



What is the evidence for chronic concussion-related changes in retired athletes: behavioural, pathological and clinical outcomes?

Paul McCrory,¹ Willem H Meeuwisse,^{2,3} Jeffrey S Kutcher,⁴ Barry D Jordan,⁵ Andrew Gardner⁶

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For numbered affiliations see end of article.

Correspondence to

Dr Paul McCrory, The Florey Institute of Neuroscience and Mental Health, Heidelberg, VIC 3084 Australia; paulmccrory@icloud.com

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ABSTRACT

Objective The purpose of this paper was to review the current state of evidence for chronic traumatic encephalopathy (CTE) in retired athletes and to consider the potential differential diagnoses that require consideration when retired athletes present with cognitive and psychiatric problems.

Data sources MEDLINE, CINAHL, EMBASE, Mosby's Index, PsycEXTRA, PsycINFO and Scopus. Key words included CTE, dementia pugilistica, punch drunk syndrome, traumatic encephalopathy, CTE, repetitive head injury, sports concussion, multiple concussions, chronic concussions, subconcussive blow and sports-related traumatic brain injury.

Results At present, there are no published epidemiological, cross-sectional or prospective studies relating to modern CTE. Owing to the nature of the published studies, being case reports or pathological case series, 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 coexisting dementing illnesses contribute to this process is largely unaccounted for in the published literature.

Conclusions At present, the interpretation of causation in the modern CTE case studies should proceed cautiously. The causal assumptions require further prospective or longitudinal studies on the topic.

INTRODUCTION

Considerable attention surrounds the potential for long-term problems in athletes with high exposure to head impacts during a career in collision sport.¹ There is evidence^{2–4} supporting an association between long-term cognitive, neurobehavioural, psychiatric problems and participation in sport.⁵ Given that sports-related concussion is a common injury and that concussive or subconcussive blows to the head or body are an inevitable consequence of sports participation, if a causal relationship between these impacts and later-life neuropsychiatric disease exists, then potentially an enormous number of retired athletes would be at risk.⁶ Based on the published case studies, however, one estimate is that fewer than 4% of retired US professional football players may be at risk for this condition⁷ rather than all exposed athletes, raising the issue that this may not be a part of impact exposure but rather due to other as yet unidentified factors.

A recent report by McKee *et al*⁸ has suggested that chronic traumatic encephalopathy (CTE) may represent a unique tauopathy with characteristic pathological stages; however, the published methodology does not allow a causal relationship to be determined between concussion or subconcussive impacts being a risk factor for CTE.

The purpose of this paper was to review the current state of evidence for CTE in retired athletes and to consider the potential differential diagnoses that require consideration when retired athletes present with cognitive and psychiatric problems.

METHODS

Articles were retrieved via online database searching, hand-searching reference lists and cited reference searches. The online databases of MEDLINE, CINAHL, EMBASE, Mosby's Index, PsycEXTRA, PsycINFO and Scopus were searched. Key words, MeSH terms and combinations of these were used to systematically search the databases. Key words included CTE, dementia pugilistica, punch drunk syndrome, traumatic encephalopathy, CTE, repetitive head injury, sports concussion, multiple concussions, chronic concussions, subconcussive blow and sports-related traumatic brain injury (TBI).

CLINICAL SYNDROMES OF LONG-TERM PROBLEMS FOLLOWING CONCUSSION

The clinical characterisation of the presentations of athletes with chronic postconcussive symptoms is poorly defined and may reflect intrinsic differences (eg, genetic) between individuals rather than the oversimplified understanding that these syndromes are due to concussive or subconcussive trauma alone. In some cases, the persistent 'postconcussive' symptoms may, in large part, be due to unrecognised depression or anxiety,⁹ which may be labelled as 'overtraining' or even athlete 'burnout'.¹⁰

If we assume concussion is the acute clinical syndrome with 90–95% of cases recovering in less than 10 days, then there is a small group where *prolonged postconcussive symptoms* exist, that is, where the symptoms persist more than 10 days after a single episode of acute concussion (5–10% of cases) but full recovery eventually ensues usually within a matter of weeks.¹¹ The clinical and neuropsychological features are those of a resolving acute injury and perhaps this entity should be considered as part of the acute syndrome.

In addition to the acute syndrome, a number of distinct but as yet poorly defined clinical subsets exist that may shed light on the process of recovery

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from concussive injury. These subsets are based on clinical experience and are not supported by hard scientific evidence at this time. Nevertheless, it may be useful to consider the full spectrum of presentations of athletes with persistent or permanent symptoms and the terminology of these states.

These include:

- ▶ Prolonged postconcussive symptoms as discussed above.
- ▶ Persistent postconcussion symptoms after one or more concussions where recovery is slow and may take months to years.¹² The DSM-IV criteria for Post Concussion Syndrome is invoked only if the symptoms last beyond 3 months. Approximately 80% of such patients recover fully with time.¹³ Cognitive testing reveals mainly attentional deficits, and structural neuroimaging is normal.
- ▶ Permanent PCS—as per above, but these individuals do not recover fully, and this has been estimated at between 10% and 20% of all cases of persistent concussion symptoms. Functional MR and/or electrophysiological change may be present, but normal structural neuroimaging is typical.¹⁴
- ▶ Proposed CTE where chronic cognitive and/or neurobehavioural dysfunction exists and a pathological diagnosis is subsequently confirmed.^{3 6} It is worth noting that there are cases where the clinical phenotype is the same as pathologically confirmed CTE cases; however, no neuro-pathological change is demonstrated at autopsy.⁸

As well as these broad categories, there are other athletes who de novo manifest mental health issues (depression, anxiety, suicide) or neurobehavioural problems in the absence of persistent or prolonged concussive symptoms dating from the time of an injury. Whether these represent a variant of the subsets above or simply reflect the high incidence of such disorders in society remains to be elucidated. The risk factors for such complications following concussion remain unclear, although they may be related to repeated concussions, at least in retrospective surveys.^{2 15} Prospective studies of head-injured individuals, with neuropathological and clinical verification, are needed to improve understanding of head trauma as a risk factor for sequelae.¹⁶

As well as clinical symptoms, there is some limited objective evidence of persistent neurophysiological, cognitive¹⁶ and radiological¹⁷ deficits up to 30 years following concussion.

PHYSIOLOGY OF CONCUSSION

Understanding the pathophysiology of concussion would be expected to lead to an improvement in the assessment of deficit and recovery following injury, and to facilitate the accurate classification of severity. For example, little is known about the anatomical localisation of common clinical features such as headache, loss of consciousness (LOC), difficulty with concentration, sleep disturbance and fatigue. Moreover, it is currently unknown whether mild TBI reflects a single clinical entity with a linear spectrum of injury or even distinct injury subtypes. It is hoped that this understanding may give some insight into whether in vivo diagnosis of CTE is possible.

In animal models following acute injury, the release of neurotransmitters and ionic fluxes occurs (known as the 'neurometabolic cascade'),¹⁸ which in turn leads to changes in cell membrane function. Animal studies suggest that, during the glucose metabolic depression phase (1–10 days postinjury), the brain is more vulnerable to repeat injury.¹⁸ Changes in the intracellular fluid status or the presence of axonal swelling may be detected using imaging techniques such as advanced diffusion weighted imaging (DWI), which also allow mapping of white

matter fibre tracts in the central nervous system.¹⁹ Preliminary studies have demonstrated DWI changes in the acute setting following mild TBI in a small cohort of adolescent patients with normal CT scans as well as in a cohort of asymptomatic professional boxers.²⁰ Functional neuroimaging techniques, for example, functional MRI (fMRI) have demonstrated changes in brain function following sport-related TBI.²¹ The main limitation of this technique is that it only reveals regions of the brain that are active in the specific cognitive task being studied. Another imaging modality, Functional Connectivity, is able to detect realtime resting state networks and may provide an alternative to fMRI for identifying brain subregions and networks that are affected in mild TBI.²² Other techniques such as MR spectroscopy (MRS) allow the detection of metabolic disturbances following mild TBI through the measurement of intracellular metabolites. Preliminary studies in a small cohort of collegiate athletes suggest a role of mitochondrial dysfunction in the postinjury metabolic depression.²³ Other studies using MRS have also demonstrated that the *N*-acetylaspartate/creatine ratio (which reflects neuronal cell damage) is related to injury severity and outcome even when white matter appears normal on MRI.²⁴

DEMENTIA RATES IN THE GENERAL POPULATION

Given that cognitive impairment is one of the key features of the proposed CTE, it is important to understand the risk of this in similar age groups in the general population. The reported incidence and prevalence rates of dementia vary according to the population studied, and prevalence approximately doubles every 5 years from the age of 65 years. The incidence of dementia (all causes) in the 30-year-old to 64-year-old group is 54/100 000, and for the 45-year-old to 64-year-old group, it is 98.1 : 100 000.²⁵

Whether mild, or repetitive mild TBI (mTBI) increases an individual's risk for developing Alzheimer's disease (AD) has been a long-standing topic of contention. While mixed results have been reported regarding the association between moderate and severe TBI and AD, the association between mTBI and AD appears to be less strong. For example, in a systematic review, Bazarian *et al*²⁶ concluded that there was limited support for the notion that mTBI (with LOC) results in an increased risk for later life AD. Further, the authors also concluded that there was insufficient evidence to determine whether an association between mTBI (without LOC) and AD exists.

DEPRESSION IN THE GENERAL POPULATION

Depression and cognitive impairment are both common conditions in older age, and they frequently occur together. A US-based epidemiology study examining major depression reported that the incidence of this disorder in men aged 25–34, 35–44 and 45–54 years was 12.3%, 11.0% and 8.6%, respectively.²⁷ This is much higher among individuals with dementia, where it has been reported that 25–50% of all patients with dementia will develop depression at some point over the course of their illness.^{28 29}

DEPRESSION, COGNITIVE IMPAIRMENT AND NEURODEGENERATIVE DISEASES IN FORMER ATHLETES

In a study of retired National Football League (NFL) players, responses to questions regarding clinical depression revealed that 269 (11.1%; 95% CI 9.9% to 12.3%) of 2434 respondents reported a previous diagnosis of clinical depression. In comparison to retired NFL players with no history of concussion, retired players with a history of one or two previous

concussions were 1.5 times more likely to be diagnosed with depression, while those with a history of three or more previous concussions were found to be three times more likely to be diagnosed with depression.¹⁵

The results of a screening survey of 513 retired NFL players (average age=61 years) reported that 35% produced scores suggesting a possibly mild cognitive impairment.² In another recent study of former NFL players, the death rate from neurodegenerative diseases was three times greater than that of the general population, although the number of cases in this study was small. More specifically, the rates of diagnosis of AD and amyotrophic lateral sclerosis (ALS) were found to be four times higher in former NFL players than the general population.³⁰ Of the 334 former athletes in this cohort, seven (2.1%) had ALS listed on their death certificates. This issue of ALS is in keeping with the TDP43 tauopathy seen in CTE cases.³¹

BRAIN PATHOLOGY IN NORMAL AGEING

The Honolulu-Asia Aging Study provides a unique longitudinal model of ageing and disease and offers considerable insight into what may be considered *normal ageing* from a pathological standpoint.³² From 1991 to 1993, 3 yearly follow-up clinical and formal neuropsychological examinations have been conducted in 3508 men who were free of dementia and a total of 593 standardised brain autopsies have been conducted.³²

Postmortem brain examination demonstrated diverse pathology, even in individuals clinically diagnosed as 'pure AD,' with fewer than 50% demonstrating the typical pathological features of AD. Furthermore, neuropathological abnormalities were also observed in approximately 40% of neuropsychologically normal patients.³²⁻³⁴ Similarly, disparity between clinical presentation (ie, living diagnosis) and postmortem neuropathology has also been demonstrated in other ageing study samples.³⁵⁻³⁶ It is now clear from these ageing studies that postmortem findings may not represent pathology and may not equate to clinical symptomatology or a syndrome³⁷ and may be seen in cognitively normal older adults. Whether the 'gold standard' of neuropathology in neurological disease is true has been recently questioned.³⁸

THE 'CLASSIC' SYNDROME OF CTE IN PROFESSIONAL BOXERS

In 1928, Dr Harrison Martland first described the 'punch drunk' or CTE state in retired boxers.³⁹ The incidence of classic CTE has proven difficult to establish, due, in the main, to a lack of prospective studies. Roberts,⁴⁰ who randomly sampled 250 retired boxers from a cohort of 16 781 UK boxers registered between 1929 and 1955, reported that in 37 boxers (17%) clinically demonstrable lesions of the nervous system were present. Notably, the oldest boxers in this cohort fought in the late 1800s, in an era where bare-knuckle championships were still conducted, frequent fights occurred even when boxers were concussed and there was little medical supervision or weight matching of boxers; however, only 11 of the 37 cases were elaborated on in this study. A close analysis of the clinical details raises suspicion regarding the certainty of the diagnosis of CTE in most cases.⁴¹

In the published cases, cognitive deterioration was typically detected 10–20 years subsequent to cessation of exposure to repetitive head trauma (ie, postretirement).⁶ Interestingly, in all cases where details were provided, the physical signs but not the cognitive deficits progressed postretirement. There are two distinct clinical syndromes that have been demonstrated in this data set; the first (which occurs in approximately 70% of cases) includes dysarthria, pyramidal problems and cognitive deficits.

As the disease manifests clinically, these cognitive abnormalities include difficulties in memory, information processing speed, insight and orientation. The second clinical syndrome (in approximately 30% of cases) includes dysarthria and pyramidal problems, but with intact cognitive abilities.⁴⁰⁻⁴²⁻⁴⁴ Movement disorders were reported to be present in approximately two in every five reported cases.³

One of the difficulties of ascribing the clinical syndrome solely to boxing is the presence of comorbidities plus risk factors for other conditions that may also result in cognitive deterioration. A case report of a champion boxer with cognitive decline highlights these issues of multifactorial causation of cognitive problems.⁴⁵

The neuropathological features of classic CTE have been described in detail⁴⁶ and typically result in a cavum septum pellucidum with septal fenestration; cerebellar scarring involving Purkinje cell loss and thinning of the granular layer; degeneration of the substantia nigra and locus caeruleus; and diffuse neurofibrillary tangles (NFT) involving the medial temporal region, uncus, amygdala, hippocampus, parahippocampal gyrus and fusiform gyrus along with the more lateral temporal, insular and frontal cortices. The extent of neuropathology appears to be positively correlated with the level of exposure.⁴⁶ Roberts *et al*⁴⁴ examined 14/15 brains originally described by Corsellis *et al*,⁴⁶ as well as six additional boxers' brains using immunocytochemistry, and 19/21 cases also demonstrated widespread diffuse amyloid deposits.

Recently, a propagation model of neurodegeneration has been proposed, suggesting that tau positive NFT phosphorylation may progressively spread from one neuron to adjacent neurons in the absence of ongoing triggering factors.⁴⁷⁻⁵⁰ The implication of this finding is that the neuropathological findings may differ or progress in different stages of the condition. This finding may help resolve the differences between reports of specific sites of tau positive NFT deposition in CTE and other studies that suggest widespread changes.

THE 'MODERN' SYNDROME OF CTE IN FOOTBALLERS

Recent publications³⁻⁵¹ on CTE in retired athletes have introduced a number of conceptual changes in the clinical features⁵²⁻⁵³ and outcomes, and also the neuropathology, as compared with the classic entity described by Roberts⁴⁰ and Corsellis *et al*⁴⁶ in their boxing subjects.

PUBLISHED MODERN CTE CASES

A number of cases of CTE in retired athletes have been published. The index case was reported by Omalu and colleagues in 2005, with additional cases reported subsequently.⁴⁻⁵¹⁻⁵⁴⁻⁵⁶ Recently, the Boston University group published their experience of CTE, with 80 athlete brain donors (22 of whom were also military veterans) with a history of repetitive brain injury, and they found that 80% of these cases demonstrated the characteristic pathology for CTE.⁸

Signs and symptoms

The modern CTE description suggests that symptoms such as gait disorders, speech slowing and extrapyramidal signs may be present; however, neuropsychiatric and behavioural symptoms tend to predominate early.⁵⁷ The most common symptoms reported are mood disorder (mainly depression), paranoia, agitation, social withdrawal, poor judgement and aggression. Cognitive impairment tends to emerge as the major neuropsychiatric feature in the latter stages⁵⁸⁻⁵⁹ and typically includes impairment across the domains of orientation, memory,

language, attention, information processing speed and executive functioning.⁶⁰ These cognitive symptoms have been proposed to progress in a somewhat predictable manner,³ whereas the classic CTE entity reported little progression of cognitive deficits.⁴⁶

Neuropathology

The reported neuropathological characteristics of both entities (classic and modern CTE) appear to be more closely related and share a number of common features such as fenestrated septum pellucidum, cerebral atrophy, tau+NFT inclusion (although found in greater amounts in modern CTE), β -amyloid deposition (found in less amounts in modern CTE), reduced pigmentation of the substantia nigra and locus caeruleus, and enlarged ventricles. The qualitative description of modern CTE characterises the neuropathological change as also including fronto-temporal lobe atrophy with extensive tau pathology distributed throughout the neocortex, medial temporal lobe, diencephalon, brainstem and spinal cord. In the 51 cases reviewed by Gavett *et al*⁷ 61 diffuse amyloid plaques were found in 24 (47%), neuritic amyloid plaques in 13 (27%) and amyloid angiopathy in 3 (6%). In the Boston study,⁸ amyloid deposition was noted in 44% of the CTE cases.

Although a number of similarities in neuropathological findings have been reported across the modern CTE cases, there are also some important differences. McKee *et al*³ have reported a marked accumulation of tau-immunoreactive astrocytes, but this has not been observed in any of the cases examined by Omalu *et al*.⁶² Omalu *et al*⁶³ have reported the skip-phenomenon, with a propensity to lobar cortical distribution in the absence of prominent periventricular topographic distribution, which has not been described in the McKee *et al*³ cases.

A defining neuropathological feature of the modern CTE entity is abundant filamentous tau lesions, of which the patterns of expression are considered unique, occurring in the absence (or at least relative scarcity) of β -amyloid deposits.³ 8 Prominent filamentous tau inclusions and brain degeneration in the absence of β -amyloid deposits are also considered the sine qua non of a number of neurodegenerative tauopathies. It is worth noting that a number of the degenerative tauopathies, such as behavioural variant fronto-temporal dementia, share many of the clinical and pathological features of 'modern' CTE.^{64–69}

DISCUSSION

The recent autopsy cases differ from the classic CTE description across a number of characteristics including age of onset, progression, assumed predominate (clinical) features and diagnostic criteria. It has also been reported that these recent cases of modern CTE, speculated to be a consequence of concussive and subconcussive blows, are characterised by a distinct neuropathological profile³ 61 63 and manifest primarily as a tauopathy.⁸ Although many of the reported macroscopic neuropathological features are common among the original and newer descriptions of CTE, the different distribution of tau-immunoreactive astrocytes distinguishes the newer description with preferential involvement of the superficial cortical layers occurring on a background of relative scarcity of β -amyloid plaques.

At present, there are no published epidemiological, cross-sectional or prospective studies relating to modern CTE. Owing to the nature of the published studies, being case reports or pathological case series, 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.⁷⁰

The extent to which age-related changes, psychiatric or mental health illness, alcohol/drug use or coexisting dementing illnesses contribute to this process is largely unaccounted for in the published literature. In addition, consideration for the potential genetic risk in those athletes with a family history of neurodegenerative disease and the extent to which this contributes to the clinical and pathological profiles also require further investigation.⁴¹

SUMMARY

At present, the interpretation of causation in the modern CTE case studies should proceed cautiously. The causal assumptions require further prospective or longitudinal studies on the topic. Ultimately, scientific research might establish that participation in contact sports leads to a distinct neuropathological syndrome, and this neuropathology causes psychiatric, cognitive and physical problems, but this cause and effect relationship remains to be shown scientifically.

Author affiliations

¹The Florey Institute of Neuroscience and Mental Health, Heidelberg, Australia

²Faculty of Kinesiology, Sport Injury Prevention Research Centre, Calgary, Alberta, Canada

³Faculty of Medicine, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

⁴Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA

⁵Burke Rehabilitation Hospital, White Plains, New York, USA

⁶Neuropsychiatry Service, HNE Mental Health Service, Newcastle, New South Wales, Australia

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REFERENCES

- Gregory S. The problem with football. Our favorite sport is too dangerous. How to make the game safer. *Time* 2010;175:36–43.
- Guskiewicz KM, Marshall SW, Bailes J, *et al*. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery* 2005;57:719–26.
- McKee AC, Cantu RC, Nowinski CJ, *et al*. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol* 2009;68:709–35.
- Omalu BI, Hamilton RL, Kambou MI, *et al*. Chronic traumatic encephalopathy (CTE) in a National Football League Player: case report and emerging medicolegal practice questions. *J Forensic Nurs* 2010;6:40–6.
- Cantu RC. Chronic traumatic encephalopathy in the National Football League. *Neurosurgery* 2007;61:223–5.
- McCroly P. Sports concussion and the risk of chronic neurological impairment. *Clin J Sport Med* 2011;21:6–12.
- Gavett BE, Cantu RC, Shenton M, *et al*. Clinical appraisal of chronic traumatic encephalopathy: current perspectives and future directions. *Curr Opin Neurol* 2011;24:525–31.
- McKee AC, Stein TD, Nowinski CJ, *et al*. The spectrum of disease in chronic traumatic encephalopathy. *Brain* 2012;136:43–64.
- Chen JK, Johnston KM, Collie A, *et al*. A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. *J Neurol Neurosurg Psychiatry* 2007;78:1231–8.
- Schwenk TL, Gorenflo DW, Dopp RR, *et al*. Depression and pain in retired professional football players. *Med Sci Sports Exercise* 2007;39:599–605.
- Makdissi M, Darby D, Maruff P, *et al*. Natural history of concussion in sport: markers of severity and implications for management. *Am J Sports Med* 2010;38:464–71.
- King N. Mild head injury: neuropathology, sequelae, measurement and recovery. *Br J Clin Psychol/Br Psychol Soc* 1997;36(Pt 2):161–84.
- Sullivan KA, Edmed SL, Cunningham LC. A comparison of new and existing mild traumatic brain injury vignettes: recommendations for research into post-concussion syndrome. *Brain Inj* 2013;27:19–30.
- King NS, Kirwilliam S. Permanent post-concussion symptoms after mild head injury. *Brain Inj* 2011;25:462–70.
- Guskiewicz KM, Marshall SW, Bailes J, *et al*. Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exercise* 2007;39:903–9.

- 16 De Beaumont L, Theoret H, Mongeon D, *et al.* Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain* 2009;132(Pt 3):695–708.
- 17 Kraus MF, Susmaras T, Caughlin BP, *et al.* White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain* 2007;130(Pt 10):2508–19.
- 18 Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train* 2001;36:228–35.
- 19 Metting Z, Rodiger LA, De Keyser J, *et al.* Structural and functional neuroimaging in mild-to-moderate head injury. *Lancet Neurol* 2007;6:699–710.
- 20 Zhang L, Heier LA, Zimmerman RD, *et al.* Diffusion anisotropy changes in the brains of professional boxers. *Am J Neuroradiol* 2006;27:2000–4.
- 21 Chen JK, Johnston KM, Collie A, *et al.* Behavioural and functional imaging outcomes in symptomatic concussed athletes measured with cogspport and functional MRI. *BJ Sport Med* 2004;38:659.
- 22 Waites AB, Briellmann RS, Saling MM, *et al.* Functional connectivity networks are disrupted in left temporal lobe epilepsy. *Ann Neurol* 2006;59:335–43.
- 23 Vagnozzi R, Signoretti S, Tavazzi B, *et al.* Temporal window of metabolic brain vulnerability to concussion: a pilot 1H-magnetic resonance spectroscopic study in concussed athletes—part III. *Neurosurgery* 2008;62:1286–95.
- 24 Garnett MR, Blamire AM, Corkill RG, *et al.* Early proton magnetic resonance spectroscopy in normal-appearing brain correlates with outcome in patients following traumatic brain injury. *Brain* 2000;123(Pt 10):2046–54.
- 25 Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. *J Neurol Neurosurg Psychiatry* 2003;74:1206–9.
- 26 Bazarian JJ, Cernak I, Noble-Haesslein L, *et al.* Long-term neurologic outcomes after traumatic brain injury. *J Head Trauma Rehabil* 2009;24:439–51.
- 27 Gonzalez HM, Tarraf W, Whitfield KE, *et al.* The epidemiology of major depression and ethnicity in the United States. *J Psychiatr Res* 2010;44:1043–51.
- 28 Olin JT, Katz IR, Meyers BS, *et al.* Provisional diagnostic criteria for depression of Alzheimer disease: rationale and background. *Am J Geriatr Psychiatry* 2002;10:129–41.
- 29 Steinberg EM, Rubinow DR, Bartko JJ, *et al.* A cross-sectional evaluation of perimenopausal depression. *J Clin Psychiatry* 2008;69:973–80.
- 30 Lehmann EJ, Hein MJ, Baron SL, *et al.* Neurodegenerative causes of death among retired National Football League players. *Neurology* 2012;79:1–5.
- 31 McKee AC, Gavett BE, Stern RA, *et al.* TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol* 2010;69:918–29.
- 32 White L. Brain lesions at autopsy in older Japanese-American men as related to cognitive impairment and dementia in the final years of life: a summary report from the Honolulu-Asia aging study. *J Alzheimers Dis* 2009;18(Pt 3):713–25.
- 33 Robinson JL, Geser F, Corrada MM, *et al.* Neocortical and hippocampal amyloid-beta and tau measures associate with dementia in the oldest-old. *Brain* 2011;134:3708–15.
- 34 Gelber RP, Launer LJ, White LR. The Honolulu-Asia Aging Study: epidemiologic and neuropathologic research on cognitive impairment. *Curr Alzheimer Res* 2012;9:664–72.
- 35 Snowden JS, Gibbons ZC, Blackshaw A, *et al.* Social cognition in frontotemporal dementia and Huntington's disease. *Neuropsychologia* 2003;41:688–701.
- 36 Sonnen JA, Larson EB, Crane PK, *et al.* Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Ann Neurol* 2007;62:406–13.
- 37 Da Cruz S, Cleveland DW. Understanding the role of TDP-43 and FUS/TLS in ALS and beyond. *Curr Opin Neurobiol* 2011;21:904–19.
- 38 Scheltens P, Rockwood K. How golden is the gold standard of neuropathology in dementia? *Alzheimers Demen* 2011;7:486–9.
- 39 Martland HS. Punch drunk. *J Am Med Assoc* 1928;19:1103–7.
- 40 Roberts AH. *Brain damage in boxers: a study of the prevalence of traumatic encephalopathy among ex-professional boxers.* London: Pitman, 1969.
- 41 McCrory P. Boxing and the risk of chronic brain injury. *BMJ* 2007;335:781–2.
- 42 Johnson J. Organic psychosyndromes due to boxing. *Br J Psychiatr* 1969;115:45–53.
- 43 Johnson J. The EEG in the traumatic encephalopathy of boxers. *Psychiatr Clin* 1969;2:204–11.
- 44 Roberts GW, Allsop D, Bruton C. The occult aftermath of boxing. *J Neurol Neurosurg Psychiatry* 1990;53:373–8.
- 45 Nowak LA, Smith GG, Reyes PF. Dementia in a retired world boxing champion: case report and literature review. *Clin Neuropathol* 2009;28:275–80.
- 46 Corsellis JA, Bruton CJ, Freeman-Browne D. The aftermath of boxing. *Psychol Med* 1973;3:270–303.
- 47 De Calignon A, Polydoro M, Suarez-Calvet M, *et al.* Propagation of tau pathology in a model of early Alzheimer's disease. *Neuron* 2012;73:685–97.
- 48 Liu L, Drouet V, Wu JW, *et al.* Trans-synaptic spread of tau pathology in vivo. *PLoS ONE* 2012;7:e31302.
- 49 Frost B, Jacks RL, Diamond MI. Propagation of tau misfolding from the outside to the inside of a cell. *J Biol Chem* 2009;284:12845–52.
- 50 Clavaguera F, Goedert M, Tolnay M. Induction and spreading of tau pathology in a mouse model of Alzheimer's disease. *Med Sci* 2010;26:121–4.
- 51 Omalu BI, Bailes J, Hammers JL, *et al.* Chronic traumatic encephalopathy, suicides and parasuicides in professional American athletes: the role of the forensic pathologist. *Am J Forensic Med Pathol* 2010;31:130–2.
- 52 Clausen H, McCrory P, Anderson V. The risk of chronic traumatic brain injury in professional boxing: change in exposure variables over the past century. *Br J Sports Med* 2005;39:661–4.
- 53 Ahmed OH, Sullivan SJ, Schneiders AG, *et al.* iSupport: do social networking sites have a role to play in concussion awareness? *Disabil Rehabil* 2010;32:1877–83.
- 54 Omalu BI, DeKosky ST, Hamilton RL, *et al.* Chronic traumatic encephalopathy in a national football league player: part II. *Neurosurgery* 2006;59:1086–92; discussion 92–3.
- 55 Omalu BI, DeKosky ST, Minster RL, *et al.* Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery* 2005;57:128–34; discussion 34..
- 56 Omalu BI, Fitzsimmons RP, Hammers J, *et al.* Chronic traumatic encephalopathy in a professional American wrestler. *J Forensic Nurs* 2010;6:130–6.
- 57 Jordan B. Neurologic aspects of boxing. *Arch Neurol* 1987;44:453–9.
- 58 Guterman A, Smith RW. Neurological sequelae of boxing. *Sports Med (Auckland, NZ)* 1987;4:194–210.
- 59 Jordan BD. Chronic traumatic brain injury associated with boxing. *Semin Neurol* 2000;20:179–85.
- 60 Costanza A, Weber K, Gandy S, *et al.* Review: contact sport-related chronic traumatic encephalopathy in the elderly: clinical expression and structural substrates. *Neuropathol Appl Neurobiol* 2011;37:570–84.
- 61 Gavett BE, Stern RA, McKee AC. Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. *Clin Sports Med* 2011;30:179–88, xi.
- 62 Omalu B, Hammers JL, Bailes J, *et al.* Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. *Neurosurg Focus* 2011;31:E3.
- 63 Omalu B, Bailes J, Hamilton RL, *et al.* Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. *Neurosurgery* 2011;69:173–83; discussion 83..
- 64 Rascovsky K, Salmon DP, Ho GJ, *et al.* Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. *Neurology* 2002;58:1801–8.
- 65 Rascovsky K, Hodges JR, Knopman D, *et al.* Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;134(Pt 9):2456–77.
- 66 Rascovsky K, Hodges JR, Kipps CM, *et al.* Diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD): current limitations and future directions. *Alzheimer Dis Assoc Disord* 2007;21:S14–8.
- 67 Hodges JR. Frontotemporal dementia (Pick's disease): clinical features and assessment. *Neurology* 2001;56(11 Suppl 4):S6–10.
- 68 Hodges JR, Davies RR, Xuereb JH, *et al.* Clinicopathological correlates in frontotemporal dementia. *Ann Neurol* 2004;56:399–406.
- 69 Hodges JR, Miller B. The classification, genetics and neuropathology of frontotemporal dementia. Introduction to the special topic papers: part I. *Neurocase* 2001;7:31–5.
- 70 Gaetz W, Macdonald M, Cheyne D, *et al.* Neuromagnetic imaging of movement-related cortical oscillations in children and adults: age predicts post-movement beta rebound. *Neuroimage* 2010;51:792–807.



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