Aging, Neurodegenerative Disease, and Traumatic Brain Injury: The Role of Neuroimaging

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Abstract

Traumatic brain injury (TBI) is a highly prevalent condition with significant effects on cognition and behavior. While the acute and sub-acute effects of TBI recover over time, relatively little is known about the long-term effects of TBI in relation to neurodegenerative disease. This issue has recently garnered a great deal of attention due to publicity surrounding chronic traumatic encephalopathy (CTE) in professional athletes, although CTE is but one of several neurodegenerative disorders associated with a history of TBI. Here, we review the literature on neurodegenerative disorders linked to remote TBI. We also review the evidence for neuroimaging changes associated with unhealthy brain aging in the context of remote TBI. We conclude that neuroimaging biomarkers have significant potential to increase understanding of the mechanisms of unhealthy brain aging and neurodegeneration following TBI, with potential for identifying those at risk for unhealthy brain aging prior to the clinical manifestation of neurodegenerative disease.

Key words: aging; Alzheimer's disease; chronic traumatic encephalopathy; neurodegenerative disease; remote traumatic brain injury

Introduction

THE RECENT SPIKING OF MEDIA INTEREST concerning the long-term effects of concussion in sport and chronic traumatic encephalopathy (CTE) has raised many questions for clinicians and researchers in the field of concussion and traumatic brain injury (TBI; we will use the terms concussion and TBI interchangeably as a concussion is a TBI. In general, the term “concussion” will be applied to milder TBIs, particularly those sustained in a sporting context.). Moreover, many patients who have sustained TBI are now concerned about the risk of dementia. If concussions sustained in high-level athletics can be linked to dementia, what about the long-term effects of TBI sustained in motor vehicle accidents and combat—the majority of which are mild in severity?

While there are many questions concerning the incidence and risk factors of CTE, a history of TBI is known to elevate the risk of neurodegenerative disease in general. Given the recent interest and wealth of research on sports-related TBI, much of what we discuss will be from the sports-related TBI literature but is relevant to TBI as defined more broadly. As such, the purpose of this article is to provide an overview of recent research on the relationship of TBI to neurodegenerative disease. We will describe the scope and limitations of this evidence, noting several challenges and future directions in this emerging body of research. We emphasize evidence from cognitive neuroscience and neuroimaging, which provide

promising biomarkers with potential for disease detection prior to the onset of clinical symptoms.

There are more than 5.2 million Americans currently living with dementia or degenerative disease. The economic costs of dementia are estimated at approximately \$203 billion dollars a year; these are anticipated to rise to \$1.2 trillion by 2050.¹ According to the Centers for Disease Control and Prevention, each year approximately 1.7 million Americans experience a TBI.² Another study using a broader surveillance of TBI, which included the number of hospitalizations, emergency department visits, and deaths due to TBI, estimated the incidence of TBI each year to be 2.4 million.^{3,4} Most TBI research has not considered the marked heterogeneity in TBI mechanisms (e.g., sports concussion versus road traffic accidents) that likely affects outcomes and the consistency of findings across studies. Nonetheless, if even a small portion of dementia outcome could be accounted for by TBI history, the public health implications would be significant. These implications broaden to the extent that TBI contributes to unhealthy brain aging causing cognitive deficits but falling short of criteria for dementia diagnosis.

Much of the research concerning CTE is based on studies of neuropathological specimens. These studies are supported by retrospective analyses of cognitive and behavior changes based on reports from family members and the deceased. While there have been high quality empirical studies of such cases,^{5–8} these do not

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reflect the spectrum of outcomes of remote effects of TBI.^{9,10} Indeed, as will be reviewed below, CTE is only one of several neurodegenerative diseases associated with TBI.

Which neurodegenerative conditions are associated with remote history of TBI?

The vast majority of research on TBI concerns effects in the acute, sub-acute, and chronic recovery phases. Neuroimaging research has identified neural correlates of deficits at the acute and chronic phases, including parenchymal volume loss,¹¹ disrupted integrity of white matter as assessed with diffusion tensor imaging (DTI),¹² and changes in brain activation associated with task performance¹³ and with resting state.¹⁴ While progressive changes (i.e., volume loss or functional changes) can be observed immediately following the injury, these are considered stable at one or at most, two years post-injury in severe cases,¹⁵ and in weeks to months following the injury in mild cases.¹⁶ Few studies have addressed longer-term degeneration or atrophy following this period.^{17,18}

The question of age-related or neurodegenerative changes occurring decades later is addressed in retrospective studies. A recent review failed to find conclusive evidence that a history of mild TBI increases the risk of developing dementia and chronic cognitive impairment.¹⁹ Yet this review included only eight studies (six of which assessed outcomes in children) with follow-up at one year and only one study directly addressing dementia risk. Below, we review the evidence for risk of select common neurodegenerative diseases across the spectrum of TBI severity: Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal lobar degeneration, and multiple sclerosis (MS), followed by amyotrophic lateral sclerosis (ALS) and CTE, which are not as common but have been linked to TBI history.

Alzheimer's disease

A remote history of TBI elevates the risk of developing AD in a dose-dependent fashion^{20,21} and lowers the age of onset of AD.^{22,23} Recent positron emission tomography (PET) and neuropathological studies also have shown that single-dose TBI may be associated with AD-related neuropathology,²⁴ although not all studies find this association.²⁵ Diffuse axonal injury (DAI), the main neuropathology of TBI,²⁶ is associated with buildup of amyloid precursor protein due to cytoskeletal disruption, which is cleaved to form amyloid- β ($A\beta$), promoting formation of amyloid plaques characteristic of AD.²⁷ This process may be enhanced in individuals with at least one copy of the *ApoE* $\epsilon 4$ allele, which is itself associated with increased release of amyloid precursor proteins and increased risk of AD by association with $A\beta$ plaques. While the risk of developing AD is increased twofold to threefold by the possession of one *ApoE* $\epsilon 4$ allele and fivefold by the presence of two *ApoE* $\epsilon 4$ alleles,²⁸ this risk increases to 10-fold in individuals with a history of TBI.²⁹ (See Guo and colleagues for a negative finding.³⁰)

Parkinson's disease

PD is characterized by damage to dopaminergic neurons in the substantia nigra and midbrain and the presence of Lewy bodies.³¹ A history of TBI has been shown to increase the risk of developing PD³² and is linked to lower age of PD onset.³³ There is evidence that the risk of PD following TBI is associated with TBI severity and that mild TBI without loss of consciousness does not confer

enhanced risk.³⁴ Individuals with a history of TBI have been shown to have an earlier onset of PD, compared with their sibling with no history of TBI.³³ Moreover, there is an association between *ApoE* genotype and the onset of PD, with *ApoE* $\epsilon 4$ carriers showing a greater risk and earlier onset of PD.³⁵ However, it remains to be determined whether there is an interaction between *ApoE* status, TBI, and risk of PD.

Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) is associated with the degeneration of the frontal and temporal lobes, with behavioral variant frontotemporal dementia (FTD), semantic dementia, or progressive non-fluent aphasia, depending on the location of pathology at the time of disease onset.³⁶ FTLD pathology includes accumulation of either tau or TAR DNA-binding protein of approximately 43 kd (TDP-43)-positive cellular inclusion bodies, with some subtypes showing ubiquitin positive inclusions and mutations to other proteins (e.g., fused in sarcoma protein, also affected in familial ALS).³⁷ A history of TBI has been associated with an increased risk of developing FTLD,³⁸ possibly due to the colocalization of anterior temporal and frontal pathology in the two diseases.³⁹ FTLD with TDP-43 inclusions has been seen in association with CTE,⁷ suggesting that there may be similar mechanisms between the two diseases. Like AD, CTE, and ALS, *ApoE* status is a risk factor for the development of FTLD. However, which allele increases FTLD risk is still debated. Lehman and colleagues⁴⁰ have shown that individuals who are *ApoE* $\epsilon 2$ positive have a higher risk of FTLD, while others have shown increased risk and earlier onset of FTLD in individuals who are *ApoE* $\epsilon 4$ positive.⁴¹

Multiple sclerosis

MS is a progressive anti-inflammatory disease of the spinal cord and brain characterized by inflammation, demyelination, astrogliosis, neuronal and axonal degeneration, and the development of sclerotic plaques in the later stages of the disease.⁴² As in CTE, an accumulation of hyperphosphorylated tau has been found in the secondary progressive stage of the disease.⁴² Recent studies have shown head injury to be a risk factor for the development of MS.^{43,44} (For a negative finding, see Pflieger and colleagues⁴⁵ and Goldacre and colleagues.⁴⁶) It is hypothesized that head trauma, even mild TBI or concussion, causes alterations in the blood brain barrier, allowing foreign elements to enter the nervous system, which can lead to the development or enlargement of lesions and make the system more vulnerable to the development of sclerotic plaques.^{47,48} As with the other neurodegenerative diseases discussed, there is an association between the *ApoE* $\epsilon 4$ allele and MS. In particular, the *ApoE* $\epsilon 4$ allele has been associated with greater cognitive impairments, more aggressive or severe forms of the disease,^{49,50} faster disease progression,^{51,52} and greater lesion load as shown on magnetic resonance imaging (MRI),⁵³ although others have failed to find a link between the *ApoE* $\epsilon 4$ allele and MS.^{54–56} To the best of our knowledge, there is no known evidence of an association between the *ApoE* $\epsilon 4$ allele, MS, and TBI.

Amyotrophic lateral sclerosis

ALS is a rapid progressive neurodegenerative disease characterized by progressive damage to motor neurons in the spinal cord, brain stem, and cortex.⁵⁷ Damage to the motor neurons produces astrogliosis in the anterior horns of the cervical and lumbar enlargements; damage to the pyramidal tracts in the spinal cord and

pyramidal cells in the precentral gyrus also is seen.⁵⁸ Like CTE, TDP-43 proteinopathy also is prevalent in ALS.⁶ Elevated rates of ALS, relative to the general population, have been noted in professional soccer players⁵⁹ and American football players,⁶⁰ as well as in military veterans,⁶¹ all of which are associated with a high risk of TBI. There is evidence that the increased risk of ALS following TBI is associated with repetitive TBI rather than a single dose, particularly when exposure occurred 10–15 years prior to diagnosis.⁶² While there is an association between the *ApoE* $\epsilon 4$ allele and ALS, there is no evidence that this association interacts with TBI dosage.⁶³

Chronic traumatic encephalopathy

CTE, formerly known as dementia pugilistica, was originally described in boxers.⁶⁴ More recently, it has been associated with repetitive concussions in other sports (e.g., American football).⁶⁵ CTE is associated with progressive changes in memory, executive functioning, emotion (particularly depression), and impulse control, as well as Parkinsonism,^{66,67} with evidence for a distinction between syndromes dominated by mood and behavior (earlier onset) versus cognitive impairment (later onset, determined retrospectively).⁸ CTE has been observed as early as the late teenage years.⁶⁸ In professional athletes, symptoms of CTE are typically seen eight to 10 years after the individual retires from play.^{5,7}

The gross neuropathology of CTE is characterized by global volume reduction and ventricular enlargement; callosal thinning; atrophy in the medial temporal lobes (MTLs), mammillary bodies, and brainstem; fenestrated cavum septum pellucidum; and scarring and neuronal loss of the cerebellar tonsils.⁵ Microscopically, CTE is characterized by deposition of hyperphosphorylated tau (in the form of neurofibrillary tangles) and glial tangles, with accompanying axonal damage distributed in the depth of the cortical sulci, around vessels, and in the subpial region—a pattern not found in other neurodegenerative conditions. Beta amyloid deposition is seen only in a subset of cases.⁵ CTE is associated with dot-like or spindle-shaped tau-positive fibrillar astrocytic tangles in white matter, which differ from the threadlike tangles typically seen in AD, suggesting that damage associated with CTE may be at the axonal level.⁵ CTE also is associated with TDP-43 proteinopathy throughout the brain and spinal cord in severe cases. This has been associated with motor neuron disease, which occurs in some individuals with CTE,⁶ AD, and frontotemporal lobar degeneration.⁶⁹ McKee and colleagues⁷ have described four stages of CTE progression based on neuropathological characteristics and behavior, although the behavioral changes were determined retrospectively. Provisional research diagnostic criteria for the diagnosis of traumatic encephalopathy also have been proposed.⁶⁷ The neuropathological presentation of CTE is often complicated with multiple comorbidities, particularly overlapping proteinopathies.^{9,10} In the largest series of CTE cases published to date, 25 of 68 cases (37%) had neuropathological evidence of ALS, AD, Lewy body disease, or FTLT.⁷

The mechanisms of CTE remain unclear but it has been associated with neuronal loss due to acceleration and deceleration forces during TBI, release of inflammatory agents and excitatory neurotransmitters, and focal ischemia.^{5,70} As is the case for AD, the changes seen with DAI could start a pathologic cascade that results in the development of CTE. Further, it has been suggested that following TBI, once these cascades begin, they continue for years, ultimately resulting in the development of CTE in individuals who are susceptible to the disease.⁵ There is evidence that *ApoE* status is

associated with CTE, although the nature of the association is unclear, with evidence showing an association with the $\epsilon 4$ allele⁸ or with the $\epsilon 3$ allele.⁶⁸ Thus, it could be suggested that *ApoE* status interacts with TBI to produce a pathological response, such as the deposition of amyloid after TBI,⁷¹ influencing the development of neurodegenerative disease such as CTE and AD as demonstrated in mouse models of TBI.⁷²

Summary

TBI is associated with increased risk of neurodegenerative disease, although research on the mechanisms conferring increased risk of neurodegenerative disease following TBI is at an early stage. While there is evidence that neurodegenerative disease may be a direct result of TBI neuropathology in the case of CTE, there also is evidence that risk is mediated indirectly by TBI neuropathology (for example in AD, especially in carriers of one or two *ApoE* $\epsilon 4$ alleles). The overlap in neuropathology (e.g., TDP-43 inclusions in FTLT, ALS, and CTE) suggests potential common mechanisms, yet in other cases the pathologies can be distinct (e.g., CTE, AD, and MS). TBI characteristics, such as dose, timing, and repetition, may exert differential influences on specific neurodegenerative conditions. For instance, there is evidence that more severe TBI (i.e., with significant loss of consciousness, at minimum) is required to detect increased risk of AD and PD, yet CTE and ALS are associated with repetitive mild TBI not necessarily involving loss of consciousness in athletes.

Neuroimaging Biomarkers

A crucial goal of dementia research is to identify people in the preclinical phase of disease progression. Although beta-amyloid and hyperphosphorylated tau are neuropathological hallmarks of dementia syndromes associated with TBI, their detection in vivo is either invasive (i.e., lumbar puncture) or expensive (i.e., amyloid imaging with PET). Promising advances also have been made in using PET imaging to measure tau protein deposits in the brains of American football players⁷³; however, the PET binding agent used (FDDNP-PET) does not yet differentiate between deposition of tau and amyloid beta proteins in the brain. The association of these biomarkers with clinical signs of dementia is imperfect. For instance, healthy adults can have positive amyloid PET scans⁷⁴ and similar levels of A β 1–42 in cerebrospinal fluid (CSF) as patients with Alzheimer's disease.⁷⁵

Standardized neuropsychological testing provides useful information concerning cognitive changes following TBI,^{76,77} yet it is inconsistently sensitive to more subtle but functionally significant deficits in speeded information processing, executive function, and attention that can be seen in association with focal frontal or diffuse damage following TBI.^{78–80} Most neuropsychological tests lack alternate forms that are necessary for serial assessments in longitudinal studies of chronic TBI effects. Very few studies have examined long-term neuropsychological outcomes in individuals with remote TBI.^{81,82}

Compared with biomarkers derived from CSF, PET imaging, or neuropsychological testing, neuroimaging measures derived from MRI and electroencephalography (EEG) are relatively non-invasive, easily administered, and repeatable, enabling application in larger-scale longitudinal studies. Research on mild cognitive impairment (MCI) and its conversion to early AD provides an example of the application of such neuroimaging biomarkers with the potential for identification of risk prior to the evolution of clinically detected dementia. For example, features of structural MRI, particularly

those involving the MTL, predict conversion from MCI to AD as well as or better than CSF markers.⁸³ At the systems level, the functional MRI technique, both at rest and in response to a memory challenge, provides additional information concerning differentiation of normal aging, MCI, and AD, even when structural measures of MTL anatomy are undifferentiated across groups.⁸⁴

Application of sensitive cognitive neuroscience methods to those at risk for neurodegenerative disease at a stage prior to disease onset would contribute to detection of risk and understanding of neural correlates of the interaction between TBI and neurodegenerative disease, enabling intervention prior to the onset of disease-related impairment. We review the sparse literature on the application of such techniques in individuals with a remote history of TBI. Although much of this research involves mild TBI, or concussion, in sport, it can be extended to TBI in general.

Quantitative structural MRI

TBI is associated with changes in cortical thickness and ventricular size, as well as abnormalities in white matter that are associated with cognitive changes in adults^{11,12} and in children and youth,⁸⁵ possibly synergistically enhancing age-related volume loss and promoting the development of cognitive deficits and neurodegenerative disease.⁸⁶ Yet few studies have examined such changes in individuals with a remote history of TBI using quantitative structural neuroimaging.

Compared with former university athletes with no history of concussion, athletes with a history of concussion sustained 30 years earlier had enlarged lateral ventricles and enhanced age-related reductions in cortical thickness in the frontal, parietal, and temporal lobes.⁸⁷ In a study of retired National Football League (NFL) players with a remote history of concussion, Hart and colleagues⁸⁸ assessed white matter lesions on fluid-attenuated inversion recovery (FLAIR) images, hemosiderin on gradient echo images, white matter integrity as assessed by fractional anisotropy (FA), a measure derived from DTI, and blood flow as assessed through arterial spin labeling (ASL). Significant effects were observed for lesion load on FLAIR, white matter integrity on FA, and blood flow on ASL but only in those already diagnosed with cognitive impairment, MCI, or depression; no differences were observed for non-cognitively-impaired NFL alumni with a concussion history. Thus, one limitation of this study is the inability to differentiate the effects of cognitive impairment and depression in general from concussion history.

Functional MRI: Blood oxygen level-dependent activation studies

Functional MRI (fMRI) is sensitive to the effects of mild TBI in the early phases of recovery, particularly on tasks of working memory, where patients with mild TBI demonstrate increased prefrontal brain activation at lower levels of task difficulty than is the case for healthy controls.⁸⁹ Concussed athletes also show working-memory-related changes in prefrontal activation during fMRI scanning.⁹⁰ (For pre- and post-injury effects in prospectively tested athletes, see Jantzen and colleagues.⁹¹) Importantly, these changes can be observed in the absence of group differences in task performance, indicating that the effects reflect a neuroimaging marker of concussion at a greater level of sensitivity than task performance.

Similar findings have been observed in recent studies of athletes with a remote history of concussion. In a study of retired American professional football players with memory complaints, those with

high (three or more concussions) concussion dose were differentiated from those with low (less than three concussions) concussion dose on a relational memory task that is sensitive to behavioral and neural changes in MCI, although these two groups were not differentiated in terms of task performance.⁹² Limitations of this study included an inability to compare the retired athletes with healthy controls due to the control group's atypical activation patterns, and restriction of the concussion sample to those with memory complaints. In a study using a well-validated test of executive functioning, retired American professional football players showed enhanced prefrontal activation relative to controls, with the former measure correlated with number of removals from play due to concussion.⁹³ Functional connectivity analyses indicated reduced frontoparietal connectivity in the athletes relative to controls. Taken together, these two studies suggest that task-related patterns of brain activation are sensitive to concussion effects in the very chronic phase following repetitive TBI, with similar patterns to that seen in the acute phase, even when task performance is matched across groups. In spite of the significant limitations in selection bias in these studies, where retired athletes self-refer due to concerns about their cognitive functioning, there is consistency in the finding of enhanced prefrontal recruitment, echoing studies in diffuse injury due to moderate-severe TBI,⁹⁴ aging,⁹⁵ and dementia,⁹⁶ where such recruitment is regarded as compensatory.⁹⁷

Electroencephalography: Event-related potential studies

Electrophysiological measures are sensitive to damage associated with TBI. The advantages of EEG over MRI include lower cost, ease of acquisition, and absence of MRI exclusion criteria (i.e., claustrophobia, metal in body, size) that result in significant data loss. Moreover, EEG has a higher temporal resolution and is therefore sensitive to neural changes at the millisecond level that may differentiate those at risk for neurodegenerative disease from those who are not.

The P300 is an evoked response demonstrated by a positive deflection over the midline electrode sites occurring between 250–500 msec in tasks that assess working memory, attention, and novelty or target detection. Abnormalities in the P3 amplitude and latency also have been shown in university alumni athletes who experienced a concussion 30 years before testing, most of whom experienced fewer than three concussions,⁹⁸ mirroring findings from more acutely concussed athletes.⁹⁹ The results were significant relative to those of a comparison group of university alumni athletes with no history of concussion and similar performance on the event-related potential (ERP) task, providing a well-matched control sample in terms of education and physical conditioning. The neurophysiological changes in working memory and attention components in the concussion group were accompanied by deficits on neuropsychological tests and by neurophysiological and behavioral evidence of motor system dysfunction.

Summary and recommendations

The results of quantitative structural MRI, fMRI, and EEG studies converge to suggest that functional neuroimaging changes can be observed *in vivo* in individuals with a very remote history of TBI. The remote changes are similar to those observed in the acute, sub-acute, and chronic (i.e., one to five years) stages following TBI. Although cognitive and neuroimaging effects of TBI recover over time, these may re-emerge with aging due to a reduction in

compensatory resources. In other words, a history of remote TBI may accelerate the process of cognitive aging.

Accordingly, enhanced prefrontal activation is noted across studies, pointing to the importance of executive control processes in the identification of candidate neuroimaging biomarkers for remote TBI effects. The effects on functional activation patterns cannot be explained as a mere byproduct of task performance differences. Moreover, as with prior studies of TBI, aging, and dementia, these findings suggest that neuroimaging measures may be sensitive to differences in groups at an earlier stage than is the case for behavioral measures. Indeed, this is expected as the neuroimaging measures are more closely coupled to brain function than behavioral measures, which are filtered through additional effects of prior exposure, training, and strategic processes. Thus, these findings support the notion that neuroimaging measures can be used to identify those with oncoming clinical signs of unhealthy brain aging associated with remote TBI prior to clinical syndrome conversion.

These consistencies notwithstanding, the few studies identified involve small sample sizes. Moreover, the samples often are drawn from those with cognitive complaints, so that the full spectrum of remote TBI effects has yet to be characterized. Recommendations to guide future functional neuroimaging research in assessing remote TBI effects are summarized in Table 1 and outlined below.

Above, we described a variety of neurodegenerative disorders associated with a history of TBI. Each of these syndromes may be associated with different biomarkers. However, at this stage of research, it is difficult to pinpoint the precise mechanisms upon which to base neuroimaging biomarker development. Our recommendations provide a starting point in the development of clinically useful neuroimaging biomarkers, with the potential for identifying those at risk, or in the preclinical phase, of unhealthy aging. It is recognized that some of these recommendations are reliant on unstandardized acquisition or processing pipelines (e.g., complexity analysis of electrophysiological data). On the other hand, consortia such as the Alzheimer's Disease Neuroimaging Initiative (adni.loni.usc.edu/methods) and Human Connectome Project (www.humanconnectome.org/documentation/tutorials) provide standardized pipelines for MRI, fMRI, EEG, and MEG data that could be applied in this area of research.

Functional MRI

Imaging cognitive control. As TBI in general effects cognitive control operations—operations that also are affected to varying degrees by the different dementia syndromes listed above—it is recommended that initial biomarker development focus on these operations. Cognitive control, the effortful use of resources to guide, organize and monitor behavior, is reliant on prefrontal function. Due to general resource reduction, there is a temporal shift in cognitive control strategies in older adults, with older adults engaging reactive cognitive control operations at an earlier level of task difficulty, compared with younger adults who employ proactive cognitive control strategies.¹⁰⁰ This shift in cognitive control strategies during aging results in different patterns of brain activation, most notably in the prefrontal cortex, that are coupled with task difficulty. Similar findings are evident in TBI.^{13,94} In both aging and TBI, these changes are considered compensatory.^{97,100,101} With the onset of dementia, however, the associated signal decreases (i.e., to hypoactivation), as this compensation is no longer effective.¹⁰² Characterization of the relationship between behavioral impairments in cognitive control

and associated brain activation changes should provide a promising functional neuroimaging biomarker indicative of unhealthy brain changes in the context of remote TBI. The detection of such changes will be enhanced by adoption of a network-based approach that is more sensitive to changes in distributed connectivity relative to univariate analyses of simple activation maps.¹⁰³ (For application of connectivity analysis in remote TBI, see Hampshire and colleagues.⁹³)

Imaging intrinsic functional connectivity. Resting state fMRI assesses brain function in the absence of a cognitively demanding task, identifying reliable intrinsic, functionally connected networks that have in turn been investigated in neurodegenerative disease.¹⁰⁴ Given the sensitivity of distributed network function to diffuse damage typical of TBI and neurodegenerative disorders, analysis of the brain's intrinsic functional networks is a valuable putative marker of pathological aging following TBI. Moreover, resting state imaging data is easily acquired, with minimal demands on participants, allowing for testing of individuals with significant impairment without the confounds of differences in task performance that can affect interpretation of activation fMRI studies. In patients with significant TBI, the default mode network (DMN)—a network involved in stimulus-independent thought that includes the anterior and posterior midline regions, the MTLs, the temporoparietal junction, and lateral temporal regions—shows less connectivity between regions within the network, greater deactivation during rest, and increased activation during tasks.^{14,105} (For a thorough review on functional connectivity in TBI, see Sharp and colleagues.¹⁰⁶) Disease-specific atrophy in a range of dementia syndromes, including AD and FTLT, is anchored to distinct networks as identified by functional connectivity in healthy controls,^{107,108} suggesting an interaction between functional abnormalities and volumetric brain changes in regions that make up these networks.

In addition to focusing on within-network changes, recent studies have examined connectivity between networks, particularly in the DMN and networks involved in external goal-oriented behavior.¹⁰⁹ Alterations in these networks also have been shown in TBI patients, whereby less deactivation in the DMN results in inhibitory control deficits.^{106,110} In FTLT, alterations in connectivity between the salience and executive control networks, as well as hyperconnectivity of both networks in the prefrontal cortex, were associated with self-regulation impairments that are a hallmark of this disease.¹¹¹ The foregoing studies support the notion of examining the interaction between the brain's intrinsic functional networks in addition to changes within independent networks.

Medial temporal lobe structure and function. Given the vulnerability of the MTLs in AD and CTE and the presence of TBI as a common risk factor for both diseases, activation studies of episodic memory, such as those that have already been studied in depth in AD and MCI, also would be profitable. Aging is associated with less distinct, more diffuse patterns of brain activation in episodic and autobiographical memory networks, which includes the MTLs, in response to different types of memory tasks.^{112,113} With the onset of AD and associated MTL dysfunction, hippocampal and MTL activation decreases further.¹¹⁴ AD patients also show reduced repetition suppression in the MTLs during episodic memory tasks.¹¹⁴ Recent work by Stern and colleagues⁸ suggest two clinical manifestations of CTE: 1) behavioral/motor impairments and 2) cognitive manifestations. In the cognitively-impaired group, a common complaint was impairments in episodic memory function.

TABLE 1. HYPOTHESIZED FINDINGS AND RECOMMENDATIONS FOR FUTURE RESEARCH INTO THE DEVELOPMENT OF FUNCTIONAL NEUROIMAGING BIOMARKERS INDICATIVE OF ACCELERATED AGING IN REMOTE TBI

<i>Neuroimaging method</i>	<i>Hypothesized findings and recommendations for future research</i>
Functional Magnetic Resonance Imaging	
A. Activation studies of cognitive control:	<ul style="list-style-type: none"> • Abnormal patterns and amount of brain activation with increasing task complexity and cognitive load • Determine whether increased activation is in fact compensatory
B. Network analysis of intrinsic connectivity:	<p>I. Task-based connectivity</p> <ul style="list-style-type: none"> • Abnormalities in task-based functional connectivity and brain dynamics <ul style="list-style-type: none"> ◦ Particularly in the default mode, salience, and executive control networks • Changes in the interaction within and between nodes of these networks • Relate changes in network dynamics to cognitive dysfunction <p>II. Resting state connectivity</p> <ul style="list-style-type: none"> • Identify abnormalities in resting state functional connectivity within specific nodes of resting state networks (e.g., default mode, salience, dorsal attention, and executive control networks) • Determine how abnormalities in connectivity between, and brain activation within, regions in these networks relate to cognitive dysfunction
C. Activation studies of episodic memory:	<ul style="list-style-type: none"> • Bilateral, and more widespread, activation patterns • Decreased activation in the hippocampus and medial temporal lobe structures • Impairments in repetition suppression in brain regions and networks associated with episodic memory deficits
Event-Related Potential	<ul style="list-style-type: none"> • Delayed P300 latency and attenuated amplitude • Identification of other ERP components sensitive to disease-specific changes <ul style="list-style-type: none"> ◦ Candidate components include: P50, N400, auditory mismatch negativity
Electrophysiology	<ul style="list-style-type: none"> • Decreases in alpha power • Increases in delta power • Determine which changes in power spectra best classify neurodegenerative disease • Identify disease-specific changes in the profile of the power spectrum
Magnetoencephalography	<ul style="list-style-type: none"> • Complexity analysis of brain noise using multiscale entropy measures • Abnormalities in theta, alpha, and delta band oscillations • Identify how changes in the power spectrum are related to cognitive function

TBI, traumatic brain injury; ERP, event-related potential.

Neuroimaging studies of MTL function are needed to better delineate the neurocognitive profile of CTE and the relationship of this disease (if any) to AD.

Electrophysiology

Long-term changes in brain electrophysiology in remote TBI also have been suggested as a potential biomarker of the conversion to unhealthy brain aging. The most studied of these changes is abnormalities in the P300 ERP component, although there is little research on this component concerning long-term TBI effects. Studies on neurodegenerative diseases using ERP have shown delayed P300 latency and decreased P300 amplitude in individuals diagnosed with AD.¹¹⁵ Other candidate ERP components to be probed include the N400, P50, and auditory mismatch negativity. The N400 component is elicited when the brain responds to semantically meaningful stimuli, with changes in N400 amplitude and latency shown in AD.¹¹⁵ Semantic processing is affected in AD and FTLT (semantic dementia variant) due to temporal neocortical damage. The N400 therefore could possibly help to distinguish these disorders from CTE, where semantic dysfunction and temporal neocortical damage has not been noted.

Golob and colleagues¹¹⁶ have shown increases in amplitude of the baseline auditory P50 component in normal aging, with greater increases found in patients with MCI who converted to AD, compared with healthy controls. The P50 is an early auditory sensory

component measured from the temporal lobe, which was thought to be sensitive to early changes in AD due to damage of the temporal cortex.¹¹⁷ In CTE, more significant pathology in the temporal cortex occurs in the later stages of the disease. Thus, it could be the case that changes in the P50 component could differentiate AD from CTE in the early stages of both diseases.

The auditory mismatch negativity component, a component sensitive to changes in deviant sound stimuli resonating from the auditory cortex, also has shown some promise as a tool for measuring impairments in change detection in AD and PD, with AD and PD patients showing abnormalities in the mismatch negativity component.¹¹⁸ Similar to the auditory P50 component, the auditory mismatch negativity also is sensitive to temporal cortex damage and could potentially be used as an electrophysiological biomarker to differentiate AD from CTE.

A further avenue for probing the remote effects of TBI is through analysis of the spectral properties of the EEG and magnetoencephalography (MEG) signals. Resting state studies using EEG have shown abnormalities in a number of frequency bands—including alpha, delta, and theta—in AD disease.^{119,120} Moreover, changes in theta power may be able to differentiate AD from healthy controls.¹²⁰ Abnormalities in alpha frequency bands during disease progression also have been shown using MEG, with changes in MEG signal thought to be related to behavioral impairments in AD.¹²¹ Although no studies to date have assessed how changes in EEG and MEG frequency bands relate to behavioral impairments

in individuals in the early stages of CTE, one would expect that similar changes to those seen in AD would occur. We expect that the identification of disease-specific profiles in spectral power would produce an even more sensitive biomarker that could potentially identify the conversion to neurodegenerative disease earlier in remote TBI.

Finally, examination of the complexity, or brain noise, also may offer a sensitive biomarker of abnormalities in patients with remote TBI. DAI following TBI weakens integrated information processing in the brain through widespread deafferentation of interconnected networks, resulting in slowing, inaccuracy, and inconsistency of behavior. Such changes can be assessed at the brain level through the complexity of neural signals or “brain noise” that enable dynamic and heterogeneous responses at brain level, promoting stable and rapid behavioral responses.¹²² TBI patients with DAI showed reduced complexity, as measured by multiscale entropy,¹²³ localized to the medial posterior region,¹²⁴ a hub region vulnerable to both TBI and AD.

Practical Barriers to the Study of Distal TBI Effects on Neurodegenerative Disease

There are numerous challenges in assessment and neuroimaging studies in TBI. It is often difficult to recruit a sample of comparison subjects that are matched to individuals with a history of TBI for education and age. TBI is most common among young males. While it is possible to recruit friends and family members that are matched to the patients for socioeconomic characteristics,⁷⁷ our experience is that individuals in this age and education range are not eager to volunteer their time for scientific research.

The recruitment of matched controls in studies of high-level or professional athletes presents additional challenges. Professional athletes may have lower education due to their pursuit of successful athletic careers; this level of education therefore does not have the same meaning as an individual who failed to pursue higher education due to lack of ability or interest. NFL players must complete a university education but their educational experience is likely different from that of non-athletes. Professional hockey players would have lower education due to recruitment opportunities at an earlier age.

In general, athletes, by definition, possess a unique profile of neurocognitive and neuromuscular capacities. Thus, they may possess superior visuospatial analysis, speeded reaction time, and decision-making capacities. Conversely, they may perform worse on measures of verbal processing that are not emphasized in sports. Additionally, athletes, especially professional athletes, are exposed to stressors and occupational characteristics that are not typical in a healthy comparison group sample. During their careers, they experience a number of injuries that have lasting physical and emotional effects and have greater wear and tear on their bodies from excessive and intense training, all of which are difficult to match with healthy control populations.

By necessity, assessment of the remote effects of TBI involves retrospective assessment of frequency and severity of TBI. This introduces a recall bias, as individuals who have experienced TBI may not accurately recall characteristics such as post-traumatic amnesia and duration of unconsciousness, especially decades later. Research in these groups can be facilitated by access to records concerning TBI characteristics, although even here such records may be inaccurate due to lack of qualified assessment of such characteristics. In professional athletics at least, many

of these injuries are documented. For example, detailed records of hockey players' injuries, penalty minutes (a proxy for the physicality of play), fights, and videos are available on the internet (www.hockeydb.com; video.nhl.com/videocenter/console?intcmpid=nav-video-main; dropyourgloves.com). Although these are proxy measures, they are clearly less subject to recall bias. However, it should be noted that at times these sources are missing or have incomplete data of injury and play history in earlier decades, and do not necessarily include adequate information from non-professional or European leagues.

TBI Characteristics and Individual Differences

Age at time of injury

The age at which a person experiences a TBI also has implications for recovery and the long-term effects of the injury. In childhood, younger age is associated with worse outcomes following TBI due to the vulnerability of the developing brain, but as children get older they show better outcomes which could be due to brain plasticity and continuing maturation.^{125,126} In adulthood, TBI experienced in middle to late age (starting as early as 40 years of age), results in worse and prolonged negative outcomes.¹²⁷ These factors make it difficult to account for injuries across the life cycle, considering the injury (or injuries) will have different effects on the brain dependent upon when they occurred.

Effect of sex

Sex effects have been documented for TBI in general¹²⁸ but the interaction of sex with remote effects of TBI has been unexplored. With the state of current research on concussions, there is a risk of significant bias in research findings that are based on professional athletes from male leagues, even though women have a higher prevalence of concussion,¹²⁹ tend to report a greater number of symptoms,¹³⁰ and recover from the injury slower.¹³¹ Little research has been done to determine why these differences occur, but differences in the sporting environment for male and female athletes, sex hormones, cerebral blood flow, and neck strength have been proposed.^{130–132}

TBI dose

Questions also remain as to whether there are differences in long-term outcomes dependent upon whether an individual experiences a single mild TBI, moderate-to-severe TBI, or repetitive TBIs. It is widely held that experiencing a single mild TBI in one's life will not lead to unhealthy brain aging; however, moderate-to-severe and repetitive TBIs have been shown to be a risk factor for unhealthy aging. It is thought that a single moderate-to-severe TBI increases the risk of developing AD, while repetitive TBIs increase the risk of developing CTE.⁷⁰ This relationship is moderated by a number of other factors, such as genetics.

Assessment and clinical rating of mild TBI/concussion

The introduction of standardized measures of depth of coma (the Glasgow Coma Scale),¹³³ documentation of loss of consciousness duration, post-traumatic amnesia, and retrograde amnesia; and acute neuroimaging studies have been important in the characterization of TBI at the acute stage. These measures have been of less utility for very mild TBI typically seen in sports. It was not until the First International Conference on Concussion in Sport in 2001 that

a consensus statement regarding the definition, diagnosis, evaluation, and treatment of concussion existed.¹³⁴

An updated consensus statement was developed at the Fourth International Conference on Concussion in Sport in 2012, which provides a clearer definition of concussion, evaluation, and treatment, as well as recommendations regarding who should be evaluating concussions, determining concussion severity, and making return-to-play decisions.¹³⁵ The implementation of these recommendations into concussion protocols will provide greater consensus on concussion diagnosis and treatment, and help to better understand the long-term implications of these injuries. The 2012 concussion statement finds little evidence for the usefulness of baseline neuropsychological testing in the management of sports concussion.¹³⁵ Yet baseline testing is useful from a research standpoint by improving assessment of intra-individual differences in recovery and contextualizing changes in neuroimaging measures.

Genetics

Having at least one copy of the *ApoE ε4* allele decreases the brain's ability to recover from TBI. Individuals who have at least one copy of the *ApoE ε4* allele show worse outcomes than individuals who do not, and this risk increases exponentially with TBI dose.¹³⁶ Further, as noted above, TBI history and possession of at least one *ApoE ε4* allele is associated with not only the development of neurodegenerative disorders, but a reduced age of onset.^{8,29} While research on genetics in TBI has focused on understanding the interaction between *ApoE* and TBI outcomes, the effect(s) other genes have on this interaction has yet to be examined. Other candidate genes that have an effect on function after TBI include catechol-O-methyl transferase (COMT)¹³⁷ and brain-derived neurotrophic factor.¹³⁸

Generalization of findings from high-level athletes

Studies of professional and other high-level athletes accounts for a very small proportion of brain injury research but it has had far-reaching impact, including the early dementia pugilistica studies through the current surge concerning CTE, with consequent policy modifications in both professional and non-professional (i.e., youth) athletics. The study of extreme conditions, such as an unusual dose of TBI sustained through high-level athletics, has provided novel information about disease processes, especially in early phases of biomedical research. By analogy, exposure to extreme psychological trauma or radiation in wartime led to increased understanding of the development of post-traumatic stress disorder and cancer that generalized beyond the military context. Athletes have unique physical and mental capacities, yet they are vulnerable to unhealthy brain aging (and other conditions), possibly to a greater degree than expected. Thus, their physical abilities and history of physical activity does not necessarily confer protection against disease.

Implications and Future Directions

While functional recovery is expected following TBI, it is now recognized that there is an association between a history of TBI and unhealthy brain aging and dementia. There are a number of brain and behavioral biomarkers that have been identified in the literature, many of which hold promise in providing a more comprehensive understanding of brain changes associated with unhealthy aging and further, in highlighting why some individuals with a history of TBI experience healthy aging, while others not only develop neurodegenerative diseases but convert at an earlier age.

We have developed a list of recommendations for future functional neuroimaging research, as well as hypothesized outcomes of this research, that we believe hold promise in providing a better understanding of the long-term effects of TBI, and in turn will enhance their use as diagnostically-sensitive neuroimaging biomarkers. (See Table 1 for specific recommendations and hypothesized findings.) These recommendations include the use of activation-based fMRI to identify abnormal brain activation patterns in cognitive control and episodic memory tasks, functional connectivity analysis to identify abnormalities in task-positive and resting state brain networks, and EEG and MEG to examine changes in temporal brain dynamics. We further recommend the use of multivariate image analysis techniques that are able to combine outcome variables from multiple brain networks to assess network dysfunction in TBI.

It has yet to be determined how the interaction between TBI and aging exacerbate and accelerate brain changes, leading to unhealthy brain aging. It has been suggested that TBI may be responsible for initiating the pathological cascade that results in unhealthy brain aging. Longitudinal prospective studies are needed to provide a more thorough understanding of the relationship between TBI and the development of neurodegenerative disorders. Future research should explore the sensitivity and specificity of neuroimaging biomarkers, particularly at the network level, to better enable the measurement of brain changes due to TBI with age. A more thorough understanding of the genetic risk factors associated with both negative outcomes following TBI and increased dementia risk will help to determine who is more vulnerable to experiencing unhealthy brain aging, as well as who may be in greater need of different treatment and rehabilitation strategies. Longitudinal studies will be crucial to enable the prediction of long-term behavioral outcomes, putatively enabling the diagnosis of oncoming neurocognitive changes before the symptoms of these diseases are seen behaviorally.

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