



University  
of Glasgow

Smith, D. H., and Stewart, W. (2016) Tackling concussion, beyond Hollywood.  
Lancet Neurology, 15(7), pp. 662-663.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/120289/>

Deposited on: 8 August 2016

Enlighten – Research publications by members of the University of Glasgow  
<http://eprints.gla.ac.uk>

## Tackling Concussion, Beyond the Movie

Douglas H. Smith<sup>1</sup>, William Stewart<sup>1,2,3</sup>

1. Penn Center for Brain Injury and Repair and Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA 19104, USA
2. Department of Neuropathology, Queen Elizabeth University Hospital, Glasgow G51 4TF, UK
3. Institute of Neuroscience and Psychology, University of Glasgow, Glasgow G12 8QQ, UK

**Corresponding Author:** Dr William Stewart, MBChB, Ph.D, FRCPath.  
Department of Neuropathology  
Queen Elizabeth University Hospital  
1345 Govan Rd  
Glasgow G51 4TF, UK.

Email: William.Stewart@glasgow.ac.uk  
Tel: +44 (0)141 354 9535

When Hollywood tackles a medical issue, such as in the movie “Concussion”<sup>1</sup>, it is worth pausing to consider the issue at question. In practice, the terms concussion and mild traumatic brain injury (mTBI) are used interchangeably. However, for the 20% or so of patients demonstrating persisting neurocognitive dysfunction after concussion, there is nothing “mild” about it. Furthermore, a history of multiple concussions is linked to increased risk of neurodegenerative disease, in particular, chronic traumatic encephalopathy (CTE)<sup>2</sup>; the subject of “Concussion”. Nevertheless, despite Hollywood movies and endless news headlines, there remains remarkable confusion over the underlying cause of concussion.

Contrary to the all too common animations illustrating the brain slamming back and forth inside the skull, the principal mechanical basis of concussion is head rotational acceleration<sup>3</sup>. A consequence of these rotational forces is rapid deformation of the brain resulting in tissue damage, particularly to vulnerable white matter axons. During normal movement, axons can stretch to at least twice their resting length and relax back, unharmed. However, very rapid stretching, such as occurs with concussion, results in components of the axon becoming stiffer, resulting in breakage of axonal microtubules; a pathology known as diffuse axonal injury (DAI). Intriguingly, computational modeling suggests that the viscoelastic “Achilles’ heel” in axons is the microtubule stabilizing protein tau<sup>4</sup>.

A consequence of this microtubule damage is interruption of normal axonal transport, leading to protein accumulation in axonal swellings at sites of injury. However, although axonal swelling is evidence of DAI, the vast majority of injured axons appear morphologically normal after TBI, even in severe cases. Nevertheless, for many of these normal-appearing axons there is dysregulation of sodium channels resulting in impaired action potential formation; a potential physiological substrate for the common symptoms of concussion, such as decreased processing speed, memory disturbance and loss of consciousness. Accompanying this sodium

influx is an increase in intra-axonal calcium, leading to activation of proteases and inevitable axonal degeneration<sup>5</sup>. As such, the so called “mild” injury of concussion can result in permanent axonal loss.

The script for “Concussion”<sup>1</sup> has the hero, Dr Omalu (played by Will Smith), proclaiming “I have found a disease that no one has ever seen.” The reality is that CTE had been recognized for many decades before being “discovered” in former American Footballers. In these earlier accounts, largely in former boxers, neuropathology examinations at autopsy described a range of abnormalities in tau and amyloid-beta contributing to “dementia puglistica”, or CTE<sup>2</sup>. Interestingly, accumulation of amyloid precursor protein (APP) in injured axons triggers amyloid-beta genesis. Further, axonal tau protein can become phosphorylated after TBI, leading to pathological aggregation. Thus, DAI-associated proteins, namely tau and APP, are implicated in both the acute injury of concussion and also the late neurodegeneration of chronic traumatic encephalopathy.

In truth, despite the Hollywood attention and increasing hyperbole regarding concussion and its long-term consequences, there remain remarkable knowledge gaps. Most notably, we are really only at the beginning of deciphering the underlying causes, one important candidate being DAI.

Supported by NIH grants, NS38104 and NS092389, NS056202, and DOD grant, PT110785.

## References

- 1 Landesman, L. Concussion. *Columbia Pictures* 2015.  
<http://www.sonypictures.com/movies/concussion/>
- 2 Smith DH, Johnson VE, Stewart W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat Rev Neurol* 2013; **9**: 211-21
- 3 Gennarelli TA, Thibault LE, Adams JH, Graham DI, Thompson CJ, Marcincin RP. Diffuse axonal injury and traumatic coma in the primate. *Ann Neurol* 1982; **12**: 564–74
- 4 Ahmadzadeh H, Smith DH, Shenoy VB. Viscoelasticity of tau proteins leads to strain rate-dependent breaking of microtubules during axonal stretch injury: predictions from a mathematical model. *Biophys J* 2014; **106**: 1123-33
- 5 Johnson, VE, Stewart, W, Weber, MT, Cullen, DK, Siman, R, Smith, DH. SNTF immunostaining reveals previously undetected axonal pathology in traumatic brain injury. *Acta Neuropathol* 2015; DOI 10.1007/s00401-015-1506-0