Clinical Pediatrics
1–9

DOI: 10.1177/0009922815589914
cpj.sagepub.com
SAGE

Prolonged Activity Restriction After Concussion: Are We Worsening Outcomes?

Marc DiFazio, MD[1], Noah D. Silverberg, PhD[2,3], Michael W. Kirkwood, PhD[4,5], Raquel Bernier, MD[1], and Grant L. Iverson, PhD[6,7,8,9]

Abstract

The current treatment of concussion or mild traumatic brain injury (mTBI) is primarily based on expert consensus. Most clinical practice guidelines advise cognitive and physical rest after injury including withdrawal from normal life activities such as school attendance, sports participation, and technology use until symptoms resolve. Some individuals who sustain an mTBI experience persistent physical, cognitive, and mental health problems. Activity restriction itself may contribute to protracted recovery and other complications. Williamson's Activity Restriction Model of Depression, formulated more than 20 years ago, is central to this hypothesis. We review research evidence for potential harms of prolonged activity restriction and report an mTBI case as an example of how an "activity restriction cascade" can unfold. According to this model, psychological consequences of removal from validating life activities, combined with physical deconditioning, contribute to the development and persistence of postconcussive symptoms after mTBI in some youth. A modification to mTBI guidelines that emphasizes prompt reengagement in life activities as tolerated is encouraged.

Keywords

concussion, mTBI, activity restriction, rest, rehabilitation, treatment

Introduction

Concussion, or mild traumatic brain injury (mTBI), is a common injury. At least 3 million cases are reported in the United States every year.[1] Recent increased media attention has raised awareness among youth, parents, coaches, and school personnel, and the injured are now encouraged and even mandated to seek medical attention.[2] Concussion therefore represents a major public health concern, with growing expenditures related to acute care, education, and management.[3] Fortunately, the majority of individuals recover swiftly.[4-8] Parental fears about concussion may be a contributing factor to decreased rates of participation in youth wrestling.[9] The President of the United States has even weighed in, indicating that "I would not let my son play football."[10]

One of the most widely implemented interventions for concussion is prescribed physical and cognitive rest, perhaps as an outcome of large-scale multimedia campaigns to disseminate expert consensus guidelines that advocate rest.[10,11] The rationale draws from the basic science findings with animal models that (*a*) the brain is in a state of neurometabolic crisis following injury,[12-14] (*b*) a second injury during recovery can result in magnified pathophysiology and behavioral deficits,[15-17] and (*c*) animals that are allowed to exercise too soon after injury do not show the expected exercise-induced increases in molecular markers of neuroplasticity.[18-21] A period of rest, then, is hypothesized to facilitate dynamic restoration of the acute neurometabolic disturbance following injury and prevent harms associated with excessive neurometabolic demand.

[1]Children's National Health System, Washington, DC, USA
[2]University of British Columbia, Vancouver, British Columbia, Canada
[3]GF Strong Rehab Centre, Vancouver, British Columbia, Canada
[4]University of Colorado School of Medicine, Aurora, CO, USA
[5]Children's Hospital Colorado, Aurora, CO, USA
[6]Harvard Medical School, Boston, MA, USA
[7]Spaulding Rehabilitation Hospital, Boston, MA, USA
[8]MassGeneral Hospital for Children, Boston, MA, USA
[9]Defense and Veterans Brain Injury Center, Bethesda, MD, USA

Corresponding Author:
Marc DiFazio, 9850 Key West Ave, Rockville, MD 20850, USA.
Email: mdifazio@childrensnational.org

As part of a concussion management strategy, youth are frequently removed from sports and physical activity and instructed to avoid activities that are perceived as cognitively demanding like schoolwork, cellular phone use, and videomatchs.[22] In our experience from different regions of the United States and Canada, primary care providers sometimes discourage exercise and cognitively challenging activities for weeks, months, or even longer, especially in children. Although well-intentioned, we believe that in many cases prolonged rest may do more harm than good, and as with other interventions, the potential benefits of prescribing long-term rest or withdrawal from activities should be weighed against the potential harms. This is our central thesis. The present article briefly reviews the basis for prescribing rest followed by a discussion of the challenges in implementing this intervention, as well as its potential for negatively impacting recovery from concussion. Negative consequences of prolonged activity restriction are discussed, and the rationale for supporting an active recovery from concussion is provided.

Case

ME was a physically and psychologically healthy youth until the winter of his second year of high school. While wrestling, he was injured when another player elbowed him in the head. He was able to finish the match, but afterwards experienced a nondebilitating headache. He reported this symptom to an athletic trainer a day later, and because of concerns regarding concussion, he was told to restrict his activity, both physically and cognitively. He was kept home from school for 2 weeks, and not allowed to participate in any wrestling, a sport he had played since childhood. (In fact, he was intending to transfer schools to improve his chances of participating at the collegiate level.) He was seen at a concussion clinic, and recommendations were made for a partial return to school with accommodations. Although exercise was allowed, he was instructed to immediately stop exercising if he experienced any of a long list of "postconcussive" symptoms that were delineated in a handout given to the family. His mood declined and he missed weeks of school. When he finally attempted to return to play several months after his initial injury, he experienced mild headache and dizziness during vigorous exercise. These symptoms were assumed to be directly attributable to his concussion, and he was told once again to stop exercising. On transferring schools, accommodations to allow for breaks and absences if necessary were put in place, and he was restricted from wrestling. After 2 weeks at the new school, his mother indicated that he was transferring back to his previous school, and he would not be wrestling again because of concerns about the risk of future concussive injury.

The case of ME demonstrates the sequence of events that some individuals who have persistent symptoms after a concussion may experience. Virtually all of ME's symptomatology, including headaches, dizziness, stress, and depressive difficulties, were consistently attributed to ongoing manifestations of concussion. In his case, we believe that the clinical management itself, including the implied messaging regarding the dangers of exertion, almost certainly contributed to his poor functional outcome.

The Evolution of Rest in Clinical Management Guidelines for mTBI

Expert opinion on the role of rest in the clinical management of traumatic brain injury has varied greatly over the past century. Early advocacy for rest in the 1920/1930s[23,24] seems to have been countered with skepticism by the 1950s, when several authors cautioned of the potential psychological[25] and physiological[26] harmful effects of prolonged rest. However, the first Consensus Statement on Concussion in Sport introduced "no activity, complete rest" as the initial step toward return to play following sport-related concussion.[27] This was recommended to continue until the athlete's symptoms resolved. The rest until asymptomatic guideline was endorsed in the next 2 iterations of the Consensus Statement on Concussion in Sport (2005, 2009). The authors of the fourth edition Consensus Statement[28] acknowledged that the evidence base for the efficacy of rest is "sparse" and the benefits of resting for more than 48 hours postinjury require further study. They add, however, that "it is appropriate to extend the amount of time of asymptomatic rest" for children. Recommendations for prolonged rest persist elsewhere. For example, DeMatteo et al[22] recently adapted return to activity guidelines specifically for children and suggested extending the period of asymptomatic rest. Primarily citing published expert opinions, this team created a protocol that involves resting until asymptomatic and then encouraging an additional week before allowing activity reengagement. A parallel return to school guideline[29] similarly advises no school attendance until the child is symptom free or after 4 weeks of persistent symptoms with physician clearance.

Empirical Evidence for Rest After mTBI

In the 1950s, Andreassen et al[30] experimented with early mobilization after mTBI in adults and reported better clinical outcomes in comparison to previous cohorts that

had enforced rest for 2 to 3 weeks. The first randomized clinical trial involved adults who presented to an emergency department with mTBI.[31] Six days of prescribed bed rest had no durable benefit over graded mobilization starting the day after injury. At follow-up, the (nonsignificant) trend favored the early mobilization group despite differential dropout that should have favored the bed rest group.[31] Three observational and pre–post studies have provided mixed evidence for the benefits of time-limited prescribed rest for adolescents and young adults who sustain a sport-related concussion.[32-34] Thomas and colleagues[35] recently published the first randomized controlled trial of rest following mTBI in adolescents. They randomized patients presenting to an emergency department to 5 days of strict rest versus usual care that consisted of 1 or 2 days of rest followed by gradual return to activity. The strict rest condition did not result in better symptom, cognitive, or balance outcomes at 3 or 10 days following injury. Unexpectedly, adolescents and young adults in the strict rest condition actually reported more postconcussive symptoms over the course of the study. In summary, the most methodologically rigorous studies to date have not demonstrated benefit of an initial period of 5 to 6 days of complete rest over an earlier return to activity. A systematic review came to a similar conclusion.[36]

Practical Challenges to Implementing Rest

Defining What "Rest" Is. Although rest is widely prescribed following mTBI, it has never been well defined and the consistency of definitions across studies and clinical practice guidelines is poor.[22,28,33-35] Some authors list specific activities to be avoided (eg, sports, homework, household chores, outings, phone use, playing a musical instrument, and drawing/artwork[34]), while others simply caution against physical and mental exertion. Anecdotally, we find that parents and certain health care providers believe that "if some rest is good, more is better" and so encourage even stricter or prolonged rest than is advised in practice guidelines. Importantly, there appears to be universal agreement that rest means withdrawal from usual preinjury life activities including academic, social, recreational, and athletic.

Complying With Prescribed Rest. Monitoring withdrawal from daily activities is challenging and typically relies on self-report of compliance. Adherence to prescribed rest in intervention studies is also incomplete.[33,35] That is, even when children and their parents are aware that compliance is being measured for a research study, they have difficulty complying with recommendations for strict rest.

Activity Restriction Does Not Keep the Brain at Rest. The presumptive rationale for the recommendation to avoid cognitive and physical activities is to lessen metabolic demand in the brain to allow healing to occur. This is based on the premise rest can minimize neurometabolic activity. In practice, it is difficult to "turn off" brain activity. Even when subjects are instructed to lay supine with their eyes closed and not think of anything in particular, functional magnetic resonance imaging reveals coordinated brain activity.[37] Although experienced meditators can volitionally reduce their brain activity,[38] the most apparent effects of meditation in novice subjects is an altered pattern of regional brain activation.[39,40] A related concern after mTBI is that cognitively demanding tasks will increase brain activation and that this brain activation is harmful. We could not find studies suggesting that thinking, reading, or studying cause neurometabolic demands or changes in the brain that could be harmful. With regard to exercise, some rodent studies illustrate that vigorous exercise (ie, running on a wheel) in the initial days following fluid percussion injury to the brain is associated with a suppression of neuromolecular markers of neuroplasticity and impaired learning.[18-21] However, translating these animal model findings into a recommendation for how long a human should rest and avoid exercise is difficult.

Determining When Rest Should End. Most recommendations for rest suggest that the period of activity restriction should only end when an individual is no longer symptomatic from the concussion. To our knowledge, there are no published studies illustrating that this practice leads to better clinical outcomes. In fact, in a large prospective sport-related concussion study examining athletes required to be symptom-free before returning to play and athletes who did not engage in a symptom-free waiting period, no differences were found for any clinical outcome including risk of reinjury, symptom duration, cognitive functioning, or postural stability.[41] Several authors have also recently highlighted the feasibility of being able to precisely determine when a patient has truly become "asymptomatic."[42-44] A major source of the challenge is that postconcussion-like symptoms are nonspecific. They occur often in healthy people and are affected by daily stress.[45-49] Symptoms following pediatric mTBI are also associated with multiple other factors unrelated to injury including the existence of premorbid symptoms,[50] premorbid learning and behavioral problems,[51,52] demographic factors,[50] maladaptive coping,[53] comorbid bodily injury and pain,[54] and parental anxiety and family stress.[55,56] Thus, some postinjury complaints are apt to be misattributed to persistent neurobiological effects of the injury and used as the rationale for ongoing activity restriction.

Possible Harmful Effects of Rest

Possible Harm #1: Anxiety, Expectations, and the Nocebo Effect. Craton N, Leslie O.[43(p203)] rather dramatically point out that "being told to stay home and that a text message may damage your brain must be quite alarming to patients." In addition to provoking anxiety in children and/or parents, expectations may influence the experience of postconcussion symptoms.[57] The "nocebo" effect (conceptualized as the causation of sickness by the expectations of sickness and by associated hyperarousal) appears to be a significant component of prolonged symptoms after concussion in some people.[58] If an individual views concussion as a serious injury that will produce lasting effects, it may in fact create or exacerbate the experience of symptoms after an injury. Indeed, there is strong evidence from adult studies that expecting a lengthy recovery may prolong actual recovery from mTBI.[59-61]

Possible Harm #2: Depression and Other Psychological Complications. Absent from much of the recent concussion literature (with notable exceptions, see Silverberg and Iverson[44]) is a consideration of the psychological impact of removal from normal life circumstances after injury, whether self-imposed or prescribed. Contemporary concussion management often involves withdrawal from everyday activities: school, employment, team involvement, and/or the use of various communication technologies (eg, phones, computers).[62] Activity withdrawal has generally been accepted as a key to successful recovery by primary care providers.[63]

However, substantial evidence suggests that withdrawal from daily validating activities has an adverse effect on the ability to cope with illness generally, and activity withdrawal is associated with psychological complications. Formally postulated more than 20 years ago, the "Activity Restriction Model of Depression" indicates that the degree to which one does not, or is unable to, participate in one's typical activities is associated with the likelihood of postillness/injury-related depressive symptoms.[64-66] In adolescents, the ability to engage in social, recreational, and sporting activities—and be increasingly independent and autonomous—is important. Activity restriction in adolescents with chronic health problems appears to directly contribute to depressive symptomatology.[66] Supporting evidence for the model has been found in several medical conditions, including amputation, cancer, and chronic pain.[65,67,68] Similar results have been found in the context of neurologic conditions, with higher risk of depression and reductions in quality of life found in the face of increased activity restriction after stroke and multiple sclerosis.[69-71] In other words, restriction from activity is a consistent determinant of depression after experiencing an injury or life-modifying medical condition.

Studies with children and adolescents with chronic health conditions have also found that social and physical activity restriction can have deleterious effects. Activity restrictions enforced by schools or parents appear to reinforce feelings of loneliness and isolation and represent a threat to a child's sense of self. In a study focused on children with medically related chronic pain, limited ability to participate in social and sporting activities was among the most distressing consequence of their health problems.[66] Evidence also indicates that being isolated is uncomfortable for most individuals, with a recent study finding that a significant number of individuals choose to experience a noxious stimulus rather than sit quietly without activities or the ability to communicate.[72] In regard to texting and phone use, recent evidence suggests that separation from the ability to communicate with others by modern technology can itself cause distress.[73]

In short, the ability to participate in normal activity appears to be a critical and independent determinant of psychological well-being for individuals after injury or illness. Yet contemporary clinical management of concussion does not adequately consider the potential negative impact of prolonged activity restriction on physical and emotional health.

Possible Harm #3: Physical Deconditioning. Rest, and specifically bed rest, results in physiologic changes in humans after a relatively short period of time.[74,75] Deconditioning and exercise intolerance can result after only 2 to 3 days of bed rest. In fact, an extended period of bed rest is considered to be contraindicated in a broad range of medical conditions, including stroke, whiplash injury, and postprocedural recovery.[76] Some of the manifestations of deconditioning mimic those reported in the postconcussion syndrome and may be misinterpreted by some as attributable to the concussion itself.

Discussion

Rest is endorsed as the primary intervention for concussion by contemporary practice guidelines and it is prescribed by many clinicians. However, there is limited and inconclusive evidence that rest improves outcomes from this injury. The central aim of the present article was to outline why there is reason to be concerned about not only a lack of efficacy for prolonged rest, but possible harms, including protracted recovery and complications. Moreover, prescribing rest is impractical and generally unacceptable to patients, especially children. The effect of withdrawal from normal life activities can

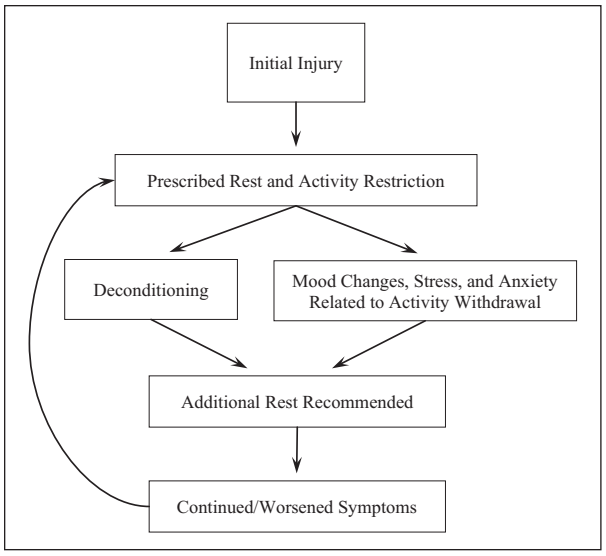

Figure 1. Theoretical model for prolonged rest and activity restriction contributing to persistent symptoms.

have iatrogenic effects, leading to some of the very symptoms typically attributed to concussion itself.

The extensive literature relating to adolescent depression is relevant to sport-related concussion because preexisting mental health problems are a risk factor for prolonged symptoms following mTBI,[50,77] and mild depression, anxiety, and stress are associated with symptoms that are very similar or identical to postconcussion symptoms.[78,79] A study by Lewinsohn and colleagues is particularly relevant. These authors examined the association between 44 variables and depression in adolescents.[80] They found 3 variables were strongly and specifically related to depression: adolescents with depression were more self-conscious, they had lower self-esteem, and they changed or decreased their activities because of physical illness or injury. This study, and the broader literature on depression in adolescents, is important because student athletes who are removed from social, educational, and sporting activities for prolonged periods of time might evolve into mild or greater depression, and mental health problems following an injury can disrupt social, recreational, and academic functioning.

In the first few days following injury, rest and reduced participation in activities might be beneficial for most children. However, *prolonged rest and activity withdrawal* may exacerbate postconcussion symptoms and produce new symptoms, at least in some people. As seen in Figure 1, we propose that an "Activity Intolerance" cascade may occur in some prone individuals after inappropriate concussion education and prolonged activity restriction. In this model, rapid physical deconditioning after withdrawal from exercise results in a significant decrease in exercise tolerance. Withdrawal from validating activities may, in prone individuals, contribute to mood deterioration, an increasing sense of vulnerability, avoidance behavior, and anxiety. When providers attribute these and other persistent symptoms to the concussive injury they often prescribe more rest, not realizing that prolonged rest can itself cause or reinforce these symptoms. Finally, on attempts at mobilization and reengagement, the return of symptoms is often ascribed to ongoing concussion-related problems rather than possible deconditioning and psychological factors, and additional rest is encouraged, further contributing to functional disruption.

We start our treatment of a child with concussion by screening for preexisting neurodevelopmental or mental health difficulties that may complicate the recovery, such as anxiety, depression, or attention deficit hyperactivity disorder. We then provide reassurance that a good recovery is expected, because education and reassurance are a common component of most effective early interventions[60,81,82] and may even be one of the active ingredients in 2 uncontrolled studies of time-limited prescribed rest.[33,34] This is important given the current media climate that often sensationalizes the purported dangers of concussion, with many parents and players worried about long-term consequences. We discourage a return to high-risk activities soon after injury because of vulnerability to reinjury.[41] However, we encourage a gradual return to activities and exercise as tolerated, and strongly recommend starting a return to school/work after only a day or two of rest in most cases. Resuming activities should ideally be gradual and at a pace that does not exacerbate symptoms. If symptoms do worsen with activity, they can be met with reassurance, minor adjustments to the return to learn plan, and symptomatic treatment (eg, of headache or sleep disturbance). If patients continue to experience symptoms weeks or months after injury, we do not believe that this represents a contraindication to exercise and activity reengagement. Indeed, in these cases, some empirical data support the use of exercise to help reduce symptomatology.[83-87] Some patients with more significant chronic pain, depression, or other functionally disruptive symptoms often need multidisciplinary workup and intervention in our experience. This may include psychological support, medical therapy, and facilitated rehabilitation. We are fairly conservative in decisions to return multiply concussed young athletes to high-risk activities given the unknown long-term risks associated with repeated concussions to the developing brain. However, we are reassuring in discussing the possibility of catastrophic outcomes with parents, because sport-related head trauma is an extremely uncommon cause of youth sports

related mortality, less common than sudden cardiac death and even lightning strikes.[88] In brief, for most young athletes, we believe that the benefit of sports involvement far outweighs the short- or long-term risks of concussions, and we encourage a return to sports and other physical recreational activities in most cases.

We encourage a balanced approach to clinical management. Using prolonged physical and cognitive rest, and activity withdrawal, is apt to do more harm than good. Health care providers can have a positive influence after concussion, based on their professional status and ability to reassure and direct patients to constructive methods of recovery. It is also critical to recognize that outcomes may be worsened by messaging of serious injury, long-term debilitation, and the need for withdrawal from reinforcing everyday activities.

Author Contributions

MDF is the communicating author. He also took up topical research, creation and editing of content. GLI, NDS, MWK and RB also contributed to topical research, creation and editing of content.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MWK receives royalties from an edited book on pediatric mild TBI referenced in the article. GLI has been reimbursed by the government, professional scientific bodies, and commercial organizations for discussing or presenting research relating to MTBI and sport-related concussion at meetings, scientific conferences, and symposiums. He has a clinical practice in forensic neuropsychology involving individuals who have sustained mild TBIs (including athletes). He has received honorariums for serving on research panels that provide scientific peer review of programs. He is a co-investigator, collaborator, or consultant on grants relating to mild TBI funded by several organizations. He has received research support from test publishing companies in the past, including ImPACT Applications Systems (not in the past 5 years). MWK has received honorariums from professional scientific bodies for discussing or presenting research relating to mild TBI at meetings, scientific conferences, and symposiums. He is an investigator or co-investigator on grants relating to pediatric TBI funded by several organizations. NDS has a clinical practice in forensic neuropsychology involving individuals who have sustained mild TBIs.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: GLI acknowledges funding support from the Mooney-Reed Charitable Foundation. NDS receives salary support from the Vancouver Coastal Health Research Institute.

References

1. Noble JM, Hesdorffer DC. Sport-related concussions: a review of epidemiology, challenges in diagnosis, and potential risk factors. *Neuropsychol Rev*. 2013;23:273-284.
2. Morrissey D, Raukar NP, Andrade-Koziol J, Mello M. Statewide assessment of the Rhode Island School and Youth Programs Concussion Act. *J Trauma Acute Care Surg*. 2014;77(3 suppl 1):S8-S11.
3. Finch CF, Clapperton AJ, McCrory P. Increasing incidence of hospitalisation for sport-related concussion in Victoria, Australia. *Med J Aust*. 2013;198:427-430.
4. Hung R, Carroll LJ, Cancelliere C, et al. Systematic review of the clinical course, natural history, and prognosis for pediatric mild traumatic brain injury: results of the international collaboration on mild traumatic brain injury prognosis. *Arch Phys Med Rehabil*. 2014;95 (3 suppl):S174-S191.
5. Cancelliere C, Hincapie CA, Keightley M, et al. Systematic review of prognosis and return to play after sport concussion: results of the international collaboration on mild traumatic brain injury prognosis. *Arch Phys Med Rehabil*. 2014;95(3 suppl):S210-S229.
6. Karr JE, Areshenkoff CN, Garcia-Barrera MA. The neuropsychological outcomes of concussion: a systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. *Neuropsychology*. 2014;28:321-336.
7. Belanger HG, Spiegel E, Vanderploeg RD. Neuropsychological performance following a history of multiple self-reported concussions: a meta-analysis. *J Int Neuropsychol Soc*. 2010;16:262-267.
8. Belanger HG, Vanderploeg RD. The neuropsychological impact of sports-related concussion: a meta-analysis. *J Int Neuropsychol Soc*. 2005;11:345-357.
9. Fainaru S, Fainaru-Wada M. Youth wrestling particiation drops. *ESPN Outside the Lines*. http://espn.go.com/espn/otl/story/_/page/popwarner/pop-warner-youth-wrestling-participation-drops-nfl-concussion-crisis-seen-causal-factor. Published November 14, 2003. Accessed February 27, 2015.
10. Lebrun CM, Mrazik M, Prasad AS, et al. Sport concussion knowledge base, clinical practises and needs for continuing medical education: a survey of family physicians and cross-border comparison. *Br J Sports Med*. 2013;47:54-59.
11. Covassin T, Elbin RJ, Sarmiento K. Educating coaches about concussion in sports: evaluation of the CDC's "Heads Up: concussion in youth sports" initiative. *J Sch Health*. 2012;82:233-238.
12. Giza CC, Hovda DA. The pathophysiology of traumatic brain injury. In: Lovell MR, Echemendia RJ, Barth JT, Collins MW, eds. *Traumatic Brain Injury in Sports*. Lisse, Netherlands: Swets & Zeitlinger; 2004:45-70.
13. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train*. 2001;36:228-235.
14. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery*. 2014;75(suppl 4):S24-S33.
15. Vagnozzi R, Tavazzi B, Signoretti S, et al. Temporal window of metabolic brain vulnerability to concussions:

mitochondrial-related impairment—part I. *Neurosurgery*. 2007;61:379-388.
16. Longhi L, Saatman KE, Fujimoto S, et al. Temporal window of vulnerability to repetitive experimental concussive brain injury. *Neurosurgery*. 2005;56:364-374.
17. Laurer HL, Bareyre FM, Lee VM, et al. Mild head injury increasing the brain's vulnerability to a second concussive impact. *J Neurosurg*. 2001;95:859-870.
18. Griesbach GS, Hovda DA, Molteni R, Wu A, Gomez-Pinilla F. Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. *Neuroscience*. 2004;125:129-139.
19. Griesbach GS, Sutton RL, Hovda DA, Ying Z, Gomez-Pinilla F. Controlled contusion injury alters molecular systems associated with cognitive performance. *J Neurosci Res*. 2009;87:795-805.
20. Griesbach GS, Gomez-Pinilla F, Hovda DA. The upregulation of plasticity-related proteins following TBI is disrupted with acute voluntary exercise. *Brain Res*. 2004;1016:154-162.
21. Griesbach GS. Exercise after traumatic brain injury: is it a double-edged sword? *PM R*. 2011;3:S64-S72.
22. DeMatteo C, Stazyk K, Singh SK, et al. Development of a conservative protocol to return children and youth to activity following concussive injury. *Clin Pediatr*. 2015;54:152-163.
23. Symonds CP. Observations on the differential diagnosis and treatment of cerebral states consequent upon head injuries. *BMJ*. 1928;2:829-832.
24. Watt J. Head injuries: a treatise from the viewpoint of diagnosis, prognosis and treatment. *Am J Surg*. 1938;41:272-274.
25. Meerloo AM. Cerebral concussion: a psychosomatic survey. *J Nerv Ment Dis*. 1949;110:347-353.
26. Voris HC. Mild head injury (concussion). *Am J Surg*. 1950;80:707-713.
27. Aubry M, Cantu R, Dvorak J, et al. Summary and agreement statement of the First International Conference on Concussion in Sport, Vienna 2001: recommendations for the improvement of safety and health of athletes who may suffer concussive injuries. *Br J Sports Med*. 2002;36:6-10.
28. McCrory P, Meeuwisse WH, Aubry M, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport, Zurich, November 2012. *J Athl Train*. 2013;48:554-575.
29. DeMatteo C, Stazyk K, Giglia L, et al. A balanced protocol for return to school for children and youth following concussive injury [published online January 18, 2015]. *Clin Pediatr (Phila)*. doi:10.1177/0009922814567305.
30. Andreassen J, Bach-Nielsen P, Heckscher H, Lindeneg O. Reassurance and short period of bed rest in the treatment of concussion: follow-up and comparison with results in other series treated by prolonged bed rest. *Acta Med Scand*. 1957;158:239-248.
31. de Kruijk JR, Leffers P, Meerhoff S, Rutten J, Twijnstra A. Effectiveness of bed rest after mild traumatic brain injury: a randomised trial of no versus six days of bed rest. *J Neurol Neurosurg Psychiatry*. 2002;73:167-172.
32. Gibson S, Nigrovic LE, O'Brien M, Meehan WP III. The effect of recommending cognitive rest on recovery from sport-related concussion. *Brain Inj*. 2013;27:839-842.
33. Moser RS, Glatts C, Schatz P. Efficacy of immediate and delayed cognitive and physical rest for treatment of sports-related concussion. *J Pediatr*. 2012;161:922-926.
34. Moser RS, Schatz P, Glenn M, Kollias KE, Iverson GL. Examining prescribed rest as treatment for adolescents who are slow to recover from concussion. *Brain Inj*. 2015;29:58-63.
35. Thomas DG, Apps JN, Hoffmann RG, McCrea M, Hammeke T. Benefits of strict rest after acute concussion: a randomized controlled trial. *Pediatrics*. 2015;135:213-223.
36. Schneider KJ, Iverson GL, Emery CA, McCrory P, Herring SA, Meeuwisse WH. The effects of rest and treatment following sport-related concussion: a systematic review of the literature. *Br J Sports Med*. 2013;47:304-307.
37. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Nat Acad Sci U S A*. 2003;100:253-258.
38. Hernandez SE, Suero J, Rubia K, Gonzalez-Mora JL. Monitoring the neural activity of the state of mental silence while practicing sahaja yoga meditation. *J Altern Complement Med*. 2015;21:175-179.
39. Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in brain and immune function produced by mindfulness meditation. *Psychosom Med*. 2003;65:564-570.
40. Baron Short E, Kose S, Mu Q, et al. Regional brain activation during meditation shows time and practice effects: an exploratory FMRI study. *Evid Based Complement Alternat Med*. 2010;7:121-127.
41. McCrea M, Guskiewicz K, Randolph C, et al. Effects of a symptom-free waiting period on clinical outcome and risk of reinjury after sport-related concussion. *Neurosurgery*. 2009;65:876-882.
42. Alla S, Sullivan SJ, McCrory P. Defining asymptomatic status following sports concussion: fact or fallacy? *Br J Sports Med*. 2012;46:562-569.
43. Craton N, Leslie O. Is rest the best intervention for concussion? Lessons learned from the whiplash model. *Curr Sports Med Rep*. 2014;13:201-204. doi:10.1249/JSR.0000000000000072.
44. Silverberg ND, Iverson GL. Is rest after concussion "the best medicine?" Recommendations for activity resumption following concussion in athletes, civilians, and military service members. *J Head Trauma Rehabil*. 2013;28:250-259.
45. Trahan DE, Ross CE, Trahan SL. Relationships among postconcussional-type symptoms, depression, and anxiety in neurologically normal young adults and victims of brain injury. *Arch Clin Neuropsychol*. 2001;16:435-445.
46. Sawchyn JM, Brulot MM, Strauss E. Note on the use of the postconcussion syndrome checklist. *Arch Clin Neuropsychol*. 2000;15:1-8.

47. Gouvier WD, Uddo-Crane M, Brown LM. Base rates of post-concussional symptoms. *Arch Clin Neuropsychol*. 1988;3:273-278.
48. Iverson GL, Lange RT. Examination of "postconcussion-like" symptoms in a healthy sample. *Appl Neuropsychol*. 2003;10:137-144.
49. Mittenberg W, DiGiulio DV, Perrin S, Bass AE. Symptoms following mild head injury: expectation as aetiology. *J Neurol Neurosurg Psychiatry*. 1992;55: 200-204.
50. McNally KA, Bangert B, Dietrich A, et al. Injury versus noninjury factors as predictors of postconcussive symptoms following mild traumatic brain injury in children. *Neuropsychology*. 2013;27:1-12.
51. Babikian T, McArthur D, Asarnow RF. Predictors of 1-month and 1-year neurocognitive functioning from the UCLA longitudinal mild, uncomplicated, pediatric traumatic brain injury study. *J Int Neuropsychol Soc*. 2013;19:145-154.
52. Yeates KO, Kaizar E, Rusin J, et al. Reliable change in postconcussive symptoms and its functional consequences among children with mild traumatic brain injury. *Arch Pediatr Adolesc Med*. 2012;166:615-622.
53. Woodrome SE, Yeates KO, Taylor HG, et al. Coping strategies as a predictor of post-concussive symptoms in children with mild traumatic brain injury versus mild orthopedic injury. *J Int Neuropsychol Soc*. 2011;17: 317-326.
54. Beaupre M, De Guise E, McKerral M. The association between pain-related variables, emotional factors, and attentional functioning following mild traumatic brain injury. *Rehabil Res Pract*. 2012;2012:924692.
55. Olsson KA, Lloyd OT, Lebrocque RM, McKinlay L, Anderson VA, Kenardy JA. Predictors of child post-concussion symptoms at 6- and 18-months following mild traumatic brain injury. *Brain Inj*. 2013;27:145-157.
56. Ponsford J, Willmott C, Rothwell A, et al. Cognitive and behavioral outcome following mild traumatic head injury in children. *J Head Trauma Rehabil*. 1999;14:360-372.
57. Suhr JA, Gunstad J. Postconcussive symptom report: the relative influence of head injury and depression. *J Clin Exp Neuropsychol*. 2002;24:981-993.
58. Vanderploeg R, Belanger H, Kaufmann P. Nocebo effects and mild traumatic brain injury: legal implications. *Psychol Inj Law*. 2014;7:245-254.
59. Hou R, Moss-Morris R, Peveler R, Mogg K, Bradley BP, Belli A. When a minor head injury results in enduring symptoms: a prospective investigation of risk factors for postconcussional syndrome after mild traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2012;83:217-223.
60. Cassidy JD, Boyle E, Carroll LJ. Population-based, inception cohort study of the incidence, course, and prognosis of mild traumatic brain injury after motor vehicle collisions. *Arch Phys Med Rehabil*. 2014;95(3 suppl): S278-S285.
61. Whittaker R, Kemp S, House A. Illness perceptions and outcome in mild head injury: a longitudinal study. *J Neurol Neurosurg Psychiatry*. 2007;78:644-646.
62. Harmon KG, Drezner J, Gammons M, et al. American medical society for sports medicine position statement: concussion in sport. *Clin J Sport Med*. 2013;23:1-18.
63. Bass P. Managing a patient after a concussion. *Contemporary Pediatrics*. http://contemporarypediatrics.modernmedicine.com/contemporary-pediatrics/content/tags/centers-disease-control-and-prevention/managing-patient-after-c. Published August 1, 2014. Accessed on May 22, 2015.
64. Lewinsohn EM, Hoberman H, Teri L, Hautzinger M. An integrative theory of depression. In: Reiss S, Bootzin R, eds. *Theoretical Issues in Behavior Therapy*. San Diego, CA: Academic Press; 1985:331-359.
65. Williamson GM. Extending the activity restriction model of depressed affect: evidence from a sample of breast cancer patients. *Health Psychol*. 2000;19:339-347.
66. Walters AS, Williamson GM. The role of activity restriction in the association between pain and depression: a study of. *Child Health Care*. 1999;28:33-50.
67. Williamson GM, Schulz R. Activity restriction mediates the association between pain and depressed affect: a study of younger and older adult cancer patients. *Psychol Aging*. 1995;10:369-378.
68. Molton IR, Hirsh AT, Smith AE, Jensen MP. Age and the role of restricted activities in adjustment to disability-related pain. *J Health Psychol*. 2013;19:1025-1034.
69. Mayo NE, Wood-Dauphinee S, Cote R, Durcan L, Carlton J. Activity, participation, and quality of life 6 months poststroke. *Arch Phys Med Rehabil*. 2002;83:1035-1042.
70. Hartman-Maeir A, Soroker N, Ring H, Avni N, Katz N. Activities, participation and satisfaction one-year post stroke. *Disabil Rehabil*. 2007;29:559-566.
71. Turner AP, Kivlahan DR, Haselkorn JK. Exercise and quality of life among people with multiple sclerosis: looking beyond physical functioning to mental health and participation in life. *Arch Phys Med Rehabil*. 2009;90: 420-428.
72. Wilson TD, Reinhard DA, Westgate EC, et al. Social psychology. Just think: the challenges of the disengaged mind. *Science*. 2014;345:75-77.
73. Clayton RB, Leshner G, Almond A. The extended iSelf: the impact of iPhone separation on cognition, emotion, and physiology. *J Comput Mediat Commun*. 2015;20: 119-135.
74. Smorawinski J, Nazar K, Kaciuba-Uscilko H, et al. Effects of 3-day bed rest on physiological responses to graded exercise in athletes and sedentary men. *J Appl Physiol*. 2001;91:249-257.
75. Fortney SM, Schneider VS, Greenleaf JE. The physiology of bed rest. *Compr Physiol*. 2011:889-939.
76. Allen C, Glasziou P, Del Mar C. Bed rest: a potentially harmful treatment needing more careful evaluation. *Lancet*. 1999;354:1229-1233.
77. Peterson RL, Connery AK, Baker DA, Kirkwood MW. Preinjury emotional-behavioral functioning of children with lingering problems following mild traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. In press.

78. Edmed S, Sullivan K. Depression, anxiety, and stress as predictors of postconcussion-like symptoms in a non-clinical sample. *Psychiatry Res*. 2012;200:41-45.
79. Gouvier WD, Cubic B, Jones G, Brantley P, Cutlip Q. Postconcussion symptoms and daily stress in normal and head-injured college populations. *Arch Clin Neuropsychol*. 1992;7:193-211.
80. Lewinsohn PM, Gotlib IH, Seeley JR. Depression-related psychosocial variables: are they specific to depression in adolescents? *J Abnorm Psychol*. 1997;106:365-375.
81. Alves W, Macciocchi SN, Barth JT. Postconcussive symptoms after uncomplicated mild head injury. *J Head Trauma Rehabil*. 1993;8:48-59.
82. Mittenberg W, Tremont G, Zielinski RE, Fichera S, Rayls KR. Cognitive-behavioral prevention of postconcussion syndrome. *Arch Clin Neuropsychol*. 1996;11:139-145.
83. Gagnon I, Galli C, Friedman D, Grilli L, Iverson GL. Active rehabilitation for children who are slow to recover following sport-related concussion. *Brain Inj*. 2009;23:956-964.
84. Leddy JJ, Kozlowski K, Donnelly JP, Pendergast DR, Epstein LH, Willer B. A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. *Clin J Sport Med*. 2010;20:21-27.
85. Baker JG, Freitas MS, Leddy JJ, Kozlowski KF, Willer BS. Return to full functioning after graded exercise assessment and progressive exercise treatment of postconcussion syndrome. *Rehabil Res Pract*. 2012;2012:705309.
86. Iverson GL, Gagnon I, Griesbach GS. Active rehabilitation for slow-to-recover children folllowing mild traumatic brain injury. In: Yeates KO, Kirkwood M, eds. *Mild Traumatic Brain Injury in Children and Adolescents: From Basic Science to Clinical Management*. New York, NY: Guilford Press; 2012:281-302.
87. Gagnon I, Grilli L, Friedman D, Iverson GL. A pilot study of active rehabilitation for adolescents who are slow to recover from sport-related concussion [published online March 3 2015]. *Scand J Med Sci Sports*. 2015. doi:10.1111/sms.12441
88. Kirkwood MW, Randolph C, Yeates KO. Sport-related concussion: a call for evidence and perspective amidst the alarms. *Clin J Sport Med*. 2012;22:383-384.