ARTICLE

Cognitive Decline and Aging: The Role of Concussive and Subconcussive Impacts

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[1]School of Kinesiology, [2]Michigan NeuroSport, [3]Department of Physical Medicine and Rehabilitation, [4]Department of Neurology, and [5]Michigan Alzheimer's Disease Center, University of Michigan at Ann Arbor, Ann Arbor, MI

BROGLIO, S.P., J.T. ECKNER, H.L. PAULSON, and J.S. KUTCHER. Cognitive decline and aging: the role of concussive and subconcussive impacts. *Exerc. Sport Sci. Rev.*, Vol. 40, No. 3, pp. 138–144, 2012. *Concussion has been viewed historically as a transient injury with no evidence supporting the existence of persistent effects. However, our recent work demonstrates electroencephalographic and motor control changes in otherwise healthy individuals with a history of concussion. We therefore hypothesize that concussive and subconcussive head impacts set about a cascade of pathological events that accelerates declines in cognitive function typically associated with the aging process.* **Key Words:** concussion, subconcussive, aging, neurometabolic cascade, cognitive and motor decline, chronic traumatic encephalopathy

INTRODUCTION

Sport-related concussions once were trivialized by athletes and coaches, and "playing through the pain" was regarded widely as a sign of an athlete's toughness and commitment to their team. As recognition and understanding of this injury improves, attitudes of minimization are changing dramatically. Sport-related concussion now is recognized widely as a major public health issue, with the Centers for Disease Control and Prevention estimating that as many as 3.8 million sport and recreation related concussions occur each year in the United States (16). This incidence rate greatly exceeds previous estimates, in part because it is now evident that a large percentage of concussions go either unrecognized or unreported to medical providers.

Although the general population is at risk for sustaining concussions through accidental trauma, contact sport participation dramatically increases this risk. Indeed, among all individuals younger than 19 yr, the risk for concussion is 0.25% per year (21). This risk increases to 5% annually with participation in a contact and collision sport such as high school football (9). Furthermore, both youth and female athletes seem to sustain concussions at a greater rate than their adult and male counterparts (9).

For the previous decade, the acute effects of concussion have been well characterized in the literature. In the immediate postinjury state, there are notable deficits to cognitive function and motor control (*e.g.*, balance), as well as increased symptom reports. In the majority of cases, these declines return to preinjury levels within 7 to 10 d of injury (20). Because of the rapid restoration to preinjury levels of functioning, little research has focused on the potential long-term consequences of concussion on brain health. In fact, the majority of investigations implementing common clinical concussion assessment tools have failed to identify differences in cognitive performance in athletes with and without a concussion history (1,13).

Recent work, however, has called into question the assertion that full recovery after sport concussion without persistent adverse effects is the norm. Initial case studies reported on brain autopsies of retired professional football athletes with significant concussion histories described diffuse amyloid plaques as well as sparse neurofibrillary tangles and tau positive neuritic threads in neocortical areas (22). This tau pathology was termed *chronic traumatic encephalopathy* and has been identified in a number of ex-athletes with a history of concussion (8). Other investigations also have linked multiple concussions to depression (12) and mild cognitive

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impairment (14) in ex-athletes with a concussion history. Although additional longitudinal research is needed to accurately document concussion history and control for other variables that may influence cognitive health, these observations suggest a link between concussions during young adulthood and adverse effects on neurocognitive health later in life.

It is not entirely clear why some individuals with a concussion history show no persistent functional impairment, whereas others experience cognitive declines and associated brain pathology later in life. In consideration of these differences, we hypothesize that concussive and subconcussive head trauma intensify the expected cognitive aging process by decreasing cognitive reserve at a faster rate, leading to premature cognitive dysfunction. As such, we will describe the known pathophysiology of concussion, the normal effect of aging on the brain, and present a theory explaining how the two ultimately may exacerbate each other. Our accelerated cognitive decline hypothesis will be supported by a number of investigations generated by our group and others.

CONCUSSION AND SUBCONCUSSIVE IMPACTS

Concussion is defined commonly as a transient disruption of brain function brought on by a direct or indirect biomechanical force acting on the brain. The neurometabolic cascade associated with concussion involves dramatic changes in intracellular and extracellular ion concentrations, glucose metabolism, and cerebral blood flow (11). Although many clinical tools are now available for concussion assessment (*e.g.*, symptom scales, computerized neurocognitive tests, balance assessment tools), there currently is no objective test that can confirm the concussion diagnosis. As such, concussion remains a clinical diagnosis, based on the athlete's presenting signs and symptoms and the impression of the evaluating medical provider. Interestingly, the definition of concussion as a pathophysiological phenomenon is separate and distinct from the clinical presentation on which diagnosis is based. Without an objective test capable of confirming the presence or absence of cellular dysfunction, there is a degree of uncertainty any time concussion is or is not diagnosed. Given the subjective, complex, and, at times, ambiguous presentations of potentially concussed individuals, clinical outcomes research studying concussion must be interpreted with a potentially significant degree of diagnostic uncertainty.

As such, individuals presenting with a clinically recognizable concussive syndrome may not represent the totality of the injured population. Indeed, some athletes having sustained one or more "subconcussive" head impacts may experience pathophysiological changes in the brain function without the clinical presentation of concussion. Although subconcussive impacts do not impart the acute morbidity of a symptomatic concussion, they may not be devoid entirely of deleterious effects. Indeed, some preliminary evidence suggests that subconcussive impacts are associated with cortical dysfunction that is not apparent clinically (32).

The acute effect of head trauma on cortical neurons likely is not limited to neuronal physiological dysfunction. Posttraumatic intracellular structural changes, such as alterations in structural support molecules and the aggregation of tau protein, also have been implicated as possible pathophysiological mechanisms (8). Tau protein aggregation establishes an identifiable link between concussions and long-term neurological sequelae, specifically the development of chronic traumatic encephalopathy. Although there currently is no research describing the long-term effects of physiological changes in brain function that are not accompanied by a clinically apparent concussion, it is possible that such physiological states can alter neuronal biology in a way that becomes clinically relevant later in life. In this regard, the possibility that both concussive and subconcussive impacts may influence the long-term cognitive health is worth investigating.

NORMAL AGING OF THE BRAIN

Aging leads to expected alterations in brain structure and function that increasingly are well described (27). For example, cortical gray matter density decreases progressively after early adulthood, although the timing and degree of this loss varies between specific brain regions (29). Similar region-specific declines in white matter volume also occur (31). These structural changes are accompanied by functional impairment of neurons. Neuronal cell loss is not an inevitable consequence of aging, but neurons do undergo many biochemical, electrophysiological, and structural changes, again differing across brain regions (3,35). Reductions in synaptic plasticity, dendritic spine density, calcium homeostasis, and the expression of neurotrophic factors all occur with aging, as do perturbations in the function of dopaminergic, serotonergic, cholinergic, and glutamatergic circuits. The degradation in neurocognitive function seen with aging likely is a consequence of both these structural and functional factors.

With age-related structural and chemical changes come the expected declines in individual cognitive abilities. Age-related changes in memory, attention, and orientation are all well documented (15), and motor function, reaction time, and balance regulation also have been shown to deteriorate with age, leading to increasingly unsteady gait and falls (7). Regardless of the performance measure, age-associated declines are expected with significant variability between individuals in terms of when the cognitive losses result in clinically apparent functional deficits. The concept of "cognitive reserve" (30) helps explain the wide clinical variability observed in practice. That is, those with more dense gray matter, with a higher number of neuronal connections, and with more robust neuronal networks can better afford to lose a fixed amount of ability before demonstrating a clinically meaningful decline.

The rate at which age-related changes progress over time is not fixed within an individual. Many behavioral and environmental factors (*e.g.*, excessive alcohol intake, smoking, sedentary lifestyle) have been postulated, to varying degrees, to influence brain physiology negatively and, thereby, to reduce neurocognitive performance (6,19). It then follows that healthy lifestyles can be accepted easily as a possible mechanism for slowing down cognitive decline. What remains unknown is whether head trauma may act in a similar fashion, negatively affecting brain physiology and, thus, potentiating the aging process.

LONG-TERM CONSEQUENCES OF CONCUSSION

Cognitive Effects of Concussion

Although sport-related concussion has been traditionally viewed as a transient injury void of long-term consequences, the relevant literature reporting on this relationship is mixed. Some investigations have demonstrated that individuals reporting a concussion history performed worse on tests evaluating executive functioning and information processing than those without a concussion history (4). Conversely, other studies have failed to differentiate between individuals with multiple concussions and those without a concussion history on pencil and paper (13) and computer-based cognitive examinations (1). Indeed, our laboratory evaluated a large sample of collegiate athletes for chronic cognitive deficits associated with concussion (1). The Headminder Concussion Resolution Index was administered to 235 individuals, and 264 participants completed the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT). Participants were divided into four groups based on self-reported history of injury (0, 1, 2, or 3 concussions), and data analyses revealed no difference between groups for either test instrument (Headminder Concussion Resolution Index or ImPACT). Collectively, the majority of studies fail to support an association between previous concussion and cognitive function (1,13). However, we note that the tests used in these studies were not designed to detect subtle long-term decrements in cognitive performance after injury. Thus, if more sensitive cognitive measures were utilized, differences in cognitive function between those with and without a history of concussion might be detected.

Electrophysiological Effects of Concussion

Electroencephalograms (EEG) have been used extensively to examine electrical activity associated with brain function, but their use to investigate the impact of concussion on brain and cognition has been limited. One particular aspect of EEG, known as event-related brain potentials (ERPs), has provided additional insight into the underlying neural mechanisms involved in cognitive function. ERPs reflect patterns of voltage change in ongoing neuroelectric activity that occurs in response to, or in preparation for, a stimulus or response. Because of their superior temporal resolution over other imaging methods, ERPs are well situated to provide information regarding the aspects of information processing that are affected by a particular variable. That is, ERPs have the temporal resolution to distinguish the cognitive processes occurring between stimulus presentation and the patient's response that are altered by differential participant characteristics.

Within the ERP assessment, the P3 is elicited when participants attend to and discriminate between stimuli approximately 300 to 800 ms after presentation. The P3 is theorized to represent the processes involved in attentional resource allocation during cognitive operations. Research findings have indicated that P3 amplitude is proportional to the amount of attentional resources devoted to a stimulus or task, with increased amplitude related to increased attention. Because the P3 occurs after a stimulus has been discriminated, the latency of this component has been theorized to reflect stimulus evaluation time, with shorter latency indicating faster cognitive processing speed. The P3 signal can be subdivided into two subcomponents: the P3a, which occurs after an unexpected event or stimulus, and the P3b occurring after an expected but infrequent event. Lastly, the N2 component represents one's ability to monitor responses and inhibit inappropriate motor responses.

A number of laboratories have conducted work evaluating the P3 response in concussed athletes both in the acute stage and after clinical recovery has occurred. Our laboratory evaluated both cognitive function and electrophysiology in young adults with and without a history of concussion (2). The 90 participants (19.7 ± 1.3 yr: 44 without concussion and 46 with previous concussion) were evaluated using the ImPACT and ERPs recorded during a Novelty Oddball Task. Those with a history of concussion reported an average of 3.4 yr since injury. Similar to our previous work with computer-based cognitive assessments, no significant differences were found between groups on the ImPACT ($P > 0.05$). Significant decrements in the P3b and N2 amplitudes were noted for those with a concussion history relative to those without a history of concussion (Fig. 1). The P3b decrement in those with previous injuries is thought to represent a lessened ability to allocate attentional resources relative to those without previous injuries. Suppression of the N2 component represents a less effective response inhibition process under more intense decision making conditions (*e.g.*, competition), which may result in a failure to inhibit an incorrect response.

In a follow-up investigation (26), we evaluated additional action monitoring measures in those with and without a history of concussion. In this investigation, we evaluated the regulatory aspects of cognitive action monitoring, or error-related negativity (ERN), the negative-going response-locked ERP component that is observed after errors are committed during choice tasks. The 30 young adults with a history of concussion (mean, 1.7 previous concussions, 3.9 yr prior) and 36 control subjects completed the ImPACT assessment and a modified flanker task, while EEG activity was recorded. Consistent with previous reports, there were no differences between groups on any of the ImPACT measures of cognitive function ($P > 0.05$). More interestingly, the previously concussed group showed poorer response accuracy on the Flanker task and poorer response accuracy after an erroneous response (*i.e.*, more errors after making an error). The underlying cognitive response was noted with suppressed ERN responses to errors in the concussion group and a significant negative correlation between concussion number and ERN amplitude. That is, as the number of concussions increased, the ERN response decreased.

Although the previously concussed participants performed equally to those without injury on the clinical measure of cognitive function (*i.e.*, ImPACT), these findings, along with our previous report (1), suggest that sport concussion can no longer be thought of as a transient injury resulting in short-lived neurological impairment. The young adults evaluated in these investigations showed a decreased ability to maintain attentional resources toward infrequent, yet expected events; less ability to inhibit incorrect responses to their environment; and a lessened ability to recognize that they had

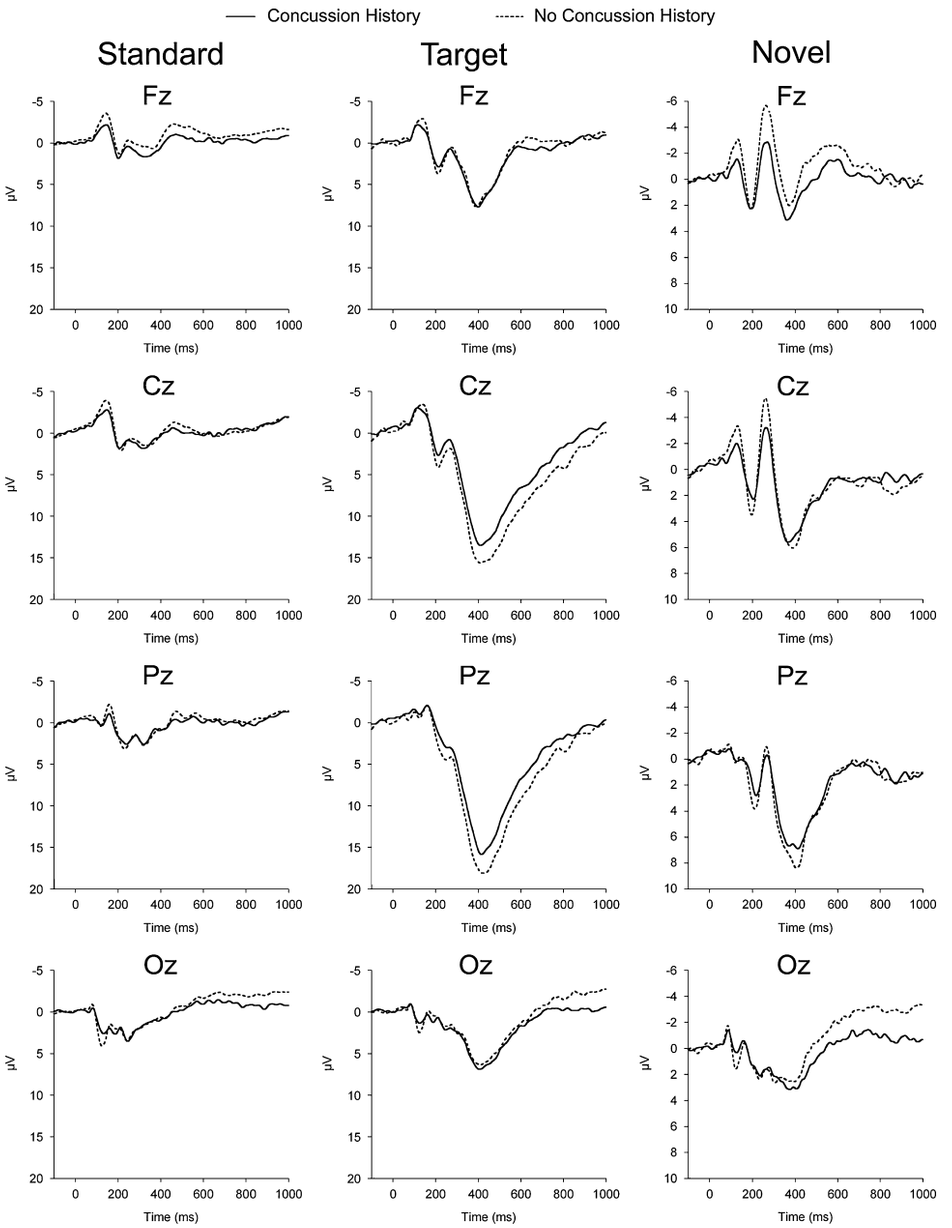

Figure 1. Event-related brain potential (ERP) waveforms showing suppressed P3b and N2 components in the concussion history group. (Reprinted from (2). Copyright © 2009 Mary Ann Liebert, Inc. Used with permission.)

made a mistake. This represents clear evidence that persistent electrophysiological changes do exist well beyond the acute injury stage.

Furthermore, the attentional resource (*i.e.*, P300) decrements documented in a young adult cohort with a concussion history mimic those seen in older adults transitioning from a stage of mild cognitive impairment (MCI) to Alzheimer's disease (AD). Gironell *et al.* (10) evaluated 94 patients (mean, 68.8 yr) at baseline and 12 and 24 months with an auditory oddball task while monitoring ERPs. The one third of the sample (n = 28) that were diagnosed with AD at the end of the study demonstrated a significantly longer P300 latency at baseline. Beyond the AD diagnosis, P300 amplitude is smaller, and latency is prolonged when compared with healthy age-matched control subjects (25). As such, the changes documented in young adults may set the stage for disease states seen in an older population.

Changes in Balance and Gait After Concussion

Combining the knowledge that concussion is a diffuse brain injury and our work showing persistent electrophysiological changes in brain function, we hypothesized that concussion also may have a lasting effect on motor control. Thus, postural control was evaluated in 224 collegiate athletes (20.0 ± 1.5 yr) using the NeuroCom Sensory Organization Test (SOT) (28). From the sample, 162 reported no previous injuries, whereas the remaining 62 reported sustaining 1 to 4 concussions (mean, 3.7 yr prior). Analysis of the general output scores from the SOT indicated only the visual ratio differed significantly between the two groups ($P < 0.05$)

but not enough to suggest a clinical balance impairment. More interestingly, when we applied a nonlinear statistics (Approximate Entropy (ApEn)) to the center of pressure pattern in the anterior-posterior (AP) and medial-lateral (ML) directions, significant differences were revealed under each of the six testing conditions ($P < 0.05$). Nonlinear statistics offer the advantage over traditional analyses by evaluating how a physiological output varies over time. In acute concussion evaluations, the use of ApEn has proven to be a more sensitive analysis of postinjury changes than the standard SOT measures; and those with a concussion history had a 16.5% decrease in ML balance complexity and 29.0% increase in AP complexity as the testing conditions became more challenging (Fig. 2).

The group differences in the pattern of AP and ML center of pressure changes indicate a shift in the balance strategy by those with a concussion history. The larger ApEn values demonstrated by the nonconcussed group suggest a greater control over medial-lateral sway. The smaller ApEn values seen in those with a concussion history suggest less control over medial-lateral sway, which is similar to what has been reported in otherwise healthy older adults and is correlated with an increased risk for falls (24). This raises the likelihood that individuals with a concussion history may be at greater risk for falls, especially as they age. These results also support our electrophysiological findings demonstrating permanent changes in cerebral function after concussion, but those changes seem to not be isolated to cognitive functioning and extend to motor functions such as postural control.

Once it was established that concussive injuries can have a lasting effect on motor control, we sought to evaluate how the injury may affect gait (17). Changes to gait are well documented in the acute stage of injury and are suggested to be more functional and sensitive to injury than static balance. Thus, we evaluated adults with (n = 28, 21.0 yr; mean, 2.0 previous concussions, 6.3 yr after injury) and without (n = 40, 20.7 yr) a concussion history using single and dual task walking conditions. All single task trials were completed on a 3.6 m GaitRite Gaitmat (CIR Systems, Inc., Havertown, PA) while the participants walked along an unobstructed path or while stepping over two (0.5 m) obstacles. The two dual task conditions implemented the same walking task, but the participants also simultaneously completed Brooks Mental Task, a visuospatial memory test. Brooks Mental Task also was completed in a resting/seated position. Performance on the cognitive test did not differ between the groups during the walking without obstacles, walking with obstacles, and the seated conditions ($P > 0.05$). However, the gait variables showed that those with a previous concussion spent a significantly greater proportion of the gait cycle in double leg stance and significantly decreased time in single leg stance. This finding was further supported by significant negative correlations between the previous number of concussions reported by the cohort and single leg stance time and a positive correlation between concussion number and double leg stance double stance time. From these data, we surmised that those with a concussion history subconsciously elect to maintain a more conservative and safer gait pattern. The motive for this action is not clear entirely, but we speculate that it is a protective mechanism to reduce the risk of further injury from falling. Unlike the balance changes that we previously documented, the changes to gait after concussion have a much greater implication for influencing injury risk with age. Indeed, there is a strong link between age-related declines in cognitive functioning that are known to influence walking negatively during dual task conditions, and impaired gait has been shown as a predictor of chronic disability, long-term nursing home care, and mortality (34).

CONCLUSIONS

Interpreting the findings from research examining the persistent changes in both cognitive and motor control function is difficult, given that longitudinal research is not available. The young adults we studied were all high functioning university students with no clinically apparent deficits

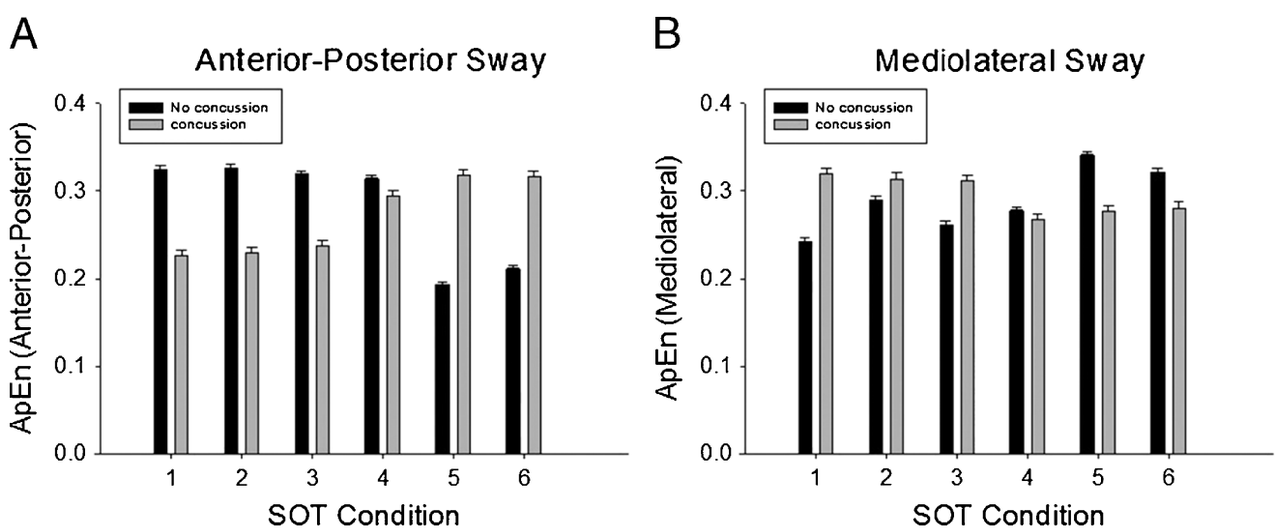

Figure 2. Differences in postural control complexity (*i.e.,* Approximate Entropy (ApEn)) in those with and without a history of concussion. A. shows changing performance in the anterior-posterior direction, and (B.) in the medial-lateral direction. SOT, NeuroCom Sensory Organization Test. (Reprinted from (28). Copyright © 2011 National Athletic Trainers' Association. Used with permission.)

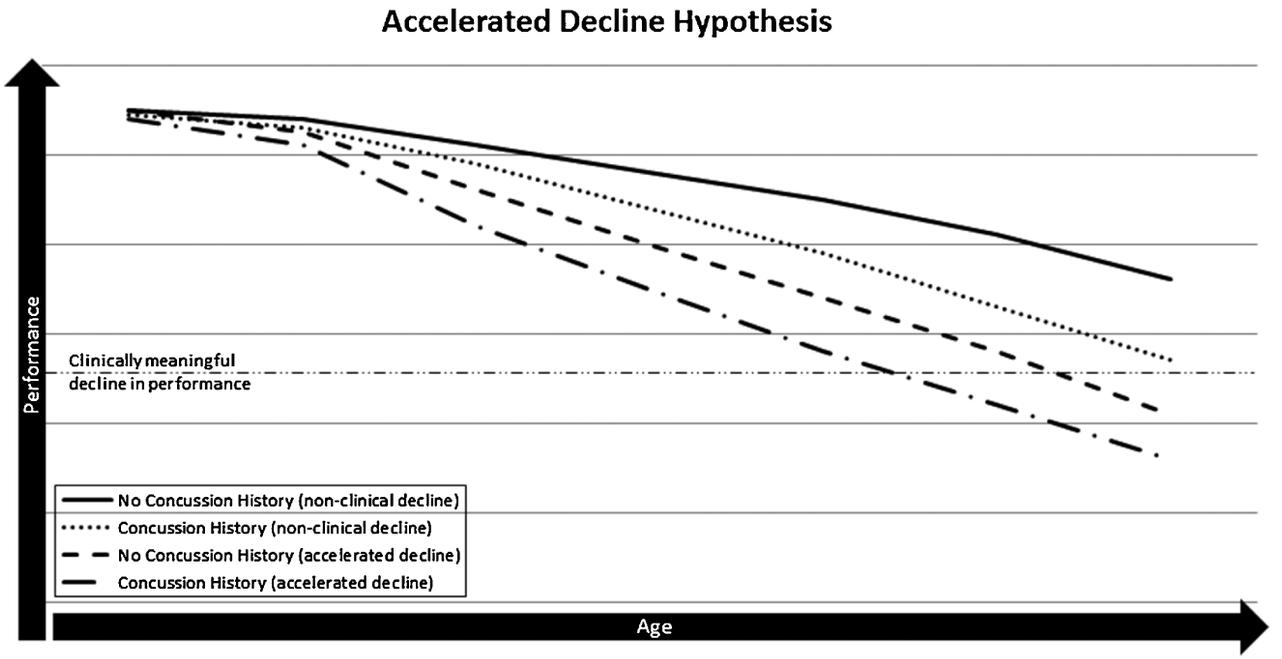

Figure 3. Hypothesis of age-related differences in cognitive and motor performance in those with and without a history of concussion. Some individuals with a concussion history may show greater performance declines, at a faster rate, with age, whereas others may benefit from cognitive reserve and show no clinical performance decrements.

after their injuries. Despite this, there are clear subclinical differences on cognitive and motor control tests between the concussed and control groups. As the concussion cohort ages, we speculate these changes may manifest into clinically significant functional impairments. For example, two studies of retired professional football athletes with a concussion history are at increased risk for an early onset of AD, MCI, and clinical depression (12,14). Others have shown motor impairment in older adults, with the last concussion occurring three decades previously (5). The cognitive reserve of previously concussed young adults likely compensates for the subtle deficits we have documented in laboratory experiments. As these individuals age and the anticipated cognitive declines associated with aging ensue, these differences may become larger and more meaningful in some portion of the population. However, others may be able to withstand a concussion without a clinically meaningful decline in function later in life. Figure 3 presents four scenarios of age-related declines: those with and without a concussion history that do and not show clinical performance impairments with age. Although intrinsic factors may play a role in the cognitive decline of otherwise healthy individuals, we hypothesize that those with a concussion history may experience a faster rate of deterioration and face clinically meaningful declines at an earlier age and to a greater degree than their uninjured counterparts. Conversely, there likely is a subset of the population that may be able to sustain a concussion without clinically meaningful declines because of their reliance on cognitive reserve.

The exact structural and chemical changes that produce these changes are not clear entirely. However, hippocampal cell death has been observed in mice within 3 d of concussion (33), and in human models, pyramidal neuron atrophy and neuronal cell death in regions of the hippocampus are seen after traumatic brain injury (18). In addition, the normal aging process is linked tightly to pyramidal cell structure declines (23). Further evidence supporting our hypothesis is provided through the postmortem assessment of cerebral tissue in athletes with a concussion history. The relationship between acute changes in metabolic and ionic changes after concussion and long-term pathological changes to the cerebral tissue is not understood fully. However, there is preliminary evidence to suggest that some individuals with a concussion history display significant tau deposits across the cerebral cortex, within the sulci, and around the cerebral vasculature. The clinical presentation of this neurodegenerative disease is one of disordered cognition, memory loss and executive dysfunction, depression, apathy, disinhibition, and irritability, as well as parkinsonian signs that appear in midlife, years after sports participation has ended (8). Ultimately, the combined damage/death to the cerebral neurons from concussive injury and aging may manifest through any number of clinical symptoms.

In the final analysis, this line of research supports the hypothesis that concussion can no longer be thought of as a transient injury void of long-term consequences. Individuals sustaining a single concussive episode in the teen years show subtle negative alterations in brain function and motor control. The magnitude of those changes in later life remains in question. Anecdotal findings suggest that many athletes with a limited number of injuries have continued on to be high-functioning adults, whereas others are at risk for earlier and more severe declines in cognitive and motor performance. In either scenario, during the young adult years, it seems as though the injury has little clinical meaning because those with an injury history can rely on their cognitive reserve to maintain a high level of functioning with no observable clinical deficits. Despite the subtle changes in brain functioning, alternate cerebral pathways are recruited to achieve

the same end goal without clinical deficit. With time, aging, and the influence of various lifestyle and environmental factors, these alternate pathways may become less effective with clinical consequences in both cognitive and motor function.

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References

1. Broglio SP, Ferrara MS, Piland SG, Anderson RB. Concussion history is not a predictor of computerized neurocognitive performance. *Br. J. Sports Med.* 2006; 40:802–5.
2. Broglio SP, Pontifex MB, O'Connor P, Hillman CH. The persistent effects of concussion on neuroelectic indices of attention. *J. Neurotrauma* 2009; 26:1463–70.
3. Burke SN, Barnes CA. Neural plasticity in the ageing brain. *Nat. Rev. Neurosci.* 2006; 7:30–40.
4. Collins MW, Grindel SH, Lovell MR, *et al.* Relationship between concussion and neuropsychological performance in college football players. *J.A.M.A.* 1999; 282:964–70.
5. De Beaumont L, Theoret H, Mongeon D, *et al.* Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain* 2009; 132:695–708.
6. Etgen T, Sander D, Bickel H, Forstl H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. *Dtsch. Arztebl. Int.* 2011; 108:743–50.
7. Fozard JL, Vercryssen M, Reynolds SL, Hancock PA, Quilter RE. Age differences and changes in reaction time: the Baltimore Longitudinal Study of Aging. *J. Gerontol.* 1994; 49:179–89.
8. Gavett BE, Stern RA, McKee AC. Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. *Clin. J. Sport Med.* 2011; 30:179–88.
9. Gessel LM, Fields SK, Collins CL, Dick RW, Comstock RD. Concussions among United States high school and collegiate athletes. *J. Athl. Train.* 2007; 42:495–503.
10. Gironell A, Garcia-Sanchez C, Estevez-Gonzalez A, Boltes A, Kulisevsky J. Usefulness of p300 in subjective memory complaints: a prospective study. *J. Clin. Neurophysiol.* 2005; 22:279–84.
11. Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J. Athl. Train.* 2001; 36:228–35.
12. Guskiewicz KM, Marshall SW, Bailes J, *et al.* Recurrent concussion and risk of depression in retired professional football players. *Med. Sci. Sports Exerc.* 2007; 39:903–9.
13. Guskiewicz KM, Marshall SW, Broglio SP, Cantu RC, Kirkendall DT. No evidence of impaired neurocognitive performance in collegiate soccer players. *Am. J. Sports Med.* 2002; 30:157–62.
14. Guskiewicz KM, Marshall SW, Bailes J, *et al.* Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery* 2005; 57:719–26.
15. Kensinger EA. Cognition in aging and age related disease. In: Hof PR, Mobbs CV, editors. *Handbook of the Neuroscience of Aging*. London, UK: Elsevier Press; 2009.
16. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: A brief overview. *J. Head Trauma. Rehabil.* 2006; 21:375–8.
17. Martini DN, Sabin MJ, DePesa SA, *et al.* The chronic effects of concussion on gait. *Arch. Phys. Med. Rehabil.* 2011; 92:585–9.
18. Maxwell WL, Dhillon K, Harper L, *et al.* There is differential loss of pyramidal cells from the human hippocampus with survival after blunt head injury. *J. Neuropathol. Exp. Neurol.* 2003; 62:272–9.
19. Mcauley E, Kramer AF, Colcombe SJ. Cardiovascular fitness and neurocognitive function in older adults: a brief review. *Brain Behav. Immun.* 2004; 18:214–20.
20. McCrory P, Meeuwisse W, Johnston K, *et al.* Consensus Statement on Concussion in Sport 3rd International Conference on Concussion in Sport Held in Zurich, November 2008. *Br. J. Sports Med.* 2009; 43:i76–90.
21. National Center for Injury Prevention and Control. *Injury Fact Book 2001–2002*. Atlanta, GA: Centers for Disease Control and Prevention; 2001, p. 110–3.
22. Omalu BI, DeKosky ST, Hamilton RL, *et al.* Chronic traumatic encephalopathy in a national football league player: Part II. *Neurosurgery* 2006; 59:1086–92.
23. Peters A. Structural changes that occur during normal aging of primate cerebral hemispheres. *Neurosci. Biobehav. Rev.* 2002; 26:733–41.
24. Piirtola M, Era P. Force platform measurements as predictors of falls among older people - a review. *Gerontology* 2006; 52:1–16.
25. Pokryszko-Dragan A, Slotwinski K, Podemski R. Modality-specific changes in P300 parameters in patients with dementia of the Alzheimer type. *Med. Sci. Monit.* 2003; 9:CR130–134.
26. Pontifex MB, O'Connor PM, Broglio SP, Hillman CH. The association between mild traumatic brain injury history and cognitive control. *Neuropsychologia* 2009; 47:3210–6.
27. Raz N, Ghisletta P, Rodrigue KM, Kennedy KM, Lindenberger U. Trajectories of brain aging in middle-aged and older adults: regional and individual differences. *Neuroimage* 2010; 51:501–11.
28. Sosnoff JJ, Broglio SP, Shin S, Ferrara MS. Previous mild traumatic brain injury and postural control dynamics. *J. Athl. Train.* 2011; 46:85–91.
29. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Tonga AW. Mapping cortical change across the human life span. *Nat. Neurosci.* 2003; 6:309–15.
30. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* 2002; 8:448–60.
31. Sullivan EV, Rohlfing T, Pfefferbaum A. Longitudinal study of callosal microstructure in the normal adult aging brain using quantitative DTI fiber tracking. *Dev. Neuropsychol.* 2010; 35:233–56.
32. Talavage TM, Nauman E, Breedlove EL, *et al.* Functionally-detected cognitive impairment in high school football players without clinically-diagnosed concussion. *J. Neurotrauma* (in press).
33. Tashlykov V, Katz Y, Gazit V, Zohar O, Schreiber S, Pick CG. Apoptotic changes in the cortex and hippocampus following minimal brain trauma in mice. *Brain Res.* 2007; 1130:197–205.
34. Topinkova E. Aging, disability and frailty. *Ann. Nutr. Metab.* 2008; 52:6–11.
35. Wong DF, Wagner HN, Dannals RF, *et al.* Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. *Science* 1984; 226:1393–6.