App. Tab 95

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF CONNECTICUT

RUSS McCULLOUGH, *et al.*,	:	No. 3:15-cv-01074 (VLB)
	:	Lead Case
Plaintiffs,	:	
	:	
vs.	:	
	:	
WORLD WRESTLING ENTERTAINMENT, INC.,	:	
	:	
Defendant.	:	

EVAN SINGLETON and VITO LOGRASSO,	:	No. 3:15-cv-00425 (VLB)
	:	Consolidated Case
Plaintiffs,	:	
	:	
vs.	:	
	:	
WORLD WRESTLING ENTERTAINMENT, INC.,	:	
	:	
Defendant.	:	

DECLARATION OF MARK R. LOVELL

Commonwealth of Pennsylvania)
) ss:
County of Allegheny)

I, Mark Lovell, do hereby declare and state as follows:

1. I am over eighteen (18) years of age. I have personal knowledge of the matters set forth herein and am competent to testify thereto.

2. I am a neuropsychologist and have been internationally recognized as an authority in the diagnosis and management of concussions in sports. In

particular, I have been recognized for my development of innovative neurocognitive testing programs and ground breaking research.

3. After graduating from Northern Michigan University with a B.S. in psychology/biology, I earned a Ph.D. in clinical psychology with an emphasis in neuropsychology from the Chicago Medical School.

4. In the early-1990s, I developed the ImPACT test, which is the first and most scientifically validated computerized concussions evaluation system. The ImPACT test has become a tool used internationally in the comprehensive clinical management of concussions.

5. I have been a neuropsychological consultant for numerous sports organizations throughout the world including, but not limited to, the National Football League, the Pittsburgh Steelers, the National Hockey League, Irish Rugby, the USA Women's Olympic Hockey team, the U.S. Ski and Snowboard team, the Indianapolis Racing League, CHAMP car racing, Major League Soccer, and World Wrestling Entertainment, Inc.

6. In 2000, I became the founding director of the University of Pittsburgh Medical Center's Sports Medicine Concussion Program, which has been regarded as the first and largest program of its kind.

7. In 2002, I co-founded ImPACT Applications, Inc. and currently serve as its Chairman of the Board and Chief Scientific Officer.

8. I have published more than 100 peer-reviewed articles, authoring or co-authoring nine textbooks and writing over 40 book chapters. I have also been

a reviewer for over 15 professional journals and I am currently serving as an editorial board member for several different journals.

9. I have been a frequent presenter at professional meetings internationally. For example, I was a member of the First and Second International Conferences on Concussion in Sport chartered by the International Olympic Committee, FIFA, and the International Ice Hockey Federation. The objectives of the symposia were to provide recommendations for the improvement of safety and health of athletes who suffer concussive injuries in sport. To this end, a range of experts were invited to both meetings to address specific issues of epidemiology, basic and clinical science, injury grading systems, cognitive assessment, new research methods, protective equipment, management, prevention, and long-term outcome.

10. The First International Conference on Concussion in Sport was held in Vienna in 2001. The Second International Conference on Concussion in Sport was held in Prague in 2004. I was a co-author of the Summary and Agreement Statements issued by the First and Second International Conferences on Concussion in Sport, copies of which are attached hereto as Exhibits 1 and 2, respectively.

11. The Third International Conference on Concussion in Sport was held in Zurich in 2008. A copy of the Consensus Statement on Concussion in Sport issued by the Third International Conference on Concussion in Sport is attached hereto as Exhibit 3.

12. The Fourth International Conference on Concussion in Sport was held in Zurich in 2012. A copy of the Consensus Statement on Concussion in Sport issued by the Fourth International Conference on Concussion in Sport is attached hereto as Exhibit 4.

13. As part of my continuing work in the area of neurocognitive research and testing, I make an effort to review current publications on the subject of concussions and, in particular, chronic traumatic encephalopathy.

14. I am familiar with a 2014 paper published by Christine M. Baugh, Clifford A. Robbins, Robert A. Stern, and Ann C. McKee, MD entitled "Current Understanding of Chronic Traumatic Encephalopathy," a copy of which is attached hereto as Exhibit 5.

15. I am familiar with a symposium presented in November 2015 by the Department of Defense Blast Injury Research Program Coordinating Office entitled "Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?" In connection with that symposium, the Department of Defense published a paper entitled "Literature Review: The Biological Basis of Chronic Traumatic Encephalopathy Following Blast Injury," a copy of which is attached hereto as Exhibit 6.

16. I am familiar with a 2015 Report published by the National Institute of Health (NIH) from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy, a copy of which is attached hereto as Exhibit 7.

I declare under penalty of perjury this 27th day of July, 2016, that the foregoing is true and correct.

Mark R. Lovell, Ph.D.

Exhibit 1

Concussion in sport

Summary and agreement statement of the first International Conference on Concussion in Sport, Vienna 2001*

M Aubry, R Cantu, J Dvorak, T Graf-Baumann, K Johnston (Chair), J Kelly, M Lovell, P McCrory, W Meeuwisse, P Schamasch (the Concussion in Sport (CIS) Group)

Recommendations for the improvement of safety and health of athletes who may suffer concussive injuries

In November 2001, the first International Symposium on Concussion in Sport was held in Vienna, Austria. This symposium was organised by the International Ice Hockey Federation (IIHF), the Federation Internationale de Football Association Medical Assessment and Research Centre (FIFA, F-MARC), and the International Olympic Committee Medical Commission (IOC).

The aim of the symposium was to provide recommendations for the improvement of safety and health of athletes who suffer concussive injuries in ice hockey, football (soccer), and other sports. To this end a range of experts were invited to address specific issues of epidemiology, basic and clinical science, grading systems, cognitive assessment, new research methods, protective equipment, management, prevention, and long term outcome, and to discuss a unitary model for understanding concussive injury. At the conclusion of the conference, a small group of experts were given a mandate by the conference delegates and organising bodies to draft a document describing the agreement position reached by those in attendance at that meeting. For the purpose of this paper, this group will be called the Concussion in Sport Group (CISG).

INTRODUCTION

This review seeks to summarise the findings of the Vienna conference and to provide a working document that will be widely applicable to sport related concussion. This document is developed for use by doctors, therapists, health professionals, coaches, and other people involved in the care of injured athletes, whether at the recreational, elite, or professional level.

During the course of the symposium, a persuasive argument was made that a comprehensive systematic approach to concussion would be of potential benefit to aid the injured athlete and direct management decisions.[1] This protocol represents a work in progress, and, as with all other guidelines or proposals, it must undergo revision as new information is added to the current literature and understanding of this injury.

The concussion in sport protocol includes:

(1) Clinical history
(2) Evaluation
(3) Neuropsychological testing
(4) Imaging procedures
(5) Research methods
(6) Management and rehabilitation
(7) Prevention
(8) Education
(9) Future directions
(10) Medicolegal considerations

A REVISED DEFINITION OF CONCUSSION

Over 35 years ago, the committee on head injury nomenclature of the Congress of Neurological Surgeons proposed a "consensus" definition of concussion.[2] The American Medical Association and the International Neurotraumatology Association subsequently endorsed this definition.[3] This definition was recognised as having a number of limitations in accounting for the common symptoms of concussion. In addition, there was an inability to include relatively minor impact injuries that result in persistent physical and/or cognitive symptoms. Seeking to transcend these limitations, the CISG has developed the following definition of concussion.

"Concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces. Several common features that incorporate clinical, pathological, and biomechanical injury constructs that may be used in defining the nature of a concussive head injury include:

(1) Concussion may be caused by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head.

(2) Concussion typically results in the rapid onset of short lived impairment of neurological function that resolves spontaneously.

(3) Concussion may result in neuropathological changes but the acute clinical symptoms largely reflect a functional disturbance rather than structural injury.

(4) Concussion results in a graded set of clinical syndromes that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course.

(5) Concussion is typically associated with grossly normal structural neuroimaging studies.

THE CISG CONCUSSION PROTOCOL

Clinical history

Recognising the importance of a detailed concussion history and appreciating the fact that many athletes will not recognise all the concussions that they may have suffered in the past, a detailed concussion history is of value. The athlete currently at a high performance level in collision sport has seldom had the first concussion on presentation in the consultant's office. The history should include specific questions as to previous symptoms of a concussion, not just perceived number of past concussions.[4] It is also worth noting that dependence on the recall of concussive injuries by teammates or coaches has been shown to be unreliable.[5] The finding that there is increased risk of subsequent concussive injuries after a first concussion is documented, although the reasons for this remain controversial. The clinical history should also include information about all previous head, face, or neck injuries as these may have clinical relevance to the present injury. It is worth emphasising that, in the setting of faciomaxillary injuries, coexistent concussive injuries may be missed unless specifically assessed.

Specific questions about disproportionate impact and matching of symptom severity may allude to progressively increasing vulnerability to injury—that is, more pronounced persistent symptoms from smaller hits. The pathophysiological nature of this phenomenon remains unclear.

* This statement is being published simultaneously with the *Clinical Journal of Sport Medicine* and the *Physician and Sportsmedicine*

Table 1 Scale of postconcussion symptoms

	Rating						
	None			Moderate			Severe
Headache	0	1	2	3	4	5	6
Nausea	0	1	2	3	4	5	6
Vomiting	0	1	2	3	4	5	6
Drowsines	0	1	2	3	4	5	6
Numbness or tingling	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sleeping more than usual	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling like "in a fog"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Trouble falling asleep	0	1	2	3	4	5	6
More emotional than usual	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervousness	0	1	2	3	4	5	6
Other	0	1	2	3	4	5	6

Adapted from Lovell and Collins.[13]

One of the issues that was speculated upon at the conference was whether concussion represents a unitary phenomenon with a linear spectrum of injury severity or whether different concussion subtypes exist. These subtypes may represent differences in clinical manifestations (confusion, memory problems, loss of consciousness), anatomical localisation (cerebral *v* brainstem, for example), biomechanical impact (rotational *v* linear force), genetic phenotype (ApoE4 positive *v* ApoE4 negative), neuropathological change (structural injury *v* no structural injury), or an as yet undefined difference. These factors may operate independently or interact with each other. It is clear that the variations in clinical outcome from the same impact force require a more sophisticated approach to the understanding of this phenomenon than is currently available.[6]

The traditional approach to severe traumatic brain injury using loss of consciousness as the primary measure of injury severity has acknowledged limitations in assessing the severity of concussive injury. Findings in this field describe association of loss of consciousness with specific early deficits but does not necessarily imply severity. Further work in this area may help to explain these findings.[7]

There is renewed interest in the role of amnesia (anterograde/retrograde) and its manifestation of injury severity.[8] Published evidence suggests that the nature, burden, and duration of the clinical postconcussive symptoms may be more important than previously recognised.[9–11]

Concussion grading scales

The CISG recognised the strengths and weaknesses of several existing concussion grading scales that attempt to characterise injury severity, but no single system was endorsed. It was the recommendation of the CISG that combined measures of recovery (see below) should be used to assess injury severity (and/or prognosis) and hence individually guide decisions on return to play.

In the absence of scientifically validated return to play guidelines, a clinical construct is recommended using an assessment of injury recovery and graded return to play. The protocol outlined below is adapted from the Canadian Academy of Sport Medicine (CASM) guidelines.[12] Sideline evaluation includes clinical evaluation of signs and symptoms, ideally using a standardised scale of postconcussion symptoms (table 1) for comparison purposes, and acute injury testing as described below under neuropsychological testing.

Evaluation

Sideline evaluation including neurological assessment and mental status testing is an essential component in the protocol. These evaluations are ideally developed in language translations for international sporting groups (an example of such a sideline evaluation developed at McGill University is available in English and French; for a copy, contact author KMJ). In the acute assessment of concussive injury—that is, concussion diagnosis—brief neuropsychological test batteries that assess attention and memory function have been shown to be practical and effective. Such tests include the Maddock's questions[14] and the Standardised Assessment of Concussion (SAC).[15] It is worth noting that standard orientation questions—for example, time, place, person—have been shown to be unreliable in the sporting situation compared with memory assessment.[14 16]

It is recognised, however, that abbreviated testing paradigms are designed for rapid evaluation of concussion on the sidelines and are not meant to replace comprehensive neuropsychological testing, which is sensitive enough to detect subtle deficits that may exist beyond the acute episode.

Signs and symptoms of acute concussion

If any one of the following symptoms or problems is present, a head injury should be suspected, and appropriate management instituted. A player does not need to have lost consciousness to suffer a concussion.

(a) Cognitive features

Unaware of period, opposition, score of game

Confusion

Amnesia

Loss of consciousness

Unaware of time, date, place

(b) Typical symptoms

Headache

Dizziness

Nausea

Unsteadiness/loss of balance

Feeling "dinged" or stunned or "dazed"

"Having my bell rung"

Seeing stars or flashing lights

Ringing in the ears

Double vision

Other symptoms such as sleepiness, sleep disturbance, and a subjective feeling of slowness and fatigue in the setting of an impact may indicate that a concussion has occurred or has not resolved.

(c) Physical signs

Loss of consciousness/impaired conscious state

Poor coordination or balance

Concussive convulsion/impact seizure

Gait unsteadiness/loss of balance

Slow to answer questions or follow directions

Easily distracted, poor concentration

Displaying unusual or inappropriate emotions, such as laughing or crying

Nausea/vomiting

Vacant stare/glassy eyed

Slurred speech

Personality changes

Inappropriate playing behavior for example, running in the wrong direction

Appreciably decreased playing ability

Neuropsychological assessment after concussion

The application of neuropsychological testing in concussion has been shown to be of value and continues to contribute significant information in concussion evaluation.[17] It has been shown that cognitive recovery may precede or follow resolution of clinical symptoms, suggesting that the assessment of cognitive function should be an important component in any return to play protocol.

In the consideration of injury recovery or return to play, such test strategies must assess the cognitive domains of information processing, planning, memory, and switching mental set. Numerous paradigms are in current use. Examples of these include paper and pencil tests (McGill ACE, SAC), condensed batteries (McGill ACE), comprehensive protocols administered by neuropsychologists (NHL, Australian football), and computerised test platforms—for example, IMPACT, CogSport, ANAM, Headminders.[18]

The consensus of the CISG was that neuropsychological testing is one of the cornerstones of concussion evaluation and contributes significantly to both understanding of the injury and management of the individual.

Overriding principles common to all neuropsychological test batteries is the need for and benefit of baseline preinjury testing and serial follow up. Recent work with computerised platforms, however, suggests that performance variability may be a key measure for diagnosis of acute concussion even in the absence of a baseline test. This strategy is currently the subject of continuing research. Inherent problems with most neuropsychological tests include the normal ranges, sensitivity and specificity of tests, and practice or learning effect, as well as the observation that players may return to baseline while still symptomatic.[17 19] In part, these may be a problem of the currently available pen and paper tests. Computerised testing using infinitely variable test paradigms may overcome these concerns. Computerised testing also has the logistical advantage that the tests may be administered by the team doctor or be web based rather than having to employ a neuropsychologist for a formal assessment. The strengths and weaknesses of such testing have been recently reviewed.[18]

The consensus of the CISG was that neuropsychological testing is one of the cornerstones of concussion evaluation and contributes significantly to both understanding of the injury and management of the individual. Organised sport federations have access to and should attempt to employ such testing as appropriate. To maximise the clinical utility of such neuropsychological assessment, baseline testing is recommended.

Neuroimaging

It was recognised by the CISG that conventional structural neuroimaging is usually normal in concussive injury. Given that caveat, the following suggestions are made. Brain computed tomography (or where available magnetic resonance imaging (MRI) brain scan) contributes little to concussion evaluation, but should be used whenever suspicion of a structural lesion exists. Examples of such situations may include prolonged disturbance of conscious state, focal neurological deficit, seisure activity, or persistent clinical or cognitive symptoms.

Newer structural MRI modalities, including gradient echo, perfusion, and diffusion weighted imaging, have greater sensitivity for structural abnormalities; however, the lack of published studies as well as the absence of preinjury neuroimaging data limits the usefulness of this approach in clinical studies at the present time. In addition, the predictive value of various MRI abnormalities that may be incidentally discovered is not established at the present time. Promising new functional imaging—for example, PET/SPECT/fMRI—technologies, while producing some compelling findings, are still at the early stages of development.[20]

Although neuroimaging may play a part in postconcussive return to play decisions or for the assessment of moderate to severe brain injury, it is not essential for otherwise uncomplicated concussive injury.

Research methods

A number of research protocols and data evaluating concussion injury assessment, injury susceptibility, and brain function after injury were presented at the Vienna conference. All of these techniques, while offering great potential for injury assessment, must be considered experimental at this time. As much as possible, elite and professional teams are well placed to contribute to these efforts through athlete recruitment for studies showing the scientific value of such approaches.

Electrophysiological recording (ERP, EEG) has shown reproducible abnormalities in the postconcussive state in brain function.[19] Similarly, balance testing has shown impairment after injury, although the mechanism for this is not established. Biochemical serum markers of brain injury (including S-100b, NSE, MBP) were proposed as means of detecting cellular damage if present.

Genetic phenotyping has been shown to be of benefit in traumatic brain injury. Published studies have shown that ApoE4 is a risk factor for adverse outcome following moderate to severe brain injury.[21] Similarly ApoE4 has been shown to be a risk factor for the development of chronic traumatic encephalopathy in boxers.[22] The significance of ApoE4 in concussion risk or injury outcome is unclear. Other published studies have noted the association of a particular calcium subunit gene abnormality with brain swelling after minor head trauma.[23]

Such research is vital in contributing to the science of concussion and will potentially provide valuable information for such important issues as clinical management, return to play guidelines, and long term outcome. Therefore research should be continued and encouraged by sporting organisations.

Management and rehabilitation

Acute response

When a player shows ANY symptoms or signs of a concussion:

(1) The player should not be allowed to return to play in the current game or practice.

(2) The player should not be left alone; and regular monitoring for deterioration is essential.

(3) The player should be medically evaluated after the injury.

(4) Return to play must follow a medically supervised stepwise process.

A player should never return to play while symptomatic. "When in doubt, sit them out!"

Rehabilitation

It was the consensus of the CISG that a structured and supervised concussion rehabilitation protocol is conducive to optimal injury recovery and safe and successful return to play. The rehabilitation principles were common to all identified programmes and are outlined below. Important principles state that the athlete be completely asymptomatic and have normal neurological and cognitive evaluations before the start of the rehabilitation programme. Therefore the more prolonged the symptom duration, the longer the athlete will have sat out. The athlete will then proceed stepwise with gradual incremental increases in exercise duration and intensity, and pause or backtrack with any recurrence of concussive symptoms. It is appreciated that, although each step may take a minimum of one day, depending on the duration of symptoms, proceeding through each step may take longer in individual circumstances.

Return to play protocol

Return to play after a concussion follows a stepwise process:

(1) No activity, complete rest. Once asymptomatic, proceed to level (2).

(2) Light aerobic exercise such as walking or stationary cycling.

(3) Sport specific training—for example, skating in hockey, running in soccer.

(4) Non-contact training drills.

(5) Full contact training after medical clearance.

(6) Game play.

With this stepwise progression, the athlete should continue to proceed to the next level if asymptomatic at the current level. If any symptoms occur after concussion, the patient should drop back to the previous asymptomatic level and try to progress again after 24 hours.

Prevention

As part of the clinical history, it is advised that details of the protective equipment used at the time of injury be sought, for both recent and remote injuries. The benefit of this approach allows modification and optimisation of protective behaviour and an opportunity for education. That said, there are relatively few methods by which concussive brain injury may be minimised in sport. The brain is not an organ that can be conditioned to withstand injury. Thus, extrinsic mechanisms of injury prevention must be sought.

> Rule changes and rule enforcement play a key role in reducing and preventing concussions.

Helmets have been proposed as a means of protecting the head and theoretically reducing the risk of brain injury. In sports in which high speed collisions can occur or which have the potential for missile injuries—for example, baseball—or for falls on to hard surfaces—for example, gridiron, ice hockey—there is published evidence that use of sport specific helmets reduces head injuries.[3] For other sports such as soccer and rugby, no sport specific helmets have been shown to be of benefit in reducing rates of head injury.[24] Some believe that the use of protective equipment may deleteriously alter playing behaviour so that the athlete actually increases his or her risk of brain injury.[25]

Although the use of correctly fitting mouthguards can reduce the rate of dental, orofacial, and mandibular injuries, the evidence that they reduce cerebral injuries is largely theoretical, and no clinical evidence for a beneficial effect in reducing concussion rates has yet been demonstrated clinically.[26]

Consideration of rule changes, such as no head checking in ice hockey, to reduce the head injury rate may be appropriate where a clear cut mechanism is implicated in a particular sport. Similarly, rule enforcement is a critical aspect of such approaches and referees play an important role.

Conditioning of the neck muscles may be of value in reducing impact forces transmitted to the brain. Biomechanical concepts dictate that the energy from an impacting object is dispersed over the greater mass of an athlete if the head is held rigidly. Although attractive from a theoretical standpoint, there is little scientific evidence for the effectiveness of such measures.

Rule changes and rule enforcement play a key role in reducing and preventing concussions.

Education

As the ability to treat or reduce the effects of concussive injury after the event is minimal, education of athletes, colleagues, and those working with them, as well as the general public is a mainstay of progress in this field. Athletes and their healthcare providers must be taught how to detect concussion, its clinical features, assessment techniques, and principles of safe return to play. Methods to improve education including various web based resources (for example, www.concussionsafety.com), educational videos, outreach programmes, concussion working groups, and the support and endorsement of enlightened sport groups such as FIFA, IOC, and IIHF who initiated this endeavour have enormous value and must be pursued vigorously.

The promotion of fair play and respect for opponents are ethical values that should be encouraged in all sports and sporting associations. Similarly coaches, parents, and managers play an important part in ensuring these values are implemented on the field of play.

Future directions

Efforts to evaluate long term outcome and any association with repeated concussion, molecular markers, imaging, and functional deficits must guide continuing investigation in this work. Efforts to expand knowledge of injury that may or may not be associated with particular manoeuvres inherent to the game, such as heading in soccer, must be elucidated.

A proposal was made that this concussion working group be identified and given a mandate to provide continuing leadership in the continued development and updating of guidelines and maintenance of the pursuit of a high standard of care in concussion.

Medicolegal considerations

Although agreement exists about the principal messages conveyed by this document, the authors acknowledge that the science of concussion is at the early stages and therefore management and return to play decisions remain largely in the realm of clinical judgment on an individual basis. It is the intention of the group to analyse the medicolegal aspect of concussions in sports and to offer here a summary of the state of the art and to direct future efforts.

ACKNOWLEDGEMENTS

The Vienna CIS Group thanks the other participants of the symposium for input and enthusiasm, which generated discussion of these ideas. We also thank Darlene Scheurich whose expert organisational abilities contributed to the success of this symposium.

Br J Sports Med 2002;**36**:6–10

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Female athlete triad syndrome

New criteria for female athlete triad syndrome?

K M Khan, T Liu-Ambrose, M M Sran, M C Ashe, M G Donaldson, J D Wark

As osteoporosis is rare, should osteopenia be among the criteria for defining the female athlete triad syndrome?

The American College of Sports Medicine (ACSM) has provided a great deal of impetus to educating healthcare providers, athletes, and the general public about the potential harm of a "serious syndrome consisting of disordered eating, amenorrhoea and osteoporosis".[1] We recognise and respect the importance of research and attention to this clinical problem and commend the ACSM on its contribution to date.[2] To their credit, the authors of the most recent position stand acknowledged that there were no data reporting prevalence on this condition,[3] and they encouraged further research. Since then, Mayo Clinic physiatrist Tamara Lauder[4] has published two important papers showing a 0% prevalence of the female athlete triad (as defined by ACSM) despite 34% of this military population being at risk of disordered eating. Therefore we re-examined the prevalence of one component of the female athlete triad, osteoporosis, in studies of athletic women with menstrual disturbance. The syndrome can be no more prevalent than any one of its diagnostic criteria alone. Thus, if osteoporosis is only present in a small proportion of the population, then it follows that the female athlete triad can only be prevalent in an equally small, or smaller, proportion of that population.

DIFFERENTIATING OSTEOPOROSIS FROM OSTEOPENIA

Because of the increasing public awareness of osteoporosis and its complications, medical practitioners must not use the term as a synonym for "low bone mass".[5] The current standard for measuring bone mass (bone mineral density; BMD) is by dual energy *x* ray absorptiometry, and since 1994 the term osteoporosis has had diagnostic criteria based on this technique.[3 6 7] Osteoporosis is defined as BMD more than 2.5 standard deviations below the mean of young adults. The term osteopenia describes BMD scores between 1 and 2.5 standard deviations below the mean of young adults. Scrutiny of many papers examining BMD data in athletes at risk of the female athlete triad syndrome (table 1) suggests that osteopenia has a significant prevalence but that osteoporosis is relatively uncommon, even in this selected population. In the substantial reviews of Bennell *et al*,[8 9] menstrual disturbance was associated with a mean 10.3% lower lumbar spine BMD, which reflects the lower limit of normal BMD and very early osteopenia (T score about −1.0). Not surprisingly, numerous authors reporting bone health of sportswomen have used osteopenia as the appropriate term.[8 10–13] Interestingly, even in the significant pathology of anorexia nervosa, the mean BMD of patients reflects osteopenia rather than osteoporosis.[11] A crucial point is that significant osteopenia—that is, T-score of −2.0—in a 20 year old may provide a worse prognosis for long term bone health than osteoporosis in a 65 year old with a T-score of −2.6.

Osteoporosis can, and does, occur in athletes[14 15] (table 1), but we argue that requiring this condition to be present in the female athlete triad syndrome relegates the syndrome to relative obscurity. It is unlikely that the prevalence of osteoporosis in athletes with disordered eating could be greater than the prevalence of osteoporosis in anorexia nervosa (table 2). Therefore, the female athlete triad, as currently defined, most likely has a lower prevalence than anorexia nervosa. This is borne out by the data of Lauder *et al*[4] showing that the prevalence of anorexia nervosa was < 8% but the prevalence of the female athlete triad was 0%. Anorexia nervosa has an overall age adjusted incidence per 100 000 person years of 14.6 for females and 1.8 for males.[16] Thus, if osteoporosis is a diagnostic criterion for the female athlete triad, the triad should have an age adjusted incidence of substantially less than 0.015% in the population at large. Note that this calculation is not based on anorexia being an essential component of the triad—it is not. These data merely recognise the fact that osteoporosis, as strictly defined, affects only a proportion

Exhibit 2

SUPPLEMENT

Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004

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Accepted 7 February 2005

Br J Sports Med 2005;**39**(Suppl I):i78–i86. doi: 10.1136/bjsm.2005.018614

In November 2001, the 1st International Symposium on Concussion in Sport was held in Vienna, Austria to provide recommendations for the improvement of safety and health of athletes who suffer concussive injuries in ice hockey, football (soccer), and other sports. The 2nd International Symposium on Concussion in Sport was organised by the same group and held in Prague, Czech Republic in November 2004. It resulted in a revision and update of the Vienna consensus recommendations, which are presented here.

This paper is a revision and update of the Vienna consensus recommendations developed after the 1st International Symposium on Concussion in Sport.[1] The Prague agreement statement is designed to build on the principles outlined in the original Vienna document and to develop further conceptual understanding of this problem. This document is developed for use by doctors, therapists, health professionals, coaches, and other people involved in the care of injured athletes, whether at the recreational, elite, or professional level.

BACKGROUND PERSPECTIVE

In November 2001, the 1st International Symposium on Concussion in Sport was held in Vienna, Austria. This meeting was organised by the International Ice Hockey Federation (IIHF) in partnership with the Federation Internationale de Football (FIFA) and the International Olympic Committee Medical Commission (IOC). As part of the resulting mandate for the future, the need for leadership and updates was identified. To meet that mandate, the 2nd International Symposium on Concussion in Sport was organised by the same group and held in Prague, Czech Republic in November 2004.

The original aims of the symposia were to provide recommendations for the improvement of safety and health of athletes who suffer concussive injuries in ice hockey, football (soccer), and other sports. To this end a range of experts were invited to both meetings in order to address specific issues of epidemiology, basic and clinical science, injury grading systems, cognitive assessment, new research methods, protective equipment, management, prevention, and long term outcome. At the conclusion of the initial conference, a small group of experts were given a mandate by the conference delegates and organising bodies to draft a document describing the agreement position reached by those in attendance at that meeting. That document was co-published in the *British Journal of Sports Medicine*, *Clinical Journal of Sport Medicine*, and *Physician and Sportsmedicine*.[1]

The wider interest base resulting from the first meeting and document was reflected by the expanded representation. New groups at the second meeting included trauma surgeons, sport psychologists, and others. This same group has produced the current document as an update of the original Vienna consensus document and includes a sideline assessment form with a pocket sized summary card for use by clinicians.

This protocol represents a work in progress, and, as with all other recommendations or proposals, it must be updated as new information is added to the current state of the literature and understanding of this injury.

First published in the main issue of *BJSM* in April (*Br J Sports Med* 2005;**39**:196–204).

BACKGROUND ISSUES

Definition of concussion

Over 35 years ago, the Committee on Head Injury Nomenclature of the Congress of Neurological Surgeons proposed a "consensus" definition of concussion.[2 3] This definition was recognised as having a number of limitations in accounting for the common symptoms of concussion. In the Vienna document, a revised consensus definition was proposed as follows: "Sports concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces". Several common features that incorporate clinical, pathological, and biomechanical injury constructs that may be used in defining the nature of a concussive head injury include the following.

(1) Concussion may be caused by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head.
(2) Concussion typically results in the rapid onset of short lived impairment of neurological function that resolves spontaneously.
(3) Concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than structural injury.
(4) Concussion results in a graded set of clinical syndromes that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course.
(5) Concussion is typically associated with grossly normal structural neuroimaging studies.

No changes were made to the definition by the Prague Group beyond noting that in some cases post-concussive symptoms may be prolonged or persistent.

Pathophysiological basis of concussion

At this time, there is no existing animal or other experimental model that accurately reflects a sporting concussive injury. It is noted that, in experimental models, of more severe injury a complex cascade of biochemical, metabolic, and gene expression changes occur.[4] Whether similar metabolic changes occur in sports concussion, however, remains speculative at this time.[5]

Concussion grading scales

The Vienna recommendation that injury grading scales be abandoned in favour of combined measures of recovery in order to determine injury severity (and/or prognosis) and hence individually guide return to play decisions received continued support.

It was also noted that concussion severity can only be determined in retrospect after all concussion symptoms have cleared, the neurological examination is normal, and cognitive function has returned to baseline.[6] There is limited published evidence that concussion injury severity correlates with the number and duration of acute concussion signs and symptoms and/or degree of impairment on neuropsychological testing.[7–12] The development of validated injury severity scales continues in the published literature.[13]

Subtypes of concussion

One of the issues speculated on at the Vienna conference was whether concussion represents a unitary phenomenon with a linear spectrum of injury severity or whether different concussion subtypes exist. These subtypes may represent differences in clinical manifestations (confusion, memory problems, loss of consciousness), anatomical localisation (such as cerebral versus brainstem), biomechanical impact (rotational versus linear force), genetic phenotype (apolipoprotein epsilon 4 (ApoE4) positive versus ApoE4 negative), neuropathological change (structural injury versus no structural injury), or an as yet undefined difference. These factors may operate independently or interact with each other. It is clear that the variations in clinical outcome with the same impact force require a more sophisticated approach to the understanding of this phenomenon than currently available.[14]

Significance of loss of consciousness

The traditional approach to severe traumatic brain injury using loss of consciousness as the primary measure of injury severity has acknowledged limitations in assessing the severity of sporting concussive injury. Findings in this field describe association of loss of consciousness with specific early deficits but does not necessarily imply severity.[13 15] As such the presence of loss of consciousness as a symptom would not necessarily classify the concussion as complex (see below).

Significance of amnesia

There is renewed interest in the role of post-traumatic amnesia and its role as a surrogate measure of injury severity.[13 16] Published evidence suggests that the nature, burden, and duration of the clinical post-concussive symptoms may be more important than the presence or duration of amnesia alone.[8 15 17] Further it must be noted that retrograde amnesia varies with the time of measurement after the injury and hence is poorly reflective of injury severity.[18 19]

Paediatric concussive injury

The general recommendations outlined in the Vienna document were originally designed for the management of adult sporting concussion. Agreement was reached, however, that identified those recommendations as relevant and useful to management of children as well. In broad terms it was felt that the recommendations should be applicable to children (defined as 5–18 years of age) whereby children should not be allowed to return to play or training until clinically completely symptom free. In addition, the concept of "cognitive rest" was introduced with special reference to a child's need to limit exertion with activities of daily living and to limit scholastic activities while symptomatic. There was also a recognition by the group that additional research is needed to better clarify the potential differences between adults and children with regard to recovery from injury and to develop cognitive assessment tools that better evaluate the younger athlete.

Formal cognitive assessment is currently problematic until late teen years because of the continuing cognitive maturation that occurs during this period, which, in turn, makes the utility of comparison with either the person's own baseline performance or population norms limited.[20]

Because of the different physiological response during childhood to head trauma, a conservative return to play approach is recommended. It may be appropriate to extend the amount of time of asymptomatic rest and/or the length of the graded exertion in children and adolescents. Future research is needed in this area.

A NEW CLASSIFICATION OF CONCUSSION IN SPORT

Historically, concussions have been classified with a number of different grading systems. In the Vienna Statement, this approach was abandoned. One of the key developments by the Prague Group is the understanding that concussion may be categorised for management purposes as either simple or complex.

Simple concussion

In simple concussion, an athlete suffers an injury that progressively resolves without complication over 7–10 days. In such cases, apart from limiting playing or training while symptomatic, no further intervention is required during the period of recovery, and the athlete typically resumes sport without further problem. Formal neuropsychological screening does not play a role in these circumstances, although mental status screening should be a part of the assessment of all concussed athletes. Simple concussion represents the most common form of this injury and can be appropriately managed by primary care physicians or by certified athletic trainers working under medical supervision.[21] The cornerstone of management is rest until all symptoms resolve and then a graded programme of exertion before return to sport. All concussions mandate evaluation by a medical doctor.

Complex concussion

Complex concussion encompasses cases where athletes suffer persistent symptoms (including persistent symptom recurrence with exertion), specific sequelae (such as concussive convulsions), prolonged loss of consciousness (more than one minute), or prolonged cognitive impairment after the injury. This group may also include athletes who suffer multiple concussions over time or where repeated concussions occur with progressively less impact force. In this group, there may be additional management considerations beyond simple return to play advice. Formal neuropsychological testing and other investigations should be considered in complex concussions. It is envisaged that such athletes would be managed in a multidisciplinary manner by doctors with specific expertise in the management of concussive injury such as a sport medicine doctor with experience in concussion, sports neurologist, or neurosurgeon.

CLINICAL ISSUES

Pre-participation physical examination

Recognising the importance of concussion history, and appreciating the fact that many athletes will not recognise all the concussions they may have suffered in the past, a detailed concussion history is of value.[22–25] Such a history may identify athletes that fit into the "complex" category outlined above and provides an opportunity for the doctor to educate the athlete about the significance of concussive injury.

A structured concussion history should include specific questions as to previous symptoms of a concussion, not just perceived number of past concussions. It is also worth noting that dependence on the recall of concussive injuries by team mates or coaches has been shown to be unreliable.[22] The clinical history should also include information about all previous head, face, or neck injuries, as these may have clinical relevance to the present injury. It is worth emphasising that, with maxillofacial and neck injuries, co-existent concussive injuries may be missed unless specifically assessed. Specific questions pertaining to disproportionate impact versus symptom severity matching may alert the clinician to a progressively increasing vulnerability to injury.

As part of the clinical history, it is advised that details on protective equipment used at the time of injury be sought, both for recent and remote injuries. The benefit of this approach allows modification and optimisation of protective behaviour and an opportunity for education.

It is specifically recommended that:

(1) both a baseline cognitive assessment (such as the Prague SCAT test in the absence of computerised neuropsychological testing) and symptom score is performed as part of the pre-participation evaluation;

(2) although formal baseline neuropsychological screening may be beyond the resources of many sports or individual athletes, it is recommended that, in organised high risk sports, consideration be given to having cognitive evaluation regardless of the age or level of performance.

Signs and symptoms of acute concussion

The suspected diagnosis of sports concussion made on the sideline is applicable to both medical and non-medical personnel and can include clinical symptoms, physical signs, cognitive impairment, and/or loss of consciousness.

If any one of the following symptoms or problems is present, a head injury should be suspected and appropriate management instituted. These will be summarised on the sideline concussion assessment tool (SCAT) that accompanies this document (fig 1).

(a) Cognitive features (see below)
- Unaware of period, opposition, score of game
- Confusion
- Amnesia
- Loss of consciousness

(b) Typical symptoms (see SCAT (fig 1) for standard symptom scale); other symptoms such as a subjective feeling of slowness and fatigue after an impact may indicate that a concussion has occurred or has not fully resolved.[26]
- Headache or pressure in the head
- Balance problems or dizziness
- Nausea
- Feeling "dinged", "foggy", stunned, or "dazed"
- Visual problems—for example, seeing stars or flashing lights, double vision
- Hearing problems—for example, ringing in the ears
- Irritability or emotional changes

(c) Physical signs
- Loss of consciousness/impaired conscious state
- Poor coordination or balance
- Concussive convulsion/impact seizure
- Gait unsteadiness/loss of balance
- Slow to answer questions or follow directions
- Easily distracted, poor concentration
- Displaying inappropriate emotions—for example, laughing, crying
- Vomiting
- Vacant stare/glassy eyed
- Slurred speech
- Personality changes
- Inappropriate playing behaviour—for example, running in the wrong direction
- Significantly decreased playing ability

Sideline evaluation of cognitive function is an essential component in the assessment of this injury. Brief neuropsychological test batteries that assess attention and memory function have been shown to be practical and effective. Such tests include the Maddocks questions[27] and the Standardised assessment of concussion.[28] It is worth noting that standard orientation questions—for example, time, place, person—have been shown to be unreliable in the sporting situation when compared with memory assessment.[27 29]

It is recognised, however, that abbreviated testing paradigms are designed for rapid concussion evaluation on the sidelines and are not meant to replace comprehensive neuropsychological testing, which is sensitive enough to detect subtle deficits that may exist beyond the acute episode, nor should they be used as a stand alone tool for the ongoing management of sports concussions. It should also be recognised that the appearance of symptoms may be delayed several hours after a concussive episode.

Convulsive and motor phenomena

A variety of acute motor phenomena—for example, tonic posturing—or convulsive movements may accompany a concussion.[30 31] Although dramatic, these clinical features are generally benign and require no specific management beyond the standard treatment for the underlying concussive injury.

Development of the sport concussion assessment tool (SCAT)

Figure 1 outlines the SCAT. The intent was to create a standardised tool that could be used for patient education as well as for physician assessment of sports concussion. The SCAT was developed by combining the following existing tools into a new standardised tool:

(1) Sideline evaluation for concussion.[28 29]

(2) Management of concussion sports palm card; American Academy of Neurology and the Brain Injury Association.[32]

(3) Standardised assessment of concussion.[33]

(4) Sideline concussion check; UPMC, Thinksafe, Sports Medicine New Zealand Inc and the Brain Injury Association.

A

This tool represents a standardized method of evaluating people after concussion in sport. This Tool has been produced as part of the Summary and Agreement Statement of the Second International Symposium on Concussion in Sport, Prague 2004

Sports concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces. Several common features that incorporate clinical, pathological and biomechanical injury constructs that may be utilized in defining the nature of a concussive head injury include:

1. Concussion may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an 'impulsive' force transmitted to the head.
2. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously.
3. Concussion may result in neuropathological changes but the acute clinical symptoms largely reflect a functional disturbance rather than structural injury.
4. Concussion results in a graded set of clinical syndromes that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course.
5. Concussion is typically associated with grossly normal structural neuroimaging studies.

Post Concussion Symptoms
Ask the athlete to score themselves based on how they feel now. It is recognized that a low score may be normal for some athletes, but clinical judgment should be exercised to determine if a change in symptoms has occurred following the suspected concussion event.

It should be recognized that the reporting of symptoms may not be entirely reliable. This may be due to the effects of a concussion or because the athlete's passionate desire to return to competition outweighs their natural inclination to give an honest response.

If possible, ask someone who knows the athlete well about changes in affect, personality, behavior, etc.

Remember, concussion should be suspected in the presence of ANY ONE or more of the following:

- Symptoms (such as headache), or
- Signs (such as loss of consciousness), or
- Memory problems

Any athlete with a suspected concussion should be monitored for deterioration (i.e., should not be left alone) and should not drive a motor vehicle.

For more information see the "Summary and Agreement Statement of the Second International Symposium on Concussion in Sport" in the:
Clinical Journal of Sport Medicine 2005; xx(xx): xxx-x
British Journal of Sports Medicine 2005; xx(xx): xxx-x
Neurosurgery 2005; ; xx(xx): xxx-x
Physician and Sportsmedicine 2005; xx(xx): xxx-x
This tool may be copied for distribution to teams, groups and organizations.

The SCAT Card

(Sport Concussion Assessment Tool)

Athlete Information

What is a concussion? A concussion is a disturbance in the function of the brain caused by a direct or indirect force to the head. It results in a variety of symptoms (like those listed below) and may, or may not, involve memory problems or loss of consciousness.

How do you feel? You should score yourself on the following symptoms, based on how you feel now.

Post Concussion Symptom Scale

	None		Moderate			Severe	
Headache	0	1	2	3	4	5	6
"Pressure in head"	0	1	2	3	4	5	6
Neck Pain	0	1	2	3	4	5	6
Balance problems or dizzy	0	1	2	3	4	5	6
Nausea or vomiting	0	1	2	3	4	5	6
Vision problems	0	1	2	3	4	5	6
Hearing problems / ringing	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Feeling "dinged" or "dazed"	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling like "in a fog"	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Fatigue or low energy	0	1	2	3	4	5	6
More emotional than usual	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6

(follow up symptoms only)

Sadness	0	1	2	3	4	5	6
Nervous or Anxious	0	1	2	3	4	5	6
Trouble falling asleep	0	1	2	3	4	5	6
Sleeping more than usual	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Other: _____	0	1	2	3	4	5	6

What should I do?
Any athlete suspected of having a concussion should be removed from play, and then seek medical evaluation.

Signs to watch for:
Problems could arise over the first 24-48 hours. You should not be left alone and must go to a hospital at once if you:

- Have a headache that gets worse
- Are very drowsy or can't be awakened (woken up)
- Can't recognize people or places
- Have repeated vomiting
- Behave unusually or seem confused; are very irritable
- Have seizures (arms and legs jerk uncontrollably)
- Have weak or numb arms or legs
- Are unsteady on your feet; have slurred speech

Remember, it is better to be safe. Consult your doctor after a suspected concussion.

What can I expect?
Concussion typically results in the rapid onset of short-lived impairment that resolves spontaneously over time. You can expect that you will be told to rest until you are fully recovered (that means resting your body and your mind). Then, your doctor will likely advise that you go through a gradual increase in exercise over several days (or longer) before returning to sport.

Figure 1 Sport concussion assessment tool (SCAT).

B

FIFA IOC IIHF

The SCAT Card

(Sport Concussion Assessment Tool)

Medical Evaluation

Name: _____ Date _____

Sport/Team: _____ Mouth guard? Y N

1) SIGNS

Was there loss of consciousness or unresponsiveness?	Y N
Was there seizure or convulsive activity?	Y N
Was there a balance problem / unsteadiness?	Y N

2) MEMORY

Modified Maddocks questions (check correct)

At what venue are we? __; Which half is it? __; Who scored last?__

What team did we play last? __; Did we win last game? __?

3) SYMPTOM SCORE

Total number of positive symptoms (from reverse side of the card) = _____

4) COGNITIVE ASSESSMENT

5 word recall	(Examples)	Immediate	Delayed (after concentration tasks)
Word 1 _____	cat	___	___
Word 2_____	pen	___	___
Word 3 _____	shoe	___	___
Word 4 _____	book	___	___
Word 5 _____	car	___	___

Months in reverse order:

Jun-May-Apr-Mar-Feb-Jan-Dec-Nov-Oct-Sep-Aug-Jul (circle incorrect)

or

Digits backwards (check correct)

5-2-8	3-9-1	_____
6-2-9-4	4-3-7-1	_____
8-3-2-7-9	1-4-9-3-6	_____
7-3-9-1-4-2	5-1-8-4-6-8	_____

Ask delayed 5-word recall now

5) NEUROLOGIC SCREENING

	Pass	Fail
Speech	___	___
Eye Motion and Pupils	___	___
Pronator Drift	___	___
Gait Assessment	___	___

Any neurologic screening abnormality necessitates formal neurologic or hospital assessment

6) RETURN TO PLAY

Athletes should not be returned to play the same day of injury. When returning athletes to play, they should follow a stepwise symptom-limited program, with stages of progression. For example:

1. rest until asymptomatic (physical and mental rest)
2. light aerobic exercise (e.g. stationary cycle)
3. sport-specific training
4. non-contact training drills (start light resistance training)
5. full contact training after medical clearance
6. return to competition (game play)

There should be approximately 24 hours (or longer) for each stage and the athlete should return to stage 1 if symptoms recur. Resistance training should only be added in the later stages. Medical clearance should be given before return to play.

Instructions:
This side of the card is for the use of medical doctors, physiotherapists or athletic therapists. In order to maximize the information gathered from the card, it is strongly suggested that all athletes participating in contact sports complete a baseline evaluation prior to the beginning of their competitive season. This card is a suggested guide only for sports concussion and is not meant to assess more severe forms of brain injury. **Please give a COPY of this card to the athlete for their information and to guide follow-up assessment.**

Signs:
Assess for each of these items and circle Y (yes) or N (no).

Memory:
Select any 5 words (an example is given). Avoid choosing related words such as "dark" and "moon" which can be recalled by means of word association. Read each word at a rate of one word per second. The athlete should not be informed of the delayed testing of memory (to be done after the reverse months and/or digits). Choose a different set of words each time you perform a follow-up exam with the same candidate.

Concentration / Attention:
Ask the athlete to recite the months of the year in reverse order, starting with a random month. Do not start with December or January. Circle any months not recited in the correct sequence.

For digits backwards, if correct, go to the next string length. If incorrect, read trial 2. Stop after incorrect on both trials.

Neurologic Screening:
Trained medical personnel must administer this examination. These individuals might include medical doctors, physiotherapists or athletic therapists. Speech should be assessed for fluency and lack of slurring. Eye motion should reveal no diplopia in any of the 4 planes of movement (vertical, horizontal and both diagonal planes). The pronator drift is performed by asking the patient to hold both arms in front of them, palms up, with eyes closed. A positive test is pronating the forearm, dropping the arm, or drift away from midline. For gait assessment, ask the patient to walk away from you, turn and walk back.

Return to Play:
A structured, graded exertion protocol should be developed; individualized on the basis of sport, age and the concussion history of the athlete. Exercise or training should be commenced only after the athlete is clearly asymptomatic with physical and cognitive rest. Final decision for clearance to return to competition should ideally be made by a medical doctor.

For more information see the "Summary and Agreement Statement of the Second International Symposium on Concussion in Sport" in the:
Clinical Journal of Sport Medicine 2005; in press
British Journal of Sports Medicine 2005;**39**:196–204
Neurosurgery 2005; in press
Physician and Sportsmedicine 2005; in press

Figure 1 Continued.

(5) McGill abbreviated concussion evaluation (ACE) (unpublished).
(6) National Hockey League physician evaluation form (unpublished).
(7) The UK Jockey Club assessment of concussion.[34]
(8) Maddocks questions.[27]

The authors gave input through a process of collaboration and iterative review. The SCAT was evaluated for face and content validity on the basis of scientific literature[35] and clinical experience of the authors. The memory questions, specifically, were modified from the validated Maddocks questions to make these questions less football-specific.[27]

INVESTIGATIONAL ISSUES

Neuropsychological assessment after concussion

The application of neuropsychological testing in concussion has been shown to be of value and continues to contribute significant information in concussion evaluation.[10 11 36 37] It has been shown that cognitive recovery may precede or follow clinical symptom resolution, suggesting that the assessment of cognitive function should be an important component in any return to play protocol.[12] It must be emphasised, however, that neuropsychological assessment should not be the sole basis of a return to play decision but rather be seen as an aid to the clinical decision making. Although neuropsychological screening may be performed or interpreted by other healthcare professionals, the final return to play decision should remain a medical one in which a multidisciplinary approach has been taken.

Neuropsychological testing should not be performed while the athlete is symptomatic because it adds nothing to return to play decisions, and it may contaminate the testing process by allowing practice effects to confound the results. In certain cases, however, serial follow up after the injury is valuable, both as a means to encourage athlete compliance and for comparison purposes.

Over-riding principles common to all neuropsychological test batteries is the need for and benefit of baseline testing before injury and serial follow up. Recent work with computerised platforms, however, suggests that performance variability may be a key measure for acute concussion diagnosis even in the absence of a baseline test. This strategy is currently the subject of research. Inherent problems with most neuropsychological tests include the normal ranges, sensitivity and specificity of tests, and practice or learning effect, as well as the observation that players may return to baseline while still symptomatic.[36] Computerised testing using infinitely variable test paradigms may overcome some of these concerns. Computerised testing also has the logistical advantage that the tests may be administered by the team doctor (or be web based) rather than requiring a neuropsychologist for a formal assessment. The strengths and weaknesses of such testing have been reviewed.[37]

It is recommended that neuropsychological testing remain one of the cornerstones of concussion evaluation in complex concussion. It is not currently regarded as important in the evaluation of simple concussion. Although this modality contributes significantly to both the understanding of the injury and management of the individual athlete, neuropsychological testing should not be the sole basis of management decisions, either for continued time out or return to play decisions.

Objective balance assessment

Balance testing, either with computerised platforms or clinical assessment, may offer additional information in concussed athletes and may be used as a part of the overall concussion management strategy, particularly where symptoms or signs indicate a balance component.[38]

Neuroimaging

It was recognised in the Vienna agreement document that conventional structural neuroimaging is usually normal in concussive injury. Given that caveat, the following suggestions are made. Computed tomography (or, where available, magnetic resonance imaging) of the brain contributes little to concussion evaluation, but should be used whenever suspicion of an intracerebral structural lesion exists. Examples of such situations may include prolonged disturbance of conscious state, focal neurological deficit, or worsening symptoms.

Newer structural magnetic resonance imaging modalities, including gradient echo, perfusion, and diffusion weighted imaging, have greater sensitivity for structural abnormalities, but the lack of published studies as well as the absence of pre-injury neuroimaging data limits the usefulness of this approach in clinical management at the present time.

In addition, the predictive value of various magnetic resonance imaging abnormalities that may be incidentally discovered is not established. Although there have been some compelling findings with promising new functional imaging technologies—for example, positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI)—they are still at early stages of development.[39–41]

Although neuroimaging may play a part in the assessment of complex sports concussions or more severe brain injury, it is not essential for simple concussive injury.

Genetic testing

Genotyping has been shown to be of benefit in traumatic brain injury. Published studies have shown that ApoE4 is a risk factor for adverse outcome after all levels of brain injury.[42–48] Similarly ApoE4 has been shown to be a risk factor for the development of chronic traumatic encephalopathy in boxers.[49] The significance of ApoE4 in sports concussion risk or injury outcome is unclear. Other published studies have noted the association of a particular calcium subunit gene abnormality with brain swelling after minor head trauma.[50] Although still in the early stages of understanding, routine genetic screening cannot be recommended at the present time. Furthermore, doctors are urged to be mindful of the ethical implications of such testing.

Experimental concussion assessment modalities

Different electrophysiological recording techniques such as evoked response potential and electroencephalogram have shown reproducible abnormalities in the post-concussive state.[51–53] However, not all studies reliably differentiated concussed athletes from controls.[54–57] The clinical significance of these changes remains to be established.

In addition, biochemical serum markers of brain injury (including S-100b, NSE, MBP, GFAP) have been proposed as means by which cellular damage may be detected if present.[58 59] However, there is currently not sufficient evidence to justify the use of these markers clinically.

CONCUSSION MANAGEMENT

Acute injury

When a player shows any symptoms or signs of a concussion, the following should be applied.

(1) The player should not be allowed to return to play in the current game or practice.

(2) The player should not be left alone, and regular monitoring for deterioration is essential over the initial few hours after injury.
(3) The player should be medically evaluated after the injury.
(4) Return to play must follow a medically supervised stepwise process.

A player should never return to play while symptomatic. "When in doubt, sit them out!"

Return to play protocol

As described above, most injuries will be simple concussions, and such injuries recover spontaneously over several days. In these situations, it is expected that an athlete will proceed rapidly through the stepwise return to play strategy.[60]

During this period of recovery in the first few days after an injury, it is important to emphasise to the athlete that physical and cognitive rest is required. Activities that require concentration and attention may exacerbate the symptoms and as a result delay recovery.

The return to play after a concussion follows a stepwise process:

(1) No activity, complete rest. Once asymptomatic, proceed to level 2.
(2) Light aerobic exercise such as walking or stationary cycling, no resistance training.
(3) Sport specific exercise—for example, skating in hockey, running in soccer; progressive addition of resistance training at steps 3 or 4.
(4) Non-contact training drills.
(5) Full contact training after medical clearance.
(6) Game play.

With this stepwise progression, the athlete should continue to proceed to the next level if asymptomatic at the current level. If any post-concussion symptoms occur, the patient should drop back to the previous asymptomatic level and try to progress again after 24 hours.

In cases of complex concussion, the rehabilitation will be more prolonged, and return to play advice will be more circumspect. It is envisaged that complex cases should be managed by doctors with a specific expertise in the management of such injuries.

An additional consideration in return to play is that concussed athletes should not only be symptom-free but also should not be taking any pharmacological agents/drugs that may affect or modify the symptoms of concussion. If antidepressant treatment is started during the management of a complex concussion, the decision to return to play while still receiving such medication must be considered carefully by the clinician concerned (see below).

In professional sport, where there are team doctors experienced in concussion management as well as access to immediate—that is, sideline—neurocognitive assessment, return to play management is often more rapid, but it must still follow the same basic principles, namely full clinical and cognitive recovery before consideration of return to play.

Role of pharmacological treatment

Pharmacological treatment in sports concussion may be applied in two distinct situations: (*a*) management of specific symptoms—for example, sleep disturbance, anxiety—in complex concussion; (*b*) to modify the underlying pathophysiology of the condition with the aim of shortening the duration of the concussion symptomatology.[61]

In broad terms, this approach to management should be only considered in complex sports concussions and by clinicians experienced in concussion management.

Sports psychology

In addition, sport psychology approaches may have potential application in this injury, particularly in complex concussion.[62] Care givers are also encouraged to evaluate the concussed athlete for affective symptoms such as depression as these may be common in concussion.[60]

OTHER ISSUES

Prevention

There is no clinical evidence that currently available protective equipment will prevent concussion. In certain sports, protective equipment may prevent other forms of head injury which may be an important issue for those sports.

Consideration of rule changes—for example, no head checking in ice hockey—to reduce the head injury rate may be appropriate where a clear-cut mechanism is implicated in a particular sport. Similarly, rule enforcement is a critical aspect of such approaches, and referees play an important role.

An important consideration in the use of protective equipment is the concept of risk compensation.[63] This is where the use of protective equipment results in behavioural change such as the adoption of more dangerous playing techniques, which can result in a paradoxical increase in injury rates. This may be a particular concern in child and adolescent athletes in whom head injury rates are often higher than in adult athletes.[64]

Medicolegal considerations

Although agreement exists on the principal messages conveyed in this document, we acknowledge that the science of concussion is at an early stage, and therefore management and return to play decisions remain largely in the realm of clinical judgment on an individualised basis.

Education

As the ability to treat or reduce the effects of concussive injury after the event is minimal, education of athletes, colleagues, and the general public is a mainstay of progress in this field. Athletes and their healthcare providers must be educated about the detection of concussion, its clinical features, assessment techniques, and principles of safe return to play. Methods to improve education including web based resources, educational videos, and international outreach programmes such as Think First (www.thinkfirst.ca) are important in delivering the message. In addition, concussion working groups plus the support and endorsement of enlightened sport groups such as FIFA, IOC, and IIHF who initiated this endeavour have enormous value and must be pursued vigorously.

The promotion of fair play and respect for opponents are ethical values that should be encouraged in all sports and sporting associations. Similarly coaches, parents, and managers play an important part in ensuring that these values are implemented on the field of play.

Research methods

A number of research protocols and data evaluating concussion injury assessment, injury susceptibility, and brain function after injury were presented at both the Vienna and Prague conferences. Although they offer great potential for injury assessment, all of these techniques must be considered experimental at this time. Elite and professional teams are well placed to contribute to these efforts through athlete

recruitment for studies showing the scientific value of such approaches.

Such research is essential in contributing to the science of concussion and will potentially provide valuable information for such important issues as clinical management, return to play guidelines, and long term outcome. Therefore research should be continued and encouraged, by both academics and sporting organisations.

Future

The issue of sports concussion management is continually evolving, and the usefulness of expert consensus in establishing a standard of care has been demonstrated by the Vienna agreement. The consensus group established at that meeting has provided continuing leadership in this field based on the initial mandate established at that time.[1] We expect that this Prague agreement will be revised and updated at future meetings.

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Competing interests: Dr Lovell is a shareholder of ImPACT, a neuropsychological testing programme. No other author has any declared conflict of interest or concussion industry affiliation.

This article will also be published in the April 2005 issues of the *Clinical Journal of Sport Medicine, Physician and Sportsmedicine,* and *Neurosurgery.*

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Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004

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Br J Sports Med 2005 39: i78-i86
doi: 10.1136/bjsm.2005.018614

Exhibit 3

Consensus Statement on Concussion in Sport: the 3rd International Conference on Concussion in Sport held in Zurich, November 2008

EDITOR'S CHOICE

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This paper is a revision and update of the recommendations developed following the 1st (Vienna) and 2nd (Prague) International Symposia on Concussion in Sport.[1 2] The Zurich Consensus statement is designed to build on the principles outlined in the original Vienna and Prague documents and to develop further conceptual understanding of this problem using a formal consensus-based approach. A detailed description of the consensus process is outlined at the end of this document. This document is developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level. While agreement exists pertaining to principal messages conveyed within this document, the authors acknowledge that the science of concussion is evolving and therefore management and return to play decisions remain in the realm of clinical judgement on an individualised basis. Readers are encouraged to copy and distribute freely the Zurich Consensus document and/or the Sports Concussion Assessment Tool (SCAT2) card and neither is subject to any copyright restriction. The authors request, however that the document and/or the SCAT2 card be distributed in their full and complete format.

The following focus questions formed the foundation for the Zurich concussion consensus statement:

Acute simple concussion

- Which symptom scale and which sideline assessment tool is best for diagnosis and/or follow up?
- How extensive should the cognitive assessment be in elite athletes?
- How extensive should clinical and neuropsychological (NP) testing be at non-elite level?
- Who should do/interpret the cognitive assessment?
- Is there a gender difference in concussion incidence and outcomes?

Return to play (RTP) issues

- Is provocative exercise testing useful in guiding RTP?
- What is the best RTP strategy for elite athletes?
- What is the best RTP strategy for non-elite athletes?
- Is protective equipment (eg, mouthguards and helmets) useful in reducing concussion incidence and/or severity?

Complex concussion and long-term issues

- Is the simple versus complex classification a valid and useful differentiation?
- Are there specific patient populations at risk of long term problems?
- Is there a role for additional tests (eg, structural and/or functional MRI, balance testing, biomarkers)?
- Should athletes with persistent symptoms be screened for depression/anxiety?

Paediatric concussion

- Which symptoms scale is appropriate for this age group?
- Which tests are useful and how often should baseline testing be performed in this age group?
- What is the most appropriate RTP guideline for elite and non-elite child and adolescent athletes?

Future directions

- What is the best method of knowledge transfer and education?
- Is there evidence that new and novel injury prevention strategies work (eg, changes to rules of the game, fair play strategies, etc)?

The Zurich document additionally examines the management issues raised in the previous Prague and Vienna documents and applies the consensus questions to these areas.

SPECIFIC RESEARCH QUESTIONS AND CONSENSUS DISCUSSION

1. Concussion

1.1 Definition of concussion

A panel discussion regarding the definition of concussion and its separation from mild traumatic brain injury (mTBI) was held. Although there was acknowledgement that the terms refer to different injury constructs and should not be used interchangeably, it was not felt that the panel would define mTBI for the purpose of this document. There was unanimous agreement, however, that concussion is defined as follows:

> Concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces. Several common features that incorporate clinical, pathologic and biomechanical injury constructs that may be utilised in defining the nature of a concussive head injury include:
> 1. Concussion may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an "impulsive" force transmitted to the head.
> 2. Concussion typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously.
> 3. Concussion may result in neuropathological changes but the acute clinical symptoms largely reflect a functional

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disturbance rather than a structural injury.
4. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course; however it is important to note that in a small percentage of cases however, post-concussive symptoms may be prolonged.
5. No abnormality on standard structural neuroimaging studies is seen in concussion.

1.2 Classification of concussion

There was unanimous agreement to abandon the simple versus complex terminology that had been proposed in the Prague agreement statement as the panel felt that the terminology itself did not fully describe the entities. The panel however unanimously retained the concept that the majority (80–90%) of concussions resolve in a short (7–10 day) period, although the recovery time frame may be longer in children and adolescents.[2]

2. Concussion evaluation

2.1 Symptoms and signs of acute concussion

The panel agreed that the diagnosis of acute concussion usually involves the assessment of a range of domains including clinical symptoms, physical signs, behaviour, balance, sleep and cognition. Furthermore, a detailed concussion history is an important part of the evaluation both in the injured athlete and when conducting a pre-participation examination. The detailed clinical assessment of concussion is outlined in the *SCAT2* form ***(see p 85)***.

The suspected diagnosis of concussion can include one or more of the following clinical domains:

a. Symptoms—somatic (eg, headache), cognitive (eg, feeling like in a fog) and/or emotional symptoms (eg, lability).
b. Physical signs (eg, loss of consciousness, amnesia).
c. Behavioural changes (eg, irritability).
d. Cognitive impairment (eg, slowed reaction times).
e. Sleep disturbance (eg, drowsiness).

If any one or more of these components is present, a concussion should be suspected and the appropriate management strategy instituted.

2.2 On-field or sideline evaluation of acute concussion

When a player shows *any* features of a concussion:

a. The player should be medically evaluated onsite using standard emergency management principles and particular attention should be given to excluding a cervical spine injury.
b. The appropriate disposition of the player must be determined by the treating healthcare provider in a timely manner. If no healthcare provider is available, the player should be safely removed from practice or play and urgent referral to a physician arranged.
c. Once the first aid issues are addressed, then an assessment of the concussive injury should be made using the SCAT2 or other similar tool.
d. The player should not be left alone following the injury and serial monitoring for deterioration is essential over the initial few hours following injury.
e. A player with diagnosed concussion should not be allowed to return to play on the day of injury. Occasionally in adult athletes, there may be return to play on the same day as the injury. See Section 4.2.

It was unanimously agreed that sufficient time for assessment and adequate facilities should be provided for the appropriate medical assessment both on and off the field for all injured athletes. In some sports this may require rule change to allow an off-field medical assessment to occur without affecting the flow of the game or unduly penalising the injured player's team.

Sideline evaluation of cognitive function is an essential component in the assessment of this injury. Brief neuropsychological test batteries that assess attention and memory function have been shown to be practical and effective. Such tests include the Maddocks questions[3 4] and the Standardized Assessment of Concussion (SAC).[5–7] It is worth noting that standard orientation questions (eg, time, place, person) have been shown to be unreliable in the sporting situation when compared with memory assessment.[4 8] It is recognised, however, that abbreviated testing paradigms are designed for rapid concussion screening on the sidelines and are not meant to replace comprehensive neuropsychological testing which is sensitive to detect subtle deficits that may exist beyond the acute episode; nor should they be used as a stand alone tool for the ongoing management of sports concussions.

It should also be recognised that the appearance of symptoms might be delayed several hours following a concussive episode.

2.3 Evaluation in emergency room or office by medical personnel

An athlete with concussion may be evaluated in the emergency room or doctor's office as a point of first contact following injury or may have been referred from another care provider. In addition to the points outlined above, the key features of this exam should encompass:

a. A medical assessment including a comprehensive history, and detailed neurological examination including a thorough assessment of mental status, cognitive functioning and gait and balance.
b. A determination of the clinical status of the patient including whether there has been improvement or deterioration since the time of injury. This may involve seeking additional information from parents, coaches, teammates and eyewitnesses to the injury.
c. A determination of the need for emergent neuroimaging in order to exclude a more severe brain injury involving a structural abnormality

In large part, these points above are included in the SCAT2 assessment, which forms part of the Zurich consensus statement.

3. Concussion investigations

A range of additional investigations may be utilised to assist in the diagnosis and/or exclusion of injury. These include the following.

3.1 Neuroimaging

It was recognised by the panellists that conventional structural neuroimaging is normal in concussive injury. Given that caveat, the following suggestions are made: brain CT (or where available, MR brain scan) contributes little to concussion evaluation but should be employed whenever suspicion of an intracerebral structural lesion exists. Examples of such situations may include prolonged disturbance of conscious state, focal neurological deficit or worsening symptoms.

Newer structural MRI modalities including gradient echo, perfusion and diffusion imaging have greater sensitivity for structural abnormalities. However, the lack of published studies as well as absent pre-injury neuroimaging data limits the usefulness of this approach in clinical management at the present time. In

addition, the predictive value of various MR abnormalities that may be incidentally discovered is not established at the present time.

Other imaging modalities such as functional MRI (fMRI) show activation patterns that correlate with symptom severity and recovery in concussion.[9–13] While not part of routine assessment at the present time, they nevertheless provide additional insight to pathophysiological mechanisms. Alternative imaging technologies (eg, positron emission tomography, diffusion tensor imaging, magnetic resonance spectroscopy, functional connectivity), while demonstrating some compelling findings, are still at early stages of development and cannot be recommended other than in a research setting.

3.2 Objective balance assessment

Published studies, using both sophisticated force plate technology and less sophisticated clinical balance tests (eg, balance error scoring system (BESS)), have identified postural stability deficits lasting approximately 72 hours following sport-related concussion. It appears that postural stability testing provides a useful tool for objectively assessing the motor domain of neurological functioning, and should be considered a reliable and valid addition to the assessment of athletes suffering from concussion, particularly where symptoms or signs indicate a balance component.[14–20]

3.3 Neuropsychological assessment

The application of neuropsychological (NP) testing in concussion has been shown to be of clinical value and continues to contribute significant information in concussion evaluation.[21–26] Although in most case cognitive recovery largely overlaps with the time course of symptom recovery, it has been demonstrated that cognitive recovery may occasionally precede or more commonly follow clinical symptom resolution, suggesting that the assessment of cognitive function should be an important component in any return to play protocol.[27 28] It must be emphasised however, that NP assessment should not be the sole basis of management decisions; rather it should be seen as an aid to the clinical decision-making process in conjunction with a range of clinical domains and investigational results.

Neuropsychologists are in the best position to interpret NP tests by virtue of their background and training. However, there may be situations where neuropsychologists are not available and other medical professionals may perform or interpret NP screening tests. The ultimate return to play decision should remain a medical one in which a multidisciplinary approach, when possible, has been taken. In the absence of NP and other (eg, formal balance assessment) testing, a more conservative return to play approach may be appropriate.

In the majority of cases, NP testing will be used to assist return to play decisions and will not be done until patient is symptom free.[29 30] There may be situations (eg, child and adolescent athletes) where testing may be performed early while the patient is still symptomatic to assist in determining management. This will normally be best determined in consultation with a trained neuropsychologist.[31 32]

3.4 Genetic testing

The significance of apolipoprotein (Apo) E4, ApoE promotor gene, tau polymerase and other genetic markers in the management of sports concussion risk or injury outcome is unclear at this time.[33 34] Evidence from human and animal studies in more severe traumatic brain injury shows induction of a variety of genetic and cytokine factors, such as: insulin-like growth factor-1 (IGF-1), IGF binding protein-2, fibroblast growth factor, Cu–Zn superoxide dismutase, superoxide dismutase-1 (SOD-1), nerve growth factor, glial fibrillary acidic protein (GFAP) and S-100. Whether such factors are affected in sporting concussion is not known at this stage.[35–42]

3.5 Experimental concussion assessment modalities

Different electrophysiological recording techniques (eg, evoked response potential (ERP), cortical magnetic stimulation and electroencephalography) have demonstrated reproducible abnormalities in the post-concussive state; however not all studies reliably differentiated concussed athletes from controls.[43–49] The clinical significance of these changes remains to be established.

In addition, biochemical serum and cerebral spinal fluid markers of brain injury (including S-100, neuron specific enolase (NSE), myelin basic protein (MBP), GFAP, tau, etc) have been proposed as means by which cellular damage may be detected if present.[50 51] There is currently insufficient evidence however, to justify the routine use of these biomarkers clinically.

4. Concussion management

The cornerstone of concussion management is physical and cognitive rest until symptoms resolve and then a graded programme of exertion prior to medical clearance and return to play. The recovery and outcome of this injury may be modified by a number of factors that may require more sophisticated management strategies. These are outlined in the section on modifiers below.

As described above, the majority of injuries will recover spontaneously over several days. In these situations, it is expected that an athlete will proceed progressively through a stepwise return to play strategy.[57] During this period of recovery while symptomatic, following an injury, it is important to emphasise to the athlete that physical *and* cognitive rest is required. Activities that require concentration and attention (eg, scholastic work, videogames, text messaging, etc) may exacerbate symptoms and possibly delay recovery. In such cases, apart from limiting relevant physical and cognitive activities (and other risk-taking opportunities for re-injury) while symptomatic, no further intervention is required during the period of recovery and the athlete typically resumes sport without further problem.

4.1 Graduated return to play protocol

Return to play protocol following a concussion follows a stepwise process as outlined in table 1.

With this stepwise progression, the athlete should continue to proceed to the next level if asymptomatic at the current level. Generally each step should take 24 hours so that an athlete would take approximately one week to proceed through the full rehabilitation protocol once they are asymptomatic at rest and with provocative exercise. If any post-concussion symptoms occur while in the stepwise programme, the patient should drop back to the previous asymptomatic level and try to progress again after a further 24-hour period of rest has passed.

4.2 Same day RTP

With adult athletes, in some settings, where there are team physicians experienced in concussion management and sufficient resources (eg, access to neuropsychologists, consultants, neuroimaging, etc) as well as access to immediate (ie, sideline) neurocognitive assessment, return to play management may be more rapid. The RTP strategy must still follow the same basic management principles,

Table 1 Graduated return to play protocol

Rehabilitation stage	Functional exercise at each stage of rehabilitation	Objective of each stage
1. No activity	Complete physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming or stationary cycling keeping intensity <70% maximum predicted heart rate No resistance training	Increase heart rate
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities	Add movement
4. Non-contact training drills	Progression to more complex training drills, eg passing drills in football and ice hockey May start progressive resistance training)	Exercise, coordination, and cognitive load
5. Full contact practice	Following medical clearance participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play	

namely full clinical and cognitive recovery before consideration of return to play. This approach is supported by published guidelines, such as the American Academy of Neurology, US Team Physician Consensus Statement, and US National Athletic Trainers Association Position Statement.[58–60] This issue was extensively discussed by the consensus panellists and it was acknowledged that there is evidence that some professional American football players are able to RTP more quickly, with even same day RTP supported by National Football League studies without a risk of recurrence or sequelae.[61] There are data however, demonstrating that at the collegiate and high school level, athletes allowed to RTP on the same day may demonstrate NP deficits post-injury that may not be evident on the sidelines and are more likely to have delayed onset of symptoms.[62–68] It should be emphasised however, that the young (<18) elite athlete should be treated more conservatively even though the resources may be the same as for an older professional athlete (see Section 6.1).

4.3 Psychological management and mental health issues

In addition, psychological approaches may have potential application in this injury, particularly with the modifiers listed below.[69 70] Caregivers are also encouraged to evaluate the concussed athlete for affective symptoms such as depression, as these symptoms may be common in concussed athletes.[57]

4.4 The role of pharmacological therapy

Pharmacological therapy in sports concussion may be applied in two distinct situations. The first of these situations is the management of specific prolonged symptoms (eg, sleep disturbance, anxiety, etc). The second situation is where drug therapy is used to modify the underlying pathophysiology of the condition with the aim of shortening the duration of the concussion symptoms.[71] In broad terms, this approach to management should only be considered by clinicians experienced in concussion management.

An important consideration in RTP is that concussed athletes should not only be symptom-free but also should not be taking any pharmacological agents/medications that may mask or modify the symptoms of concussion. Where antidepressant therapy may be commenced during the management of a concussion, the decision to return to play while still on such medication must be considered carefully by the treating clinician.

4.5 The role of pre-participation concussion evaluation

Recognising the importance of a concussion history, and appreciating the fact that many athletes will not recognise all the concussions they may have suffered in the past, a detailed concussion history is of value.[72–75] Such a history may preidentify athletes that fit into a high risk category and provides an opportunity for the healthcare provider to educate the athlete in regard to the significance of concussive injury. A structured concussion history should include specific questions as to previous symptoms of a concussion; not just the perceived number of past concussions. It is also worth noting that dependence on the recall of concussive injuries by teammates or coaches has been shown to be unreliable.[72] The clinical history should also include information about all previous head, face or cervical spine injuries as these may also have clinical relevance. It is worth emphasising that in the setting of maxillofacial and cervical spine injuries, coexistent concussive injuries may be missed unless specifically assessed. Questions pertaining to disproportionate impact versus symptom severity matching may alert the clinician to a progressively increasing vulnerability to injury. As part of the clinical history it is advised that details regarding protective equipment employed at time of injury be sought, for both recent and remote injuries. A comprehensive pre-participation concussion evaluation allows for modification and optimisation of protective behaviour and an opportunity for education.

5. Modifying factors in concussion management

The consensus panel agreed that a range of 'modifying' factors may influence the investigation and management of concussion and in some cases, may predict the potential for prolonged or persistent symptoms. These modifiers would also be important to consider in a detailed concussion history and are outlined in Table 2.

In this setting, there may be additional management considerations beyond simple RTP advice. There may be a more important role for additional investigations, including formal NP testing, balance assessment and neuroimaging. It is envisioned that athletes with such modifying features would be managed in a multidisciplinary manner coordinated by a physician with specific expertise in the management of concussive injury.

The role of female gender as a possible modifier in the management of concussion was discussed at length by the panel. There was not unanimous agreement that the current published research evidence is conclusive that this should be included as a modifying factor, although it was accepted that gender may be a risk factor for injury and/or influence injury severity.[76–78]

5.1 The significance of loss of consciousness (LOC)

In the overall management of moderate to severe traumatic brain injury, duration of LOC is an acknowledged predictor of outcome.[79] While published findings in concussion describe LOC associated with specific early cognitive deficits it has not been noted as a measure of injury severity.[80 81] Consensus discussion determined that prolonged (>1 minute duration) LOC would be considered as a factor that may modify management.

5.2 The significance of amnesia and other symptoms

There is renewed interest in the role of post traumatic amnesia and its role as a

Table 2 Concussion modifiers

Factors	Modifier
Symptoms	Number
	Duration (>10 days)
	Severity
Signs	Prolonged loss of consciousness (>1 min), amnesia
Sequelae	Concussive convulsions
Temporal	Frequency—repeated concussions over time
	Timing—injuries close together in time
	"Recency"—recent concussion or traumatic brain injury
Threshold	Repeated concussions occurring with progressively less impact force or slower recovery after each successive concussion
Age	Child and adolescent (<18 years old)
Co- and pre-morbidities	Migraine, depression or other mental health disorders, attention deficit hyperactivity disorder, learning disabilities, sleep disorders
Medication	Psychoactive drugs, anticoagulants
Behaviour	Dangerous style of play
Sport	High risk activity, contact and collision sport, high sporting level

surrogate measure of injury severity.[67 82 83] Published evidence suggests that the nature, burden and duration of the clinical post-concussive symptoms may be more important than the presence or duration of amnesia alone.[80 84 85] Further it must be noted that retrograde amnesia varies with the time of measurement post-injury and hence is poorly reflective of injury severity.[86 87]

5.3 Motor and convulsive phenomena

A variety of immediate motor phenomena (eg, tonic posturing) or convulsive movements may accompany a concussion. Although dramatic, these clinical features are generally benign and require no specific management beyond the standard treatment of the underlying concussive injury.[88 89]

5.4 Depression

Mental health issues (such as depression) have been reported as a long-term consequence of traumatic brain injury, including sports related concussion. Neuroimaging studies using fMRI suggest that a depressed mood following concussion may reflect an underlying pathophysiological abnormality consistent with a limbic-frontal model of depression.[52 90–100]

6. Special populations

6.1 The child and adolescent athlete

There was unanimous agreement by the panel that the evaluation and management recommendations contained herein could be applied to children and adolescents down to the age of 10 years. Below that age children report different concussion symptoms from adults and would require age appropriate symptom check lists as a component of assessment. An additional consideration in assessing the child or adolescent athlete with a concussion is that in the clinical evaluation by the healthcare professional there may be the need to include both patient and parent input as well as teacher and school input when appropriate.[101–107]

The decision to use NP testing is broadly the same as the adult assessment paradigm. However, timing of testing may differ in order to assist planning in school and home management (and may be performed while the patient is still symptomatic). If cognitive testing is performed, it must be developmentally sensitive until the late teen years due to the ongoing cognitive maturation that occurs during this period which, in turn, makes the utility of comparison to either the person's own baseline performance or to population norms limited.[20] In this age group it is more important to consider the use of trained neuropsychologists to interpret assessment data, particularly in children with learning disorders and/or attention deficit hyperactivity disorder (ADHD) who may need more sophisticated assessment strategies.[31 32 101]

The panel strongly endorsed the view that children should not be returned to practice or play until clinically completely symptom-free, which may require a longer time frame than for adults. In addition, the concept of "cognitive rest" was highlighted with special reference to a child's need to limit exertion with activities of daily living and to limit scholastic and other cognitive stressors (eg, text messaging, videogames, etc) while symptomatic. School attendance and activities may also need to be modified to avoid provocation of symptoms.

Because of the different physiological response and longer recovery after concussion and specific risks (eg, diffuse cerebral swelling) related to head impact during childhood and adolescence, a more conservative return to play approach is recommended. It is appropriate to extend the amount of time of asymptomatic rest and/or the length of the graded exertion in children and adolescents. It is not appropriate for a child or adolescent athlete with concussion to RTP on the same day as the injury regardless of the level of athletic performance. Concussion modifiers apply even more to this population than adults and may mandate more cautious RTP advice.

6.2 Elite versus non-elite athletes

The panel unanimously agreed that all athletes regardless of level of participation should be managed using the same treatment and return to play paradigm. A more useful construct was agreed whereby the available resources and expertise in concussion evaluation were of more importance in determining management than a separation between elite and non-elite athlete management. Although formal baseline NP screening may be beyond the resources of many sports or individuals, it is recommended that in all organised high risk sports consideration be given to having this cognitive evaluation regardless of the age or level of performance.

6.3 Chronic traumatic brain injury

Epidemiological studies have suggested an association between repeated sports concussions during a career and late life cognitive impairment. Similarly, case reports have noted anecdotal cases where neuropathological evidence of chronic traumatic encephalopathy was observed in retired football players.[108–112] Panel discussion was held and no consensus was reached on the significance of such observations at this stage. Clinicians need to be mindful of the potential for long-term problems in the management of all athletes.

7. Injury prevention

7.1 Protective equipment: mouthguards and helmets

There is no good clinical evidence that currently available protective equipment will prevent concussion although mouthguards have a definite role in preventing dental and orofacial injury. Biomechanical studies have shown a reduction in impact forces to the brain with the use of head gear and helmets, but these findings have not been translated to show a reduction

in concussion incidence. For skiing and snowboarding there are a number of studies to suggest that helmets provide protection against head and facial injury and hence should be recommended for participants in alpine sports.[113–116] In specific sports such as cycling, motor and equestrian sports, protective helmets may prevent other forms of head injury (eg, skull fracture) that are related to falling on hard road surfaces; these may be an important injury prevention issue for those sports.[116–128]

7.2 Rule change

Consideration of rule changes to reduce the head injury incidence or severity may be appropriate where a clear-cut mechanism is implicated in a particular sport. An example of this is in football (soccer) where research studies demonstrated that upper limb to head contact in heading contests accounted for approximately 50% of concussions.[129] As noted earlier, rule changes may also be needed in some sports to allow an effective off-field medical assessment to occur without compromising the athlete's welfare, affecting the flow of the game or unduly penalising the player's team. It is important to note that rule enforcement may be a critical aspect of modifying injury risk in these settings; referees play an important role in this regard.

7.3 Risk compensation

An important consideration in the use of protective equipment is the concept of risk compensation.[130] This is where the use of protective equipment results in behavioural change, such as the adoption of more dangerous playing techniques, which can result in a paradoxical increase in injury rates. This may be a particular concern in child and adolescent athletes where head injury rates are often higher than in adult athletes.[131–133]

7.4 Aggression versus violence in sport

The competitive/aggressive nature of sport which makes it fun to play and watch should not be discouraged. However, sporting organisations should be encouraged to address violence that may increase concussion risk.[154 155] Fair play and respect should be supported as key elements of sport.

8. Knowledge transfer

As the ability to treat or reduce the effects of concussive injury after the event is minimal, education of athletes, colleagues and the general public is a mainstay of progress in this field. Athletes, referees, administrators, parents, coaches and healthcare providers must be educated regarding the detection of concussion, its clinical features, assessment techniques and principles of safe return to play. Methods to improve education, including web-based resources, educational videos and international outreach programmes are important in delivering the message. In addition, concussion working groups plus the support and endorsement of enlightened sport groups, such as Fédération Internationale de Football Association (FIFA), International Olympic Commission (IOC), International Rugby Board (IRB) and International Ice Hockey Federation (IIHF), who initiated this endeavour have enormous value and must be pursued vigorously. Fair play and respect for opponents are ethical values that should be encouraged in all sports and sporting associations. Similarly coaches, parents and managers play an important part in ensuring these values are implemented on the field of play.[57 136–148]

9. Future directions

The consensus panellists recognise that research is needed across a range of areas in order to answer some critical research questions. The key areas for research identified include:

- Validation of the SCAT2.
- Gender effects on injury risk, severity and outcome.
- Paediatric injury and management paradigms.
- Virtual reality tools in the assessment of injury.
- Rehabilitation strategies (eg, exercise therapy).
- Novel imaging modalities and their role in clinical assessment.
- Concussion surveillance using consistent definitions and outcome measures.
- Clinical assessment where no baseline assessment has been performed.
- "Best-practice" neuropsychological testing.
- Long-term outcomes.
- On-field injury severity predictors.

10. Medico-legal considerations

This consensus document reflects the current state of knowledge and will need to be modified according to the development of new knowledge. It provides an overview of issues that may be of importance to healthcare providers involved in the management of sports related concussion. It is not intended as a standard of care, and should not be interpreted as such. This document is only a guide, and is of a general nature, consistent with the reasonable practice of a healthcare professional. Individual treatment will depend on the facts and circumstances specific to each individual case.

It is intended that this document will be formally reviewed and updated prior to 1 December 2012.

11. Statement on background to consensus process

In November 2001, the 1st International Conference on Concussion in Sport was held in Vienna, Austria. This meeting was organised by the IIHF in partnership with FIFA and the Medical Commission of the IOC. As part of the resulting mandate for the future, the need for leadership and future updates was identified. The 2nd International Conference on Concussion in Sport was organised by the same group with the additional involvement of the IRB and was held in Prague, Czech Republic in November 2004. The original aims of the symposia were to provide recommendations for the improvement of safety and health of athletes who suffer concussive injuries in ice hockey, rugby, football (soccer) and other sports. To this end, a range of experts were invited to both meetings to address specific issues of epidemiology, basic and clinical science, injury grading systems, cognitive assessment, new research methods, protective equipment, management, prevention and long-term outcome.[1 2]

The 3rd International Conference on Concussion in Sport was held in Zurich, Switzerland on 29–30 October 2008 and was designed as a formal consensus meeting following the organisational guidelines set forth by the US National Institutes of Health. (Details of the consensus methodology can be obtained at: http://consensus.nih.gov/ABOUTCDP.htm) The basic principles governing the conduct of a consensus development conference are summarised below:

1. A broad based non-government, non-advocacy panel was assembled to give balanced, objective and knowledgeable attention to the topic. Panel members excluded anyone with scientific or commercial conflicts of interest and included researchers in clinical medicine, sports medicine, neuroscience, neuroimaging, athletic training and sports science

2. These experts presented data in a public session, followed by inquiry and discussion. The panel then met in an executive session to prepare the consensus statement.
3. A number of specific questions were prepared and posed in advance to define the scope and guide the direction of the conference. The principle task of the panel was to elucidate responses to these questions. These questions are outlined above.
4. A systematic literature review was prepared and circulated in advance for use by the panel in addressing the conference questions.
5. The consensus statement is intended to serve as the scientific record of the conference.
6. The consensus statement will be widely disseminated to achieve maximum impact on both current healthcare practice and future medical research.

The panel chairperson (WM) did not identify with any advocacy position. The chairperson was responsible for directing the consensus session and guiding the panel's deliberations. Panellists were drawn from clinical practice, academic and research in the field of sports related concussion. They do not represent organisations per se but were selected for their expertise, experience and understanding of this field.

Competing interests: None.

Consensus panellists (listed in alphabetical order): In addition to the authors above, the consensus panellists were S Broglio, G Davis, R Dick, J Dvorak, R Echemendia, G Gioia, K Guskiewicz, S Herring, G Iverson, J Kelly, J Kissick, M Makdissi, M McCrea, A Ptito, L Purcell, M Putukian. Also invited but not in attendance: R Bahr, L Engebretsen, P Hamlyn, B Jordan, P Schamasch.

This article has been co-published in the following journals: *Clinical Journal of Sport Medicine, Physician and Sportsmedicine, Neurosurgery, Physical Medicine and Rehabilitation, Journal of Athletic Training, Scandinavian Journal of Medicine & Science in Sport, Journal of Clinical Neuroscience, Journal of Science & Medicine in Sport.*

Accepted 2 February 2009

Br J Sports Med 2009;**43**:i76–i84.
doi:10.1136/bjsm.2009.058248

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APPENDIX 1

Sport Concussion Assessment Tool (SCAT2) form: a clinical tool used by practitioners managing athletes with concussion.

APPENDIX 2

Pocket SCAT2: a pocket card designed for lay practitioners to suspect the diagnosis of a concussion.

Consensus Statement on Concussion in Sport: the 3rd International Conference on Concussion in Sport held in Zurich, November 2008

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Br J Sports Med 2009 43: i76-i84
doi: 10.1136/bjsm.2009.058248

Exhibit 4

Editor's choice
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Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012

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► Additional material is published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/bjsports-2013-092313).

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Received 8 February 2013
Accepted 8 February 2013

To cite: McCrory P, Meeuwisse WH, Aubry M, *et al*. *Br J Sports Med* 2013;47:250–258.

PREAMBLE

This paper is a revision and update of the recommendations developed following the 1st (Vienna 2001), 2nd (Prague 2004) and 3rd (Zurich 2008) International Consensus Conferences on Concussion in Sport and is based on the deliberations at the 4th International Conference on Concussion in Sport held in Zurich, November 2012.[1–3]

The new 2012 Zurich Consensus statement is designed to build on the principles outlined in the previous documents and to develop further conceptual understanding of this problem using a formal consensus-based approach. A detailed description of the consensus process is outlined at the end of this document under the Background section. This document is developed primarily for use by physicians and healthcare professionals who are involved in the care of injured athletes, whether at the recreational, elite or professional level.

While agreement exists pertaining to principal messages conveyed within this document, the authors acknowledge that the science of concussion is evolving, and therefore management and return to play (RTP) decisions remain in the realm of clinical judgement on an individualised basis. Readers are encouraged to copy and distribute freely the Zurich Consensus document, the Concussion Recognition Tool (CRT), the Sports Concussion Assessment Tool V3 (SCAT3) and/or the Child SCAT3 card and none are subject to any restrictions, provided they are not altered in any way or converted to a digital format. The authors request that the document and/or the accompanying tools be distributed in their full and complete format.

This consensus paper is broken into a number of sections

1. A summary of concussion and its management, with updates from the previous meetings;
2. Background information about the consensus meeting process;
3. A summary of the specific consensus questions discussed at this meeting;
4. The Consensus paper should be read in conjunction with the SCAT3 assessment tool, the Child SCAT3 and the CRT (designed for lay use).

SECTION 1: SPORT CONCUSSION AND ITS MANAGEMENT

The Zurich 2012 document examines the sport concussion and management issues raised in the previous Vienna 2001, Prague 2004 and Zurich 2008 documents and applies the consensus questions from section 3 to these areas.[1–3]

Definition of concussion

A panel discussion regarding the definition of concussion and its separation from mild traumatic brain injury (mTBI) was held. There was acknowledgement by the Concussion in Sport Group (CISG) that although the terms mTBI and concussion are often used interchangeably in the sporting context and particularly in the US literature, others use the term to refer to different injury constructs. Concussion is the historical term representing low-velocity injuries that cause brain 'shaking' resulting in clinical symptoms and that are not necessarily related to a pathological injury. Concussion is a subset of TBI and will be the term used in this document. It was also noted that the term *commotio cerebri* is often used in European and other countries. Minor revisions were made to the definition of concussion, which is defined as follows:

> Concussion is a brain injury and is defined as a complex pathophysiological process affecting the brain, induced by biomechanical forces. Several common features that incorporate clinical, pathologic and biomechanical injury constructs that may be utilised in defining the nature of a concussive head injury include:

1. Concussion may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an "impulsive' force transmitted to the head.
2. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, symptoms and signs may evolve over a number of minutes to hours.
3. Concussion may result in neuropathological changes, but the acute clinical symptoms

largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies.

4. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course. However, it is important to note that in some cases symptoms may be prolonged.

Recovery of concussion

The majority (80–90%) of concussions resolve in a short (7–10 day) period, although the recovery time frame may be longer in children and adolescents.[2]

Symptoms and signs of acute concussion

The diagnosis of acute concussion usually involves the assessment of a range of domains including clinical symptoms, physical signs, cognitive impairment, neurobehavioural features and sleep disturbance. Furthermore, a detailed concussion history is an important part of the evaluation both in the injured athlete and when conducting a preparticipation examination. The detailed clinical assessment of concussion is outlined in the SCAT3 and Child SCAT3 forms, which are given in the appendix to this document.

The suspected diagnosis of concussion can include one or more of the following clinical domains:

1. Symptoms—somatic (eg, headache), cognitive (eg, feeling like in a fog) and/or emotional symptoms (eg, lability);
2. Physical signs (eg, loss of consciousness (LOC), amnesia);
3. Behavioural changes (eg, irritability);
4. Cognitive impairment (eg, slowed reaction times);
5. Sleep disturbance (eg, insomnia).

If any one or more of these components are present, a concussion should be suspected and the appropriate management strategy instituted.

On-field or sideline evaluation of acute concussion

When a player shows ANY features of a concussion:

A. The player should be evaluated by a physician or other licensed healthcare provider onsite using standard emergency management principles and particular attention should be given to excluding a cervical spine injury.
B. The appropriate disposition of the player must be determined by the treating healthcare provider in a timely manner. If no healthcare provider is available, the player should be safely removed from practice or play and urgent referral to a physician arranged.
C. Once the first aid issues are addressed, an assessment of the concussive injury should be made using the SCAT3 or other sideline assessment tools.
D. The player should not be left alone following the injury and serial monitoring for deterioration is essential over the initial few hours following injury.
E. A player with diagnosed concussion should not be allowed to RTP on the day of injury.

Sufficient time for assessment and adequate facilities should be provided for the appropriate medical assessment both on and off the field for all injured athletes. In some sports, this may require rule change to allow an appropriate off-field medical assessment to occur without affecting the flow of the game or unduly penalising the injured player's team. The final determination regarding concussion diagnosis and/or fitness to play is a medical decision based on clinical judgement.

Sideline evaluation of cognitive function is an essential component in the assessment of this injury. Brief neuropsychological test batteries that assess attention and memory function have been shown to be practical and effective. Such tests include the SCAT3, which incorporates the Maddocks' questions[4 5] and the Standardized Assessment of Concussion (SAC).[6–8] It is worth noting that standard orientation questions (eg, time, place and person) have been shown to be unreliable in the sporting situation when compared with memory assessment.[5 9] It is recognised, however, that abbreviated testing paradigms are designed for rapid concussion screening on the sidelines and are not meant to replace comprehensive neuropsychological testing which should ideally be performed by trained neuropsychologists who are sensitive to subtle deficits that may exist beyond the acute episode; nor should they be used as a stand-alone tool for the ongoing management of sports concussions.

It should also be recognised that the appearance of symptoms or cognitive deficit might be delayed several hours following a concussive episode and that concussion should be seen as an evolving injury in the acute stage.

Evaluation in the emergency room or office by medical personnel

An athlete with concussion may be evaluated in the emergency room or doctor's office as a point of first contact following injury or may have been referred from another care provider. In addition to the points outlined above, the key features of this examination should encompass:

A. A medical assessment including a comprehensive history and detailed neurological examination including a thorough assessment of mental status, cognitive functioning, gait and balance.
B. A determination of the clinical status of the patient, including whether there has been improvement or deterioration since the time of injury. This may involve seeking additional information from parents, coaches, teammates and eyewitnesses to the injury.
C. A determination of the need for emergent neuroimaging in order to exclude a more severe brain injury involving a structural abnormality.

In large part, these points above are included in the SCAT3 assessment.

Concussion investigations

A range of additional investigations may be utilised to assist in the diagnosis and/or exclusion of injury. Conventional structural neuroimaging is typically normal in concussive injury. Given that caveat, the following suggestions are made: Brain CT (or where available an MR brain scan) contributes little to concussion evaluation but should be employed whenever suspicion of an intracerebral or structural lesion (eg, skull fracture) exists. Examples of such situations may include prolonged disturbance of the conscious state, focal neurological deficit or worsening symptoms.

Other imaging modalities such as fMRI demonstrate activation patterns that correlate with symptom severity and recovery in concussion.[10–14] Although not part of routine assessment at the present time, they nevertheless provide additional insight to pathophysiological mechanisms. Alternative imaging technologies (eg, positron emission tomography, diffusion tensor imaging, magnetic resonance spectroscopy, functional connectivity), while demonstrating some compelling findings, are still at early stages of development and cannot be recommended other than in a research setting.

Published studies, using both sophisticated force plate technology, as well as those using less sophisticated clinical balance tests (eg, Balance Error Scoring System (BESS)), have identified acute postural stability deficits lasting approximately 72 h following sports-related concussion. It appears that postural stability testing provides a useful tool for objectively assessing the motor domain of neurological functioning, and should be considered as a reliable and valid addition to the assessment of athletes suffering from concussion, particularly where the symptoms or signs indicate a balance component.[15–21]

The significance of Apolipoprotein (Apo) E4, ApoE promoter gene, Tau polymerase and other genetic markers in the management of sports concussion risk or injury outcome is unclear at this time.[22 23] Evidence from human and animal studies in more severe traumatic brain injury demonstrates induction of a variety of genetic and cytokine factors such as: insulin-like growth factor 1 (IGF-1), IGF binding protein 2, Fibroblast growth factor, Cu-Zn superoxide dismutase, superoxide dismutase 1 (SOD-1), nerve growth factor, glial fibrillar acidic protein (GFAP) and S-100. How such factors are affected in sporting concussion is not known at this stage.[24–31] In addition, biochemical serum and cerebral spinal fluid biomarkers of brain injury (including S-100, neuron-specific enolase (NSE), myelin basic protein (MBP), GFAP, tau, etc) have been proposed as a means by which cellular damage may be detected if present.[32–38] There is currently insufficient evidence, however, to justify the routine use of these biomarkers clinically.

Different electrophysiological recording techniques (eg, evoked response potential (ERP), cortical magnetic stimulation and electroencephalography) have demonstrated reproducible abnormalities in the postconcussive state; however, not all studies reliably differentiated concussed athletes from controls.[39–45] The clinical significance of these changes remains to be established.

Neuropsychological assessment

The application of neuropsychological (NP) testing in concussion has been shown to be of clinical value and contributes significant information in concussion evaluation.[46–51] Although cognitive recovery largely overlaps with the time course of symptom recovery in most cases, it has been demonstrated that cognitive recovery may occasionally precede or more commonly follow clinical symptom resolution, suggesting that the assessment of cognitive function should be an important component in the overall assessment of concussion and, in particular, any RTP protocol.[52 53] It must be emphasised, however, that NP assessment should not be the sole basis of management decisions. Rather, it should be seen as an aid to the clinical decision-making process in conjunction with a range of assessments of different clinical domains and investigational results.

It is recommended that all athletes should have a clinical neurological assessment (including assessment of their cognitive function) as part of their overall management. This will normally be performed by the treating physician often in conjunction with computerised neuropsychological screening tools.

Formal NP testing is not required for all athletes; however, when this is considered necessary, it should ideally be performed by a trained neuropsychologist. Although neuropsychologists are in the best position to interpret NP tests by virtue of their background and training, the ultimate RTP decision should remain a medical one in which a multidisciplinary approach, when possible, has been taken. In the absence of NP and other (eg, formal balance assessment) testing, a more conservative RTP approach may be appropriate.

NP testing may be used to assist RTP decisions and is typically performed when an athlete is clinically asymptomatic; however, NP assessment may add important information in the early stages following injury.[54 55] There may be particular situations where testing is performed early to assist in determining aspects of management, for example, return to school in a paediatric athlete. This will normally be best determined in consultation with a trained neuropsychologist.[56 57]

Baseline NP testing was considered by the panel and was not felt to be required as a mandatory aspect of every assessment; however, it may be helpful to add useful information to the overall interpretation of these tests. It also provides an additional educative opportunity for the physician to discuss the significance of this injury with the athlete. At present, there is insufficient evidence to recommend the widespread routine use of baseline neuropsychological testing.

Concussion management

The cornerstone of concussion management is physical and cognitive rest until the acute symptoms resolve and then a graded programme of exertion prior to medical clearance and RTP. The current published evidence evaluating the effect of rest following a sports-related concussion is sparse. An initial period of rest in the acute symptomatic period following injury (24–48 h) may be of benefit. Further research to evaluate the long-term outcome of rest, and the optimal amount and type of rest, is needed. In the absence of evidence-based recommendations, a sensible approach involves the gradual return to school and social activities (prior to contact sports) in a manner that does not result in a significant exacerbation of symptoms.

Low-level exercise for those who are slow to recover may be of benefit, although the optimal timing following injury for initiation of this treatment is currently unknown.

As described above, the majority of injuries will recover spontaneously over several days. In these situations, it is expected that an athlete will proceed progressively through a stepwise RTP strategy.[58]

Graduated RTP protocol

RTP protocol following a concussion follows a stepwise process as outlined in table 1.

With this stepwise progression, the athlete should continue to proceed to the next level if asymptomatic at the current level. Generally, each step should take 24 h so that an athlete would take approximately 1 week to proceed through the full rehabilitation protocol once they are asymptomatic at rest and with provocative exercise. If any postconcussion symptoms occur while in the stepwise programme, then the patient should drop back to the previous asymptomatic level and try to progress again after a further 24 h period of rest has passed.

Same day RTP

It was unanimously agreed that no RTP on the day of concussive injury should occur. There are data demonstrating that at the collegiate and high school levels, athletes allowed to RTP on the same day may demonstrate NP deficits postinjury that may not be evident on the sidelines and are more likely to have delayed onset of symptoms.[59–65]

'Difficult' or persistently symptomatic concussion patient

Persistent symptoms (>10 days) are generally reported in 10–15% of concussions. In general, symptoms are not specific to concussion and it is important to consider other pathologies

Table 1 Graduated return to play protocol

Rehabilitation stage	Functional exercise at each stage of rehabilitation	Objective of each stage
1. No activity	Symptom limited physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming or stationary cycling keeping intensity <70% maximum permitted heart rate No resistance training	Increase HR
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities	Add movement
4. Non-contact training drills	Progression to more complex training drills, eg, passing drills in football and ice hockey May start progressive resistance training	Exercise, coordination and cognitive load
5. Full-contact practice	Following medical clearance participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play	

Cases of concussion in sport where clinical recovery falls outside the expected window (ie, 10 days) should be managed in a multidisciplinary manner by healthcare providers with experience in sports-related concussion.

Psychological management and mental health issues

Psychological approaches may have potential application in this injury, particularly with the modifiers listed below.[66 67] Physicians are also encouraged to evaluate the concussed athlete for affective symptoms such as depression and anxiety as these symptoms are common in all forms of traumatic brain injury.[58]

Role of pharmacological therapy

Pharmacological therapy in sports concussion may be applied in two distinct situations. The first of these situations is the management of specific and/or prolonged symptoms (eg, sleep disturbance, anxiety, etc). The second situation is where drug therapy is used to modify the underlying pathophysiology of the condition with the aim of shortening the duration of the concussion symptoms.[68] In broad terms, this approach to management should be only considered by clinicians experienced in concussion management.

An important consideration in RTP is that concussed athletes should not only be symptom-free, but also they should not be taking any pharmacological agents/medications that may mask or modify the symptoms of concussion. Where antidepressant therapy may be commenced during the management of a concussion, the decision to RTP while still on such medication must be considered carefully by the treating clinician.

Role of preparticipation concussion evaluation

Recognising the importance of a concussion history, and appreciating the fact that many athletes will not recognise all the concussions they may have suffered in the past, a detailed concussion history is of value.[69–72] Such a history may preidentify athletes who fit into a high-risk category and provides an opportunity for the healthcare provider to educate the athlete in regard to the significance of concussive injury. A structured concussion history should include specific questions as to previous symptoms of a concussion and length of recovery, not just the perceived number of past concussions. It is also worth noting that dependence on the recall of concussive injuries by teammates or coaches has been demonstrated to be unreliable.[69] The clinical history should also include information about all previous head, face or cervical spine injuries as these may also have clinical relevance. It is worth emphasising that in the setting of maxillofacial and cervical spine injuries, coexistent concussive injuries may be missed unless specifically assessed. Questions pertaining to disproportionate impact versus symptom severity matching may alert the clinician to a progressively increasing vulnerability to injury. As part of the clinical history, it is advised that details regarding protective equipment employed at the time of injury be sought, both for recent and remote injuries.

There is an additional and often unrecognised benefit of the preparticipation physical examination insofar as the evaluation allows for an educative opportunity with the player concerned as well as consideration of modification of playing behaviour if required.

Modifying factors in concussion management

A range of 'modifying' factors may influence the investigation and management of concussion and, in some cases, may predict the potential for prolonged or persistent symptoms. However, in some cases, the evidence for their efficacy is limited. These modifiers would be important to consider in a detailed concussion history and are outlined in table 2.

Female gender

The role of female gender as a possible modifier in the management of concussion was discussed at length by the panel. There was no unanimous agreement that the current published research evidence is conclusive enough for this to be included as a modifying factor, although it was accepted that gender may be a risk factor for injury and/or influence injury severity.[73–75]

Significance of LOC

In the overall management of moderate-to-severe traumatic brain injury, duration of LOC is an acknowledged predictor of

Table 2 Concussion modifiers

Factors	Modifier
Symptoms	Number Duration (>10 days) Severity
Signs	Prolonged loss of consciousness (LOC) (>1 min), Amnesia
Sequelae	Concussive convulsions
Temporal	Frequency—repeated concussions over time Timing—injuries close together in time 'Recency'—recent concussion or traumatic brain injury (TBI)
Threshold	Repeated concussions occurring with progressively less impact force or slower recovery after each successive concussion
Age	Child and adolescent (<18 years old)
Comorbidities and premorbidities	Migraine, depression or other mental health disorders, attention deficit hyperactivity disorder (ADHD), learning disabilities (LD), sleep disorders
Medication	Psychoactive drugs, anticoagulants
Behaviour	Dangerous style of play
Sport	High risk activity, contact and collision sport, high sporting level

outcome.[76] Although published findings in concussion describe LOC associated with specific, early cognitive deficits, it has not been noted as a measure of injury severity.[77 78] Consensus discussion determined that prolonged (>1 min duration) LOC would be considered as a factor that may modify management.

Significance of amnesia and other symptoms

There is renewed interest in the role of post-traumatic amnesia and its role as a surrogate measure of injury severity.[64 79 80] Published evidence suggests that the nature, burden and duration of the clinical postconcussive symptoms may be more important than the presence or duration of amnesia alone.[77 81 82] Further, it must be noted that retrograde amnesia varies with the time of measurement postinjury and hence is poorly reflective of injury severity.[83 84]

Motor and convulsive phenomena

A variety of immediate motor phenomena (eg, tonic posturing) or convulsive movements may accompany a concussion. Although dramatic, these clinical features are generally benign and require no specific management beyond the standard treatment of the underlying concussive injury.[85 86]

Depression

Mental health issues (such as depression) have been reported as a consequence of all levels of traumatic brain injury including sports-related concussion. Neuroimaging studies using fMRI suggest that a depressed mood following concussion may reflect an underlying pathophysiological abnormality consistent with a limbic-frontal model of depression.[34 87–97] Although such mental health issues may be multifactorial in nature, it is recommended that the treating physician consider these issues in the management of concussed patients.

SPECIAL POPULATIONS

Child and adolescent athlete

The evaluation and management recommendations contained herein can be applied to children and adolescents down to the age of 13 years. Below that age, children report concussion symptoms different from adults and would require age-appropriate symptom checklists as a component of assessment. An additional consideration in assessing the child or adolescent athlete with a concussion is that the clinical evaluation by the healthcare professional may need to include both patient and parent input, and possibly teacher and school input when appropriate.[98–104] A child SCAT3 has been developed to assess concussion (see appendix) for individuals aged 5–12 years.

The decision to use NP testing is broadly the same as the adult assessment paradigm, although there are some differences. The timing of testing may differ in order to assist planning in school and home management. If cognitive testing is performed, then it must be developmentally sensitive until late teen years due to the ongoing cognitive maturation that occurs during this period, which in turn limits the utility of comparison to either the person's own baseline performance or to population norms.[20] In this age group, it is more important to consider the use of trained paediatric neuropsychologists to interpret assessment data, particularly in children with learning disorders and/or ADHD who may need more sophisticated assessment strategies.[56 57 98]

It was agreed by the panel that no return to sport or activity should occur before the child/adolescent athlete has managed to return to school successfully. In addition, the concept of 'cognitive rest' was highlighted with special reference to a child's need to limit exertion with activities of daily living that may exacerbate symptoms. School attendance and activities may also need to be modified to avoid provocation of symptoms. Children should not be returned to sport until clinically completely symptom-free, which may require a longer time frame than for adults.

Because of the different physiological response and longer recovery after concussion and specific risks (eg, diffuse cerebral swelling) related to head impact during childhood and adolescence, a more conservative RTP approach is recommended. It is appropriate to extend the amount of time of asymptomatic rest and/or the length of the graded exertion in children and adolescents. It is not appropriate for a child or adolescent athlete with concussion to RTP on the same day as the injury, regardless of the level of athletic performance. Concussion modifiers apply even more to this population than adults and may mandate more cautious RTP advice.

Elite versus non-elite athletes

All athletes, regardless of the level of participation, should be managed using the same treatment and RTP paradigm. The available resources and expertise in concussion evaluation are of more importance in determining management than a separation between elite and non-elite athlete management. Although formal NP testing may be beyond the resources of many sports or individuals, it is recommended that, in all organised high-risk sports, consideration be given to having this cognitive evaluation, regardless of the age or level of performance.

Chronic traumatic encephalopathy

Clinicians need to be mindful of the potential for long-term problems in the management of all athletes. However, it was agreed that chronic traumatic encephalopathy (CTE) represents a distinct tauopathy with an unknown incidence in athletic populations. It was further agreed that a cause and effect relationship has not as yet been demonstrated between CTE and concussions or exposure to contact sports.[105–114] At present, the interpretation of causation in the modern CTE case studies should proceed cautiously. It was also recognised that it is important to address the fears of parents/athletes from media pressure related to the possibility of CTE.

INJURY PREVENTION

Protective equipment—mouthguards and helmets

There is no good clinical evidence that currently available protective equipment will prevent concussion, although mouthguards have a definite role in preventing dental and orofacial injury. Biomechanical studies have shown a reduction in impact forces to the brain with the use of head gear and helmets, but these findings have not been translated to show a reduction in concussion incidence. For skiing and snowboarding, there are a number of studies to suggest that helmets provide protection against head and facial injury and hence should be recommended for participants in alpine sports.[115–118] In specific sports such as cycling, motor and equestrian sports, protective helmets may prevent other forms of head injury (eg, skull fracture) that are related to falling on hard surfaces and may be an important injury prevention issue for those sports.[118–130]

Rule change

Consideration of rule changes to reduce the head injury incidence or severity may be appropriate where a clear-cut mechanism is implicated in a particular sport. An example of this is in football (soccer) where research studies demonstrated that upper limb to head contact in heading contests accounted for approximately 50% of concussions.[131] As noted earlier, rule changes

may also be needed in some sports to allow an effective off-field medical assessment to occur without compromising the athlete's welfare, affecting the flow of the game or unduly penalising the player's team. It is important to note that rule enforcement may be a critical aspect of modifying injury risk in these settings, and referees play an important role in this regard.

Risk compensation

An important consideration in the use of protective equipment is the concept of risk compensation.[132] This is where the use of protective equipment results in behavioural change such as the adoption of more dangerous playing techniques, which can result in a paradoxical increase in injury rates. The degree to which this phenomenon occurs is discussed in more detail in the review published in this supplement of the journal. This may be a matter of particular concern in child and adolescent athletes where the head injury rates are often higher than in adult athletes.[133–135]

Aggression versus violence in sport

The competitive/aggressive nature of sport that makes it fun to play and watch should not be discouraged. However, sporting organisations should be encouraged to address violence that may increase concussion risk.[136 137] Fair play and respect should be supported as key elements of sport.

Knowledge transfer

As the ability to treat or reduce the effects of concussive injury after the event is minimal, education of athletes, colleagues and the general public is a mainstay of progress in this field. Athletes, referees, administrators, parents, coaches and healthcare providers must be educated regarding the detection of concussion, its clinical features, assessment techniques and principles of safe RTP. Methods to improve education including web-based resources, educational videos and international outreach programmes are important in delivering the message. In addition, concussion working groups, plus the support and endorsement of enlightened sport groups such as Fédération Internationale de Football Association (FIFA), International Olympic Commission (IOC), International Rugby Board (IRB) and International Ice Hockey Federation (IIHF), who initiated this endeavour, have enormous value and must be pursued vigorously. Fair play and respect for opponents are ethical values that should be encouraged in all sports and sporting associations. Similarly, coaches, parents and managers play an important part in ensuring that these values are implemented on the field of play.[58 138–150]

SECTION 2: STATEMENT ON BACKGROUND TO THE CONSENSUS PROCESS

In November 2001, the 1st International Conference on Concussion in Sport was held in Vienna, Austria. This meeting was organised by the IIHF in partnership with FIFA and the Medical Commission of the IOC. As part of the resulting mandate for the future, the need for leadership and future updates was identified. The 2nd International Conference on Concussion in Sport was organised by the same group with the additional involvement of the IRB and was held in Prague, the Czech Republic, in November 2004. The original aims of the symposia were to provide recommendations for the improvement of safety and health of athletes who suffer concussive injuries in ice hockey, rugby, football (soccer) as well as other sports. To this end, a range of experts were invited to both meetings to address specific issues of epidemiology, basic and clinical science, injury grading systems, cognitive assessment, new research methods, protective equipment, management, prevention and long-term outcome.[1 2]

The 3rd International Conference on Concussion in Sport was held in Zurich, Switzerland on 29/30 October 2008 and was designed as a formal consensus meeting following the organisational guidelines set forth by the US National Institutes of Health. (Details of the consensus methodology can be obtained at: http://consensus.nih.gov/ABOUTCDP.htm.) The basic principles governing the conduct of a consensus development conference are summarised below:

1. A broad-based non-government, non-advocacy panel was assembled to give balanced, objective and knowledgeable attention to the topic. Panel members excluded anyone with scientific or commercial conflicts of interest and included researchers in clinical medicine, sports medicine, neuroscience, neuroimaging, athletic training and sports science.
2. These experts presented data in a public session, followed by inquiry and discussion. The panel then met in an executive session to prepare the consensus statement.
3. A number of specific questions were prepared and posed in advance to define the scope and guide the direction of the conference. The principal task of the panel was to elucidate responses to these questions. These questions are outlined below.
4. A systematic literature review was prepared and circulated in advance for use by the panel in addressing the conference questions.
5. The consensus statement is intended to serve as the scientific record of the conference.
6. The consensus statement will be widely disseminated to achieve maximum impact on both current healthcare practice and future medical research.

The panel chairperson (WM) did not identify with any advocacy position. The chairperson was responsible for directing the consensus session and guiding the panel's deliberations. Panellists were drawn from clinical practice, academics and research in the field of sports-related concussion. They do not represent organisations per se, but were selected for their expertise, experience and understanding of this field.

The 4th International Conference on Concussion in Sport was held in Zurich, Switzerland on 1–3 November 2012 and followed the same outline as for the third meeting. All speakers, consensus panel members and abstract authors were required to sign an ICMJE Form for Disclosure of Potential Conflicts of Interest. Detailed information related to each author's affiliations and conflicts of interests will be made publicly available on the CISG website and published with the BJSM supplement.

Medical legal considerations

This consensus document reflects the current state of knowledge and will need to be modified according to the development of new knowledge. It provides an overview of issues that may be of importance to healthcare providers involved in the management of sports-related concussion. It is not intended as a standard of care, and should not be interpreted as such. This document is only a guide, and is of a general nature, consistent with the reasonable practice of a healthcare professional. Individual treatment will depend on the facts and circumstances specific to each individual case.

It is intended that this document will be formally reviewed and updated prior to 1 December 2016.

SECTION 3: ZURICH 2012 CONSENSUS QUESTIONS

Note that each question is the subject of a separate systematic review that is published in the *BJSM* (2013:47:5). As such, all citations and details of each topic will be covered in those reviews.

When you assess an athlete acutely and they do not have a concussion, what is it? Is a cognitive injury the key component of concussion in making a diagnosis?

The consensus panel agreed that concussion is an evolving injury in the acute phase with rapidly changing clinical signs and symptoms, which may reflect the underlying physiological injury in the brain. Concussion is considered to be among the most complex injuries in sports medicine to diagnose, assess and manage. A majority of concussions in sport occur without LOC or frank neurological signs. At present, there is no perfect diagnostic test or marker that clinicians can rely on for an immediate diagnosis of concussion in the sporting environment. Because of this evolving process, it is not possible to rule out concussion when an injury event occurs associated with a transient neurological symptom. All such cases should be removed from the playing field and assessed for concussion by the treating physician or healthcare provider as discussed below. It was recognised that a cognitive deficit is not necessary for acute diagnosis as it either may not be present or detected on examination.

Are the existing tools/examination sensitive and reliable enough on the day of injury to make or exclude a diagnosis of concussion?

Concussion is a clinical diagnosis based largely on the observed injury mechanism, signs and symptoms. The vast majority of sports-related concussions (hereafter, referred to as *concussion*) occur without LOC or frank neurological signs.[151–154] In milder forms of concussion, the athlete might be slightly confused, without clearly identifiable amnesia. In addition, most concussions cannot be identified or diagnosed by neuroimaging techniques (eg, CT or MRI). Several well-validated neuropsychological tests are appropriate for use in the assessment of acute concussion in the competitive sporting environment. These tests provide important data on symptoms and functional impairments that clinicians can incorporate into their diagnostic formulation, but should not solely be used to diagnose concussion.

What is the best practice for evaluating an adult athlete with concussion on the 'field of play' in 2012?

Recognising and evaluating concussion in the adult athlete on the field is a challenging responsibility for the healthcare provider. Performing this task is often a rapid assessment in the midst of competition with a time constraint and the athlete eager to play. A standardised objective assessment of injury, which includes excluding more serious injury, is critical in determining disposition decisions for the athlete. The on-field evaluation of sports-related concussion is often a challenge given the elusiveness and variability of presentation, difficulty in making a timely diagnosis, specificity and sensitivity of sideline assessment tools, and the reliance on symptoms. Despite these challenges, the sideline evaluation is based on recognition of injury, assessment of symptoms, cognitive and cranial nerve function, and balance. Serial assessments are often necessary. Concussion is often an evolving injury, and signs and symptoms may be delayed. Therefore, erring on the side of caution (keeping an athlete out of participation when there is any suspicion for injury) is important. An SAC is useful in the assessment of the athlete with suspected concussion but should not take the place of the clinician's judgement.

How can the SCAT2 be improved?

It was agreed that a variety of measures should be employed as part of the assessment of concussion to provide a more complete clinical profile for the concussed athlete. Important clinical information can be ascertained in a streamlined manner through the use of a multimodal instrument such as the Sport Concussion Assessment Tool (SCAT). A baseline assessment is advised wherever possible. However, it is acknowledged that further validity studies need to be performed to answer this specific issue.

A future SCAT test battery (ie, SCAT3) should include an initial assessment of injury severity using the Glasgow Coma Scale (GCS), immediately followed by observing and documenting concussion signs. Once this is complete, symptom endorsement and symptom severity, as well as neurocognitive and balance functions, should be assessed in any athlete suspected of sustaining a concussion. It is recommended that these latter steps be conducted following a minimum 15 min rest period on the sideline to avoid the influence of exertion or fatigue on the athlete's performance. Although it is noted that this time frame is an arbitrary one, the expert panel agreed nevertheless that a period of rest was important prior to assessment. Future research should consider the efficacy for inclusion of vision tests such as the King Devick Test and clinical reaction time tests.[155 156] Recent studies suggest that these may be useful additions to the sideline assessment of concussion. However, the need for additional equipment may make them impractical for sideline use.

It was further agreed that the SCAT3 would be suitable for adults and youths aged 13 and over and that a new tool (Child SCAT3) be developed for younger children.

Advances in neuropsychology: are computerised tests sufficient for concussion diagnosis?

Sports-related concussions are frequently associated with one or more symptoms, impaired balance and/or cognitive deficits. These problems can be measured using symptom scales, balance testing and neurocognitive testing. All three modalities can identify significant changes in the first few days following injury, generally with normalisation over 1–3 weeks. The presentation of symptoms and the rate of recovery can be variable, which reinforces the value of assessing all three areas as part of a comprehensive sport concussion programme.

Neuropsychological assessment has been described by the CISG as a 'cornerstone' of concussion management. Neuropsychologists are uniquely qualified to interpret neuropsychological tests and can play an important role within the context of a multifaceted-multimodal and multidisciplinary approach to managing sports-related concussion. Concussion management programmes that use neuropsychological assessment to assist in clinical decision-making have been instituted in professional sports, colleges and high schools. Brief computerised cognitive evaluation tools are the mainstay of these assessments worldwide, given the logistical limitation in accessing trained neuropsychologists; however, it should be noted that these are not substitutes for formal neuropsychological assessment. At present, there is insufficient evidence to recommend the widespread routine use of baseline neuropsychological testing.

What evidence exists for new strategies/technologies in the diagnosis of concussion and assessment of recovery?

A number of novel technological platforms exist to assess concussion including (but not limited to) iPhone/smart phone apps, quantitative electroencephalography, robotics sensory motor

assessment, telemedicine, eye-tracking technology, functional imaging/advanced neuroimaging and head impact sensors. At this stage, only limited evidence exists for their role in this setting and none have been validated as diagnostic. It will be important to reconsider the role of these technologies once evidence is developed.

Advances in the management of sport concussion: what is evidence for concussion therapies

The current evidence evaluating the effect of rest and treatment following a sports-related concussion is sparse. An initial period of rest may be of benefit. However, further research to evaluate the long-term outcome of rest, and the optimal amount and type of rest, is needed. Low-level exercise for those who are slow to recover may be of benefit, although the optimal timing following injury for initiation of this treatment is currently unknown. Multimodal physiotherapy treatment for individuals with clinical evidence of cervical spine and/or vestibular dysfunction may be of benefit. There is a strong need for high-level studies evaluating the effects of a resting period, pharmacological interventions, rehabilitative techniques and exercise for individuals who have sustained a sports-related concussion.

The difficult concussion patient—What is the best approach to investigation and management of persistent (>10 days) postconcussive symptoms?

Persistent symptoms (>10 days) are generally reported in 10–15% of concussions. This may be higher in certain sports (eg, elite ice hockey) and populations (eg, children). In general, symptoms are not specific to concussion and it is important to consider and manage co-existent pathologies. Investigations may include formal neuropsychological testing and conventional neuroimaging to exclude structural pathology. Currently, there is insufficient evidence to recommend routine clinical use of advanced neuroimaging techniques or other investigative strategies. Cases of concussion in sport where clinical recovery falls outside the expected window (ie, 10 days) should be managed in a multidisciplinary manner by healthcare providers with experience in sports-related concussion. Important components of management after the initial period of physical and cognitive rest include associated therapies such as cognitive, vestibular, physical and psychological therapy, consideration of assessment of other causes of prolonged symptoms and consideration of commencement of a graded exercise programme at a level that does not exacerbate symptoms.

Revisiting concussion modifiers: how should the evaluation and management of acute concussion differ in specific groups?

The literature demonstrates that the number and severity of symptoms and previous concussions are associated with prolonged recovery and/or increased risk of complications. Brief LOC, duration of post-traumatic amnesia and/or impact seizures do not reliably predict outcome following concussion, although a cautious approach should be taken in an athlete with prolonged LOC (ie, >1 min). Children generally take longer to recover from concussions and assessment batteries have yet to be validated in the younger age group. Currently, there are insufficient data on the influence of genetics and gender on outcome following concussion. Several modifiers are associated with prolonged recovery or increased risk of complications following concussion and have important implications for management. Children with concussion should be managed conservatively, with the emphasis on return to learn before return to sport. In cases of concussion managed with limited resources (eg, non-elite players), a conservative approach should also be taken such that the athlete does not return to sport until fully recovered.

What are the most effective risk reduction strategies in sport concussion?—from protective equipment to policy?

No new valid evidence was provided to suggest that the use of current standard headgear in rugby, or of mouthguards in American football, can significantly reduce players' risk of concussion. No evidence was provided to suggest an association between neck strength increases and concussion risk reduction. There was evidence to suggest that eliminating body checking from Pee Wee ice hockey (ages 11–12 years) and fair-play rules in ice hockey were effective injury prevention strategies. Helmets need to be able to protect from impacts resulting in a head change in velocity of up to 10 m/s in professional American football, and up to 7 m/s in professional Australian football. It also appears that helmets must be capable of reducing head-resultant linear acceleration to below 50 g and angular acceleration components to below 1500 rad/s^2 to optimise their effectiveness. Given that a multifactorial approach is needed for concussion prevention, well-designed and sport-specific prospective analytical studies of sufficient power are warranted for mouthguards, headgear/helmets, facial protection and neck strength. Measuring the effect of rule changes should also be addressed by future studies, not only assessing new rule changes or legislation, but also alteration or reinforcement to existing rules.

What is the evidence for chronic concussion-related changes?—behavioural, pathological and clinical outcomes

It was agreed that CTE represents a distinct tauopathy with an unknown incidence in athletic populations. It was further agreed that CTE was not related to concussions alone or simply exposure to contact sports. At present, there are no published epidemiological, cohort or prospective studies relating to modern CTE. Owing to the nature of the case reports and pathological case series that have been published, it is not possible to determine the causality or risk factors with any certainty. As such, the speculation that repeated concussion or subconcussive impacts cause CTE remains unproven. The extent to which age-related changes, psychiatric or mental health illness, alcohol/drug use or co-existing medical or dementing illnesses contribute to this process is largely unaccounted for in the published literature. At present, the interpretation of causation in the modern CTE case studies should proceed cautiously. It was also recognised that it is important to address the fears of parents/athletes from media pressure related to the possibility of CTE.

From consensus to action—how do we optimise knowledge transfer, education and ability to influence policy?

The value of knowledge transfer (KT) as part of concussion education is increasingly becoming recognised. Target audiences benefit from specific learning strategies. Concussion tools exist, but their effectiveness and impact require further evaluation. The media is valuable in drawing attention to concussion, but efforts need to ensure that the public is aware of the right information. Social media as a concussion education tool is becoming more prominent. Implementation of KT models is one approach organisations can use to assess knowledge gaps; identify, develop and evaluate education strategies; and use the outcomes to facilitate decision making. Implementing KT strategies requires a defined plan. Identifying the needs, learning styles and preferred learning strategies of target audiences, coupled with evaluation, should be

a piece of the overall concussion education puzzle to have an impact on enhancing knowledge and awareness.

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Competing interests See the supplementary online data for competing interests (http://dx.doi.org/10.1136/bjsports-2013-092313).

Provenance and peer review Commissioned; internally peer reviewed.

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Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012

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Br J Sports Med 2013 47: 250-258
doi: 10.1136/bjsports-2013-092313

Exhibit 5

Curr Treat Options Neurol (2014) 16:306
DOI 10.1007/s11940-014-0306-5

Traumatic Brain Injury (JR Couch, Section Editor)

Current Understanding of Chronic Traumatic Encephalopathy

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This article is part of the Topical Collection on *Traumatic Brain Injury*

Keywords Chronic traumatic encephalopathy (CTE) · Concussion · Brain trauma · Traumatic brain injury (TBI) · APOE · Biomarker · Tau · Football

Opinion statement

Chronic traumatic encephalopathy (CTE) is a unique neurodegenerative disease found in individuals with a history of repetitive head impacts. The neuropathology of CTE is increasingly well defined. Prospective, longitudinal studies with post-mortem neuropathologic validation as well as in vivo diagnostic techniques are needed in order to advance the understanding of CTE clinically. Given the large number of individuals who incur concussions and other forms of brain trauma, this is an important area for scientific and public health inquiry.

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease thought to be associated with a history of repetitive head impacts [1, 8, 9••, 10, 11, 12•] such as those sustained through contact sports or military combat. CTE, a distinct neurodegeneration, was first introduced in the literature as "punch drunk" or dementia pugilistica in the early 1900s because of its association with boxing [13]. In fact, much of the

Published online: 15 July 2014

early literature about the disease focused on the boxing population [1, 13, 14]. However, the disease is found in a more diverse group of individuals with a history of repetitive head impacts including a variety of contact sport athletes, military veterans, domestic abuse victims, and individuals with self-inflicted head banging behavior [7]. Although significant media attention has been brought to this disease, there is relatively little known regarding the pathobiological mechanisms underlying CTE, and a large number of questions remain. The preponderance of the literature has consisted of postmortem neuropathologic assessments with retrospective clinical interviews. As such, the neuropathology of CTE is currently better understood than the clinical presentation or course, and there is a need for prospective longitudinal clinical studies with in vivo diagnostic techniques or neuropathologic validation. This article reviews the current state of our knowledge concerning CTE, including neuropathologic characteristics, clinical features, proposed clinical and pathologic diagnostic criteria, possible risk factors, and future research needs.

Neuropathologic characteristics

Much of the scientific literature on CTE, to-date, is derived from clincopathologic case series of the disease [1–4, 6–8, 9••, 15]. The neuropathology of CTE is increasingly well defined. In 2013, McKee and colleagues published the largest case report to date of individuals with neuropathologically confirmed CTE, presenting proposed criteria for four stages of CTE pathology based on the severity of the findings [9••]. Formal validation of the reliability of these criteria and the staging system are currently being performed by a team of nine neuropathologists, funded by a National Institutes of Health (NIH) U01 grant (1U01NS086659-01, National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Biomedical Imaging and Bioengineering (NIBIB); PI, Ann McKee). Detailed criteria of McKee et al.'s pathologic staging criteria can be found in Table 1.

CTE is characterized by the deposition of hyperphosphorylated tau (p-tau) protein as neurofibrillary tangles (NFT) beginning perivascularly and at the depths of the cortical sulci. Later stage p-tau pathology becomes more widespread, particularly dense in the medial temporal lobes, also present in the white matter, and leads to prominent neuronal loss and gliosis. The irregular and perivascular nature of the p-tau neurofibrillary tangles, the proclivity for the sulcal depths, and the marked subpial and periventricular involvement are unique features of the disease that distinguish it from other tauopathies. TAR DNA-binding protein 43 (TDP-43) is present in about 80 % of cases. Early stages show sparse TDP-43 positive neurites in cortex, medial temporal lobe, and brainstem. Late-stage pathology presents with TDP-43 intraneuronal and intraglial inclusions in the frontal subcortical white matter and fornix, brainstem, and medial temporal lobe. In most cases of CTE, there are no beta amyloid 1–42 ($A\beta_{1-42}$) positive neuritic plaques. Evidence of axonal injury is common and ranges from multifocal axonal varicosities in earlier stage pathology to severe axonal loss in later stage pathology. Stage I and II CTE can present macroscopically with mild enlargement of the lateral ventricles or third ventricle and/or mild septal abnormalities. Grossly, advanced CTE is characterized by enlargement of the lateral and third ventricles, cavum septum pellucidum, septal perforations, and pallor of the substantia nigra and locus coeruleus. In addition, severe

Table 1. Description of McKee et al.'s (2013) proposed neuropathologic staging of CTE

	Stage I	Stage II	Stage III	Stage IV
P-Tau	Focal perivascular NFTs at depths of cortical sulci	NFTs adjacent to focal epicenters and in nuclei outside of Meynert and locus coeruleus	Dense in medial temporal lobes and widespread in cortex, diencephalon, brainstem, and spinal cord	P-tau pathology widespread including in white matter; prominent neuronal loss and gliosis of cortex; hippocampal sclerosis
Macroscopic	Mild lateral ventricle enlargement in some cases	Mild enlargement of the frontal horn of the lateral ventricles or thinning of the corpus callosum in a majority of cases; small cavum septum pellucidum in some cases	Mild cerebral atrophy, enlarged ventricles, depigmentation of locus coeruleus and substantia nigra, septal abnormalities in some cases	Increased cerebral, medial temporal lobe, hypothalamus, thalamus, and mammillary body atrophy; septal abnormalities; enlarged ventricles; pallor of locus coeruleus and substantia nigra
TDP-43	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Severe intraneuronal and intraglial inclusions in cortex, white matter, diencephalon, basal ganglia, brainstem
Axonal injury	Multifocal axonal varicosities in cortex and subcortical white matter	Multifocal axonal varicosities in cortex and subcortical white matter	Severe axonal loss in cortex and white matter	Severe axonal loss in cortex and white matter
Aβ-42	Present in less than half of subjects with CTE and less than one-third of pure CTE cases; those with Aβ-42 deposits were significantly older than those without			

cases may also show profound atrophy of the medial temporal lobes or profound global atrophy. In reports examining former football players [9••] and former boxers [1], the severity of pathology appears to correlate to duration of athletic career. McKee et al. also found an association between severity of pathology to years since retirement from athletics and age at death [9••].

Clinical presentation

Clinical symptoms of CTE generally present years or decades after exposure to trauma [1, 9••, 16••]. Although there are some symptom overlaps between the acute concussive injury and the later-life neurodegenerative process of CTE (eg, attention and concentration loss, headache), it is thought that CTE is distinct from the acute concussion or postconcussion sequelae [17]. That is,

although a history of repetitive brain trauma is thought to be necessary to cause CTE (ie, all neuropathologically confirmed cases of CTE to date have had a history of repetitive brain trauma), CTE symptoms are not just the cumulative effects of this process. Furthermore, there is no clear relationship between prolonged acute concussion symptoms (eg, postconcussion syndrome) and the pathology of CTE.

Evidence to-date suggests that CTE presents clinically with symptoms in one or more of four possible domains: mood, behavior, cognition, and motor [9••, 16••]. Commonly noted mood features include depression, irritability, and hopelessness. Behavioral features may include impulsivity, explosivity, and aggression. Cognitive features can include memory impairment, executive dysfunction, and in severe cases dementia. Motor features, including parkinsonism, ataxia, and dysarthria, appear in a subset of cases, predominantly boxers. In addition, chronic headache is also experienced in some cases [7, 9••, 15, 18, 16••, 19, 20•, 21•]. Two distinct clinical presentations of CTE have been described in a recent study by Stern et al., substantiating evidence from earlier literature regarding this possibility [1, 16••, 22–24] According to Stern and colleagues, the first type of clinical presentation initially presents with mood and behavioral symptoms earlier in life (mean age approximately 35) and progresses to include cognitive symptoms later in the disease course. The second clinical presentation begins with cognitive impairment later in life (mean age approximately 60), which may progress to include mood and behavioral symptoms [16••].

Earlier cases of CTE tended to report a higher prevalence of motor features than more recent reports. Differences in symptom profile have led some researchers to differentiate "classic" and "modern" CTE clinically [25•]. It is worth noting that "classic" cases were predominantly boxers, whereas more recent descriptions have been dominated by football players. Differences in the nature of exposure could account for differences in presentation— biomechanical comparisons of head impact dynamics in boxing and football have shown that boxers experience proportionally more rotational acceleration than in football [26, 27]. Further, computational modeling of boxing impacts suggests that stress in boxing impacts is greatest on midbrain structures, and midbrain damage may account for the parkinsonian features found in CTE [27, 28]. Supporting this theory, in the case series of neuropathologically confirmed CTE by McKee and colleagues [9••], professional boxers and professional football players with neuropathologically confirmed CTE, professional boxers exhibited significantly more motor symptoms (eg, ataxia dysarthria) relative to football players. This clinical difference between boxers and football players was mirrored in the pathology: boxers displayed more cerebellar scarring than football players. Thus, although there is a notable difference in the presence of motor symptoms between the earlier and more recent CTE literature, this may be attributable, at least in part, to the variance in head impact exposure types experienced by boxers and football players.

The question of suicide in CTE remains contentious [29•]. Several CTE case series have included victims of suicide.[6, 7, 9••, 16••] However, our lack of understanding of the population incidence of CTE limits our ability to attribute a complex and multifactorial behavior such as suicide to underlying CTE proteinopathy. The issue is further complicated considering that well

established risk factors for suicide and suicidal ideation such as substance use and depression [30, 31] are often comorbid in cases of CTE [9••, 16••]. The current literature does not provide means to separate the contribution (or lack thereof) of these different potential factors to the act of completing suicide. Further, premature association between repetitive brain trauma and suicidality could result in a 'self-fulfilling prophecy' prompting wider suicides in exposed individuals irrespective of contribution (or noncontribution) from CTE symptoms. Available scientific evidence cannot wholly support the notion that CTE *causes* suicidal thoughts or behaviors, and such assumptions or assertions should be avoided without further evidence.

All efforts to define the clinical presentation of CTE are also limited due to the lack of in vivo diagnosis and use of retrospective reviews of case reports[15, 20•, 21•] or family interviews [9••, 16••]. This information is valuable to determine initial correlations between presence of neuropathology and clinical manifestation; however, because of their retrospective third-party nature, there are significant limitations to these data. Although some of the earlier literature includes clinical evaluations [13, 32], the findings and their generalizability is limited by the technology of the era [25•]. Increased prospective and longitudinal clinical research in this area is critically needed.

Clinical diagnosis and in vivo biomarkers

Several important studies are underway to develop reliable biomarkers for CTE during life, although like most neurodegenerative diseases, the definitive diagnosis of CTE is based on neuropathologic examination. To date, three groups of authors have proposed preliminary clinical and/or research diagnostic criteria [20•, 21•, 33•]. The three independently proposed criteria are largely comparable and follow a structure similar to the National Institutes on Aging—Alzheimer's Association clinical diagnostic criteria [34] by differentiating between probable and possible cases based on endorsement of various signs and symptoms. All criteria require a patient to have a history of brain trauma, and to exhibit symptoms consistent with the clinical presentation of CTE described in the literature that could not likely be explained by another condition. All three criteria identified behavioral and cognitive disturbances as important for a diagnosis of CTE. Research groups differ concerning the importance of motor features; Jordan has suggested that motor features resulting from injury to the pyramidal tracts, extrapyramidal system, and cerebellum are necessary for CTE, whereas both Montenigro et al. and Victoroff have suggested a less central role of motor features in diagnosing clinical CTE [20•, 21•, 33•]. Montinegro et al. suggested codifying the clinical syndrome associated with repetitive brain trauma as Traumatic Encephalopathy Syndrome (TES), and reserving CTE for postmortem neuropathologic diagnoses [33•]. In order to confirm the utility of these criteria in either research or clinical settings, future studies will need to demonstrate an ability to reliably differentiate between cases and noncases with a high degree of specificity. A comparison of these proposed criteria can be found in Table 2.

Table 2. Description of existing proposed research or clinical diagnostic criteria for CTE

	Jordan (2013)	Montenigro et al. (2014)	Victoroff (2013)
Disease/disorder	CTE	Traumatic encephalopathy syndrome (TES), a clinical syndrome associated with history of repetitive brain trauma	CTE
Subclassifications	Definite, Probable, Possible, Improbable	behavioral/mood variant (BMv), cognitive variant (COGv), mixed variant (MIXv), dementia (D); differentiated depending on the presence of motor features or clinical course; or probable, possible, or unlikely CTE based on biomarkers	Clinically probable, clinically possible, acute onset, delayed onset, apparently persistent, apparently progressive, apparently improving
History of brain trauma	No specific guidance as to the specific type or amount of brain trauma required	History of multiple head impacts (mTBI, TBI, or subconcussive trauma) from high exposure contact sports, other significant exposure to repetitive hits, or any activity resulting in TBI	Probable or definite exposure to one or more of the following: TBI, concussion, subconcussions
Duration of symptoms/ onset of symptoms	No guidance provided Typically manifest later in life after a period of latency	Symptoms must be present for a minimum of 12 months Symptom onset must be delayed by at least 2 years from exposure to brain trauma	Symptoms must last for at least two years after impact Acute onset cases have no period of recovery in the 6–12 months following concussion. Delayed onset cases have evidence of decline following apparent recovery post-impact
Differential diagnosis	*Definite* (neuropathologically confirmed) and *Probable*: Cases of CTE involve ruling out of other possible neurological causes. *Possible*: CTE can potentially be explained by other known neurological causes. *Improbable*: CTE can be explained by a pathophysiological process unrelated to brain trauma.	Must rule out other neurological disorders, including residual symptoms from acute TBI or postconcussion syndrome that could account for symptoms. Comorbidities such as substance use, other neurodegenerative diseases can be present	Must rule out other medical or psychiatric diagnosis that could explain symptoms
Clinical features	*Behavioral and psychiatric features*: aggression or agitation, apathy, impulsivity, depression, delusions, suicidality	*Core clinical features*: Difficulties in cognition substantiated with scores of ≥1.5 SD below norms on standardized mental status	Symptoms: headache, speech changes, tremor, deterioration in stance or gait, falls, cognitive decline, mood changes, anxiety

Table 2. (Continued)

	Jordan (2013)	Montenigro et al. (2014)	Victoroff (2013)
	Cognitive features: impaired attention and concentration, memory problems, executive dysfunction, dementia, visuospatial difficulties, language impairment. *Motor features*: dysarthria, spasticity, ataxia, parkinsonism, gait disturbance, motor neuron disease (possibly)	of neuropsychological tests, behavioral issues (eg, short fuse, violence), mood disturbance (eg, depression). *Supportive features*: impulsivity, anxiety, apathy, paranoia, suicidality, chronic headache, motor signs (eg, parkinsonism), documented functional decline, delayed onset. *Potential Biomarkers for diagnosis of Probable CTE*: cavum septi pellucidi, abnormal beta amyloid CSF levels, elevated CSF p-tau/tau ratio, negative amyloid imaging, positive tau imaging, cortical atrophy based on neuroimaging, cortical thinning based on neuroimaging	*Personality change* (eg, irritability, apathy), alcohol abuse dependence or sensitivity, anger or aggression. *Neurological signs*: nystagmus, dysarthria, reduced facial expression, hypertonia or rigidity, hyperreflexia, hemiparesis, tremor, limb ataxia, disorders of gait or stance. *Neurobehavioral signs*: memory loss, other cognitive impairment (eg, disorientation, confusion), mood disturbance (eg, depression), thought disorder, pathological personality traits (eg, irritability, apathy), anger or aggression
Symptom requirements for diagnosis	*Definite*: neurological process consistent with clinical presentation of CTE along with pathological confirmation. *Probable*: two or more of the following conditions: cognitive and/or behavioral impairment, cerebellar dysfunction, pyramidal tract disease or extrapyramidal disease, distinguishable from other disease processes and consistent with the clinical presentation of CTE. *Possible*: neurological process consistent with clinical presentation of CTE but potentially explained by other neurological disorders. *Improbable*: inconsistent with clinical description of CTE and be explained by a process unrelated to brain trauma	At least one core clinical feature must be present and considered a change from baseline functioning, at least two supportive features must be present. *TES-BMo*: behavioral and/or mood core features without cognitive core features. *TES-COGv*: cognitive core features without behavioral and/or mood core features. *TES-MIXc*: both cognitive core features and behavioral and/or mood core features. *TES-D*: progressive course of cognitive core features, evidence of functional impairment. *Probable CTE*: meets TES criteria, progressive, >1 positive CTE biomarker. *Possible CTE*: meets TES criteria, either has not undergone biomarker testing or has had a negative biomarker (other than tau imaging), or has another disorder that may account for presentation. *Unlikely CTE*: does not meet TES criteria and/or has had negative tau imaging	*Clinically probable diagnosis* requires at least two symptoms and three signs. *Clinically possible diagnosis* requires at least one symptom and two signs. Cases should be identified as acute onset or delayed onset. (See onset of symptoms above.) Cases should be identified as either apparently persistent (clinical features last more than two years), apparently progressive (clinical features last for more than two years and are unequivocally progressive), or apparently improving
CTE clinical features and reliability			

To date, there are no objective, validated in vivo biomarkers of CTE. However, important work in the area of CTE biomarkers is currently underway. Several research groups[18, 21•, 35•, 36] have suggested that negative amyloid PET imaging in the presence of positive tau PET imaging could provide a reliable way to differentiate between cases of CTE and Alzheimer's disease (AD). Small and colleagues published preliminary findings in a study of five former professional football players using the PET ligand ^{18}F-FDDNP, which binds to both tau and amyloid [35•, 37]. Although they suggested that positive findings (higher signals) using this technology could be indicative of underlying CTE pathology, the nonspecific binding of ^{18}F-FDDNP means that the signal cannot be solely attributed to the presence of tau. Thus, neuropathologic confirmation is needed to determine the underlying pathology. Alternatively, a tau-specific PET ligand, such as those in preliminary studies by Chien et al. [38••], may be used to measure tau in vivo as a potential biomarker for CTE. Preliminary work using diffusion tensor imaging has shown evidence of persistent changes in white matter integrity after periods of head impact exposure [39•, 40•], which may prove useful in distinguishing CTE. Magnetic resonance spectroscopy (MRS), a method of measuring brain metabolites, has shown promise in preliminary studies by Lin and colleagues [41•]. Cerebrospinal fluid (CSF) markers have been useful in the AD diagnostic process [34] and CSF p-tau levels have been shown to correlate with levels of p-tau NFT deposition in the brain [42]. Thus, CSF protein measures may useful biomarkers for CTE, and in the differentiation of CTE from other neurodegenerative diseases.

Risk factors

As stated above, to-date, all individuals with neuropathologically confirmed CTE have a history of repetitive head impacts. Although this type of exposure seems to be *necessary* for the occurrence of CTE, it does not appear to be *sufficient*. That is, not all individuals with a history of repetitive head impact exposure get CTE. As previously noted, detailed relation between head impact exposure (eg, frequency, magnitude, age of first exposure) and later-life neurologic outcomes is not well understood. To date, other risk factors for CTE, beyond head impact exposure, are unknown.

Genetics

Genetic risk factors may play a role in development of CTE. The apolipoprotein (ApoE) ε4 allele is the most powerful predictor of sporadic AD [43]. There have been several reports linking the ApoE ε4 allele and head injury with a variety of negative outcomes, including prolonged recovery and poor cognitive performance [44–47]; however, these studies lacked neuropathologic disease confirmation of disease. Findings in neuropathologically confirmed studies are mixed. In the series studied by Stern et al. [16••] and McKee et al. [7], there was an overrepresentation of ε4 carriers in a cohort of neuropathologically confirmed CTE relative to population norms. However, in a study with a larger sample size (N=103), the effect failed to reach significance [9••]. While early clinical findings established a link between clinical outcomes and APOE ε4

expression, the literature has not definitively established a link between APOE genotype and CTE pathology. Future research should examine the association between APOE genotype and CTE, as well as other possible genetic risk factors for CTE such as the MAPT gene or the TARDBP gene.

Lifestyle

One important challenge to accurately describing the clinical presentation and course of CTE are the lifestyle comorbidities associated with contact sport athletes and military veterans, in whom the disease has been most studied. Comorbidities such as alcohol abuse or dependence, recreational drug use, and performance enhancing drug use can all lead to personality changes and neuropsychiatric difficulties [48–51]. A non-negligible portion of individuals with neuropathologically confirmed CTE have had reported substance abuse [16••]. However, there are neuropathologically confirmed cases of CTE without a history of any of these afflictions, indicating that they are not causative factors. Therefore, understanding whether and to what extent lifestyle issues, such as those noted, influence the clinical manifestations of CTE is necessary.

Conclusions

Both in CTE and other neurodegenerative diseases, neuropathologic abnormalities are not always directly correlated with specific clinical signs and symptoms. There are likely other factors that influence disease occurrence, progression, and clinical presentation. To date, our understanding of the clinical presentation of CTE is heavily reliant on retrospective interviews with family members of individuals with neuropathologically confirmed CTE. Currently, our neuropathologic understanding of CTE is based on a biased sample of individuals who are who are predominantly among those most exposed to repetitive head impacts (eg, professional football players, professional boxers). What we understand less well is how repetitive head impacts from other less severe and less predictable exposures, such as the occasional concussion or fall, may or may not relate to the development of CTE. However, despite these limitations, there is sufficient scientific evidence to reasonably conclude that CTE is a distinct pathology that is caused, at least in part, by repetitive head impacts.

Our understanding of CTE has progressed considerably in the last several years. However, important gaps still exist in our understanding such as the incidence and prevalence of CTE, nonhead trauma risk factors for the disease, and in vivo diagnostic techniques. There are a variety of factors beyond a history of repetitive head impacts (eg, personality, lifestyle) that differentiate collegiate or professional contact sport athletes from the general public. Understanding to what extent these other factors influence clinical signs and symptoms is critical. Furthermore, there are other non-CTE results of repetitive head impacts. For example, in a 2012 study by Lehman et al. retired NFL athletes were found to have a neurodegenerative mortality rate three-times that of the U.S. population generally, and when AD and amyotrophic lateral sclerosis were examined specifically NFL mortality rates were four times that of the general population [52••]. Differentiating the clinical manifestations of CTE and non-CTE results of head impacts is needed. In order to facilitate clinical understanding of CTE, the most

pressing issue we are faced with is developing an in vivo diagnostic tool. With an in vivo diagnosis, we could begin to directly assess clinical symptomatology and progression, research incidence and prevalence in a living population, and begin therapeutic studies. Without an in vivo diagnosis, the questions we can accurately address are limited by the methodologies we are able to employ.

As CTE research has a particular ability to be misunderstood by the lay public and sensationalized in the media, caution needs to be exercised when discussing results of scientific studies and generalizing the results to the population as a whole. Many individuals have some history of head impacts incurred through sports participation or other activities [53]. However, the pathophysiological mechanism linking this initial trauma, whether concussive or subconcussive, to later-life CTE pathology has yet to be elucidated. Furthermore, without a more complete understanding of the incidence, prevalence, and possible risk factors that lead to the development of CTE, it is impossible for the general population to accurately assess their risk of CTE. Unfortunately the popular media, which has reported on CTE because of its association with professional athletics, often does not present findings with the same accuracy, caution, or contextualization as the original peer-reviewed scientific publications. In order to avoid causing undue panic in individuals who have a history of concussions or other traumatic brain injuries, the scientific community and the media need to clearly address the considerable gaps that exist in our understanding of CTE [54].

Compliance with Ethics Guidelines

Conflict of Interest

Christine M. Baugh and Clifford A. Robbins declare that their institution has received R01 grant support from the NIH. Robert A. Stern declares that his institution has received R01 grant support from the NIH. Dr. Stern also declares the receipt of consulting fees from Athena Diagnostics, as well as gifts to his institution from the National Football League, the Andlinger Foundation, and the NFL Players Association. Dr. Stern also receives royalties from Psychological Assessment Resources, Inc., for psychological tests developed, and he has received consulting fees from law firms in cases involving sports-related brain trauma. Ann C. McKee declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Exhibit 6

DEPARTMENT OF DEFENSE

BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

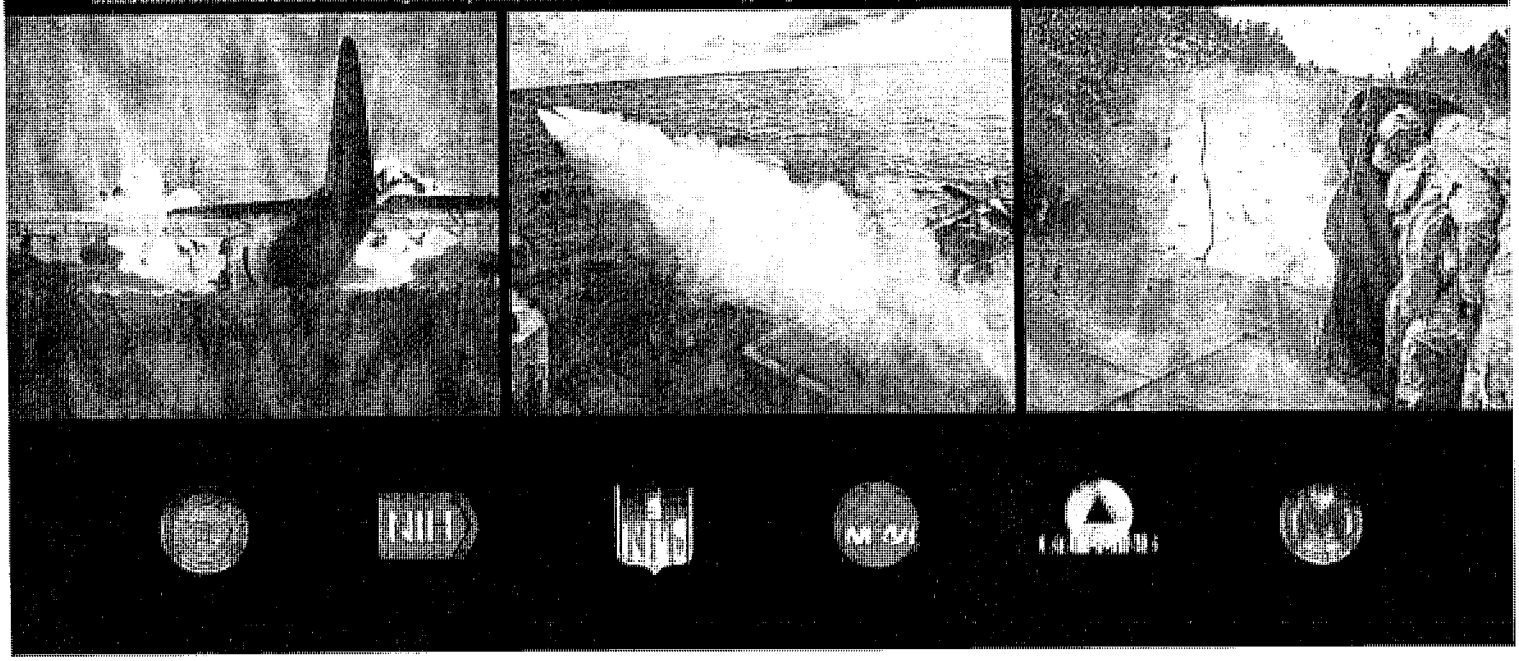
Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

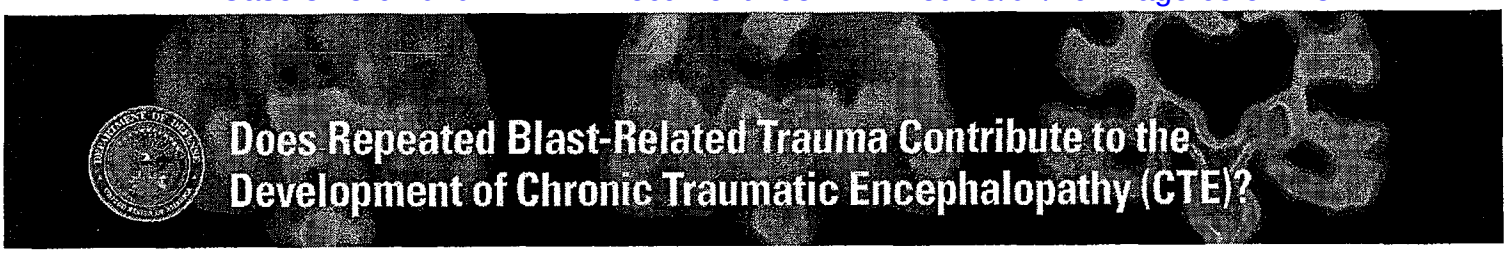
3–5 NOVEMBER 2015

LITERATURE REVIEW

The Pathological Basis of Chronic Traumatic Encephalopathy Following Blast Injury

Above image reproduced with permission from Dr. Vladimir Kepe and Dr. Jorge Barrio of the University of California, Los Angeles. ©2015 Proceedings of the National Academy of Sciences of the United States of America. Below left: Tech. Sgt. Jeffrey Allen, U.S. Air Force. Below center: Cryptologic Technician 1st Class Carl T. Jacobson, U.S. Navy. Below right: Pfc. Erik Warren, U.S. Army.





Executive Summary

To inform the 2015 International State-of-the-Science Meeting, the United States Department of Defense Blast Injury Research Program Coordinating Office requested a review of recent research literature on chronic traumatic encephalopathy (CTE). This literature review addresses specific research questions about (1) the pathophysiological basis of CTE and (2) associations between the mechanism(s) of head injury (e.g., single or multiple exposures, impact or nonimpact injury) and the development of CTE. CTE is described as a neurodegenerative disorder affecting individuals exposed to head injury that can result in a range of cognitive, behavioral, and/or motor deficits. Broad scientific consensus about CTE has not been established; however, multiple academic and government organizations are investigating links between exposure to brain injuries, CTE-associated pathology, and reported clinical symptoms.

The current state of the science has generated an initial consensus on the neuropathology of CTE (NINDS, 2015). However, the evidence does not allow for a conclusive determination of whether exposure to head injury is sufficient and causative in the development of CTE pathology. All existing clinical neuropathological evidence associated with CTE has been gathered from postmortem autopsy of subjects with histories of exposure to head injury. Unique pathological characteristics of CTE have not been comprehensively determined, in part because observations of macroscopic (i.e., gross anatomical) and microscopic (i.e., molecular) abnormalities vary to some degree across different studies and research groups. Based on existing observations, research groups have proposed classification frameworks describing CTE as a progressive disease or as a collection of related neuropathologies.

Existing research does not substantively inform whether the development of CTE is potentially associated with head injury frequency (e.g., single versus multiple exposures) or head injury type (e.g., impact, nonimpact, blast). Head injury exposure data is not consistent across case studies, which prevents systematic analysis. Many CTE studies characterize head injury exposure as exposure to sport or occupation and do not include data describing injury frequency, severity, or the time elapsed between injuries.

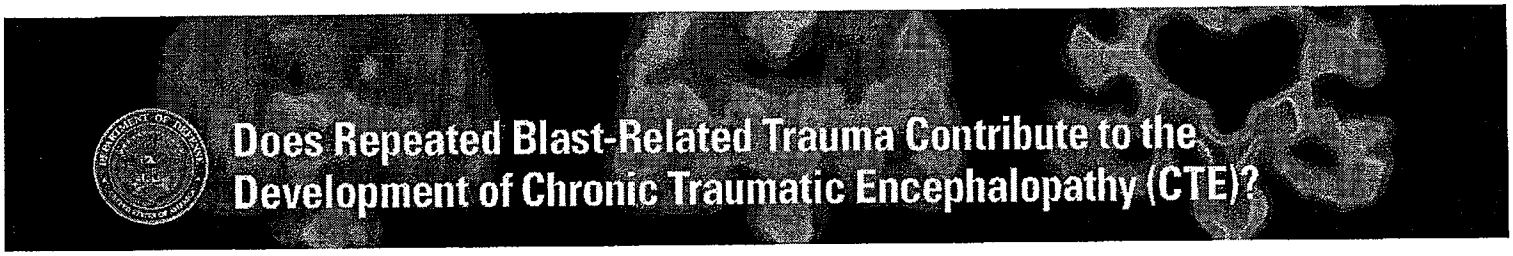
The incidence of CTE-associated pathology and/or symptoms in at-risk populations cannot be determined from existing literature and highlights a need for population-based studies. While the primary risk factor for CTE is thought to be exposure to head injury, additional research is needed to investigate other potential risk factors, such as genetic predisposition. The broad range of clinical symptoms associated with CTE overlap with those of multiple neurodegenerative disorders. Animal models may also offer insights to neuropathological and neurobehavioral abnormalities thought to be associated with CTE. While animal models do not accurately exhibit the neuropathology of CTE, animal

models of traumatic brain injury (TBI) may reflect some associated head injury exposure conditions (e.g., blunt force or blast-induced) and tau pathology.

Successful development of biomarkers to identify CTE pathology in living persons would benefit the research and development of potential diagnosis, prevention, and treatment strategies. Investigators are pursuing neuroimaging modalities and biospecimen analytes as potential predictive biomarkers of CTE by targeting pathophysiological phenomena associated with CTE and the biological processes affected by head injury exposure.

Because no established treatment for CTE exists, current mitigation strategies focus on preventing head injury and/or concussion. Although consensus on the understanding of CTE is still being established, researchers are investigating potential treatment approaches that target the pathophysiological mechanisms associated with CTE. Because of the neuropathological similarities with Alzheimer's disease and TBI, potential pharmacological and behavioral interventions for these conditions are also being investigated for CTE.

The current state of the science does not allow for a conclusive determination of whether exposure to head injury is associated with the development of CTE pathology or clinical symptoms. Existing clinical data are limited, observational in nature, and subject to several methodological concerns, leading some researchers to question whether CTE is a unique neurodegenerative disease. CTE has drawn significant public and media attention given the large at-risk population (e.g., military service members, contact sport athletes). Experts have noted concern over the potential clinical and legal consequences of widespread misunderstanding of CTE. In light of these factors, the need for additional research is clear, particularly population-based studies, the use of standardized pathology protocols, and the development of clinical diagnostic criteria.



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Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Purpose

The mission of the United States Department of Defense (DoD) Blast Injury Research Program Coordinating Office (Blast PCO) is to assist in fulfilling the DoD Executive Agent responsibilities and functions related to medical research to prevent, mitigate, and treat blast injuries in accordance with DoD Directive 6025.21E. The Blast PCO coordinates and manages relevant DoD medical research efforts and programs, including identifying blast injury knowledge gaps, shaping medical research programs to fill identified gaps, facilitating collaboration among diverse communities within and outside the DoD, and widely disseminating blast injury research information.

To achieve these objectives, the Blast PCO convenes an annual International State-of-the-Science (SoS) Meeting to assist in identifying knowledge gaps pertaining to key blast injury issues. These annual SoS meetings are highly focused to help determine what is known and unknown about particular blast injury topics. The topic of the 2015 International SoS Meeting is chronic traumatic encephalopathy (CTE) and how this condition may relate to head injuries arising from blast exposure. The Blast PCO requested a review of recent research literature to inform meeting participants on the current scientific knowledge of the underlying pathophysiological changes in the brain that may be associated with CTE following head injury. It seeks to address the following research questions:

- What is the current evidence describing the pathophysiological basis of CTE?
  - What biological processes following head injury are associated with the development of CTE?
  - What advances in neuroimaging or biomarkers of CTE may lead to the development of diagnostic tools or therapeutic strategies?
- What associations are known between the mechanism(s) of head injury (e.g., single or multiple exposures, impact or nonimpact injury) and the development of CTE?
  - Does the frequency of exposure to head injury correlate with the development of CTE?
  - Are there any known distinctions between how impact injury, nonimpact injury, and blast-induced injury are associated with the development of CTE?

Methodology

This literature review searched PubMed, the Defense Technical Information Center (DTIC), Google, and Google Scholar using search terms (see Appendix 1) to identify English language clinical and basic science articles published in the last 10 years (between 2005 and 2015, inclusive). Among DTIC documents, only those assigned for

public distribution (Distribution A) were included. Identified articles published prior to 2005 were included in the literature review only if they were determined to be potentially critical to addressing the research questions or understanding the topic. Search terms were generated in collaboration with the Blast PCO and the 2015 SoS Meeting Planning Committee. In addition to the search terms listed in Appendix 1, ad hoc searches on key principal investigators or on specific topics were performed. Publications identified in the bibliographies of reviewed articles were also included in this literature review. Table 1 lists the search inclusion and exclusion criteria for the review.

Table 1. Literature Search Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. English language articles only 2. Articles published between 2005 and 2015 (inclusive)* 3. Clinical and animal model studies 4. DTIC documents assigned Distribution A: Approved for public release: distribution unlimited	1. Articles not directly addressing research questions 2. DTIC documents not approved for public release

*Older publications were included when potentially critical to addressing the research questions or understanding the topic.

Articles meeting the inclusion criteria were further reviewed to determine whether they directly informed the research questions and merited inclusion in the literature review. Articles were reviewed for the following elements:

- Study design
- Study population (e.g., military, athletes)
- Outcome measures (e.g., histology, cognitive/behavioral symptoms)
- Results and statistics (when available)
- Conclusions, study limitations, and recommendations relevant to research questions.

Following this strategy, the literature search yielded 359 articles that met the parameters of the search terms and inclusion/exclusion criteria (see Table 1). This literature review report includes a total of 164 articles.

Neuropathology

CTE is described as a progressive neurodegenerative disorder affecting individuals exposed to head injury and resulting in cognitive, behavioral and/or motor deficits. Broad consensus on the existence of, and diagnostic criteria for, CTE has not been firmly established in the clinical and scientific community (Hazrati et al., 2013; Karantzoulis & Randolph, 2013; McCrory, Meeuwisse, Kutcher, Jordan, & Gardner, 2013; Randolph, 2014; Wortzel, Brenner, & Arciniegas, 2013); however, multiple academic research groups and government organizations are gathering and analyzing evidence that may provide significant insights about potential links between exposure to

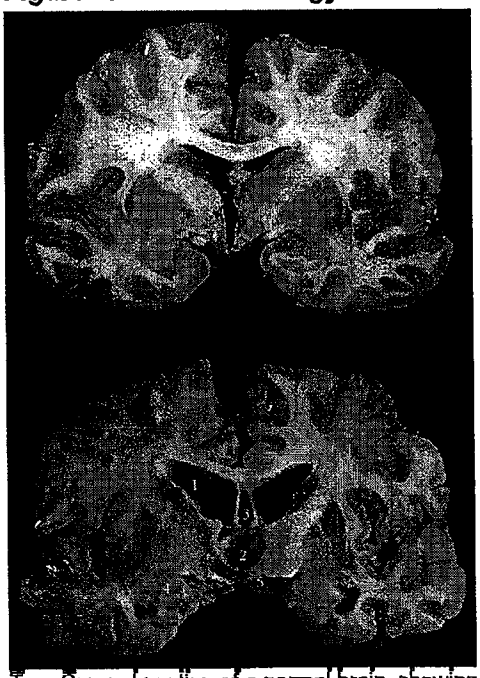
head injury and the development of CTE (Hinds, 2014; McKee et al., 2013; McKee, Stein, Kiernan, & Alvarez, 2015; Omalu, Bailes, et al., 2011; Riley, Robbins, Cantu, & Stern, 2015; Saigal & Berger, 2014). A recent National Institutes of Health (NIH) consensus workshop began to establish the pathognomonic features of CTE required for diagnosis (NINDS, 2015).

To date, all existing clinical neuropathological evidence describing CTE has been gathered from postmortem autopsy of subjects with a history of exposure to head injury (Gardner, Iverson, & McCrory, 2014). Pathological abnormalities associated with CTE include macroscopic (i.e., gross anatomical) and microscopic (i.e., cellular and molecular) changes. While CTE shares a number of characteristics with other neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Frontotemporal Lobar Degeneration (FTLD), it is thought to have unique pathological features (McKee et al., 2013, 2015; NINDS, 2015).

Macroscopic Neuropathology

Recent consensus work determined that "Macroscopic abnormalities in the septum pellucidum (cavum, fenestration), disproportionate dilatation of the IIIrd ventricle or signs of previous brain injury" were supportive criteria for diagnosis of CTE (NINDS, 2015). Prior to this consensus work, multiple investigators described gross anatomical abnormalities associated in the postmortem autopsy of brains with neuropathologically confirmed CTE (McKee et al., 2015; Stern et al., 2011). These abnormalities (see Figure 1), which may result from underlying neurodegenerative processes, include an overall reduction in brain weight (Corsellis, Bruton, & Freeman-Browne, 1973), the enlargement of ventricles (Williams & Tannenberg, 1996), atrophy of functional brain structures (Roberts, Whitwell, Acland, & Bruton, 1990), cavum septum pellucidum (Hof et al., 1992), and depigmentation of the locus coeruleus and substantia nigra (Corsellis et al., 1973). Other observations describe relatively more modest gross anatomical findings in neuropathologically confirmed CTE (Wortzel, Brenner, et al., 2013), including a lack of cerebral atrophy and milder depigmentation of

Figure 1. Gross Pathology of CTE



Top: Coronal section of a normal brain, showing the expected size and relationship of the cerebral cortex and ventricles. Bottom: Coronal section from the brain of a retired professional football player showing characteristic gross pathology of CTE, including severe dilatation of ventricles II (1) and III (2) and cavum septum pellucidum (3); adapted from Stern et al. 2011; permissions pending

the substantia nigra and locus coeruleus (Omalu, Bailes, et al., 2011; Omalu, Bailes, Hammers, & Fitzsimmons, 2010).

Microscopic Neuropathology

Postmortem examination of brains revealing microscopic pathological abnormalities associated with CTE has included histological observations thought to reflect intracellular and intercellular processes of neurodegeneration.

Tau Protein Aggregation

Abnormal aggregation of hyperphosphorylated tau protein, including neurofibrillary tangles (NFTs) and/or astrocytic tangles (ATs), is considered to be a neuropathological hallmark of CTE (Kiernan, Montenigro, Solomon, & McKee, 2015). A recent NIH consensus workshop determined that perivascular accumulation of tau proteins in neurons, astrocytes, and cell processes in an irregular pattern at the depths of cortical sulci was pathognomonic (i.e., uniquely indicative) of CTE (NINDS, 2015). Autopsy examinations of neuropathologically confirmed CTE across multiple studies describe abnormal tau aggregates in several brain areas, including superficial layers of the cerebral cortex, subcortical nuclei, and brainstem (McKee et al., 2013, 2015; Omalu, Bailes, et al., 2011; Stein, Alvarez, & McKee, 2014). However, there remain some differences in the literature about the volume and location of these tau protein aggregates (Iverson, Gardner, McCrory, Zafonte, & Castellani, 2015; Wortzel, Brenner, et al., 2013).

Tauopathies are a class of neurodegenerative diseases characterized by the aggregation of hyperphosphorylated tau protein (Takashima, 2013) that are thought to be associated with head injury (Abisambra & Scheff, 2014). The normal function of tau protein is to stabilize microtubules; however, aberrant hyperphosphorylation of tau causes the formation of protein aggregates and NFTs, which are thought to contribute to the development of CTE (Lucke-Wold et al., 2014). Other tauopathies include AD, progressive supranuclear palsy (Hauw et al., 1994; Litvan et al., 1996), Pick's disease (Rizzini et al., 2000), and Huntington's disease (Fernández-Nogales et al., 2014). Recent efforts to establish a neuropathological distinction between AD and CTE suggests that the latter is distinguished by the widespread presence of NFTs in perivascular areas, particularly at the depths of sulci, and in superficial cortical laminae and astrocytes (McKee et al., 2013; NINDS, 2015). Table 2 describes in greater detail the observed pathological differences between AD and CTE.

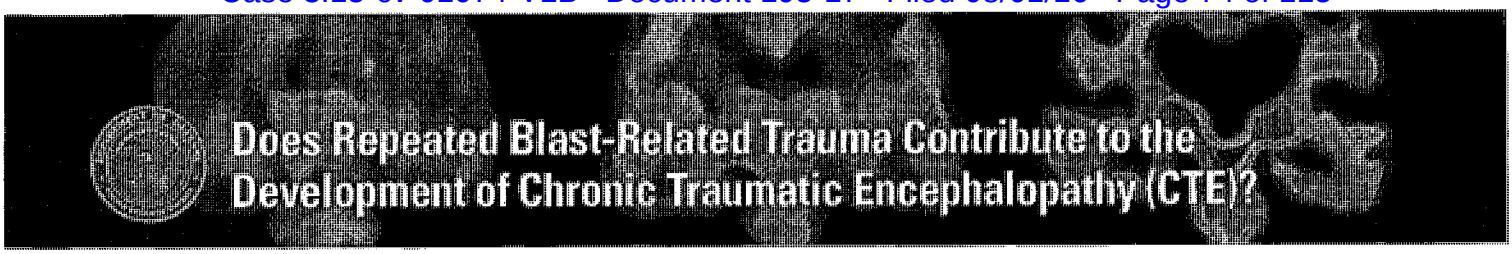
Table 2. Distinctions in Tau Pathology between AD and CTE

Pathological Features	AD	CTE
Tau Protein		
Six isoforms	All present	All present
3 or 4 repeat tau	Both present	Both present
Cell Origin		
Neuronal	NFTs and pretangles	NFTs and pretangles
Astrocytic	Not present	Prominent
Neuronal Domain		
Cell body	Prominent	Prominent
Dendrite	Prominent	Prominent
Axon	Sparse	Prominent
Cell Pattern		
Perivascular	Not present	Prominent NFTs and astrocytic tangles
Foci at depths of cerebral sulci	Not present	Prominent NFTs and astrocytic tangles
Irregular, patchy cortical distribution	Not present	Prominent
Cortical laminae	NFTs predominantly in laminae III and V	NFTs predominantly laminae II and III
Subpial astrocytic tangles	Not present	Prominent
Periventricular astrocytic tangles	Not present	Present
Distribution		
Mild pathology	Braak stages I and III: NFTs in entorhinal cortex, amygdala, and hippocampus	CTE stages I and II: NFTs in focal epicenters in cerebral cortex, usually frontal lobe
Advanced pathology	Braak stages IV and VI: • High densities of NFTs in widespread cortical areas and medial temporal lobe; uniform distribution • Low densities of NFTs in basal ganglia and brainstem • NFTs in mammillary bodies not present • White matter tracts relatively uninvolved	CTE stages III and IV: • High densities of NFTs in widespread cortical areas and medial temporal lobe; patchy irregular distribution • High densities of NFTs in basal ganglia, especially nucleus accumbens • Prominent p-tau pathology in white matter tracts

Adapted from McKee et al., 2013; reprint permissions pending

TAR DNA-Binding Protein 43 Aggregation

The presence of TAR DNA-binding protein (TDP-43) aggregates is another pathological abnormality observed in postmortem examination of neuropathologically confirmed CTE cases (Kiernan et al., 2015). McKee et al. (2010) were the first to report the presence of TDP-43 aggregates as a pathological feature of CTE. Distribution of these aggregates was reported in the brainstem; basal ganglia; diencephalon; medial temporal lobe; frontal, temporal, and insular cortices; and subcortical white matter.



TDP-43 functions as a transcriptional regulator in the central nervous system (Sephton, Cenik, Cenik, Herz, & Yu, 2012). Aberrant TDP-43 aggregates have also been reported in studies of other neurodegenerative diseases (Armstrong et al., 2009; Bosque, Boyer, & Priya, 2013), including Motor Neuron Disease (MND) (McKee et al., 2010), Amyotrophic Lateral Sclerosis, and FTLD (Baloh, 2011).

Beta-Amyloid Plaque Formation

The presence of beta-amyloid (Aβ) plaques has been reported at various levels and distributions in neuropathologically confirmed CTE cases (McKee et al., 2009, 2015; Omalu, Bailes, et al., 2011; Stein et al., 2015). Whether Aβ pathology has a unique association with the development of CTE has been called into question given that these peptide plaques are also associated with AD (Stein et al., 2014). However, a recent study suggests that Aβ deposition is associated with a pathological and clinical progression of CTE and in an accelerated trajectory compared to normal aging (Stein et al., 2015).

Axonal Injury

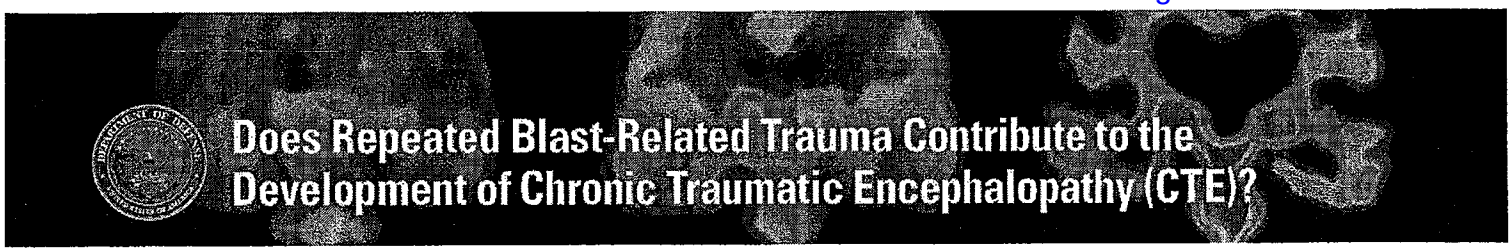
Evidence of axonal injury has been described in neuropathologically confirmed CTE cases. Multifocal axonal varicosities have been observed in the frontal and temporal cortex and in subcortical white matter tracts in the brains of CTE cases (McKee et al., 2009, 2013; Omalu, Bailes, et al., 2011). The extent of axonal injury is thought to be associated with the progression of CTE (McKee et al., 2013). Intercellular events following axonal injury, including microglial and astrocyte activation, are thought to be potential mechanistic links between TBI and CTE (Ling, Hardy, & Zetterberg, 2015; Lucke-Wold et al., 2014).

Neuroinflammation

Evidence of neuroinflammation has been reported in neuropathologically confirmed CTE cases (McKee, Daneshvar, Alvarez, & Stein, 2014; McKee et al., 2015). It is unclear whether inflammation is driving protein deposition of tau or if it is a compensatory repair mechanism of the neurodegenerative processes underlying CTE (Coughlin et al., 2015). TBI is known to induce neuroinflammation, which may persist for years in humans (Smith, Johnson, & Stewart, 2013). Neuroinflammation, which is associated with microglial and astroglial activation, may play a role in long-term neurodegeneration (Faden, Wu, Stoica, & Loane, 2015).

Classifications of CTE

Two research groups have proposed classification frameworks of CTE based on neuropathological observations. Omalu et al. (2011) describe four CTE phenotypes thought of as parallel pathologies. McKee et al. (2013) classify CTE into four stages that describe progressive neuropathological changes. These frameworks reflect an emerging understanding of the neuropathology of CTE, not rigid or absolute classifications (Wortzel, Brenner, et al., 2013). Indeed, criteria for both of these



classification frameworks is informed by the presence of Aβ plaques and related neuritic plaques despite the recent understanding that these features may not be associated with CTE (Stein et al., 2014).

In the phenotypic classification framework (see Table 3), the first phenotype of CTE is described as sparse to frequent NFTs and neuritic threads (NTs) in the cerebral cortex and brainstem (Omalu, Bailes, et al., 2011). The second phenotype also includes NFTs and NTs in the basal ganglia and cerebellum in addition to diffuse amyloid plaques. The third phenotype is defined by a combination of moderate to frequent NFTs and NTs predominately in the brainstem with none to sparse NFTs and NTs in the cerebral cortex and basal ganglia and none in the cerebellum. The fourth phenotype is defined by a combination of none to sparse NFTs and NTs in the cerebral cortex, brainstem, and basal ganglia and a lack of NFTs and NTs in the cerebellum. There are no diffuse amyloid plaques in the cerebral cortex. In all described phenotypes, there is a possibility of observing varying degrees of NFTs and NTs in the hippocampus with or without diffuse amyloid plaques.

Table 3. Phenotypic Classification of CTE

Phenotype	Characteristics
Phenotype I	• Sparse to frequent NFT and NT in the cerebral cortex and brainstem but without involvement of basal ganglia and cerebellum • No diffuse amyloid plaques in the cerebral cortex
Phenotype II	• Sparse to frequent NFTs and NTs in the cerebral cortex and brainstem and may include pathology in the basal ganglia and cerebellum • Presence of diffuse amyloid plaques in the cerebral cortex
Phenotype III	• Brainstem predominant: moderate to frequent NFTs and NTs in the brainstem nuclei, absent or sparse NFTs and NTs in the cerebral cortex, basal ganglia, and cerebellum • No diffuse amyloid plaques in the cerebral cortex
Phenotype IV	• Incipient: absent or sparse NFTs and NTs in the cerebral cortex, brainstem, and basal ganglia • No cerebellar involvement • No diffuse amyloid plaques in the cerebral cortex

Adapted from Omalu, Bailes, et al. 2011; reprint permissions pending

According to the classification framework of progressive pathological stages that McKee et al. (2013) propose (see Table 4), CTE begins focally, usually perivascularly at the depth of the sulci in the frontal cerebral cortex, as well as in the superficial layers of the cerebral cortex. The pathology develops over time to involve widespread regions of the medial cortex, medial temporal lobe, diencephalon, basal ganglia, brainstem, and spinal cord. Stages I and II are considered to be mild pathologies and are characterized by NFTs in focal epicenters of the frontal cortices. Stages III and IV represent severe forms of CTE, with more widespread tau involvement.

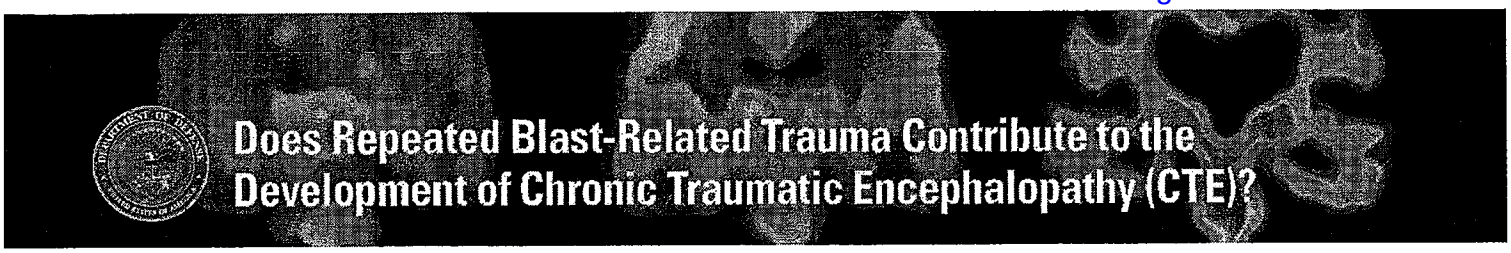


Table 4. Progressive Classification of CTE

Stage	Macroscopic Pathology	Microscopic Pathology
Stage I	• Normal brain weight • Brain pathology is unremarkable	• Focal epicenters of perivascular p-tau and neurofibrillary and astrocytic tangles involving the sulcal depths and typically affecting the superior and dorsolateral frontal cortices • Approximately half of Stage I p-tau pathology also shows rare TDP-43 neurites • No presence of Aβ plaques, except in subjects over 50 years of age
Stage II	• Normal brain weight • Subtle brain pathology exhibited • Mild enlargement of the frontal horns of the lateral and third ventricles, cavum septum pellucidum, and pallor of the locus coeruleus and substantia nigra	• Multiple epicenters of perivascular foci of p-tau NFT and neurites at the depths of the sulci with localized spread from epicenters to the superficial layers of the adjacent cortex • Mild TDP-43 pathology as abnormal neurites and neuronal inclusions • No neurofibrillary p-tau involvement in the medial temporal lobe • Aβ plaques found in 19% of subjects if over 50 years of age
Stage III	• Mild reduction in brain weight • Mild cerebral atrophy with dilatation of the lateral and third ventricles • Septal abnormalities • Moderate depigmentation of the locus coeruleus and mild depigmentation of the substantia nigra • Atrophy of the mammillary bodies and thalamus	• Widespread p-tau pathology in the frontal, insular, temporal, and parietal cortices • Neurofibrillary pathology in the amygdala, hippocampus, and entorhinal cortex • Aβ plaques found in 13% of cases
Stage IV	• Marked reduction in brain weight • Atrophy of the cerebral cortex • Marked atrophy of the medial temporal lobe, thalamus, hypothalamus, and mammillary bodies • Diffuse atrophy of the white matter and thinning of the corpus callosum, particularly the isthmus • Severe thinning of the hypothalamic floor	• Severe p-tau pathology affecting most regions of the cerebral cortex and the medial temporal lobe, sparing the calcarine cortex • Severe p-tau pathology in the diencephalon, basal ganglia, brainstem, and spinal cord • Astrocytosis of the white matter • Neuronal loss in the cerebral cortex • Marked axonal loss of subcortical white matter tracts • Widespread TDP-43 deposits • Marked loss of myelinated nerve fibers

Adapted from McKee et al., 2013; reprint permissions pending

Neuropathological Diagnosis

Currently, there are no premortem diagnostic criteria for CTE. Recent proposals for postmortem CTE diagnostic criteria (McKee et al., 2013) have been followed by a recent NIH consensus workshop (NINDS, 2015), which established diagnostic criteria for CTE, supportive criteria for a diagnosis of CTE, and exclusions to a primary diagnosis of CTE (see Table 5).

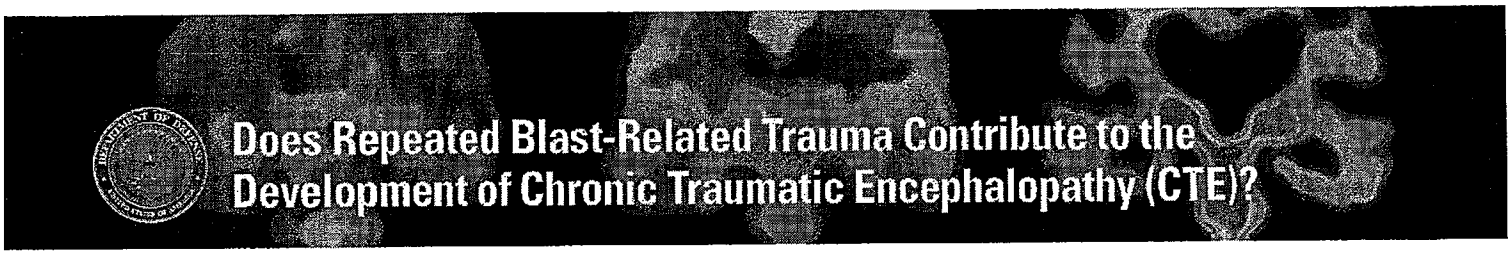


Table 5. Neuropathological Criteria for Diagnosis of CTE

Required criteria for diagnosis of CTE:

- Abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci

Supportive criteria for a diagnosis of CTE:

- Macroscopic abnormalities in the septum pellucidum (cavum fenestration), discoloration of the third ventricle, or signs of previous brain injury
- Abnormal tau immunoreactive neuronal lesions affecting the neocortex predominantly in superficial layers 2 and 3 as opposed to layers 3 and 5 as in AD
- Abnormal tau (or silver positive) neuropil threads in the hippocampus, especially in CA2 and CA4 regions, which differ from the preferential involvement of CA1 and subiculum in AD
- Abnormal tau immunoreactive neuronal and astrocytic lesions in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, and substantia nigra
- Tau immunoreactive thorny astrocytes in subpial perivascular locations

Exclusions to the diagnosis of primary CTE:

- CAA, predominant neurofibrillary degeneration in the hippocampus in association with amyloid plaques as seen in AD
- Cerebellar ataxia, cell loss, prominent coiled bodies in oligodendroglia, and tufted astrocytes as seen in progressive supranuclear palsy
- Severe involvement of striatum and pallidum with astrocytic plaques in cortical and subcortical structures as seen in cortical basal degeneration

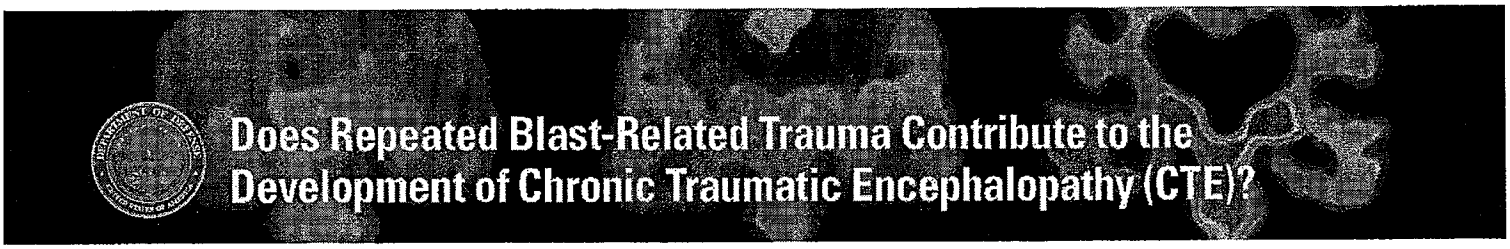
Adapted from NINDS 2015; reprint permissions pending

Exposure to Head Injury

Existing clinical literature describing neuropathologically confirmed CTE does not substantively inform whether the condition is potentially associated with head injury frequency (e.g., single versus multiple exposures) or head injury type (e.g., impact, nonimpact, blast). Data about the frequency or type of head injury exposure is not collected systematically or consistently across, or sometimes even within, CTE case series or case studies. Most CTE studies characterize head injury exposure simply as exposure to sport or occupation (e.g., football, boxing) without including data describing head injury frequency, severity, or the time elapsed between multiple injuries. Head injury exposure in these cases is assumed, but not necessarily quantified. Among the studies that do include data about the incidence of head injuries in CTE cases, including frequency, type, and/or severity, this information is gathered retrospectively from family interviews and/or medical records, which are subjective and carry other potential biases. Additionally, a high rate of duplication (i.e., re-reporting cases across multiple publications) exists in the clinical CTE literature (Maroon et al., 2015).

Head Injury Exposure Data in CTE Cases

A recent review analyzing 153 unique cases of neuropathologically confirmed CTE characterizes exposure to head injury by categorizing cases according to sports participation, Veteran status, or miscellaneous exposure types (Maroon et al., 2015). Additional information about head injury incidence (e.g., motor vehicle accidents, improvised explosive devices [IEDs]) was included when available, but not consistently across cases. The authors also note that while all neuropathologically confirmed CTE



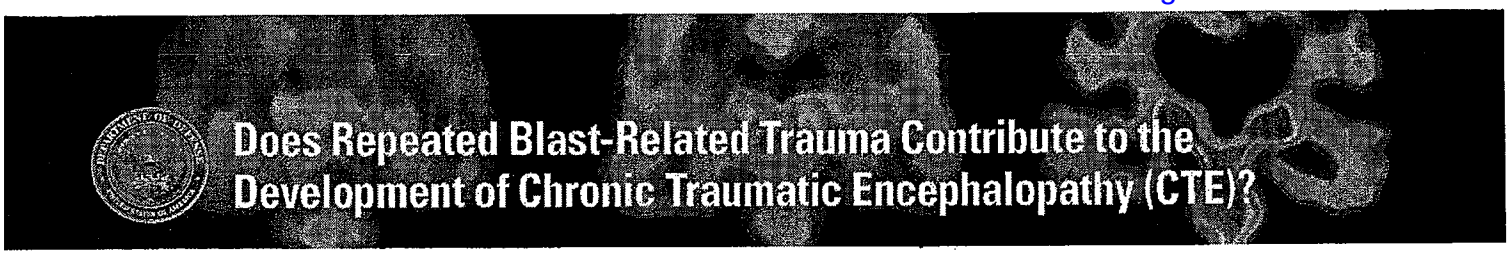
cases had a "history of head trauma," documentation of severity, frequency, and concussion was "highly variable" in the literature.

McKee & Robinson (2014) provide postmortem case reports for four military Veterans with pathological signs of CTE, three of which were previously reported (Goldstein et al., 2012). Exposure to head injury across the four cases is described in McKee & Robinson (2014) as exposure to blast (from single to "several"), as well as concussion symptoms and/or history, if experienced. The authors also review a single case study from Omalu, Hammers, et al. (2011) of a Veteran exposed to "multiple mortar blasts and IEDs" whose autopsy showed neuropathological changes consistent with CTE. Additionally, McKee & Robinson (2014) review 23 postmortem cases of Veterans neuropathologically diagnosed with CTE from the Boston VA Brain Bank. In this cohort, exposure to head injury is characterized by sports participation in 16 subjects, exposure to IED blast or military concussion in 5 subjects (3 of whom also played high school football), and other exposures, such as assault, motor vehicle accident, and posttraumatic epilepsy. Frequency and severity of head injury in these cases was not reported.

A case series of six retired football players from the Canadian Football League includes three with neuropathologically confirmed CTE at autopsy (Hazrati et al., 2013). These three cases are reported to have been exposed to multiple concussions; however, the authors note that additional frequency or severity information could not be determined. While clinical details of these cases were gathered retrospectively from family interviews, treating physicians, and medical records, the source of the concussion history was not specified by the authors.

The case series review by McKee et al. (2013) includes 35 football players with neuropathologically confirmed CTE for which head injury exposure information was available from structured retrospective interviews of family members. Statistical analyses among these cases finds that the family-reported number of concussions is not correlated with the pathological stage of CTE (concussion frequency data was not provided by authors). However, the number of years played, the number of years since retirement, and the age at death is correlated with CTE stage in these cases. The authors also did not report the collection of head injury exposure information for 17 football players included in the case series review who did not exhibit neuropathologically confirmed CTE. This case series also includes 21 military Veterans, 16 of whom were athletes (8 professional football players) and 9 of whom experienced combat. The authors note that three veterans sustained TBI and four were exposed to IEDs or explosive munitions.

Characterization of head injury exposure for 11 cases of neuropathologically confirmed CTE by Omalu et al. (2011) is limited to that of contact sports participation. While the



authors collected retrospective clinical symptom information through next-of-kin interviews, analysis to correlate symptoms with pathology was not performed.

McKee et al. (2009) present case reports of one football player and two boxers with neuropathologically confirmed CTE. Retrospectively collected head injury exposure information is documented for the football player (at least 11 concussions during college and the professional career, only one medically confirmed) and one of the boxers (a mild injury during the teenage years). The authors also review 47 cases previously documented in the literature, including boxing, football, and other sport activities. A review of these cases reveals that the characterization of exposure to head injury was limited to that of exposure to sport, with the exception of a soccer player (a single severe head injury) and a circus dwarf (knocked unconscious approximately a dozen times).

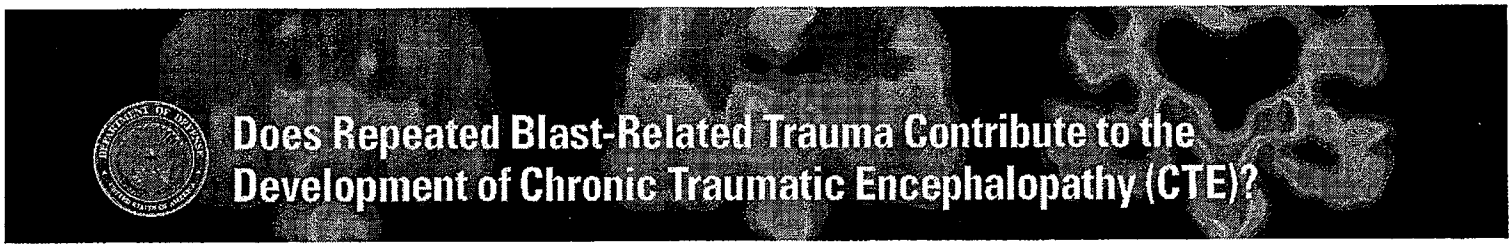
Frequency of Head Injury Exposure

Existing studies of neuropathologically confirmed cases do not provide evidence comparing single versus multiple head injury exposures in the development of CTE. Some investigators have explored associations between injury frequency and other neurological outcomes thought to be related to CTE; however, few firm conclusions can be drawn given mixed evidence and methodological concerns. A meta-analysis comparing the effect of exposure to multiple versus single mild TBI (mTBI) in athletes finds minimal, nonsignificant differences in cognitive function and symptom complaints between the two exposure frequencies, although secondary analysis finds poorer performance in delayed memory and executive measures in the multiple mTBI exposure group (Belanger, Spiegel, & Vanderploeg, 2010). Previously, investigators have reported an association between the number of sustained concussions and cognitive impairments, as well as self-reported clinical depression (Guskiewicz et al., 2005, 2007). However, methodological limitations attributed to errors inherent in self-reporting have subsequently put these findings in question (Kerr, Marshall, & Guskiewicz, 2012; Wortzel, Brenner, et al., 2013).

Type of Head Injury Exposure

Existing studies of neuropathologically confirmed cases do not provide evidence comparing head injury type in the development of CTE. Understanding how injury type may contribute to CTE is further complicated by observations that, in football players with pathologically confirmed CTE, some have a history of concussion and some do not (Stein et al., 2014), raising the possibility that subconcussive injury, or another exposure in the population, is potentially associated with the induction of CTE. Additionally, some football players with a documented history of multiple concussions do not exhibit neuropathologically confirmed CTE upon postmortem examination (Hazrati et al., 2013).

Investigation of blast-related CTE is relatively immature (Gandy et al., 2014), given that the first case of military CTE was reported fewer than five years ago (Omalu, Hammers,



et al., 2011). Goldstein et al. (2012) describe case studies of four military Veterans with neuropathologically confirmed CTE that, according to case history, were exposed to one or multiple IED blast exposures and/or one or multiple concussions; however, comparison between blast and nonblast injury in this limited cohort was not made. Observations by these authors in animal model data indicate that rotational forces, in addition to the blast wave, are necessary to induce injury and resulting sequelae, including CTE. Goldstein et al. (2012) also suggest that a single blast exposure may induce CTE, while other investigators have identified methodological problems with this conclusion (Wortzel, Brenner, et al., 2013). Additionally, a study by Ryu et al. (2014) includes neuropathology examinations from five Veterans exposed to blast injury that were absent the tau pathology associated with CTE.

Epidemiology

The incidence of CTE-associated pathology and/or symptoms in at-risk populations cannot be determined from existing literature, which has prompted investigators to call for population-based studies (Iverson et al., 2015; Lenihan & Jordan, 2015). Early observations in boxers estimating a prevalence of CTE at 17% (Roberts, 1969) are likely inapplicable to modern realities given changes to factors over the past several decades, including the nature of boxing, diagnostic criteria, the inclusion of other at-risk populations in the field (e.g., football), and an evolving understanding of CTE (Clausen, McCrory, & Anderson, 2005; Gardner et al., 2014; Lenihan & Jordan, 2015). Studies investigating the risk of neurodegenerative disorders secondary to repetitive head injury exposure yield mixed results (Jordan, 2014), as some investigators have observed greater rates of neurodegenerative symptoms in contact sport athletes (Guskiewicz et al., 2005; Lehman, Hein, Baron, & Gersic, 2012), while others find no increased rates in similar populations (Savica, Parisi, Wold, Josephs, & Ahlskog, 2012).

Despite inconclusive epidemiological evidence, the primary risk factor for CTE appears to be exposure to head impacts from concussive or subconcussive events. This determination is largely the result of observations that all neuropathologically confirmed CTE cases have a history of brain trauma (Baugh, Robbins, Stern, & McKee, 2014). Other factors related to or influencing injury exposure may play a role as well, including the length of boxing or professional football career (Lenihan & Jordan, 2015).

Studies of genetic CTE risk factors have primarily focused on the apolipoprotein E (ApoE) genotyping, particularly the ε4 allele, which is a known risk factor for AD (Michaelson, 2014), but when taken together, existing studies yield inconclusive evidence. ApoEε4 variations have been observed in case studies of neuropathologically confirmed CTE (Omalu, Bailes, et al., 2011), and some evidence suggests neuropathological impairment in contact sport athletes with the ApoEε4 variation (Jordan et al., 1997; Kuhnel, Erlanger, Tsai, Jordan, & Relkin, 2000). However, more recent studies have noted that abnormal ApoE allelic variation in CTE cases does not

appear to be greater than that of the general population (see Table 6) (Maroon et al., 2015; McKee et al., 2013).

Table 6. ApoE Allelic Distribution in Confirmed CTE Cases

ApoE Genotype	Overall Cases n (%)		Football Cases n (%)		% of Normal Population
ε3/ε3	49	(62.0%)	32	(60.4%)	58.5%
ε2/ε3	4	(5.1%)	4	(7.5%)	13.6%
ε2/ε2	0	(0.0%)	0	(0.0%)	0.3%
ε2/ε4	2	(2.5%)	1	(1.9%)	2.4%
ε3/ε4	20	(25.3%)	11	(20.8%)	22.2%
ε4/ε4	5	(6.3%)	5	(9.4%)	2.9%
Total	**80**		**53**		

Adapted from Maroon et al. 2015; reprint permissions pending

Clinical Manifestations

Numerous clinical symptoms have been associated with CTE, which are often variable and nonspecific, and that overlap with symptoms of multiple neurodegenerative disorders, including AD, PD, FTLD, MND, as well as postconcussive syndrome (Iverson et al., 2015; Lenihan & Jordan, 2015; Maroon et al., 2015). Clinical symptoms associated with CTE include chronic psychiatric illnesses (e.g., depression), headache, cognitive problems, and motor impairment (Iverson et al., 2015; Lenihan & Jordan, 2015; Maroon et al., 2015; McKee et al., 2013; Omalu, Bailes, et al., 2011). Experts have noted an extensive overlap of clinical symptoms associated with CTE and post-traumatic stress disorder in military populations (McKee & Robinson, 2014; Omalu, Hammers, et al., 2011). While suicidality is commonly reported, links between CTE and suicide have been questioned in the literature (Iverson, 2014; Maroon et al., 2015; Wortzel, Shura, & Brenner, 2013).

Investigators are working to establish clear links between clinical changes and CTE neuropathology. McKee et al. (2013) correlates clinical findings with a proposed framework of progressive neuropathological staging for CTE. Additionally, Stern et al. (2013) proposes two types of clinical presentation variants, one termed "behavior/mood" and one termed "cognitive." Stein et al., (2015) subsequently reported that the cognitive variant may be associated with Aβ deposition. While the broad range of symptoms associated with CTE has been questioned as clinically meaningless (Randolph, 2014), investigators have recently suggested diagnostic criteria for CTE (Jordan, 2013; Victoroff, 2013), including the proposal of Traumatic Encephalopathy Syndrome (Montenigro et al., 2014; Montenigro, Bernick, & Cantu, 2015).

To address existing questions about links between CTE neuropathology and clinical/behavioral changes, established diagnostic criteria for longitudinal studies are needed (Antonius et al., 2014). Additionally, numerous methodological gaps in the existing body of case reports must be addressed. Data reporting is inconsistent across case studies, and a high rate (43%) of duplication (i.e., re-reporting cases across

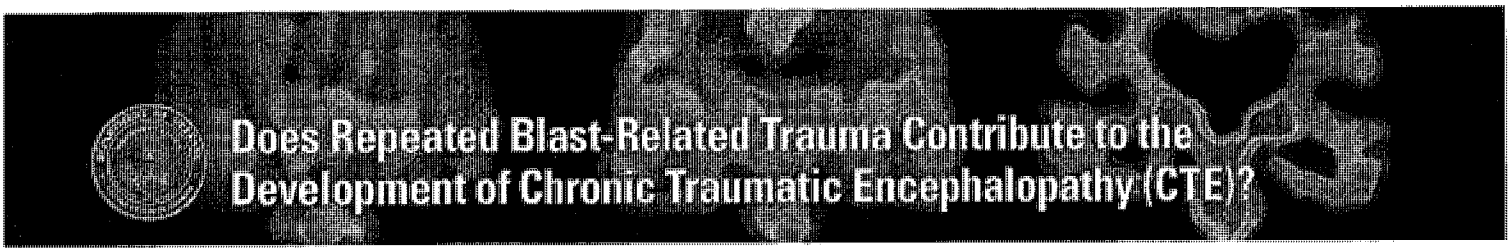
multiple publications) has been described (Maroon et al., 2015). Conclusions derived from case studies, which are often referred to researchers by families with concerns about neurobehavioral problems (Antonius et al., 2014), are limited by the significant likelihood of selection (ascertainment) biases (Daneshvar et al., 2011; Maroon et al., 2015). Additionally, premortem symptom data, which is often derived from interviews with family members, is not objective and is subject to recall biases (McCrory, Zazryn, & Cameron, 2007).

Animal Models

Animal models may offer insights into neuropathological and neurobehavioral abnormalities thought to be associated with CTE. To date, few investigators have developed animal models designed to reflect CTE specifically (Goldstein et al., 2012; Petraglia, Plog, Dayawansa, Dashnaw, et al., 2014), which highlights opportunities for further preclinical research (Goldstein, McKee, & Stanton, 2014). However, certain animal models of TBI may be useful because they reflect some injury exposure conditions associated with CTE, such as blunt force or blast-induced TBI.

Animal models of blunt force-induced TBI are commonly used to study single and repetitive closed head injury (Ojo, Mouzon, & Crawford, 2015). Injury is induced in an anesthetized animal from impact to the skull or scalp (with or without a protective plate). The impact can be generated by dropping a weight through a tube positioned above the head or by using an electromagnetically or pneumatically powered probe (Mouzon et al., 2012; Petraglia, Plog, Dayawansa, Dashnaw, et al., 2014). The specific pathology and behavioral effects observed in each model vary with the impact severity, frequency, anatomical site, age, and linear or rotational movement of the head.

Existing animal models of blast-induced TBI include the shock-tube and open-field model. The shock-tube model induces injury by delivering highly reproducible blast waves from a gas-driven pneumatic tube system to the head of an anesthetized animal. Some investigators secure the neck, head, torso, and abdomen of the animal to minimize movement and tertiary blast effects (Cernak et al., 2011). Others use a Kevlar vest to protect the thorax of the anesthetized animal from the blast shock wave (Long et al., 2009). The open-field model typically involves placing anesthetized animals in compartments on a platform in close proximity (e.g., 4 to 7 meters) to an ordinance (e.g., TNT) and then exposing the animal to blast waves from a controlled explosion (Rubovitch et al., 2011). Recently, application of a lithotripsy machine has been developed to generate shock waves that induce brain injuries in mice (Divani et al., 2015).



Neuropathological Analysis

Animal models of blunt force-induced and blast-induced TBI described above have revealed few histological abnormalities consistent with observations in neuropathologically confirmed CTE cases.

Tau

Animal model research characterizing tau aggregation in the brain following TBI results in inconsistent findings. Several studies in rodents demonstrate an increase in tau following single impact TBI (Goldstein et al., 2012; Liliang et al., 2010; Luo et al., 2014; Perez-Polo et al., 2015) or blast-related TBI (Goldstein et al., 2012). Other studies fail to demonstrate a difference in tau aggregation when comparing single-impact TBI and sham-injury groups (Gama Sosa et al., 2014; Mannix et al., 2013; Mouzon et al., 2014).

Similarly, animal model studies investigating the impact of repeated TBI on tau aggregation in the brain report mixed findings. Animals exposed to repeated TBI did not have elevated brain levels of phosphorylated tau (as measured by immunohistochemistry, ELISA, and western blot) 24 hours, 34 days, 10 weeks, 4 months, 6 months, and 12 months postinjury (Bolton & Saatman, 2014; Mouzon et al., 2014; Xu et al., 2014). However, other studies reported that repeated TBI increases tau levels in the brain postinjury (Arun et al., 2013; Kane et al., 2012; Luo et al., 2014; Namjoshi et al., 2014; Zhang, Teng, Song, Hu, & Chen, 2015). Of these studies that found increased tau postinjury, one reported region-specific increases (cortex, amygdala, and hippocampus) of tau immunoreactivity in up to six months following repeated TBI (Petraglia, Plog, Dayawansa, Dashnaw, et al., 2014).

One reason rodent models do not accurately reflect the neuropathology of confirmed CTE cases may be that the endogenous rodent tau aggregates differently from the human protein. In an attempt to generate a more precise rodent model of head injury, two mouse models expressing human tau isoforms have been created. The hTau mouse expresses all six human tau isoforms (Andorfer et al., 2003), and the T44 mouse expresses the shortest human tau isoform (Ishihara et al., 2001). In hTau mice, Ojo et al. (2013) demonstrated increased expression of phosphorylated tau 21 days after repetitive injury; however, tau expression in these animals did not increase after a single head injury.

Axonal Injury

Axonal injury is a common neuropathological consequence of closed head injury (Johnson, Stewart, & Smith, 2013; Povlishock & Katz, 2005). Because axonal injury and subsequent intercellular events, including activation of microglia and astrocytes, are thought to be potential mechanistic links between TBI and CTE (Ling et al., 2015; Lucke-Wold et al., 2014), animal models may provide a means to study these associations.

Traditionally, axonal injury was thought to be limited to acute periods following head injury; however, recent evidence has identified axonal degeneration in human brains many years postinjury (Johnson, Stewart, Begbie, et al., 2013; Johnson, Stewart, & Smith, 2013). Evidence of chronic axonal injury indicates a potential pathology contributing to chronic symptoms of CTE. In closed head injury animal models, the presence of persistent axon damage with corresponding activation of astrocytes and microglial cells has been described in mice subjected to single and repetitive mTBI exposure (Donovan et al., 2014; Fidan et al., 2015; Luo et al., 2014; Mierzwa, Marion, Sullivan, McDaniel, & Armstrong, 2015; Mouzon et al., 2014). Activation of astrocytes and microglial cells suggestive of CTE pathology also appears to be a common feature of blast injuries in rodents (Goldstein et al., 2012; Sajja et al., 2014; Svetlov et al., 2010).

Neurobehavioral Analysis

Animal model studies have also described neurobehavioral abnormalities reflecting clinical manifestations thought to be associated with CTE. Two common neurobehavioral tests used with rodent models are the Morris water maze test for cognitive assessment (i.e., spatial learning and memory) (Vorhees & Williams, 2006) and the accelerating rotarod test for motor assessment (i.e., balance and sensorimotor coordination) (Hamm, Pike, O'dell, Lyeth, & Jenkins, 1994). Multiple investigators have demonstrated cognitive (Laurer et al., 2001; Meehan, Zhang, Mannix, & Whalen, 2012; Petraglia, Plog, Dayawansa, Chen, et al., 2014) and motor (Laurer et al., 2001; Mouzon et al., 2012) deficits in animal models following exposures to impact-related TBI. Neurobehavioral deficits have also been observed following blast-related TBI exposure in rodents (Goldstein et al., 2012; Koliatsos et al., 2011; Long et al., 2009; Säljö, Bolouri, Mayorga, Svensson, & Hamberger, 2009).

Additionally, animal model studies have explored the impact of TBI exposure frequency on neurobehavioral abnormalities. Numerous investigators have demonstrated that multiple TBI impact-related exposures result in more pervasive and long-lasting neurobehavioral deficits when compared to single-exposure injuries (Laurer et al., 2001; Meehan et al., 2012; Mouzon et al., 2012, 2014; Petraglia, Plog, Dayawansa, Chen, et al., 2014). Studies also suggest greater cognitive impairments when the interval between multiple impacts to the head is shorter (Longhi et al., 2005; Mannix et al., 2013).

Biomarkers

Successful development of objective *in vivo* biomarkers could enable the identification of CTE pathology in living persons, which would greatly enhance understanding of the underlying biological mechanisms and would inform potential diagnostic, treatment, and prevention strategies. Investigators are pursuing neuroimaging modalities and biospecimen analytes as potential predictive biomarkers of CTE.

Neuroimaging

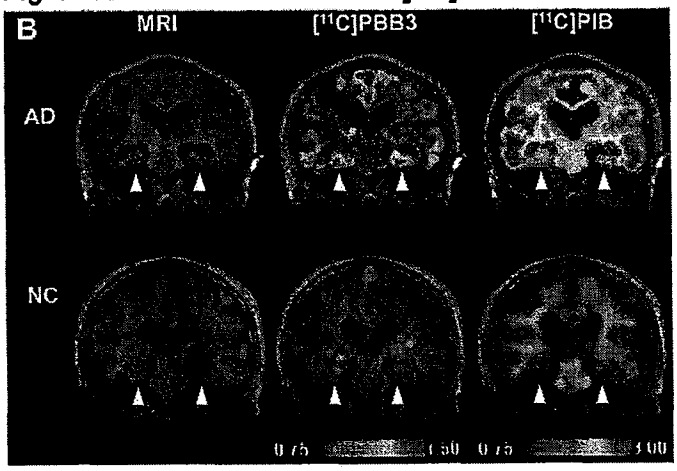
There are no longitudinal studies correlating *in vivo* neuroimaging data directly with postmortem CTE-associated pathology. Current neuroimaging research relevant to CTE biomarkers generally focuses on two approaches. One approach is the detection of molecules associated with CTE pathology (e.g., tau, Aβ). The second approach is detecting structural or molecular changes associated with head injury, which is thought to contribute to the development of CTE.

Positron Emission Tomography

Positron emission tomography (PET) can detect the presence and distribution of specific molecules using trace amounts of radioactive ligands that bind to molecules of interest. Investigators are developing PET radioligands to image pathology associated with CTE (Turner et al., 2013), including aggregations of tau (Villemagne & Okamura, 2014) and Aβ (Barrio, Hunag, & Cole, 1999). PET is also being used to assess changes in metabolic activity in the brain associated with exposure to head trauma.

Several PET radioligands targeting tau have shown potential as CTE biomarkers, and some are being investigated in clinical trials. For example, Maruyama et al. (2013) demonstrated that the [^{11}C]PBB3 radioligand exhibits specificity for tau in transgenic mouse models and human subjects with probable AD (see Figure 2). Investigators are conducting a Phase II clinical trial to determine whether [^{11}C]PBB3 can detect tau aggregates in patients with a history of TBI (National Institute of Mental Health, 2015).

Figure 2. PET Accumulation of [^{11}C]PBB3



Coronal [^{11}C]PBB3 PET scan of patients with probable AD and controls (Maruyama et al., 2014)

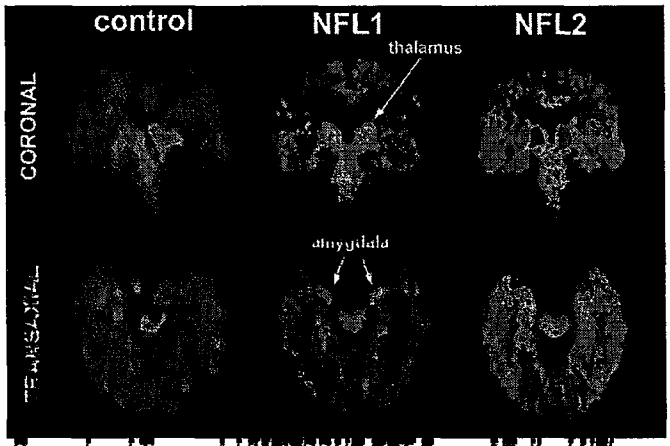
Additionally, [^{18}F]T807 and [^{18}F]T808 are two related radioligands with high affinity and selectivity for hyperphosphorylated tau in humans (Chien et al., 2013, 2014). Multiple

clinical trials are investigating the use of [^{18}F]T807 as a potential biomarker of CTE (Avid Radiopharmaceuticals, 2015; Di Carli, 2015; Molecular NeuroImaging, 2015).

PET imaging of tau faces several challenges (Villemagne, Fodero-Tavoletti, Masters, & Rowe, 2015). Tau protein aggregates are intracellularly expressed, which requires the corresponding ligand to cross the blood–brain barrier and cell membrane to bind. Tau aggregates are also subject to several post-translational modifications that alter the ultrastructural conformation of the aggregates and affect radioligand binding. Tau ligands have an affinity for Aβ aggregates as well, which poses a challenge for characterization of CTE pathology as both protein aggregates may be present in different anatomical locations and Aβ pathology is significant in AD. Nevertheless, at least six new classes of tau radioligands have been developed, each with different levels of affinity and specificity to tau relative to Aβ (Shah & Catafau, 2014).

PET imaging of Aβ aggregates has been demonstrated using a [^{18}F]FDDNP radioligand (Barrio et al., 1999); however, unlike [18F]T807, binding is relatively nonselective and also labels NFTs (i.e., tau) (Smid et al., 2013). In football players with a history of head injury exposure, [^{18}F]FDDNP PET demonstrates increased signaling in the amygdala and subcortical brain regions (see Figure 3), which is potentially indicative of CTE (Small et al., 2013). Barrio et al. (2015) describe differences in [^{18}F]FDDNP signal patterns between football players with mTBI and Veterans with blast-induced mTBI. These observations suggest that the radioligand may be useful in identifying and characterizing CTE. The [^{18}F]FDDNP radioligand also binds with extracellular Aβ plagues and intracellular NTFs in patients with AD (Shoghi-Jadid et al., 2002; Smid et al., 2013) and Down's syndrome (Nelson, Siddarth, & Kepe, 2011), so discrimination between tauopathies must rely on regional signal differences.

Figure 3. PET Imaging in Retired NFL Players



Coronal and Transaxial [^{18}F]-FDDNP PET Scan of Retired NFL Players (Small et al., 2013)

PET imaging with [^{18}F]FDG PET can measure the glucose metabolic activity, which reflects the functional states of brain structures (Turner et al., 2013). [^{18}F]FDG PET imaging has found hypometabolism (relative to controls) in the brain regions of boxers, which is thought to be affected by impacts to the side of the head, including the frontal lobe anterior to Broca's area, the posterior cingulate cortex, the posterior parietal lobe, and the cerebellum (Provenzano et al., 2010). This pattern of hypometabolism differs from other types of TBI exposures, such as motor vehicle accidents and falls, which affect orbitofrontal and anterior temporal lobe areas. However, the hypometabolism of the posterior cingulate cortex and the posterior parietal lobes is similar to that seen in patients with AD, which may be responsible for the AD-like cognitive decline seen in boxers (Bonte, Harris, Roney, & Hynan, 2004). Unlike boxers, patients with AD do not typically show hypometabolism in the cerebellum, which may be unique to boxers presenting with AD-like cognitive impairments. Together, these results suggest that [^{18}F]FDG PET could potentially be used as a biomarker for TBI-related neurodegenerative processes resulting from exposure to head injury.

Researchers have also pursued the use of PET to characterize TBI-related neuroinflammation through use of radioligands selective for activated microglia. Elevated uptake of [^{11}C]R-PK11195, which binds to a transmembrane protein expressed in activated microglia, was observed in the brains of patients with moderate to severe TBI from several months to years postinjury (Folkersma et al., 2011; Ramlackhansingh et al., 2011). Increased binding of [^{11}C]-DPA-713, a second-generation radioligand with greater specificity for activated microglia, was observed in the brain regions associated with TBI of nine former NFL players compared to controls (Coughlin et al., 2015).

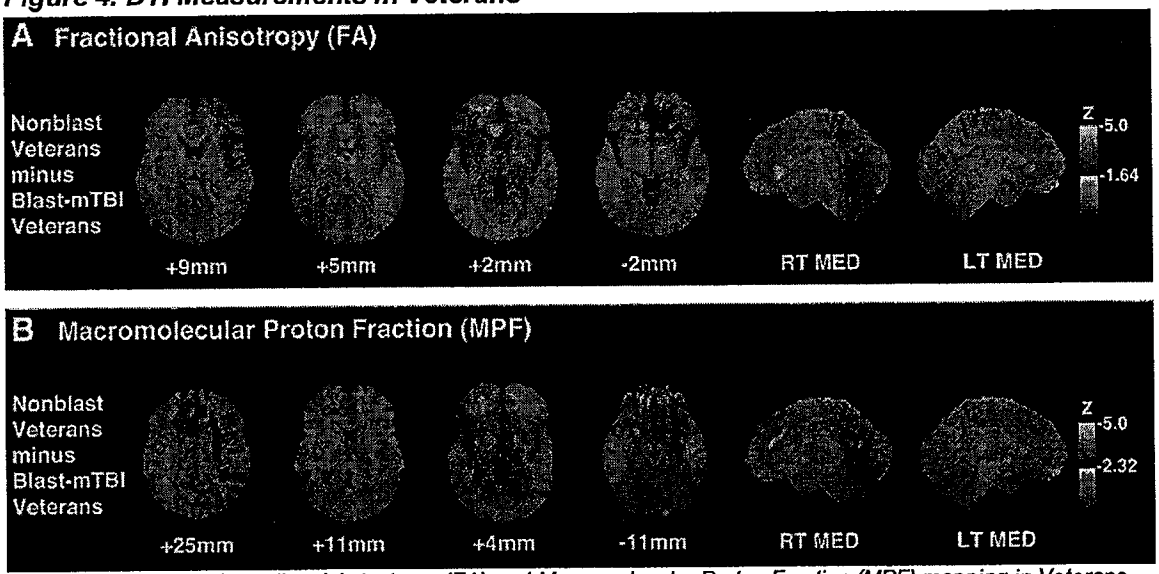
Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) can visualize white matter axon tracts, in turn enabling investigators to detect abnormalities not visible on conventional magnetic resonance imaging or computed tomography imaging methodologies (Turner et al., 2013). DTI revealed significant white matter changes in a high-school contact sport athlete following a single concussion (Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012). Furthermore, significant white matter changes can be detected in contact sport athletes exposed to multiple subconsussive injuries in the absence of clinically evident concussion (Bazarian et al., 2014, 2012). DTI findings have also supported a link between axonal abnormalities and executive impairment following TBI (Lipton et al., 2009).

Several DTI studies that have investigated white matter integrity in Veterans with exposure to blast- and/or impact-related injuries report different findings. Some studies detect abnormalities in multiple, diffuse areas (see Figure 4) (Davenport, Lim, Armstrong, & Sponheim, 2012; Hayes, Miller, Lafleche, Salat, & Verfaellie, 2015; Morey et al , 2013; Petrie et al , 2014), while MacDonald et al. (2013) report abnormalities restricted to the cerebellum. Detection of spatially heterogeneous areas of decreased

fractional anisotropy may indicate a potential DTI-based biomarker for blast-related mTBI (Jorge et al., 2012). In contrast, one recent DTI study found no significant differences in white matter integrity between Veterans exposed to blast-related injury and controls (Levin et al., 2010).

Figure 4. DTI Measurements in Veterans

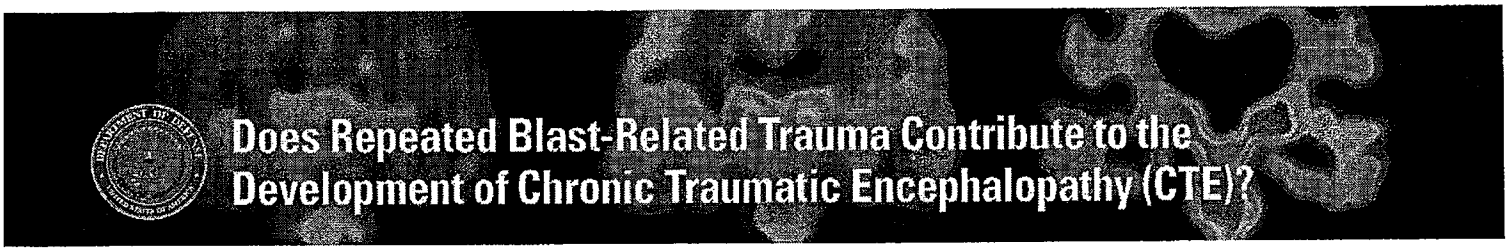


DTI measurements of Fractional Anisotropy (FA) and Macromolecular Proton Fraction (MPF) mapping in Veterans with or without blast-induced mTBI. (A) FA (metric of white matter structural integrity) is reduced in the right genu of the corpus callosum of blast-induced mTBI. (B) MPF values (metric of white matter myelin compositional integrity) are lower in blast-induced mTBI in multiple brain regions. Image from Petrie et al., 2014.

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a noninvasive method of measuring brain chemistry *in vivo* that can be applied to detect changes in brain metabolites following TBI (Gavett et al., 2011; Turner et al., 2013). Common brain metabolites altered by brain injury that MRS can detect include decreased N-acetyl aspartate (NAA; indicating neuronal damage), increased choline (Ch) and lipid (indicating membrane damage and diffuse axonal injury), increased combined glutamate and glutamine (Glx; indicating excitotoxic effects of the brain) and increased myo-inositol (indicating brain injury from membrane damage and/or as a result of astrocytosis) (Gavett et al., 2011).

One-dimensional (1D) MRS has demonstrated a significant decrease in Glx and NAA in the primary motor cortex and NAA in the prefrontal cortex in concussed athletes as compared with nonconcussed athletes (Henry, Tremblay, Boulanger, Ellemberg, & Lassonde, 2009). In retired professional athletes with CTE symptoms, 1D MRS has found increased levels of Ch and Glx when compared to age-matched, healthy controls (Lin et al., 2010). Use of advanced spectroscopy methods, specifically two dimensional localized correlated spectroscopy, illustrated changes in Glx and Ch typically captured



with conventional 1D MRS, but also recorded increases in phenylalanine and fucose from the brains of former athletes, which cannot be measured by 1D MRS (Gavett et al., 2011; Lin et al., 2015). While imaging changes in these brain metabolites using MRS may help describe pathological changes following single or repetitive brain injury, it can be difficult to distinguish between natural changes with aging and those of injury (Tremblay et al., 2013).

Researchers have been investigating MRS to study the effects of blast injury in Veterans. Reductions of NAA relative to brain metabolites Ch and creatine (Cr), NAA/Ch and NAA/Cr ratios, respectively, are thought to indicate brain injury (Signoretti et al., 2008). Significant hippocampal reductions of NAA/Ch and NAA/Cr have been observed in Veterans when compared to controls (de Lanerolle et al., 2014; Hetherington et al., 2014).

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) can investigate structural and functional changes of the brain following brain injury (Bruce et al., 2015; Gandy et al., 2014). Researchers have used fMRI to evaluate functional disruptions in both concussive and subconcussive injury groups, even in the absence of overt clinical symptoms (Talavage et al., 2010). Given its ability to detect deficits in subconcussive injury, fMRI may hold promise for future investigations of CTE-related changes (Gavett et al., 2011).

Biospecimens

Effective biospecimen-based biomarkers would provide a more accessible, cost-effective, and deployable method for identifying CTE *in vivo* than neuroimaging modalities that are resource intensive and located in fixed brick-and-mortar facilities. There are few studies focused on biospecimen-based CTE biomarkers, in part due to the pathological and symptological similarities to established neurodegenerative diseases (Turner et al., 2013). However, investigators have been pursuing the measurement of proteins and/or microRNAs found in cerebrospinal fluid (CSF) or blood plasma as potential biomarkers of TBI, which may lend insight into identification of CTE pathology *in vivo* (Baugh et al., 2012; Mez, Stern, & McKee, 2013).

Cerebrospinal Fluid

While CSF is considered a potential source of TBI biomarker identification given its direct contact with the brain and nervous system (Turner et al., 2013), the lumbar puncture required to sample CSF poses obvious disadvantages. Research on CSF biomarkers of TBI focus on axonal proteins, such as neurofilament light and tau (DeKosky, Blennow, Ikonomovic, & Gandy, 2013). A longitudinal study of amateur boxers demonstrates increased CSF levels of neurofilament light and tau after bouts (Zetterberg & Blennow, 2015). While the increases of neurofilament light suggested dose dependency (increases were more pronounced in boxers who sustained several head punches), the utility of this marker is called into question given that protein levels returned to normal after three months of no bouts. Additional studies in amateur boxers

have described increases in CSF proteins, in particular neurofilament light, tau, and glial fibrillary acidic protein (GFAP), that correlated with exposure to head trauma (Neselius et al., 2012, 2013; Zetterberg, Hietala, & Jonsson, 2006). The number of days in which the proteins remained elevated varied, indicating that they may be best used as markers of acute injury. Additional studies are needed to validate blast biomarkers and determine the most effective time to take CSF samples following exposure.

Blood Plasma

While blood-based biomarker sampling poses lower risk than the lumbar punctures that CSF approaches require, plasma biomarkers have their drawbacks, including (1) dilution of the brain-specific protein by the large volume of plasma and in the extracellular fluid of peripheral organs, (2) degradation of the biomarker candidate by blood proteases, (3) clearance of the protein by hepatic metabolism or renal excretion, and (4) analyses of brain proteins in blood that can be confounded by release of the same protein from peripheral tissues (DeKosky et al., 2013). Recent research has identified several potential blood plasma-based biomarkers of TBI. Serum levels of S-100β were increased in patients with severe TBI and demonstrate a strong correlation to clinical outcome (Anderson, Hansson, Nilsson, Dijlai-Merzoug, & Settergren, 2001; Naeimi, Weinhofer, Sarahrudi, Heinz, & Vécsei, 2006). Additionally, the ratio of GFAP to ubiquitin carboxy-terminal hydrolase-L1 in plasma may be characteristic of a focal or diffuse TBI (Mondello et al., 2012) and may change after multiple concussive or subconcussive head injuries. This ratio may potentially offer insight into the development of CTE (Turner et al., 2013). Transient, severity-dependent, and time-dependent elevations of tau levels in serum were detected following TBI in rats (Liliang et al., 2010). Additionally, Olivera et al. (2015) reported elevated concentrations of plasma tau protein in military personnel with TBI.

Another plasma-based TBI biomarker of potential relevance to CTE is neuron-specific enolase (Zetterberg et al., 2009). Elevated levels of this protein were detected in boxers after they abstained from boxing for two months when compared to healthy controls. However, S-100β, brain-derived neurotrophic factor, and heart-type fatty acid binding protein did not change. These results suggest that neuron-specific enolase may remain elevated for an extended period of time postinjury and could be a useful biomarker for diagnosing athletes and patients who have suffered multiple concussive and subconcussive head injuries.

Treatment and Prevention Strategies

There is no established treatment for CTE, and for this reason, current mitigation strategies focus on prevention of head injury and/or concussion (DeKosky et al., 2013; Jordan, 2014). While protective headgear can prevent severe injuries (e.g., penetrating injury, skull fracture, intracranial hemorrhage), helmets do not appear to mitigate the incidence or severity of sports related concussion (Harmon et al., 2013, McCrory,

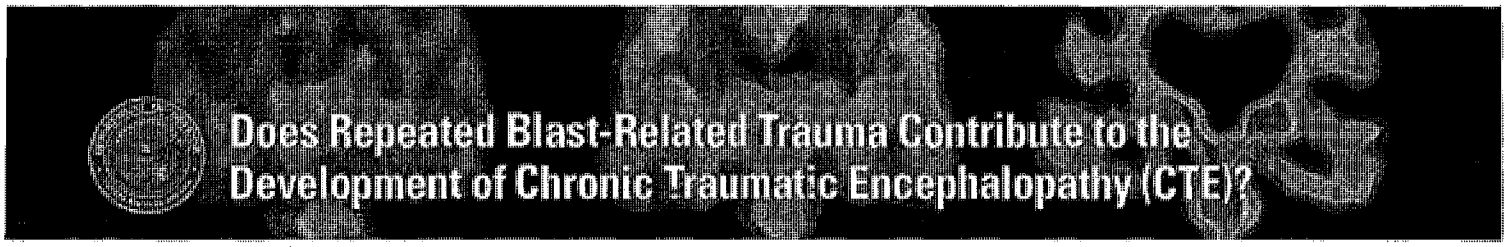
Meeuwisse, Aubry, et al., 2013). Some investigators have suggested that the use of helmets in sports enables or promotes aggressive play and increases the risk for head injury (Herring et al., 2011). Other prevention strategies in sports include rule changes and return-to-play guidelines (McCrory, Meeuwisse, Aubry, et al., 2013). The DoD is also developing return-to-activity guidelines for service members following mTBI (McCulloch et al., 2015).

Although consensus on the understanding of CTE is still being established and diagnostic criteria are still under development, researchers are investigating potential treatment approaches. Several animal model studies target tau pathology as a potential intervention strategy. Kondo et al. (2015) blocked tauopathy progression in mice with the application of an antibody that interrupted an early stage of tau development, termed "cistauosis," following TBI. Recent work describing the impact of acetylation on tau aggregation suggests a potential therapeutic target for CTE (Cook, Carlomagno, et al., 2014; Cook, Stankowski, Carlomagno, Stetler, & Petrucelli, 2014). Additionally, pharmacologic inhibition of a metabolic enzyme (monoacylglycerol lipase) in a mouse model of repetitive closed-head injury reduced several neuropathological hallmarks of CTE, including tau phosphorylation and TDP-43 protein aggregation (Zhang et al., 2015). Because of the neuropathological similarities with AD and TBI, potential pharmacological and behavioral interventions for these conditions could also be applied to CTE (Antonius et al., 2014; Levin & Bhardwaj, 2014).

Discussion

CTE represents a major potential public health issue considering the number of athletes, service members, and Veterans exposed to single and/or multiple concussive and/or subconcussive head injuries. The current state of the science has generated an initial consensus on the neuropathology of CTE (NINDS, 2015). However, the evidence does not allow for a conclusive determination of whether exposure to head injury is sufficient and causative in the development of CTE pathology. Existing clinical data are limited, observational in nature, and subject to methodological concerns. These realities have led some investigators to question whether existing data are adequate to confirm CTE as a unique neurodegenerative disease (Iverson et al., 2015; Karantzoulis & Randolph, 2013; Randolph, 2014).

Existing neuropathological evidence describes abnormalities in the brain following exposure to head injury that may be associated with CTE development and that may reflect underlying biological processes. Recent consensus establishing perivascular tau aggregation in cortical sulci depths as unique indications of CTE represents the most conclusive pathological evidence to date (NINDS, 2015). Pathophysiological mechanisms explaining how tau aggregation causes or contributes to clinical symptoms of tauopathies, including AD, have yet to be determined, and it is not definitively established whether or how tau pathology drives or causes clinical manifestations of



CTE (Iverson et al., 2015). More broadly, it is still not clear what other macroscopic and microscopic (e.g., Aβ, TDP-43) pathological findings are unique to CTE, given that autopsy reports are inconsistent (Karantzoulis & Randolph, 2013) and that these pathological findings are also associated with aging (McCrory, Meeuwisse, Kutcher, et al., 2013) and multiple other neurodegenerative diseases (Karantzoulis & Randolph, 2013).

Identification of biomarkers enabling *in vivo* detection of CTE pathology would advance ongoing research needs. Investigators are working to develop neuroimaging and biospecimen-based biomarkers, targeting the pathophysiological mechanisms associated with CTE (e.g., tau aggregates) and the biological processes following head injury exposure. Premortem identification of CTE could potentially benefit prevention and treatment. Current preclinical and clinical development of therapeutic or rehabilitative strategies are also targeting pathophysiological mechanisms associated with CTE and the biological processes following head injury exposure.

Existing clinical evidence does not inform whether variations in head injury frequency (e.g., single versus multiple exposures) or head injury type (e.g., impact, nonimpact, blast) are differentially associated with CTE. Data about frequency or type of head injury exposure is not collected systematically or consistently across, or sometimes even within, CTE case series or case studies. Most CTE studies characterize head injury exposure simply as exposure to sport or occupation (e.g., football, boxing) without including data describing head injury frequency, severity, or the time elapsed between injuries.

Other fundamental questions exist about the links between exposure to head injury, CTE-associated pathology, and clinical symptoms. For example, evidence does not conclusively support that retired athletes exhibit a unique neurodegenerative pathology or have higher rates of associated clinical symptoms (Randolph, 2014). Alternative hypotheses have been described recently by Iverson et al. (2015), such as the possibility that neurotrauma reduces a cerebral reserve normally protecting persons from development of neurodegenerative disorders, or that tau pathology is clinically silent such that symptoms are due to other, potentially multifactorial, causes.

Research Needs

Limitations to the conclusions that can be drawn about links between exposure to head injury, CTE-associated pathology, and clinical symptoms stem in part from the characteristics of existing evidence and methodological issues. For example, postmortem CTE autopsy cases, which are often referred to researchers by families with concerns about neurobehavioral problems (Antonius et al., 2014), are limited by significant selection (ascertainment) biases (Daneshvar et al., 2011; Karantzoulis & Randolph, 2013; Maroon et al., 2015). Data about the clinical symptoms associated with

CTE are retrospective and often derived from interviews with family members, which make the data subjective and limited by recall biases (McCrory et al., 2007).

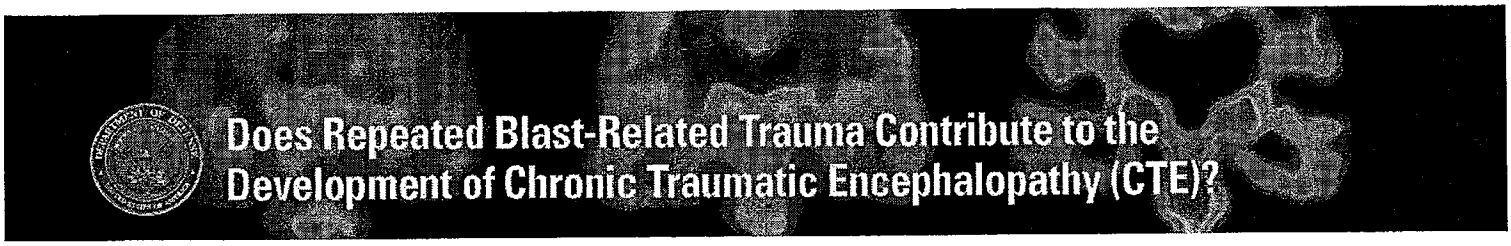
CTE has drawn significant public and media attention given the large at-risk population (e.g., military service members, contact sport athletes). Experts have noted concern over the potential clinical and legal consequences of a widespread misunderstanding of CTE (Wortzel, Brenner, et al., 2013). Given these factors, the need for additional research is clear and investigators have called for specific actions (Iverson et al., 2015; Montenigro et al., 2014; Randolph, 2014):

- Initiation of cross-sectional, prospective, longitudinal, and/or epidemiological studies; initial work could compare retired athletes to demographically matched controls without exposure to head injury and assess whether a higher risk for clinical symptoms is supported; additional work could investigate links between CTE-associated pathology and observed clinical symptoms
- Development of standardized protocols for studying pathology, including establishing control data
- Development of clinical diagnostic research criteria
- Continued biomarker development, such as determining whether PET imaging can detect differences in tau between groups with and without head injury exposure, with different clinical manifestations, including comorbidities (as well as control subjects)

Appendices

Appendix 1: Search Terms

Condition		Pathology	Outcome Measure(s)	Study Population(s)
Alzheimer's disease	Motor neuron disease	Activated kinases	Assessment	Animal models
Auditory	Neurodegeneration	Apolipoprotein E (ApoE) genotype	Computational models	Athletes
Behavioral disorder	Neurodegenerative	Astrocytes	Diagnostic	Boxing
Blast event	Parkinsonism	Astroglial tangles	Diffraction spectrum imaging or DSI	Breacher
Blast exposure	Post-concussion syndrome or PCS	Axonopathy	Diffusion Tensor Imaging or DTI	Football
Chronic TBI	Post-traumatic stress disorder or PTSD	Beta-amyloid	Magnetic Resonance Imaging or MRI	International Space Program
Chronic traumatic encephalopathy or CTE	Potentially concussive event or PCE	Biomarker	Screening	Military
Cognition	Proteinopathies	Epigenetics	Positron Emission Tomography or PET	NASA
Cognitive deficits	Repetitive head injury	Glymphatics	Treatment	NCAA
Concussion	Suicide	Microglia		NFL
Headache/ migraine	Tauopathy	Neuroendocrine		Occupational blast
Head trauma	Traumatic brain injury or TBI	Neurofibrillary tangles		Post-mortem
Hearing	Traumatic encephalopathy	Neuropathology		Sports
Inflammation	Vascular injury	Neurosensory		Soccer
Late effects of TBI	Vertigo or dizziness	TDP-43		Veteran
Mild traumatic brain injury or mTBI	Eye, retina, optic nerve, retinal ganglion cells, photoreceptors			



Appendix 2: Selected Acronyms and Abbreviations

Aβ	Beta-amyloid
AD	Alzheimer's disease
ApoE	Apolipoprotein E
ATs	Astrocytic tangles
BBB	Blood–brain barrier
Blast PCO	DoD Blast Injury Research Program Coordinating Office
Ch	Choline
Cr	Creatine
CSF	Cerebrospinal fluid
CTE	Chronic traumatic encephalopathy
DoD	Department of Defense
DTI	Diffusion tensor imaging
DTIC	Defense Technical Information Center
FA	Fractional Anisotropy
fMRI	Functional magnetic resonance imaging
FTLD	Frontotemporal lobar degeneration
GFAP	Glial fibrillary acidic protein
Glx	Glutamine
MND	Motor neuron disease
MPF	Macromolecular proton fraction
MRS	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
NFTs	Neurofibrillary tangles
NIH	National Institutes of Health
NINDS	National Institute for Neurological Disorders and Stroke
NTs	Neuritic threads
PD	Parkinson's disease
PET	Positron emission tomography
pTau	Phosphorylated tau
SoS	State of the science
TBI	Traumatic brain injury
TDP-43	TAR DNA-binding protein-43

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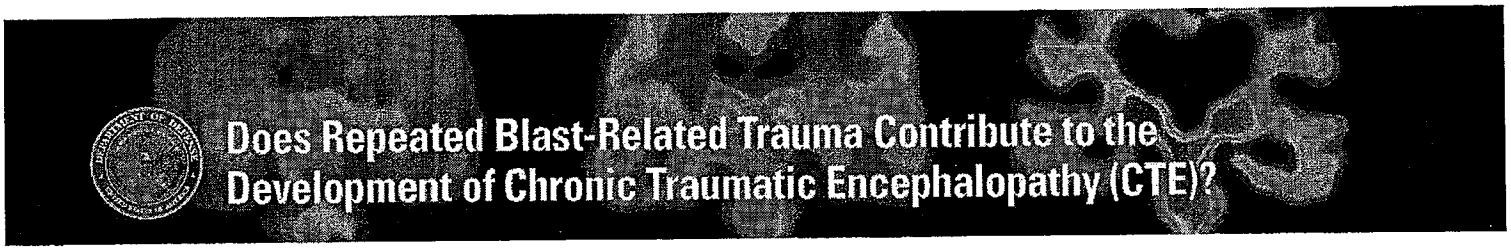

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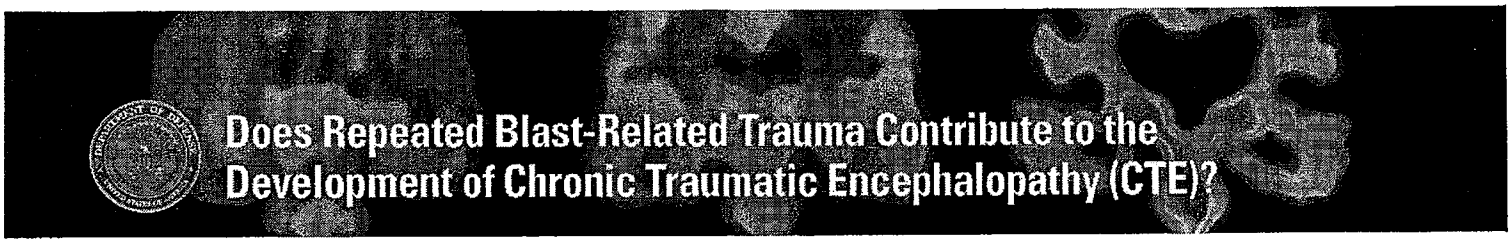

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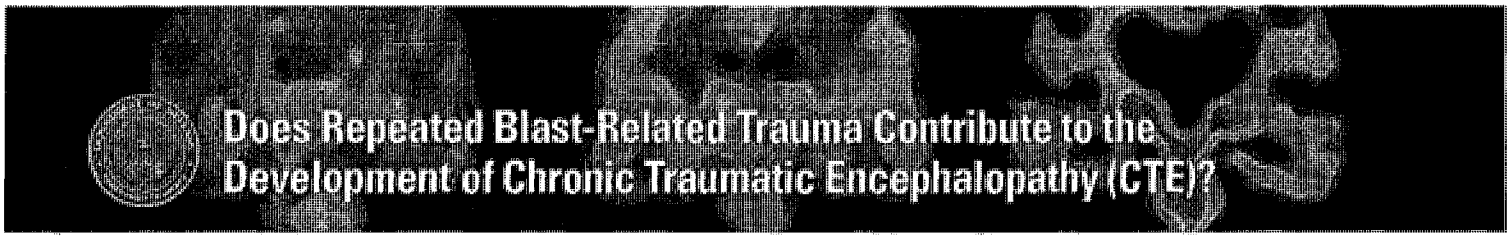

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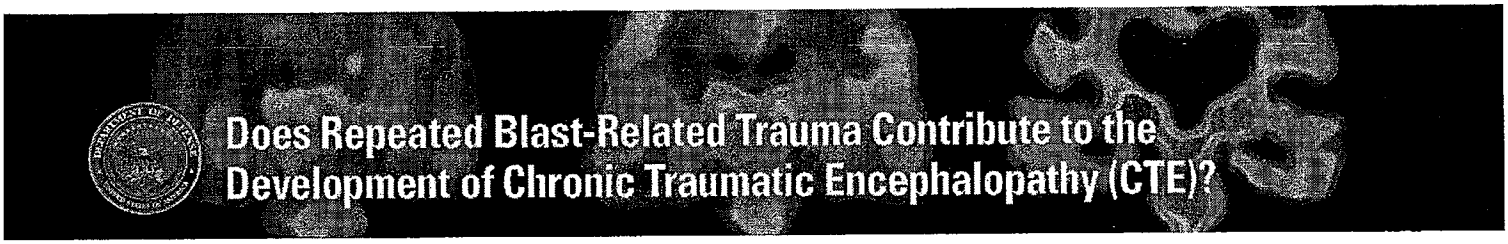

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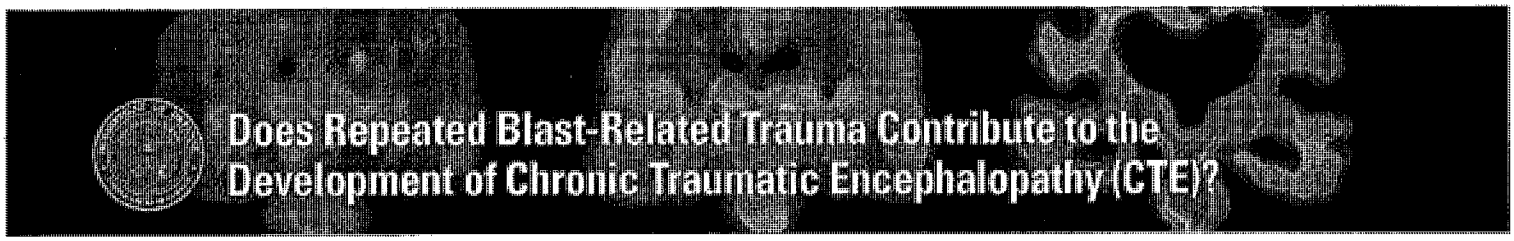

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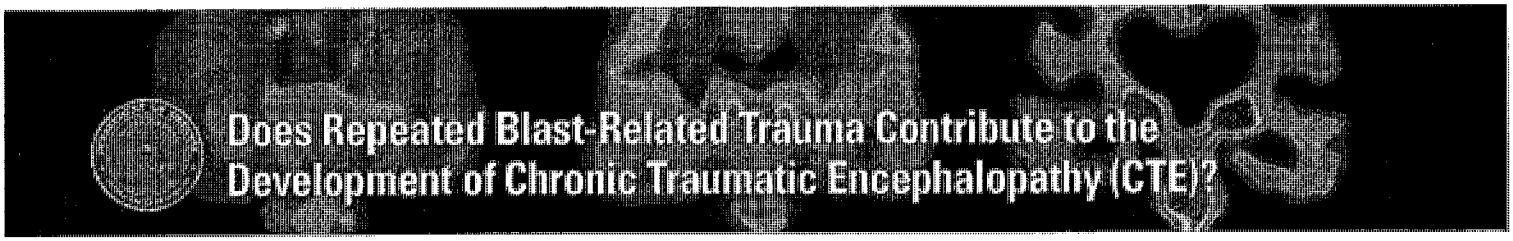

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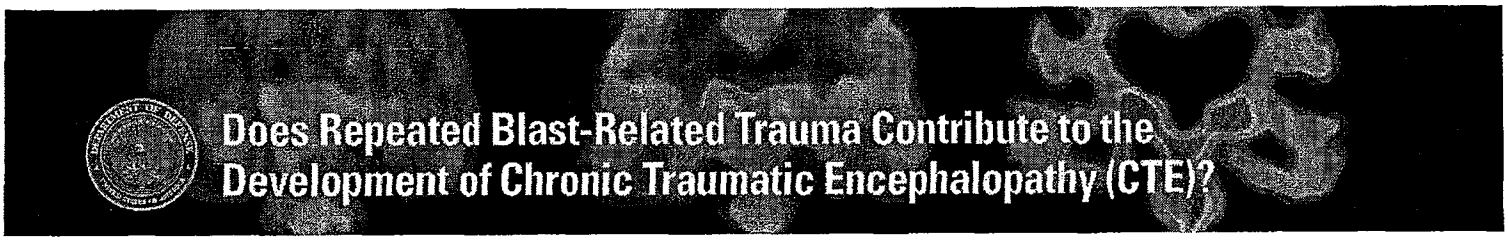

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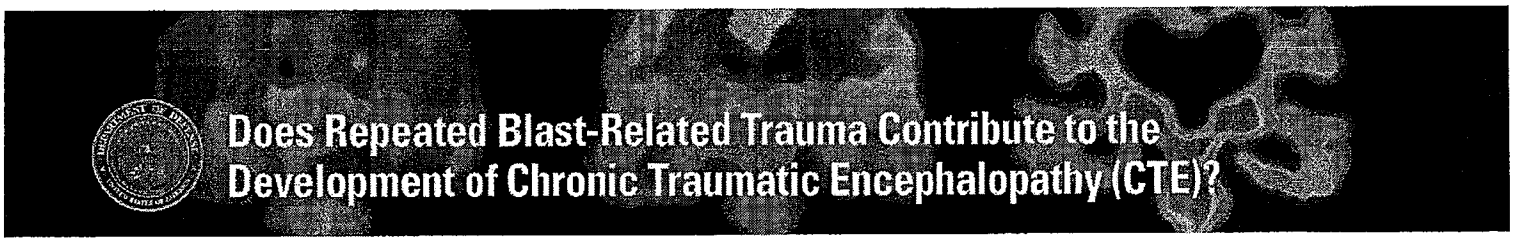

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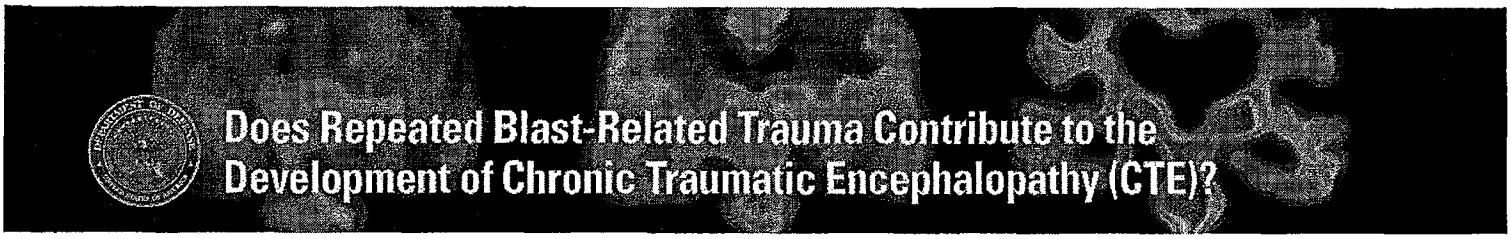

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Exhibit 7

Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy

In 1928, the pathologist Harrison Stanford Martland described the clinical features of a distinct neuropsychiatric disorder in boxers known as the "punch-drunk syndrome." Several decades later this became known as "dementia pugilistica," reflecting a belief that it was a disease almost exclusive to former boxers. More recent neuropathological studies have identified this condition in persons with other forms of head injury, including athletes exposed to repetitive brain injury in a wide range of sports. Thus, almost 90 years after Dr. Martland's first account in boxers, there is a realization that sustained brain injury raises the risk of developing this condition, rather than the environment or sport in which brain injury is occurs.

Despite the passage of time, this condition, now called chronic traumatic encephalopathy (CTE), remains a diagnosis that can only be made during neuropathological examination of the brain at autopsy. Early accounts of the pathology of dementia pugilistica/CTE described nerve cell loss and accumulation of abnormal tau protein forming neurofibrillary tangles in affected brain regions. How and where the degeneration began in the brain was never clear. More recent reports include cases in persons with substantial exposures to trauma who did not develop dementia, but in whom tau positive neurofibrillary tangles are seen in the brain at autopsy. The pathologic characteristics of CTE remain poorly defined. Its recognition at autopsy remains limited and as a result it is not clear how often evidence of CTE goes undetected in autopsy cases.

In April 2013, the NIH launched a major effort to define the pathologic characteristics of CTE. With support from the Foundation for NIH's Sports Health Research Program with funding from the National Football League, the NIH awarded grants to two teams of neuropathologists and TBI experts to better understand this condition. A major goal of this research is to use advanced neuroimaging techniques to correlate pathologic changes with imaging abnormalities so that imaging tools might someday be used to examine living persons for the presence of CTE. Defining the brain abnormalities that are specific for CTE is key to advancing medical research and care. To this end, the neuropathology teams have started a process to generate consensus guidelines for the pathological diagnosis of CTE that will allow a more complete picture to be formulated over the grant period. The first consensus workshop occurred in Boston on February 26 and 27, 2015.

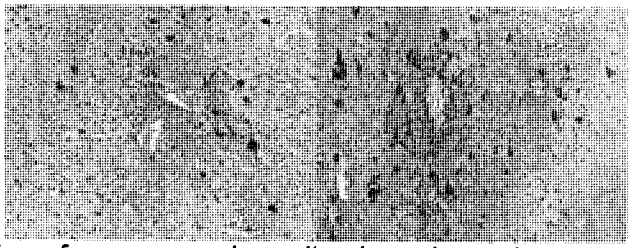
The process included a review of the literature, individual review of relevant pathologic cases using digital imaging technology, and a face-to-face review of cases from the same digital images, followed by discussion and recommendations. The team assembled slides stained with Luxol fast blue/Hematoxylin & eosin (LH&E), a silver stain (Bielschowsky), and immunostains for phospho-tau (AT8), amyloid-beta and phospho-TDP-43. The slides were prepared using standardized protocols by a single laboratory. Digitized images of the slides were then provided to the consensus neuropathology group whose members were blinded to all information, including age, sex, and clinical history. Slides included 19 brain regions from 25 cases of CTE and other disorders that might be in the differential diagnosis

of CTE, all having significant tau aggregates. The non-CTE cases included Alzheimer's disease (AD), Parkinson-dementia complex of Guam, progressive supranuclear palsy, corticobasal degeneration, primary age-related tauopathy and argyrophilic grain disease. The pathologists independently reviewed the slides and diagnosed each case using provisional criteria for CTE and established criteria for other tauopathies. The teams of pathologists then met in Boston to review the pathology slides and diagnoses as a group. In general, there was excellent agreement among the pathologists with regard to distinguishing CTE from the other tauopathies. Discussions led to refinements in the provisional neuropathological criteria for CTE, as well as "best practice" recommendations for neuropathologists examining brains for evidence of CTE.

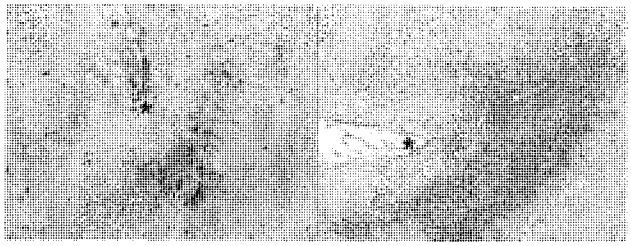
Required criteria for pathological diagnosis of CTE:

The feature considered the most specific for CTE, and the one that distinguished the disorder from the other tauopathies, was the regional distribution of tau aggregates. **In CTE, the tau lesion considered pathognomonic was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci.** Many other abnormalities were seen, especially in the more severely affected brains, but the group consensus was that abnormal tau immunoreactivity in neurons and glia, in an irregular, focal, perivascular distribution and at the depths of cortical sulci, was required for the diagnosis of CTE. There was frequentsly evidence of TDP-43-immunoreactive neuronal cytoplasmic inclusions, amyloid pathologies, and severe hippocampal neurofibrillary degeneration, including extracellular tangles best seen with silver stains.

Recommendations were also made for conducting a neuropathologic examination for CTE. Of note, the Bielschowsky silver stain did not detect the diagnostically significant focal perivascular cortical tau lesions, so the group recommended phospho-tau immunohistochemistry. They also discussed how extensive the sampling must be to rule out CTE, but no data were available to make this determination. All things considered, except for centers specializing in CTE research, the group felt that the sampling protocol recommended by Alzheimer's Disease Centers (NIA-AA recommendations) was reasonable at this stage. Tissue blocks, including the sulcal depth from superior and middle frontal gyrus, superior and middle temporal gyrus and inferior parietal gyrus, were considered to be most informative for detecting the earliest or most mild lesions of CTE..



Tau antibody staining of neurons and neurites in perivascular pattern (arrow pointing to blood vessel).



Lower field photo illustrating the focal nature of the tau staining at depth of sulci (asterisk at bottom of sulcus).

Supportive criteria for a diagnosis of CTE:

To complement the required criteria, the group also defined supportive pathological features that were frequent in CTE brains, especially in the more severely affected cases. These include:

1. Macroscopic abnormalities in the septum pellucidum (cavum, fenestration), disproportionate dilatation of the IIIrd ventricle or signs of previous brain injury;
2. Abnormal tau immunoreactive neuronal lesions affecting the neocortex predominantly in superficial layers 2 and 3 as opposed to layers 3 and 5 as in AD;
3. Abnormal tau (or silver-positive) neurofibrillary lesions in the hippocampus, especially in CA2 and CA4 regions, which differ from preferential involvement of CA1 and subiculum in AD;
4. Abnormal tau immunoreactive neuronal and astrocytic lesions in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum and substantia nigra, and
5. Tau immunoreactive in thorny astrocytes in subpial periventricular and perivascular locations.

Findings considered exclusions to the diagnosis of primary CTE:

1. CA1 predominant neurofibrillary degeneration in the hippocampus in association with amyloid plaques, as seen in AD;
2. Cerebellar dentate cell loss, prominent coiled bodies in oligodendroglia, and tufted astrocytes as seen in PSP, and
3. Severe involvement of striatum and pallidum with astrocytic plaques in cortical and subcortical structures as seen in CBD.

Conclusion:

The criteria described above constitute the first step in the process of fully characterizing the neuropathology of CTE, just as the Boston meeting was the first of a series of consensus conferences of the investigators funded by the NIH research initiative. However, it was noted that, **thus far, this pathology has only been found in individuals exposed to brain trauma, typically multiple episodes.** How common this pathology occurs at autopsy and the nature and degree of trauma necessary to cause this neurodegeneration remain to be determined.

In concluding the meeting, the investigators identified numerous important as areas that need to be addressed to more fully understand CTE. These include questions about the involvement of spinal cord, neuronal cell loss, gliosis, inflammation, hemosiderin

deposition, specific pathologic stages of the disorder, further characterization of amyloid and TDP-43 pathologies, etc. It is also especially important for the community to understand that it is not yet possible to correlate clinical symptoms or future brain health with the signature pathologic feature of CTE. NIH, again with funding from the Foundation for NIH Sports Health Research Program, issued a solicitation for teams of clinical and imaging investigators to address this important issue in persons with neuropsychiatric symptoms and history of multiple concussion to attempt to determine the core clinical symptoms of CTE and how they progress over time.

The following neuropathology experts took part in the First Consensus Conference to Evaluate the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy:

Nigel J. Cairns - Washington University, St. Louis
Dennis W. Dickson - Mayo Clinic, Jacksonville
Rebecca Folkerth – Brigham and Women's Hospital, Boston
C. Dirk Keene - University of Washington, Seattle
Ann McKee - Boston University (Principal Investigator of one of the NIH CTE grants)
Daniel Perl - Uniformed Services University of the Health Sciences, Bethesda
Thor Stein - Boston University
Willie Stewart - University of Glasgow, Scotland
Jean Paul Vonsattel - Columbia University, New York

In addition to neuropathologists, the group included Irene Litvan – University of California San Diego, who is a neurologist with significant expertise in devising research criteria for neurodegenerative tauopathies, and Wayne Gordon-Mount Sinai Hospital, New York, an expert in TBI as well as Principal Investigator of the other NIH CTE grant.

The following NINDS staff also participated in the conference:

Patrick Bellgowan
Deborah Babcock
Walter Koroshetz

Last Modified March 31, 2015