# Long-term Neurocognitive Dysfunction in Sports: What Is the Evidence?

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**KEYWORDS**

- Neurocognitive dysfunction • Computerized assessment
- Athletes • Concussive injury

Perhaps no issue in sports medicine has attracted so much attention in the media and popular press as the issue of potential long-term consequences of sports-related mild traumatic brain injury (mTBI or concussion). This issue resulted in several congressional hearings in 2009 and 2010 and has led to changes in management policies at the professional, collegiate, and high-school sports levels. For the 2010 football season, no athlete at any level of competition (ie, high school, collegiate, or professional) was allowed to return to play in the same game (or practice) once a concussion had been diagnosed. Similarly, no athlete who sustained a concussion was allowed to return to play before being cleared by a health care professional. At the time of the writing of this article, 6 states in the United States had passed laws mandating medical evaluation and clearance of concussed high-school athletes before their return to play.

Although it can be argued that many of the changes in rules of play and in the management of concussive injuries are long overdue and may lead to a reduction in disability in athletes at all levels of play, the state of scientific investigation regarding the long-term consequences of brain injury in athletes is still in its infancy and the state of affairs is far from clear. Despite public opinion to the contrary, many questions have yet to be answered regarding the actual risk of long-term disability caused by repeated concussion, factors that may influence outcome, and why some athletes seem to develop trauma-related difficulties and others do not. This issue is of significant

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importance to athletes of all ages as we certainly want to better understand and limit the potential for chronic brain-related dysfunction in athletes. However, on the other side of the issue, the notion that repeated concussions lead to irreversible brain dysfunction could have the unfortunate consequence of limiting participation in contact or collision sports for generations of children for whom participation in athletics provides the basis for personal, physical, and social growth.

The purpose of this article is to summarize the published data on the long-term effects of sports concussive injuries, with a focus on high-school/collegiate athletes, professional boxers, and (American) football players. The systematic study of the potential long-term effects of concussive injury on younger/amateur athletes is in its infancy, and little long-term data are available. Thus, the available data on amateur high-school and collegiate athletes is referred to as intermediate effects, and the available data on professional boxing and (American) football players is referred to as long-term effects. The immediate neurocognitive effects of sports-related concussion have been well documented (see Belanger and Vanderploeg[1] for a meta-analysis of studies).

The current state of knowledge regarding intermediate and long-term disability in athletes is summarized and reviewed, and the available scientific evidence is reviewed. More specifically, recent neuropsychological studies on high-school and collegiate athletes as well as survey and neuropathologic research of older boxers and football athletes are reviewed. Future lines of scientific inquiry that may help to increase our knowledge base in the not so distant future are also discussed.

## AMATEUR HIGH-SCHOOL AND COLLEGIATE ATHLETES

Several studies have addressed the issue of potential cumulative effects of concussion on neurocognitive test performance in high-school and collegiate athletes. Macciocchi and colleagues[2] matched a group of college football players with a history of 1 grade 1 concussion (according to American Association of Neurology guidelines) with a group of players with 2 grade 1 concussions. This study was part of a larger study of 2300 division 1-A collegiate football players who were retrospectively examined and followed for 4 years in an effort to investigate the neuropsychological effects of concussive injuries. Participants in this study were matched by age, education, and years in competitive football. All athletes underwent preseason baseline assessment of neurocognitive function by completing several traditional paper-pencil cognitive tests. Baseline assessment also included a history questionnaire and a symptom checklist. Following concussion, players were assessed at 24 h, 5 days, and 10 days after injury. Performance on neuropsychological tests and self-reported symptoms of players who sustained 2 concussions were compared with those players who only sustained 1 concussion. There were no statistically significant differences in test scores between players who sustained 2 concussive injuries versus those with 1 concussive injury. Although there was an expected increase in postconcussive symptoms compared with baseline symptom endorsement, symptoms returned to baseline levels within 10 days for both groups. The investigators also examined within-group differences for players with 2 concussions and found no difference in neurocognitive test performance in players who sustained concussions in close proximity (mean = 33 days) or in subsequent seasons (mean = 532 days). In addition, there was no significant difference found in the number of symptoms endorsed after the first or second concussion in players who sustained 2 injuries.

In the prospective cohort National Collegiate Athletic Association study that evaluated duration of symptoms of collegiate football players after recurrent concussion, Guskiewicz and colleagues[3] found that players with a history of previous concussions were more likely to sustain subsequent concussions than counterparts who did not have any history of concussion. A total of 2905 football players from 25 US colleges (including athletes from Division I, II, and III schools) were followed during their college careers.

All players underwent baseline measures that included a Graded Symptom Checklist (GCS) and an extensive health questionnaire. However, the athletes did not seem to undergo any objective baseline neuropsychological assessment. The GCS was again administered 1, 2, 3, 5, and 7 days after injury. Out of the 2905 college football players who were followed for 3 football seasons, 196 concussions were reported in 184 players. Twelve players sustained repeated concussions within the same season, with 11 players experiencing a second concussion within 10 days of the first injury and 9 concussions occurred within 7 days of the first injury. The rate of concussions occurred with greater frequency in Division III athletes than in Divisions I and II. Many of the concussions that occurred in the sample of athletes could not be retrospectively graded because of insufficient or missing data. The investigators reported that, on average, most athletes who suffered a concussion indicated they were symptom free within 1 week after their injury.

The investigators found that athletes with a history of 3 or more concussions appeared 3 times more likely to sustain a subsequent concussion than those without prior history of concussion. In addition, athletes with a history of multiple concussions experienced a longer duration of symptoms as assessed by athletic trainers. The investigators concluded that college football players with a history of concussion seem more likely to experience another concussive injury. Results from the study also led investigators to conclude that a history of concussion was not only associated with a greater likelihood of future concussive injury but also a slower recovery as indicated by self-report of symptoms.

Iverson and colleagues[4] matched a group of 19 high-school and collegiate athletes with a history of 3 or more concussions with a group of nonconcussed athletes. Subjects were matched by gender, age, education, and sport. All athletes completed a preseason computerized neuropsychological (ImPACT) baseline and were retested within 5 days after concussion (mean = 1.7 days). Baseline differences in symptom scores were noted, with athletes having a positive 3+ history of concussion reporting more symptoms than nonconcussed athletes. There were no statistically significant differences in baseline scores, although a trend toward lower baseline memory test scores was noted in the concussed group. The investigators speculated that the small sample size (and subsequently limited statistical power) precluded the attainment of statistical significance. There was a significant difference on ImPACT memory scores after concussion for the athletes with a history of multiple concussions. The investigators reported that athletes with a history of multiple concussions were 7.7 times more likely to show a major decline in postconcussion memory test performance than athletes with no history of concussion. Iverson and colleagues[4] interpreted this finding as preliminary evidence suggestive of a cumulative effect of multiple concussions.

Moser and colleagues[5] studied 223 high-school athletes who had undergone baseline testing with a symptom checklist and paper-pencil neuropsychological tests. Cumulative grade point averages (GPA) were also available fors all students. Athletes were grouped into those with a recent concussion (1 week before testing; n = 40), athletes with no history of concussion (n = 82), and asymptomatic athletes who had experienced 1 (n = 56), 2, or more (n = 45) prior concussions. The results indicated that asymptomatic athletes with a history of 2 or more concussions performed similarly to athletes with a recent concussive injury. Athletes with a rich history of concussion had lower GPAs than athletes with no history of concussion. The investigators concluded that multiple concussions may have enduring neuropsychological effects in this age group.

Three studies appeared in the *British Journal of Sports Medicine* in 2006 addressing the issue of cumulative effects of concussion on neurocognitive test performance. The first study published was by Iverson and colleagues.[6] Subjects were 867 high-school and collegiate athletes who had completed preseason baseline neuropsychological testing (ImPACT). Athletes were grouped according to self-reported history of concussion. There were 664 athletes with no prior concussions, 149 athletes with 1 prior concussion, and 54 athletes with 2 prior concussions. A multivariate analysis of variance revealed no significant effect, leading the investigators to conclude that if there was indeed a cumulative effect for multiple concussions, it was small and undetectable using computerized neurocognitive test methodology.

The second study was published by Collie and colleagues,[7] who studied 521 Australian Rules footballers. Athletes were divided into groups based on self-reported history of concussion: no concussion (n = 244), 1 concussion (n = 95), 2 concussions (n = 72), 3 concussions (n = 48), and 4 or more concussions (n = 62). All athletes completed baseline neurocognitive measures (CogSport) for 2 consecutive seasons. There were no statistically significant differences in reaction time and total error rates among the groups, leading the investigators to conclude that there was no association between number of previous concussions and current neurocognitive test performance.

The third study was reported by Broglio and colleagues.[8] They retrospectively studied 235 university athletes with a HeadMinder CRI neurocognitive baseline test, and 264 university athletes with a baseline ImPACT test. The athletes were divided into groups based on self-reported history of concussion. No history of concussion was reported by 336 athletes, 105 reported a history of 1 concussion, 36 reported 2 concussions, and 22 reported having had 3 concussions. A multivariate analysis of variance revealed no effect for history of concussion on neurocognitive test performance on either HeadMinder or ImPACT. The investigators concluded that there is either no effect of multiple concussions on neurocognitive test performance or that the decrements may be so subtle that they are undetectable by these neurocognitive measures.

In a more recent study, Bruce and Echemendia[9] investigated the relationship between self-reported history of concussion and performance on neurocognitive tests in a multisport (eg, ice hockey, soccer, lacrosse, football basketball, and so forth) sample of college athletes. The researchers conducted 3 studies as part of their project. First, the association between self-reported history of concussion and performance on computerized neuropsychological tests (ImPACT) was examined. A second study included examination of the association between self-reported history of concussion and performance on traditional paper-pencil neurocognitive tests. The paper-pencil battery of neuropsychological assessment tools included Digit Symbol, Symbol Modalities Test, Stroop Test, Controlled Oral Word Association Test, Trail Making Test A & B, and the Hopkins Verbal Learning Test. As part of the third study, a separate group of athletes were administered both traditional neuropsychological tests and computerized neuropsychological tests (ImPACT) and the relationship between performance on both of these measures and reported history of concussion was examined. The results from the studies did not find an association between a history of self-reported concussion and performance on ImPACT or paper-pencil neuropsychological tests. Based on their findings, the investigators concluded that a history of multiple concussive injuries did not result in clear neurocognitive deficits in their sample of athletes.

In summary, 5 of the 8 studies reviewed revealed no evidence for cumulative adverse effects on neurocognitive function in sports-related concussion. Two studies raised the possibility of a cumulative effect, and another suggested a protracted recovery period following multiple concussions. Our informal analysis is consistent with the results of a recent meta-analysis of athletes reporting multiple concussions.[10] In this study of 614 multiply concussed athletes culled from 8 published studies meeting the investigators' inclusion criteria (6 of which have been reviewed earlier), the overall effect of multiple concussions was determined to be minimal. However, the investigators reported that follow-up analyses indicated that multiple concussions were associated with poorer neurocognitive performance on tests of delayed memory and executive functioning.

## PROFESSIONAL ATHLETES

In this section, the available data on professional boxers and professional (American) football players are reviewed.

### *Boxing*

Perhaps in no other area of sports is the evidence more compelling for long-term adverse neurocognitive effects than in professional boxing. One stated objective in boxing is to inflict a concussion on one's opponent, preferably with loss of consciousness for longer than a count of 10. In 1928 Martland[11] coined the term punch drunk to refer to the long-term neurocognitive effects of boxing. The term dementia pugilistica was introduced by Millspaugh[12] in 1937 and in 1962 Courville[13] referred to the "psychopathic deterioration of pugilists." Jordan and colleagues[14] referred to this disorder as "chronic traumatic brain injury" in boxers. The most recent iteration of this diagnostic classification has been termed chronic traumatic encephalopathy (CTE).[15]

In any discussion of possible long-term cognitive effects from boxing, it is important to distinguish between amateur and professional boxers. A recent meta-analysis of neurocognitive studies of amateur boxers revealed little or no evidence of chronic neurocognitive effects.[16] Conversely, in 1969[17] Roberts reported that 17% of retired professional boxers who had active careers in the earlier part of the twentieth century developed CTE. Clausen and colleagues[18] pointed out that the incidence of CTE in professional boxers was likely on the decline, given that the average duration of a boxer's career in the 1930s was 19 years (currently at 5 years), and that the average number of bouts has been reduced from 336 to 13.

A comprehensive review of studies related to dementia pugilistica was published by Erlanger and colleagues.[19] They estimated the prevalence of moderate to severe dementia in boxers at 20%.

The study by Jordan and colleagues[14] published in *JAMA* is particularly remarkable and worthy of review. Jordan and colleagues[14] studied 30 professional boxers, aged 23 to 76 years, assessing genetic typing (apolipoprotein E4 alleles, a known risk factor for late onset Alzheimer dementia) and neurobehavioral functioning (a combination of motor, cognitive, and neuropsychiatric symptoms). The results indicated that the boxers with the highest exposure (defined as 12 or more professional bouts) had lower neurobehavioral scores than those with less than 12 bouts. The ApoE E4 genotype frequencies among the boxers were reported to parallel the typical distribution in the general population. High-exposure boxers who were positive for at least 1 ApoE allele had the worst neurobehavioral functioning of any subgroup assessed. Jordan and colleagues[14] concluded that boxing exposure and possession of an ApoE E4 allele interacted to result in greater impairment in neurobehavioral functioning.

***Survey Research with National Football League Athletes***

Several major survey studies of National Football League (NFL) retirees' cognitive and biopsychosocial characteristics have been conducted and published in the past decade. These studies have been cited as evidence of long-term adverse effects on mood and/or cerebral functioning in professional athletes. The data presented in these surveys merit a detailed review.

The first study was conducted by a multidisciplinary group associated with the Center for the Study of Retired Athletes at the University of North Carolina at Chapel Hill.[20] In the spring and summer of 2001 and in early 2002, the investigators sent out a general health questionnaire to 3683 living members of the National Football League's Retired Player's Association. A total of 2552 players responded, yielding a response rate of 69.3%. History of concussion was assessed through self-reports, and a concussion was defined as "… an injury resulting from a blow to the head that caused an alteration in mental status and one or more of the following symptoms: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering, and difficulty concentrating" [(p720)].

The results regarding concussion indicated that 1513 retirees (60.8%) reported having sustained at least 1 concussion during their professional playing career, and 597 (24%) reported sustaining 3 or more concussions. About half of those athletes sustaining concussions experienced either loss of consciousness or memory loss. Subjectively, about 17.6% of those athletes sustaining a concussion believed that the concussion had a permanent effect on their thinking and memory skills as they aged.

The health questionnaire also included the SF-36 Measurement Model for Functional Assessment of Health and Well-Being, an index of health, well-being, and activities of daily living. The investigators derived a "… mental health component score, which includes scores of vitality, social functioning, role emotional, and mental health" [(p720)], and compared the scores of the retired athletes with age- and gender-matched norms provided by prior research.[21] A review of the SF-36 reveals that the vitality domain includes 4 items, the social functioning domain includes 2 items, the role-emotional domain includes 3 items, and the mental health domain includes 5 items. The respondent answers each item with a frequency score, with 6 response options available in the original version of the SF-36, and 5 response options available in version 2 of the test.

The Mental Component Scale (MCS) scores on the SF-36 for the NFL retirees aged 50 years and older were similar to those of the general population for all age groups. However, when players were grouped according to the number of reported concussions sustained while playing professional football, the MCS scores of the retired players with 3 or more concussions were worse than those retirees with 0, 1, or 2 concussions at a statistical probability level of less than .001. Inspection of the group means, however, reveals that the average score of the normative group was 52.42 (SD not reported), and the average score of the NFL retirees with 3 or more concussions was 50.31 (SD = 11.26), a mean difference of roughly 2 points. The standard deviations of the MCS scores of the concussion groups ranged from 8.50 to 11.26. Although the mean difference between the groups was statistically significant (with subject numbers ranging from 374 to 814 per group), the question arises as to whether this 2-point mean difference between groups is of any clinical, functional, or practical significance. In 2005, Guskiewicz and colleagues[22] interpreted this finding as evidence of a "… progressive decline in mental health functioning …" [(p722)]. This conclusion may be debatable.

The potential relationship between a history of concussions in professional football and the emergence of late-life depression was discussed in greater detail in a paper published by Guskiewicz and colleagues,[22] in 2007. However, as pointed out by Casson,[23] the data presented in the 2007 paper was based on the same data presented in the 2005 publication; those findings have been addressed earlier in this article.

Approximately 4 months later a second survey focusing on memory and issues related to mild cognitive impairment (MCI) was sent to a subset of 1754 NFL retirees aged 50 years or older, with a copy sent to the player's informant, defined as a spouse or close relative. MCI is a diagnostic classification believed to represent the intermediate domain or transitional phase between normal aging and dementia.[24] Generally speaking, MCI involves the presence of subjectively reported and objectively assessed impairment in at least 1 area of cognitive functioning (typically memory) with preservation of basic activities of daily living.

MCI and memory questionnaire data were available for 758 players and from 641 retired players' spouses/informants. There were 22 cases of physician-diagnosed MCI among the retirees (3 cases involving cerebrovascular accident) and 77 cases of retirees who had significant memory impairment based on informant data. Although percentages are not reported by the investigators, we calculate a rate of physician-diagnosed MCI at 2.9% among retiree-reported data (22/758), and a rate of 12.01% (77/641) based on the informant data.

Plassman and colleagues[25] assessed the prevalence of cognitive impairment without dementia (a functional diagnostic equivalent of MCI) in the US population in a longitudinal study conducted from 2001 to 2005. Overall, they found a 22.2% prevalence rate for cognitive impairment without dementia. They found a 16% prevalence rate in the 71- to 79-year-old cohort (the youngest cohort reported), which is closest to the older NFL retirees in age (mean age of 62.4 years). For the NFL retirees, the physician-based diagnosis rate of MCI (2.9%) and the informant-based rate (12.01%) are less than those reported by Plassman and colleagues[25] for the general population (16%).

Age is a critical variable in the prevalence of MCI, as it is the greatest single risk factor for this diagnosis.[26] The authors were unable to locate a study of prevalence rates of MCI in the Unites States among the 60- to 69-year age range, as most studies use age 70 years as the lower limit for inclusion. Thus, the rates reported earlier based on the Plassman data may not be ideally comparable with the NFL retirees, because the Plassman cohort is, on average, a decade older than the NFL cohort. However, if the rates reported by the NFL retirees were increased by 50% in an inelegant attempt to make age-appropriate prevalence estimates, the NFL retirees' prevalence data remain consistent with (and certainly do not exceed) the general US population data reported by Plassman and colleagues.[25]

In assessing the relationship between number of concussions reported and the presence of Alzheimer disease (AD), the investigators reported that there was no association between the number of concussions sustained as a professional football player and a diagnosis of AD. Thirty-three retirees (1.3%) reported a physician's diagnosis of AD, and about half of those were receiving nootropic (memory-enhancing) therapy. However, the investigators reported that there was a higher prevalence of AD in the retiree cohort than in the corresponding general population, leading the investigators to conclude that "… this group may have an earlier onset of AD than the general American male population" [(p721)]. Plassman and colleagues[25] reported a 5.5% prevalence rate for prodromal AD in the general population. The term prodromal AD is said to be the equivalent of the clinical criteria for a diagnosis of AD, but lacks biopsy or autopsy confirmation. The 1.3% prevalence rate of AD among NFL retirees reported by Guskiewicz and colleagues[20] is less than the age-matched population rate of 5.5% reported by Plassman and colleagues.[25] Again, however, the age variable must be kept in mind, as the retirees were on average, younger than those in the Plassman study.

The second study was conducted in November and December 2008 by the University of Michigan Institute for Social Research.[27] The investigators presented a stratified random survey of 1063 retired NFL players. A wide array of demographic, health, religious, financial, and psychosocial data were collected, including information on depression, intermittent explosive disorder, and dementia. The researchers split the NFL retirees into younger (age 30–49 years) and older (age 50+ years) groups. The data are reported in terms of percentages, and the NFL retirees' data are compared with all US men in similar age brackets (30–49 years and 50+ years). No statistical analyses were conducted to determine if any group differences were statistically significant.

Depression was assessed using a combination of 4 screener items from the National Study of American Life along with items from the Patient Health Questionnaire. There was a higher rate of endorsement of all 4 screener questions for depression among the younger retired players (37.6%) versus the comparable group from all US men (20.7%). Among older retirees, 23% endorsed all 4 screener questions in the positive direction versus 15% in the age-matched all US men group. Current major depression was reported by 3.9% and 3.6% of the younger and older retirees, respectively. The corresponding rates for all US men were 3.0% for the younger group and 3.9% for the older group. The investigators suggested that younger retirees may have a higher rate of depression than age-matched counterparts. This was not the case for the older retirees.

The investigators also screened for intermittent explosive disorder (IED), defined as "episodes of unpremeditated and uncontrollable anger" [(p32)]. A 3-question screening test was used. Irrespective of age, the NFL retirees scored lower on any of the 3 screening items than their age-matched counterparts from the general population. More than half (54.8%) of the younger men from the general population endorsed at least 1 of the screening questions, whereas the corresponding figure for younger NFL retirees was 30.7%). Among older individuals, NFL retirees endorsed at least 1 of the screening questions 29.3% of the time, whereas the corresponding figure for the general male population was 47.2%. The investigators concluded that "... NFL retirees are much less likely to report symptoms of anger than the general population" [(p32)].

The investigators acknowledged that individuals with dementia were more difficult to diagnose than those with depression or IED because dementia directly affects an individual's ability to participate in such a survey. The investigators also acknowledge that they did not administer cognitive tests, neurologic examinations, or review medical records. Weir and colleagues[27] interviewed a proxy reporter (generally the wife) of the retired player. The respondent was asked if a diagnosis of dementia, AD, or other memory-related disease had ever been made. In the younger age group, 0.1% of the general population and 1.9% of the NFL retirees reported these diagnoses. The corresponding figures for the older groups were 1.2% for the general male population and 6.1% for the NFL retirees. The 6.1% rate of dementia diagnoses is similar to the 5.5% rate reported by Plassman and colleagues.[25]

From a research methodological perspective, there are many limitations to survey research. A partial list of the limitations (as pointed out by Guskiewicz and colleagues[20]) include retrospective analysis, the self-reporting nature of responses (often without objective verification), response bias (including socially desirable responding), and sampling error. The authors view survey data as quite useful in the exploratory aspects of a field of inquiry. However, survey data do not typically allow for cause and effect scientific analysis. Although we applaud the investigators of these surveys for making scientific inquiries, we do not believe that survey results allow for cause and effect statements of an evidence-based sort. Our goal is not to criticize the investigators of these surveys for their research; our goal is to clarify the justifiable conclusions from their data.

## NEUROPATHOLOGIC STUDIES OF ATHLETES

In the past several years, neuropathologic studies of retired athletes have appeared in the literature, and significant media attention has been focused on these reports. More specifically, the tragic deaths and subsequent autopsies of 3 retired NFL athletes fueled speculation that NFL athletes were at an increased risk for premature dementia, presumably secondary to multiple blows to the head (concussive or subconcussive) throughout their playing careers. The first reports were individual autopsy studies of 3 NFL athletes.[28–30] The first published report generated a heated rebuttal by Casson and colleagues,[31] criticizing the study on definitional and methodological grounds. These autopsy studies pointed toward CTE as the neuropathologic substrate of premature dementia and death in these athletes. A fourth case involving an NFL athlete was reported in 2007,[32] and a fifth NFL case was reported by McKee and her colleagues[15] in 2009.

The most comprehensive article on CTE was published by McKee and colleagues,[15] who reviewed data from 48 previously published and autopsy-verified cases of CTE and presented data on 3 additional athletes. McKee and colleagues[15] described CTE as a "… neuropathologically distinct slowly progressive tauopathy with a clear environmental etiology" [(p709)]. They described the neurobehavioral manifestations of CTE as changes in memory, behavior, personality, gait, and speech, along with parkinsonism. Neuropathologically, atrophic changes are noted in the cerebral hemispheres, mamillary bodies, medial temporal lobe, and brainstem, with ventricular dilatation and a fenestrated cavum septum pellucidum. Microscopically, CTE involves extensive tau-immunoreactive neurofibrillary and astrocytic tangles along with spindle and thread-like neurites throughout the brain. Beta-amyloid deposition (plaques), 1 of the hallmark features of AD, are said to occur in less than half the cases.

The autopsy-verified cases of CTE reviewed by McKee and colleagues[15] included 39 boxers, 5 NFL players (4 previously published cases and 1 new case), and 1 case each from the sports of wrestling and soccer. Two of the cases reviewed from the literature were head bangers (1 autistic), 1 case died of physical abuse, 1 case had epilepsy, and 1 case was a circus clown with alcoholism who had a history of repeatedly being shot out of a cannon. McKee and colleagues[15] present a detailed comprehensive review of the clinical manifestations in each of the previously published and the 3 newly presented cases. Thus, of the 51 autopsy-verified cases of CTE reviewed by McKee and colleagues,[15] 46 (90%) were athletes, and 39 of the 46 athletes (85%) were boxers.

These initial NFL cases have led to the more systematic recruitment of athletes for eventual postmortem study. This effort has been gaining momentum steadily in the past 5 years and has resulted in the establishment of 2 formal programs at West Virginia University and at Boston University (the latter in conjunction with the Sports Legacy Institute of Boston). These programs have been structured to recruit living athletes for inclusion in the postmortem studies on their deaths.

## LIMITATIONS OF OUR REVIEW

Our review has several limitations. First, our review is restricted to the sports concussion literature, and we have not reviewed the published studies of the intermediate and long-term neurocognitive effects of concussion in nonathletes (civilian and military). Second, not all of the available studies of the effects of concussive injury have been reviewed; studies based on the sport and quality of the research were chosen. Third, a formal meta-analysis of available studies was not done (see Ref.[10] for a recent meta-analysis), as our goal was simply to provide an overview of the research in this area. The emerging data on intermediate neurophysiologic changes in sports-related concussion have not been discussed, as several studies have emerged recently documenting persistent changes in cortical electrophysiologic functions after concussion.[33–35]

## FUTURE DIRECTIONS

As we reviewed the sports concussion literature, we found several moderator variables that could affect the state of the knowledge base regarding the potential adverse long-term effects of multiple concussions. First, many studies contain mixed groups of athletes. For example, published studies have an admixture of men and women, various sports, different ages, and multiple comorbid medical and psychiatric conditions (eg, migraine headaches, attention deficit hyperactivity disorder, learning disabilities). It has been shown in several studies that these biopsychosocial variables may have systematic effects on response to concussive injury, and ultimately may be relevant in determining long-term outcome. For example, gender differences in incidence and response to concussive injury are emerging and it seems that women may have a more protracted outcome.[36,37] Age has been posited to be a significant factor in determining response to sports concussive injury, as some empiric studies[38] and consensus clinical experience[39] have suggested that younger (child and adolescent) athletes may have a lengthier course of recovery than older athletes. Collins and colleagues[40] reported that collegiate athletes with learning disabilities and/or attention deficit spectrum disorders who sustained multiple concussions may have poorer neurocognitive test performances. Mihalik and colleagues[41] found that concussed high-school and collegiate athletes classified as having posttraumatic migraine headache had significantly poorer neurocognitive performances after concussion than those with uncomplicated headache or no headache. The most recent position paper from the Concussion in Sport Group[39] indicated that depression or other psychiatric or sleep disorders may be considered significant modifiers of response to concussive injury. A history of emotional disturbance or psychological illness that predates concussion may also influence the recovery process. In some cases, the athlete's emotional issues may have been fairly controlled until the injury and associated stress results in reemergence of previous emotional difficulties. The elucidation of the role of genetic factors in the incidence and response to concussive injury is another area in need of further study. For example, Terrell and colleagues[42] reported that collegiate athletes with an APOE promoter G-219T TT genotype may be at increased risk for sustaining concussion, and raised the question of the role of tau Ser-50-Pro polymorphism as a risk factor for concussive injury.

Further prospective studies on the intermediate and long-term effects of concussive injuries in various athletic populations are awaited, and it is to be hoped that researchers will include and assess the biopsychosocial factors discussed earlier as potential moderator variables in these studies. In the interim, it is our conclusion based on the literature reviewed that adverse long-term neurocognitive effects of concussive injury have been demonstrated empirically in professional boxers only.

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