usage 'concussion' describes a clinical presentation, but does not identify the underlying pathological process and therefore cannot be considered a true diagnosis. However, mounting evidence indicates diffuse axonal injury as a likely pathological substrate for concussion, thereby providing a framework to develop true diagnostic criteria.

Although more than two million individuals experience a concussion in the U.S. each year[1], the condition has only burst into the spotlight in the past decade, with numerous headline news stories and even a Hollywood film. Concussion is often regarded as a form of mild traumatic brain injury (TBI); however, there is nothing 'mild' about this condition for many individuals. Indeed, more than 15% of individuals with concussion go on to experience persisting neurocognitive dysfunction[2]. Furthermore, a history of exposure to multiple concussions and head impacts, for example through participation in contact sports, has been linked to an increased risk of a number of neurodegenerative conditions[3], including chronic traumatic encephalopathy[3].

The Oxford English Dictionary defines diagnosis as "the identification of the nature of an illness or other problem by examination of the symptoms". Therefore, as the current concept of 'concussion' does not encompass the "nature" of the illness with respect to an underlying pathological process, concussion should not be considered a true diagnosis. Indeed, the current, purely descriptive, use of the term concussion is arguably no more sophisticated than the old use of the term 'consumption' to describe the once mysterious condition that we now know to be caused by *mycobacterium tuberculosis*. Nonetheless, mounting evidence suggests

that the symptoms of concussion reflect structural and physiological disruption of brain networks. In particular, mechanical damage to axons throughout the white matter, known as diffuse axonal injury (DAI), is increasingly acknowledged as a primary contributor to both the short-term and long-term clinical manifestations of concussion[4,5]. Therefore, the time is right to acknowledge the contribution of this pathology in order to improve approaches to concussion diagnosis and management.

DAI was first observed over 60 years ago when varicose swellings along white matter axons were detected in post-mortem brain tissue from individuals with moderate and severe TBI[4,5]. Subsequently, the unique biomechanical origin of DAI was revealed by use of preclinical models of TBI, in which immediate loss of consciousness and persisting coma were shown to be dependent on the rapid deformation of brain tissue caused by rotational acceleration of the head[4,5]. In these models, injury severity and the durations of loss of consciousness and coma directly correlated with the extent of axonal pathology identified in tissue preparations. Given that similar, albeit milder, biomechanical forces have been implicated in the induction of concussion, interest in examining the presence and importance of DAI in this condition has been rapidly growing.

In 1994, post-mortem examination of the brains of five mostly elderly individuals who died shortly after a concussion, but from other causes, revealed surprisingly extensive axonal pathology throughout the white matter in the absence of other neuropathological changes[6]. More recently, DAI was identified as the predominant pathology in a pig model of head rotational acceleration that was designed to mimic the biomechanics of human concussion[4,5]. Importantly, in this model, immediate loss of consciousness was associated with the presence of axonal pathology in the brainstem.

Under the unique mechanical loading conditions of concussion, axons have been found to be selectively vulnerable to damage owing, in part, to their highly anisotropic organization and viscoelastic properties. During normal daily activities, axons tolerate stretching of up to twice their resting length; however, under the rapid or ‘dynamic’ deformation caused by rotational acceleration (Fig. 1a, adapted with permission[5]), the axon becomes stiffer and more brittle, making it more prone to injury[4,5]. This high rate of stretching results in immediate mechanical damage to the axonal cytoskeleton, loss of ionic homeostasis and metabolic crisis[4,5]. In turn, axonal transport is interrupted, leading to accumulation of proteins in swellings, which is

followed by proteolysis and, eventually, axonal degeneration[4,5,7] (Fig. 1b, adapted with permission[7]). However, even in severe TBI, this pathological sequence affects only a minority of axons[4]. The remainder continue to look structurally normal, but might nonetheless be dysfunctional. This collective axonal dysfunction can induce immediate and persisting disruption of signaling across brain networks, resulting in loss of consciousness and/or alterations in cognitive status, such as decreased processing speed[2].

Perhaps the most extensive body of evidence supporting DAI as a key substrate of concussion is from advanced neuroimaging studies. The microscopic nature of the axonal swellings renders DAI nearly invisible to conventional brain imaging examinations. However, in a small proportion of individuals with concussion, subtle white matter changes can be observed with standard MRI, leading to a tentative diagnosis of DAI[4,5]. These observations precipitated extensive efforts to use enhanced neuroimaging to identify this otherwise 'stealth' pathology. For over 20 years, multiple advanced MRI techniques, such as diffusion tensor imaging, have consistently identified white matter changes after concussion in animal models[4,5] and in humans[8]. For the former, histopathological examination indicated that these MRI signal changes corresponded with regions of axonal pathology[4]. However, despite so many years of success and refinement, none of these advanced neuroimaging techniques have been included in routine assessment of patients with suspected concussion, owing, in part, to the highly sophisticated nature of the techniques, the length of time needed for image processing and the difficulty in calibration between MRI scanners.

Blood biomarker studies have also implicated DAI as an underlying pathology in concussion. Specifically, the blood concentrations of axonal proteins — including calpain-cleaved αII-spectrin N-terminal fragment (SNTF) and the microtubule-associated proteins tau and neurofilament light chain — were higher in samples from individuals with symptoms of concussion than in pre-injury samples or samples from healthy individuals[9,10]. In another study, elevated SNTF levels measured in plasma samples taken within 24h of injury identified a subset of concussion patients with persisting neurocognitive dysfunction when assessed at 3 months[9,10]. Of note, histology studies in moderate to severe TBI in humans and in mild TBI in swine have now identified damaged axons as the source of this SNTF, tau and neurofilament light[10]. Thus, the identification of axonal proteins in the serum serves as a marker of axon lysis and degeneration. As damaged axons in the brain do not regenerate, these observations indicate that permanent brain damage occurs in some individuals with concussion. These

findings also raise the likelihood that concussion involves a range of axonal pathophysiology, including reversible changes (such as ionic imbalance), the presence of intact but dysfunctional axons, and axon degeneration, which might be associated with persisting and potentially progressive symptoms.

The identification of *mycobacterium tuberculosis* in the late 19th century revealed the source of 'consumption' and led to a true diagnostic entity and, eventually, treatment. In much the same way, now is the time for the term 'concussion' to embody the nature of the disorder. This improvement is now possible as a result of the progress made in the past decade, from characterization of the pathological processes underlying the injury through to advances in diagnostic neuroimaging and blood biomarker studies. Ideally, this new approach to diagnosis will include broad implementation of non-invasive techniques to identify individuals at risk of persisting neurocognitive dysfunction, thus improving clinical management and providing a rational basis for selective enrollment in clinical trials. Furthermore, advanced imaging and fluid biomarker approaches will be important to follow potential long-term changes that might lead to neurodegenerative disorders like chronic traumatic encephalopathy, which could be driven by progressive axonal pathology[4,5]. We anticipate that other pathological processes, such as disruption of the blood–brain barrier and inflammation[4], will be shown to have a role in concussion symptoms; however, for now, objective identification of degenerative DAI and its aftermath can provide a framework for operational diagnostic criteria that can be refined over time. Indeed, based on the rate of development, we anticipate that blood biomarker techniques that identify degenerative DAI will be ready for broad application in the near future. Therefore, now is the time to transform the diagnosis of concussion.

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Competing interests

The authors declare no competing interests.

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Figure 1: Diffuse axonal injury in concussion a | The principal mechanical trigger of traumatic brain injury is head rotational acceleration, which induces dynamic deformation of brain tissue. **b |** Axonal microtubules (blue and red) are ruptured at the moment of head impact, leading to interruption of protein transport, accumulation of cargos proteins (green) and the development of periodic varicose swelling along white matter axons. Part a adapted from ref[5], part b adapted from ref[7].