Received Date : 18-Jul-2016

Accepted Date : 18-Jul-2016

Article type : Featured Paper Commentary

Invited Commentary for Mychasiuk et al., EJM-2016-03-23472:

Challenging the dogma that 'rest is best' after concussion

Bridgette D. Semple, Ph.D.

Department of Medicine (Royal Melbourne Hospital)

The University of Melbourne

Level 1, Melbourne Brain Centre

Royal Parade, Parkville VIC 3050, Australia

Phone: +61 3 8344 4108

Email: Bridgette.Semple@unimelb.edu.au

Number of words: 757

Keywords: concussion, mild traumatic brain injury, rats, animal models, return-to-play, management guidelines, exercise, rehabilitation, voluntary, motor recovery, cognition.

Clinical management of concussions or mild traumatic brain injuries (mTBI) is currently guided by expert-derived consensus statements (Giza *et al.*, 2013; McCrory *et al.*, 2013; Graham *et al.*, 2014). At present, concussed patients are advised to undergo an initial post-injury period of physical and cognitive rest, until asymptomatic at rest and able to return to maximal exercise without symptom exacerbation. This conservative standard of care is in line with the Latin concept of *primum non nocere*, or 'first, do no harm,' and has been widely accepted particularly for brain injuries in children and adolescents, who may be more susceptible to the potential lasting consequences of concussion (Graham *et al.*, 2014). However,

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ejm.13346](https://doi.org/10.1111/ejm.13346)

This article is protected by copyright. All rights reserved

such guidelines have been constructed in the absence of solid empirical evidence (Schneider *et al.*, 2013). As a result, what exactly constitutes optimal management of a concussion remains unclear, including whether rest is the best approach, or whether active rehabilitation may provide greater therapeutic benefit.

In this issue, Mychasiuk *et al* (*in press*) present preclinical evidence that early voluntary exercise after mTBI is not detrimental, and indeed, appears to promote rehabilitation. Using a clinically-relevant model of concussion incorporating impact-acceleration and rotational forces in the juvenile rat, the authors examined the effect of voluntary exercise on post-concussive behaviors and gene expression changes. Access to voluntary running wheels was provided to mTBI rats either immediately after injury, or after a delay of 3 or 7 days, and compared to mTBI rats without wheel access as well as those deprived of both exercise and peer-to-peer social interactions. In general, access to voluntary exercise at any time post-injury was found to be beneficial, ameliorating motor and cognitive impairments and restoring the aberrant post-injury expression of genes involved in mitochondrial bioenergetics, growth factors and DNA degradation. Rats deprived of peer social activity also performed poorly on functional outcome measures, comparable to those without voluntary exercise.

This timely study challenges the widely-accepted but inadequately supported concept that rest is necessary for brain recovery after injury. Indeed, others have previously suggested that a prolonged period of rest after injury may exacerbate secondary symptoms such as fatigue, depression, and physiological de-conditioning (Silverberg & Iverson, 2013; Thomas *et al.*, 2015; DiFazio *et al.*, 2016). In contrast, although the focus has primarily been on patients with persistent post-concussive symptoms, preliminary clinical studies have demonstrated that sub-symptom threshold aerobic exercise during the sub-acute post-injury phase is both safe and may enhance recovery (Majerske *et al.*, 2008; Gagnon *et al.*, 2009; Leddy *et al.*, 2010; Kurowski *et al.*, 2016). Of note, after moderate-to-severe TBI, both physical and cognitive rehabilitation are considered integral to promoting recovery (Fogelman & Zafonte, 2012), and targeted rehabilitation of vestibular dysfunction after sports-related injuries have also yielded positive outcomes (McCrory *et al.*, 2013; Schneider *et al.*, 2014).

How exercise rehabilitation could be implemented in concussed patients prior to symptom resolution, as modeled in the study by Mychasiuk and colleagues, is likely to be controversial. Epidemiological evidence suggests that early activity after a concussion can exacerbate symptoms, prolong neurocognitive recovery, and increase vulnerability of the brain to a recurrent concussion [see review by (Semple *et al.*, 2015)]. From a pathophysiological perspective, both preclinical and clinical studies have demonstrated a window of increased susceptibility to impaired cellular metabolism acutely after a mTBI (Vagnozzi *et al.*,

2008; Prins *et al.*, 2013). Future studies are needed to dissect the influence of pre-injury versus post-injury exposure to voluntary exercise, as pre-training may explain the neuroprotective effects observed in the current study, in comparison to previous findings that delayed but not acute onset post-injury exercise was most beneficial (Griesbach *et al.*, 2004). Further, the physiological and chronic effects of acute exercise rehabilitation after concussion must be carefully monitored, as compromised cardiac and temperature autonomic regulation have been reported during exercise within the first two weeks after mTBI (Griesbach *et al.*, 2013; 2014). Lastly, sex-specific effects of mTBI as observed in the current study support the growing concept that outcomes are influenced by a range of factors including sex, age, and pre-existing health status, such that the timing of return-to-play/learn should ultimately be individually tailored.

In summary, the study by Mychasiuk and colleagues adds to increasing evidence that complete abstinence of physical and cognitive activity may be unnecessary and in fact hinder optimal recovery after concussion (Silverberg & Iverson, 2013; Leddy *et al.*, 2016). High quality, randomized controlled trials are needed to guide the resumption of activity after concussions in adults and children. Future studies to investigate the optimal timing and efficacy of voluntary, sub-threshold exercise and cognitive activity are warranted.

References:

- DiFazio, M., Silverberg, N.D., Kirkwood, M.W., Bernier, R. & Iverson, G.L. (2016) Prolonged Activity Restriction After Concussion: Are We Worsening Outcomes? *Clinical pediatrics*, **55**, 443-451.
- Fogelman, D. & Zafonte, R. (2012) Exercise to enhance neurocognitive function after traumatic brain injury. *Pm R*, **4**, 908-913.
- Gagnon, I., Galli, C., Friedman, D., Grilli, L. & Iverson, G.L. (2009) Active rehabilitation for children who are slow to recover following sport-related concussion. *Brain Injury*, **23**, 956-964.
- Giza, C.C., Kutcher, J.S., Ashwal, S., Barth, J., Getchius, T.S., Gioia, G.A., Gronseth, G.S., Guskiewicz, K., Mandel, S., Manley, G., McKeag, D.B., Thurman, D.J. & Zafonte, R. (2013) Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of

the Guideline Development Subcommittee of the American Academy of Neurology. *Neurol*, **80**, 2250-2257.

- Graham, R., Rivara, F.P., Ford, M.A. & Spicer, C.M. (2014) Sports-related concussions in youth: Improving the science, changing the culture *Institute of Medicine and National Research Council* The National Academies Press, Washington DC.
- Griesbach, G.S., Gomez-Pinilla, F. & Hovda, D.A. (2004) The upregulation of plasticity-related proteins following TBI is disrupted with acute voluntary exercise. *Brain Res*, **6**, 154-162.
- Griesbach, G.S., Tio, D.L., Nair, S. & Hovda, D.A. (2013) Temperature and heart rate responses to exercise following mild traumatic brain injury. *J Neurotrauma*, **30**, 281-291.
- Griesbach, G.S., Tio, D.L., Nair, S. & Hovda, D.A. (2014) Recovery of stress response coincides with responsiveness to voluntary exercise after traumatic brain injury. *J Neurotrauma*, **31**, 674-682.
- Kurowski, B.G., Hugentobler, J., Quatman-Yates, C., Taylor, J., Gubanich, P.J., Altaye, M. & Wade, S.L. (2016) Aerobic Exercise for Adolescents With Prolonged Symptoms After Mild Traumatic Brain Injury: An Exploratory Randomized Clinical Trial. *The Journal of head trauma rehabilitation*.
- Leddy, J.J., Baker, J.G. & Willer, B. (2016) Active Rehabilitation of Concussion and Post-concussion Syndrome. *Physical medicine and rehabilitation clinics of North America*, **27**, 437-454.
- Leddy, J.J., Kozłowski, D.A., Donnelly, J.P., Pendergast, D.R., Epstein, L.H. & Willer, B. (2010) A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. *Clin J Sport Med*, **20**, 21-27.
- Majerske, C.W., Mihalik, J.P., Ren, D., Collins, M.W., Reddy, C.C., Lovell, M.R. & Wagner, A.K. (2008) Concussion in sports: postconcussive activity levels, symptoms, and neurocognitive performance. *J Athl Train*, **43**, 265-274.
- McCrory, P., Meeuwisse, W., Aubry, M., Cantu, B., Dvorak, J., Echemendia, R.J. & Engebretsen, L.e.a. (2013) Consensus Statement on Concussion in Sport-the 4th International Conference on Concussion in Sport Held in Zurich, November 2012. *Clin J Sport Med*, **23**, 89-117.

- Prins, M.L., Alexander, D., Giza, C.C. & Hovda, D.A. (2013) Repeated mild traumatic brain injury: mechanisms of cerebral vulnerability. *J Neurotrauma*, **30**, 30-38.
- Schneider, K.J., Iverson, G.L., Emery, C.A., McCrory, P., Herring, S.A. & Meeuwisse, W.H. (2013) The effects of rest and treatment following sport-related concussion: a systematic review of the literature. *Br J Sports Med*, **47**, 304-307.
- Schneider, K.J., Meeuwisse, W.H., Nettel-Aguirre, A., Barlow, K., Boyd, L., Kang, J. & Emery, C.A. (2014) Cervicovestibular rehabilitation in sport-related concussion: a randomised controlled trial. *Br J Sports Med*, **22**, 2013-093267.
- Semple, B.D., Lee, S., Sadjadi, R., Fritz, N., Carlson, J., Griep, C., Ho, V., Jang, P., Lamb, A., Popolizio, B., Saini, S., Bazarian, J.J., Prins, M.L., Ferriero, D.M., Basso, D.M. & Noble-Haeusslein, L.J. (2015) Repetitive concussions in adolescent athletes - translating clinical and experimental research into perspectives on rehabilitation strategies. *Front Neurol*, **6**, 69.
- Silverberg, N.D. & Iverson, G.L. (2013) Is rest after concussion "the best medicine?": recommendations for activity resumption following concussion in athletes, civilians, and military service members. *The Journal of head trauma rehabilitation*, **28**, 250-259.
- Thomas, D.G., Apps, J.N., Hoffmann, R.G., McCrea, M. & Hammeke, T. (2015) Benefits of strict rest after acute concussion: a randomized controlled trial. *Pediatrics*, **135**, 213-223.
- Vagnozzi, R., Signoretti, S., Tavazzi, B., Floris, R., Ludovici, A., Marziali, S., Tarascio, G., Amorini, A.M., Di Pietro, V., Delfini, R. & Lazzarino, G. (2008) Temporal window of metabolic brain vulnerability to concussion: a pilot 1H-magnetic resonance spectroscopic study in concussed athletes--part III. *Neurosurgery*, **62**, 1286-1295.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Semple, BD

Title:

Challenging the dogma that 'rest is best' after concussion (Commentary on Mychasiuk et al.).

Date:

2016-10

Citation:

Semple, B. D. (2016). Challenging the dogma that 'rest is best' after concussion (Commentary on Mychasiuk et al.). Eur J Neurosci, 44 (7), pp.2405-2406. <https://doi.org/10.1111/ejn.13346>.

Persistent Link:

<http://hdl.handle.net/11343/291612>