BRAIN INJURY AS A NEURODEGENERATIVE DISORDER

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BRAIN INJURY AS A NEURODEGENERATIVE DISORDER

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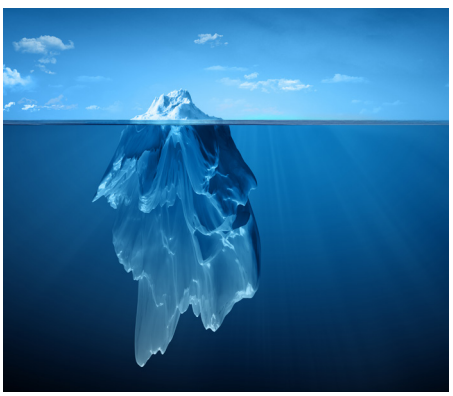

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It has been long assumed that following the resolution of acute injuries, traumatic brain injury represents a stable neural entity. However, there is growing evidence that a single moderate-severe brain injury may instead trigger an ongoing deteriorative process that commences sub-acutely, and occurs regardless of age. For scientists and clinicians, it is critical to examine this body of evidence and to explore its implications. Do the findings represent a neurodegenerative process or can they be alternatively explained? What are the neural, behavioural and functional characteristics of this progressive deterioration? Such information is needed to develop treatments to prevent or mitigate decline, and to inform the clinical care of brain injured patients. Research and clinical practice are influenced by the assumption that moderate-severe TBI is non-progressive, with few studies exploring treatments to prevent progression, and rehabilitation typically concentrated in the early stages of injury. Brain injuries can never be fully prevented. However, understanding that such progressive deterioration occurs opens a novel area of research - prevention of secondary decline - offering new possibilities for the improvement of long-term outcomes in people with traumatic brain injury.

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EDITORIAL
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Editorial: Brain Injury as a Neurodegenerative Disorder

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Keywords: neurodegeneration, traumatic brain injury, TBI, chronic TBI, atrophy, TBI as disease process, chronic traumatic encephalopathy, CTE: dementia in sports concussions

INTRODUCTION

The acute stage of moderate-severe traumatic brain injury (TBI) entails the rapid unfolding of pathophysiological processes secondary to biomechanical damage that eventually stabilize, typically leaving a combination of focal damage (visible as encephalomalacia) and more widespread lesions, both to the white matter (known as traumatic axonal injury) and to the microvasculature of the brain (Povlishock and Katz, 2005). It has long been assumed that following resolution of these acute neuropathological events, that the brain then remains stable throughout the chronic stages of injury. However, a growing body of research, much of it from the groups represented in this special topic, has revealed ongoing losses to volume and white matter integrity of the brain (Bendlin et al., 2008; Ng et al., 2008; Farbota et al., 2012a,b; Adnan et al., 2013). Findings from these longitudinal studies do not appear to reflect simply the brain's *healing* for example, the process of gliosis or the resolution of edema. Rather, deterioration is observed in a number of studies between two time points that are well within the chronic stages of injury (e.g., Greenberg et al., 2008; Green et al., 2014), thereby representing progressive and possibly neurodegenerative changes.

With these important scientific developments in mind, the broad aims of this special topic of Frontiers in Human Neuroscience were three-fold: (i) To challenge the assumption of stability of the brain in chronic TBI and to advance a reconceptualization of moderate-severe TBI as a progressive, deteriorative disorder; (ii) to provide preliminary data on the characteristics and causes of deteriorative changes; and, (iii) to open a discussion about the clinical implications of these progressive changes observed in the chronic stages of TBI. The overarching goal of the issue is to stimulate further research into decline in the chronic stages of TBI, with a longer-term view to intervention research aimed at prevention or mitigation.

THE FINDINGS

The special topic focuses on research in patients with *moderate-severe TBI*, illustrating progressive losses to both white matter (Farbota et al., 2012a; Green et al., 2014) and gray matter (Green et al., 2014). A particularly concerning finding is the ubiquity of neurodegeneration: In one study (Green et al., 2014), the authors found significant atrophy in the chronic stages of injury in over 95% of their sample. A second line of related research in the issue focuses on the cumulative and chronic effects of *multiple milder* injuries (i.e., concussions/mild TBIs and sub-concussive blows), and the elevated risk of chronic traumatic encephalopathy (CTE) and other dementias (Hazrati et al., 2013; Tartaglia et al., 2014). Here, multiple mild TBIs are sustained—often in the context of professional contact sports, and in the second to fourth decades of life—but the neurodegeneration is typically observed many years after the last concussion has been sustained (though see McKee et al., 2013 for case studies of CTE in mid- and early-career athletes). Here again, the prevalence of neurodegeneration

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is noteworthy. In a recent study, 80% of the 85 brains of people with a history of high mild TBI exposure showed evidence of CTE (McKee et al., 2013). As noted by the authors, the study contained ascertainment biases, largely examining the brains of people with known neurological findings prior to death, for example. However, even if the findings represent an overestimate, they raise the specter of a considerably higher prevalence rate for neurodegeneration in this context than previously considered.

Discussing questions of prevalence, methodological challenges, and the history of CTE, Tartaglia et al. (2014) have provided a review of the CTE literature, one that is placed in the broader etiological context of tauopathies. On the same topic, Hazrati et al. (2013) have presented a post-mortem case series of retired professional football players, a population in whom a great deal of the CTE research has focused, with findings supporting the hypothesis that multiple concussions lead to neurodegeneration, but not exclusively to CTE.

In addition to these adult studies, there was preliminary evidence of neurodegeneration presented in the mini-review by Keightley et al. (2014). Interestingly, the totality of these findings (i.e., preliminary evidence for high incidence of neurodegeneration; and, neurodegeneration cutting across injury mechanisms [single severe vs. multiple mild] and across the age spectrum) suggests that neither a genetic nor demographic risk factor can fully account for neurodegeneration in TBI. Rather, the findings raise the question whether it is *post-injury* factors, set in motion by the injury (e.g., neuroinflammation—Johnson et al., 2013, or mood alterations), that may put many at risk, with "protective" factors potentially preventing or mitigating these effects in some. Bigler (2013b), who has studied the brain's instability after injury for over a decade (e.g., Tate and Bigler, 2000; Bigler, 2013a), examines in this special issue mechanisms of deterioration, and discusses the impact of TBI on age-typical brain development (mediated in part by the age at which the TBI is sustained) and on the aging process.

The challenges that lie ahead in understanding these mechanisms are illustrated well by an apparent paradox: Neurodegeneration in moderate-severe TBI is often observed within the first year or years of injury; thus, neural declines are often happening concurrently with behavioral *recovery* (see Bendlin et al., 2008). The co-occurrence of brain decline and behavioral recovery in moderate-severe TBI underscores that there are *multiple* mechanisms that the underlie brain changes during the chronic stages of injury, both beneficial and deleterious, and most likely interdependent.

With regard to the behavioral and clinical implications of this topic, Farbota et al. (2012a,b) have presented behavioral correlates of neurodegeneration (but also of recovery), while Miller et al. (2013) have revealed that environmental enrichment, and in particular cognitive enrichment, is negatively associated with volume loss in the hippocampi during the chronic stages of TBI—offering a new modifiable target of neuro rehabilitation (i.e., environmental enrichment for prevention of hippocampal atrophy in chronic TBI). Of note, Frasca et al. (2013) argue that the environments patients enter after clinical rehabilitation services have ended may contain reduced environmental enrichment, and thereby exacerbate neurodegeneration.

Lastly, in examining longitudinal degenerative change *in vivo*, it is essential to acknowledge the limitations in our imaging and analytic approaches. Junghoon et al. (2013) offer a potential solution to these challenges with a novel approach to MRI acquisition and analysis.

CONCLUSIONS

We have presented a number of papers that illustrate the need to consider chronic moderate-severe TBI as a progressive, neurodegenerative disorder. This re-conceptualization opens new avenues for research, for example into the patterns and mechanisms of degeneration, and into protective factors and treatments. Clinically, the notion questions the prevailing approach to the delivery of clinical care, whereby services are concentrated in the early weeks and months of injury. If TBI patients are indeed declining in the chronic stages of injury, a re-evaluation of the current distribution of services is much needed.

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REFERENCES

Adnan, A., Crawley, A., Mikulis, D., Moscovitch, M., Colella, B., and Green, R. E. (2013). Moderate-severe traumatic brain injury causes delayed loss of white matter integrity: evidence of fornix deterioration in the chronic stage of injury. *Brain Inj.* 27, 1415–1422. doi: 10.3109/02699052.2013.823659

Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., et al. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *Neuroimage* 42, 503–514. doi: 10.1016/j.neuroimage.2008.04.254

Bigler, E. D. (2013a). Neuroinflammation and the dynamic lesion in traumatic brain injury. *Brain* 136, 9–11. doi: 10.1093/brain/aws342

Bigler, E. D. (2013b). Traumatic brain injury, neuroimaging, and neurodegeneration. *Front. Hum. Neurosci.* 7:395. doi: 10.3389/fnhum.2013.00395

Farbota, K. D., Bendlin, B. B., Alexander, A. L., Rowley, H. A., Dempsey, R. J., and Johnson, S. C. (2012a). Longitudinal diffusion tensor imaging and neuropsychological correlates in traumatic brain injury patients. *Front. Hum. Neurosci.* 6:160. doi: 10.3389/fnhum.2012.00160

Farbota, K. D., Sodhi, A., Bendlin, B. B., McLaren, D. G., Xu, G., Rowley, H. A., et al. (2012b). Longitudinal volumetric changes following traumatic brain injury: a

tensor-based morphometry study. *J. Int. Neuropsychol. Soc.* 18E, 1006–1018. doi: 10.1017/S1355617712000835

Frasca, D., Tomaszczyk, J., McFadyen, B. J., and Green, R. E. A. (2013). Traumatic brain injury and post-acute decline: what role does environmental enrichment play? A scoping review. *Front. Hum. Neurosci.* 7:31. doi: 10.3389/fnhum.2013.00031

Green, R. E. A., Colella, B., Maller, J. J., Bayley, M., Glazer, J., and Mikulis, D. J. (2014). Scale and pattern of atrophy in the chronic stages of moderate-severe TBI. *Front. Hum. Neurosci.* 8:67. doi: 10.3389/fnhum.2014.00067

Greenberg, G., Mikulis, D. J., Ng, K., DeSouza, D., and Green, R. E. (2008). Use of diffusion tensor imaging to examine subacute white matter injury progression in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S45–S50. doi: 10.1016/j.apmr.2008.08.211

Hazrati, L. N., Tartaglia, M. C., Diamandis, P., Davis, K. D., Green, R. E. A., Wennberg, R., et al. (2013). Absence of chronic traumatic encephalopathy in retired football players with multiple concussions and neurological symptomatology. *Front. Hum. Neurosci.* 7:222. doi: 10.3389/fnhum.2013.00222

Johnson, V. E., Stewart, J. E., Begbie, F. D., Trojanowski, J. Q., Smith, D. H., and Stewart, W. (2013). Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain* 136, 28–42. doi: 10.1093/brain/aws322

Kim J., Avants, B., Whyte, J., and Gee, J. C. (2013). Methodological considerations in longitudinal morphometry of traumatic brain injury. *Front. Hum. Neurosci.* 7:52. doi: 10.3389/fnhum.2013.00052

Keightley, M., Sinopoli, K., Davis, K., Green, R. E., Mikulis, D., Wennberg, R., et al. (2014). Is there evidence for neurodegenerative change following traumatic brain injury in children and youth? A scoping review. *Front. Hum. Neurosci.* 8:139. doi: 10.3389/fnhum.2014.00139

McKee, A. C., Stern, R. A., Nowinski, C. J., Stein, T. D., Alvarez, V. E., Daneshvar, D. H., et al. (2013) The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136(Pt 1), 43–64. doi: 10.1093/brain/aws307

Miller, L. S., Colella, B., Mikulis, D., Maller, J., and Green, R. E. (2013). Environmental enrichment may protect against hippocampal atrophy in the chronic stages of traumatic brain injury. *Front. Hum. Neurosci.* 7:506. doi: 10.3389/fnhum.2013.00506

Ng, K., Mikulis, D. J., Glazer, J., Kabani, N., Till, C., Greenberg, G., et al. (2008). Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S35–S44. doi: 10.1016/j.apmr.2008.07.006

Povlishock, J. T., and Katz, D. I. (2005). Update of neuropathology and neurological recovery after traumatic brain injury. *J. Head Trauma Rehabil.* 20, 76–94. doi: 10.1097/00001199-200501000-00008

Tartaglia, M. C., Hazrati, L. N., Davis, K., Green, R., Wennberg, R., Mikulis, M., et al. (2014). Chronic trafumatic encephalopathy and other neurodegenerative proteinopathies. *Front. Hum. Neurosci.* 7:30. doi: 10.3389/fnhum.2014.00030

Tate, D. F., and Bigler, E. D. (2000). Fornix and hippocampal atrophy in traumatic brain injury. *Learn. Mem.* 7, 442–446. doi: 10.1101/lm.33000

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REVIEW ARTICLE
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Traumatic brain injury, neuroimaging, and neurodegeneration

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Depending on severity, traumatic brain injury (TBI) induces immediate neuropathological effects that in the mildest form may be transient but as severity increases results in neural damage and degeneration. The first phase of neural degeneration is explainable by the primary acute and secondary neuropathological effects initiated by the injury; however, neuroimaging studies demonstrate a prolonged period of pathological changes that progressively occur even during the chronic phase. This review examines how neuroimaging may be used in TBI to understand (1) the dynamic changes that occur in brain development relevant to understanding the effects of TBI and how these relate to developmental stage when the brain is injured, (2) how TBI interferes with age-typical brain development and the effects of aging thereafter, and (3) how TBI results in greater frontotemporolimbic damage, results in cerebral atrophy, and is more disruptive to white matter neural connectivity. Neuroimaging quantification in TBI demonstrates degenerative effects from brain injury over time. An adverse synergistic influence of TBI with aging may predispose the brain injured individual for the development of neuropsychiatric and neurodegenerative disorders long after surviving the brain injury.

Keywords: traumatic brain injury, TBI, brain development, neuroimaging, neurodegeneration, neuropsychiatric disorders

Neuronal damage from traumatic brain injury (TBI) induces pathophysiological as well as anatomical changes (Blennow et al., 2012) that may set the stage that eventually leads to dementia (Shively et al., 2012). It is well-established and long-known that the damage from a TBI may be severe enough that the cognitive deficits experienced by the individual never return to pre-injury levels; thereby meeting *Diagnostic and Statistical Manual—Fourth Edition—Text Revision* (DSM-IV-TR) criteria for *Dementia Due to Head Trauma* (DSM-IV-TR 294.1x; see Bigler, 2007b, 2009). In the *DSM-5*, this is now classified as *Major Neurocognitive Disorder Due to TBI* (see American Psychiatric Association, 2013). However, accumulating evidence suggests with prior TBI, even in the individual that returns to presumed pre-injury cognitive ability that an increased risk for later in life degeneration occurs increasing the likelihood for a dementing illness (Plassman et al., 2000; Wang et al., 2012). It is this latter aspect of the long term effects of TBI on the aging process that will be the focus of this review. Since the majority of head injuries resulting in TBI occur before middle-age, the basic question examined in this review is the potential role that prior TBI plays in the aging process and the mechanisms whereby prior TBI would adversely influence aging.

When neural tissue is injured and reparative and restorative mechanisms fail to work, cellular morphology changes; this may ultimately result in cell death (Stoica and Faden, 2010). With change in cellular morphology or cell death, either regional or whole brain atrophy results, depending on the severity and type of injury (Pitkanen et al., 1998; Bramlett and Dietrich, 2007; Lifshitz et al., 2007; Tata and Anderson, 2010). In a human post-mortem TBI study of brain volume, Maxwell et al. (2010) examined brain weight of TBI patients who survived several months to years post-injury but were moderately to severely disabled or in a vegetative state. The following brain weights (± standard deviation) were reported: 1442.7 ± 105.0 g for controls, 1329.6 ± 202.9 g for moderately disabled, 1330 ± 140.7 g for severely disabled, and 1275 ± 135.5 g for vegetative state patients. On average moderate-to-severe TBI resulted in approximately a 112 cc of generalized volume loss at post mortem in these relatively young TBI patients (on average 44 years of age at the time of injury and 52 years at the time of death), when compared to age-matched controls who died from non-TBI related causes. While the Maxwell et al. sample was middle age at the time of death, as a group the amount of overall volume loss documented at post-mortem was comparable to that observed in patients 20–30 years older (mean age 71.1 ± 8.3) with various types of dementia at the time of death (see Purohit et al., 2011).

The Maxwell et al. study confirms TBI associated total brain volume (TBV) loss at post-mortem in the patient with chronic brain injury that approximates the degree of brain volume loss in those with brain atrophy from various types of age-related degenerative diseases much later in life. Fortunately, contemporary neuroimaging provides methods for ante-mortem detection of volume loss and its relationship to outcome following TBI,

including the prediction of adverse neurological and neuropsychiatric outcome. Having sustained a TBI raises the potential for serious long-term neurobehavioral sequelae (Moretti et al., 2012). Since smaller TBV or brain volume loss from injury, disease or disorder may be a factor associated with a host of neurological and neuropsychiatric disorders (Kempton et al., 2008; Okonkwo et al., 2010; Olesen et al., 2011; Gunther et al., 2012; Skoog et al., 2012), if TBI reduces brain volume, such reductions likely relate to adverse outcome.

For the individual who sustains a TBI and survives the injury, the post-injured brain has to navigate the remainder of life with potentially less resiliency and reserve because of the parenchymal loss (Bigler, 2007b, 2009). Since aging alone—even healthy disease-free aging—is nonetheless associated with brain volume loss, does having TBI-related volume loss accelerate the loss associated with aging? Since less brain volume later in life increases the risk of dementia (Skoog et al., 2012) does brain volume loss from TBI relate to increased dementia and possibly induce further degenerative changes?

TBI induces a number of neuropathological changes like the aggregation of β-amyloid and tau along with neuroinflammatory changes that resemble the pathology of degenerative diseases (Blennow et al., 2012). Do the combination of effects that resemble later in life neurodegenerative changes in the young individual who sustains a TBI become associated with a greater likelihood for transition to a progressive dementing illness later in life?

These questions are addressed in this review which examines volume loss from brain injury, its role in the aging process, and how neuroimaging methods may be used to document such changes.

TBI AND PARENCHYMAL VOLUME LOSS

SIGNIFICANT TBI RESULTS IN BRAIN VOLUME LOSS

Figure 1 is from an adult male who sustained a severe TBI (GCS = 3) but in whom a pre-injury magnetic resonance imaging (MRI) scan had been performed, so pre-injury quantification of ventricular and brain volume could be established. An excellent global measure of brain integrity is the ventricle-to-brain ratio (VBR; Bigler and Tate, 2001), calculated as the total of ventricular volume divided by total brain volume (TBV), multiplied by 100 so that the ratio is reported in whole numbers. Overall, normal VBR for the adult is around 1.5 with a 0.5 standard deviation (Blatter et al., 1995). In cerebral atrophy the reduction in brain volume is accompanied by a passive, compensatory increase in ventricular volume (referred to as hydrocephalus ex vacuo) thereby resulting in increased VBR. Acutely in TBI, presence of cerebral edema results in increased parenchymal volume because of tissue expansion from swelling combined with ventricular compression, reducing the size of the ventricle. In the mildest forms of TBI when edema occurs, this swelling may be transient and brain parenchyma and ventricular volume return to pre-injury levels. If injury is of sufficient severity, however, over time parenchymal degeneration occurs, reflected by brain volume loss in conjunction with hydrocephalus ex vacuo and increased VBR. As seen in this illustration, the pre-injury scan VBR was well within normal limits. However, post-injury computed tomography (CT) findings reflect distinctly reduced VBR, indicative of whole brain edema and ventricular compression, which remained throughout the first week post-injury. However, by 16 weeks post-injury substantial ventricular increase is evident along with a higher VBR score, which continued to increase over the next 2 years post-injury.

Over time, these scans, as shown in **Figure 1**, demonstrate several important points. Compared to the pre-injury brain, post-injury generalized swelling and ventricular compression in the acute and early sub-acute timeframe clearly indicate the non-specific edema and generalized neuroinflammation affects the entirety of the brain. Furthermore, this type of swelling likely compromises overall cerebral perfusion, thereby affecting neural integrity, cellular degradation and apoptosis (Xu et al., 2010) and in rodent TBI models exacerbates hippocampal damage beyond what occurs directly from the TBI (Foley et al., 2013). By the time of the first scan was obtained more than an hour post-injury in the case shown in **Figure 1**, obviously the instantaneous biomechanical shear/strain deformation injuries had occurred and what is primarily being viewed in the first acute scan are the combinations of primary and the initial secondary effects of the injury. By day 7, there is a low density lesion, likely an infarction beginning to evolve adjacent to the caudate, which is particularly evident 2 years post-injury. This demonstrates another TBI principle in that distinctly focal effects, either from shearing and/or vascular effects, may occur within the backdrop of global pathological changes. What is reflected in the scan 2 years post-injury is the summation of all of the pathological effects of TBI—mechanical deformation, axonal shearing resulting in primary axotomy, and likely focal lesion effects as well as the combined effects of secondary axotomy, ischemic damaged from compromised cerebral blood flow and whatever pathological neuroexcitatory effects may have occurred in combination with other neuroinflammatory reactions (Bigler and Maxwell, 2011, 2012). The pathological cascade is complex and as shown in this illustration plays out over an extended period of time. The end-product, however, is a brain reflective of non-specific damage with considerable overall TBV loss.

In a living veteran sample with penetrating brain injury and post-traumatic epilepsy, as a group TBI patients were found to exhibit approximately a 52 cc whole brain volume loss based on neuroimaging findings obtained years post-injury (Raymont et al., 2010). The TBI subjects in the Raymont et al. investigation had sustained injuries not as severe as in the subjects in the Maxwell et al. (2010) investigation and were penetrating in nature, but still exhibited substantial volume loss based on quantitative neuroimaging. Thus, when assessed with *in vivo* neuroimaging methods, TBI may result in substantial volume loss of brain parenchyma, which in turn relates to neurocognitive outcome (Tate et al., 2011), to be reviewed below. Furthermore, *in vivo* quantitative neuroimaging provides methods to examine the course of neurodegenerative changes over time post-injury in those who survive the brain injury.

If the trauma induced volume loss associated with TBI were just the effects of the initial injury, once the acute cascade of degeneration occurred it would be assumed that the injured brain should exhibit no further degeneration. However, if TBI has produced something more than a static brain injury,

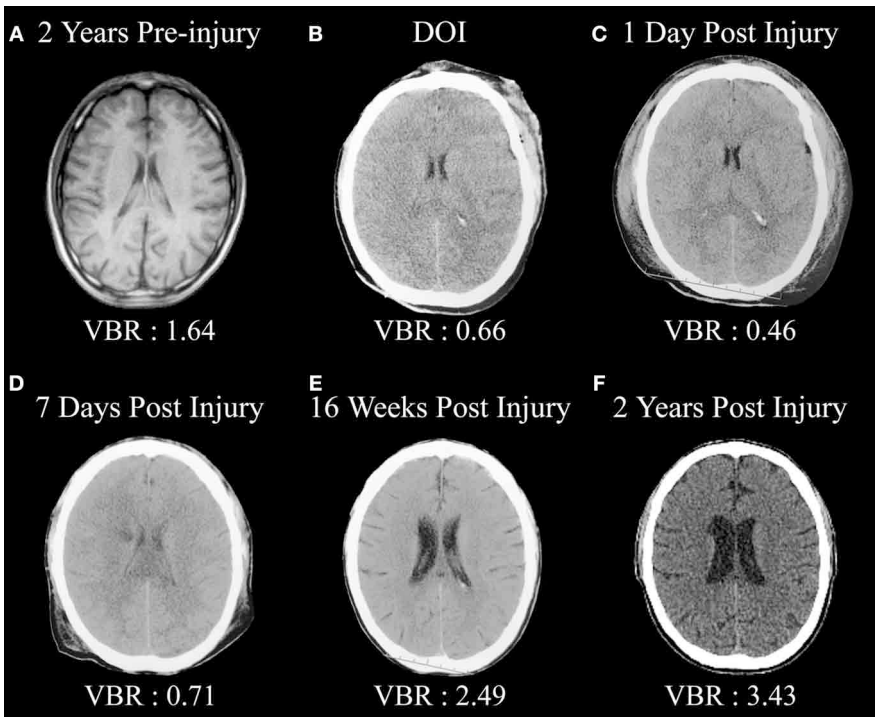

FIGURE 1 | (A) Pre-injury magnetic resonance image (MRI) approximately 2 years prior to a severe traumatic brain injury (TBI). Note the normal size of the ventricular system and ventricle-to-brain (VBR) ratio of 1.64 (normal is approximately 1.5 with a 0.5 standard deviation). **(B)** Day-of-injury initial CT demonstrating brain edema and reduced VBR, which continues to be reflected in **(C,D)**. **(E)** Distinct neurodegeneration has occurred by 16 weeks post-injury, reflected as ventricular dilation and increased VBR, with continued neurodegeneration out to 2 years post-injury as seen in **(F)**.

longitudinal neuroimaging would exhibit progressive changes over time (Greenberg et al., 2008). This would implicate neurodegenerative processes extending well-beyond the point of acute TBI, and the sub-acute timeframe necessary for those initial pathological effects to run their course (Bendlin et al., 2008; Ng et al., 2008; Farbota et al., 2012). Recently, chronic neuroinflammation, particularly involving white matter (WM) has been implicated in some of these progressive changes, including volume loss in the corpus callosum (Johnson et al., 2011, 2013). Since the shear-strain influences of TBI are more likely to damage axons, producing what is referred to as traumatic axonal injury (TAI; see Bigler and Maxwell, 2012) any chronic neuroinflammatory response influencing WM integrity would likely have adverse influences on recovery.

Longer-term pathological effects from TBI, regardless of their nature, would likely interact with the aging process and may set the stage for adverse neuropsychiatric and neurocognitive outcome after injury along with increased risk for age-related neurodegenerative diseases (Lucas et al., 2006; Johnson et al., 2012; Shively et al., 2012). Based on neuroimaging studies of normal brain development over the life span in comparison to the pathological effects of TBI, this review will address three basic issues: (1) dynamic changes in brain volume relate to age, with "normal" age-related reductions in brain volume occurring after the third decade in life, (2) TBI interferes with age-typical brain development depending on the age when injury occurs and while both gray matter (GM) and WM are damaged, trauma selectively damages axons; thereby more disruptive to WM neural connectivity during the aging process post-injury (see Ramlackhansingh et al., 2011), and (3) along with whole-brain, WM and GM volume reductions from TBI, traumatic injury results in more selective frontotemporolimbic damage, atrophic changes identifiable via neuroimaging. Diffuse damage, along with the frontotemporolimbic locus of damage from TBI, pre-disposes the brain injured individual for increased neuropsychiatric morbidity with aging and increased risk for dementia later in life.

DYNAMIC CHANGES IN BRAIN VOLUME OVER THE LIFE SPAN

At birth, TBV is approximately 25% of what it will become in adulthood but the volume increase in brain growth occurs rapidly, where based on magnetic resonance imaging (MRI) volumetric studies by 8 years of age, TBV approximates adulthood (Courchesne et al., 2000). Over the remaining childhood years and throughout adolescence, a dynamic interaction between cellular maturation and pruning along with myelination results in reduced overall GM with increased WM (see **Figure 2**). Knowing the influence of age-typical effects on brain, WM and GM volumes and the fact that all three are in decline later in the aging process (>6th decade of life) indicates their utility as neuroimaging markers of brain parenchymal health earlier in life. Quantitative neuroimaging methods that measure volumetric brain changes demonstrate these effects as shown in **Figure 2**. For

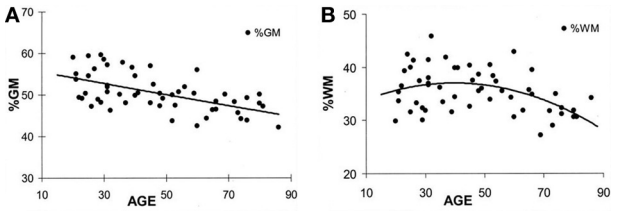

FIGURE 2 | (A,B) These plots are from Ge et al. (2002) and reflect different trajectories of white matter (WM) and gray matter (GM) over the life-span. The percent of GM volume total brain (TBV) volume declines with age whereas the percentage of WM to TBV shows and increase followed by decline later in life. Note that the age at which an individual is injured occurs not in a static brain, but rather in a brain that has age-dependent changes occurring simultaneously with the age when injury occurs. Reproduced with permission from The American Society of Neuroradiology.

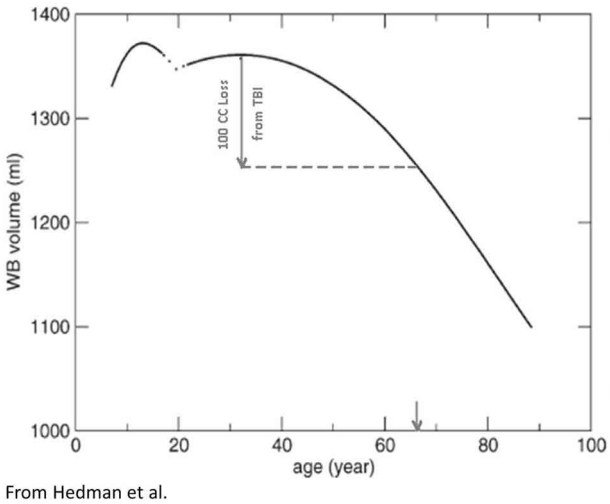

FIGURE 3 | Based on a meta-analysis Hedman et al. (2011) constructed the following TBV plots over the life span from approximately age 4 through 90 years of age. A hypothetical TBI patient injured in their 20's sustaining a volume loss of a 100 cc is depicted with the inference being that although only chronologically a young adult, because of the brain loss, the total reduction of TBV is similar to someone in their 7th decade of life (downward arrow, X-axis). In other words, purely from a TBV perspective, TBI accelerated brain volume loss. Reproduced with permission from Wiley.

example, Ge et al. (2002) plotted the percentage of whole brain WM and GM volume by age from approximately 10 through 90 years, as shown in **Figure 2**. Note that by mid-childhood GM has already started to decrease, which in childhood is thought to reflect normal neuronal pruning, all-the-while WM from late childhood through early adulthood increases and does not peak until early mid-adulthood but thereafter in decline just as GM. Throughout childhood and adolescence TBV reflects several dynamic phases of pruning, modeling and myelination but following peak development in adulthood thereafter a steady decline in TBV occurs as shown in **Figure 3**, adapted from Hedman et al. (2011). The Hedman et al. investigation examined 56 longitudinal MRI studies involving 2211 subjects from four to 88 years of age where they determined that after 35 years of age, a 0.2% per annum volume loss occurred which accelerated to 0.5% per annum after age 60.

Therefore, the early dynamic interplay between GM pruning and increased WM connectivity underlies much of the early ebb-and-flow of overall brain volume within the first three decades of life (see **Figures 2**, **3**). However, after stabilization around mid-adulthood, brain volume follows an inexorable decline, which is age dependent. In the developing healthy brain, maturational changes may be measured as volumetric changes, including WM volume; WM connectivity also can be measured with metrics such as fractional anisotropy (FA) based on diffusion tensor imaging (DTI; Shi et al., 2012), MRI structural covariance functions (Zielinski et al., 2010) and functional MRI (fMRI; Rubia, 2012).

Since intracranial volume peaks in mid-childhood, around 8 years of age, and basically remains invariant for the remainder of life (Courchesne et al., 2000), any reduction in TBV is met with increased cerebrospinal fluid (CSF) volume, where notably increasing age results in a linear CSF increase (Inglese and Ge, 2004). Increased whole brain CSF with aging, disease or injury is a reflection of cerebral atrophy (Driscoll et al., 2011). When a significant TBI occurs with resulting volume loss from the injury that injury occurs amidst a developmental backdrop of changing TBV, ventricular and total CSF volume, WM and GM volumes at the time of injury (Tasker, 2006).

Prospective, life-span neuroimaging studies on the effects of TBI have not been done but inferences can be made from longitudinal and childhood developmental studies that have examined TBI patients in the chronic phase post-injury. In child TBI the injury perturbs developmental trajectories which may never return to their pre-injury trajectories (Tasker, 2006; Ewing-Cobbs et al., 2008; Wu et al., 2010; Beauchamp et al., 2011). In adults, any volume loss from brain injury is superimposed on whatever the age-typical volume loss would be, potentially resulting in an acceleration of any age-mediated decline (Bigler, 2007b, 2009). For example, returning to **Figure 3**, if a typical 25-year-old with a pre-injury TBV of 1350 cc (average adult brain volume) lost 100 cc because of a severe TBI (thereby approximating the volume loss for moderately-to-severely disabled individuals with TBI from the Maxwell et al. (2010) study mentioned above) as determined by quantitative neuroimaging several months post-injury that 25-year-old individual would have a TBV equivalent to a 65-year-old (note the point of intercept in **Figure 3** and the down-pointing arrow). Did the brain injury with a 100 cc volume loss impose a 40+ aging effect on the brain in what should be a 25-year-old brain?

Figures 2, **3** are straightforward volumetric markers of brain development, and while they reflect gross anatomy, there are other neuroimaging biomarkers of both WM and GM integrity more sensitive to microstructure and neuronal health that also map onto these volume changes. Such changes show age-related dynamic alterations in energy metabolism including magnetic resonance spectroscopy findings (MRS), magnetization transfer ratios that directly assess WM integrity along with DTI, and resting state fMRI or rs-fMRI (Inglese and Ge, 2004; Rosazza and

Minati, 2011). DTI and rs-fMRI findings in normal development and TBI are particularly important because these neuroimaging tools provide techniques for more directly assessing brain connectivity (Van Den Heuvel and Sporns, 2011; Irimia et al., 2012b). How brain connectivity is either maintained, adapted to or damaged is key to understanding the effects of TBI at any point in the life span as well as normal aging and neurodegenerative disorders (Liu et al., 2013; Steffener et al., 2012; Levin and Smith, 2013; Pandit et al., 2013). Fortunately overall parenchymal volume positively correlates with DTI metrics, especially WM volume (see Harrison et al., 2011, 2013) and thereby TBV and WM volumes likely represent proxies that reflect brain connectivity. Based on the age-dependent volume changes shown in **Figures 2**, **3**, volume measures may be used as biomarkers of underlying brain health, developmental stage and brain connectivity. Reductions in brain volume from TBI would reflect reduced brain connectivity (Palacios et al., 2012, 2013).

As already introduced, the VBR metric represents a simple neuroimaging measurement sensitive to brain parenchymal volume loss as well as changes in CSF that relates to cognitive outcome in TBI (Tate et al., 2011). As rendered from a volume acquisition T1-weighted MRI, **Figure 4** depicts a three-dimensional surface appearance of the brain along with the cerebral ventricles (in blue) in a healthy control compared to a TBI patient with severe brain injury, global cerebral atrophy (note the prominence of the cortical sulci and inter-hemispheric fissure) and increased VBR. What is important about this image of the brain injured patient shown in **Figure 4** is that the TBI occurred when this individual was 12 years of age and the MRI obtained approximately 2 years post-injury. So the distinctly visible atrophic brain is that of a 14-year-old, but the degree of atrophy is similar to an individual seven or eight decades older. The advantage of using the VBR metric is that it automatically adjusts for head size differences due to height, body type and sex differences that influence head and brain size (Lainhart et al., 2006). In typical developing individuals, because normal brain development fills the cranial vault and ventricular size is minimal, VBR findings during childhood are relatively constant after age six and remain so throughout childhood, adolescence and early adulthood. Increases in VBR do occur in normal aging that become overtly notable by middle age but sharply increase after age 65. Chronic VBR changes reflective of generalized atrophy in TBI are directly proportional to the severity of injury (Bigler et al., 2006; Wilde et al., 2006a; Ghosh et al., 2009). Likewise, pathological increases in VBR are found in neurodegenerative disorders (Bigler et al., 2004; Carmichael et al., 2007; Olesen et al., 2011). The VBR in this child was calculated to be 5.55, which in comparison to a "normal" aging VBR would not have occurred until after the 8th decade of life. What will become of this brain as it ages?

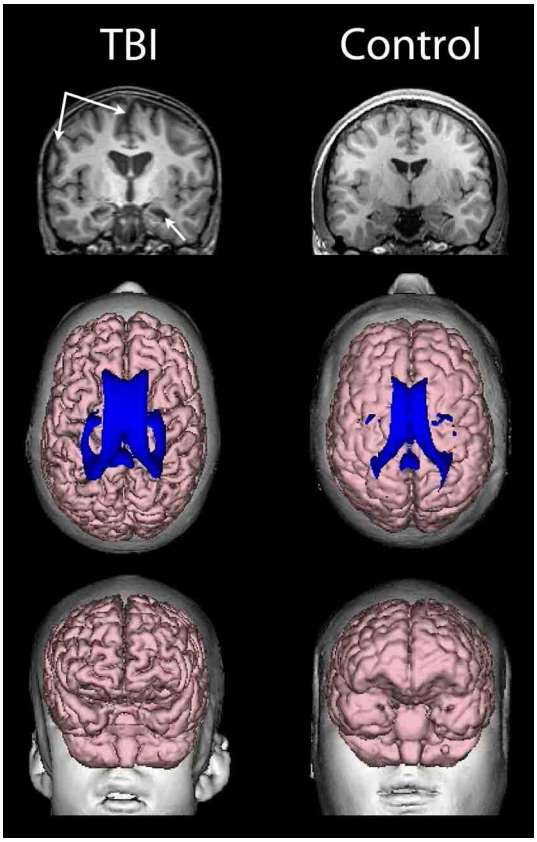

FIGURE 4 | (Top) T1-weighted coronal images of a TBI patient on the left and an age-matched control on the right, both young adolescent males. Upper left-hand arrows point to a prominent interhemispheric fissure and cortical sulci, reflective of whole brain volume loss and generalized cerebral atrophy in the TBI patient. The lower arrow points to an atrophic hippocampus and dilated temporal horn, bilaterally in the TBI patient. **(Middle)** Dorsal view of a 3-D reconstruction of the ventricle in shown in blue superimposed on the flesh-tone brain surface 3-D reconstruction. Calculating whole brain volume and dividing it by total ventricular volume and multiplying by 100 results in a ventricle-to-brain ratio (VBR) of 5.55, which is markedly deviant from normal, which in typical developing controls is generally in the range of 1.5 with a 0.5 standard deviation [see Blatter et al. (1995) and Chang et al. (2005)]. The control subject VBR was 1.45. Frontal view of the 3-D reconstructed brain **(Bottom)** of the individual with TBI showing global frontal atrophy with visibly larger cortical sulci compared to the age-match control subject on the right, again reflective of generalized cerebral atrophy. Increased VBR reflects this type of global brain volume loss, ventricular enlargement, gyral shrinkage and sulcal enlargement.

BRAIN VOLUME REDUCTIONS IN TBI

Presumably, as injury severity increases more numerous and potentially widely distributed pathological effects occur throughout the brain (Adams et al., 2011). This fact likely characterizes the association between injury severity and reduced TBV as reflected by increased VBR. Regardless of how severity is defined (GCS, LOC or PTA) increased severity is associated with increased cerebral atrophy (Bigler et al., 2006), where VBR may triple or more in those with the most severe injury.

Examining VBR changes at different time points post-injury provides insight into the more long-term neurodegenerative effects from sustaining a brain injury. Blatter et al. (1997) examined in a cross-sectional sample VBR at different times post-injury showing dynamic atrophic changes with VBR increases more than 2 years post-injury. The steepest VBR increases post-injury occurred by approximately 3 weeks clearly reflecting the initial neuropathological effects of neuronal death and cellular

phagocytosis that results in reduced TBV. However, VBR changes continued to increase in this study beyond 2 years after injury.

Once trauma passes a pathological threshold, *in vitro* studies show that the primary trauma-induced cell loss begins immediately or within hours of injury depending on mechanism of injury, injury severity and the type of induced pathological effects (Cullen et al., 2011). However, as discussed by Bigler and Maxwell (2012) there are any number of potential secondary pathological pathways that could result in more long-term neurodegenerative effects. Confirmation of these long-term effects comes from other investigations as well. For example, Ng et al. (2008) first quantified CSF volume at approximately 4.5 months post-injury, long past the initial sub-acute time frame where Blatter et al. and others (see also Gale et al., 1995) have shown the greatest degree of degenerative change occurs from TBI, continued to show volumetric differences out to 2.5 years post-injury. In severe TBI these visible changes are readily viewed in the individual patient by sequential neuroimaging studies as shown in **Figure 5**. This patient sustained a severe TBI and while significant neurodegenerative effects had occurred by one month post-injury, visible changes progressed over the next 20 months based on scan findings.

In terms of actual volume loss, Sidaros et al. (2009) examined a group of severe TBI patients at approximately 8 weeks post-injury and then again at 12 months. In comparison to controls TBV was reduced by approximately 8.4% within this initial 2-month post-injury timeframe; however, using the patient's 2-month post-acute MRI as the baseline, by 12 months post-injury an additional overall 4% volume loss occurred (range from −0.6 to −9.4%). Translating this into actual brain parenchymal tissue loss (refer to **Figure 3** again), in the typical 1350 cc brain, moderate-to-severe TBI would result on average in more than a 100 cc loss of brain parenchyma. Accordingly, the example given in **Figure 3** actually does reflect a type of reduction in TBV that would occur in the typical young adult sustaining a severe TBI.

From the above discussion of brain volume loss, returning to the Hedman et al. (2011) investigation, given their report of a 0.2–0.5% per annum whole brain volume loss, if severe TBI results in a ∼10% volume reduction this far exceeds any per annum "normal" volume loss. In fact that would induce a volume loss that in normal aging would have taken decades to achieve. In adulthood, depending on the age at the time of injury, such a volume loss likely adds to the aging burden on the brain and may accelerate age-effects by several decades. Although overly simplistic, the argument can be made that this volume loss is registered against whatever brain reserve capacity might have been present at the time of the original TBI (Bigler, 2007b), predisposing the individual with TBI to age-mediated neuropsychiatric and neurodegenerative disorders (Bigler, 2009). Traumatic-induced TBV reductions that occur within the first few months post-injury likely occur as a direct effect of the initial pathological response but more long-term TBV reductions would also reflect potential complex interactive age, neuroinflammation and neurodegenerative effects (Amor et al., 2010; Johnson et al., 2013).

In the longest follow-up TBI study to date involving structural neuroimaging, Tomaiuolo et al. (2012) compared patients at one and then 8 years post-injury. **Figure 6** from that study shows progressive changes in the corpus callosum, clearly implicating that further WM degeneration occurs long after the initial active pathological changes within the acute and sub-acute timeframe. Within a year post-injury, as also clearly visible in **Figure 6**, the corpus callosum goes through an initial loss of tracts and overall significant size reduction compared to an age-matched non-TBI control. For comparison, **Figure 6**, at the bottom, also shows normal appearance of DTI-derived fiber tracts involving the corpus callosum and the distinct loss of tracts that may occur in TBI taken from the study by Wilde et al. (2006a). The initial changes within the corpus callosum would mostly be attributable to the acute/sub-acute neuropathological effects including cell death and Wallerian degeneration of WM tracts. However, as shown in the Tomaiuolo et al. study, the continuation of WM degenerative changes from one out to eight years post-injury—as reflected in the continued reduction of the corpus callosum—could not be explained by the initial acute/sub-acute effects and implicates more long-term neurodegenerative sequelae. Tomaiuolo et al. also examined the volume of the hippocampus which interestingly, although significantly smaller than controls in the TBI subjects, did not show additional volume loss out to 8 years post-injury. Such findings are consistent with the progressive yet selective damaging effects of TBI on WM, including long-term neurodegenerative effects which will be discussed next.

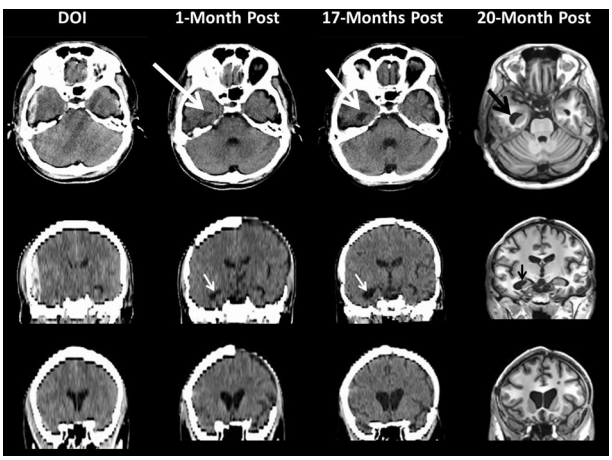

FIGURE 5 | This patient sustained a severe TBI as a consequence of a fall. Note on the day of injury (DOI) the computed tomography (CT) scan demonstrates the presence of a large epidural hematoma with brain displacement. Repeat scanning was performed at 1-month (CT scan), 17 (CT scan) and 20 months (MRI) post-injury. For the CT scans in the middle and bottom rows the coronal sections shown are based on re-sampled axial images with degradation in image resolution but sufficient to depict ventricular changes over time. Note how in the DOI scan the temporal horn is basically undetectable from parenchymal shift from the epidural as well as edema but clearly visible and dilated by 1-Month (white arrow) which increases by 17-months and even more prominent by 20 months as shown in the MRI findings. The bottom coronal images clearly depict increasing dilation of the anterior horns of the lateral ventricular system reflecting brain parenchymal volume loss that progresses from DOI through 20-months post-injury. Note at 1 month the patient still has missing bone-flap from the original craniotomy to treat a contra coup hemorrhagic contusion and subdural hematoma.

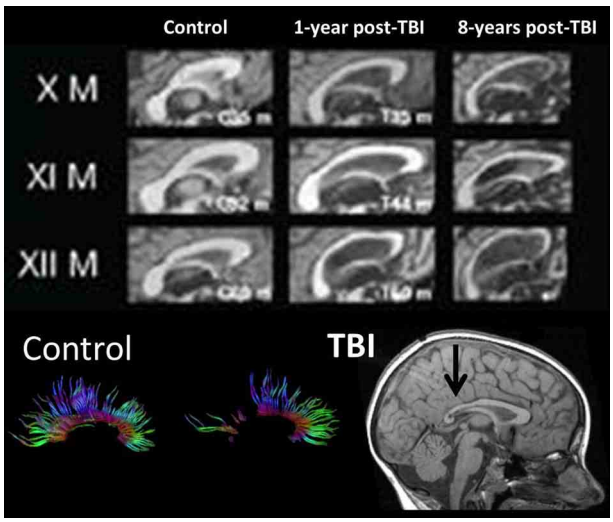

FIGURE 6 | (TOP) Mid-sagittal section through the corpus callosum showing initial atrophy 1-year from TBI, but increasing atrophy within this WM structure expressed over the next 8 years, indicating late neurodegenerative effects on WM. Images reproduced with permission from Tomaiuolo et al. (2012) and Elsevier Science. **(BOTTOM)** Corpus callosum tractography extracted from DTI in a control, compared to a child with severe TBI. The mid-sagittal MRI shows gross thinning of the posterior corpus callosum (dark arrow) but DTI actually demonstrates that this reduced area actually has regions of no DTI-identifiable aggregate WM tracts. Adapted from Wilde et al. (2006b) used with permission from Mary Ann Liebert Publishing.

The vulnerability of the corpus callosum in TBI is of particular interest, because some of the greatest shear/strain effects from trauma occur within the corpus callosum (McAllister et al., 2012; Rowson et al., 2012) and reductions in the size and/or integrity of the corpus callosum, even in mild TBI is well-documented (Aoki et al., 2012). The Tomaiuolo et al. (2012) study demonstrates that whatever initial traumatic effects there are on WM, damage to corpus callosum tracts may progress long after the injury, reflected as corpus callosum volume loss and atrophic changes (see also Tasker, 2006). Furthermore, Galanaud et al. (2012) show that pathological findings on DTI 1 year post-injury predict poor outcome from severe TBI. Interestingly, as already mentioned, Tomaiuolo et al. did not observe progressive changes in the hippocampus. It is very likely that different regions will have different resiliencies and/or vulnerabilities to the effects of injury and aging.

For example, progressive changes in the corpus callosum, long after injury, implicate active degenerative effects that are probably more than just age-mediated degenerative changes specific to WM (Farbota et al., 2012). Given the sensitivity of the DTI technique to detect abnormalities of myelin integrity and gliosis from TBI (Budde et al., 2011; Budde and Frank, 2012), DTI studies of abnormal WM in TBI should be able to document progressive degenerative changes in inter- and intra-hemispheric pathways (see Kim et al., 2008) when prospectively done.

WHITE MATTER VULNERABILITY, DIMINISHED BRAIN CONNECTIVITY OF TBI AND CHANGES OVER TIME

While hemispheric interconnectivity occurs across the corpus callosum, large intra-hemispheric fasciculi connect multiple regions within each hemisphere and likewise, there are long-coursing WM tracts integrating the brainstem and cerebellum with subcortical nuclei and the cerebrum. Shorter U-fibers connect adjacent gyral regions. The previously mentioned study by Bendlin et al., 2008 examined TBI patients (GCS of 13 or below) at 2 months post-injury and followed for more than 1 year post-injury showing longitudinal differences occurred not just within the corpus callosum, but also involving long white matter tracts as well as more short U-fibers. Follow-up with this same cohort out to 4 years post-injury has shown that the degeneration continues years post injury (Farbota et al., 2012). Wang et al. (2011) examined TBI patients earlier in their course of injury (from day-of-injury to within 9 days) and as with Bendlin et al. they followed-up within 14 months post injury and likewise documented ongoing degeneration. Thus, progressive WM degradation has now been documented that extends well into the chronic phase of having sustained a TBI (see also Sidaros et al., 2008, 2009) and Palacios et al. (2012, 2013).

Probably the most salient clinical effect of WM vulnerability is the loss of overall brain connectivity that occurs with TBI (Bonnelle et al., 2012; Caeyenberghs et al., 2012; Irimia et al., 2012a; Palacios et al., 2012). Caeyenberghs et al. (2012) not only showed the presence of disrupted WM integrity in TBI but that this disruption results in diminished cognitive control in those with brain injury. Furthermore, Wang et al. (2011) demonstrated that WM abnormalities both acutely and chronically were predictive of outcome.

The degree of WM integrity inferred directly or indirectly has been the focus of numerous studies in aging and dementia. Given improvements in image quantification the degree of WM lesion burden in the elderly individual is associated with increased levels of dementia and in those where changes in WM are quantified over time, the degree of WM burden predicts transition from mild cognitive impairment (MCI) to Alzheimer's disease (Carlson et al., 2008; Price et al., 2012; Silbert et al., 2012). Silbert et al. (2012), in a longitudinal, prospective neuroimaging study that measured WM volume as well as CSF, identified WM changes 10 years prior to MCI onset. Silbert et al. concluded that "acceleration in WM burden, a common indicator of cerebrovascular disease in the elderly, is a pathological change that emerges early in the presymptomatic phase leading to MCI (p. 741)." In the Silbert et al. investigation, they began neuroimaging studies at age 70, but if the change from 70 to 80 predicts who converts to MCI, what does this mean if baseline WM burden has already been compromised in a TBI patient injured at a much younger age? **Figure 7** shows WM burden in terms of the fluid attenuated inversion recovery or FLAIR signal abnormality and susceptibility weighted imaging (SWI) sequences in TBI patients only one of whom is an adult.

FRONTOTEMPOROLIMBIC LOCUS OF DAMAGE FROM TBI

McAllister (2011) reviews the neuropathological as well as neuroimaging studies that demonstrate a frontotemporolimbic locus

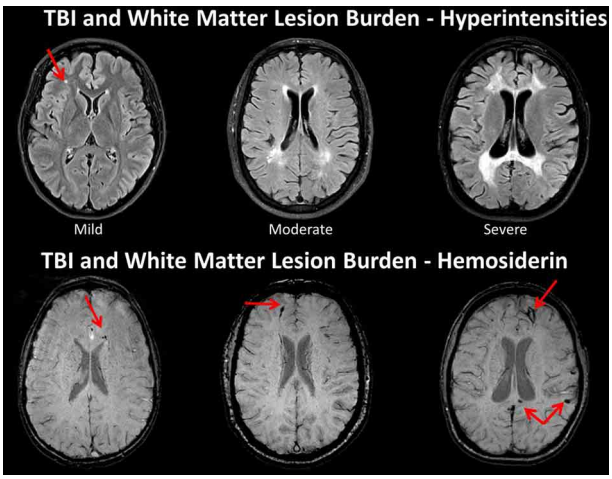

FIGURE 7 | TOP: Fluid attenuated inversion recovery (FLAIR) sequence in three traumatic brain injury (TBI) cases depicting different levels of white matter burden. (Left) a child with mild TBI (mTBI) indicating a solitary, focal white matter hyperintensity (WMH). (Middle) a 62-year-old male with a severe TBI with no white matter abnormalities noted on admission CT. Patient had a GCS of 7 prior to intubation, meeting criteria for severe TBI (Right) 17-year-old injured 2 years prior with an admission GCS of 3. Note the prominent and extensive WMHs widely distributed. **BOTTOM**: The middle and right hand subjects are the same as above, but subject on the left side is a different child with a mild TBI, who did not have a WMH, but did show hemosiderin in the corpus callosum (arrow). Note that both patients with severe injury have some generalized atrophy and ventricular dilation as a reflection of generalized brain volume loss as a consequence of severe TBI along with multiple hemosiderin deposits.

of injury from TBI. Anatomically, Bigler (2007a, 2008) has shown that because of the location of the cranial fossa and dura mater, trauma induced movement of the frontal and temporal lobes creates a mechanical vulnerability for damage to frontotemporolimbic regions of the brain following trauma. Brain deformations involving these structures, in turn increases the likelihood for focal pathology including surface contusions in these regions. Additionally, because of a unique confluence of major WM fasciculi that course through key brain regions in conjunction with network hubs and nodes involving frontotemporolimbic circuitry, even small but strategic WM lesions may have dramatic effects in TBI (Bigler et al., 2010).

The hippocampus has long been recognized as a fundamental limbic system structure. Hippocampal atrophy is a common finding in TBI (Bigler and Maxwell, 2011). As shown in **Figures 3**, **4**, marked bilateral hippocampal atrophy may occur in severe TBI. The selective damage to the hippocampus in TBI is in part related to its positioning within the medial temporal lobe and the above mentioned biomechanical vulnerability of the medial temporal lobe to compression injury, but there are also intrinsic excitotoxic, neurotransmitter and metabolic factors specific to the hippocampus that predispose it to injury as well (see Diaz-Arrastia et al., 2009). Controlled animal experiments show that the hippocampus is particularly sensitive to the effects of trauma, even in mild TBI (Chen et al., 2012), with progressive neuronal death and hippocampal atrophy beyond the acute/sub-acute timeframe (Smith et al., 1997; Immonen et al., 2009). Additionally, given its high metabolic demands combined with over-expression of excitotoxic effects, greater hippocampal damage in TBI is often the outcome (Deng and Xu, 2011; Marquez de la Plata et al., 2011). In children, Wilde et al. (2006b) have shown that hippocampal volume loss from TBI was proportionally the greatest in comparison to all other brain regions examined.

Hippocampal and medial temporal lobe pathology plays a role in many neuropsychiatric and neurodegenerative disorders. For example, obvious pathological changes within the hippocampal formation occur in Alzheimer's disease and related dementias, associated with the memory impairments observed in these disorders (Hodges, 2012). Some level of hippocampal pathology is thought to contribute to major depression that occurs late in life, which also may relate to mild cognitive impairment (MCI; Morra et al., 2009). Additionally, a very complex interplay exists between TBV, aging and hippocampal volume and the transitions from healthy aging to MCI, and from MCI to frank dementia (Apostolova et al., 2012). Successful "aging" of the hippocampal complex and its multimodal efferent and afferent connections is considered a key element of brain plasticity with advancing age (Goh and Park, 2009). Oppositely, any injury to the hippocampus or its afferent/efferent connections such as from TBI likely adds to or advances the aging burden.

Lastly, when the limbic system is viewed in its entirety, it is a complex, highly interconnected system dependent on the integrity of numerous WM pathways. While the hippocampus is central to limbic system integrity, note that functional hippocampal disruption in TBI may occur by lesions quite distal to the hippocampus but occurring within other structures or limbic pathways that either input or output the hippocampus. For example, Wilde et al. (2010) have shown the vulnerability of frontal projections from the anterior cingulum in TBI. Such pathological changes would be a minimum of three synaptic connections from the hippocampus, and while the axonal injury may be specific to the cingulum bundle, it potentially would have some similar effects as if the damage actually had occurred in the hippocampus since part of hippocampal output to frontal cortex projects via the anterior cingulum. More directly, the fornix is vulnerable in TBI (Yallampalli et al., 2013), thereby disrupting the direct output of the hippocampus. Because of the interdependence of the limbic network on each of its constituent parts, intactness at one level does not insure that transfer of information occurs at another. Because of the increased likelihood of hippocampal damage in TBI, even minimal hippocampal damage could be highly disruptive to limbic connectivity and overtime, add to the burden of age effects.

AGING, TBI AND NEURODEGENERATIVE DISORDERS

At the beginning of this discussion it was shown that whole-brain volume is age-dependent, which over time, even in the healthy individual declines. Brain atrophy outside the parameters of that related to normal aging is associated with a host of disease processes and potential adverse age-mediated genetic factors. As such, any environmental condition, such as a TBI that has the

potential to influence brain volume loss likely adds to the disease burden that accompanies reduced brain volume during the normal aging process. This is graphically depicted in **Figure 8** when the 14-year-old atrophic brain from a severe TBI is compared side-by-side with the MRI findings from an 86-year-old patient with Alzheimer's disease.

The initial, direct effect of brain injury induces neuroinflammatory reactions that may set the stage for long-term neuroinflammatory effects and neurodegeneration (see Ramlackhansingh et al., 2011; Johnson et al., 2013). The initial direct neurodegenerative changes that occur following TBI are manifested by significant brain atrophy that occurs within the first 6 months post-injury (Gale et al., 1995). While these effects can be accounted for by acute/sub-acute injury mechanisms and their pathological consequences, given the above observations, neuroinflammatory and neurodegenerative processes may extend for years beyond the initial post-injury injury time frame in the TBI patient. These more chronic effects do set the stage for important interactions that occur between the age at the time of injury, aging and age-related vulnerabilities, to later in life neuropsychiatric and progressive neurodegenerative disorders indicating that the lesion in TBI may be much more dynamic (Bigler, 2013). The frontotemporolimbic locus of where TBI induced degenerative changes are most likely to occur in the brain, has a most interesting overlap with brain areas observed in older individuals with increased risk for a variety of age-related neurological and neuropsychiatric disorders. Two examples are given that demonstrate this overlap. Sperling et al. (2011) review the pre-clinical stages of Alzheimer's disease in relationship to key biomarkers that, overtime, increase the likelihood for developing dementia.

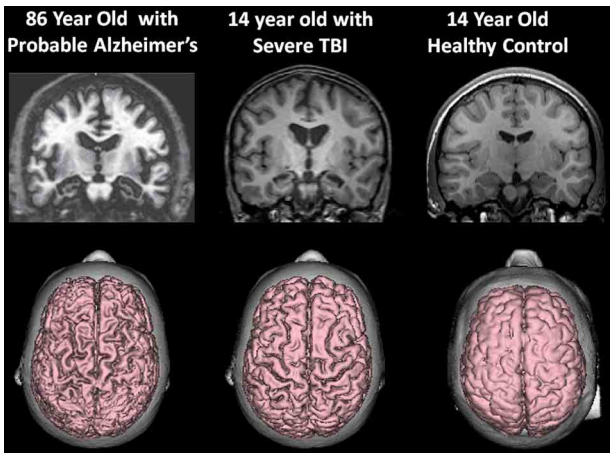

FIGURE 8 | (Top) T1-weighted coronal images approximately at the same level showing hippocampal atrophy in the 86-year-old patient with a clinical diagnosis of Alzheimer's disease and the 14-year-old patient with severe traumatic brain injury (TBI). Note compared to the control coronal image on the right, both the TBI case and the Alzheimer's exhibit hippocampal atrophy, ventricular dilation and sulcal widening. **(Bottom)** All images are 3-D renderings from volume acquisition magnetic resonance imaging (MRI) depicting the dorsal view of the brain in each subject described above. Note the similarity of the diffuse pattern of atrophic change that has occurred in both the patient with Alzheimer's disease and the adolescent who survived severe TBI. Clearly, the elderly patient with Alzheimer's has more severe atrophy but nonetheless the atrophy in the TBI adolescent is substantial, especially when compared to the typical developing adolescent control. Note: The patient with Alzheimer's disease is taken from Jacobson et al. (2009); this patient's clinical findings, including additional neuroimaging and neuropsychological details are described in that publication. Reproduced with permission from John Wiley and Sons.

As in the Jack et al. (2013) review, each of the biomarkers associated with the development of Alzheimer's disease, is also associated with biomarkers relevant to TBI; in particular, the deposition of the amyloid-beta (Aβ), neuroimaging based findings of pathology and presence of cognitive impairment. Aβ, tau pathologies, reduced brain volume, and impaired memory are all part of the pathological and clinical picture of TBI *and* age-associated degenerative diseases (Smith et al., 1999; Emmerling et al., 2000; Ikonomovic et al., 2004; Dekosky et al., 2010), creating the potential association between TBI and Alzheimer's disease and related dementias (Sivanandam and Thakur, 2012). In the Jack et al. review, two individuals are shown at the identical time-point—one with low risk for developing dementia, the other with high risk, for example, a prior history of TBI. Given the associations reviewed above, if the high risk individual were someone with a significant TBI who has recovered to some pre-injury baseline, yet had increased burden because of brain atrophy, mildly reduced cognitive ability and various biomarkers of neuronal injury, given this model the TBI individual would be at higher risk for developing dementia.

Smith (2013) reviewed the long-term consequences of microglial activation associated with TBI and summarized the potential findings as shown in **Figure 9**. This diagram uses the cognitive reserve hypothesis (see Bigler, 2007b) that assumes an inexorable yet normal decline in function with age. Although the brain adapts when injured except in cases of severe catastrophic injuries, the individual may never return to baseline and then as depicted in the illustration the adverse effects may be either synergistic or additive. Regardless of the mechanism, having a brain injury shortens the time for when the dementia threshold would be achieved.

A second example comes from the review by Bozzali et al. (2008) on regional and global atrophy that accompanies cognitive decline in degenerative disease, its frontotemporolimbic distribution and a more direct link between having sustained TBI earlier in life and developing a dementing illness (Plassman et al., 2000; Magnoni and Brody, 2010; Esiri and Chance, 2012; Sivanandam and Thakur, 2012; Wang et al., 2012). The implication from these studies and reviews is that overlapping trauma-induced neurodegenerative effects occur within the same frontotemporolimbic areas associated with age-related neurodegenerative disorders. This association between TBI and later onset of dementia may also relate to the selective WM damage that occurs with TBI and the role that WM pathology plays in the expression of dementia via a breakdown in neural connectivity and networks (Carmichael and Salloway, 2012; Shively et al., 2012; Weinstein et al., 2013).

The above discussion focused mostly on a single event, moderate-to-severe TBI, but since mild TBI (mTBI) constitutes the majority of injuries, if mTBI contributes adversely to the aging process, this could be a major public health concern

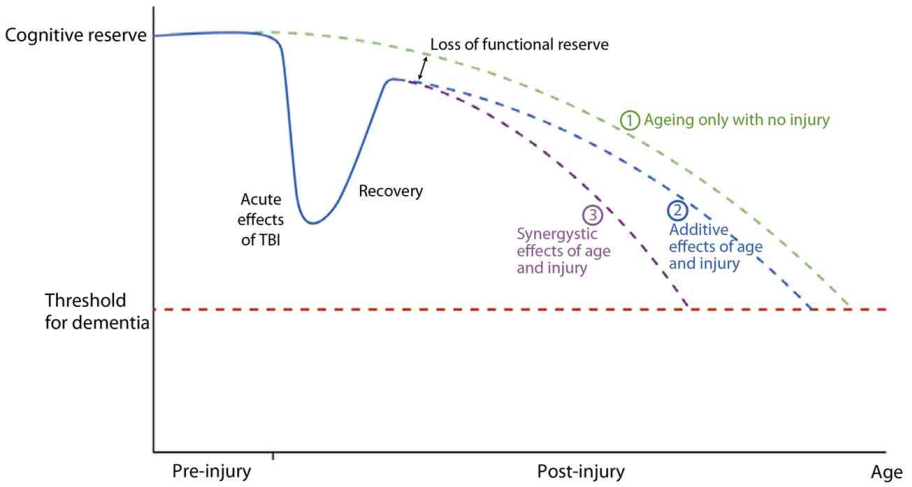

FIGURE 9 | A graphical representation of a postulated cognitive reserve and how head injury may increase the risk of cognitive decline. The broken green line (1) represents the "normal" situation. There is loss of cognitive function with aging until a threshold point is crossed (broken red line) resulting clinically in dementia. After an episode of traumatic brain injury there is a significant decline in cognitive function which recovers, the degree of recovery being dependent on the severity of the head injury. Recovery is, however, not complete resulting in a loss of functional reserve. After this point cognitive decline may be as for normal ageing [broken blue line (2)] with the dementia threshold being crossed earlier due to loss of functional reserve, or there may be a continued synergistic effect of mechanisms initiated by the head injury which accelerates cognitive decline [broken purple line (3)]. Reproduced with permission from John Wiley and Sons and Smith (2013).

(Bazarian et al., 2009). Similarly, multiple concussions or mTBIs are commonplace in some sports (Harmon et al., 2013). Chronic traumatic encephalopathy (CTE) has been demonstrated in athletes with repetitive blows to the head (Victoroff, 2013), yet not necessarily meeting criteria for a clinically diagnosed concussion (McKee et al., 2012). In the largest post-mortem study to date of 85 individuals with CTE, McKee and colleagues have shown that CTE, while it may in some cases be the solitary neuropathological diagnosis, CTE was also associated with cases of Alzheimer's disease, Lewy body disease, frontotemporal lobar degeneration and motor neuron disease. In a subset of American National Football League players who had sustained concussions while playing found that CTE was associated with increased duration of football play and age at time of death. This observation suggests incubation and interactive effect of the prior injury with time and aging effects. McKee et al. (2012) conclude that the association of CTE "... with other neurodegenerative disorders suggests that repetitive brain trauma and hyperphosphorylated tau protein deposition promote the accumulation of other abnormally aggregated proteins including TAR DNA-binding protein 43, amyloid beta protein and alpha-synuclein (p. 43)." Dementia pugilistica has been diagnosed in as high as 20% of retired boxers and may have its onset long after the last boxing match (Kokjohn et al., 2013).

Lehman et al. (2012) found in retired National Football League (NFL) players, a rate of death associated with a neurodegenerative disorder 3 times higher than the general U.S. population. Hart et al. (2013) have also shown in aging, retired NFL players that WM pathology in DTI analyses is related to cognitive dysfunction and depression. While the Plassman et al. (2000) study (which verified presence of TBI in the medical record) reported a positive relationship between prior brain injury and development of dementia, some studies that include self-report of prior TBI do not (Dams-O'Connor et al., 2012). The issue is likely complicated because in the Plassman et al. study, when the mild TBI subjects were assessed independently, as a group they did not have a significantly increased hazard ratio for developing dementia. Returning to the model offered by Jack et al. (2013) and shown in **Figure 8**, those within the mild end of the TBI spectrum with a single head injury would likely have the least risk. Since mTBI constitutes the majority of those with brain injury, the high presence of mTBI with potentially minimal risk factors may be an explanation why some studies do not find an association. Using a retrospective cohort design with documented TBI, Wang et al. (2012) did demonstrate an increased risk for dementia. Sayed et al. (2013) examined a large cohort of individuals with TBI from the National Alzheimer's Coordinating Center Uniform Data set and observed that those with chronic cognitive deficit were those who met criteria for developing dementia. The Sayed et al. study may show that TBI alone may be insufficient to develop dementia, but TBI plus risk factors as outlined in **Figure 9**, reproduced from Smith (2013), such as residual cognitive impairment may be the combination needed for the transition from recovered but not demented to developing dementia post-injury.

Currently, all of the degenerative disorders including CTE require post-mortem confirmation, but ante-mortem neuroimaging studies may provide important insights into how brain injury interacts with the aging process and the development of late neuropathological sequelae. Koerte et al. (2012a,b) have shown DTI changes in athletes, even without symptomatic concussion. What it means to have abnormal

DTI findings in the athlete with a history of concussive or sub-concussive blows to the head is not known at this time, but raises the specter of potential later-in-life reduced brain reserve capacity and increased vulnerability for neuropsychiatric disorder (Bigler et al., 2013).

Recently, Bailey et al. (2012) demonstrated in relatively young professional boxers (∼28 years of age) that impaired cerebral hemodynamic function related to history and intensity of sparring and reduced neuropsychological performance. More than three decades after their last concussion, Tremblay et al. (2013) examined athletes with a history of prior concussion compared to those without. Athletes with prior concussions had abnormally enlarged ventricular size, cortical thinning in regions more vulnerable to the aging process and diminished episodic memory and verbal fluency compared to age matched athletes without prior history of concussion, yet demographically matched. Gardner et al. (2012) review the literature on sport-related concussions and DTI showing residuals in terms of WM damage even in this mild end of the TBI spectrum. In a within-subject prospective design, Toth et al. (2013) have shown a statistically significant subtle loss of brain volume by 1 month post injury in mTBI, where TBV was reduced by 1% and ventricular volume increased by 3.4%. However, without pre-injury baseline imaging, what role inflammation may have played in this is not known. These observations indicate that even mild injuries have the potential to initiate a cascade of neuropathological events that influence ageing and the potential to develop a neurodegenerative disorder. Complex genetic (Toth et al., 2013) factors are also likely related to how even mild injury influences outcome and the risk for late in life dementia (Ponsford et al., 2011; Schipper, 2011).

Finally, neuroinflammation specific to WM may play a role in the progression of degenerative brain changes for months to years' post-injury (Smith et al., 2012; Bigler, 2013; Johnson et al., 2013). There may be differential effects of WM inflammatory reactions between child and adult brain injury (Mayer et al., 2012) and DTI may provide a method for *in vivo* tracking of these changes (Voelbel et al., 2012).

SUMMARY

Directly related to the effects of trauma and its severity, TBI may induce widespread neuronal loss and disrupted WM connectivity as part of the primary and secondary effects of the injury along with injury-initiated neuroinflammation and neurodegeneration. Thus, TBI, especially toward the severe end of the spectrum, becomes a major risk factor for untoward effects later in life by reducing brain reserve capacities and diminished neuroplasticity to offset age-mediated decline. In fact, TBI may initiate an adverse synergistic effect with aging to predispose the earlier development of neuropsychiatric symptoms and age-related neurodegenerative diseases in the brain injured individual.

REFERENCES

Adams, J. H., Jennett, B., Murray, L. S., Teasdale, G. M., Gennarelli, T. A., and Graham, D. I. (2011). Neuropathological findings in disabled survivors of a head injury. *J. Neurotrauma* 28, 701–709. doi: 10.1089/neu.2010.1733

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 5th Edn.* Washington, DC: American Psychiatric Publishing.

Amor, S., Puentes, F., Baker, D., and van der Valk, P. (2010). Inflammation in neurodegenerative diseases. *Immunology* 129, 154–169. doi: 10.1111/j.1365-2567.2009.03225.x

Aoki, Y., Inokuchi, R., Gunshin, M., Yahagi, N., and Suwa, H. (2012). Diffusion tensor imaging studies of mild traumatic brain injury: a meta-analysis. *J. Neurol. Neurosurg. Psychiatry* 83, 870–876. doi: 10.1136/jnnp-2012-302742

Apostolova, L. G., Green, A. E., Babakchanian, S., Hwang, K. S., Chou, Y. Y., Toga, A. W., et al. (2012). Hippocampal atrophy and ventricular enlargement in normal aging, mild cognitive impairment (MCI), and Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 26, 17–27. doi: 10.1097/WAD.0b013e3182163b62

Bailey, D. M., Jones, D. W., Sinnott, A., Brugniaux, J. V., New, K. J., Hodson, D., et al. (2012). Impaired cerebral haemodynamic function associated with chronic traumatic brain injury in professional boxers. *Clin. Sci. (Lond.)* 124, 177–189. doi: 10.1042/CS20120259

Bazarian, J. J., Cernak, I., Noble-Haeusslein, L., Potolicchio, S., and Temkin, N. (2009). Long-term neurologic outcomes after traumatic brain injury. *J. Head Trauma Rehabil.* 24, 439–451. doi: 10.1097/HTR.0b013e3181c15600

Beauchamp, M. H., Ditchfield, M., Catroppa, C., Kean, M., Godfrey, C., Rosenfeld, J. V., et al. (2011). Focal thinning of the posterior corpus callosum: normal variant or post-traumatic? *Brain Inj.* 25, 950–957. doi: 10.3109/02699052.2011.589791

Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., et al. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *Neuroimage* 42, 503–514. doi: 10.1016/j.neuroimage.2008.04.254

Bigler, E. D. (2007a). Anterior and middle cranial fossa in traumatic brain injury: relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. *Neuropsychology* 21, 515–531. doi: 10.1037/0894-4105.21.5.515

Bigler, E. D. (2007b). "Traumatic brain injury and cognitive reserve," in *Cognitive Reserve: Theory and Applications*, ed Y. Stern (New York, NY: Taylor and Francis), 85–116.

Bigler, E. D. (2008). Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *J. Int. Neuropsychol. Soc.* 14, 1–22. doi: 10.1017/S135561770808017X

Bigler, E. D. (2009). "Traumatic brain injury," in *Textbook of Alzheimer Disease and Other Dementias*, eds M. F. Weiner and A. M. Lipton (Washington, DC: The American Psychiatric Publishing, Inc.), 229–246.

Bigler, E. D. (2013). Neuroinflammation and the dynamic lesion in traumatic brain injury. *Brain* 136, 9–11. doi: 10.1093/brain/aws342

Bigler, E. D., Deibert, E., and Filley, C. M. (2013). When is a concussion no longer a concussion? *Neurology* 81, 14–15. doi: 10.1212/WNL.0b013e318299cd0e

Bigler, E. D., and Maxwell, W. L. (2011). Neuroimaging and neuropathology of TBI. *NeuroRehabilitation* 28, 63–74. doi: 10.3233/NRE-2011-0633

Bigler, E. D., and Maxwell, W. L. (2012). Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings. *Brain Imaging Behav.* 6, 108–136. doi: 10.1007/s11682-011-9145-0

Bigler, E. D., McCauley, S. R., Wu, T. C., Yallampalli, R., Shah, S., MacLeod, M., et al. (2010). The temporal stem in traumatic brain injury: preliminary findings. *Brain Imaging Behav.* 4, 270–282. doi: 10.1007/s11682-010-9105-0

Bigler, E. D., Neeley, E. S., Miller, M. J., Tate, D. F., Rice, S. A., Cleavinger, H., et al. (2004). Cerebral volume loss, cognitive deficit and neuropsychological performance: comparative measures of brain atrophy: I. Dementia. *J. Int. Neuropsychol. Soc.* 10, 442–452. doi: 10.1017/S1355617704103111

Bigler, E. D., Ryser, D. K., Gandhi, P., Kimball, J., and Wilde, E. A. (2006). Day-of-injury computerized tomography, rehabilitation status, and development of cerebral atrophy in persons with traumatic brain injury. *Am. J. Phys. Med. Rehabil.* 85, 793–806. doi: 10.1097/01.phm.0000237873.26250.e1

Bigler, E. D., and Tate, D. F. (2001). Brain volume, intracranial volume, and dementia. *Invest. Radiol.* 36, 539–546. doi: 10.1097/00004424-200109000-00006

Blatter, D. D., Bigler, E. D., Gale, S. D., Johnson, S. C., Anderson, C. V., Burnett, B. M., et al. (1995). Quantitative volumetric analysis of brain MR: normative database spanning 5 decades of life. *AJNR Am. J. Neuroradiol.* 16, 241–251.

Blatter, D. D., Bigler, E. D., Gale, S. D., Johnson, S. C., Anderson, C. V., Burnett, B. M., et al. (1997). MR-based brain and cerebrospinal fluid measurement after traumatic brain injury: correlation with neuropsychological outcome. *AJNR Am. J. Neuroradiol.* 18, 1–10.

Blennow, K., Hardy, J., and Zetterberg, H. (2012). The neuropathology and neurobiology of traumatic brain injury. *Neuron* 76, 886–899. doi: 10.1016/j.neuron.2012.11.021

Bonnelle, V., Ham, T. E., Leech, R., Kinnunen, K. M., Mehta, M. A., Greenwood, R. J., et al. (2012). Salience network integrity predicts default mode network function after traumatic brain injury. *Proc. Natl. Acad. Sci. U.S.A.* 109, 4690–4695. doi: 10.1073/pnas.1113455109

Bozzali, M., Cercignani, M., and Caltagirone, C. (2008). Brain volumetrics to investigate aging and the principal forms of degenerative cognitive decline: a brief review. *Magn. Reson. Imaging* 26, 1065–1070. doi: 10.1016/j.mri.2008.01.044

Bramlett, H. M., and Dietrich, W. D. (2007). Progressive damage after brain and spinal cord injury: pathomechanisms and treatment strategies. *Prog. Brain Res.* 161, 125–141. doi: 10.1016/S0079-6123(06)61009-1

Budde, M. D., and Frank, J. A. (2012). Examining brain microstructure using structure tensor analysis of histological sections. *Neuroimage* 63, 1–10. doi: 10.1016/j.neuroimage.2012.06.042

Budde, M. D., Janes, L., Gold, E., Turtzo, L. C., and Frank, J. A. (2011). The contribution of gliosis to diffusion tensor anisotropy and tractography following traumatic brain injury: validation in the rat using Fourier analysis of stained tissue sections. *Brain* 134, 2248–2260. doi: 10.1093/brain/awr161

Caeyenberghs, K., Leemans, A., Heitger, M. H., Leunissen, I., Dhollander, T., Sunaert, S., et al. (2012). Graph analysis of functional brain networks for cognitive control of action in traumatic brain injury. *Brain* 135, 1293–1307. doi: 10.1093/brain/aws048

Carlson, N. E., Moore, M. M., Dame, A., Howieson, D., Silbert, L. C., Quinn, J. F., et al. (2008). Trajectories of brain loss in aging and the development of cognitive impairment. *Neurology* 70, 828–833. doi: 10.1212/01.wnl.0000280577.43413.d9

Carmichael, O. T., Kuller, L. H., Lopez, O. L., Thompson, P. M., Dutton, R. A., Lu, A., et al. (2007). Cerebral ventricular changes associated with transitions between normal cognitive function, mild cognitive impairment, and dementia. *Alzheimer Dis. Assoc. Disord.* 21, 14–24. doi: 10.1097/WAD.0b013e318032d2b1

Carmichael, O. T., and Salloway, S. (2012). Imaging markers of incipient dementia: the white matter matters. *Neurology* 79, 726–727. doi: 10.1212/WNL.0b013e3182662020

Chang, K., Barnea-Goraly, N., Karchemskiy, A., Simeonova, D. I., Barnes, P., Ketter, T., et al. (2005). Cortical magnetic resonance imaging findings in familial pediatric bipolar disorder. *Biol. Psychiatry* 58, 197–203. doi: 10.1016/j.biopsych.2005.03.039

Chen, Z., Leung, L. Y., Mountney, A., Liao, Z., Yang, W., Lu, X. C., et al. (2012). A novel animal model of closed-head concussive-induced mild traumatic brain injury: development, implementation, and characterization. *J. Neurotrauma* 29, 268–280. doi: 10.1089/neu.2011.2057

Courchesne, E., Chisum, H. J., Townsend, J., Cowles, A., Covington, J., Egaas, B., et al. (2000). Normal brain development and aging: quantitative analysis at *in vivo* MR imaging in healthy volunteers. *Radiology* 216, 672–682.

Cullen, D. K., Vernekar, V. N., and Laplaca, M. C. (2011). Trauma-induced plasmalemma disruptions in three-dimensional neural cultures are dependent on strain modality and rate. *J. Neurotrauma* 28, 2219–2233. doi: 10.1089/neu.2011.1841

Dams-O'Connor, K., Gibbons, L. E., Bowen, J. D., McCurry, S. M., Larson, E. B., and Crane, P. K. (2012). Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. *J. Neurol. Neurosurg. Psychiatry* 84, 177–182. doi: 10.1136/jnnp-2012-303938

Dekosky, S. T., Ikonomovic, M. D., and Gandy, S. (2010). Traumatic brain injury–football, warfare, and long-term effects. *N. Engl. J. Med.* 363, 1293–1296. doi: 10.1056/NEJMp1007051

Deng, P., and Xu, Z. C. (2011). Contribution of Ih to neuronal damage in the hippocampus after traumatic brain injury in rats. *J. Neurotrauma* 28, 1173–1183. doi: 10.1089/neu.2010.1683

Diaz-Arrastia, R., Agostini, M. A., Madden, C. J., and Van Ness, P. C. (2009). Posttraumatic epilepsy: the endophenotypes of a human model of epileptogenesis. *Epilepsia* 50(Suppl. 2), 14–20. doi: 10.1111/j.1528-1167.2008.02006.x

Driscoll, I., Zhou, Y., An, Y., Sojkova, J., Davatzikos, C., Kraut, M. A., et al. (2011). Lack of association between 11C-PiB and longitudinal brain atrophy in non-demented older individuals. *Neurobiol. Aging* 32, 2123–2130. doi: 10.1016/j.neurobiolaging.2009.12.008

Emmerling, M. R., Morganti-Kossmann, M. C., Kossmann, T., Stahel, P. F., Watson, M. D., Evans, L. M., et al. (2000). Traumatic brain injury elevates the Alzheimer's amyloid peptide A beta 42 in human CSF. A possible role for nerve cell injury. *Ann. N.Y. Acad. Sci.* 903, 118–122. doi: 10.1111/j.1749-6632.2000.tb06357.x

Esiri, M. M., and Chance, S. A. (2012). Cognitive reserve, cortical plasticity and resistance to Alzheimer's disease. *Alzheimers Res. Ther.* 4, 7. doi: 10.1186/alzrt105

Ewing-Cobbs, L., Prasad, M. R., Swank, P., Kramer, L., Cox, C. S. Jr., Fletcher, J. M., et al. (2008). Arrested development and disrupted callosal microstructure following pediatric traumatic brain injury: relation to neurobehavioral outcomes. *Neuroimage* 42, 1305–1315. doi: 10.1016/j.neuroimage.2008.06.031

Farbota, K. D., Bendlin, B. B., Alexander, A. L., Rowley, H. A., Dempsey, R. J., and Johnson, S. C. (2012). Longitudinal diffusion tensor imaging and neuropsychological correlates in traumatic brain injury patients. *Front. Hum. Neurosci.* 6:160. doi: 10.3389/fnhum.2012.00160

Foley, L. M., Iqbal O'Meara, A. M., Wisniewski, S. R., Kevin Hitchens, T., Melick, J. A., Ho, C., et al. (2013). MRI assessment of cerebral blood flow after experimental traumatic brain injury combined with hemorrhagic shock in mice. *J. Cereb. Blood Flow Metab.* 33, 129–136. doi: 10.1038/jcbfm.2012.145

Galanaud, D., Perlbarg, V., Gupta, R., Stevens, R. D., Sanchez, P., Tollard, E., et al. (2012). Assessment of white matter injury and outcome in severe brain trauma: a prospective multicenter cohort. *Anesthesiology* 117, 1300–1310. doi: 10.1097/ALN.0b013e3182755558

Gale, S. D., Johnson, S. C., Bigler, E. D., and Blatter, D. D. (1995). Trauma-induced degenerative changes in brain injury: a morphometric analysis of three patients with preinjury and postinjury MR scans. *J. Neurotrauma* 12, 151–158. doi: 10.1089/neu.1995.12.151

Gardner, A., Kay-Lambkin, F., Stanwell, P., Donnelly, J., Williams, W. H., Hiles, A., et al. (2012). A systematic review of diffusion tensor imaging findings in sports-related concussion. *J. Neurotrauma* 29, 2521–2538. doi: 10.1089/neu.2012.2628

Ge, Y., Grossman, R. I., Babb, J. S., Rabin, M. L., Mannon, L. J., and Kolson, D. L. (2002). Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. *AJNR Am. J. Neuroradiol.* 23, 1327–1333.

Ghosh, A., Wilde, E. A., Hunter, J. V., Bigler, E. D., Chu, Z., Li, X., et al. (2009). The relation between Glasgow Coma Scale score and later cerebral atrophy in paediatric traumatic brain injury. *Brain Inj.* 23, 228–233. doi: 10.1080/02699050802672789

Goh, J. O., and Park, D. C. (2009). Neuroplasticity and cognitive aging: the scaffolding theory of aging and cognition. *Restor. Neurol. Neurosci.* 27, 391–403. doi: 10.3233/RNN-2009-0493

Greenberg, G., Mikulis, D. J., Ng, K., Desouza, D., and Green, R. E. (2008). Use of diffusion tensor imaging to examine subacute white matter injury progression in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S45–S50. doi: 10.1016/j.apmr.2008.08.211

Gunther, M. L., Morandi, A., Krauskopf, E., Pandharipande, P., Girard, T. D., Jackson, J. C., et al. (2012). The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: the VISIONS cohort magnetic resonance imaging study*. *Crit. Care Med.* 40, 2022–2032. doi: 10.1097/CCM.0b013e318250acc0

Harmon, K. G., Drezner, J. A., Gammons, M., Guskiewicz, K. M., Halstead, M., Herring, S. A., et al. (2013). American Medical

Society for Sports Medicine position statement: concussion in sport. *Br. J. Sports Med*. 47, 15–26. doi: 10.1136/bjsports-2012-091941

Harrison, D. M., Caffo, B. S., Shiee, N., Farrell, J. A., Bazin, P. L., Farrell, S. K., et al. (2011). Longitudinal changes in diffusion tensor-based quantitative MRI in multiple sclerosis. *Neurology* 76, 179–186. doi: 10.1212/WNL.0b013e318206ca61

Harrison, D. M., Shiee, N., Bazin, P. L., Newsome, S. D., Ratchford, J. N., Pham, D., et al. (2013). Tract-specific quantitative MRI better correlates with disability than conventional MRI in multiple sclerosis. *J. Neurol.* 260, 397–406. doi: 10.1007/s00415-012-6638-8

Hart, J., Kraut, M. A., Womack, K. B., Strain, J., Didehbani, N., Bartz, E., et al. (2013). Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: a cross-sectional study. *JAMA Neurol.* 70, 326–335. doi: 10.1001/2013.jamaneurol.340

Hedman, A. M., van Haren, N. E., Schnack, H. G., Kahn, R. S., and Hulshoff Pol, H. E. (2011). Human brain changes across the life span: a review of 56 longitudinal magnetic resonance imaging studies. *Hum. Brain Mapp*. 33, 1987–2002. doi: 10.1002/hbm.21334

Hodges, J. R. (2012). Alzheimer's disease and the frontotemporal dementias: contributions to clinico-pathological studies, diagnosis, and cognitive neuroscience. *J. Alzheimers Dis.* 33(Suppl. 1), S211–S217. doi: 10.3233/JAD-2012-129038

Ikonomovic, M. D., Uryu, K., Abrahamson, E. E., Ciallella, J. R., Trojanowski, J. Q., Lee, V. M., et al. (2004). Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury. *Exp. Neurol.* 190, 192–203. doi: 10.1016/j.expneurol.2004.06.011

Immonen, R. J., Kharatishvili, I., Niskanen, J. P., Grohn, H., Pitkanen, A., and Grohn, O. H. (2009). Distinct MRI pattern in lesional and perilesional area after traumatic brain injury in rat–11 months follow-up. *Exp. Neurol.* 215, 29–40. doi: 10.1016/j.expneurol.2008.09.009

Inglese, M., and Ge, Y. (2004). Quantitative MRI: hidden age-related changes in brain tissue. *Top. Magn. Reson. Imaging* 15, 355–363. doi: 10.1097/01.rmr.0000168069.12985.15

Irimia, A., Chambers, M. C., Torgerson, C. M., Filippou, M., Hovda, D. A., Alger, J. R., et al. (2012a). Patient-tailored connectomics visualization for the assessment of white matter atrophy in traumatic brain injury. *Front. Neurol.* 3:10. doi: 10.3389/fneur.2012.00010

Irimia, A., Chambers, M. C., Torgerson, C. M., and Van Horn, J. D. (2012b). Circular representation of human cortical networks for subject and population-level connectomic visualization. *Neuroimage* 60, 1340–1351. doi: 10.1016/j.neuroimage.2012.01.107

Jack, C. R. Jr., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., et al. (2013). Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* 12, 207–216. doi: 10.1016/S1474-4422(12)70291-0

Jacobson, M. W., Delis, D. C., Peavy, G. M., Wetter, S. R., Bigler, E. D., Abildskov, T. J., et al. (2009). The emergence of cognitive discrepancies in preclinical Alzheimer's disease: a six-year case study. *Neurocase* 15, 278–293. doi: 10.1080/13554790902729465

Johnson, V. E., Stewart, J. E., Begbie, F. D., Trojanowski, J. Q., Smith, D. H., and Stewart, W. (2013). Inflamation and white matter degeneration persist for years after a single traumatic brain injury. *Brain* 136, 28–42.

Johnson, V. E., Stewart, W., and Smith, D. H. (2012). Axonal pathology in traumatic brain injury. *Exp. Neurol.* 246, 35–43. doi: 10.1016/j.expneurol.2012.01.013

Johnson, V. E., Stewart, W., Trojanowski, J. Q., and Smith, D. H. (2011). Acute and chronically increased immunoreactivity to phosphorylation-independent but not pathological TDP-43 after a single traumatic brain injury in humans. *Acta Neuropathol.* 122, 715–726. doi: 10.1007/s00401-011-0909-9

Kempton, M. J., Geddes, J. R., Ettinger, U., Williams, S. C., and Grasby, P. M. (2008). Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. *Arch. Gen. Psychiatry* 65, 1017–1032. doi: 10.1001/archpsyc.65.9.1017

Kim, J., Avants, B., Patel, S., Whyte, J., Coslett, B. H., Pluta, J., et al. (2008). Structural consequences of diffuse traumatic brain injury: a large deformation tensor-based morphometry study. *Neuroimage* 39, 1014–1026. doi: 10.1016/j.neuroimage.2007.10.005

Koerte, I. K., Ertl-Wagner, B., Reiser, M., Zafonte, R., and Shenton, M. E. (2012a). White matter integrity in the brains of professional soccer players without a symptomatic concussion. *JAMA* 308, 1859–1861. doi: 10.1001/jama.2012.13735

Koerte, I. K., Kaufmann, D., Hartl, E., Bouix, S., Pasternak, O., Kubicki, M., et al. (2012b). A prospective study of physician-observed concussion during a varsity university hockey season: white matter integrity in ice hockey players. Part 3 of 4. *Neurosurg. Focus* 33, E3. doi: 10.3171/2012.10.FOCUS12303

Kokjohn, T. A., Maarouf, C. L., Daugs, I. D., Hunter, J. M., Whiteside, C. M., Malek-Ahmadi, M., et al. (2013). Neurochemical profile of dementia pugilistica. *J. Neurotrauma* 30, 981–997. doi: 10.1089/neu.2012.2699

Lainhart, J. E., Bigler, E. D., Bocian, M., Coon, H., Dinh, E., Dawson, G., et al. (2006). Head circumference and height in autism: a study by the Collaborative Program of Excellence in Autism. *Am. J. Med. Genet. A* 140, 2257–2274. doi: 10.1002/ajmg.a.31465

Lehman, E. J., Hein, M. J., Baron, S. L., and Gersic, C. M. (2012). Neurodegenerative causes of death among retired National Football League players. *Neurology* 79, 1970–1974. doi: 10.1212/WNL.0b013e31826daf50

Levin, H., and Smith, D. (2013). Traumatic brain injury: networks and neuropathology. *Lancet Neurol.* 12, 15–16. doi: 10.1016/S1474-4422(12)70300-9

Lifshitz, J., Kelley, B. J., and Povlishock, J. T. (2007). Perisomatic thalamic axotomy after diffuse traumatic brain injury is associated with atrophy rather than cell death. *J. Neuropathol. Exp. Neurol.* 66, 218–229. doi: 10.1097/01.jnen.0000248558.75950.4d

Liu, C. Y., Krishnan, A. P., Yan, L., Smith, R. X., Kilroy, E., Alger, J. R., et al. (2013). Complexity and synchronicity of resting state blood oxygenation level-dependent (BOLD) functional MRI in normal aging and cognitive decline. *J. Magn. Reson. Imaging* 38, 36–45. doi: 10.1002/jmri.23961

Lucas, S. M., Rothwell, N. J., and Gibson, R. M. (2006). The role of inflammation in CNS injury and disease. *Br. J. Pharmacol.* 147(Suppl. 1), S232–S240. doi: 10.1038/sj.bjp.0706400

Magnoni, S., and Brody, D. L. (2010). New perspectives on amyloid-beta dynamics after acute brain injury: moving between experimental approaches and studies in the human brain. *Arch. Neurol.* 67, 1068–1073. doi: 10.1001/archneurol.2010.214

Marquez de la Plata, C. D., Garces, J., Shokri Kojori, E., Grinnan, J., Krishnan, K., Pidikiti, R., et al. (2011). Deficits in functional connectivity of hippocampal and frontal lobe circuits after traumatic axonal injury. *Arch. Neurol.* 68, 74–84. doi: 10.1001/archneurol.2010.342

Maxwell, W. L., MacKinnon, M. A., Stewart, J. E., and Graham, D. I. (2010). Stereology of cerebral cortex after traumatic brain injury matched to the Glasgow outcome score. *Brain* 133, 139–160. doi: 10.1093/brain/awp264

Mayer, A. R., Ling, J. M., Yang, Z., Pena, A., Yeo, R. A., and Klimaj, S. (2012). Diffusion abnormalities in pediatric mild traumatic brain injury. *J. Neurosci.* 32, 17961–17969. doi: 10.1523/JNEUROSCI.3379-12.2012

McAllister, T. W. (2011). Neurobiological consequences of traumatic brain injury. *Dialogues Clin. Neurosci.* 13, 287–300.

McAllister, T. W., Ford, J. C., Ji, S., Beckwith, J. G., Flashman, L. A., Paulsen, K., et al. (2012). Maximum principal strain and strain rate associated with concussion diagnosis correlates with changes in corpus callosum white matter indices. *Ann. Biomed. Eng.* 40, 127–140. doi: 10.1007/s10439-011-0402-6

McKee, A. C., Stein, T. D., Nowinski, C. J., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., et al. (2012). The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136, 43–64.

Moretti, L., Cristofori, I., Weaver, S. M., Chau, A., Portelli, J. N., and Grafman, J. (2012). Cognitive decline in older adults with a history of traumatic brain injury. *Lancet Neurol.* 11, 1103–1112. doi: 10.1016/S1474-4422(12)70226-0

Morra, J. H., Tu, Z., Apostolova, L. G., Green, A. E., Avedissian, C., Madsen, S. K., et al. (2009). Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. *Hum. Brain Mapp.* 30, 2766–2788. doi: 10.1002/hbm.20708

Ng, K., Mikulis, D. J., Glazer, J., Kabani, N., Till, C., Greenberg, G., et al. (2008). Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89,

S35–S44. doi: 10.1016/j.apmr.2008.07.006

Okonkwo, O. C., Alosco, M. L., Jerskey, B. A., Sweet, L. H., Ott, B. R., and Tremont, G. (2010). Cerebral atrophy, apolipoprotein E varepsilon4, and rate of decline in everyday function among patients with amnestic mild cognitive impairment. *Alzheimers Dement*. 6, 404–411. doi: 10.1016/j.jalz.2010.02.003

Olesen, P. J., Guo, X., Gustafson, D., Borjesson-Hanson, A., Sacuiu, S., Eckerstrom, C., et al. (2011). A population-based study on the influence of brain atrophy on 20-year survival after age 85. *Neurology* 76, 879–886. doi: 10.1212/WNL.0b013e31820f2e26

Palacios, E. M., Sala-Llonch, R., Junque, C., Roig, T., Tormos, J. M., Bargallo, N., et al. (2012). White matter integrity related to functional working memory networks in traumatic brain injury. *Neurology* 78, 852–860. doi: 10.1212/WNL.0b013e31824c465a

Palacios, E. M., Sala-Llonch, R., Junque, C., Fernandez-Espejo, D., Roig, T., Tormos, J. M., et al. (2013). Long-term declarative memory deficits in diffuse TBI: correlations with cortical thickness, white matter integrity and hippocampal volume. *Cortex* 49, 646–657. doi: 10.1016/j.cortex.2012.02.011

Pandit, A. S., Expert, P., Lambiotte, R., Bonnelle, V., Leech, R., Turkheimer, F. E., et al. (2013). Traumatic brain injury impairs small-world topology. *Neurology* 80, 1826–1833. doi: 10.1212/WNL.0b013e3182929f38

Pitkanen, A., Tuunanen, J., Kalviainen, R., Partanen, K., and Salmenpera, T. (1998). Amygdala damage in experimental and human temporal lobe epilepsy. *Epilepsy Res*. 32, 233–253. doi: 10.1016/S0920-1211(98)00055-2

Plassman, B. L., Havlik, R. J., Steffens, D. C., Helms, M. J., Newman, T. N., Drosdick, D., et al. (2000). Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology* 55, 1158–1166. doi: 10.1212/WNL.55.8.1158

Ponsford, J., McLaren, A., Schonberger, M., Burke, R., Rudzki, D., Olver, J., et al. (2011). The association between apolipoprotein E and traumatic brain injury severity and functional outcome in a rehabilitation sample. *J. Neurotrauma* 28, 1683–1692. doi: 10.1089/neu.2010.1623

Price, C. C., Mitchell, S. M., Brumback, B., Tanner, J. J., Schmalfuss, I., Lamar, M., et al. (2012). MRI-leukoaraiosis thresholds and the phenotypic expression of dementia. *Neurology* 79, 734–740. doi: 10.1212/WNL.0b013e3182661ef6

Purohit, D. P., Batheja, N. O., Sano, M., Jashnani, K. D., Kalaria, R. N., Karunamurthy, A., et al. (2011). Profiles of Alzheimer's disease-related pathology in an aging urban population sample in India. *J. Alzheimers Dis.* 24, 187–196. doi: 10.3233/JAD-2010-101698

Ramlackhansingh, A. F., Brooks, D. J., Greenwood, R. J., Bose, S. K., Turkheimer, F. E., Kinnunen, K. M., et al. (2011). Inflammation after trauma: microglial activation and traumatic brain injury. *Ann. Neurol.* 70, 374–383. doi: 10.1002/ana.22455

Raymont, V., Salazar, A. M., Lipsky, R., Goldman, D., Tasick, G., and Grafman, J. (2010). Correlates of posttraumatic epilepsy 35 years following combat brain injury. *Neurology* 75, 224–229. doi: 10.1212/WNL.0b013e3181e8e6d0

Rosazza, C., and Minati, L. (2011). Resting-state brain networks: literature review and clinical applications. *Neurol. Sci.* 32, 773–785. doi: 10.1007/s10072-011-0636-y

Rowson, S., Duma, S. M., Beckwith, J. G., Chu, J. J., Greenwald, R. M., Crisco, J. J., et al. (2012). Rotational head kinematics in football impacts: an injury risk function for concussion. *Ann. Biomed. Eng.* 40, 1–13. doi: 10.1007/s10439-011-0392-4

Rubia, K. (2012). Functional brain imaging across development. *Eur. Child Adolesc. Psychiatry*. doi: 10.1007/s00787-012-0291-8. [Epub ahead of print].

Sayed, N., Culver, C., Dams-O'Connor, K., Hammond, F., and Diaz-Arrastia, R. (2013). Clinical phenotype of dementia after traumatic brain injury. *J. Neurotrauma* 30, 1117–1120. doi: 10.1089/neu.2012.2638

Schipper, H. M. (2011). Apolipoprotein E: implications for AD neurobiology, epidemiology and risk assessment. *Neurobiol. Aging* 32, 778–790. doi: 10.1016/j.neurobiolaging.2009.04.021

Shi, Y., Short, S. J., Knickmeyer, R. C., Wang, J., Coe, C. L., Niethammer, M., et al. (2012). Diffusion tensor imaging-based characterization of brain neurodevelopment in primates. *Cereb. Cortex* 23, 36–48. doi: 10.1093/cercor/bhr372

Shively, S., Scher, A. I., Perl, D. P., and Diaz-Arrastia, R. (2012). Dementia resulting from traumatic brain injury: what is the pathology? *Arch. Neurol.* 69, 1245–1251.

Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., et al. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain* 131, 559–572. doi: 10.1093/brain/awm294

Sidaros, A., Skimminge, A., Liptrot, M. G., Sidaros, K., Engberg, A. W., Herning, M., et al. (2009). Long-term global and regional brain volume changes following severe traumatic brain injury: a longitudinal study with clinical correlates. *Neuroimage* 44, 1–8. doi: 10.1016/j.neuroimage.2008.08.030

Silbert, L. C., Dodge, H. H., Perkins, L. G., Sherbakov, L., Lahna, D., Erten-Lyons, D., et al. (2012). Trajectory of white matter hyperintensity burden preceding mild cognitive impairment. *Neurology* 79, 741–747. doi: 10.1212/WNL.0b013e3182661f2b

Sivanandam, T. M., and Thakur, M. K. (2012). Traumatic brain injury: a risk factor for Alzheimer's disease. *Neurosci. Biobehav. Rev.* 36, 1376–1381. doi: 10.1016/j.neubiorev.2012.02.013

Skoog, I., Olesen, P. J., Blennow, K., Palmertz, B., Johnson, S. C., and Bigler, E. D. (2012). Head size may modify the impact of white matter lesions on dementia. *Neurobiol. Aging* 33, 1186–1193. doi: 10.1016/j.neurobiolaging.2011.01.011

Smith, C. (2013). Review: the long-term consequences of microglial activation following acute traumatic brain injury. *Neuropathol. Appl. Neurobiol.* 39, 35–44. doi: 10.1111/nan.12006

Smith, C., Gentleman, S. M., Leclercq, P. D., Murray, L. S., Griffin, W. S., Graham, D. I., et al. (2012). The neuroinflammatory response in humans after traumatic brain injury. *Neuropathol. Appl. Neurobiol.* doi: 10.1111/nan.12008. [Epub ahead of print].

Smith, D. H., Chen, X. H., Nonaka, M., Trojanowski, J. Q., Lee, V. M., Saatman, K. E., et al. (1999). Accumulation of amyloid beta and tau and the formation of neurofilament inclusions following diffuse brain injury in the pig. *J. Neuropathol. Exp. Neurol.* 58, 982–992. doi: 10.1097/00005072-199909000-00008

Smith, D. H., Chen, X. H., Pierce, J. E., Wolf, J. A., Trojanowski, J. Q., Graham, D. I., et al. (1997). Progressive atrophy and neuron death for one year following brain trauma in the rat. *J. Neurotrauma* 14, 715–727. doi: 10.1089/neu.1997.14.715

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 7, 280–292. doi: 10.1016/j.jalz.2011.03.003

Steffener, J., Habeck, C. G., and Stern, Y. (2012). Age-related changes in task related functional network connectivity. *PLoS ONE* 7:e44421. doi: 10.1371/journal.pone.0044421

Stoica, B. A., and Faden, A. I. (2010). Cell death mechanisms and modulation in traumatic brain injury. *Neurotherapeutics* 7, 3–12. doi: 10.1016/j.nurt.2009.10.023

Tasker, R. C. (2006). Changes in white matter late after severe traumatic brain injury in childhood. *Dev. Neurosci.* 28, 302–308. doi: 10.1159/000094156

Tata, D. A., and Anderson, B. J. (2010). The effects of chronic glucocorticoid exposure on dendritic length, synapse numbers and glial volume in animal models: implications for hippocampal volume reductions in depression. *Physiol. Behav.* 99, 186–193. doi: 10.1016/j.physbeh.2009.09.008

Tate, D. F., Khedraki, R., Neeley, E. S., Ryser, D. K., and Bigler, E. D. (2011). Cerebral volume loss, cognitive deficit, and neuropsychological performance: comparative measures of brain atrophy: II. Traumatic brain injury. *J. Int. Neuropsychol. Soc.* 17, 308–316. doi: 10.1017/S1355617710001670

Tomaiuolo, F., Bivona, U., Lerch, J. P., Di Paola, M., Carlesimo, G. A., Ciurli, P., et al. (2012). Memory and anatomical change in severe non missile traumatic brain injury: approximately 1 vs. approximately 8 years follow-up. *Brain Res. Bull.* 87, 373–382. doi: 10.1016/j.brainresbull.2012.01.008

Toth, A., Kovacs, N., Perlaki, G., Orsi, G., Aradi, M., Komaromy, H., et al. (2013). Multi-modal magnetic resonance imaging in the acute and sub-acute phase of mild traumatic brain injury: can we see the difference? *J. Neurotrauma* 30, 2–10. doi: 10.1089/neu.2012.2486

Tremblay, S., De Beaumont, L., Henry, L. C., Boulanger, Y., Evans, A. C., Bourgouin, P., et al. (2013).

Sports concussions and aging: a neuroimaging investigation. *Cereb. Cortex* 23, 1159–1166. doi: 10.1093/cercor/bhs102

Van Den Heuvel, M. P., and Sporns, O. (2011). Rich-club organization of the human connectome. *J. Neurosci*. 31, 15775–15786. doi: 10.1523/JNEUROSCI.3539-11.2011

Victoroff, J. (2013). Traumatic encephalopathy: review and provisional research diagnostic criteria. *NeuroRehabilitation* 32, 211–224.

Voelbel, G. T., Genova, H. M., Chiaravalotti, N. D., and Hoptman, M. J. (2012). Diffusion tensor imaging of traumatic brain injury review: implications for neurorehabilitation. *NeuroRehabilitation* 31, 281–293.

Wang, H. K., Lin, S. H., Sung, P. S., Wu, M. H., Hung, K. W., Wang, L. C., et al. (2012). Population based study on patients with traumatic brain injury suggests increased risk of dementia. *J. Neurol. Neurosurg. Psychiatry* 83, 1080–1085. doi: 10.1136/jnnp-2012-302633

Wang, J. Y., Bakhadirov, K., Abdi, H., Devous, M. D. Sr., Marquez de la Plata, C. D., Moore, C., et al. (2011). Longitudinal changes of structural connectivity in traumatic axonal injury. *Neurology* 77, 818–826. doi: 10.1212/WNL.0b013e31822c61d7

Weinstein, G., Wolf, P. A., Beiser, A. S., Au, R., and Seshadri, S. (2013). Risk estimations, risk factors, and genetic variants associated with Alzheimer's disease in selected publications from the Framingham Heart Study. *J. Alzheimers Dis*. 33(Suppl 1), S439–S445. doi: 10.3233/JAD-2012-129040

Wilde, E. A., Bigler, E. D., Pedroza, C., and Ryser, D. K. (2006a). Post-traumatic amnesia predicts long-term cerebral atrophy in traumatic brain injury. *Brain Inj*. 20, 695–699. doi: 10.1080/02699050600744079

Wilde, E. A., Chu, Z., Bigler, E. D., Hunter, J. V., Fearing, M. A., Hanten, G., et al. (2006b). Diffusion tensor imaging in the corpus callosum in children after moderate to severe traumatic brain injury. *J. Neurotrauma* 23, 1412–1426. doi: 10.1089/neu.2006.23.1412

Wilde, E. A., Ramos, M. A., Yallampalli, R., Bigler, E. D., McCauley, S. R., Chu, Z., et al. (2010). Diffusion tensor imaging of the cingulum bundle in children after traumatic brain injury. *Dev. Neuropsychol*. 35, 333–351. doi: 10.1080/87565641003696940

Wu, T. C., Wilde, E. A., Bigler, E. D., Li, X., Merkley, T. L., Yallampalli, R., et al. (2010). Longitudinal changes in the corpus callosum following pediatric traumatic brain injury. *Dev. Neurosci*. 32, 361–373.

Xu, Y., McArthur, D. L., Alger, J. R., Etchepare, M., Hovda, D. A., Glenn, T. C., et al. (2010). Early nonischemic oxidative metabolic dysfunction leads to chronic brain atrophy in traumatic brain injury. *J. Cereb. Blood Flow Metab*. 30, 883–894. doi: 10.1038/jcbfm.2009.263

Yallampalli, R., Wilde, E. A., Bigler, E. D., McCauley, S. R., Hanten, G., Troyanskaya, M., et al. (2013). Acute white matter differences in the fornix following mild traumatic brain injury using diffusion tensor imaging. *J. Neuroimaging* 23, 224–227. doi: 10.1111/j.1552-6569.2010.00537.x

Zielinski, B. A., Gennatas, E. D., Zhou, J., and Seeley, W. W. (2010). Network-level structural covariance in the developing brain. *Proc. Natl. Acad. Sci. U.S.A*. 107, 18191–18196. doi: 10.1073/pnas.1003109107

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Scale and pattern of atrophy in the chronic stages of moderate-severe TBI

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Background: Moderate-severe traumatic brain injury (TBI) is increasingly being understood as a progressive disorder, with growing evidence of reduced brain volume and white matter (WM) integrity as well as lesion expansion in the chronic phases of injury. The scale of these losses has yet to be investigated, and pattern of change across structures has received limited attention.

Objectives: (1) To measure the percentage of patients in our TBI sample showing atrophy from 5 to 20 months post-injury in the whole brain and in structures with known vulnerability to acute TBI, and (2) To examine relative vulnerability and patterns of volume loss across structures.

Methods: Fifty-six TBI patients [complicated mild to severe, with mean Glasgow Coma Scale (GCS) in severe range] underwent MRI at, on average, 5 and 20 months post-injury; 12 healthy controls underwent MRI twice, with a mean gap between scans of 25.4 months. Mean monthly percent volume change was computed for whole brain (ventricle-to-brain ratio; VBR), corpus callosum (CC), and right and left hippocampi (HPC).

Results: (1) Using a threshold of 2 z-scores below controls, 96% of patients showed atrophy across time points in at least one region; 75% showed atrophy in at least 3 of the 4 regions measured. (2) There were no significant differences in the proportion of patients who showed atrophy across structures. For those showing decline in VBR, there was a significant association with both the CC and the right HPC ($P < 0.05$ for both comparisons). There were also significant associations between those showing decline in (i) right and left HPC ($P < 0.05$); (ii) all combinations of genu, body and splenium of the CC ($P < 0.05$), and (iii) head and tail of the right HPC ($P < 0.05$ all sub-structure comparisons).

Conclusions: Atrophy in chronic TBI is robust, and the CC, right HPC and left HPC appear equally vulnerable. Significant associations between the right and left HPC, and within substructures of the CC and right HPC, raise the possibility of common mechanisms for these regions, including transneuronal degeneration. Given the 96% incidence rate of atrophy, a genetic explanation is unlikely to explain all findings. Multiple and possibly synergistic mechanisms may explain findings. Atrophy has been associated with poorer functional outcomes, but recent findings suggest there is potential to offset this. A better, understanding of the underlying mechanisms could permit targeted therapy enabling better long-term outcomes.

Keywords: atrophy, chronic, degeneration, traumatic brain injury, progression, MRI

INTRODUCTION

Traumatic brain injury (TBI) is increasingly being understood as a chronic and possibly progressive disease, rather than an injury with a circumscribed period of recovery and a static course thereafter (Ng et al., 2008; Masel and Dewitt, 2010; Bigler, 2013a). Evidence is accumulating from several laboratories including our own that following early cognitive recovery, many patients show statistically and clinically significant cognitive decline in the ensuing months (Ruff et al., 1991) and years (Millis et al., 2001; Till et al., 2008). We and others have also demonstrated that the brain's structure is not static after resolution of acute injuries, with TBI patients showing volume loss and reduced white matter (WM) integrity during the sub-acute and chronic stages of injury (Bendlin et al., 2008; Greenberg et al., 2008; Ng et al., 2008; Sidaros et al., 2009; Farbota et al., 2012; Adnan et al., 2013). Given that such atrophy is observed in some studies

well after the resolution of acute events (Greenberg et al., 2008; Ng et al., 2008; Ross et al., 2012), and that sub-acute structural deterioration has been correlated with functional and behavioral outcomes (Bendlin et al., 2008; Sidaros et al., 2009), these changes cannot be attributed simply to encephalomalacia (i.e., scar formation associated with gliosis) or to resolution of edema. The evidence is thus supportive of a progressive neuropathology, possible mechanisms of which have been recently reviewed (Smith et al., 2013).

This very different course of TBI than has been traditionally assumed has clinical and scientific implications for how we understand and treat TBI patients, in both the short and longer term. Therefore, it is important to gain an understanding of the scale of atrophy: What proportion of TBI patients demonstrates progressive loss of brain volume? Previous studies have demonstrated group differences in atrophy and/or WM integrity loss between TBI patients and controls. What has yet to be investigated is the actual prevalence of patients who show decline, and moreover, who do so at what might be considered a clinically significant degree. Such information is needed to understand whether it is a subset of TBI patients who are at risk of degeneration or the majority. While atrophy in a subset would direct researchers (and clinicians) to evaluate risk factors for degeneration; ubiquitous atrophy would suggest that TBI itself is a degenerative disorder. The central aim of this study, therefore, was to begin to shed light on this question of scale.

To address the question, we undertook volumetric MRI measurements in TBI patients at approximately 5 and 20 months post-injury and compared the extent of volume loss across time for each patient to a normative control sample, also measured at two time points. We called patients showing significant volume loss "decliners." In both samples, we examined the whole brain using ventricle-to-brain ratio (VBR), as well as the hippocampi and corpus callosum (CC) and their sub-structures, areas with demonstrated vulnerability to the acute mechanical and neurochemical effects of injury (e.g., axonal deformation, hypoxia, excitotoxic cascades Povlishock and Katz, 2005). Our cohort ranged in severity from complicated mild to severe, but was overall a severely injured group of patients.

With regard to prediction of the scale of atrophy, in a previous study in which we examined lesion expansion, we found that in our sample of 14 patients, 10 showed lesion expansion across time within the chronic stages of injury (Ng et al., 2008). We therefore predicted that at least half of our sample in the current study would show significant volume loss on at least one measure.

We were also interested in the relative vulnerability of the individual structures and sub-structures, and in their pattern of deterioration. With regard to relative vulnerability, we measured the number of decliners (i.e., people who showed atrophy across time points as compared to normative controls) for each structure in order to ascertain whether one structure showed a greater frequency of decliners than another structure.

We speculated that those regions most vulnerable to *acute* injury would show the greatest chronic atrophy. This is because of growing evidence that while "use" increases brain (and in particular hippocampal) volume (Draganski et al., 2006; Maguire et al., 2006), "disuse" mediates volume loss (Underwood and Coulson, 2008; Miller et al., 2013). Therefore, we reasoned that regions most susceptible to initial damage, should sustain greater disuse, and therefore greater later atrophy. Both the CC and the hippocampi are commonly affected in TBI, especially when rotational forces are involved. In one study in children, the hippocampus was identified as the most vulnerable structure to TBI (Wilde et al., 2006), and it is vulnerable to acute phase damage from a variety of mechanisms, (e.g., mechanical deformation, hypoxic/excitotoxic injury, afferent and efferent disconnection of projections, and compromised neurogenesis Greer et al., 2012). The hippocampal head has been shown to be disproportionately vulnerable, as compared to the body and tail (Ariza et al., 2006). We therefore predicted that more individuals would show chronic degeneration in the hippocampal head than any other structure/sub-structure examined.

With regard to the pattern of deterioration, we asked whether the volumes of those regions measured in the study shrink commensurately with one another, and whether their sub-regions would shrink commensurately. In other words, did individuals who showed atrophy on one structure, also necessarily show atrophy on another?

In our previous research into sub-acute cognitive decline (Till et al., 2008), we observed marked variability in the cognitive and psychomotor functions that showed decline from 12 to 24 months post-injury, both within and between subjects. This suggested that atrophy might not have a predictable pattern. On this basis, we predicted that decline in one region would *not* be associated with decline in another, although we expected VBR—as an index that subsumes all other structures—to be associated with the hippocampi and CC.

MATERIALS AND METHODS

All participants gave their informed consent, except where participants were clinically judged as unable to provide informed consent; here, a substitute decision maker provided informed consent. In such cases, all patients gave their assent to participate. The study was approved by the Research Ethics Board of the Toronto Rehabiltation Institute where the research took place

PARTICIPANTS

TBI Patient group

Patient participants were 56 males and females with clinically confirmed TBI. See **Table 1** for injury and demographic characteristics of the sample, which were ascertained through medical records, clinical interview and direct testing. Overall, this was a typical group of adult TBI patients with more males than females, more motor-vehicle accidents than other causes of injury, estimated pre-morbid IQ (as measured by the Wechsler Test of Adult Reading (WTAR) Weschler, 2001; Green et al., 2008) in the average range, and just over high-school education. TBI severity for participants was based on the lowest Glasgow Coma Scale (GCS) score obtained from the acute care medical chart, where GCS was available and valid, or from length of post-traumatic amnesia (PTA), which was obtained from medical records and/or from clinical interview with the patient and family members at approximately 2 months post-injury. PTA classifications were based on

Table 1 | Injury and demographic characteristics of TBI sample (*N* = 56).

Variable	Proportion/mean	*SD* (range)
Age (years)	*M* = 40.16	15.63 (17–73)
Education (years)	*M* = 13.63	3.36 (6–21)
Estimated pre-morbid IQ (WTAR) (*N* = 51)	*M* = 98.45	18.26 (67–125)
Sex	73% = male 27% = female	
SOCIO-ECONOMIC STATUS (BASED ON HOLLINGSHEAD CLASSIFICATION Hollingshead and Redlich, 1958)		
1. Major business/professional	3.8%	
2. Medium business/minor professional, technical	41.5%	
3. Skilled craftsperson, clerical, sales worker	17%	
4. Machine operator, semiskilled worker	18.9%	
5. Unskilled laborer, menial service worker	18.9%	
TYPE OF INJURY		
Motor vehicle accident	57.1%	
Fall	37.5%	
Assault	3.6%	
Sports injury	1.8%	
SEVERITY OF INJURY VARIABLES		
Acute care length of stay (days)	*M* = 37.44days	20.01 (5–98)
GCS (lowest of recorded scores)	*M* = 6.19	3.42(3–13)
Mild (13–15)	10.7	
Moderate (9–12)	5.4%	
Severe (≤8)	69.6%	
Missing data	14.3%	
LENGTH OF POST-TRAUMATIC AMNESIA		
Less then 5 min, very mild	3.6%	
1–24 h, moderate	1.8%	
1–7 days, severe	21.4%	
1–4 weeks, very severe	44.6%	
>4 weeks, extremely severe	23.2%	
Missing data	5.4%	

Lezak (2004). As indicated in **Table 1**, patients ranged in severity from complicated mild to severe or greater, with mean TBI severity based on GCS in the severe range ($M = 6.2$).

All patient participants were recruited at a large, urban rehabilitation teaching hospital in Toronto from the in-patient Acquired Brain Injury service. The patients were part of an ongoing, prospective study on recovery from TBI (*The Toronto Rehab Traumatic Brain Injury Recovery Study*), which includes cognitive, motor, and neuro-imaging assessments at multiple time points. Inclusion criteria for the larger study comprise: clinically confirmed TBI with central (as opposed to orthopedic) injuries severe enough to warrant in-patient neurorehabilitation; out of PTA by 3 months post-injury; aged between 17 and 75; able to use at least one upper extremity; and, functional command of English. An additional inclusion criterion for the present study was completion of two or more MRIs. Exclusion criteria for the larger study include: past history of TBI; history of psychotic or neurological illness; and, TBI sustained secondary to another neurological event (e.g., a stroke). An additional exclusion criterion for the current study was an intervening neurological event between the first and follow-up MRI with the potential to influence the structural status of the brain (e.g., another TBI or intra-cranial infection).

Healthy control group

Twelve healthy adult control participants were recruited to the current study. These individuals were students and staff members at the rehabilitation hospital or friends or family members of students and staff members. Controls were excluded if they had a previous history of TBI, including concussion, or any other disease affecting the central nervous system. The control group was 50% male, with a mean age of 36.3 years ($SD = 12.5$, range 18–60), and a mean education of 17.5 years ($SD = 2.2$, range 11–21).

DESIGN AND PROCEDURES

The study was a prospective, repeated measures design. The normative control group was used to establish the level of decline in each patient for each structure. This was computed for each subject for each structure, as described below. MRIs were administered at two time points. The first was completed for all patients at a mean of 5.2 months post-injury, ($SD = 1.15$; range: 3.7–10.4). The second scan was at a mean of 20 months post-injury ($SD = 4.7$; range = 10.5–56.1), with a mean gap between scans of 14.8 months ($SD = 10.9$; range = 4.4–52.2). For control participants, the mean gap between scans was 25.4 months ($SD = 10.0$; range = 10.4–39.4). The relatively greater gap in the controls biased hypotheses against Type I errors. The longer gap between control scans allowed for greater non-specific decline to transpire, thereby increasing the threshold for reaching decline in the patients.

The MRI outcome measures were as follows: computed monthly percent change for ventricle to brain ratio (VBR), volumes of the left hippocampus (HPC-L; i.e., HPC-L total, HPC-L head, HPC-L body, HPC-L tail), volumes of the right hippocampus (HPC-R; i.e., HPC-R total, HPC-R head, HPC-R body, HPC-R tail), and CC volumes (i.e., CC total, CC genu, CC body, CC splenium).

All participants were required to pass a rigorous, clinical screening procedure prior to the first MRI assessment. All MRIs were conducted at a separate site (Toronto Western Hospital), which is part of the same center. All equipment and acquisition parameters were identical for the initial and follow-up assessments. One of two MRI technologists performed all MRIs.

Acquisition protocol

MRI scans were acquired on a General Electric (GE) Signa-Echospeed 1.5 Tesla HD scanner (SIGNA EXCITE, GE Healthcare, Milwaukee WI), using an eight channel head coil. Sequences included sagittal T1 ($TR/TE = 300/13$ ms), slice thickness = 5 mm, space 2.5 mm, matrix 256 × 128 axial

gradient recalled echo (GRE) $TR/TE = 450/20$, flip angle = 20°, slice thickness = 3 mm no gap, matrix 256 × 192 axial fluid-attenuated-inversion-recovery (FLAIR) TR/TE = 9000/45 ms, TI (inversion time) = 2200 ms, slice thickness = 5 mm no gap, matrix 256 × 192 axial fast spin echo (FSE) proton density (PD)/T2 TR/TE 5500/30,90 ms, slice thickness = 3 mm no gap, matrix 256 × 192. All above mentioned sequences were obtained with a 22 cm field of view (FOV). The high-resolution isotropic T1 weighted, three-dimensional IR prepped radio-frequency spoiled-gradient recalled-echo (3D IRSPGR) images $TI/TR/TE =$ 12/300/5,TI, $FA = 20$, slice thickness = 1 mm no gap, matrix = 256 × 256 were acquired in the axial plane utilizing a 25 cm FOV. The entire scanning session lasted approximately 55 min.

Image processing and analysis

The MR images were transferred to a workstation for image processing. The scans were received in the Digital Imaging and Communications in Medicine (DICOM) file format and were subsequently converted into (Medical Imaging Network Common Data Form; MINC) file format that was created at McConnell Brain maging Centre of the Montreal Neurological Institute. Following this procedure, the files were anonymized.

A number of image processing steps were performed in order to make MRI data usable for image analysis. The first step was the intensity non-uniformity correction (Sled et al., 1998). These images were then linearly registered (aligned) into stereotaxic coordinates (Collins et al., 1994) based on the Talairach atlas (Talairach and Tournoux, 1988). The linear registration to Talairach coordinates was accomplished through 3D cross-correlation between a given volume and an average MR brain image previously converted into the Talairach coordinate system (Collins et al., 1994). After the registration the images had the same size and orientation, allowing for direct anatomical comparisons between subjects. A second non-uniformity correction was performed after the registration, which helped to remove any residual non-uniformity artifacts.

Every voxel in a non-uniformity corrected and registered image was then classified into one of the three classes: cerebrospinal fluid (CSF), gray matter (GM), and WM using an automated tissue classification algorithm (Zijdenbos et al., 1998). Subsequently, cortical surface extraction from the tissue-classified images was performed, resulting in a 3D reconstruction of the cortical surface. Next, the skull and scalp were removed in the tissue-classified images using the 3D surface extraction as a mask in order to obtain the tissue volumes of the whole brain. Thus, the volumes of CSF, GM, and WM reported in this study were calculated using the tissue-classified images, which excluded the skull, scalp, cerebellum, and brainstem. The combination of the GM and WM was used as the whole brain volume in the VBR analysis.

The hippocampi were manually outlined using Analyze TM 8.1 (Brain Imaging Resource, Mayo Clinic, MN) by an experienced tracer (JM) from coronally orientated MR images in the anterior-posterior direction. Calculations of volumes were computed automatically by multiplying the number of voxels traced in each slice, by their depth (i.e., slice thickness). As described by Watson et al. (1992, 1997), the anterior tip of the HPC until the slice before the opening of the crux of the fornix was measured as the HPC head and body and included the subiculum, CA1-areas, and dentate gyrus. The HPC tail was measured from the slice immediately posterior to that which represented the last slice according to the Watson protocol (see Maller et al., 2007 for a more detailed description of this procedure) (Maller et al., 2007).

The CC was manually traced on the midline sagittal slice of the T1 images using anatomical landmarks in an hierarchical order on a Windows XP Professional workstation (Core2Duo CPU, 2GIG RAM) using the Region of Interest module within analyzetm 8.1 (Brain Imaging Resource, Mayo Clinic, MN, USA). The landmarks based on the midline sagittal slice were, first, no WM or only minimal WM in the cortical mantle surrounding the CC, second, the interthalamic adhesion, and third, the transparent septum and the visibility of the aqueduct of Sylvius. To adjust for total brain volume, total midsagittal CC area and every subregional area in the analyses data were normalized by dividing by each individual's total intracranial volume (ICV). ICV was calculated from the total of GM, WM, and cerebrospinal fluid volumes which were estimated from processing the T1-weighted scans through FSL 4.0 (Analysisgroup, 2012), using the FAST module.

Analyses

Percentage of people showing significant decline in volume. As noted above, patients were classified as "decliners" if they showed atrophy in parenchymal tissue at a threshold of at least 2 z-scores below that of controls. (Note that we use the term "below" here rather than "greater than" for clarity of exposition.) We calculated a z-score for each patient participant using the following method: First, for each structure and substructure, percent change from time 1 to time 2 was calculated for patients and controls using the following formula: $[t2 - t1/(t1 + t2)] * 100$. Second, *monthly* percent change was then calculated in order to compare subjects with differing temporal gaps between scans. Third, a z-score was calculated for each patient using his/her *observed* score (i.e., percent change per month), the *expected* score (i.e., mean monthly percent change for controls), and the standard deviation for monthly percent change in the control group. We used a conservative z-score cut-off to classify decliners. Only if the patient was at least 2 z-scores below that of controls was he/she classified as a decliner. This enabled us to compute the percentage of decliners in our sample, in order to address the primary objective of our study.

Relative vulnerability of decline of structures/sub-structures and pattern of deterioration. To examine whether structures were equally vulnerable to decline or whether the number of decliners varied across structures, we calculated 95% confidence intervals for each proportion of decliners across structures, and substructures. To examine whether decline in one structure was associated with decline in another, we calculated PHI coefficients and their 95% confidence intervals between structures and between substructures. This enabled us to measure the degree of overlap within subjects in decliner classification across the structures (i.e., is there a correlation between those classified as decliners and non-decliners in one structure and those in another?). The PHI coefficient is a measure of association for two binary variables, interpreted similarly to the Pearson Correlation Coefficient.

Presentation of findings. Results are presented by each of the three research questions: (1) the overall percentage of people showing decline on at least one structure, and the number of structures on which subjects declined; (2) the relative vulnerability of structures (i.e., respective number of decliners in each structure), and (3) the pattern of atrophy (i.e., whether decline in one structure was associated with decline in another).

RESULTS

DEMOGRAPHIC COMPARISONS BETWEEN CONTROLS AND PATIENTS

There was no significant difference between the patients and controls for age, $t = 0.897$ ($df = 72$), $p = 0.373$, Cohen's $d = 0.211$. The controls had significantly more education than the patients, $t = -4.25$ ($df = 72$), $p < 0.001$, Cohen's $d = -1.00$.

DECLINERS: PERCENTAGE OF PATIENTS WHO SHOW ATROPHY THAT IS AT LEAST 2 z-SCORES BELOW THAT OF CONTROLS

Table 2 shows the monthly percent atrophy in the control group. The control group monthly percent changes were extremely small, with all scores close to 0, consistent with stability over time. [Note that while the primary aim of the study was to ascertain the *percentage* of decliners in our sample, we have included patient means with unpaired *t*-test results (all assuming unequal variances based on Levene's tests) to permit group mean comparisons]. These illustrate highly significant group differences.

Table 3 shows that compared to the normative group, over 96% of patients showed decline in at least one region. The majority (75%) showed decline in at least three of the four regions measured.

In **Table 4** the absolute number and percentage of decliners by structure are presented. Over 70% of patients showed atrophy within each of the right and left HPC, the CC and the whole brain; moreover, the lower bounds of the confidence intervals for each of these values was greater than 50%. Therefore, the results strongly support our hypothesis that more than 50% of patients would show atrophy of the brain.

RELATIVE VULNERABILITY TO DECLINE OF STRUCTURES AND SUB-STRUCTURES

Examining similarities and differences across structures in the number of decliners, **Table 4** shows that, the highest absolute number of decliners is in VBR; this is not surprising as VBR is an index of total brain volume loss that subsumes all structures. However, none of the structures (including VBR) differed significantly from one another with respect to the number of decliners, with confidence intervals overlapping substantially. Within the substructures, it is interesting to note that only the genu of the CC was different from its respective sub-structures, with significantly fewer decliners than in either the body or the splenium. These results did not support our hypothesis that the hippocampus, and particularly the hippocampal head would show greatest vulnerability.

PATTERN OF ATROPHY ACROSS STRUCTURES

Examining whether atrophy across structures and sub-structures was related, we examined the association between decliners. If a patient showed atrophy across time on one structure, were they likely to also show atrophy on another structure? **Table 5A** shows the PHI coefficients and their 95% confidence intervals between regions measured. There was an overarching relationship, that

Table 2 | Percent decline (by group) across structures and substructures.

Structure	Percent atrophy per month in healthy control participants ($N = 12$)	Percent atrophy per month in patients ($N = 56$)
VBR[a]	0.18 (0.21)	1.32 (1.21)*****
HPC-L head	−0.008 (0.03)	−0.300 (0.63)**
HPC-L body	−0.004 (0.04)	−0.364 (0.59)*****
HPC-L tail	0.054 (0.08)	−0.676 (1.44)*****
HPC-L total	−0.002 (0.02)	−0.348 (0.48)*****
HPC-R head	0.004 (0.03)	−0.248 (0.60)**
HPC-R body	0.005 (0.03)	−0.331 (0.83)**
HPC-R tail	−0.023 (0.05)	−0.662 (1.05)*****
HPC-R total	0.002 (0.03)	−0.324 (0.53)*****
CC genu	−0.14 (0.11)	−0.855 (1.24)*****
CC body	0.09 (0.09)	−0.765 (1.33)*****
CC splenium	0.08 (0.09)	−0.805 (0.81)*****
CC total	−0.02 (0.04)	−0.812 (0.88)*****

[a] *Positive change for VBR denotes atrophy.*

***P < 0.005; *****P < 0.00001.*

Table 3 | The number of patients who show atrophy.

	Number/(percentage) of decliners
Decline in at least 1 structure	**54/56 (96.4%)**
Decline in 4/4 structures	22/56 (39.3%)
Decline in 3/4 structures	20/56 (35.7%)
Decline in 2/4 structures	8/56 (9%)
Decline in 1/4 structures	4/56 (7%)
Decline in 0/4 structures	2/56 (3.6%)

Table 4 | The number of patients who show decline in each structure and substructure.

Structure/ substructure	Number/(percentage) of decliners by structure	Lower and upper 95% CI at 2 z-score < controls
VBR	**45** (80.4)	67.6–89.9
HPC-L head	31 (55.4)	41.5–68.7
HPC-L body	24 (42.9)	29.7–56.8
HPC-L tail	32 (57.1)	43.2–70.3
HPC-L total	**40** (71.4)	57.8–82.7
HPC-R head	38 (67.9)	54.0–79.7
HPC-R body	39 (69.6)	55.9–81.2
HPC-R tail	36 (64.3)	50.4–76.6
HPC-R total	**41** (73.2)	59.7–84.2
CC genu	26 (46.4)*	33.0–60.3
CC body	42 (75.0)	61.6–85.6
CC splenium	42 (75.0)	61.6–85.6
CC total	**43 (76.8)**	63.6–87.0

Table 5A | PHI coefficients across the structures measured.

	PHI coefficients (95% CI)			
	VBR	**HPC-L total**	**HPC-R total**	**CC total**
VBR	–	$r = -0.01$ ($CI = -0.28$–0.25)	$r = 0.31$* ($CI = 0.05$–0.53)	$r = 0.37$* ($CI = 0.12$–0.57)
HPC-L total	–	–	$r = 0.33$* ($CI = 0.08$–0.55)	$r = 0.03$ ($CI = -0.24$–0.29)
HPC-R total	–	–	–	$r = 0.15$ ($CI = -0.12$–0.39)

is, significant overlap, between VBR with both the CC and the right (but not left) HPC. The right and left hippocampus also overlapped significantly. There was no relationship between the CC and the hippocampi. These results partially supported our hypotheses, namely a relationship between VBR and individual structures, and the absence of relationship between some (though not all) of the structures measured.

Table 5B presents the PHI coefficients and their 95% confidence intervals between substructures. Here, significant overlap was observed between the right hippocampus head and tail, and between the genu and body and the genu and splenium of the CC, findings which overall did not support our hypothesis.

Table 5B | PHI coefficients for sub-structures of the left and right hippocampus and the corpus callosum.

	PHI coefficients (95% CI)		
	HPC-L head	**HPC-L body**	**HPC-L tail**
HPC-L head	–	$r = -0.02$ ($CI = -0.28$–0.24)	$r = 0.02$ ($CI = -0.24$–0.28)
HPC-L body	–	–	$r = -0.05$ ($CI = -0.31$–0.21)
	HPC-R head	**HPC-R body**	**HPC-R tail**
HPC-R head	–	$r = 0.13$ ($CI = -0.14$–0.38)	$r = 0.29$* ($CI = 0.02$–0.51)
HPC-R body	–	–	$r = 0.16$ ($CI = -0.11$–0.40)
	CC genu	**CC body**	**CC splenium**
CC genu	–	$r = 0.29$* ($CI = 0.03$–0.51)	$r = 0.37$* ($CI = 0.12$–0.58)
CC body	–	–	$r = 0.14$ ($CI = -0.13$–0.39)

DISCUSSION

The primary purpose of the current study was to gain a better understanding of the scale of atrophy in the chronic phase of TBI. Our cohort was a Canadian sample of patients with brain injuries ranging from complicated mild to severe. More than 96% of our sample showed atrophy over time in at least one region and the large majority showed atrophy in at least three of the four regions measured. Therefore, these findings indicate substantive atrophy—we employed a threshold of at least two z-scores below that of controls—across several structures. Given the relationship between sub-acute atrophy and behavioral and functional outcomes (Sidaros et al., 2008, 2009; Farbota et al., 2012), and between total brain volume loss and clinical impairment (Tate et al., 2011), these findings are clinically concerning, especially as brain atrophy is a known predictor of Alzheimer's Disease (Frisoni et al., 2010).

A secondary purpose of the study was to begin to characterize this chronic atrophy by examining two related features of the data: (i) the extent to which the number of decliners in each structure and sub-structure differed, allowing us to evaluate preliminarily the relative vulnerability of structures examined, and (ii) the extent to which decline in one structure was associated with decline in another. With regard to the first question, we found few differences in the number of decliners across structures and sub-structures, with only the genu differing significantly from the other sub-structures of the CC. Thus, contrary to our hypothesis, the findings in the small number of regions examined in our study do not suggest that one region is more vulnerable to chronic volume loss than another, with the exception of the genu. However, it is possible that limited power may have elevated Type II errors; given the rather large confidence intervals secondary to sample size, the results may under-represent differences between structures.

Regarding the second question, we found more associations across structures than we had predicted. Subjects showing atrophy in the whole brain also showed atrophy in other structures measured (i.e., CC and right HPC) as expected, which likely does not speak to underlying mechanisms, but rather to VBR's inclusive relationship with the other structures measured. However, we also found that those who declined in one HPC were more likely to also decline in the other. Within the sub-structures, those who declined in the right HPC head were more likely to decline in the tail, and those who declined in genu of the CC were more likely to decline in the body and the splenium. It is important to note that wide confidence intervals secondary to sample size bias the findings in favor of Type II errors, and that these findings may actually *underestimate* the degree of association between the structures.

These findings offer some direction for future research into mechanisms. A great deal of research has examined the *acute* primary and secondary mechanical, chemical, and electrophysiological changes in the brain following TBI, which in more serious injuries are ultimately associated with necrotic or apoptotic death (Povlishock and Katz, 2005; Griesbach et al., 2007). In contrast, there has been relatively limited research directly investigating mechanisms of later atrophy of the brain (but see Johnson et al., 2013; Smith et al., 2013).

MECHANISMS OF ATROPHY IN THE CHRONIC STAGE OF TBI

In broad strokes, atrophy in the chronic stages of injury may reflect volume loss, neuronal death or a reduction in neuronal proliferation and/or survival. Cell death may occur due to delayed apoptotic mechanisms (Colicos et al., 1996; Bramlett et al., 1997a,b; Dixon et al., 1999; Williams et al., 2001; Coulson et al., 2008) secondary to trans-neuronal degeneration (Gennarelli and Graham, 1998; Tate and Bigler, 2000) arising from disconnections within or between functionally related structures (Tate and Bigler, 2000; Duering et al., 2012; Bigler, 2013b). Volume loss may reflect decreased complexity of the neuropil, with decreased spines, synapses and arborization or reduced fluid as a result of diminished protein production. Vascular changes might also contribute to volumetric changes over time. For example, reduced functional hyperemia (because of reduced neuronal demand) would reduce blood volume as would disrupted neurovascular coupling. A mechanism receiving increasing scientific attention for chronic stage losses in TBI is persisting inflammation, associated with cytokine release and microglial activation (Gentleman et al., 2004; Rodriguez-Paez et al., 2005; Johnson et al., 2013; Smith et al., 2013). Genetic causes of poorer clinical outcomes have been advanced for a number of years (Ponsford et al., 2011). A highly probable cause of volume losses are the synergistic effects of aging and TBI, as described in detail by Bigler (2013b); such effects may exacerbate the burden of normal and pathological aging, and thereby account for observed volume losses, with such losses also hastening the onset of dementia. Links between TBI and dementia are being increasingly made (Fakhran et al., 2013), with proteins implicated in dementias (e.g., amyloid-beta, amyloid precursor protein, tau), for example, found to accumulate in damaged axons and other neuronal compartments in the chronic stages of TBI (Bramlett et al., 1997b; Smith et al., 2003; Uryu et al., 2007; Johnson et al., 2012; Bennett et al., 2013).

Importantly, these candidate mechanisms of atrophy are empirically testable. Ultimately, an understanding is needed of whether a single mechanism or multiple mechanisms influence atrophy, whether different mechanisms affect different regions, and if multiple mechanisms do influence atrophy, whether they are additive or synergistic.

The findings in the current study favor some mechanisms over others, helping at least to constrain hypotheses for future research. The *ubiquity* of atrophy across patients would not support an exclusive genetic explanation of atrophy; for example, base rates of the e-4 allele that has been implicated in the relationship between TBI and dementia are considerably lower than the 96% incidence of patients who showed volume loss in this study.

With regard to neuroinflammation, Johnson et al. (2013) showed evidence of increasing neuroinflammation in the CC from the sub-acute to the more chronic stages of injury (i.e., 2 weeks to 1 year vs. > 1–18 years post-injury), and inflammation correlated with WM integrity losses and visible pathology. The prevalence of unequivocal markers of neuroinflammation appeared to be substantively lower than the 76.8% of patients in our study showing CC volume loss. However, neuroinflammation is likely one of multiple causes of volume loss in our study.

In humans, the identification of behavioral factors that may exacerbate or buffer against volume loss is of high importance given the potential for clinical intervention. It has been postulated that a downward spiral of negative neuroplastic change secondary to disuse may play a role in chronic decline (Evans, 2008; Miller et al., 2013). Supporting this putative mechanism, our group observed a significant negative correlation between self-reported hours of environmental enrichment in the first year post-injury and the degree of hippocampal atrophy observed from 5 to 20 months post-injury (Miller et al., 2013). Compounding disuse is physiological disconnection of healthy tissue from damaged tissue. Given that all of our patients had sustained brain damage and were therefore at risk of both disconnection and disuse, and moreover, that the CC and hippocampus are frequently affected acutely, and are associated with discrete cognitive functions, this explanation is consistent with the high prevalence of chronic atrophy observed. Within the substructures of the (right) hippocampus, the significant association observed is consistent with this interpretation, with the unique pattern of interconnectivity within the hippocampus meaning that damage to one area may deafferent another; if the disconnected tissue does not functionally re-organize, then it is vulnerable to transneuronal degeneration (McCarthy, 2003; Amaral et al., 2008).

However, other aspects of our findings do not support the interpretations above. For example, we found that hippocampal volume loss on the right was positively associated with volume loss on the left. Experience-dependent volume increases in the hippocampus (Draganski et al., 2006; Maguire et al., 2006) would have predicted that greater reliance on the less damaged hippocampus would result in volumetric increases to it, giving rise to a *negative* association between hippocampi. The positive association between hippocampi suggests a common mechanism deleteriously affecting both. One such mechanism is reduction in new neuronal growth, survival and integration. As is the case for many TBI patients, many of the patients in our cohort at 5 months post-injury and later, had residual physical impairments, reduced volition, had neither returned to work or school, were less socially engaged, and had limited access to resources (Frasca et al., 2013), Therefore, many underwent less physical activity, and many were engaged in less cognitively demanding activity. Since physical and cognitive enrichment have been associated, respectively, with enhanced neuronal proliferation and survivorship (Curlik and Shors, 2010, 2013), this reduced enrichment may have offset hippocampal growth. Moreover, widespread damage to networks might have further impeded integration of new neurons.

The array of possible interpretations for these findings indicates that much further research is needed to understand mechanisms of atrophy in sub-acute and chronic TBI. Such an understanding is critical for the development of treatment research to avert or abate this atrophy.

There were limitations of the current study. The size of the control group was relatively small and may have compromised the reliability of our findings. As well, because the timelines of the two assessments of controls and patients differed, we calculated monthly percent change to compare patients with controls. This calculation assumes a linear month-to-month change, which is not substantiated. There were significant education, but not age, differences between the patient and control groups. However, we

speculate that this difference did not contribute to our findings. In a previous study by our group Miller et al. (2013) using overlapping participants, there was no relationship between years of education and degree of hippocampal atrophy. Moreover, the weight of evidence suggests that education confers protection against the clinical (cognitive) expression of disease, but not against the development of neuropathology or neurodegeneration itself (Members et al., 2010). As well, our findings do not permit us to distinguish between cell death versus volume loss without death. Other methodological approaches, including neuropathological ones, are needed to examine this distinction.

CONCLUSIONS

In the chronic stage of moderate-severe atrophy, loss of volume is substantive and ubiquitous across patients. Changes may be attributable to tissue shrinkage—the result of lost neuropil, protein and/or fluids—or to cell death, with disconnection and disuse, inflammation and delayed apoptosis contributing independently or interactively. Environmental enrichment could play a role in offsetting these changes, and in the chronic stages of injury is a "no-harm" intervention that warrants investigation. Further research is needed to identify precise mechanisms of atrophy that would help us to develop targeted clinical interventions.

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REFERENCES

Adnan, A., Crawley, A., Mikulis, D., Moscovitch, M., Colella, B., and Green, R. E. (2013). Moderate-severe traumatic brain injury causes delayed loss of white matter integrity: evidence of fornix deterioration in the chronic stage of injury. *Brain Inj.* 27, 1415–1422. doi: 10.3109/02699052.2013.823659

Amaral, O. B., Vargas, R. S., Hansel, G., Izquierdo, I., and Souza, D. O. (2008). Duration of environmental enrichment influences the magnitude and persistence of its behavioral effects on mice. *Physiol. Behav.* 93, 388–394. doi: 10.1016/j.physbeh.2007.09.009

Analysisgroup. (2012). *FMRIB Software Library v4.0 [Online]. Oxford: Nuffield Department of Clinical Neurosciences, University of Oxford*. Accessed 2012. Available online at: http://www.fmrib.ox.ac.uk/fsl

Ariza, M., Serra-Grabulosa, J. M., Junqué, C., Ramírez, B., Mataró, M., Poca, A., et al. (2006). Hippocampal head atrophy after traumatic brain injury. *Neuropsychologia* 44, 1956–1961. doi: 10.1016/j.neuropsychologia.2005.11.007

Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., et al. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *Neuroimage* 42, 503–514. doi: 10.1016/j.neuroimage.2008.04.254

Bennett, R. E., Esparza, T. J., Lewis, H. A., Kim, E., Mac Donald, C. L., Sullivan, P. M., et al. (2013). Human apolipoprotein E4 worsens acute axonal pathology but not amyloid-beta immunoreactivity after traumatic brain injury in 3xTG-AD mice. *J. Neuropathol. Exp. Neurol.* 72, 396–403. doi: 10.1097/NEN.0b013e31828e24ab

Bigler, E. D. (2013a). Neuroinflammation and the dynamic lesion in traumatic brain injury. *Brain* 136, 9–11. doi: 10.1093/brain/aws342

Bigler, E. D. (2013b). Traumatic brain injury, neuroimaging, and neurodegeneration. *Front. Hum. Neurosci.* 7:395. doi: 10.3389/fnhum.2013.00395

Bramlett, H. M., Dietrich, W. D., Green, E. J., and Busto, R. (1997a). Chronic histopathological consequences of fluid-percussion brain injury in rats: effects of post-traumatic hypothermia. *Acta Neuropathol.* 93, 190–199. doi: 10.1007/s004010050602

Bramlett, H. M., Kraydieh, S., Green, E. J., and Dietrich, W. D. (1997b). Temporal and regional patterns of axonal damage following traumatic brain injury: a beta-amyloid precursor protein immunocytochemical study in rats. *J. Neuropathol. Exp. Neurol.* 56, 1132–1141. doi: 10.1097/00005072-199710000-00007

Colicos, M. A., Dixon, C. E., and Dash, P. K. (1996). Delayed, selective neuronal death following experimental cortical impact injury in rats: possible role in memory deficits. *Brain Res.* 739, 111–119. doi: 10.1016/S0006-8993(96)00819-0

Collins, D. L., Neelin, P., Peters, T. M., and Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J. Comput. Assist. Tomogr.* 18, 192–205. doi: 10.1097/00004728-199403000-00005

Coulson, E. J., May, L. M., Osborne, S. L., Reid, K., Underwood, C. K., Meunier, F. A., et al. (2008). p75 neurotrophin receptor mediates neuronal cell death by activating GIRK channels through phosphatidylinositol 4,5-bisphosphate. *J. Neurosci.* 28, 315–324. doi: 10.1523/JNEUROSCI.2699-07.2008

Curlik, D. M. 2nd., and Shors, T. J. (2010). Learning increases the survival of newborn neurons provided that learning is difficult to achieve and successful. *J. Cogn. Neurosci.* 23, 2159–2170. doi: 10.1162/jocn.2010.21597

Curlik, D. M. 2nd., and Shors, T. J. (2013). Training your brain: Do mental and physical (MAP) training enhance cognition through the process of neurogenesis in the hippocampus? *Neuropharmacology* 64, 506–514. doi: 10.1016/j.neuropharm.2012.07.027

Dixon, C. E., Kochanek, P. M., Yan, H. Q., Schiding, J. K., Griffith, R. G., Baum, E., et al. (1999). One-year study of spatial memory performance, brain morphology, and cholinergic markers after moderate controlled cortical impact in rats. *J. Neurotrauma* 16, 109–122. doi: 10.1089/neu.1999.16.109

Draganski, B., Gaser, C., Kempermann, G., Kuhn, H. G., Winkler, J., Buchel, C., et al. (2006). Temporal and spatial dynamics of brain structure changes during extensive learning. *J. Neurosci.* 26, 6314–6317. doi: 10.1523/JNEUROSCI.4628-05.2006

Duering, M., Righart, R., Csanadi, E., Jouvent, E., Herve, D., Chabriat, H., et al. (2012). Incident subcortical infarcts induce focal thinning in connected cortical regions. *Neurology* 79, 2025–2028. doi: 10.1212/WNL.0b013e3182749f39

Evans, J. E. A. (2008). Research digest. *Neuropsychol. Rehabil.* 18, 372–384. doi: 10.1080/09602010801909153

Fakhran, S., Yaeger, K., and Alhilali, L. (2013). Symptomatic white matter changes in mild traumatic brain injury resemble pathologic features of early Alzheimer dementia. *Radiology* 269, 249–257. doi: 10.1148/radiol.13122343

Farbota, K. D., Bendlin, B. B., Alexander, A. L., Rowley, H. A., Dempsey, R. J., and Johnson, S. C. (2012). Longitudinal diffusion tensor imaging and neuropsychological correlates in traumatic brain injury patients. *Front. Hum. Neurosci.* 6:160. doi: 10.3389/fnhum.2012.00160

Frasca, D., Tomaszczyk, J., McFadyen, B. J., and Green, R. E. A. (2013). Traumatic brain injury and post-acute decline: what role does environmental enrichment play? A scoping review. *Front. Hum. Neurosci.* 7:31. doi: 10.3389/fnhum.2013.00031

Frisoni, G. B., Fox, N. C., Jack, C. R. Jr., Scheltens, P., and Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nat. Rev. Neurol.* 6, 67–77. doi: 10.1038/nrneurol.2009.215

Gennarelli, T. A., and Graham, D. I. (1998). Neuropathology of the head injuries. *Semin. Clin. Neuropsychiatry* 3, 160–175.

Gentleman, S. M., Leclercq, P. D., Moyes, L., Graham, D. I., Smith, C., Griffin, W. S. T., et al. (2004). Long-term intracerebral inflammatory response after traumatic brain injury. *Forensic Sci. Int.* 146, 97–104. doi: 10.1016/j.forsciint.2004.06.027

Green, R. E., Melo, B., Christensen, B., Ngo, L. A., Monette, G., and Bradbury, C. (2008). Measuring premorbid IQ in traumatic brain injury: an examination of the validity of the Wechsler Test of Adult Reading (WTAR). *J. Clin. Exp. Neuropsychol.* 30, 163–172. doi: 10.1080/13803390701300524

Greenberg, G., Mikulis, D. J., Ng, K., Desouza, D., and Green, R. E. (2008). Use of diffusion tensor imaging to examine subacute white matter injury progression in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S45–S50. doi: 10.1016/j.apmr.2008.08.211

Greer, J. E., Povlishock, J. T., and Jacobs, K. M. (2012). Electrophysiological abnormalities in both axotomized and nonaxotomized pyramidal neurons following mild traumatic brain injury. *J. Neurosci.* 32, 6682–6687. doi: 10.1523/JNEUROSCI.0881-12.2012

Griesbach, G. S., Gomez-Pinilla, F., and Hovda, D. A. (2007). Time window for voluntary exercise-induced increases in hippocampal neuroplasticity

molecules after traumatic brain injury is severity dependent. *J. Neurotrauma* 24, 1161–1171. doi: 10.1089/neu.2006.0255

Hollingshead, A. B., and Redlich, F. C. (1958). *Social Class and Mental Illness.* New York, NY: John Wiley. doi: 10.1037/10645-000

Johnson, V. E., Stewart, J. E., Begbie, F. D., Trojanowski, J. Q., Smith, D. H., and Stewart, W. (2013). Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain* 136, 28–42. doi: 10.1093/brain/aws322

Johnson, V. E., Stewart, W., and Smith, D. H. (2012). Widespread tau and amyloid-Beta pathology many years after a single traumatic brain injury in humans. *Brain Pathol.* 22, 142–149. doi: 10.1111/j.1750-3639.2011.00513.x

Lezak, M. D. (2004). *Neuropsychological Assessment.* New York, NY: Oxford University Press.

Maguire, E. A., Woollett, K., and Spiers, H. J. (2006). London taxi drivers and bus drivers: a structural MRI and neuropsychological analysis. *Hippocampus* 16, 1091–1101. doi: 10.1002/hipo.20233

Maller, J. J., Daskalakis, Z. J., and Fitzgerald, P. B. (2007). Hippocampal volumetrics in depression: the importance of the posterior tail. *Hippocampus* 17, 1023–1027. doi: 10.1002/hipo.20339

Masel, B. E., and Dewitt, D. S. (2010). Traumatic brain injury: a disease process, not an event. *J. Neurotrauma* 27, 1529–1540. doi: 10.1089/neu.2010.1358

McCarthy, M. M. (2003). Stretching the truth. Why hippocampal neurons are so vulnerable following traumatic brain injury. *Exp. Neurol.* 184, 40–43. doi: 10.1016/j.expneurol.2003.08.020

Members, E. C. C., Brayne, C., Ince, P. G., Keage, H. A., McKeith, I. G., Matthews, F. E., et al. (2010). Education, the brain and dementia: neuroprotection or compensation? *Brain* 133, 2210–2216. doi: 10.1093/brain/awq185

Miller, L. S., Colella, B., Mikulis, D., Maller, J., and Green, R. E. (2013). Environmental enrichment may protect against hippocampal atrophy in the chronic stages of traumatic brain injury. *Front. Hum. Neurosci.* 7:506. doi: 10.3389/fnhum.2013.00506

Millis, S. R., Rosenthal, M., Novack, T. A., Sherer, M., Nick, T. G., Kreutzer, J. S., et al. (2001). Long-term neuropsychological outcome after traumatic brain injury. *J. Head Trauma Rehabil.* 16, 343–355. doi: 10.1097/00001199-200108000-00005

Ng, K., Mikulis, D. J., Glazer, J., Kabani, N., Till, C., Greenberg, G., et al. (2008). Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S35–S44. doi: 10.1016/j.apmr.2008.07.006

Ponsford, J., McLaren, A., Schonberger, M., Burke, R., Rudzki, D., Olver, J., et al. (2011). The association between apolipoprotein E and traumatic brain injury severity and functional outcome in a rehabilitation sample. *J. Neurotrauma* 28, 1683–1692. doi: 10.1089/neu.2010.1623

Povlishock, J. T., and Katz, D. I. (2005). Update of neuropathology and neurological recovery after traumatic brain injury. *J. Head Trauma Rehabil.* 20, 76–94. doi: 10.1097/00001199-200501000-00008

Rodriguez-Paez, A. C., Brunschwig, J. P., and Bramlett, H. M. (2005). Light and electron microscopic assessment of progressive atrophy following moderate traumatic brain injury in the rat. *Acta Neuropathol.* 109, 603–616. doi: 10.1007/s00401-005-1010-z

Ross, D. E., Ochs, A. L., Seabaugh, J. M., Demark, M. F., Shrader, C. R., Marwitz, J. H., et al. (2012). Progressive brain atrophy in patients with chronic neuropsychiatric symptoms after mild traumatic brain injury: a preliminary study. *Brain Inj.* 26, 1500–1509. doi: 10.3109/02699052.2012.694570

Ruff, R. M., Young, D., Gautille, T., Marshall, L. F., Barth, J., Jane, J. A., et al. (1991). Verbal learning deficits following severe head injury: heterogeneity in recovery over 1 year. *J. Neurosurg.* 75, S50–S58.

Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., et al. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain* 131, 559–572. doi: 10.1093/brain/awm294

Sidaros, A., Skimminge, A., Liptrot, M. G., Sidaros, K., Engberg, A. W., Herning, M., et al. (2009). Long-term global and regional brain volume changes following severe traumatic brain injury: a longitudinal study with clinical correlates. *Neuroimage* 44, 1–8. doi: 10.1016/j.neuroimage.2008.08.030

Sled, J. G., Zijdenbos, A. P., and Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans. Med. Imaging* 17, 87–97. doi: 10.1109/42.668698

Smith, D. H., Johnson, V. E., and Stewart, W. (2013). Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat. Rev. Neurol.* 9, 211–221. doi: 10.1038/nrneurol.2013.29

Smith, D. H., Uryu, K., Saatman, K. E., Trojanowski, J. Q., and McIntosh, T. K. (2003). Protein accumulation in traumatic brain injury. *Neuromolecular Med.* 4, 59–72. doi: 10.1385/NMM:4:1-2:59

Talairach, J., and Tournoux, P. (1988). *Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: an Approach to Cerebral Imaging.* New York, NY: Thieme Medical Publishers.

Tate, D. F., and Bigler, E. D. (2000). Fornix and hippocampal atrophy in traumatic brain injury. *Learn. Mem.* 7, 442–446. doi: 10.1101/lm.33000

Tate, D. F., Khedraki, R., Neeley, E. S., Ryser, D. K., and Bigler, E. D. (2011). Cerebral volume loss, cognitive deficit, and neuropsychological performance: comparative measures of brain atrophy: II. Traumatic brain injury.*J. Int. Neuropsychol. Soc.* 17, 308–316. doi: 10.1017/S1355617710001670

Till, C., Colella, B., Verwegen, J., and Green, R. E. (2008). Postrecovery cognitive decline in adults with traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S25–S34. doi: 10.1016/j.apmr.2008.07.004

Underwood, C. K., and Coulson, E. J. (2008). The p75 neurotrophin receptor. *Int. J. Biochem. Cell Biol.* 40, 1664–1668. doi: 10.1016/j.biocel.2007.06.010

Uryu, K., Chen, X. H., Martinez, D., Browne, K. D., Johnson, V. E., Graham, D. I., et al. (2007). Multiple proteins implicated in neurodegenerative diseases accumulate in axons after brain trauma in humans. *Exp. Neurol.* 208, 185–192. doi: 10.1016/j.expneurol.2007.06.018

Watson, C., Andermann, F., Gloor, P., Jones-Gotman, M., Peters, T., Evans, A., et al. (1992). Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. *Neurology* 42, 1743–1750. doi: 10.1212/WNL.42.9.1743

Watson, C., Cendes, F., Fuerst, D., Dubeau, F., Williamson, B., Evans, A., et al. (1997). Specificity of volumetric magnetic resonance imaging in detecting hippocampal sclerosis. *Arch. Neurol.* 54, 67–73. doi: 10.1001/archneur.1997.00550130049015

Weschler, D. (2001). *Wechsler Test of Adult Reading (WTAR).* San Antonio, TX: Harcourt Assessment.

Wilde, E. A., Chu, Z., Bigler, E. D., Hunter, J. V., Fearing, M. A., Hanten, G., et al. (2006). Diffusion tensor imaging in the corpus callosum in children after moderate to severe traumatic brain injury. *J. Neurotrauma* 23, 1412–1426. doi: 10.1089/neu.2006.23.1412

Williams, S., Raghupathi, R., Mackinnon, M. A., McIntosh, T. K., Saatman, K. E., and Graham, D. I. (2001). *In situ* DNA fragmentation occurs in white matter up to 12 months after head injury in man. *Acta Neuropathol.* 102, 581–590. doi: 10.1007/s004010100410

Zijdenbos, A. P., Forghani, R., and Evans, A. C. (1998). "MRI brain data sets: validation of INSECT," in *Medical Image Computing and Computer-Assisted Intervetion - Miccai '98*, eds W. M. Wells, A. Colchester, and S. Delps (Cambridge: Springer), 439–448.

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Longitudinal diffusion tensor imaging and neuropsychological correlates in traumatic brain injury patients

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Traumatic brain injury (TBI) often involves focal cortical injury and white matter (WM) damage that can be measured shortly after injury. Additionally, slowly evolving WM change can be observed but there is a paucity of research on the duration and spatial pattern of long-term changes several years post-injury. The current study utilized diffusion tensor imaging to identify regional WM changes in 12 TBI patients and nine healthy controls at three time points over a four year period. Neuropsychological testing was also administered to each participant at each time point. Results indicate that TBI patients exhibit longitudinal changes to WM indexed by reductions in fractional anisotropy (FA) in the corpus callosum, as well as FA increases in bilateral regions of the superior longitudinal fasciculus (SLF) and portions of the optic radiation (OR). FA changes appear to be driven by changes in radial (not axial) diffusivity, suggesting that observed longitudinal FA changes may be related to changes in myelin rather than to axons. Neuropsychological correlations indicate that regional FA values in the corpus callosum and sagittal stratum (SS) correlate with performance on finger tapping and visuomotor speed tasks (respectively) in TBI patients, and that longitudinal increases in FA in the SS, SLF, and OR correlate with improved performance on the visuomotor speed (SS) task as well as a derived measure of cognitive control (SLF, OR). The results of this study showing progressive WM deterioration for several years post-injury contribute to a growing literature supporting the hypothesis that TBI should be viewed not as an isolated incident but as a prolonged disease state. The observations of long-term neurological and functional improvement provide evidence that some ameliorative change may be occurring concurrently with progressive degeneration.

Keywords: traumatic brain injury, diffusion tensor imaging, longitudinal, neuropsychology, recovery, DTI, TBI

INTRODUCTION

Traumatic brain injury (TBI) affects more than 1.4 million people every year in the United States (CDC, 2006). These injuries are the most common source of neurological impairment among young and middle-aged adults, and can produce long-term cognitive deficits that hinder patients' ability to function independently, lower their quality of life and increase the risk of developing co-morbid neurological disorders (Anderson et al., 1995; Kiraly and Kiraly, 2007; Bombardier et al., 2010; Malec et al., 2010; Risdall and Menon, 2010; Sharp and Ham, 2011). Previous research has shown that the progression of structural pathology in the first year following injury includes decreased white matter (WM) integrity throughout the brain (Povlishock and Christman, 1995; Trivedi et al., 2007; Xu et al., 2007; Marquez de la Plata et al., 2008; Sidaros et al., 2008; Lin et al., 2010), but little is known about WM changes that occur after this first year. Concomitant to slowly occurring atrophy and WM degradation, TBI patients typically demonstrate measurable cognitive and motor improvements in the first and subsequent years post-injury. This study aims to identify long-term patterns of WM change following TBI, as well as how variations in WM integrity correlate with both neuropsychological test performance and change in test performance over time (Levin, 2003; Staudt, 2010).

Diffusion tensor imaging (DTI) is sensitive to WM damage immediately following TBI and useful in monitoring longitudinal changes (Filippi et al., 2001; Xu et al., 2007; Bendlin et al., 2008). DTI, which is based on the principle that water molecule movement is restricted by barriers to diffusion that vary in the brain depending on tissue type or pathology, [for review see Le Bihan (1991)], is sensitive to changes in the microstructure of WM.

Several studies have shown that DTI accurately detects damage in tissue that may appear normal when measured with conventional MRI (Arfanakis et al., 2002; Chan et al., 2003) and that DTI can be of clinical importance when tracing recovery (Filippi et al., 2001; Arfanakis et al., 2002; Field et al., 2003). These capabilities make DTI well suited for assessing WM damage caused by TBI and for tracking how WM changes progress longitudinally following injury.

The current study is an extension of a prior study conducted on this same cohort of TBI patients. The previous paper (Bendlin et al., 2008), included whole-brain DTI and volumetric analyses of patients at two months and one year post-injury. Results showed gray and WM alterations over time in TBI compared to control. Regions of reduced WM integrity included corpus callosum, forceps major and minor, anterior corona radiata, external capsule, cerebral peduncle, superior longitudinal fasciculus (SFL), uncinate fasciculus, and corticopontine tract. The current study extends the previous work with the addition of a third time point approximately four years post-injury. Furthermore, the current study includes axial and radial diffusivity analyses (which may allow inference concerning the cause of WM changes), and increases the power to detect group-wise effects by restricting analyses to the WM.

The primary metric used to assess WM integrity in this study is fractional anisotropy (FA). FA describes the extent to which a diffusion process is anisotropic or directionally constrained. In brain WM, higher FA is associated with greater WM integrity (Alexander et al., 2007). As noted above, we also employed two secondary metrics: axial diffusivity and radial diffusivity. Axial diffusivity refers to the movement of water along the principle axis of a WM tract. Animal studies have demonstrated that high axial diffusivity is associated with healthy axons, and low axial diffusivity is associated with axonal damage (Song et al., 2002, 2003). Radial diffusivity refers to the movement of water perpendicular to the principle axis of a WM tract. Animal studies have demonstrated that low radial diffusivity is associated with healthy myelin, and high radial diffusivity is associated with myelin damage (Wheeler-Kingshott and Cercignani, 2009). Investigating how these secondary metrics change over time in brain regions demonstrating longitudinal differences in FA can provide additional insight into the processes underlying WM change.

The first major goal of the current study was to characterize longitudinal changes in regional brain WM microstructure using DTI in conjunction with neuropsychological testing. Due to previous reports of volume loss and WM decline in the corpus callosum, as well as the emergent theory of TBI as the initiation of a disease state, we predicted that this structure would demonstrate continued decline throughout the duration of the study within the TBI group (Gale et al., 1995; Bigler et al., 1996; Kim et al., 2008; Kumar et al., 2010; Masel and DeWitt, 2010; Matsukawa et al., 2011; Ljungqvist et al., 2011). While decline in many regions is likely, patients typically continue to improve cognitively; thus we also sought to determine whether FA increases may occur in other regions, which may suggest consolidation or remodeling of WM tracts associated with recovery. Candidate regions include corticospinal tract regions (cerebral peduncle, internal capsule) and longitudinal tracts (superior and inferior longitudinal fasciculi) due to previous research indicating improvements in certain diffusion metrics in a subset of these regions (Sidaros et al., 2008) and the presence of damage in these regions observed in cross-sectional studies done close to the time of injury but not in those done several years post-TBI (Kraus et al., 2007; Bendlin et al., 2008).

The second major goal of this study was to identify correlations between FA and neuropsychological task performance cross-sectionally at each time point studied, as well as determine whether changes in task performance over time correlated with changes in FA longitudinally. Due to previous research indicating that higher corpus callosum FA is associated with better performance on manual motor tasks in brain injury patients, we predicted that scores on a fine motor finger tapping task employed in this study would correlate with FA in this region among TBI patients (Caeyenberghs et al., 2011a,b). Furthermore, we predicted that increases in FA within the longitudinal tracts would correlate with improved performance on the more complex neuropsychological tasks such as the Cognitive Oral Word Association Test (COWAT), or the cognitive component of the Trail Making Test. Finally, we expected patients who had sustained more severe injuries, as measured by the 24 h post-resuscitation Glasgow Coma Score (GCS), to demonstrate a greater degree of initial microstructural damage and longitudinal WM change than patients who sustained less severe injuries.

METHODS

TBI PATIENTS

Forty-six TBI patients participated in an initial MRI scan, thirty-six returned for a second visit, and twenty returned for a third visit. DTI was acquired in sixteen individuals at all three time points (three were subsequently excluded due to excessive motion, and one more was excluded due to a second head injury sustained in a motor vehicle accident between visits 2 and 3). The mean age of the final group of twelve patients (ten males and two females) was 35.00 ± 12.76 years at the beginning of the study; mean education was 13.17 ± 1.75 years. The majority of the patients received acute treatment at the University of Wisconsin Hospital and Clinics level 1 trauma center and were referred from the departments of Neurosurgery, Trauma and/or Rehabilitation. The inclusion criteria for TBI consisted of involvement in a rapid impact injury to the brain (such as a motor vehicle accident or fall) causing a loss of consciousness. Evidence of brain injury included admittance for emergency medical attention following loss of consciousness in the field, a GCS score either at the emergency room (ER) or upon hospital admission of less than or equal to 13, and a post-resuscitation GCS score of 5 or above. All patients had day of injury CT scans that were positive for visible brain injury. All TBI patients were less than three months post-injury at their first visit, and most were studied between eight and twelve weeks post-injury depending on their availability and other medical issues related to the injury. Exclusion criteria consisted of current major Axis I psychiatric disease or history of major medical condition (e.g., cancer, diabetes, or diagnosed neurological condition), as well as any previous diagnosis of substance dependence, or an undiagnosed pattern of behavior

demonstrating longstanding maladaptive use of alcohol or other drugs. All patients gave informed written consent under a protocol approved by the University of Wisconsin Health Sciences Institutional Review Board.

HEALTHY CONTROLS

Thirty-six control participants were recruited from the community and from the University of Wisconsin Madison campus via advertisement. Twenty of these participants returned for two additional visits. Acquisition errors resulted in the loss of four participants who did not have adequate DTI at all three time points; and in seven cases DTI was not acquired at one of the visits due to time constraints; DTI scans acquired from nine participants at all three time points were used in the final analysis. The mean age of the final group of nine healthy controls (four males, five females) was 31.44 ± 12.38 years at the beginning of the study; education was 14.77 ± 2.22 years. Exclusion criteria were identical to the TBI group (with the exception of head injury also being exclusionary for controls). MR scanning of control participants occurred on approximately the same schedule as that of TBI patients. All participants gave informed written consent under a protocol approved by the University of Wisconsin Health Sciences Institutional Review Board.

PROCEDURES

Volunteers participated in three testing sessions, each consisting of MR imaging and neuropsychological testing. TBI patients were tested at three visits, Visit 1, acquired approximately two months (mean = 63 days) post-injury (ranging from 28 to 81 days), Visit 2, approximately one year (mean = 318 days) after Visit 1 (ranging from 226 to 381 days) and Visit 3, approximately three years (mean = 1187 days) after Visit 2 (ranging from 956 to 1651 days). Controls also participated in three visits with approximately one year (mean = 286 days) between Visit 1 and 2 (ranging from 74 to 374 days) and three years (mean = 1096 days) between Visit 2 and 3 (ranging from 778 to 2011 days).

NEUROPSYCHOLOGICAL EXAMINATION

On the day of each scan, a neuropsychological battery that included: COWAT, WRAT-III (Wide Range Achievement Test-reading subtest, an approximation of pre-morbid intelligence), Finger Tapping (during which participants tapped a lever for 10 s as fast as possible for three trials and the average was used), Digit Span (a measure of working memory) and Trail Making Tests A (a visual-motor speed task) and B (a combination task requiring both visual-motor skill and rapid cognitive set shifting) was administered to each participant. These tests were selected based on previous research in our laboratory suggesting their probable relevance to TBI induced behavioral changes. Some of our analyses also included Trails B cognitive component scores which were calculated by subtracting each subject's Trails A score (visuomotor) from his or her Trails B score (visuomotor and cognitive) to isolate the cognitive component of the Trails B task. Statistical analysis of neuropsychological test results was performed as follows: for each test, a general linear model repeated measures test was carried out in SPSS 20.0. From these models, main effects of group and time as well as a group by time interaction were derived. Simple effects analyses were performed by using independent samples one-tailed *t*-tests to assess between-groups differences in task performance at each time point, and by using paired samples one-tailed *t*-tests to assess within groups changes in task performance across time points.

MAGNETIC RESONANCE IMAGING

All participants underwent magnetic resonance on a General Electric 3.0 T (Waukesha, WI) MRI system with a quadrature birdcage head coil. Structural scans included an axial T1-weighted inversion recovery-prepped spoiled gradient echo scan (inversion time = 600 ms, repetition time (TR)/echo time (TE)/flip angle = 9 ms/1.8 ms/20°; acquisition matrix = 256 × 192 interpolated to 256 × 256; field of view (FOV) = 240 mm; and 124 slices 1.2 mm thick). Diffusion tensor imaging was performed using a cardiac-gated, diffusion-weighted sequence with the following parameters: 12 directions with diffusion weighting of 1114 s/mm^2 and a non-diffusion-weighted reference image (B0); TR = 10–15 s; TE = 78.2 ms; number of averages: 3; acquisition matrix = 120 × 120 interpolated to 256 × 256; FOV = 240 mm; 39 contiguous 3 mm thick axial slices. The scan resulted in 0.9375 × 0.9375 × 3 mm voxels. Prior to the diffusion-weighted scan, high order shimming was performed to minimize EPI distortions. A neuroradiologist (HR) reviewed all structural MRI images to identify the location and extent of lesions associated with the TBI and to identify non-injury related brain abnormalities that might exclude participants from the statistical analyses. Additionally, a high resolution 2D axial T2* gradient echo sequence sensitive to both DAI and contusions was collected for evaluation by a neuroradiologist who confirmed the presence of brain injury. Imaging parameters were as follows: gradient echo read-out with TR = 325 ms, TE = 20 ms; flip angle = 15°; acquisition matrix = 256 × 192 interpolated to 256 × 256; FOV = 240 mm; 22 5 mm thick axial slices, with a 1 mm skip between slices; and receiver bandwidth = ±15.83 kHz.

DIFFUSION TENSOR IMAGE PROCESSING

Image distortions in the DTI-data caused by eddy currents were corrected using a 2D affine co-registration function, align linear, in the Automated Image Registration software package (http://www.loni.ucla.edu/Software/AIR). Non-linear image distortion from static field (B0) inhomogeneities was corrected using the acquired field map and implemented in the prelude (Phase Region Expanding Labeller for Unwrapping Discrete Estimates) and fugue (FMRIB's Utility for Geometrically Unwarping EPIs) tools from the FSL software suite (Smith et al., 2004). After distortion corrections, 3D maps of the diffusion tensor and derived measures, FA, axial diffusivity (determined using the principle eigenvalue, L1) and radial diffusivity (determined using the average of the secondary and tertiary eigenvalues, L2 and L3), were calculated. For each subject, the FA, radial diffusivity, and axial diffusivity maps from Visits 2 and 3 were then co-registered to the corresponding maps from Visit 1 using flirt (FSL) 12-parameter affine co-registration. Normalization was then performed using fNIRT in FSL. Normalization of the Visit 1 maps to the FSL FMRIB58_FA_1 mm template was performed

for each subject. The transformation derived from this normalization was then applied to the co-registered maps acquired during Visits 2 and 3. The maps from each time point for each measure were visually checked for alignment to each other and the template.

STATISTICAL ANALYSIS

Primary statistical analyses were performed on FA maps using factorial ANOVA statistical modules in SPM8. Gender was used as a covariate in all analyses. Because this study focused only on WM change, all SPM analyses were restricted to regions within a WM mask to increase our power to detect longitudinal change. The WM mask was created by applying a threshold of 0.5 (**Figure 1**) to the mean FA map of all subjects, and then binarizing the resulting image using fslmaths (FMRIB Software Library). To determine whether there were overall group differences in longitudinal FA change, we tested for an interaction between group and time within the factorial model. The hypothesis that there would be longitudinal change within the TBI group was tested using simple effects analyses, also within the factorial model framework.

Secondary statistical analyses using axial and radial diffusivity maps were also performed using factorial ANOVA statistical modules in SPM8. Because these analyses were employed to further examine the causes of FA change, axial, and radial diffusivity analyses were restricted to regions where significant FA results were observed. We hypothesized that increases in FA would be driven by decreased radial diffusivity and/or increased axial diffusivity, and also conversely that decreases in FA would be driven by increased radial diffusivity and/or increased axial diffusivity.

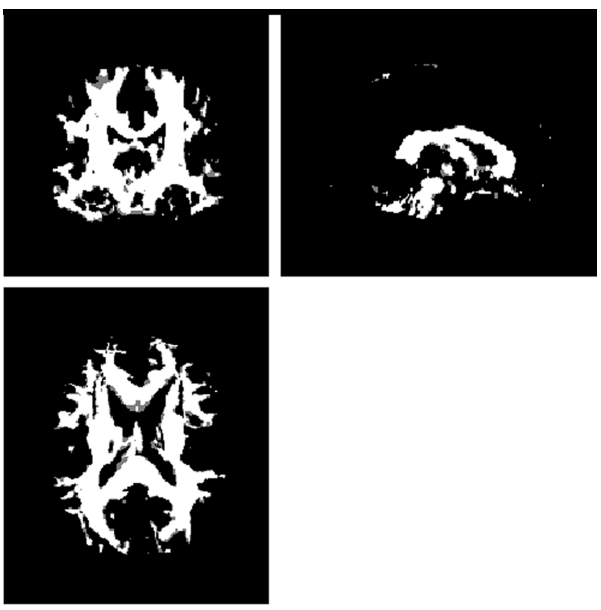

FIGURE 1 | Because this study focused only on white matter change, all SPM analyses were restricted to regions within a white matter mask to increase our power to detect longitudinal change. The white matter mask was created by applying a threshold of 0.5 to the mean FA map of all subjects, and then binarizing the resulting image. This figure shows the white matter mask in three orthogonal directions. The left side of the mask is patient left and the right is patient right.

Correlations with neuropsychological test scores were assessed using linear regression implemented in SPM8, where test scores were independent variables and FA maps were the dependent variables. We hypothesized that we would see positive regional correlations between FA and task performance. In addition to direct correlations between neuropsychological test scores and FA values, we also tested hypotheses concerning how changes in FA and changes in neuropsychological performance might correlate. In these cases, differences in neuropsychological test scores between two time points were calculated for each subject, as were differences in FA during the same interval. FA differences were determined by subtracting the later maps from the earlier maps for each subject. Correlations between FA change maps and changes in neuropsychological test scores were also assessed using linear regression implemented in SPM8, where changes in test scores were independent variables and FA change maps were the dependent variables. All correlation analyses of neuropsychological measures were limited to regions within the WM mask used in general FA analyses.

STATISTICAL THRESHOLD

A voxel-level threshold of $\alpha = 0.001$ (uncorrected) was used for all contrasts. Multiple-comparison correction for FA analyses was performed using estimates from a Monte-Carlo simulation performed with AlphaSim to achieve a corrected cluster-level threshold of $\alpha = 0.05$ (Forman et al., 1995). The Monte-Carlo simulation determined based on randomly computed images that a cluster with 581 voxels with the same dimensions, voxel probability threshold, and smoothness parameters as FA images inputted for analysis would be unlikely (at the $\alpha = 0.05$ cluster-level corrected threshold) to be significant only by chance. Thus, a cluster-level threshold of 581 voxels was used in all FA analyses. For secondary factorial analyses of axial and radial diffusivity and regression analyses used to test neuropsychological correlations cluster-levels were determined individually for each SPM at the significance levels noted above.

RESULTS

DEMOGRAPHIC AND BEHAVIORAL RESULTS

There were no significant differences in age ($t = -1.131$, df $= 19$, two-tailed $p = 0.272$) or years of education ($t = -1.861$, df $= 19$, two-tailed $p = 0.078$) between the TBI and control groups. There were significantly more males in the TBI group compared to the control group ($\chi^2_{(1,\ 12)} = 4.535$, $p = 0.033$). Demographic results are shown in **Table 1**. Repeated measures analyses of neuropsychological test results indicated a main effect of group in the DSPAN, Trails B, and COWAT tasks, as well as a group by time interaction for the COWAT task (**Table 2**). Simple effects analyses of neuropsychological tests performance indicated that TBI patients' performance was significantly worse than that of controls on Digit Span, Trails A and B at Visits 1, 2, and 3. TBI patients also differed from controls on the COWAT at Visits 1 and 2. No significant group differences were seen in WRAT-III or Finger Tapping. TBI patients demonstrated

Table 1 | Individual level subject demographics for patients and controls and select patient injury characteristics.

Subject	Age	Education	Sex	GCSadmit	GCS24	Hrs15	Injury notes
PATIENTS							
1	19	12	M	3T	7	334	DAI
2	49	12	M	15	15	0	DAI, subarachnoid hemorrhage, CC damage
3	19	14	F	3T	11	91	Subarachnoid hemorrhage, subdural hematoma
4	24	14	M	3	7	662	DAI, contusions, epidural hematoma, subarachnoid hemorrhage
5	39	10	M	3T	6	835	Extensive contusions, subdural hematoma
6	45	12	M	3T	14	270	Skull fracture, frontal contusion, CC damage
7	29	13	M	3	14	179	DAI, contusions, skull fracture
8	52	16	F	11	13	97	Skull fracture, subarachnoid hemorrhage, subdural hematoma,
9	51	12	M	7	7	726	Depressed skull fracture, subdural and epidural hematomas
10	19	13	M	3T	5	49	Extensive hemorrhages, CC shearing
11	37	14	M	9	7	116	DAI, subarachnoid hemorrhage, subdural hematoma, shearing
Mean (SD)	35.0 (12.8)	13.2 (1.5)	83% M	5.7 (4.2)	9.6(3.8)	305.4(297.8)	
CONTROLS							
12	22	19	F				
13	22	15	M				
14	29	13	F				
15	27	16	F				
16	25	12	F				
17	19	16	F				
18	36	16	M				
19	24	13	M				
20	51	13	M				
Mean (SD)	29.2 (9.7)	14.8 (2.2)	44% M				
p	0.272	0.078	0.033				

Age of participants indicates the mean age of participants at the start of the study. P-values are based on the results of two-tailed independent-samples t-tests for age and education and a chi-squares test for gender proportions. Abbreviations are as follows: GCSadmit = Glasgow Coma Scale score at hospital admission, GCS24 = Glasgow Coma Scale score 24 h post-injury, 15 h = Number of hours before patient reached a GCS score of 15, DAI = Diffuse axonal injury, CC = corpus callosum, T = Patient was intubated at the time of GCS assessment.

significant improvements on the DSPAN, Trails A, B, and COWAT tests between Visit 1 and 2, and also showed significant improvement on the Trails A, B and COWAT tests between Visit 1 and 3. Controls demonstrated significant improvement on the Trails A and B tasks between Visit 1 and 2. All neurological test results are shown in **Table 2**.

DTI RESULTS

The FA factorial analysis revealed a group by time interaction in the genu of the corpus callosum (**Figure 2**). Analyses of the secondary metrics (using separate factorial models for axial diffusivity and radial diffusivity maps) demonstrated that there was also a group by time interaction in this region in the radial diffusivity model, but not the axial diffusivity model (**Figure 2**). Together these analyses indicate that the group by time interaction observed in the genu in the FA analysis was driven by changes in radial (not axial) diffusivity.

A main effect of time was observed throughout the corpus callosum in the primary FA analysis (**Figure 3**). A corresponding main effect of time was observed in this region in the radial, but not the axial, diffusivity analysis (**Figure 3**). A main effect of group was observed in WM tracts throughout the brain, including the cerebral peduncle, inferior and superior longitudinal fascicule (ILF and SLF), internal and external capsule, inferior fronto-occipital fasciculus, sagittal stratum (SS), corpus callosum, fornix, optic radiations (ORs), thalamic radiations, uncinate fasciculus, and corona radiata (**Figure 4**). Axial and radial diffusivity analyses revealed a main effect of group in genu, fornix, and ILF in the axial model and a main effect of group throughout the corpus callosum, as well as in the fornix, ILF, ORs, and thalamic radiations in the radial model (**Figure 4**).

Simple effects analyses within the FA factorial model demonstrated that TBI subjects exhibited a significant decrease in FA throughout the corpus callosum between the first and third visits (**Figure 5A**). We hypothesized that this change would be driven either by a decrease in axial diffusivity, an increase in radial diffusivity, or some combination of the two. Analyses of the secondary metrics limited to this corpus callosum region were used to test this hypothesis. Results showed that TBI subjects did not demonstrate any decreases in axial diffusivity in this region, while they did exhibit significant increases in radial diffusivity in both the genu and isthmus of the corpus callosum (**Figure 5A**). Controls did not demonstrate significant longitudinal FA decreases in any brain regions.

Table 2 | Neuropsychological test results.

Task	Time 1 *n*, **Mean** (SD)	Time 2 *n*, **Mean** (SD)	Time 3 *n*, **Mean** (SD)
TBI GROUP RESULTS			
WRAT-III	12, **44.7** (6.5)	12, **44.5** (12.3)	11, **45.6** (5.7)
DSPAN[a]	12, **14.3*****† (3.6)	12, **15.6*** (3.7)	11, **15.6*** (4.6)
Trails A	12, **42.0***† (21.5)	12, **30.8*** (6.4)	12, **28.7*****† (7.1)
Trails B[a]	11, **101.3***† (29.0)	12, **78.6*** (20.9)	12, **68.8***† (36.4)
COWAT[b]	12, **21.2***††† (10.2)	12, **33.8*** (10.6)	12, **39.6**†† (12.4)
FT	10, **44.1** (14.7)	12, **45.9** (7.6)	12, **45.7** (6.9
CONTROL GROUP RESULTS			
WRAT-III	8, **50.0** (5.1)	7, **50.0** (6.1)	9, **55.7** (5.2)
DSPAN	8, **20.1** (3.4)	7, **20.6** (3.9)	9, **20.4** (5.2)
Trails A	8, **25.1** (6.9)	7, **24.6**†† (5.4)	9, **20.3** (4.5)
Trails B	8, **55.0** (25.6)	7, **51.5**† (20.4)	9, **38.6** (7.1)
COWAT	8, **41.8** (7.8)	7, **44.6** (8.9)	9, **45.9** (11.9)
FT	6, **45.6** (10.8)	7, **48.9** (6.9)	9, **48.3** (6.8)

Test abbreviations are as follows: WRAT-III = Wide Range Achievement Test (reading subtest), DSPAN = Digit Span Test, Trails A = Trail Making Test A (motor), Trails B = Trail Making Test B (motor and cognitive), COWAT = Cognitive Oral Word Association Test, FT DOM = Dominant Hand Finger Tapping Test. Means are of raw scores. Repeated measures analyses based on general linear models were carried out for each neuropsychological test and significant results ($p < 0.05$) are noted next to task names in the following manner: [a]indicates a main effect of group and [b]indicates a group by time interaction. None of the models demonstrated a significant effect of time. Between-groups differences were calculated using independent samples one-tailed t-tests, and significance levels are denoted as follows: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Between groups differences are noted by the patient average scores only. Within-groups differences were calculated using paired samples one-tailed t-tests, and significance levels are denoted as follows: $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$. Differences between time 1 and 2 are noted by the first time point average, differences between time 2 and 3 are noted by the second time point average, and differences between time 1 and 3 are noted by the third time point average.

In order to determine whether the decrease in FA in the corpus callosum within the TBI group between the first and third visits was driven primarily by early changes during the first interval or late changes during the second interval, each interval was assessed individually within the FA factorial model. These secondary analyses were limited to the corpus callosum region where a change had been observed between the first and third time points. Results demonstrated that significant changes could be seen in the genu and body of the corpus callosum during the first interval (**Figure 5B**), but no significant clusters were identified during the second interval. Axial and radial diffusivity analyses within this region indicated that an increase in radial diffusivity was present in the genu during the first interval among TBI subjects (**Figure 5B**), however, no accompanying decrease in axial diffusivity was observed.

Simple effects analyses within the FA factorial model also demonstrated that TBI subjects exhibited significant FA increases in bilateral regions of the SLF as well as in an OR region on the left side of the brain between the first and third visits (**Figure 6**). Again, we hypothesized that changes observed among TBI patients would be driven either by decreases in axial diffusivity, increases in radial diffusivity, or some combination of the two. Analyses of the secondary metrics limited to these regions were used to test this hypothesis. Results showed that TBI subjects did not demonstrate any increases in axial diffusivity in these regions between the first and third visits, however, significant decreases in radial diffusivity were observed in all regions tested (**Figure 6**). Controls did not exhibit significant longitudinal FA increases in any brain regions.

In order to determine whether the increases in FA in the bilateral SLF and left OR within the TBI group between the first and third visits were driven primarily by early changes during the first interval or late changes during the second interval, each interval was assessed individually within the FA factorial model. These secondary FA increase analyses were limited to the regions where a change had been observed between the first and third time points. No significant clusters were identified during either the first or second intervals individually, suggesting that the observed change occurred gradually over the four year study duration.

Between-groups simple effects analyses demonstrated that the TBI group had reduced FA compared to the control group in the cerebral peduncle, ILF, SLF, internal and external capsule, inferior fronto-occipital fasciculus, SS, corpus callosum, fornix, ORs, thalamic radiations, uncinate fasciculus, and corona radiata at all three visits. There were no regions in which the TBI group had greater FA than the control group at any of the three time points. We hypothesized that FA reductions would be driven by a combination of reduced axial and increased radial diffusivity. Secondary analyses confirmed this hypothesis, demonstrating that the TBI group had reduced axial diffusivity compared to controls in parts of the cerebral peduncle, external capsule, internal capsule, OR, fornix, SLF, and ILF at all three time points. Increased radial diffusivity among TBI patients was observed in all regions in which group differences in FA were observed at all three time points.

NEUROPSYCHOLOGICAL CORRELATIONS

Contrary to our hypothesis, we did not observe any correlations between an individual's GCS score and regional WM FA at any of the three time points. Of the seven neuropsychological measures tested for correlation with FA, two tests, Trails A and dominant hand finger tapping, were significantly correlated with regional FA values among the TBI subjects. No significant correlations were observed between FA and neuropsychological test performance among control subjects. Finger tapping scores correlated positively with FA in the splenium of the corpus callosum at the second time point (**Figure 7**). A lowered statistical threshold $\alpha = 0.01$ enabled observation of smaller splenium clusters when the equivalent correlational tests were run for the first and third time points, however, only the second time point result surpassed significance levels employed in this study. Trails A performance correlated positively with FA in bilateral regions of the SS at the first time point, and a unilateral region in the left SS at the second time point (**Figure 8A**).

Correlations between FA changes and changes in neuropsychological measures over time were also significant for two neuropsychological measures, Trails A and B cognitive component. No equivalent correlations were observed among controls for any measure. There was a positive correlation between change in the

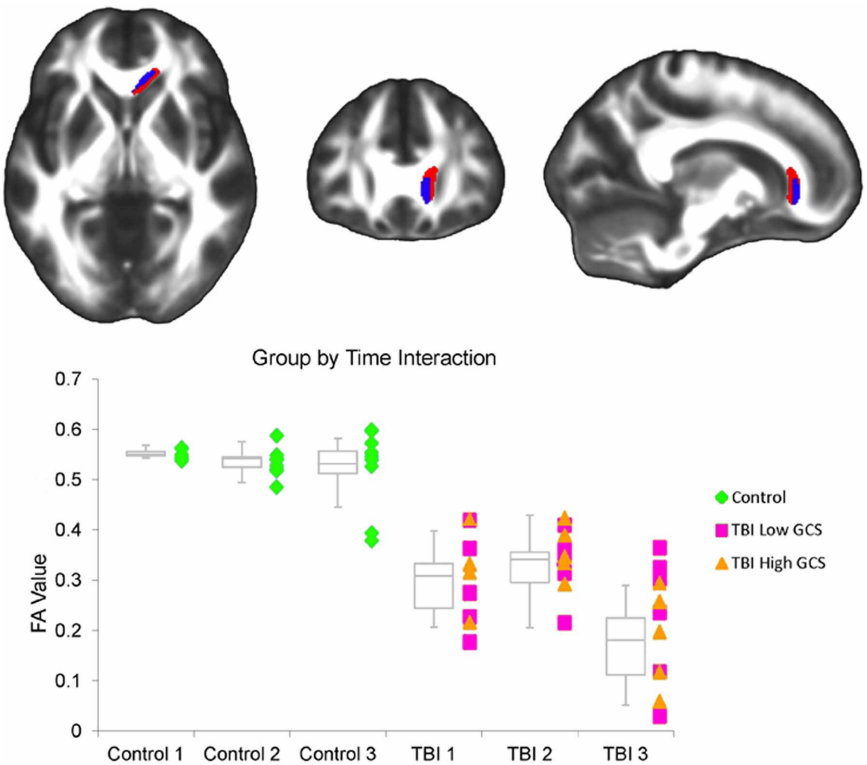

FIGURE 2 | (Top) A significant interaction between group and interval was observed within the FA factorial model. There were inter-interval dissimilarities in group-wise patterns of FA change in the genu of the corpus callosum (red). Axial and radial diffusivity analyses were restricted to regions demonstrating an FA effect. Within this region, a significant interaction was also observed in the radial diffusivity factorial model (overlapping blue region), but not the axial diffusivity factorial model. The left side of the statistical map is patient left and right is patient right. (**Bottom**) This graph shows the average FA value for each subject at each of the three time points within the corpus callosum cluster demonstrating an FA effect. Controls are marked as green diamonds, TBI patients with a 24 h GCS score of 7 or lower are marked as pink squares, and patients with a 24 h GCS score of 10 or higher are marked as orange triangles. Box plots indicate the 75th percentile, median, and 25th percentile FA values of each group at each time point, and whiskers indicate 1.5 times inter-quartile ranges.

Trails A score between the first and third time points and change in FA over the same duration (where an increase in FA was associated with a reduction in time to complete Trails A) in the right SS (**Figure 8B**). No significant correlations were observed between change in Trails A score and change in FA during either sub-interval of the study (from time one to time two or from time two to time three). A positive correlation between FA change and change in the Trails B cognitive component between time one and time three was observed in the left superior SLF and the right OR (**Figure 9**). Analysis of this correlation during each of the sub-intervals did not reveal any regions of significant clusters between the first and second time point, but a significant cluster was observed in the right posterior SLF between the second and third time points (**Figure 9**).

DISCUSSION

Longitudinal brain changes following TBI are sparsely documented. In this study we examined TBI patients over a period of four years and found that rather than showing a circumscribed period of brain degeneration following injury, TBI involves a protracted period of brain change that continues for several years. The results of this study suggest that studying alterations in brain WM may provide clues to neuropsychological function following TBI, and potentially inform upon the clinical course of patients following injury.

In our study, we found significant effects in the corpus callosum, which is commonly injured in TBI. The group by time interaction observed in the FA factorial model combined with the simple effects analyses indicates that the TBI subjects demonstrated a significantly greater reduction in FA in the genu of the corpus callosum during the first year post-injury than during the subsequent three years of the total follow-up period. This result is commensurate with previous work on a different subset of individuals in this cohort indicating FA reductions in this region during the first year post-injury (Bendlin et al., 2008), as well as other previous studies that have also found longitudinal WM decline in this region during the first year (Xu et al., 2007; Wu et al., 2010). Our results also demonstrated that the observed FA effect was driven by increased radial, rather than decreased axial, diffusivity, which is consistent with previous observations (Sidaros et al., 2008; Kumar et al., 2010). Other recent research has indicated that initial injury to the genu is highly predictive of patient outcome (in terms of general disability), however, we did not

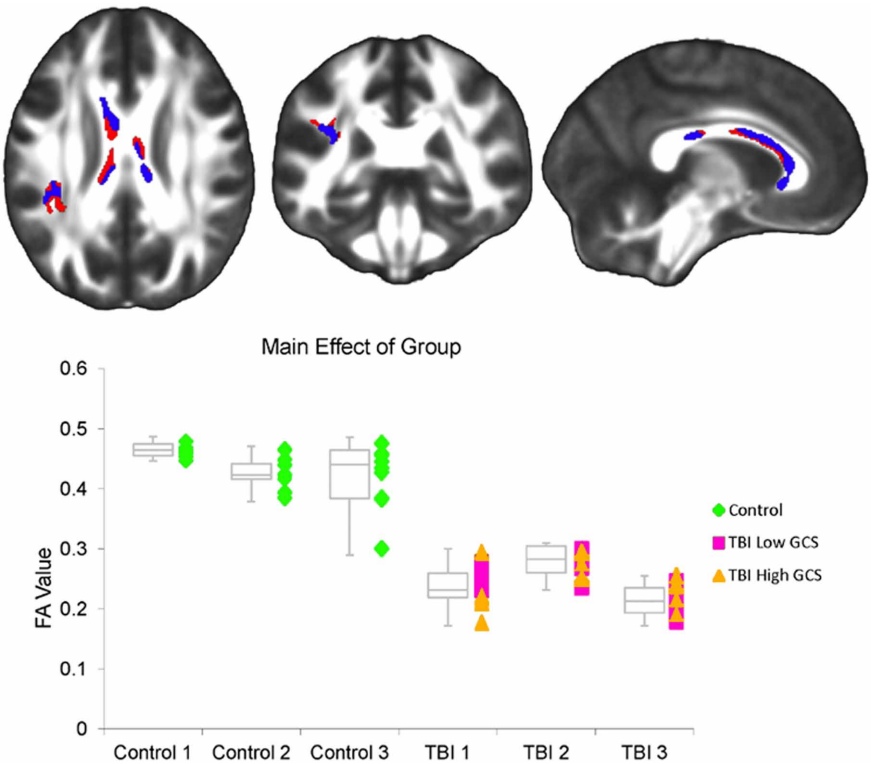

FIGURE 3 | (Top) A significant effect of time was observed throughout the corpus callosum as well as in the left SLF within the FA factorial model (red). Axial and radial diffusivity analyses were restricted to regions demonstrating an FA effect. Within this region, a significant effect of time was also observed within the radial diffusivity factorial model (overlapping blue region), but not the axial diffusivity factorial model. The left side of the statistical map is patient left and right is patient right. (**Bottom**) This graph shows the average FA value for each subject at each of the three time points within the corpus callosum cluster demonstrating an FA effect. Controls are marked as green diamonds, TBI patients with a 24 h GCS score of 7 or lower are marked as pink squares, and patients with a 24 h GCS score of 10 or higher are marked as orange triangles. Box plots indicate the 75th percentile, median, and 25th percentile FA values of each group at each time point, and whiskers indicate 1.5 times inter-quartile ranges.

observe correlations between FA change in this region over time and change in neuropsychological task performance (Matsukawa et al., 2011).

The main effect of time combined with simple effects analyses indicate that TBI patients experienced a continued decline in FA throughout the corpus callosum that continued throughout the duration of the four year period studied, and that this decrease was driven by increases in radial diffusivity. It has been suggested that initial tearing, shearing, and misalignment of axons initiates an inflammatory cascade that leads to further WM damage, myelin loss, and gliosis, and we expect that these processes were critical to the gradual, long-term FA reductions observed here (Povlishock, 2000).

The main effect of group combined with between-groups simple effects analyses indicate that TBI subjects exhibited reduced FA in several major tracts, that this difference was persistent for at least four years post-injury, and that a combination of reduced axial and increased radial diffusivity gave rise to these FA differences. These results collectively demonstrate that in several major tracts there is reduced directional coherence of WM among our TBI subjects that is both widespread and long-lasting. These between-groups differences are consistent with cross-sectional observations (Chan et al., 2003; Nakayama et al., 2006; Kiraly and Kiraly, 2007; Xu et al., 2007; Bendlin et al., 2008; Sidaros et al., 2008; Wang et al., 2011).

Our simple effects results also demonstrate that TBI subjects demonstrated increases in FA in the SLF bilaterally as well as in a portion of the OR during the course of the study, potentially signifying improvement of WM integrity or alternatively showing loss of crossing fibers in these brain regions. No previous study that we are aware of has demonstrated longitudinal increases in FA among TBI patients. This is likely because no previous study that we are aware of followed patients for four years as the current study did, and the FA increases we observed appear to have taken place gradually during the four year study duration. Previous research has, however, identified apparent improvements in FA in animal models of TBI (Rubovitch et al., 2011), and in either axial or radial diffusivity among human TBI patients (Sidaros et al., 2008; Kumar et al., 2010), indicating that our present finding is potentially replicable. This evidence of subtle neurological recovery merits further investigation, particularly in clinical settings. The secondary result indicating that this increase in FA was driven by a longitudinal decrease in radial diffusivity (rather than an increase in axial diffusivity) could suggest improved myelin integrity within the tract, however, it is equally plausible that progressive loss of damaged axons that is observed in animal models

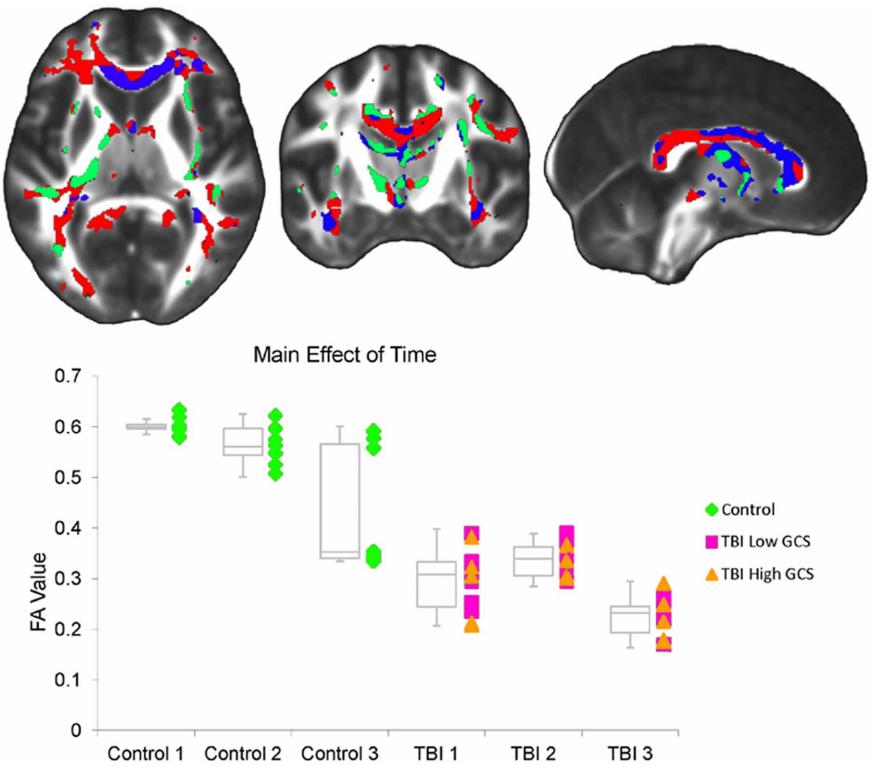

FIGURE 4 | (Top) A significant effect of group was observed within the FA factorial model in several white matter tracts throughout the brain, including the cerebral peduncle, inferior and superior longitudinal fascicule (ILF and SLF), internal and external capsule, inferior fronto-occipital fasciculus, sagittal stratum, corpus callosum, fornix, optic radiations, thalamic radiations, uncinate fasciculus, and corona radiata (red). Axial and radial diffusivity analyses were restricted to regions demonstrating an FA effect. Within this set of regions, a significant effect of group was also observed within the radial diffusivity factorial model (overlapping blue regions), as well as the axial diffusivity factorial model (overlapping green yellow regions). Regions in which a significant effect was seen in the FA, radial diffusivity, and axial diffusivity models are shown in green. The left side of the statistical map is patient left and right is patient right. (**Bottom**) This graph shows the average FA value for each subject at each of the three time points within the regions demonstrating an FA effect. Controls are marked as green diamonds, TBI patients with a 24 h GCS score of 7 or lower are marked as pink squares, and patients with a 24 h GCS score of 10 or higher are marked as orange triangles. Box plots indicate the 75th percentile, median, and 25th percentile FA values of each group at each time point, and whiskers indicate 1.5 times inter-quartile ranges.

of TBI (Creed et al., 2011) may underlie the observed FA changes in our TBI cohort.

The fact that longitudinal changes in radial (rather than axial) diffusivity were found in the same regions where FA changes were found warrants further attention. In the literature, findings concerning radial diffusivity and TBI tend to be relatively consistent across studies, whereas findings relating to axial diffusivity are inconsistent. Many studies have reported longitudinal increases in radial diffusivity in the absence of changes in axial diffusivity and like in the current study these changes have frequently been localized to the corpus callosum (Mac Donald et al., 2007; Newcombe et al., 2007; Ewing-Cobbs et al., 2008; Tasker et al., 2010). Differences in axial diffusivity, however, have been inconsistent, with some groups finding increases (Sidaros et al., 2008; Tasker et al., 2010), decreases (Li et al., 2011) or no change (Mac Donald et al., 2007) in both the corpus callosum and other regions. These inconsistencies may be due to differences in how long after injury patient scans were obtained. While FA variations may be related to myelin change, axonal change, or differences in directional coherence of fibers (e.g., presence of absence of crossing fibers), changes in axial diffusivity are thought to be associated primarily with axonal changes while changes in radial diffusivity are thought to relate to myelin changes (Song et al., 2002; Alexander et al., 2007; Xie et al., 2010). These findings indicate that progressive FA loss observed among our subjects was likely driven by progressive myelin pathology, possibly due to persistent inflammation (Ramlackhansingh et al., 2011). While progressive FA increases observed could have been driven by improvements in myelin integrity, the removal of axons with damaged myelin by phagocytotic processes likely also contributed to our result.

While it is not plausible to determine why some regions showed FA increases while others showed decreases with imaging data alone, it is nonetheless instructive to speculate on this matter. One likely contributing factor is the specific injuries sustained by this cohort of TBI patients. The corpus callosum is frequently that center of severe damage during TBI, and the subjects in this cohort were no exception. Several subjects' initial radiology notes included mentions of corpus callosal damage, but none mentioned other tracts specifically. It is possible, therefore,

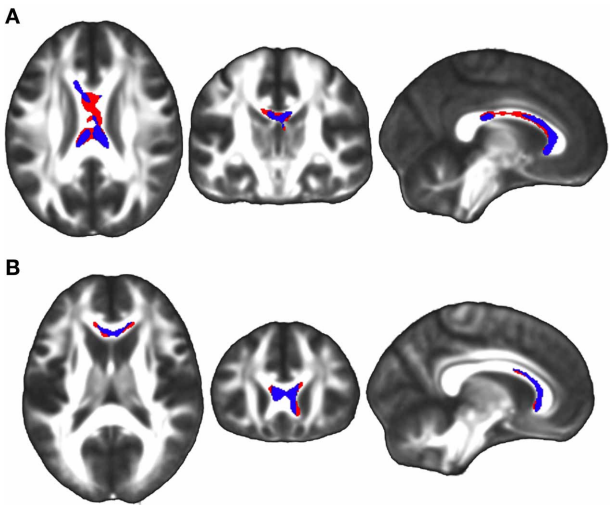

FIGURE 5 | (A) Simple effects analysis within the FA factorial model revealed a significant region of the corpus callosum in which TBI subjects exhibited greater FA at the first time point compared to the third time point (red), indicating a longitudinal FA reduction during the four year study duration. The equivalent test in controls did not produce any significant clusters. Secondary axial and radial diffusivity analyses were renstricted to regions demonstrating an FA effect. Axial and radial diffusivity analyses demonstrated that in this region there was a significant increase in radial diffusivity, but no decrease in axial diffusivity, during the four year study (overlapping blue region). **(B)** Analysis of this region during the two sub-intervals revealed that there was a significant FA reduction between the first and second time points in the genu of the corpus callosum among TBI subjects (red), but no clusters between the second and third time points. Secondary axial and radial diffusivity analyses were restricted to regions demonstrating an FA effect. Axial and radial diffusivity analyses demonstrated that in this region there was a significant increase in radial diffusivity, but no decrease in axial diffusivity, between the first and second time points (overlapping blue region). The left side of the statistical map is patient left and right is patient right.

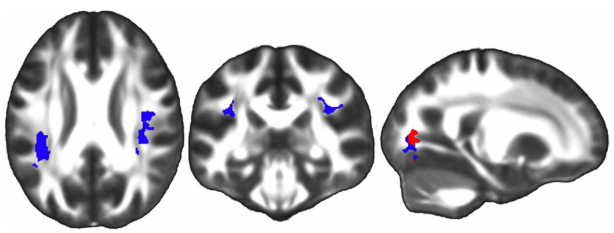

FIGURE 6 | Simple effects analysis within the FA factorial model revealed significant regions in the bilateral SLF in which TBI subjects exhibited greater FA at the third time point compared to the first time point (red), indicating a longitudinal FA increase during the four year study duration. The equivalent test in controls did not produce any significant clusters. Secondary axial and radial diffusivity analyses were restricted to this region demonstrating an FA effect. Axial and radial diffusivity analyses demonstrated that in this region there was a significant decrease in radial diffusivity during the four year study period (overlapping blue region), but no accompanying increase in axial diffusivity. The left side of the statistical map is patient left and right is patient right.

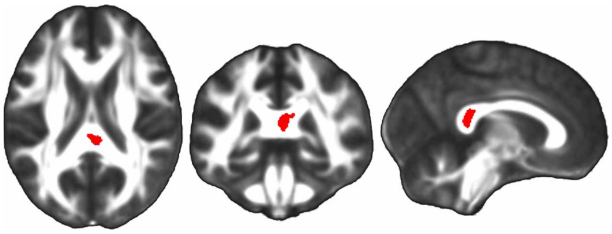

FIGURE 7 | Linear regression analyses, in which neuropsychological test scores were the independent variables and FA maps were the dependent variables, demonstrated a significant correlation between performance on a finger tapping task and FA in the splenium of the corpus callosum among TBI patients at the second time point (red). The left side of the statistical map is patient left and right is patient right.

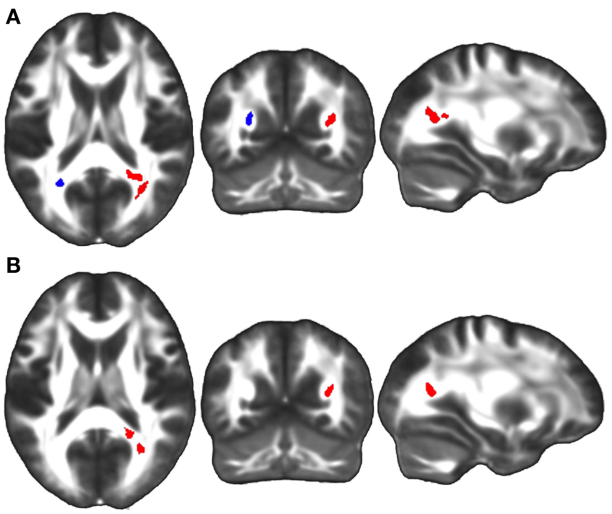

FIGURE 8 | (A) Linear regression analyses demonstrated a significant positive correlation between TBI patients' performance on the Trails A visuomotor speed task and FA in bilateral regions of the sagittal stratum at the first time point (red), and in a unilateral region of the left sagittal stratum at the second time point (overlapping blue region). **(B)** A positive correlation was also observed between change in Trails A score between the first and third time points and change in sagittal stratum FA over the same four year study duration (red). The left side of the statistical map is patient left and right is patient right.

the continued deterioration was observed in regions with greater initial damage. Another complementary possibility is that differential tract properties promote different responses to insult. Research with animal models has demonstrated that astrocytic proliferation can occur in responses to focal injury, but only certain subclasses of neurons are capable of this type of structural remodeling (Blizzard et al., 2011). Further research, most likely in animal models, is necessary to determine why certain regions continue to deteriorate post-injury while others remain static or even improve.

GCS score and WM integrity were not correlated in TBI patients, likely due to the heterogeneity of patients' injuries. It is probable that more severely injured individuals had greater WM

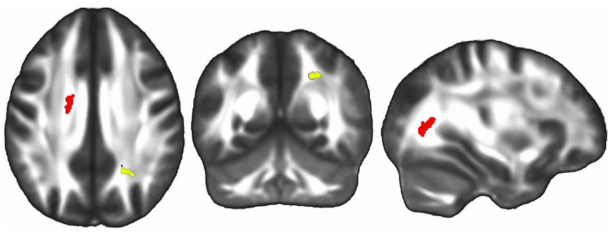

FIGURE 9 | Linear regression analyses revealed a significant positive correlation between change in the cognitive component of the Trails B score between time one and time three and FA change in the left superior SLF and right optic radiation over the same four year study duration (red). Analyses of sub-intervals revealed there was also a significant positive correlation between change in the Trails B cognitive component between the first and second time points, and FA change in the right posterior SLF over the same one year first interval duration (yellow). The left side of the statistical map is patient left and right is patient right.

damage near impact sites, but variable injury locations across subjects precluded group-wise identification of these differences. The neuropsychological correlations we observed were consistent with our hypothesis that FA and neuropsychological task performance would correlate positively. In TBI patients, damage to the splenium indexed by lower FA was associated with slower finger tapping speed, consistent with previous studies linking corpus callosum to manual motor tasks (Muetzel et al., 2008; Caeyenberghs et al., 2011a,b).

Faster performance on the Trails A test was associated with higher FA in the SS, an interesting finding given that this tract is known to be implicated in visuomotor functions. Individuals with greater damage to this tract likely had more difficulty completing the task (Makris et al., 2005; Hao et al., 2011). Over time, this relationship held, with a subset of TBI patients showing longitudinal improvements in Trails A completion speed between the first and third time points and a corresponding increase in FA in the SS over the same interval.

Correlations were also observed between change in the Trails B cognitive component score over time and change in FA values among TBI patients. A correlation was observed between the first and third time points in the left SLF and the right OR, as well as in the right SLF between the second and third time points. Previous work has demonstrated that FA in the SLF is is associated with complex functions such as attentiveness, working memory and reading skills (Karlsgodt et al., 2008; Frye et al., 2010). The SLF subserves a wide variety of connective functions, and the longitudinal improvements in directional coherence of fibers within this tract among TBI patients in this study may have contributed to improved scores on the Trails B cognitive component measure. Interestingly, we also found a relationship in the OR (a tract relevant to the relay of visual information from the lateral geniculate nucleus to the visual cortex); this may suggest that subtracting Trails A scores from Trails B scores does not entirely remove the visuomotor element of the task, or possibly that this tract is important for subserving the cognitive component of a visuomotor task. Overall, our neuropsychological correlations demonstrate that the differences in FA observed in our study do indeed have an impact on cognitive and motor function, and that subtle increases in FA over time reflect WM change that is related to improved functionality in patients. While it should be noted that the neuropsychological correlations reported in the current study may be specific to the set of patients included and their particular patterns of WM damage, it is nonetheless informative to identify functional relevancies of WM change.

In addition to the primary analyses and results presented in this paper, we also conducted an investigatory simple effects analysis of whole-brain radial diffusivity changes within our patients. This analysis was carried out within the radial diffusivity factorial model used in our primary analysis, but the search was not restricted to regions demonstrating FA change. The results of this analysis, which used the same statistical parameters as our primary FA analysis, indicated that within our cohort longitudinal decreases in radial diffusivity (approximating improvements in myelin integrity) were found in regions throughout the brain during the four year study duration. Regions included superior and inferior longitudinal fasiculi, internal and external capsules, the descending corticospinal tract, and forceps major and minor (**Figure A1**). While this analysis is beyond the planned scope and goals of the current study, it is provocative and may be informative to future research.

The results of this study likely have significant clinical relevance. Specifically, it is notable that we observed WM changes occurring for several years post-injury because the continued malleability of the injured brain holds promise for the effectiveness of treatments well beyond the three to six month window in which treatments are typically prescribed. The FA increase observed in this study has particular relevance to treatment options, as it reflects plasticity and represents a potential physiological basis of rehabilitation. In order to truly assess the relevance of these results to clinical applications, a clinical trial study would be necessary. In such a study, DTI would be used as an outcome measure with the expectation that patients undergoing treatment would exhibit less deterioration or greater improvement in regional brain WM integrity. A positive result would underscore the clinical relevance of our findings.

The current study has methodological limitations that should be considered. Firstly, the results of our study may be limited by methodological limitations imposed by performing a patient and control comparison. For example, it is possible that preprocessing of imaging data and even MR signal of interest can be affected differentially by group. Voxel-wise comparisons of brain images are dependent upon accurate alignment to a template; in order to minimize error, all FA maps were visually inspected for within-subject tract alignment to the template and alignment across all participants. Another potential limitation concerns the greater ratio of women to men in the control group compared to the TBI group. Due to this, we used gender as a covariate in all analyses. In this study we were not able to account for the intensity or duration of rehabilitations programs in which some of our patients participated. Future clinical trials are critical to understanding how rehabilitation programs impact neurological recovery.

Concurrent volume loss exhibited by TBI patients could also have confounded our results. Volume loss following injury is well

established in the TBI literature (Levine et al., 2008; Merkley et al., 2008; Sidaros et al., 2009), and has also been observed in this particular cohort of patients (Bendlin et al., 2008). While any DTI study done on this patient population will have results obtained in the context of volume loss, it is nonetheless important to acknowledge that tissue contraction, in addition to microstructural reorganization, may contribute to observed changes in DTI metrics. To ensure that our results were not due solely to volumetric changes, we conducted a native space region of interest analysis on the genu of the corpus callosum. The genu was selected because it is a functionally relevant region and is easily identifiable. FA values were extracted from 3 mm spherical ROIs placed in the center of the genu in each participant's native space DTI images from Visits 1, 2, and 3. Independent samples two-tailed *t*-tests showed that TBI patients had reduced FA compared to controls at all three time points (Visit 1: Controls-$m = 0.77$, TBIs-$m = 0.67$, $p = 0.005$; Visit 2: Controls-$m = 0.79$, TBIs-$m = 0.63$, $p = 0.0003$; Visit 3: Controls-$m = 0.79$, TBIs-$m = 0.61$, $p = 0.001$). Paired samples two-tailed *t*-tests showed that TBI patients demonstrated a reduction in FA between Visits 1 and 2 ($p = 0.01$) as well as between visits 1 and 3 ($p = 0.04$). Paired samples *t*-tests showed no longitudinal changes within the control group. These results mirror the observations made in our whole-brain analysis, and partially allay concerns about the confounding effects of concurrent volume change.

Finally, the results of this study may be limited by the small number of participants that were followed through all three time points. The TBI population and college aged controls are both itinerant populations, and therefore, difficult to track for long periods of time. Notwithstanding this limitation, follow-up of TBI patients over three time points makes this an extremely valuable sample. Furthermore, we did not find significant differences in age, education or injury severity within either group between those who dropped out of the study and those who completed all three visits, suggesting that selective drop-out did not bias the results.

In this study, we show that TBI patients exhibit longitudinal WM changes that continue for at least four years post-injury. These changes include both progressive reductions in FA (observed in the corpus callosum) as well as progressive FA increases (observed in the bilateral SLF). Within the regions where FA changes were found, radial diffusivity alterations were present—suggesting myelin changes continued to occur throughout the period studied. Furthermore, neuropsychological correlations indicate that diffusion metrics are related to cognitive and motor abilities, and that improved directional coherence within tracts is relevant to improved task performance in certain brain regions among TBI patients. The fact that changes continued to develop for several years post-injury provides support for the hypothesis that TBI is not merely an event but rather the initiation of a prolonged disease state with potentially lifelong systemic impacts. FA increases are of particular note due to the unprecedented nature of these findings. TBI is generally conceptualized as strictly a degenerative condition and evidence of what might be long-term neurological improvement could be of significant clinical importance. We strive to continue to improve our understanding of these long-term effects following traumatic injury. An important area of work going forward will be to capitalize on signs of gradual long-term neurological and functional improvement observed in TBI, and to further understand the brain correlates of ameliorative change, which likely occurs alongside progressive degeneration.

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REFERENCES

Alexander, A. L., Lee, J. E., Lazar, M., and Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics* 4, 316–329.

Anderson, C. V., Bigler, E. D., and Blatter, D. D. (1995). Frontal lobe lesions, diffuse damage, and neuropsychological functioning in traumatic brain-injured patients. *J. Clin. Exp. Neuropsychol.* 17, 900–908.

Arfanakis, K., Haughton, V. M., Carew, J. D., Rogers, B. P., Dempsey, R. J., and Meyerand, M. E. (2002). Diffusion tensor MR imaging in diffuse axonal injury. *AJNR Am. J. Neuroradiol.* 23, 794–802.

Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., Sherman, J. E., and Johnson, S. C. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *Neuroimage* 42, 503–514.

Bigler, E. D., Blatter, D. D., Johnson, S. C., Anderson, C. V., Russo, A. A., Gale, S. D., Ryser, D. K., MacNamara, S. E., and Bailey, B. J. (1996). Traumatic brain injury, alcohol and quantitative neuroimaging: preliminary findings. *Brain Inj.* 10, 197–206.

Blizzard, C. A., Chuckowree, J. A., King, A. E., Hosie, K. A., McCormack, G. H., Chapman, J. A., Vickers, J. C., and Dickson, T. C. (2011). Focal damage to the adult rat neocortex induces wound healing accompanied by axonal sprouting and dendritic structural plasticity. *Cereb. Cortex* 21, 281–291.

Bombardier, C. H., Fann, J. R., Temkin, N. R., Esselman, P. C., Barber, J., and Dikmen, S. S. (2010). Rates of major depressive disorder and clinical outcomes following traumatic brain injury. *JAMA* 303, 1938–1945.

Caeyenberghs, K., Leemans, A., Coxon, J., Leunissen, I., Drijkoningen, D., Geurts, M., Gooijers, J., Michiels, K., Sunaert, S., and Swinnen, S. P. (2011a). Bimanual coordination and corpus callosum microstructure in young adults with traumatic brain injury: a diffusion tensor imaging study. *J. Neurotrauma* 28, 897–913.

Caeyenberghs, K., Leemans, A., Geurts, M., Linden, C. V., Smits-Engelsman, B. C., Sunaert, S., and Swinnen, S. P. (2011b). Correlations between white matter integrity and motor function in traumatic brain injury patients. *Neurorehabil. Neural Repair* 25, 492–502.

Chan, J. H., Tsui, E. Y., Peh, W. C., Fong, D., Fok, K. F., Leung, K. M., Yuen, M. K., and Fung, K. K. (2003). Diffuse axonal injury: detection of changes in anisotropy of water diffusion by diffusion-weighted imaging. *Neuroradiology* 45, 34–38.

Creed, J. A., DiLeonardi, A. M., Fox, D. P., Tessler, A. R., and Raghupathi, R. (2011). Concussive brain trauma in the mouse results in acute cognitive deficits and sustained impairment of axonal function. *J. Neurotrauma* 28, 547–563.

Ewing-Cobbs, L., Prasad, M. R., Swank, P., Kramer, L., Cox, C. S. Jr., Fletcher, J. M., Barnes, M., Zhang, X., and Hasan, K. M. (2008). Arrested development and disrupted callosal microstructure following pediatric traumatic brain injury: relation to neurobehavioral outcomes. *Neuroimage* 42, 1305–1315.

Field, A. S., Hasan, K., Jellison, B. J., Arfanakis, K., and Alexander, A. L. (2003). Diffusion tensor imaging in an infant with traumatic brain swelling. *AJNR Am. J. Neuroradiol.* 24, 1461–1464.

Filippi, C. G., Ulug, A. M., Ryan, E., Ferrando, S. J., and van Gorp, W. (2001). Diffusion tensor imaging of patients with HIV and normal-appearing white matter on MR images of the brain. *AJNR Am. J. Neuroradiol.* 22, 277–283.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., and Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn. Reson. Med.* 33, 636–647.

Frye, R. E., Hasan, K., Malmberg, B., Desouza, L., Swank, P., Smith, K., and Landry, S. (2010). Superior longitudinal fasciculus and cognitive dysfunction in adolescents born preterm and at term. *Dev. Med. Child Neurol.* 52, 760–766.

Gale, S. D., Johnson, S. C., Bigler, E. D., and Blatter, D. D. (1995). Nonspecific white matter degeneration following traumatic brain injury. *J. Int. Neuropsychol. Soc.* 1, 17–28.

Hao, X., Xu, D., Bansal, R., Dong, Z., Liu, J., Wang, Z., Kangarlu, A., Liu, F., Duan, Y., Shova, S., Gerber, A. J., and Peterson, B. S. (2011). Multimodal magnetic resonance imaging: the coordinated use of multiple, mutually informative probes to understand brain structure and function. *Hum. Brain Mapp.* doi: 10.1002/hbm.21440. [Epub ahead of print].

Karlsgodt, K. H., van Erp, T. G., Poldrack, R. A., Bearden, C. E., Nuechterlein, K. H., and Cannon, T. D. (2008). Diffusion tensor imaging of the superior longitudinal fasciculus and working memory in recent-onset schizophrenia. *Biol. Psychiatry* 63, 512–518.

Kim, J., Avants, B., Patel, S., Whyte, J., Coslett, B. H., Pluta, J., Detre, J. A., and Gee, J. C. (2008). Structural consequences of diffuse traumatic brain injury: a large deformation tensor-based morphometry study. *Neuroimage* 39, 1014–1026.

Kiraly, M., and Kiraly, S. J. (2007). Traumatic brain injury and delayed sequelae: a review–traumatic brain injury and mild traumatic brain injury (concussion) are precursors to later-onset brain disorders, including early-onset dementia. *ScientificWorldJournal* 7, 1768–1776.

Kraus, M. F., Susmaras, T., Caughlin, B. P., Walker, C. J., Sweeney, J. A., and Little, D. M. (2007). White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain* 130(Pt 10), 2508–2519.

Kumar, R., Saksena, S., Husain, M., Srivastava, A., Rathore, R. K., Agarwal, S., and Gupta, R. K. (2010). Serial changes in diffusion tensor imaging metrics of corpus callosum in moderate traumatic brain injury patients and their correlation with neuropsychometric tests: a 2-year follow-up study. *J. Head Trauma Rehabil.* 25, 31–42.

Le Bihan, D. (1991). Molecular diffusion nuclear magnetic resonance imaging. *Magn. Reson. Q.* 7, 1–30.

Levin, H. S. (2003). Neuroplasticity following non-penetrating traumatic brain injury. *Brain Inj.* 17, 665–674.

Levine, B., Kovacevic, N., Nica, E. I., Cheung, G., Gao, F., Schwartz, M. L., and Black, S. E. (2008). The Toronto traumatic brain injury study: injury severity and quantified MRI. *Neurology* 70, 771–778.

Li, J., Li, X. Y., Feng, D. F., and Gu, L. (2011). Quantitative evaluation of microscopic injury with diffusion tensor imaging in a rat model of diffuse axonal injury. *Eur. J. Neurosci.* 33, 933–945.

Lin, M. R., Chiu, W. T., Chen, Y. J., Yu, W. Y., Huang, S. J., and Tsai, M. D. (2010). Longitudinal changes in the health-related quality of life during the first year after traumatic brain injury. *Arch. Phys. Med. Rehabil.* 91, 474–480.

Ljungqvist, J., Nilsson, D., Ljungberg, M., Sorbo, A., Esbjornsson, E., Eriksson-Ritzen, C., and Skoglund, T. (2011). Longitudinal study of the diffusion tensor imaging properties of the corpus callosum in acute and chronic diffuse axonal injury. *Brain Inj.* 25, 370–378.

Mac Donald, C. L., Dikranian, K., Bayly, P., Holtzman, D., and Brody, D. (2007). Diffusion tensor imaging reliably detects experimental traumatic axonal injury and indicates approximate time of injury. *J. Neurosci.* 27, 11869–11876.

Makris, N., Kennedy, D. N., McInerney, S., Sorensen, A. G., Wang, R., Caviness, V. S. Jr., and Pandya, D. N. (2005). Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, *in vivo*, DT-MRI study. *Cereb. Cortex* 15, 854–869.

Malec, J. F., Brown, A. W., Moessner, A. M., Stump, T. E., and Monahan, P. (2010). A preliminary model for posttraumatic brain injury depression. *Arch. Phys. Med. Rehabil.* 91, 1087–1097.

Marquez de la Plata, C. D., Hart, T., Hammond, F. M., Frol, A. B., Hudak, A., Harper, C. R., O'Neil-Pirozzi, T. M., Whyte, J., Carlile, M., and Diaz-Arrastia, R. (2008). Impact of age on long-term recovery from traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, 896–903.

Masel, B. E., and DeWitt, D. S. (2010). Traumatic brain injury: a disease process, not an event. *J. Neurotrauma* 27, 1529–1540.

Matsukawa, H., Shinoda, M., Fujii, M., Takahashi, O., Yamamoto, D., Murakata, A., and Ishikawa, R. (2011). Genu of corpus callosum in diffuse axonal injury induces a worse 1-year outcome in patients with traumatic brain injury. *Acta Neurochir. (Wien)* 153, 1687–1693. discussion 1693–1694.

Merkley, T. L., Bigler, E. D., Wilde, E. A., McCauley, S. R., Hunter, J. V., and Levin, H. S. (2008). Diffuse changes in cortical thickness in pediatric moderate-to-severe traumatic brain injury. *J. Neurotrauma* 25, 1343–1345.

Muetzel, R. L., Collins, P. F., Mueller, B. A. M., Schissel, A., Lim, K. O., and Luciana, M. (2008). The development of corpus callosum microstructure and associations with bimanual task performance in healthy adolescents. *Neuroimage* 39, 1918–1925.

Nakayama, N., Okumura, A., Shinoda, J., Yasokawa, Y. T., Miwa, K., Yoshimura, S. I., and Iwama, T. (2006). Evidence for white matter disruption in traumatic brain injury without macroscopic lesions. *J. Neurol. Neurosurg. Psychiatry* 77, 850–855.

Newcombe, V. F., Williams, G. B., Nortje, J., Bradley, P. G., Harding, S. G., Smielewski, P., Coles, J. P., Maiya, B., Gillard, J. H., Hutchinson, P. J., Pickard, J. D., Carpenter, T. A., and Menon, D. K. (2007). Analysis of acute traumatic axonal injury using diffusion tensor imaging. *Br. J. Neurosurg.* 21, 340–348.

Povlishock, J. T. (2000). Pathophysiology of neural injury: therapeutic opportunities and challenges. *Clin. Neurosurg.* 46, 113–126.

Povlishock, J. T., and Christman, C. W. (1995). The pathobiology of traumatically induced axonal injury in animals and humans: a review of current thoughts. *J. Neurotrauma* 12, 555–564.

Ramlackhansingh, A. F., Brooks, D. J., Greenwood, R. J., Bose, S. K., Turkheimer, F. E., Kinnunen, K. M., Gentleman, S., Heckemann, R. A., Gunanayagam, K., Gelosa, G., and Sharp, D. J. (2011). Inflammation after trauma: microglial activation and traumatic brain injury. *Ann. Neurol.* 70, 374–383.

Risdall, J. E., and Menon, D. K. (2010). Traumatic brain injury. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 366, 241–250.

Rubovitch, V., Ten-Bosch, M., Zohar, O., Harrison, C. R., Tempel-Brami, C., Stein, E., Hoffer, B. J., Balaban, C. D., Schreiber, S., Chiu, W. T., and Pick, C. G. (2011). A mouse model of blast-induced mild traumatic brain injury. *Exp. Neurol.* 232, 280–289.

Sharp, D. J., and Ham, T. E. (2011). Investigating white matter injury after mild traumatic brain injury. *Curr. Opin. Neurol.* 24, 558–563.

Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., Paulson, O. B., Jernigan, T. L., and Rostrup, E. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain* 131(Pt 2), 559–572.

Sidaros, A., Skimminge, A., Liptrot, M. G., Sidaros, K., Engberg, A. W., Herning, M., Paulson, O. B., Jernigan, T. L., and Rostrup, E. (2009). Long-term global and regional brain volume changes following severe traumatic brain injury: a longitudinal study with clinical correlates. *Neuroimage* 44, 1–8.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., and Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 23(Suppl. 1), S208–S219.

Song, S. K., Sun, S. W., Ju, W. K., Lin, S. J., Cross, A. H., and Neufeld, A. H. (2003). Diffusion

tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage* 20, 1714–1722.

Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., and Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17, 1429–1436.

Staudt, M. (2010). Brain plasticity following early life brain injury: insights from neuroimaging. *Semin. Perinatol.* 34, 87–92.

Tasker, R. C., Westland, A. G., White, D. K., and Williams, G. B. (2010). Corpus callosum and inferior forebrain white matter microstructure are related to functional outcome from raised intracranial pressure in child traumatic brain injury. *Dev. Neurosci.* 32, 374–384.

Trivedi, M. A., Ward, M. A., Hess, T. M., Gale, S. D., Dempsey, R. J., Rowley, H. A., and Johnson, S. C. (2007). Longitudinal changes in global brain volume between 79 and 409 days after traumatic brain injury: relationship with duration of coma. *J. Neurotrauma* 24, 766–771.

Wang, J. Y., Bakhadirov, K., Abdi, H., Devous, M. D. Sr., Marquez de la Plata, C. D., Moore, C., Madden, C. J., and Diaz-Arrastia, R. (2011). Longitudinal changes of structural connectivity in traumatic axonal injury. *Neurology* 77, 818–826.

Wheeler-Kingshott, C. A., and Cercignani, M. (2009). About "axial" and "radial" diffusivities. *Magn. Reson. Med.* 61, 1255–1260.

Wu, T. C., Wilde, E. A., Bigler, E. D., Li, X., Merkley, T. L., Yallampalli, R., McCauley, S. R., Schnelle, K. P., Vasquez, A. C., Chu, Z., Hanten, G., Hunter, J. V., and Levin, H. S. (2010). Longitudinal changes in the corpus callosum following pediatric traumatic brain injury. *Dev. Neurosci.* 32, 361–373.

Xie, M., Tobin, J. E., Budde, M. D., Chen, C. I., Trinkaus, K., Cross, A. H., McDaniel, D. P., Song, S. K., and Armstrong, R. C. (2010). Rostrocaudal analysis of corpus callosum demyelination and axon damage across disease stages refines diffusion tensor imaging correlations with pathological features. *J. Neuropathol. Exp. Neurol.* 69, 704–716.

Xu, J., Rasmussen, I. A., Lagopoulos, J., and Haberg, A. (2007). Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. *J. Neurotrauma* 24, 753–765.

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APPENDIX

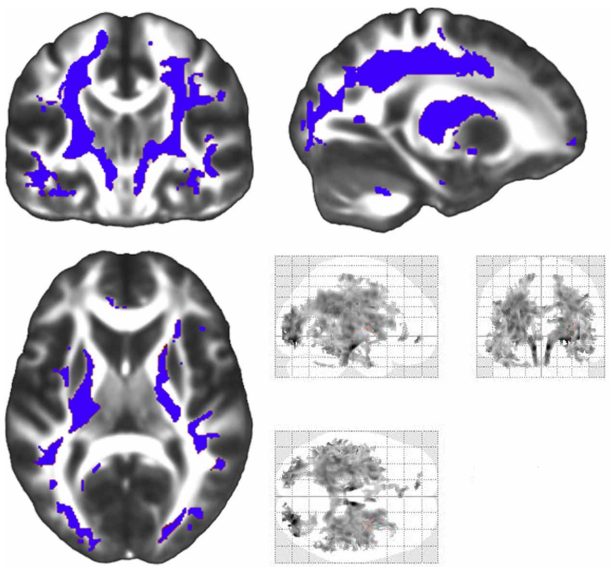

FIGURE A1 | A supplementary whole-brain analysis of radial diffusivity change among patients that was not restricted to regions demonstrating an FA effect was conducted. This analysis was carried out in the same radial diffusivity factorial model used in the restricted radial diffusivity analyses, and statistical thresholds used in FA analyses were employed. This analysis examined decreases in radial diffusivity during the four year study duration. Regions of decreased radial diffusivity included significant longitudinal decreases in radial diffusivity in superior and inferior longitudinal fasiculi, internal and external capsules, forceps major and minor and the descending corticospinal tract (blue). The tubular regions of change that extend through the descending corticospinal tract were not constrained on any side by the white matter mask employed in our analyses. The left side of the statistical map is patient left and right is patient right.

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Is there evidence for neurodegenerative change following traumatic brain injury in children and youth? A scoping review

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While generalized cerebral atrophy and neurodegenerative change following traumatic brain injury (TBI) is well recognized in adults, it remains comparatively understudied in the pediatric population, suggesting that research should address the potential for neurodegenerative change in children and youth following TBI. This focused review examines original research findings documenting evidence for neurodegenerative change following TBI of all severities in children and youth. Our relevant inclusion and exclusion criteria identified a total of 16 articles for review. Taken together, the studies reviewed suggest there is evidence for long-term neurodegenerative change following TBI in children and youth. In particular both cross-sectional and longitudinal studies revealed volume loss in selected brain regions including the hippocampus, amygdala, globus pallidus, thalamus, periventricular white matter, cerebellum, and brain stem as well as overall decreased whole brain volume and increased CSF and ventricular space. Diffusion Tensor Imaging (DTI) studies also report evidence for decreased cellular integrity, particularly in the corpus callosum. Sensitivity of the hippocampus and deep limbic structures in pediatric populations are similar to findings in the adult literature and we consider the data supporting these changes as well as the need to investigate the possibility of neurodegenerative onset in childhood associated with mild traumatic brain injury (mTBI).

Keywords: traumatic brain injury, neurodegeneration, magnetic resonance imaging

INTRODUCTION

One of the most commonly reported injuries in children who participate in sports is concussion or mild traumatic brain injury (mTBI) (Browne and Lam, 2006). Children and youth (<19 years) involved in organized contact sports are nearly six times more likely to suffer a severe concussion compared to other leisure physical activities (Browne and Lam, 2006). The recovery profile and breadth of consequences in children and youth remains largely unknown (McCrory et al., 2004). This dearth of literature is compounded by the recent scrutiny youth participation in competitive contact sports (such as boxing, hockey and football) has received, due primarily to case study and media reports linking repeat concussions to a distinct neurodegenerative disease known as chronic traumatic encephalopathy (CTE).

This condition was initially described in boxers in 1928 by Martland and known as dementia pugilistica (Martland, 1928). In some cases, a constellation of symptoms typical of neurodegenerative disease were observed in a syndrome, and Miller coined the term "CTE" (Miller, 1966). It is now recognized in many sports in which there are repetitive concussions. CTE is defined as a slowly progressive neurodegenerative disorder associated with repeated brain trauma that manifests years after implicated concussive events (McKee et al., 2009). CTE is a neurodegenerative disease with a distinct distribution of atrophy along the amygdalo-hippocampal-septo-hypothalamic-mesencephalic continuum (McKee et al., 2009). CTE shows some similarity to the chronic effects of moderate and severe traumatic brain injury (TBI). There is demonstrated evidence for neurodegeneration in the chronic phase of moderate to severe TBI, ensuing months to years after brain injury with sub-acute atrophy within the limbic system hippocampi (Ng et al., 2008) and elsewhere (Greenberg et al., 2008; Farbota et al., 2012; Green et al., 2014). The corpus callosum (unmyelinated axons in particular) is vulnerable to the deposition of protein post-TBI, suggesting

commonality with CTE (Reeves et al., 2007). Thus, generalized cerebral atrophy is a well-established consequence of moderate-to-severe TBI in adults that can be quantified from MRI studies that assess total brain volume (e.g., Bigler et al., 2010).

To the best of our knowledge, there are currently no scientific studies published of CTE following repetitive concussions/mTBI in children. The popularity of competitive sports coupled with the dearth of literature investigating long-term outcomes following mTBI in the pediatric population, suggests that research addressing the potential for CTE in youth following multiple mTBIs should be a public priority. This mini-review examines the available evidence on atrophy and neurodegenerative change in children and adolescents (<19 years) in the chronic stages of mild, moderate and severe TBI compared to typically developing youths. Research findings describe widespread volume reductions (e.g., Levin et al., 2000; Verger et al., 2001; Serra-Grabulosa et al., 2005; Tasker et al., 2005; Wilde et al., 2005, 2006, 2007, 2010, 2012; Braga et al., 2007; Spanos et al., 2007; Yuan et al., 2007; Fearing et al., 2008; Bigler et al., 2010; Beauchamp et al., 2011a,b) and clearly indicate that childhood TBI disrupts normal age-related neuronal processes that may persist across the life-span (see Bigler, 2013).

METHODS

IDENTIFYING RELEVANT STUDIES

We chose a scoping review methodology (Mays et al., 2001) and entered the keywords mild, traumatic, brain, injury, MRI, child, chronic, long-term, and concussion combined with the Boolean operators AND and OR into PubMed, Ovid, PsychInfo, and Medline as the search engines. We also hand searched each reference list and included only published articles from January 1, 2000 to May 2, 2012 that contained human participants and were published in English. The start date of 2000 was chosen as studies published following this date contained imaging technology and methods sufficiently advanced in terms of sensitivity to detect more subtle structural changes. Foreign language material was excluded because of the cost and time in translating material. We adopted these methods for practical reasons and acknowledge that key articles may have been missed.

The various mechanisms for searching in our scoping study generated a total of 16 publications. No additional publications were identified as the study progressed. All publications were originally identified on the PubMed electronic databases and confirmed by subsequent databases searched.

STUDY SELECTION

Our initial examination of the studies indicated that our search strategy had identified a large number of irrelevant studies. Criteria to eliminate studies that did not address our central research question were developed *post-hoc* in three stages, based on increasing familiarity with the literature (Arksey and O'Malley, 2005). In Stage One we included original research articles and case studies that examined structural changes using MRI following mild, moderate and severe TBI. We included imaging studies examining adults only if the methods informed imaging techniques that could be applied to pediatric cases. We excluded meta-analyses and review articles as well as non-TBI forms of brain injury. These criteria identified 201 articles for review. During Stage Two, we narrowed our inclusion criteria to a TBI sustained during childhood and youth (defined as under the age of 19) and excluded metabolic studies which identified 71 articles. Finally during Stage Three we included only those studies that were cross-sectional or longitudinal in design and reported on neuroimaging findings of neurological degeneration obtained at least 1 year post-injury in order to identify those studies focused on the chronic effects following TBI for all subjects examined. We also excluded studies focusing solely on intentional brain trauma (i.e., inflicted abuse) to try and keep injury mechanism more similar to the biomechanical forces observed in concussion/mTBI. These criteria resulted in 16 articles for review.

Two reviewers (first and second authors) applied the inclusion and exclusion criteria to all the citations and copies of the full articles were obtained for those studies felt to "best fit" the research question. Having read the articles in full, all 16 articles were selected for inclusion in the review.

CHARTING THE DATA

We charted key items of information obtained from the primary research reports being reviewed (Arksey and O'Malley, 2005). We recorded information as follows:

- Author(s), year of publication and study location
- Study population (Brain Injury (TBI) Severity, Time Since Injury, and Mechanism)
- Study Population (Demographic Characteristics)
- Aims
- Study Design
- Structural Feature Assessed
- Behavioral Outcome Measure(s)
- Neurodegenerative Findings

RESULTS

NUMERICAL ANALYSIS OF THE EXTENT, NATURE, AND DISTRIBUTION OF STUDIES

Study design

Supplementary Table 1 summarizes the data obtained from each study. With respect to study design, 14 of the 16 studies reviewed utilized a cross-sectional design, of which 10 included a comparison group. Of the 10 studies containing a control group, seven studies individually matched participants across a number of demographic variables including age, sex, education (maternal or child), and socioeconomic status. One study matched on age and sex combined, with one study matching on age alone. Two studies described a control group consisting of children and youth of similar age who had sustained orthopedic injuries. All cross sectional studies included participants who were under the age of 19 years at the time of scanning. Two of the sixteen studies were prospective longitudinal investigations of the same cohort of children re-imaged at two time-points. One study re-imaged at 3 and 18 months post-injury while the second re-imaged at 3 and 36 months post-injury. Of these two longitudinal studies only one included a control group comprised of children of similar age who had sustained an orthopedic injury.

Of the 16 studies reviewed, eight examined volumetric properties of selected brain regions only, while three considered multiple brain regions and/or all gray and white matter (see **Figure 1**). Two studies report on diffusion tensor imaging (DTI) in selected brain regions (corpus callosum Wilde et al., 2006 and cingulum bundle Wilde et al., 2010, respectively), while one study used DTI to examine selected white matter regions including the corpus callosum, interior capsule, superior longitudinal fasciculus and inferior fronto-occipital fasciculus (Yuan et al., 2007). Two studies employed both volumetric and DTI methods to explore evidence for impaired brain growth across the whole brain following TBI.

Patient population

Of the sixteen studies reviewed, five present various findings from a single cohort of sixteen children and youth who previously sustained a moderate-severe TBI. Six studies in total considered the moderate to severe patient population. Three studies included mild, moderate and severe case while two included "complicated mTBI" [defined as children exhibiting focal pathology on acute computed tomography (CT), regardless of having GCS scores in the range of 13–15] in addition to children and youth survivors of moderate and severe TBI. One study considered the full spectrum of TBI including mild, moderate and severe TBI. One study defined their patient population as mild to moderate and severe, while a final three studies considered severe TBI only.

Behavioral outcome measures

Just over two thirds (11/16) of the studies correlated a measure of behavioral function with the MRI findings. A total of five studies did not include a behavioral outcome measure and three studies (Wilde et al., 2005, 2006; Yuan et al., 2007) correlated MRI findings with GCS or Glasgow Outcome Scale (GOS) alone (see Supplementary Table 1). Most studies that included a behavioral outcome measure reported positive correlations with the structural features assessed (see **Figure 2**). For example, Wilde et al. (2012) found a significant positive correlation between the emotional control subscale of the Behavior Rating Inventory of Executive Function (BRIEF) and right medial frontal and right anterior cingulate gyrus volume. Levin et al. (2000) reported that the uncorrected corpus callosum area was correlated with acute TBI severity and Vineland Adaptive Behavior Scale (VABS) score at 36 months postinjury. Wilde et al. (2010) reported a significant correlation between a low GCS score and high apparent diffusion coefficient (ADC). Furthermore, for the TBI group, significant correlations were found between DTI parameters and behavioral measures. Fearing et al. (2008) found a decreased baseline RT on the Sternberg task to be associated with total brainstem volume for both the control and TBI groups. Yuan et al. (2007) found GCS scores to be positively correlated with FA in several white matter areas including the inferior fronto-occipital fasciculus. Braga et al. (2007) observed lesion volume and presence of lesions left supramarginal gyrus in splenium to be significantly associated with dyscalculia. Wilde et al. (2006) found higher FA was related to increased cognitive processing speed and faster interference resolution. In the TBI patients, higher FA was also related to better functional outcome as measured by the GOS. Serra-Grabulosa et al. (2005) reported verbal long term memory to be significantly correlated with volume of cerebrospinal fluid (CSF) in the TBI group only. Hippocampal volume also correlated with visual and verbal long term recall for TBI subjects. Wilde et al. (2005) observed that greater tissue preservation predicted better recovery on the GOS. Finally, Verger et al. (2001) found that corpus callosum area strongly correlated with several measures involving processing speed and visuospatial function.

CHRONIC ATROPHY AND NEURODEGENERATIVE FINDINGS

Longitudinal studies

Cortical thickness and volumetric changes. Longitudinal investigation of cortical thickness revealed that at 18 months (relative to 3 months) post-injury, bilateral frontal, fusiform, and

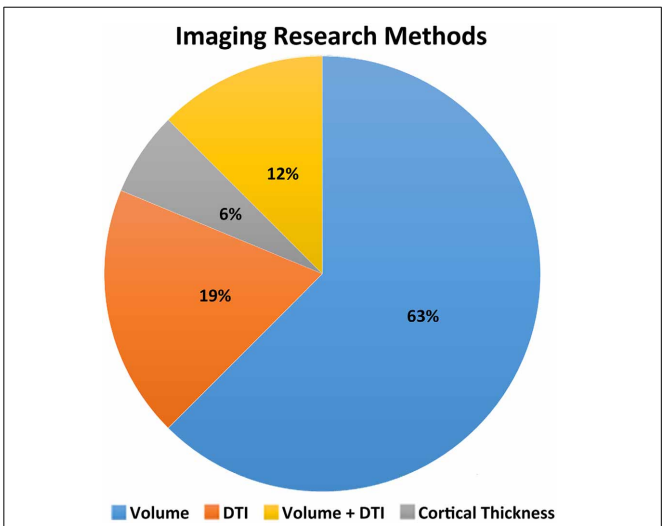

FIGURE 1 | Illustrative summary of imaging research methods.

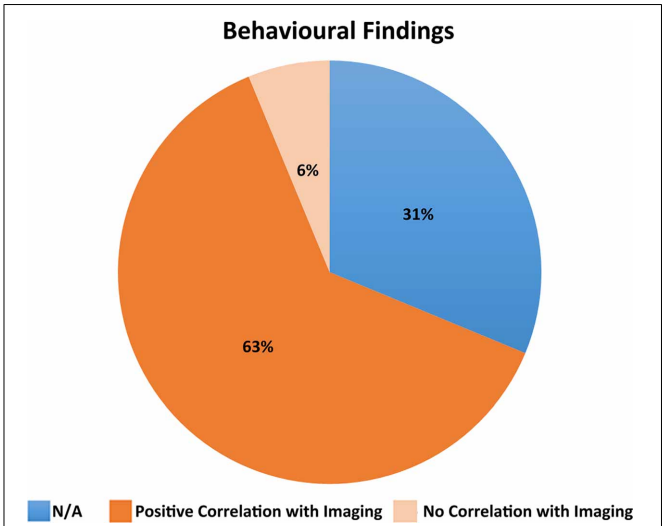

FIGURE 2 | Illustrative summary of behavioral findings.

lingual regions remained significantly decreased in TBI relative to orthopedic controls with additional areas of cortical thinning emerging in bilateral frontal regions, fusiform gyrus and left parietal regions. Wilde et al. (2012) found large bilateral regions of the medial aspects of the frontal lobes and anterior cingulate were attenuated. Most notably, there were also cortical thickness increases in aspects of the medial orbital frontal lobes and bilateral cingulate and right lateral orbital frontal lobe (Wilde et al., 2012) which could be interpreted as either compensatory hypertrophy or random effects. In addition, Levin et al. (2000) report that corpus callosum area decreased from 3 to 36 months in severely injured children and increased in the mild to moderate group. Uncorrected corpus callosum area was correlated with acute TBI severity and functional outcome at 36 months post-injury.

White matter integrity assessed by diffusion tensor imaging (DTI). None of the longitudinal studies examined this parameter.

Cross-sectional studies

Cortical thickness and volumetric changes. All eleven studies focusing on volumetric changes reported positive findings indicative of long-term degeneration in selected brain regions. More specifically, relative to a control group with similar demographic characteristics and in some cases, an orthopedic or extracranial injury, volume loss was evident in the hippocampus, amygdala, globus pallidus, thalamus (gray matter only), periventricular white matter, cerebellum, and the midbrain of the brainstem. Whole brain volume was found to be significantly decreased in TBI patients relative to controls while CSF and ventricular space was observed to be significantly greater. A number of studies attempted to control for the presence of focal lesions by analyzing volumes in brain regions with no focal lesions, as well as patients who did not have focal injuries. These, studies reported reduced volumes in selected brain regions suggesting that the degeneration was not secondary to acute injury and resulting atrophy. Finally in the one study that included mTBI and stratified results according to severity (Beauchamp et al., 2011a,b), significantly reduced gray matter and left hippocampal volume was reported for mild injuries as well as significantly increased CSF compared to an age and sex matched sample.

White matter integrity assessed by diffusion tensor imaging (DTI). All five studies employing DTI reported positive findings indicating compromised white matter integrity at least 1 year following TBI compared to demographically similar control subjects, some of whom sustained an orthopedic or extracranial injury. More specifically, fractional anisotropic (FA) values were significantly reduced in the genu, body and splenium of the corpus callosum, anterior limb of the posterior capsule, posterior limb of the anterior capsule, superior fronto-occipital fasciculus, superior longitudinal fasciculus, superior fronto-occipital fasciculus, and centrum semiovale. Moreover, FA values were significantly reduced bilaterally in the cingulum bundles, while ADC values were significantly increased. Similarly, TBI patients demonstrated significantly higher mean diffusivity in the right cerebral white matter, bilaterally in the forceps major and in the body and splenium of the corpus callosum.

DISCUSSION

Taken together, the studies reviewed suggest there is evidence for long-term neurodegenerative change following TBI in children and youth. In particular both cross-sectional and longitudinal studies revealed volume loss in selected brain regions including the hippocampus, amygdale, globus pallidus, thalamus, periventricular white matter, cerebellum, and brain stem as well as overall decreased whole brain volume and increased CSF and ventricular space. DTI studies also report evidence for decreased axonal integrity, particularly in the corpus callosum (Wilde et al., 2006; Yuan et al., 2007; Porto et al., 2011). Although fewer in number, longitudinal investigations are of critical importance and those reviewed here (i.e., Wilde et al., 2012) highlight the dynamic and disruptive interplay between childhood TBI and normal developmental neuronal processes such as axonal thinning and increased myelination (see Bigler, 2013).

Taken together, the findings appear to highlight a sensitivity of the hippocampus and deep limbic structures in pediatric populations, which like adults, show similarities to CTE where there is a distinct distribution of atrophy along the amygdalo-hippocampal-septo-hypothalamic-mesencephalic continuum (McKee et al., 2009). They also corroborate findings in the chronic phase of moderate to severe TBI in adults, where sub-acute atrophy within the limbic system hippocampi (Ng et al., 2008), corpus callosum (Reeves et al., 2007), and elsewhere (i.e., Greenberg et al., 2008; Bigler et al., 2010; Green et al., 2014) have been documented.

A major limitation of the studies reviewed is the lack of studies focused specifically on repetitive concussions or mTBIs. Only one study (Beauchamp et al., 2011a,b) reported results specific to mTBI where reduced gray matter and left hippocampal volume was reported for mild injuries as well as significantly increased CSF compared to an age and sex matched sample. The second important limitation is that the methods of only a subset of the studies speak directly to a progressive, and putatively neurodegenerative entity. Chronic findings in the rest of the studies reviewed may alternatively reflect the enduring effects of the initial injuries. These findings indicate that long-term investigation of neurodegenerative change following repetitive concussions and mTBIs in children is warranted (Tartaglia et al., 2014).

There is widespread belief that children are at an advantage to adults when inflicted with significant brain damage, such as repeat concussions or mTBIs, as the developing brain has a higher chance of reorganization or plasticity (McCrory et al., 2004). This view is becoming increasingly challenged. The developing brain is cognitively maturing throughout childhood and any impact may cause a disruption in this neuronal maturation (Anderson et al., 2001). Although the injury may occur in the same way, the outcome needs to be treated differently as the composition and mechanical properties of the head and brain differ in an adult and youth (Kirkwood et al., 2006). These differences include increased brain water content, decreased level of myelination,

skull geometry, suture elasticity, and neck strength (Bauer and Fritz, 2004; Kirkwood et al., 2006).

In conclusion, the mini-review provides strong evidence for neurodegenerative change following TBI of all severities in children and youth while clearly highlighting repetitive and chronic mTBI in children and youth as an overlooked population. Future research should employ multi-centerd strategies to longitudinally investigate the possibility of neurodegenerative onset and CTE in childhood associated with repeat mTBIs by developing age specific normal databases for each of the imaging parameters under assessment.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnhum.2014.00139/abstract

REFERENCES

Anderson, V., Catroppa, C., Morse, S., Haritou, F., and Rosenfeld, J. (2001). Outcome from mild head injury in young children: a prospective study. *J. Clin. Exp. Neuropsychol.* 23, 705–717. doi: 10.1076/jcen.23.6.705.1015

Arksey, H., and O'Malley, L. (2005). Scoping studies: towards a methodological framework. *Int. J. Soc. Res. Methodol.* 8, 19–32. doi: 10.1080/1364557032000119616

Bauer, R., and Fritz, H. (2004). Pathophysiology of traumatic injury in the developing brain: an introduction and short update. *Exp. Toxicol. Pathol.* 56, 65–73. doi: 10.1016/j.etp.2004.04.002

Beauchamp, M. H., Ditchfield, M., Catroppa, C., Kean, M., Godfrey, C., Rosenfeld, J. V., et al. (2011b). Focal thinning of the posterior corpus callosum: normal variant or post-traumatic? *Brain Inj.* 25, 950–957. doi: 10.3109/02699052.2011.589791

Beauchamp, M. H., Ditchfield, M., Maller, J. J., Catroppa, C., Godfrey, C., Rosenfeld, J. V., et al. (2011a). Hippocampus, amygdala and global brain changes 10 years after childhood traumatic brain injury. *Int. J. Dev. Neurosci.* 29, 137–143. doi: 10.1016/j.ijdevneu.2010.12.003

Bigler, E. D. (2013). Traumatic brain injury, neuroimaging, and neurodegeneration. *Front. Hum. Neurosci.* 7:395. doi: 10.3389/fnhum.2013.00395

Bigler, E. D., Abildskov, T. J., Wilde, E. A., McCauley, S. R., Li, X., Merkley, T. L., et al. (2010). Diffuse damage in pediatric traumatic brain injury: a comparison of automated versus operator-controlled quantification methods. *Neuroimage* 50, 1017–1026. doi: 10.1016/j.neuroimage.2010.01.003

Braga, L. W., Souza, L. N., Najjar, Y. J., and Dellatolas, G. (2007). Magnetic resonance imaging (MRI) findings and neuropsychological sequelae in children after severe traumatic brain injury: the role of cerebellar lesion. *J. Child Neurol.* 22, 1084–1089. doi: 10.1177/0883073807306246

Browne, G. J., and Lam, L. T. (2006). Concussive head injury in children and adolescents related to sports and other leisure physical activities. *Br. J. Sports Med.* 40, 163–168. doi: 10.1136/bjsm.2005.021220

Farbota, K. D., Bendlin, B. B., Alexander, A. L., Rowley, H. A., Dempsey, R. J., and Johnson, S. C. (2012). Longitudinal diffusion tensor imaging and neuropsychological correlates in traumatic brain injury patients. *Front. Hum. Neurosci.* 6:160. doi: 10.3389/fnhum.2012.00160

Fearing, M. A., Bigler, E. D., Wilde, E. A., Johnson, J. L., Hunter, J. V., Li, X., et al. (2008). Morphometric MRI findings in the thalamus and brainstem in children after moderate to severe traumatic brain injury. *J. Child Neurol.* 23, 729–737. doi: 10.1177/0883073808314159

Green, R. E. A., Colella, B., Maller, J., Bayley, M., Glazer, J., and Mikulis, D. J. (2014). Scale and pattern of atrophy in the chronic stages of moderate-Severe traumatic brain injury. *Front. Hum. Neurosci.* 8:67. doi: 10.3389/fnhum.2014.00067

Greenberg, G., Mikulis, D. J., Ng, K., DeSouza, D., and Green, R. E. (2008). Use of diffusion tensor imaging to examine subacute white matter injury progression in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S45–S50. doi: 10.1016/j.apmr.2008.08.211

Kirkwood, M., Yeates, K., and Wilson, P. (2006). Pediatric sport-related concussion: A review of the clinical management of an oft-neglected population. *Pediatrics* 117, 1359–1371. doi: 10.1542/peds.2005-0994

Levin, H. S., Benavidez, D., Verger-Maestre, K., Perachio, N., Song, J., Mendelsohn, D. B., et al. (2000). Reduction of corpus callosum growth after severe traumatic brain injury in children. *Neurology* 54, 647–653 doi: 10.1212/WNL.54.3.647

Martland, H. (1928). Punchdrunk. *JAMA* 91, 1103–1107. doi: 10.1001/jama.1928.02700150029009

Mays, N., Roberts, E., and Popay, J. (2001). "Synthesising research evidence," in *Studying the Organisation and Delivery of Health Services: Research Methods,* eds N. Fulop, P. Allen, A. Clarke, and N. Black (London: Routledge), 188–220.

McCrory, P., Collie, A., Anderson, V., and Davis, G. (2004). Can we manage sport related concussion in children the same as in adults? *Br. J. Sports Med.* 38, 516–519. doi: 10.1136/bjsm.2004.014811

McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, E. T., Gavett, B. E., Budson, A. E., et al. (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J. Neuropathol. Exp. Neurol.* 68, 709–735. doi: 10.1097/NEN.0b013e3181a9d503

Miller, H. (1966). Mental after-effects of head injury. *Proc. R. Soc. Med.* 59, 257–261.

Ng, K., Mikulis, D. J., Glazer, J., Kabani, N., Till, C., Greenberg, G., et al. (2008). Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S35–S44. doi: 10.1016/j.apmr.2008.07.006

Porto, L., Jurcoane, A., Margerkurth, J., Althaus, J., Zanella, F., Hattingen, E., et al. (2011). Morphometry and diffusion MR imaging years after childhood traumatic brain injury. *Eur. J. Paediatr. Neurol.* 15, 493–501. doi: 10.1016/j.ejpn.2011.06.004

Reeves, T. M., Phillips, L. L., Lee, N. N., and Povlishock, J. T. (2007). Preferential neuroprotective effect of tacrolimus (FK506) on unmyelinated axons following traumatic brain injury. *Brain Res.* 1154, 225–236. doi: 10.1016/j.brainres.2007.04.002

Serra-Grabulosa, J. M., Junqué, C., Verger, K., Salgado-Pineda, P., Mañeru, C., and Mercader, J. M. (2005). Cerebral correlates of declarative memory dysfunctions in early traumatic brain injury. *J. Neurol. Neurosurg. Psychiatry* 76, 129–131. doi: 10.1136/jnnp.2004.027631

Spanos, G. K., Wilde, E. A., Bigler, E. D., Cleavinger, H. B., Fearing, M. A., Levin, H. S., et al. (2007). Cerebellar atrophy after moderate-to-severe pediatric traumatic brain injury. *AJNR Am. J. Neuroradiol.* 28, 537–542.

Tartaglia, M. C., Hazrati, L., Davis, K. D., Green, R. E. A., Wennberg, R., Mikulis, D., et al. (2014). Chronic traumatic encephalopathy and other neurodegenerative proteinopathies. *Front. Hum. Neurosci.* 8:30. doi: 10.3389/fnhum.2014.00030

Tasker, R. C., Salmond, C. H., Westland, A. G., Pena, A., Gillard, J. H., Sahakian, B. J., et al. (2005). Head circumference and brain and hippocampal volume after severe traumatic brain injury in childhood. *Pediatr. Res.* 58, 302–308. doi: 10.1203/01.PDR.0000169965.08854.25

Verger, K., Junqué, C., Levin, H. S., Jurado, M. A., Pérez-Gómez, M., Bartrés-Faz, D., et al. (2001). Correlation of atrophy measures on MRI with neuropsychological sequelae in children and adolescents with traumatic brain injury. *Brain Inj.* 15, 211–221. doi: 10.1080/02699050010004059

Wilde, E. A., Bigler, E. D., Hunter, J. V., Fearing, M. A., Scheibel, R. S., Newsome, M. R., et al. (2007). Hippocampus, amygdala, and basal ganglia morphometrics in children after moderate-to-severe traumatic brain injury. *Dev. Med. Child Neurol.* 49, 294–299. doi: 10.1111/j.1469-8749.2007.00294.x

Wilde, E. A., Chu, Z., Bigler, E. D., Hunter, J. V., Fearing, M. A., Hanten, G., et al. (2006). Diffusion tensor imaging in the corpus callosum in children after moderate to severe traumatic brain injury. *J. Neurotrauma* 23, 1412–1426. doi: 10.1089/neu.2006.23.1412

Wilde, E. A., Hunter, J. V., Newsome, M. R., Scheibel, R. S., Bigler, E. D., Johnson, J. L., et al. (2005). Frontal and temporal morphometric findings on MRI in children after moderate to severe traumatic brain injury. *J. Neurotrauma* 22, 333–344. doi: 10.1089/neu.2005.22.333

Wilde, E. A., Merkley, T. L., Bigler, E. D., Max, J. E., Schmidt, A. T., Ayoub, K. W., et al. (2012). Longitudinal changes in cortical thickness in children after traumatic brain injury and their relation to behavioral regulation and

emotional control. *Int. J. Dev. Neurosci.* 30, 267–276. doi: 10.1016/j.ijdevneu.2012.01.003

Wilde, E. A., Ramos, M. A., Yallampalli, R., Bigler, E. D., McCauley, S. R., Chu, Z., et al. (2010). Diffusion tensor imaging of the cingulum bundle in children after traumatic brain injury. *Dev. Neuropsychol.* 35, 333–351. doi: 10.1080/87565641003696940

Yuan, W., Holland, S. K., Schmithorst, V. J., Walz, N. C., Cecil, K. M., Jones, B. V., et al. (2007). Diffusion tensor MR imaging reveals persistent white matter alteration after traumatic brain injury experienced during early childhood. *AJNR Am. J. Neuroradiol.* 28, 1919–1925. doi: 10.3174/ajnr.A0698

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Environmental enrichment may protect against hippocampal atrophy in the chronic stages of traumatic brain injury

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Objective: To examine the relationship between environmental enrichment (EE) and hippocampal atrophy in the chronic stages of moderate to severe traumatic brain injury (TBI).

Design: Retrospective analysis of prospectively collected data; observational, within-subjects.

Participants: Patients ($N = 25$) with moderate to severe TBI.

Measures: Primary predictors: (1) An aggregate of self-report rating of EE (comprising hours of cognitive, physical, and social activities) at 5 months post-injury; (2) pre-injury years of education as a proxy for pre-morbid EE (or cognitive reserve). Primary outcome: bilateral hippocampal volume change from 5 to 28 months post-injury.

Results: As predicted, self-reported EE was significantly negatively correlated with bilateral hippocampal atrophy ($p < 0.05$), with greater EE associated with less atrophy from 5 to 28 months. Contrary to prediction, years of education (a proxy for cognitive reserve) was not significantly associated with atrophy.

Conclusion: Post-injury EE may serve as a buffer against hippocampal atrophy in the chronic stages of moderate-severe TBI. Clinical application of EE should be considered for optimal maintenance of neurological functioning in the chronic stages of moderate-severe TBI.

Keywords: traumatic brain injury, environmental enrichment, subacute atrophy, adult, moderate to severe

INTRODUCTION

Conventionally, moderate-severe traumatic brain injury (TBI) has been viewed as a non-progressive brain disorder with a predictable trajectory of recovery leading to a stable course thereafter (Lezak et al., 2004). However, growing research findings show progressive gray matter atrophy and loss of white matter integrity in the post-acute and chronic phases of injury (Trivedi et al., 2007; Greenberg et al., 2008; Ng et al., 2008; Farbota et al., 2012; Adnan et al., in press). Further, some individuals with TBI also show progressive cognitive and functional declines in the ensuing months and years following injury (Corkin et al., 1989; Millis et al., 2001; Himanen et al., 2006; Till et al., 2008), supporting the notion that TBI is not a stable condition (Ng et al., 2008; Till et al., 2008).

A brain structure of key importance in TBI is the hippocampus. Memory impairment is one of the most common complaints following TBI, in part due to the acute effects of hippocampal injury, which include excitotoxic and hypoxic insult (Rosenfeld et al., 2012). On top of these acute injuries, post-acute atrophy of the hippocampus has now been demonstrated in several TBI studies (Bigler et al., 1997; Ng et al., 2008). Tate and Bigler (2000) have suggested that post-acutely, hippocampal cell loss may be the result of transneuronal degeneration secondary to hippocampal deafferentation and/or deefferentation. Indeed, the unique pattern of neuronal projections within the hippocampus (Duvernoy et al., 2005), which is comprised of six architecturally distinct regions linked via unidirectional projections (Amaral and Witter, 1995), has been referred to as an Achilles' heel of sorts, whereby damage to one region of the hippocampus can lead to downstream damage to other regions via loss of activity-dependent survival factors (McCarthy, 2003). Thus, disuse-mediated loss, either secondary to disconnection or to a dearth of behavioral stimulation, may be an important factor in observed hippocampal volume loss in the post-acute stages of injury.

Disuse-mediated loss—or "use it or lose it"—is a concept that has received extensive attention in the older adult literature. It has been argued for decades that greater day-to-day cognitive stimulation is associated with less cognitive decline and delayed onset of dementia. The "negative neuroplasticity" framework of

Mahncke et al. (2006), advanced to explain functional losses in normal aging, offers a disuse-mediated framework that can also be applied to atrophy in the chronic stages of TBI (Evans et al., 2008). In their framework, the authors posit that cognitive, perceptual, emotional, physical, psychosocial, and vocational changes associated with aging limit engagement in the busy schedules and complexity of activities of earlier life, leading to a cycle of behavioral inactivation and avoidance—or learned disuse (Taub et al., 2006), and resulting in reduced activation of brain networks (Blake et al., 2006). Although behavioral losses are more sudden in brain injury, moderate-severe TBI patients, too, are commonly unable to engage in the complex activities of work, school and social activities as a result of TBI-induced decrements in cognitive, physical, perceptual and emotional functioning. These patients are especially at risk of reduced behavioral (and thereby neural) stimulation in the sub-acute and chronic stages of injury (after discharge from in-patient rehabilitation facilities), where there is often reduced environmental stimulation and/or reduced supports to foster engagement in the environment (Evans et al., 2008; Frasca et al., 2013).

Related to the above, the concept of environmental enrichment (EE) refers to exposure to and engagement with complex and stimulating environments, and there is extensive evidence that EE can beneficially influence the size, morphology and function of the brain, through synaptic modification and synaptogenesis, the shape and size of dendritic spines (or spine remodeling), axon collateral sprouting, hippocampal (dentate gyrus) neurogenesis and survival of neurons, and brain network connectivity; and such changes have been associated with improvements in functional performance (Rosenzweig and Bennett, 1996; Diamond, 2001; Mohammed et al., 2002; Draganski et al., 2006; Kasai et al., 2010; Kolb et al., 2010; Berlucchi, 2011). Indeed, seminal reviews of the literature conclude that brains that have received increased stimulation, via enhanced mental and physical activity, are better able to mount neuroprotective responses against neurodegenerative processes, traumatic insults and other forms of adult-onset neural dysfunction (Nithianantharajah and Hannan, 2009).

Taken together, the above literature (Mohammed et al., 2002; Kolb et al., 2010; Berlucchi, 2011) suggests that environmental influences, such as intensified cognitive stimulation, might buffer against chronic stage atrophy in moderate-severe TBI. The primary objective of the present study, therefore, was to examine the relationship between post-injury EE, and hippocampal atrophy in the chronic stages of injury. To our knowledge, no studies have yet examined this relationship. We hypothesized that greater EE (i.e., frequency of cognitive, physical, and social engagement) measured in the early post-acute stages of injury (i.e., 5 months post-injury) would be associated with less long-term bilateral hippocampal atrophy over the ensuing years (measured from 5 to 28 months post-injury).

The secondary objective concerned pre-injury EE factors, namely exposure to higher levels of education in development and early adulthood, which has been associated with better cognitive recovery following TBI (Kesler et al., 2003). Given evidence of (1) a positive association between education and cognitive and functional recovery following TBI (Green et al., 2008) and stroke (Elkins et al., 2006), (2) a positive association between education and dendritic branching in healthy adult humans (Jacobs et al., 1993), and (3) a positive correlation between years of education and cognitive functioning in normal aging (Corral et al., 2006; Fritsch et al., 2007), it was hypothesized that greater years of education would be associated with less bilateral hippocampal atrophy, measured from 5 to 28 months post-injury.

METHODS

PARTICIPANTS

The 25 clinical participants in this study (see **Table 1**) were part of a larger research study being conducted at the Toronto Rehabilitation Institute, a large publicly-funded inpatient neurorehabilitation hospital. The focus of the larger study was to investigate the natural history and mechanisms of recovery following moderate-severe TBI. Informed consent was obtained from all participants in the study, and procedures for the present study were approved by the Research Ethics Board of the Toronto Rehabilitation Institute and the Office of Research Ethics at the University of Toronto. Participants underwent prospective assessments at approximately 5, 12, and 28 months post-injury. As the current design was a retrospective analysis of data collected in the course of the larger study data were *only* available at the 5, 12, and 28 month time points.

Inclusion criteria for the larger study comprised: (1) acute care medical diagnosis of TBI; (2) posttraumatic amnesia (PTA) of 1 h or more and/or Glasgow Coma Scale (GCS) score of 12 or less either at emergency or at the scene of the accident and/or positive CT or MRI findings; (3) age between 17 and 80 years old; (4) able to follow simple commands in English based upon Speech Language Pathologist intake assessment; and, (5) competent to provide informed consent for study or availability of a legal decision maker.

Exclusion criteria for the larger study included: (1) orthopaedic injuries affecting both upper extremities; (2) diseases primarily or frequently affecting the central nervous system, including dementia of Alzheimer's type, Parkinson's disease, multiple sclerosis, Huntington's disease, lupus, or stroke; (3) a history of psychotic disorder; (4) non-emergence from posttraumatic amnesia by 6 weeks post-injury, as measured by the Galveston Orientation Amnesia Test (Levin et al., 1979); (5) TBI secondary to another neurological event, such as a fall due to stroke; and, (6) failure on a symptom validity test (Test of Memory Malingering) (Tombaugh, 1996) at any of the assessments. The demographic and injury characteristics of the clinical sample are shown in **Table 1**. The additional inclusion criteria for the current study were: relevant behavioral and MRI outcome measures at 5 months post-injury plus MRI data at 28 months post-injury.

There were 30 individuals from the larger study with all relevant outcome measures at 5 months post-injury who had reached or surpassed the 28 month post-injury time-point at the time of data analysis. Of those, 25 underwent the 28-month post-injury MRI and were, therefore, eligible for inclusion in the present study, indicating a retention rate of 83%.

Of the sample included in the present study, none showed evidence of severe anxiety or depression, and less than 30% reported experiencing mild or moderate depression or anxiety during the

Table 1 | Demographic information and hippocampal volume loss.

Subject ID	Age/sex	Education	GCS	PTA	IQ (WTAR)	% Change in bilateral hippocampal volume from 5–28 months post-injury
368	68/M	8	Unknown	5	ESL	−19.79
380	48/M	12	3	4	89	−14.45
358	59/F	17	4	5	107	−14.27
376	29/M	16	3	4	124	−11.06
364	54/M	20	7	5	120	−8.82
369	25/M	12	Unknown	5	LD	−7.91
362	60/M	15	Unknown	5	111	−7.05
337	17/M	12	4	1	83	−6.85
363	46/M	17	3	5	Dysarthria	−6.01
389	48/M	11	6	6	105	−5.49
353	27/F	18	3	5	117	−5.35
352	59/M	12	3	6	104	−4.79
339	37/M	12	3	6	89	−4.46
333	44/F	16	6	4	120	−4.06
379	31/M	16	8	6	108	−3.31
349	50/F	17	10	3	120	−3.29
338	57/F	12	13	6	98	−3.27
359	18/F	12	6	5	LD	−2.55
329	19/M	9	Unknown	4	103	−0.97
346	28/F	14	7	5	106	0.27
374	66/M	12	6	5	Aphasia	0.83
331	30/M	16	6	6	97	2.77
327	41/M	11	3	4	99	2.98
330	40/F	13	3	0	116	3.34
335	25/M	16	7	4	124	5.43
	($M = 41$yrs; $SD = 16$)	($M = 14$yrs; $SD = 3$)	($M = 5$; $SD = 3$)	($M = 4.6$days; $SD = 1.5$)	*($M = 109$; $SD = 11.4$)*	($M = -4.7\%$; $SD = 6.0$)

first year post-injury based on the Beck Depression Inventory (Beck, 1987) and Beck Anxiety Inventory (Beck, 1990).

MATERIALS

Lifestyle activities questionnaire

Assessment of post-injury EE was based on participants' self-reported frequency of engagement in a variety of activities involving cognitive, physical, and social demands. Given the absence of reliable or valid published measures of EE in humans at the time of data analysis, EE activities were listed on a self-report questionnaire designed for the purpose of the present study, entitled the Lifestyle Activities Questionnaire (LAQ). Cognitive, physical, and social activities on the LAQ were obtained from a theoretically-derived and empirically-tested inventory developed by Salthouse et al. (2002), which was constructed by specifying 22 common activities that a sample of 1200 adults, ranging from the age of 18–97 years, rated in terms of their cognitive demand (where 1 = low demand, corresponding to sleeping, and 5 = high demand, corresponding to working on a tax form). An activity added to the LAQ that was not on Salthouse's inventory was the frequency of engagement in sports or physical activity at the gym. Participants were asked to rate the frequency with which they engaged in each of the listed activities on an ordinal scale ranging from 1 to 5.

The scale comprised descriptors that ranged from (1) *didn't do at all* to (5) *several hours, every day of the week*. For statistical analysis, each number of the scale was weighted based on estimated associated hours. "Didn't do at all and less than once a week" was assigned a weight of zero; "once or twice a week" was assigned a weight of 1 (i.e., for 1 h/week); "several times a week" was assigned a weight of 3 (3 h/week); "an hour or so most days" was assigned a weight of 7; and "several hours a day" was assigned a weight of 20 (20 h/week). Transformation of ordinal scores into weighted scale scores corresponding to estimated hours/week provided a meaningful and more ecological marker of EE. However, for patient responses, the scale was kept as ordinal (i.e., 1–5), because self-reported ratings were deemed by clinical experts consulted to be more easily understood by patients and less likely to result in missing or inaccurate data. We suggest that this approach enabled us to provide richer data than previous methods of aggregating EE activities, in which individuals were classified as "active" if they endorsed doing even one mentally-challenging activity for 1 h per week or more, for example (Bosma et al., 2002; Richards et al., 2003).

Items were sub-classified into cognitive, social or physical activity types to allow for a comparison of the respective influences of each on hippocampal volume loss. For all items,

consensus was reached by two trained clinicians regarding assignment to a cognitive, social or physical aggregate. Nineteen items were classified as cognitive activities, 8 items were classified as social activities, and 2 items were classified as physical activities. For each subject, the weighted score for each item type (i.e., social, cognitive, physical) was summed to create a sub-aggregate score for each component of EE; the grand sum was the total score for the larger EE aggregate.

MRI acquisition protocol

MRI scans were acquired on a General Electric (GE) Signa-Echospeed 1.5 Tesla HD scanner (SIGNA EXCITE, GE Healthcare, Milwaukee WI), using an eight channel head coil. Sequences included sagittal T1 (TR/TE = 300/13 ms), slice thickness = 5 mm, space 2.5 mm, matrix 256 × 128 axial gradient recalled echo TR/TE = 450/20, flip angle = 20°, slice thickness = 3 mm no gap, matrix 256 × 192 axial fluid-attenuated-inversion-recovery TR/TE = 9000/45 ms, TI (inversion time) = 2200 ms, slice thickness = 5 mm no gap, matrix 256 × 192 axial fast spin echo proton density (PD)/T2 TR/TE 5500/30, 90 ms, slice thickness = 3 mm no gap, matrix 256 × 192. All above mentioned sequences were obtained with a 22 cm field of view. The high-resolution isotropic T1 weighted, three-dimensional IR prepped radio-frequency spoiled-gradient recalled-echo images TI/TR/TE = 12/300/5, TI, FA = 20, slice thickness = 1 mm no gap, matrix = 256 × 256 were acquired in the axial plane utilizing a 25 cm field of view. The entire scanning session lasted ∼55 min.

Image processing and analysis

The MR images were transferred to a workstation for image processing. The scans were received in the Digital Imaging and Communications in Medicine file format and were subsequently converted into (Medical Imaging Network Common Data Form) file format that was created at McConnell Brain Imaging Centre of the Montreal Neurological Institute. Following this procedure, the files were anonymized.

A number of image processing steps were performed in order to make the MRI data usable for image analysis. First, an intensity non-uniformity correction was performed, followed by linear registration of the images into stereotaxic coordinates based on the Talairach atlas. The linear registration to Talairach coordinates was accomplished through 3D cross-correlation between a given volume and an average MR brain image previously converted into the Talairach coordinate system allowing for direct anatomical comparisons between subjects. Finally, a second non-uniformity correction was performed after the registration, which helped to remove any residual non-uniformity artifacts.

The hippocampi were manually outlined using Analyze 7.0 (Brain Imaging Resource, Mayo Clinic, MN) by an experienced tracer (JM) from coronally orientated MR images in the anterior-posterior direction. Calculations of volumes were computed automatically by multiplying the number of voxels traced in each slice, by their depth (i.e., slice thickness). As described by Watson et al. (1992, 1997), the anterior tip of the hippocampus until the slice before the opening of the crux of the fornix was measured as the hippocampal head and body and included the subiculum, CA1-(4) areas, and dentate gyrus. The hippocampus tail was measured from the slice immediately posterior to that which represented the last slice according to the Watson protocol (Watson et al., 1992, 1997) (see Maller et al., 2007 for a more detailed description of this procedure).

All raw hippocampal volumes were expressed in mm^3. For the purpose of the present study, hippocampal volume change between 5 months (T1) post-injury and 28 months (T2) post-injury was measured using the following formula:

$$\text{Hippocampal volume change} = \frac{(\text{Vol T2} - \text{Vol T1})}{(\text{Vol T2} + \text{Vol T1})/2} * 100$$

DESIGN AND PROCEDURES

The study employed a retrospective, within subjects, longitudinal design. For clinical participants, LAQs were collected and initial MRI scans were acquired at a mean of 5.3 months ($SD = 1.2$; range = 4.3–10.3 months) post-injury; follow-up MRI scans were acquired at 28.48 months ($SD = 5.5$; range = 24–42 months) post-injury.

The primary dependent measure for the study was bilateral hippocampal volume. The primary independent measures were (1) EE as measured by the total score of the LAQ at 5 months post-injury and (2) years of education prior to the injury. We also examined the relative contributions of the cognitive, social and physical EE sub-aggregate scores.

The primary control variables were injury severity (measured by the Glasgow Coma Scale, duration of PTA, and duration of acute care length of stay), estimated premorbid intelligence (based on the mean score on the Wechsler Test of Adult Reading administered [Wechsler, 2001] at 12 and 28 months post-injury), socioeconomic status, and age at injury.

RESULTS

Using Pearson product moment correlation, primary control variables were correlated with hippocampal atrophy and with the measure of overall EE. Each variable was correlated separately due to limited power secondary to sample size. Any variables with significant correlation were included in subsequent analyses. No significant correlations were observed between any of the primary control variables and EE or hippocampal atrophy, with the exception of age, which correlated significantly with the EE aggregate ($r = -0.45$, $p < 0.05$, $N = 25$) whereby increasing age was associated with less overall EE. As well, there was a trend for higher age at injury to be associated with greater bilateral hippocampal atrophy ($r = 0.39$, $p = 0.06$, $N = 25$). These findings, combined with previous research findings of greater deleterious effects of injury on aging brains (Popa-Wagner et al., 2007; Onyszchuk et al., 2008; Petcu et al., 2008), necessitated controlling for age at injury in the present study analyses.

Partial correlation was used to test the primary hypothesis of the study, namely the relationship between the EE aggregate and bilateral hippocampal atrophy, while controlling for age at injury. A significant negative correlation was observed ($r = -0.42$, $p < 0.05$, $df = 21$) whereby greater general activity level at 5 months post-injury was associated with less bilateral hippocampal atrophy from 5 to 28 months post-injury.

Partial correlation between years of education and hippocampal atrophy, controlling for age at injury was used to examine the secondary hypothesis. Contrary to prediction, no significant relationship was observed ($r = -0.05$, $p = 0.82$, $df = 22$).

Lastly, we also explored preliminarily the respective contribution to hippocampal atrophy of the cognitive, social and physical sub-aggregates. Here, a hierarchical linear regression was conducted, which revealed significant negative correlations between bilateral hippocampal atrophy and cognitive activity ($r = -0.53$, $p < 0.01$), and between bilateral hippocampal atrophy and social activity ($r = -0.47$, $p < 0.05$) but no significant correlation between bilateral hippocampal atrophy and physical activity.

DISCUSSION

Consistent with our prediction, there was a significant negative association between EE (i.e., engagement in cognitive, physical, and social activities) at 5 months post-injury and bilateral hippocampal atrophy from 5 to 28 months post-injury. Although the observational design of the present study precludes conclusions regarding causality, our findings are consistent with previous associations found between EE and enhanced hippocampal structure, and they are potentially explained by increased production, survival and integration of newly generated dentate gyrus neurons (Kempermann et al., 2002; Olson et al., 2006; Tanti et al., 2013); findings in animals—where EE has been correlated with neurogenesis in TBI and moreover correlated with better recovery (Kovesdi et al., 2011; Matter et al., 2011)—bolster such an interpretation. At a behavioral level, the current findings are consistent with use-it-or-lose-it frameworks, and support the extrapolation of the Mahncke et al. (2006) framework—where reduced schedules of activities and avoidance of cognitively-challenging activities were purported to lead to under-stimulation of critical neural networks and loss of associated functions—to chronic TBI (Evans et al., 2008). The findings are also consistent with Robertson and Murre's (1999) computational model of brain plasticity and guided recovery of function, whereby damaged, but potentially viable circuits may be repaired via cognitive activity, cognitive arousal, and Hebbian learning mechanisms. As well, these findings converge with findings from the cognitive-training literature, which shows evidence that engagement in cognitively-demanding tasks is associated with increased cerebral volume in brain areas that are functionally-related to the demands of the task (Draganski et al., 2006).

Unexpectedly, the results of the present study showed no significant relationship between hippocampal atrophy and pre-injury cognitive reserve, as measured by level of education. This finding was surprising given the extensive evidence of a positive association between level of education and cognitive functioning in normal aging (Corral et al., 2006; Fritsch et al., 2007), stroke recovery (Elkins et al., 2006), and TBI recovery (Kesler et al., 2003). Therefore, the study findings do not offer evidence that this proxy for pre-injury EE protects against the structural progression of subacute hippocampal atrophy following TBI. One interpretation of this null finding is that a fixed degree of neural reserve at the time of brain injury does not confer neuroprotection against progressive pathology (e.g., disconnection, [Tate and Bigler, 2000]; neuroinflammation [Bigler, 2013; Johnson et al., 2013]) as would be logically predicted by conventional theories of brain reserve (Satz, 1993; Stern, 2002) and by negative associations found between premorbid cognitive reserve and progression of pathology in Alzheimers disease (Stern, 2006), multiple sclerosis (Amato et al., 2013) and stroke (Willis and Hakim, 2013). In particular, our findings suggest that in order for EE to positively modulate brain disorders via neuroprotective and/or compensatory mechanisms, EE exposure must occur after the disorder has commenced, and during the period of progression of neuropathology (Nithianantharajah and Hannan, 2009). Such an explanation is consistent with EE influences on neurogenesis, as discussed above (Kovesdi et al., 2011; Matter et al., 2011). As neurogenesis is an active process, it may be that temporally congruent factors, namely current EE, but not past education, play a more significant role (Lee et al., 2009; Surget et al., 2011). Unfortunately, our retrospective analysis did not allow us to quantitate the dentate gyrus, the site of neurogenesis.

EE in humans is viewed conventionally as being comprised of three primary elements: cognitive, physical, and social stimulation (Scarmeas and Stern, 2003; Studenski et al., 2006). Of the three conventional elements of EE, our preliminary findings indicated that cognitive activity accounted for the most outcome variance in bilateral hippocampal atrophy. The question whether it is cognitive, social or physical enrichment that confers the greatest neuroplastic advantage is under active debate; our findings are consistent with those comparison studies in animals that found greater survival and integration of new hippocampal neurons after cognitive stimulation than exercise (Kempermann et al., 2002, 2010; Olson et al., 2006; Curlik and Shors, 2011; Shors et al., 2012; Tanti et al., 2013).

A limitation of the present study was the small sample size and relatively small (albeit typical) representation of female subjects, which limits the generalizability of the study findings and precluded examination of gender as a control variable.

It is important to note that in our preliminary and exploratory analysis of the relative contributions of the sub-aggregates (cognitive vs. social vs. physical stimulation), the greater number of cognitive items on the LAQ may have conferred greater analytic stability to the cognitive outcome measure, with the very small number of physical items (2) providing limited stability. Therefore, further research into the relationship between cognitive vs. other types of stimulation and atrophy in the chronic stages of TBI is needed.

Many studies of EE in humans are observational and correlational in design, including the present study. Future EE research would benefit from inclusion of elements that would permit conclusions regarding causality and directionality of relationships, as offered by Salthouse et al. (2002). They suggested that random assignment to experimental and control groups would minimize influences of relevant pre-existing individual differences, such as initial level of cognitive ability and amount of education. Further, rigorous control of enrichment groups, in terms of type and amount of EE, is needed as well as long-term objective monitoring of the amount and frequency of EE activities. Though, given that objective monitoring of lifestyle activities is often unfeasible, experience sampling might offer greater

accuracy than retrospective self-report (Csikszentmihalyi and Larson, 1987). Further general challenges in the measurement and manipulation of EE in humans pertain to inter-individual differences in motivation, interest and engagement: what is cognitively challenging, stimulating, and enjoyable to one may be overly difficult and thus stressful for another, or excessively easy and thus insufficiently stimulating to confer neural benefits to another. These limitations affect the strength of conclusions in our own study and warrant future experimental studies with the controls described above.

With regard to models of rehabilitation, the present study arguably provides preliminary empirical support for the contextualized model of cognitive rehabilitation proposed by Ylvisaker et al. (2002), in which therapeutic activities embedded in the patient's real life outside of the clinical setting may lead to greater recovery following brain injury. Cognitive rehabilitation researchers have recommended that rehabilitation strategies should be embedded in real-life contexts in order to maximize far transfer of learned skills and to impact real-life functioning (Murre and Robertson, 1999; Mateer and Sira, 2006). Consistent with these recommendations and with the Ylvisaker et al. (2002) contextualized model of rehabilitation, the majority of activities examined in the present study were embedded in real-life contexts, thus increasing the practical utility of the present study findings. Future prospective research should compare augmentation or intensification of those activities that are a part of patients' day to day life, with EE conferred by more conventional interventions such as computerized cognitively stimulating activities. Longitudinal measures of EE are also needed. Here, we inferred that EE at 5 months post-injury is a proxy for ongoing EE.

Regarding future research avenues, preliminary findings indicate that the default mode network (DMN; Raichle et al., 2001) in humans is implicated in TBI, with functional connectivity decrements within the DMN predicting sustained attention deficits (Bonnelle et al., 2011; Sandrone and Bacigaluppi, 2012). Future studies could investigate the benefits of EE factors purported to impact connectivity within the DMN, such as meditation practice (Taylor et al., 2013), an area of burgeoning interest in the literature on recovery from TBI.

CONCLUSIONS

The present study is the first to examine EE factors and their relationship with hippocampal atrophy in the chronic stages of moderate-severe TBI. EE that followed TBI and was temporally proximal to injury had a negative association with hippocampal atrophy, while years of education, a proxy for pre-injury EE (or cognitive reserve) was not significantly associated. Validation of the present findings through replication with larger samples of TBI patients is needed, ideally in a study in which the type and duration of EE is experimentally manipulated. EE is intimately associated with modification of existing synapses, synaptogenesis as well as neurogenesis. Its role in neurorehabilitation appears critical. The findings of this correlational study can be used to generate testable hypotheses regarding the directional impact of EE, as well as the active ingredients of EE for buffering against cerebral atrophy, and its functional consequences. Such questions have significant implications for the development of effective rehabilitation methods for people suffering the long-term consequences of moderate-severe TBI.

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REFERENCES

Adnan, A., Crawley, A., Mikulis, D., Moscovitch, M., Colella, B., and Green, R. E. A. (in press). Moderate-severe traumatic brain injury causes delayed loss of white matter integrity: evidence of fornix deterioration in the chronic stage of injury. *Brain Injury*.

Amaral, D. G., and Witter, M. P. (1995). "Hippocampal formation," in *The Rat Nervous System*, ed G. Paxinos (New York, NY: Academic Press), 443–493.

Amato, M. P., Razzolini, L., Goretti, B., Stromillo, M. L., Rossi, F., Giorgio, A., et al. (2013). Cognitive reserve and cortical atrophy in multiple sclerosis: a longitudinal study. *Neurology* 80, 1728–1733. doi: 10.1212/WNL.0b013e3182918c6f

Beck, A. T. (1987). *Beck Depression Inventory*. San Antonio, TX: The Psychological Corporation.

Beck, A. T. (1990). *Beck Anxiety Inventory*. San Antonio, TX: Psychological Corporation.

Berlucchi, G. (2011). Brain plasticity and cognitive neurorehabilitation. *Neuropsychol. Rehabil.* 21, 560–578. doi: 10.1080/09602011.2011.573255

Bigler, E. D. (2013). Neuroinflammatin and the dynamic lesion. *Brain* 136, 9–11. doi: 10.1093/brain/aws342

Bigler, E. D., Blatter, D. D., Anderson, C. V., Johnson, S. C., Gale, S. D., Hopkins, R. O., et al. (1997). Hippocampal volume in normal aging and traumatic brain injury. *AJNR Am. J. Neuroradiol.* 18, 11–23.

Blake, D. T., Heiser, M. A., Caywood, M., and Merzenich, M. M. (2006). Experience-dependent adult cortical plasticity requires cognitive association between sensation and reward. *Neuron* 52, 371–381. doi: 10.1016/j.neuron.2006.08.009

Bonnelle, V., Leech, R., Kinnunen, K. M., Ham, T. E., Beckmann, C. F., De Boissezon, X., et al. (2011). Default mode network connectivity predicts sustained attention deficits after traumatic brain injury. *J. Neurosci.* 31, 13442–13451. doi: 10.1523/JNEUROSCI.1163-11.2011

Bosma, H., Van Boxtel, M. P., Ponds, R. W., Jelicic, M., Houx, P., Metsemakers, J., et al. (2002). Engaged lifestyle and cognitive function in middle and old-aged, non-demented persons: a reciprocal association? *Z. Gerontol. Geriatr.* 35, 575–581. doi: 10.1007/s00391-002-0080-y

Corkin, S., Rosen, T. J., Sullivan, E. V., and Clegg, R. A. (1989). Penetrating head injury in young adulthood exacerbates cognitive decline in later years. *J. Neurosci.* 9, 3876–3883.

Corral, M., Rodriguez, M., Amenedo, E., Sanchez, J. L., and Diaz, F. (2006). Cognitive reserve, age, and neuropsychological performance in healthy participants. *Dev. Neuropsychol.* 29, 479–491. doi: 10.1207/s15326942dn2903_6

Csikszentmihalyi, M., and Larson, R. (1987). Validity and reliability of the experience-sampling method. *J. Nerv. Ment. Dis.* 175, 526–536. doi: 10.1097/00005053-198709000-00004

Curlik, D. M., and Shors, T. J. (2011). Learning increases the survival of newborn neurons provided that learning is difficult to achieve and successful. *J. Cogn. Neurosci.* 23, 2159–2170. doi: 10.1162/jocn.2010.21597

Diamond, M. C. (2001). Response of the brain to enrichment. *An. Acad. Bras. Cienc.* 73, 211–220.

Draganski, B., Gaser, C., Kempermann, G., Kuhn, H. G., Winkler, J., Buchel, C., et al. (2006). Temporal and spatial dynamics of brain structure changes during extensive learning. *J. Neurosci.* 26, 6314–6317. doi: 10.1523/JNEUROSCI.4628-05.2006

Duvernoy, H. M., Cattin, F., and Naidich, T. (2005). *Human Hippocampus: Functional Anatomy, Vascularization and Serial Sections with MRI*. Heidelberg: Springer-Verlag.

Elkins, J. S., Longstreth, W. T. Jr., Manolio, T. A., Newman, A. B.,

Bhadelia, R. A., et al. (2006). Education and the cognitive decline associated with MRI-defined brain infarct. *Neurology* 67, 435–440. doi: 10.1212/01.wnl.0000228246.89109.98

Evans, J. J., Bateman, A., Turner, G., and Green, R. E. A. (2008). Understanding brain injury resources and evidence base. *Neuropsychol. Rehabil. Res. Dig.* 18, 372–384. doi: 10.1080/09602010801909153

Farbota, K. D., Bendlin, B. B., Alexander, A. L., Rowley, H. A., Dempsey, R. J., and Johnson, S. C. (2012). Longitudinal diffusion tensor imaging and neuropsychological correlates in traumatic brain injury patients. *Front. Hum. Neurosci.* 6:160. doi: 10.3389/fnhum.2012.00160

Frasca, D., Tomaszczyk, J., McFadyen, B. J., and Green, R. E. A. (2013). Traumatic brain injury and post-acute decline: what role does environmental enrichment play? A scoping review. *Front. Hum. Neurosci.* 7:31. doi: 10.3389/fnhum.2013.00031

Fritsch, T., McClendon, M. J., Smyth, K. A., Lerner, A. J., Friedland, R. P., and Larsen, J. D. (2007). Cognitive functioning in healthy aging: the role of reserve and lifestyle factors early in life. *Gerontologist* 47, 307–322. doi: 10.1093/geront/47.3.307

Green, R. E. A., Colella, B., Herbert, D. A., Bayley, M., Kang, H. S., Till, C., et al. (2008). Prediction of return to productivity after severe traumatic brain injury: investigations of optimal neuropsychological tests and timing of assessment. *Arch. Phys. Med. Rehabil.* 89, S51–S60.

Greenberg, G., Mikulis, D. J., Ng, K., Desouza, D., and Green, R. E. (2008). Use of diffusion tensor imaging to examine subacute white matter injury progression in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, 45–50. doi: 10.1016/j.apmr.2008.09.552

Himanen, L., Portin, R., Isoniemi, H., Helenius, H., Kurki, T., and Tenovuo, O. (2006). Longitudinal cognitive changes in traumatic brain injury: a 30-year follow-up study. *Neurology* 66 187–192. doi: 10.1212/01.wnl.0000194264.60150.d3

Jacobs, B., Schall, M., and Scheibel, A. B. (1993). A quantitative dendritic analysis of Wernicke's area in humans. II. Gender, hemispheric, and environmental factors. *J. Comp. Neurol.* 327, 97–111. doi: 10.1002/cne.903270108

Johnson, V. E., Stewart, J. E., Begbie, F. D., Trojanowski, J. Q., Smith, D. H., and Stewart, W. (2013). Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain* 136(Pt 1), 28–42. doi: 10.1093/brain/aws322

Kasai, H., Fukuda, M., Watanabe, S., Hayashi-Takagi, A., and Noguchi, J. (2010). Structural dynamics of dendritic spines in memory and cognition. *Trends Neurosci.* 33 121–129.

Kempermann, G., Fabel, K., Ehninger, D., Babu, H., Leal-Galicia, P., Garthe, A., et al. (2010). Why and how physical activity promotes experience-induced brain plasticity. *Front. Neurosci.* 4:189. doi: 10.3389/fnins.2010.00189

Kempermann, G., Gast, D., and Gage, F. H. (2002). Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann. Neurol.* 52, 135–143. doi: 10.1002/ana.10262

Kesler, S. R., Adams, H. F., Blasey, C. M., and Bigler, E. D. (2003). Premorbid intellectual functioning, education, and brain size in traumatic brain injury: an investigation of the cognitive reserve hypothesis. *Appl. Neuropsychol.* 10, 153–162. doi: 10.1207/S15324826AN1003_04

Kolb, B., Teskey, G. C., and Gibb, R. (2010). Factors influencing cerebral plasticity in the normal and injured brain. *Front. Hum. Neurosci.* 4:204. doi: 10.3389/fnhum.2010.00204

Kovesdi, E., Gyorgy, A. B., Kwon, S. C., Wingo, D. L., Kamnaksh. A., Long, J. B., et al. (2011). The effect of enriched environment on the outcome of traumatic brain injury; a behavioral, proteomics, and histological study. *Front. Neurosci.* 5:42. doi: 10.3389/fnins.2011.00042

Lee, T., Jarome, T., Li, S. J., Kim, J. J., and Helmstetter, F. J. (2009). Chronic stress selectively reduces hippocampal volume in rats: a longitudinal magnetic resonance imaging study. *Neuroreport* 20, 1554–1558. doi: 10.1097/WNR.0b013e328332bb09

Levin, H. S., O'donnell, M. A., and Grossman, R. G. (1979). The Galveston orientation and amnesia test: a practical scale to assess cognition after head injury. *J. Nerv. Ment. Dis.* 167, 675–684. doi: 10.1097/00005053-197911000-00004

Lezak, M. D., Howieson, D. B., and Loring, D. W. (2004). *Neuropsychological Assessment*. New York, NY: Oxford University Press.

Mahncke, H. W., Bronstone, A., and Merzenich, M. M. (2006). Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. *Prog. Brain Res.* 157, 81–109.

Maller, J. J., Daskalakis, Z. J., and Fitzgerald, P. B. (2007). Hippocampal volumetrics in depression: the importance of the posterior tail. *Hippocampus* 17, 1023–1027.

Mateer, C. A., and Sira, C. S. (2006). Cognitive and emotional consequences of TBI: intervention strategies for vocational rehabilitation. *Neurorehabilitation* 21, 315–326.

Matter, A. M., Folweiler, K. A., Curatolo, L. M., and Kline, A. E. (2011). Temporal effects of environmental enrichment–mediated functional improvement after experimental traumatic brain injury in rats. *Neurorehabil. Neural Repair* 25, 558–564. doi: 10.1177/1545968310397206

McCarthy, M. M. (2003). Stretching the truth. Why hippocampal neurons are so vulnerable following traumatic brain injury. *Exp. Neurol.* 184, 40–43. doi: 10.1016/j.expneurol.2003.08.020

Millis, S. R., Rosenthal, M., Novack, T. A., Sherer, M., Nick, T. G., Kreutzer, J. S., et al. (2001). Long-term neuropsychological outcome after traumatic brain injury. *J. Head Trauma Rehabil.* 16, 343–355. doi: 10.1097/00001199-200108000-00005

Mohammed, A. H., Zhu, S. W., Darmopil, S., Hjerling-Leffler, J., Ernfors, P., Winblad, B., et al. (2002). Environmental enrichment and the brain. *Prog. Brain Res.* 138, 109–133. doi: 10.1016/S0079-6123(02)38074-9

Murre, R., and Robertson, I. (1999). Rehabilitation of brain damage: brain plasticity and principles of guided recovery. *Psychol. Bull.* 125, 544–575. doi: 10.1037/0033-2909.125.5.544

Ng, K., Mikulis, D. J., Glazer, J., Kabani, N., Till, C., Greenberg, G., et al. (2008). Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S35–S44. doi: 10.1016/j.apmr.2008.07.006

Nithianantharajah, J., and Hannan, A. J. (2009). The neurobiology of brain and cognitive reserve: mental and physical activity as modulators of brain disorders. *Prog. Neurobiol.* 89, 369–382. doi: 10.1016/j.pneurobio.2009.10.001

Olson, A. K., Eadie, B. D., Ernst, C., and Christie, B. R. (2006). Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. *Hippocampus* 16, 250–260. doi: 10.1002/hipo.20157

Onyszchuk, G., He, Y. Y., Berman, N. E., and Brooks, W. M. (2008). Detrimental effects of aging on outcome from traumatic brain injury: a behavioral, magnetic resonance imaging, and histological study in mice. *J. Neurotrauma* 25, 153–171. doi: 10.1089/neu.2007.0430

Petcu, E. B., Sfredel, V., Platt, D., Herndon, J. G., Kessler, C., and Popa-Wagner, A. (2008). Cellular and molecular events underlying the dysregulated response of the aged brain to stroke: a mini-review. *Gerontology* 54, 6–17. doi: 10.1159/000112845

Popa-Wagner, A., Carmichael, S. T., Kokaia, Z., Kessler, C., and Walker, L. C. (2007). The response of the aged brain to stroke: too much, too soon? *Curr. Neurovasc. Res.* 4, 216–227.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., and Shulman, G. L. (2001). A default mode of brain function. *Proc. Natl. Acad. Sci. U.S.A.* 98, 676–682. doi: 10.1073/pnas.98.2.676

Richards, M., Hardy, R., and Wadsworth, M. E. (2003). Does active leisure protect cognition? Evidence from a national birth cohort. *Soc. Sci. Med.* 56, 785–792.

Robertson, I. H., and Murre, J. M. (1999). Rehabilitation of brain damage: brain plasticity and principles of guided recovery. *Psychol. Bull.* 125, 544–575. doi: 10.1037/0033-2909.125.5.544

Rosenzweig, M. R., and Bennett, E. L. (1996). Psychobiology of plasticity: effects of training and experience on brain and behavior. *Behav. Brain Res.* 78, 57–65. doi: 10.1016/0166-4328(95)00216-2

Rosenfeld, J. V., Maas, A. I., Bragge, P., Morganti-Kossmann, M. C., Manley, G. T., and Gruen, R. L. (2012). Early management of severe traumatic brain injury. *Lancet* 380, 1088–1098. doi: 10.1016/S0140-6736(12)60864-2

Salthouse, T. A., Berish, D. E., and Miles, J. D. (2002). The role of cognitive stimulation on the relations between age and cognitive functioning. *Psychol. Aging* 17, 548–557. doi: 10.1037/0882-7974.17.4.548

Sandrone, S., and Bacigaluppi, M. (2012). Learning from default mode network: the predictive value of resting state in traumatic brain injury. *J. Neurosci.* 32, 1915–1917. doi: 10.1523/JNEUROSCI.5637-11.2012

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. *Neuropsychology* 7, 273–295. doi: 10.1037/0894-4105.7.3.273

Scarmeas, N., and Stern, Y. (2003). Cognitive reserve and lifestyle. *J. Clin. Exp. Neuropsychol.* 25, 625–633. doi: 10.1076/jcen.25.5.625.14576

Shors, T. J., Anderson, M. L., Curlik, D. M., and Nokia, M. S. (2012). Use it or lose it: How neurogenesis keeps the brain fit for learning. *Behav. Brain Res.* 227, 450–458. doi: 10.1016/j.bbr.2011.04.023

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* 8, 448–460. doi: 10.1017/S1355617702813248

Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 20, 112–117.

Studenski, S., Carlson, M. C., Fillit, H., Greenough, W. T., Kramer, A., and Rebok, G. W. (2006). "From bedside to bench: does mental and physical activity promote cognitive vitality in late life?" in *Proceeding of the Conference on Science Aging Knowledge Environment 2006* (Philadelphia, PA), pe21.

Surget, A., Tanti, A., Leonardo, E. D., Laugeray, A., Rainer, Q., Touma, C., et al. (2011). Antidepressants recruit new neurons to improve stress response regulation. *Mol. Psychiatry* 16, 1177–1188. doi: 10.1038/mp.2011.48

Tanti, A., Westphal, W. P., Girault, V., Brizard, B., Devers, S., Leguisquet, A. M., et al. (2013). Region-dependent and stage-specific effects of stress, environmental enrichment and antidepressant treatment on hippocampal neurogenesis. *Hippocampus* 23, 797–811. doi: 10.1002/hipo.22134

Tate, and Bigler, E. D. (2000). Fornix and hippocampal atrophy in traumatic brain injury. *Learn. Mem.* 7, 442–446. doi: 10.1101/lm.33000

Taub, E., Uswatte, G., Mark, V. W., and Morris, D. M. (2006). The learned nonuse phenomenon: implications for rehabilitation. *Eura. Medicophys.* 42, 241–256.

Taylor, V. A., Daneault, V., Grant, J., Scavone, G., Breton, E., Roffe-Vidal, S., et al. (2013). Impact of meditation training on the default mode network during a restful state. *Soc. Cogn. Affect. Neurosci.* 8, 4–14. doi: 10.1093/scan/nsr087

Till, C., Colella, B., Verwegen, J., and Green, R. E. (2008). Postrecovery cognitive decline in adults with traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89(12 Suppl.), S25–S34. doi: 10.1016/j.apmr.2008.07.004

Tombaugh, T. N. (1996). *Test of Memory Malingering (TOMM).* New York, NY: Multi-Health Systems, Inc.

Trivedi, M. A., Ward, M. A., Hess, T. M., Gale, S. D., Dempsey, R. J., Rowley, H. A., et al. (2007). Longitudinal changes in global brain volume between 79 and 409 days after traumatic brain injury: relationship with duration of coma. *J. Neurotrauma* 24, 766–771. doi: 10.1089/neu.2006.0205

Watson, C., Andermann, F., Gloor, P., Jones-Gotman, M., Peters, T., Evans, A., et al. (1992). Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. *Neurology* 42, 1743–1750. doi: 10.1212/WNL.42.9.1743

Watson, C., Cendes, F., Fuerst, D., Dubeau, F., Williamson, B., Evans, A., et al. (1997). Specificity of volumetric magnetic resonance imaging in detecting hippocampal sclerosis. *Arch. Neurol.* 54, 67–73. doi: 10.1001/archneur.1997.00550130049015

Wechsler, D. (2001). *Wechsler Test of Adult Reading (WTAR).* San Antonio, TX: The Psychological Corporation.

Willis, K. J., and Hakim, A. M. (2013). Stroke prevention and cognitive reserve: emerging approaches to modifying risk and delaying onset of dementia. *Front. Neurol.* 4:13. doi: 10.3389/fneur.2013.00013

Ylvisaker, M., Hanks, R., and Johnson-Greene, D. (2002). Perspectives on rehabilitation of individuals with cognitive impairment after brain injury: rationale for reconsideration of theoretical paradigms. *J. Head Trauma Rehabil.* 17, 191–209.

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Traumatic brain injury and post-acute decline: what role does environmental enrichment play? A scoping review

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Objectives: While a growing number of studies provide evidence of neural and cognitive decline in traumatic brain injury (TBI) survivors during the post-acute stages of injury, there is limited research as of yet on environmental factors that may influence this decline. The purposes of this paper, therefore, are to (1) examine evidence that environmental enrichment (EE) can influence long-term outcome following TBI, and (2) examine the nature of post-acute environments, whether they vary in degree of EE, and what impact these variations have on outcomes.

Methods: We conducted a scoping review to identify studies on EE in animals and humans, and post-discharge experiences that relate to barriers to recovery.

Results: One hundred and twenty-three articles that met inclusion criteria demonstrated the benefits of EE on brain and behavior in healthy and brain-injured animals and humans. Nineteen papers on post-discharge experiences revealed that variables such as insurance coverage, financial, and social support, home therapy, and transition from hospital to home, can have an impact on clinical outcomes.

Conclusion: There is evidence to suggest that lack of EE, whether from lack of resources or limited ability to engage in such environments, may play a role in post-acute cognitive and neural decline. Maximizing EE in the post-acute stages of TBI may improve long-term outcomes for the individual, their family and society.

Keywords: traumatic brain injury, environmental enrichment, post-acute decline, adult, moderate to severe, post-discharge, transition home

INTRODUCTION

Moderate to severe traumatic brain injury (TBI) is a ubiquitous injury: studies suggest an annual incidence of upwards of 20–60 per 100,000 (Narayan et al., 2002; Bruns and Hauser, 2003; Cassidy et al., 2004; C.I.H.I., 2006). Many of these injuries are sustained in young adulthood (C.I.H.I., 2006; Faul et al., 2010) and result in significant impairment to cognitive, motor, and emotional functioning. Predominant and persisting deficits to executive functioning, attention, memory, and speed of processing compromise psychosocial functioning and quality of life (Sander et al., 2001; Hawthorne et al., 2009; Resch et al., 2009). Because these deficits prevent many TBI survivors from returning to pre-injury levels of activity and participation (Dikmen et al., 1983, 1995; Lezak, 2004; Christensen et al., 2008), successful community integration is now recognized as a primary goal of rehabilitation for persons with brain injury (Sander et al., 2010).

The consequences of brain injury are particularly concerning given the high incidence of TBI. Murray and Lopez (1997) predicted that by 2020, TBI will be the third leading cause of disability in the world. Considering that males aged 15–24 years have the highest incidence of TBI (Pickett et al., 2004; C.I.H.I., 2006; Faul et al., 2010), this can mean decades of disability and lost productivity. Not surprisingly, the annual burden of acute care and rehabilitation in North America is estimated to be in the billions of dollars (SMARTRISK, 2006; Faul et al., 2010).

A theoretically intriguing and clinically important question that is emerging from the literature is whether an impediment to recovery and a contributing factor to failed community integration after moderate to severe TBI is cognitive and brain deterioration in the post-acute stages after brain injury. TBI recovery studies typically show an asymptotic pattern of recovery, with rapid improvement within the first weeks and months of injury, followed by a slower rate of improvement and then a plateau with limited measureable recovery thereafter (Basso, 1989; Heinemann et al., 1995; Blatter et al., 1997; Holbrook et al., 1999; Christodoulou et al., 2001; Farne et al., 2004). However, not only do many fail to return to pre-injury levels of function when they reach that plateau (Christensen et al., 2008), but there is growing evidence that a subset of TBI survivors show cognitive deterioration.

A number of studies that have examined post-acute cognitive changes in TBI survivors have demonstrated that across domains of functioning, a combination of maintenance, further recovery and frank declines are observed (Ruff et al., 1991; Millis et al., 2001; Sander et al., 2001; Himanen et al., 2006; Salmond et al., 2006; Till et al., 2008). For example, Till et al. (2008) showed

that nearly 30% of their sample of moderate-severe TBI patients showed clinically significant decline (as measured by the reliable change index) in two or more domains of cognitive functioning.

In examining changes of the brain during the post-acute stages of TBI, imaging studies have also shown evidence of deterioration, including decreased cerebral blood flow (Kim et al., 2010), declines in whole brain volume (Blatter et al., 1997; Mackenzie et al., 2002; Trivedi et al., 2007; Ng et al., 2008; Sidaros et al., 2009; Hudak et al., 2011), atrophy of discrete gray, and white matter structures including the hippocampus and corpus callosum (Wilson et al., 1988; Bigler et al., 1997; Levine et al., 2008; Ng et al., 2008; Sidaros et al., 2008), lesion expansion (Ng et al., 2008); and reduced white matter integrity as measured by diffusion tensor imaging (Bendlin et al., 2008; Greenberg et al., 2008; Sidaros et al., 2008; Warner et al., 2010; Farbota et al., 2012).

Correlations between brain and behavioral decline have also been observed. In one study, 24 TBI survivors underwent MRI scans at 8 weeks and 12 months post-injury. The authors not only demonstrated increased atrophy during this time period, but also negatively correlated outcomes on the Glasgow Outcome Scale (Sidaros et al., 2009). In other studies, Hudak et al. (2011) found that decreases in brain volume correlated with depressive symptoms in the post-acute phase, and Farbota et al. (2012) demonstrated that diffusion tensor imaging findings (fractional anisotropy values) and neuropsychological task performance were positively correlated.

Given mounting evidence revealing post-acute decline, we suggest that it is important at this stage of research to begin to consider what factors may hold the potential to influence, and in particular, offset this decline.

One factor that may play a role is "environmental enrichment" (EE). As we will discuss further in the next section, EE broadly refers to enhanced stimulation, associated with (1) environments that provide access to cognitive as well as physical and social stimulation, and (2) conditions that encourage maximal participation. An extensive body of literature shows positive correlations between EE and cognitive and neuronal status. (Scarmeas and Stern, 2003; Will et al., 2004; Simpson and Kelly, 2011). There have also been some findings to suggest that EE influences post-acute decline. In Till et al.'s (2008) study of post-injury cognitive decline, the authors found a relationship between hours of therapy at 5 months post-injury and degree of cognitive decline from 12 to 24 months. They concluded that lack of access to complex and enriched environments, due in part to limited access to resources, may play a critical a role in decline. In another study, Miller and Green (in press) found that greater hippocampal volume loss in the chronic stages of TBI (12–24 months post-injury) was negatively correlated with degree of cognitive stimulation reported at 5 months post-injury.

These few but important findings raise the question whether post-acute decline in these survivors was influenced by the extent of enrichment, or lack thereof, in the environments to which they were discharged following the early and intensive months of therapy. A reduction in the level of enrichment in the later stages of recovery from TBI might occur when the number and hours of therapies are reduced or when patients move from in-patient neurorehabilitation back to the home environment. Additionally, TBI survivors may return to environments that are indeed complex and enriched, but without the expertise of therapists actively providing supports and adaptations to the environments, patients may be unable to engage due to cognitive, emotional and/or physical impairments that render the environments overwhelming or inaccessible.

The purposes of this paper, therefore, are to (1) examine evidence that EE can influence long-term outcome following TBI, and (2) examine the nature of post-acute environments, whether they vary in degree of EE, and what impact these variations have on outcomes. To accomplish these aims, we will undertake a scoping review summarizing literature related to EE and post-acute environments.

SCOPING REVIEW METHODS

This paper addresses two of the reasons for undertaking a scoping review identified by Arksey and O'Malley (2005): to summarize and disseminate research findings and to identify research gaps in the existing literature. The scoping review typically unfolds in five steps: (1) identify the research question; (2) identify all pertinent studies; (3) select the studies for detailed analysis; (4) chart the data according to key concepts; and (5) collate and summarize the findings of the selected studies (Arksey and O'Malley, 2005; Rumrill et al., 2010):

IDENTIFY THE RESEARCH QUESTION

The research questions addressed in this paper are whether (1) EE can influence long-term recovery, and (2) post-discharge environments vary in degree of EE, and whether such variations influence outcomes.

IDENTIFY ALL PERTINENT STUDIES

The literature review aimed to identify a comprehensive set of articles detailing the effects of EE in animals and humans, and the post-discharge experiences related to recovery and regaining independence in the post-acute stages after TBI. Articles that addressed these topics were obtained through use of a traditional keyword-driven electronic search guided by the following terms: TBI; recovery; EE; environmental complexity; active lifestyle; stimulation; neuroplasticity; cognitive reserve; intervention; multi-disciplinary; multi-contextual; post-rehabilitation; transition home; barriers; community integration; re-engagement. Peer-reviewed journals were searched using the PubMed and Cochrane Collaboration research databases as well as the Google Scholar search engine, for articles published between 1987 and 2012. Additionally, hand searches were conducted of references from key articles to follow up on seminal work and promising literature that might not have been captured by the databases used.

SELECT STUDIES FOR DETAILED ANALYSIS

To be considered for inclusion in the review, articles had to meet the following criteria: (1) describe EE (or components of EE) in animals or adult humans or (2) describe the post-discharge experience, and more specifically, the transition from hospital to home in adult brain-injury survivors; and (3) be available in English. No methodological limitations were applied to screen for levels of evidence.

CHART DATA ACCORDING TO KEY CONCEPTS

Articles that met the inclusion criteria were reviewed in detail and categorized based on population examined, methodology, and study objectives to discover commonalities and provide connections between the sets of literatures reviewed.

COLLATE AND SUMMARIZE FINDINGS

The results are presented to correspond with the objectives of this paper. A numerical summary of the articles included is followed by a summary of the literature.

RESULTS

Database searches identified 2053 articles. Of these, 142 were included in the review based on the selection criteria listed above. **Table 1** provides a brief summary of the articles that were included. **Tables 2** and **3** provide a more detailed summary of the papers that specifically addressed EE in brain-injured animals and humans, as well as EE and post-discharge experiences, respectively. **Tables 2** and **3** detail the populations, methods, objectives, and main findings of the articles that were included.

ENVIRONMENTAL ENRICHMENT HAS BENEFICIAL EFFECTS ON BRAIN AND BEHAVIOR IN ANIMALS AND HUMANS

DEFINING ENVIRONMENTAL ENRICHMENT

A number of definitions have been proposed for EE, and it is often defined in relative terms. In animal studies, EEs (e.g., cages with running wheels, novel toys, several animals) are typically contrasted with standard or impoverished environments (e.g., cages with a single animal, and only the basic necessities for living). In these studies, researchers have stressed the importance of having cognitive, social and physical stimulation for environments to be considered enriched and a key property is the maintenance of novelty, for example through regularly changing toys and food (Diamond, 2001; Simpson and Kelly, 2011).

Kramer et al. (2004) have suggested that while numerous positive changes in cognitive functioning, neuroanatomy, and neurochemistry have been demonstrated as a result of exposure to EE in animals, we must examine the degree to which these findings translate to humans, and that an operational definition of EE applicable to humans needs to be established. Whereas novel toys and food, running wheels, and housing several animals together maps on well to cognitive, physical, and social stimulation in animals, identification of such concrete mappings in humans has proven more difficult. Subject factors, such as motivation and mental effort play a large role in reaping the benefits of EE. Thus, personality and earlier life experiences may influence engagement with the environment, such that what is a stimulating and engaging environment for one person may not be for another (Johansson, 2003). Thus, for humans, the definition of EE is more complex, addressing both the nature of the environment and factors that influence engagement with it.

These ideas of Kramer et al. (2004) are consistent with earlier work by Schooler (1987), who defined the related concept of environmental complexity as being determined by stimulus and demand characteristics. He theorized that greater diversity of stimuli in one's environment could lead to more options/plans of action to consider and decisions to make. When cognitive efforts are reinforced and rewarded, people are motivated to continue engaging in complex environments, which in turn enhances cognitive functioning. Thus, enhancing cognitive functioning further promotes participation in complex environments, illustrating a dynamic facet of EE and its benefits. Enrichment, therefore, reflects environmental complexity (e.g., opportunity to participate in different sports, clubs or social networks, and to engage in intellectually demanding activities), one's inclination to participate in the environment, and the frequency of participation.

Given the limitations in defining, manipulating and controlling EE in human studies, animal studies have arguably provided the most compelling evidence for the causal effects of EE.

Table 1 | Numerical summary of articles reviewed.

Literature topic	Number of studies	Methodologies	Populations
Beneficial effects of EE	123: animals—55; humans—68	*Animal literature*: quantitative, experimental; *Human literature:* quantitative, correlational, observational, intervention	Healthy and brain-injured animals, humans
Post-discharge experiences	19	Qualitative, observational, correlational, reviews, case study	Brain-injured humans

BENEFITS OF ENVIRONMENTAL ENRICHMENT

Environmental enrichment in healthy animals

In 1947, Hebb examined if rats exposed to EE would improve behaviorally on problem-solving tasks, compared to a control group (Hebb, 1947). EE rats were free to roam his home while control rats were housed in standard laboratory cages. Hebb found performance was superior in the EE group. Since then, more systematically controlled studies have had similar findings.

Exposure to EE has been associated with increases in cognitive functioning, specifically improvements in response selectivity, learning ability, spatial and problem solving skills, memory, and processing speed (Mohammed et al., 1990; Rosenzweig and Bennett, 1996; Nilsson et al., 1999; Van Praag et al., 2000; Kobayashi et al., 2002; Milgram, 2003; Valero et al., 2011; Leger et al., 2012; Speisman et al., 2012; Yang et al., 2013). Reductions in boredom (Meagher and Mason, 2012) and frustration (Latham and Mason, 2010) have been demonstrated as well. The benefits of EE are also observable at cellular and molecular levels. There is evidence of increased neurogenesis, synaptogenesis and dendritic spine density in parts of the brain associated with memory and learning (i.e., hippocampus, dentate gyrus and cerebellar Purkinje cells) in response to EE (Kolb and Whishaw, 1998; Johansson, 2000, 2002; Van Praag et al., 2000; Churchill et al., 2002; Kempermann et al., 2002; Valero et al., 2011; Eckert and Abraham, 2012; Jung and Herms, 2012; Leger et al., 2012; Speisman et al., 2012; Fares et al., 2013; Yang et al., 2013). Increases in brain weight and cortical thickness

Table 2 | Detailed summary of articles included in "Brain-injured animals and EE" and "Brain-injured humans and EE" scoping review.

Authors	Methods	(1) Main objectives and (2) Findings
BRAIN-INJURED ANIMALS AND EE		
Hamm et al., 1996	Brain-injured and sham-injured rats in EE and standard environment (SE)	(1) Determine whether exposure to EE would promote recovery of cognitive function; (2) Brain-injured rats in EE vs. SE: EE rats showed more improvement in Morris Water Maze task; Brain-injured rats in EE vs. sham-injured: performed at same level.
Johansson and Ohlsson, 1996	Brain-injured rats randomly assigned to EE, social-stimulation only or physical-stimulation only environment	(1) Determine relative importance of social and physical activity to EE; (2) No difference in infarct size between groups. EE group performed better than physical group in all tests, better than social group on rotating pole. With time EE group performed better than social group in limb placement, climbing, inclined plane. Social group performed better than physical group on inclined plane and in climbing at all times, by 13 weeks also in limb placement test and on beam.
Passineau et al., 2001	Brain-injured and sham-injured rats randomly assigned to EE and SE	(1) Examine effect of EE on behavior and on histological integrity of brain tissue selectively vulnerable to brain trauma; (2) Injured animals in EE showed shorter latencies to find platform in Morris Water Maze task vs. injured/SE animals on day 12 post-TBI. Both injured groups showed deficits vs. sham groups. At 14 days post-TBI, EE animals had approximately 2× smaller lesion areas in regions of cerebral cortex posterior to injury epicenter compared to injured/SE animals. Overall lesion volume for entire injured cortical hemisphere was smaller in animals recovering in EE.
Dobrossy and Dunnett, 2001	Brain-injured rodents; review	(1) Review degree to which housing conditions or behavioral training can modify survival, integration or function of transplanted tissue; (2) Behavioral training experience can promote behavioral, and functional compensation, and influence neuroplasticity at cellular, and systems levels of neuronal reorganization.
Johansson, 2003	Brain-injured rats; review	(1) Review influence of post-ischemic environmental factors, possible clinical implications; (2) EE improves functional outcome, increases dendrite branching, number of dendritic spines in contralateral cortex, influences expression of many genes, modifies lesion-induced stem cell differentiation in hippocampus.
Dobrossy and Dunnett, 2004	Brain-injured rats with and without neural grafts randomly assigned to EE and SE	(1) Examine effects of differential housing conditions on striatal graft morphology and functional recovery; (2) Functional recovery accompanied by reduction in infarct size and more afferent connections.
Will et al., 2004	Brain-injured rats; review	(1) Compare three main non-invasive therapeutic strategies for achieving rehabilitation after brain damage: EE, physical exercise, specific formal training; (2) EE increased neurogenesis in hippocampus and up-regulation of neurotropic factors (e.g., NGF) that result in decreased spontaneous apoptosis and increased neuronal survival.
Gobbo and O'Mara, 2004	Brain-injured rats housed under EE or SE, 6 weeks before, 4 weeks after surgery	(1) Investigate if EE can protect rats against the cognitive and neurological consequences of transient ischemia; (2) EE improved learning and memory; does not protect against actual loss of CA1 pyramidal cells. Brain-derived neurotrophic factor levels were increased.
Lippert-Gruener et al., 2007	Brain-injured and sham-injured rats assigned to EE, EE + multi-modal early onset stimulation (MEOS), or SE	(1) Investigate effects of EE, EE+ MEOS, and SE on cognitive and motor function, and cortical lesion volume; (2) Rats in EE and EE+MEOS demonstrated improvement over SE, but no change in lesion size.
Pereira et al., 2007	Brain-injured and sham-injured rats randomly assigned to EE and SE	(1) Examine effects of daily EE on memory deficits in water maze and cerebral damage; (2) Spatial reference, working memory impairments were completely reversed by EE; Reduction of both hippocampal volume and cortical area, ipsilateral to arterial occlusion, no EE effect on morphological measurements.
Hoffman et al., 2008	Brain-injured and sham-injured rats randomly assigned to early EE, delayed EE, continuous EE or no EE	(1) Examine whether EE-mediated benefits are dependent on exposure to EE during neurobehavioral training; (2) A3 cell loss significantly attenuated in TBI + continuous EE group vs. TBI + no EE group. Beam-walking was facilitated in TBI groups that received early or continuous EE vs. those receiving delayed or no EE. Cognitive training enhanced in TBI groups that received continuous or delayed EE vs. early or no EE groups.

(Continued)

Table 2 | Continued

Authors	Methods	(1) Main objectives and (2) Findings
Sozda et al., 2010	Brain-injured and sham-injured rats assigned to typical EE, EE –social, EE –stimuli, SE, SE +stimuli	(1) Investigate effects of typical EE, EE –social, EE –stimuli, SE, SE +stimuli on motor and cognitive function, lesion volume, brain volume loss; (2) Typical EE groups performed same as sham group, and showed most improvement compared to other TBI groups in terms of spatial learning and memory retention, lesion size reduction.
Sun et al., 2010	Brain-injured rats randomly assigned to EE or SE	(1) Investigate effects of EE on cognitive impairment, levels of BDNF and NMDA receptor subunit 1 (NR1) and subunit 2B (NR2B) in hippocampus; (2) EE exposure improved spatial cognitive performance and non-spatial memory performance. EE increased levels of BDNF and NR1 protein in hippocampus.
Matter et al., 2010	Brain-injured or sham-injured rats randomly assigned to 8 groups receiving continuous, early or delayed EE with either 1 or 2 weeks of exposure	(1) Further assess effects of time of initiation and duration of EE on neurobehavioral recovery by evaluating and directly comparing all the temporal permutations; (2) Motor ability was enhanced in TBI groups that received early EE (i.e., during testing) vs. standard housing. Acquisition of spatial learning facilitated in groups receiving delayed EE (i.e., during training).
De Witt et al., 2011	Brain-injured and sham-injured rats randomly assigned to EE, EE (2 h), EE (4 h), EE (6 h), or SE	(1) Determine whether abbreviated EE (i.e., rehab-relevant dose response) confers benefits similar to typical EE; (2) TBI + EE (2 h) and TBI + EE (4 h) groups not different from TBI + STD group in behavioral assessment. TBI + EE (6 h) group exhibited enhancement of motor and cognitive performance when compared with TBI + STD group, TBI + EE (2 h) and TBI + EE (4 h) groups, and did not differ from TBI + EE (typical) group.
Cheng et al., 2012	Brain-injured and sham-injured rats randomly assigned to 3 weeks of EE or SE. In phase 2: half of rats in EE transferred to SE conditions (TBI + EE + SE and sham + EE + SE; re-assessed 1/month for 6 months)	(1) Determine whether EE-mediated motor and cognitive benefits persist after its withdrawal; (2) TBI + EE and TBI + EE + STD groups performed better in the water maze than the TBI + STD group, did not differ from one another. Data replicate several studies showing that EE enhances recovery after brain injury, and extend by demonstrating that cognitive benefits are maintained for at least 6 months post-rehabilitation.
Shin et al., 2013	Brain-injured and sham-injured rats assigned to EE or SE	(1) Investigate effects of EE on substantia nigra gene expression; (2) EE-induced gene alterations after TBI included genes important for signal transduction, in particular calcium signaling pathways, membrane homeostasis, and metabolism.
Monaco et al., 2013	Brain-injured and sham-injured rats assigned to EE or SE	(1) Assess effect of EE on functional and histological outcome in female rats after TBI; (2) EE improved motor function and spatial learning; reduced lesion size and increased hippocampal cell survival.
BRAIN-INJURED HUMANS AND EE		
Blackerby, 1990	Acute moderate-severe TBI ($n = 145$); retrospective; quantitative	(1) Investigate effects of different levels of rehabilitation intensity on length of stay in two hospital-based coma and acute rehabilitation populations; (2) After increasing treatment intensity and changes in case management, patients were discharged an average of 1.5 months earlier than before changes.
Toglia, 1991	Brain injury; concept paper	(1) Review literature on learning and generalization and direct applications to treatment; (2) Five components identified in cognitive psychology literature as critical to process of generalization: (a) use of multiple environments, (b) identification of criteria for transfer, (c) meta-cognitive training, (d) emphasis on processing strategies, and (e) use of meaningful activities.
Spivack et al., 1992	Acute moderate-severe TBI ($n = 95$); prospective; quantitative: repeated measures	(1) Examine effects of intensity of treatment and length of stay during inpatient rehabilitation hospitalization; (2) Patients with longer length of stay (LOS) made more progress across all outcome variables than patients with shorter LOS; In long LOS group, two treatment-intensity groups initially equivalent, and at discharge high-intensity treatment group surpassed low-intensity treatment group.

(Continued)

Table 2 | Continued

Authors	Methods	(1) Main objectives and (2) Findings
Willer et al., 1999	Post-acute/chronic severe TBI ($n = 46$); prospective; quantitative: case control matched design, repeated measures	(1) Compare outcomes of a post-acute residential rehabilitation program with a matched sample receiving limited services in their homes or on an outpatient basis; (2) Individuals who received intensive rehabilitation services in community-based residential program exhibited considerable improvement in functional abilities (cognitive skills, motor skills). Treatment group showed greater improvement in community integration.
Sohlberg et al., 2000	Chronic moderate-severe TBI, ABI ($n = 14$); prospective; quantitative: repeated measures	(1) Compare attention processing training with an educational and support method; (2) 10 weeks of brain injury education seemed most effective in improving self-reports of psychosocial function. Attention process training influenced self-reports of cognitive function, had stronger influence on performance of executive attention tasks. Vigilance, orienting networks showed little specific improvement.
Cicerone et al., 2000	TBI/Stroke; review	(1) Establish evidence-based recommendations for clinical practice of cognitive rehabilitation from methodical review of scientific literature concerning effectiveness of cognitive rehabilitation; (2) Attention deficits: limited evidence exists for generalization of benefits attributable to attention remediation, tendency to observe gains on tasks most closely related to training tasks; Multi-modal interventions: can significantly improve neuropsychological performance in many skill areas. Maintenance, generalization of benefits from cognitive rehabilitation greatest when treatment is provided for appropriately long periods of time, when efforts are made by clinician and patient to identify and apply interventions to personally relevant areas of functioning, when patients are able to assume responsibility for using compensatory strategies in everyday functioning.
De Weerdt et al., 2000	Acute stroke ($n = 56$); prospective; quantitative: observational	(1) Observe how stroke patients spend their time in a rehabilitation unit; (2) Patients most frequently involved in therapeutic activities, Belgium: 28% of day, Switzerland: 45%. Belgian patients: 27% of day in own room, Swiss: 49% of day. Swiss patients spent nearly 1.5 h per day more in therapy. Differences between two settings could only partially be explained by more favorable patient-staff ratios in Swiss setting.
Fasotti et al., 2000	Post-acute/chronic severe TBI ($n = 22$); prospective; quantitative: repeated measures	(1) Compare the effectiveness of Time Pressure Management (TPM) training with concentration training in which verbal instruction was the key element; (2) TPM produces greater gains than concentration training and appears to generalize to other measures of speed and memory function.
Zhu et al., 2001	Post-acute moderate-severe TBI ($n = 36$); prospective; quantitative: repeated measures	(1) Evaluate effects of different levels of intensive rehabilitation treatment on functional outcome; (2) Increasing amount of rehabilitation from conventional 2–4 h/day improved functional outcome as measured by GOS. More patients in intensive group returned to gainful work, either original or modified job. Improvement most significant in early post-injury period at 2–3 months.
Shiel et al., 2001	Moderate-severe TBI ($n = 56$); prospective; quantitative: repeated measures	(1) Investigate effect of increased intensity of rehabilitation on rate at which independence was regained and duration of hospital admission; (2) Increasing hours per week of therapy can accelerate rate of recovery of personal independence and result in being discharged from hospital sooner. No evidence of ceiling effect of therapeutic intensity beyond which no further response observed.
Park and Ingles, 2001	ABI; meta-analysis	(1) Examine the efficacy of attention rehabilitation; (2) Direct-retraining methods produced only small non-significant improvements in performance. Few studies that attempted to rehabilitate specific skills requiring attention showed statistically significant improvements after training and had considerably larger effect sizes. Results suggest learning that occurs as a function of training is specific, does not tend to generalize or transfer to tasks that differ considerably from those used in training.

(Continued)

Table 2 | Continued

Authors	Methods	(1) Main objectives and (2) Findings
Powell et al., 2002	Post-acute/chronic severe TBI ($n = 94$); prospective; quantitative: RCT	(1) Evaluation of multidisciplinary community based outreach rehabilitation; (2) Outreach participants significantly more likely to show gains on Barthel Index, BICRO-39 total score, self-organization, psychological well-being subscales. Strong trends for BICRO personal care and mobility, on FIM+FAM for personal care and cognitive functions.
Slade et al., 2002	Acute stroke/TBI ($n = 161$); prospective; quantitative: RCT	(1) Examined if increased intensity of therapy would decrease length of stay; (2) Accounting for impairment/disability mix, and consequent response of therapy, enhanced levels of physiotherapy and occupational therapy led to benefits for experimental group, resulting in decrease length of stay.
Cifu et al., 2003	Moderate-severe TBI ($n = 491$); prospective; quantitative: RCT	(1) Identify factors relating to intensity of rehabilitation services received and to ascertain relation between injury outcomes, demographics, types of therapy, and intensity of rehabilitation services provided; (2) Findings support assertions that increased therapy intensity, particularly physical and psychological therapies, enhances functional outcomes.
Rath et al., 2003	Chronic mild-severe TBI ($n = 60$); prospective; quantitative: repeated measures	(1) Compare efficacy of a group-treatment protocol using a remedial programme that aims to reduce difficulties in emotional self-regulation, and to facilitate steps used in problem solving with a conventional neuropsychological rehabilitation programme; (2) Participants in innovative group improved in problem solving as assessed using a variety of measures, including (i) executive function, (ii) problem-solving self-appraisal, (iii) self-appraised emotional self-regulation and clear thinking, (iv) objective observer ratings of role-played scenarios. Improvements were maintained at follow-up.
Boman et al., 2004	Mild-moderate TBI ($n = 10$); prospective; experimental: repeated measures	(1) Examine efficacy of cognitive rehabilitation in the patient's home or vocational environment; (2) Positive effect on some measures on impairment level, no differences on activity or participation levels at follow-up; indicates home-based cognitive training improves some attentional and memory functions and facilitates learning of strategies.
Cicerone et al., 2004	Post-acute/chronic moderate-severe TBI ($n = 56$); prospective; quantitative: repeated measures	(1) Evaluate effectiveness of an intensive cognitive rehabilitation program (ICRP) compared with standard neurorehabilitation (SRP); (2) ICRP participants over twice as likely to show clinical benefit on Community Integration Questionnaire. ICRP participants showed improvement in overall neuropsychological functioning; participants with clinically significant improvement on Community Integration Questionnaire showed greater improvement of neuropsychological functioning. Satisfaction with cognitive functioning made significant contribution to post-treatment community integration.
De Wit et al., 2005	Stroke ($n = 60$); prospective; quantitative: observational	(1) Identify differences in use of time by stroke patients in 4 rehabilitation centers in 4 countries; (2) Patients in Belgium and UK spent more time in passive behavior, in rooms, without any interaction compared with patients in Germany and Switzerland. Latter centers had more structured rehabilitation program. May have resulted in more therapy time, more challenging environment for patients, physically and mentally.
Turner-Stokes et al., 2005	Mild-severe ABI; Cochrane review	(1) Assess effects of multi-disciplinary rehabilitation in adults aged 16–65 years; (2) For patients with moderate- severe ABI already in therapy, there was strong evidence that more intensive programmes are associated with earlier functional gains, and "moderate evidence" that continued outpatient therapy could help to sustain gains made in early post-acute rehabilitation.
Cicerone et al., 2005	TBI, stroke; review	(1) Update previous evidence-based recommendations of the Brain Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine for cognitive rehabilitation; (2) Consensus that cognitive rehabilitation should focus on reducing disability, helping restore social role functioning, rather than exclusively on remediation of impairments. Most studies evaluated outcome of interventions at impairment level rather than effect on performance of activities or changes in social participation.

(Continued)

Table 2 | Continued

Authors	Methods	(1) Main objectives and (2) Findings
Zhu et al., 2007	Acute/post-acute moderate-severe TBI ($n = 68$); Prospective; RCT	(1) Evaluate the effects of an increase in the intensity of rehabilitation on functional outcome; (2) More patients in the high intensity group than in the control group who achieved a maximum FIM total score at the third month and a maximum Glasgow Outcome Scale score at the second and third months.
Kleim and Jones, 2008	Healthy adult/TBI; review	(1) Review 10 principles of experience-dependent neural plasticity and considerations in applying them to the damaged brain; (2) Optimism that the nature of brain plasticity can be capitalized upon to improve rehabilitation efforts and to optimize functional outcome.
Kennedy et al., 2008	TBI; Systematic review, meta-analysis	(1) Review studies that focused on executive functions of problem solving, planning, organizing and multitasking; (2) Compelling evidence from 10 intervention studies that using step-by-step meta-cognitive strategy instruction improves problem solving, etc. for personally relevant activities or problem situations; Changes more likely to be observed at level of activities and participation in daily living than on standardized tests (i.e., impairment outcomes).
Spikman et al., 2009	ABI ($n = 75$); prospective; quantitative: RCT, repeated measures	(1) Evaluate the effects of a treatment for dysexecutive problems on daily life functioning; (2) Experimental patients resumed previous roles significantly more than before treatment. From post-treatment to follow-up, only experimental group showed further improvement over time; DEX showed decrease of executive complaints similar for both groups. On DEX-therapist, significantly less executive problems after treatment for experimental group. Executive abilities observed by professionals improved more in experimental group.
Toglia et al., 2010	Chronic moderate TBI ($n = 4$); quantitative: single-subject design; repeated measures	(1) Refine, explore and provide preliminary testing of the multi-context approach in promoting strategy use across situations and increasing self-regulation, awareness and functional performance; (2) Participants demonstrated positive changes in self-regulatory skills and strategy use across tasks. Examination of individual participants revealed important, varying patterns of change in strategy use, learning transfer and self-awareness across intervention.
Cernich et al., 2010	Review; TBI	(1) Review of available evidence of cognition following TBI; (2) Recommendations: (i) Access to sub-acute rehabilitation that is holistic in nature and involves multi-disciplinary team to in work in an integrated fashion to support physical, cognitive and social skill retraining is vital to support positive outcome following TBI; (ii) Trials of medication to assist with attention, memory impairment appear well-supported by the available evidence; (iii) RCTs demonstrate utility of specific rehabilitation approached to attention retraining and retraining of executive function; (iv) Training in use of supportive devices to support individual's daily activities remains central to independent function.
Leon-Carrion et al., 2012	Acute severe TBI ($n = 19$); quantitative: observational	(1) Explore the course and timing of functional recovery in patients who have emerged from coma; (2) To achieve a good response and outcome nearing normalcy, a patient needs over 300 h of intensive rehabilitation.
Hayden et al., 2013	Acute-chronic mild-severe TBI ($n = 1274$); retrospective; quantitative	(1) Evaluate functional improvement after admission to post-acute rehabilitation; (2) Improved functioning after post-acute rehabilitation, regardless of severity of impairment or time since injury to admission to program. Rate of improvement greater for those admitted within 3 months of injury. Individuals with severe impairment demonstrated less improvement when admitted later in time after injury.

Acute, 0–3 months post-injury; post-acute, 3–12 months post-injury; chronic, greater than 12 months post-injury.

have also been demonstrated, as have increases in the amount of nerve growth factor, brain derived neurotropic factor, myelination, acetylcholinesterase activity, neurotransmitters, glial proliferation, blood vessels (number and size), and protein synthesis (Rosenzweig, 1966; West and Greenough, 1972; Bennett et al., 1974; Mohammed et al., 1990; Rosenzweig and Bennett, 1996; Kolb and Whishaw, 1998; Van Praag et al., 2000; Diamond, 2001; Churchill et al., 2002; Pietropaolo et al., 2004; Will et al., 2004; Bennett et al., 2006; Hoffman et al., 2008; Gabriel et al., 2009a,b; Lores-Arnaiz et al., 2010; Qiu et al., 2011, 2012; Williamson et al.,

Table 3 | Detailed summary of articles included in "Post-discharge experiences and EE" scoping review.

Authors	Methods	(1) Main objectives and (2) Findings
POST-DISCHARGE FACTORS THAT INFLUENCE STIMULATION		
Corrigan et al., 2004	Chronic mild-severe TBI ($n = 1802$); prospective; quantitative	(1) Provide population-based estimates of perceived needs following TBI and the prevalence of unmet needs; (2) Many reported still requiring help managing cognitive changes, emotional changes, and managing finances.
Staudenmayer et al., 2007	Post-acute severe TBI ($n = 211$); prospective; quantitative	(1) Determine whether there are specific types of functional deficits that disproportionately affect ethnic minorities after TBI; (2) Minorities demonstrated worse long-term functional outcome, less social and financial resources suggested as related/causal variables.
Shafi et al., 2007	Post-acute severe TBI ($n = 344$); prospective; quantitative	(1) Analyze whether racial or ethnic disparities exist in trauma care, specifically related to access to rehabilitation services and functional outcomes of patients with TBI; (2) Ethnic minorities less likely to be insured; more likely to have moderate-severe disability at follow-up. Data suggest insured patients less likely to be disabled, relationship strongest for private insurance.
Till et al., 2008	Post-acute moderate -severe TBI ($n = 33$); quantitative: observational cohort: 5, 12, 24 months post-injury	(1) Assess prospectively degree of post-acute long-term cognitive decline after TBI; (2) Amount of therapy received at 5 months post-injury significantly higher in group of non-decliners vs. decliners; individuals who were insured received more hours of therapy after discharge than those not insured.
Sander et al., 2009	Post-acute mild-severe TBI ($n = 151$); prospective; quantitative	(1) Determine contribution of race/ethnicity and income to community integration at approximately 6 months following TBI; (2) After controlling for age, education, injury severity, race/ethnicity, income made a significant contribution to variance in social integration, total score and scores on Belonging and Independent Participation scales of the Community Integral Measure. Lower income was associated with worse community integration.
Keightley et al., 2011	TBI, ABI + caregivers ($n = 17$); qualitative	(1) Explore barriers and enablers surrounding transition from health care to home community settings for Aboriginal clients recovering from ABI in northwestern Ontario; (2) Lack of awareness, education and resources acknowledged as key challenges to successful transitioning by clients and healthcare providers.
Sander et al., 2011	Post-acute mild-severe TBI ($n = 167$); prospective; mixed methods	(1) Investigate meaning of community integration in an ethnically diverse sample; (2) Financial issues, such as home ownership and insufficient funds, were perceived as contributing to decreased participation in the community.
Turner et al., 2009b	Post-acute mild-severe TBI, ABI + caregivers ($n = 38$); qualitative; pre-discharge, 1, 3 months post-discharge	(1) Explore people's lived experiences of reengagement in meaningful occupations during hospital-to-home transition phase after ABI; (2) Not being able to participate in desired occupations was source of stress and frustration. Many family caregivers reported participation in meaningful occupations was fundamental element of recovery gains. Other key elements: establishing routines or schedules and occupying one's time. Participation in meaningful occupations perceived to enhance functional recovery during transition.
POST-DISCHARGE FACTORS THAT INFLUENCE ENGAGEMENT		
Freeman, 1997	Severe TBI; Concept paper	(1) Explore methods used to establish a rehabilitation program in the home, the initial moves, the family dynamics, the advantages, and some of the programs required for the restoration of function of sensory, cognitive and motor abilities; (2) Family environment provides wide variety of activities, which are inclusive of person, guarantees provision of stimulation over a wide spectrum of inputs and activities.
Rotondi et al., 2007	Chronic moderate-severe TBI + caregivers ($n = 185$); qualitative	(1) Determine expressed needs of persons with TBI and their primary family caregivers; (2) Inadequate preparation of primary support persons and persons who experienced TBI for personality and behavioral sequelae prior to discharge from the hospital appeared to be a common complaint.
McCormack and Liddiard, 2009	Chronic severe TBI ($n = 1$); case study	(1) Examines a model of community rehabilitation; (2) Supportive and effective familial care system and specialist community interdisciplinary rehabilitation was effective in facilitating recovery.

(Continued)

Table 3 | Continued

Authors	Methods	(1) Main objectives and (2) Findings
Keightley et al., 2011	TBI, ABI + caregivers ($n = 17$); qualitative	(1) Explore barriers and enablers surrounding transition from health care to home community settings for Aboriginal clients recovering from ABI in north western Ontario; (2) Lack of awareness, education and resources acknowledged as key challenges to successful transitioning by clients and healthcare providers.
Sander et al., 2011	Post-acute mild-severe TBI ($n = 167$); prospective; mixed methods	(1) Investigate meaning of community integration in an ethnically diverse sample; (2) Feeling integrated into the community relates to aspects of the environment as much as to involvement in specific activities.
Turner et al., 2011b	Post-acute mild-severe TBI, ABI + caregivers ($n = 38$); qualitative; pre-discharge, 1, 3 months post-discharge	(1) Explore service and support needs of individuals with ABI and family caregivers during transition phase from hospital to home; (2) Individuals with ABI experience a range of service and support needs during the early transition phase, many of which are currently unmet. Findings also indicated that support for family caregivers and access to early community rehabilitation were the two areas in which participants most commonly reported experiencing unmet needs.
Rusconi and Turner-Stokes, 2003	Post-acute/chronic TBI, ABI, SCI ($n = 53$); quantitative: cross-sectional cohort survey	(1) Evaluate aftercare of patients discharged from specialist rehabilitation unit with respect to use of equipment and follow-up by therapy and care services and to assess change in dependency and care needs; (2) Many patients observed they were ill-prepared for sudden change from an intensive therapy programme on unit to a much less frequent and more self-reliant programme in community.
Rittman et al., 2004	Post-acute stroke + caregivers ($n = 51$); qualitative	(1) Evaluate the transition from hospital to home during the first month after discharge following acute stroke; (2) When routines are not re-established, survivors and caregivers experience more chaos, disruption during the transition. When talking about ways days are spent, most survivors describe problems with boredom and not having meaningful activities in their lives.
Turner et al., 2007	Chronic TBI, ABI + caregivers ($n = 24$); qualitative	(1) Explore transition experiences from hospital to home of a purposive sample of individuals with ABI; (2) Many participants found it difficult to locate and access suitable post-discharge therapy services. Friendship and social networks played important role during transition process. Post-discharge boredom, particularly during first 1–2 months at home, commonly expressed.
Turner et al., 2009b	Post-acute mild-severe TBI, ABI + caregivers ($n = 38$); qualitative; pre-discharge, 1, 3 months post-discharge	(1) Explore people's lived experiences of reengagement in meaningful occupations during hospital-to-home transition phase after ABI; (2) Not being able to participate in desired occupations was source of stress, frustration for many participants. Many family caregivers reported participation in meaningful occupations was fundamental element of recovery gains. Other key elements of transition success included establishing routines or schedules and occupying one's time. Results demonstrated participation in meaningful occupations was perceived to enhance functional recovery during transition; underscores importance of encouraging and facilitating participation in meaningful occupations.
Hoogerdijk et al., 2011	Chronic mild-severe TBI ($n = 4$); qualitative	(1) Better understand how individuals with TBI make sense of adaptation process and their performance of occupations within this process; (2) Results indicate adaptation process following TBI is a necessary struggle to gain new identity; facilitated by engagement in familiar occupations in familiar environments; a protracted learning process that continues long after rehabilitation ends; individual, situated.
Turner et al., 2011a	Post-acute mild-severe TBI, ABI + caregivers ($n = 38$); qualitative; pre-discharge, 1, 3 months post-discharge	(1) Explore perspectives of individuals with ABI and their family caregivers concerning recovery and adjustment during the early transition phase from hospital to home; (2) Findings highlight that while returning home was typically perceived to facilitate ongoing recovery, process of adjusting emotionally to life at home posed significant challenge for many participants during transition phase.

(Continued)

Table 3 | Continued

Authors	Methods	(1) Main objectives and (2) Findings
Nalder et al., 2012a	Post-acute moderate -severe TBI + caregivers ($n = 210$); prospective; quantitative: repeated measures: discharge, 1, 3, 6 months post-discharge	(1) Identify factors associated with perceived success of transition from hospital to home after TBI; (2) Greater perceived success of transition associated with higher levels of health-related quality of life, level of community integration, more severe injury. Sentinel events (e.g., returning to work, independent community access, changing living situation) associated with greater perceived success; financial strain, difficulty accessing therapy services associated with less success.
Nalder et al., 2012b	Post-acute moderate -severe TBI + caregivers ($n = 210$); prospective; quantitative: repeated measures: discharge, 1, 3, 6 months post-discharge	(1) Describe timing and factors associated with occurrence of sentinel events (financial strain, difficulty accessing therapy, return to work, accommodation change and independent transport use) during transition to community for individuals with TBI; (2) General positive sentinel events (e.g., regaining independence, returning to work) more likely experienced by individuals with higher levels of global functioning and psychosocial integration. Individuals with lower levels of functioning at greater risk of experiencing more negative sentinel events (e.g. financial strain). Individuals with more severe injury and poorer adjustment more likely to report difficulty accessing therapy.

Acute, 0–3 months post-injury; post-acute, 3–12 months post-injury; chronic, greater than 12 months post-injury.

2012; Fares et al., 2013; Vazquez-Sanroman et al., 2013; Yang et al., 2013).

In examining properties of EE that produce beneficial effects, factors such as *intensity* and *duration* emerge as critical for reaping the most benefits. Bennett et al. (2006) examined the effects of long-term continuous EE on memory performance in aged mice. Mice received a 10-week treatment of either 5 min of daily handling housed in impoverished environments (i.e., clear plastic shoe boxes), 3 h of daily exposure to a basic EE (i.e., small bin with fresh bedding, a running wheel, a plastic rodent dwelling, a plastic tube for climbing, a few toys), or continuous complex EE (i.e., larger bin to allow for more mice to be housed together, and for larger and more complex objects). Continuously enriched older mice performed significantly better than other groups of aged mice in spatial memory tasks, and were indistinguishable from younger control mice in their performance.

Amaral et al. (2008) examined durations of EE in mice and influences on behavioral changes (open field habituation and locomotion). They compared mice exposed to 1, 4, and 8 weeks of EE. While mice exposed to 4 and 8 weeks showed behavioral effects, the 1-week group did not. Furthermore, mice in the 4-week exposure group demonstrated effects lasting 2 months post-EE, but only mice in the 8-week EE group demonstrated effects lasting up to 6 months. The authors concluded that *(1) a minimum EE period is necessary to induce beneficial behavioral effects, (2) the effect of EE can persist at least partially for many months after its cessation, and (3) the degree of persistence is greater in animals exposed to longer durations of EE*. Relevant to the discharge environment of humans and the importance of ongoing therapy/stimulation, these findings showed that the benefits of EE are lost when animals are removed from enriched environments.

Environmental enrichment in healthy humans

Scarmeas and Stern (2003) undertook a review of the relationship between lifestyle and cognitive reserve, which they defined as the degree to which the brain can create and use networks or cognitive paradigms that are more efficient or flexible, and thus less susceptible to disruption. They asked whether exercising the brain had the same healthy effects as exercising the body. They found that greater participation in intellectual and social leisure activities was associated with less cognitive decline in healthy older adults and a lower incidence of dementia. These important "use it or lose it" findings support the need for EE in the sub-acute and chronic stages of TBI to avert decline. The authors proposed that leisure activities and an active lifestyle might buffer against cognitive decline by: (1) increasing synaptic density, which results in more efficient cognitive functioning of unaffected neurons; (2) more efficient use of the same brain networks; and (3) more efficient use of alternative brain networks. They also found that although it is a very active area of research, our understanding of the specific active ingredients that buffer against cognitive decline has not been fully elucidated.

In addition to studies examining how mentally active lifestyles are associated with cognitive benefits (Gribbin et al., 1980; Pushkar et al., 1997; Wang et al., 2002; Wilson et al., 2002, 2003; Crowe et al., 2003; Verghese et al., 2003; Newson and Kemps, 2005; Fujiwara et al., 2009), studies have also illustrated the benefits of maintaining physically active (Clarkson-Smith and Hartley, 1989; Schuit et al., 2001; Pignatti et al., 2002; Voss et al., 2011; Xu et al., 2011) and socially active lifestyles (Bassuk et al., 1999; Fratiglioni et al., 2000; Mahoney et al., 2000; Seeman et al., 2001). However, they are correlational in design and leave open the possibility that higher functioning people seek out the continuous exposure.

A number of further studies have shown the benefits of EE for healthy older adults (Huppert, 1991; Christensen and Mackinnon, 1993; Davidson and Bar-Yam, 2006; Sampson et al., 2009; Marioni et al., 2012a,b; Paillard-Borg et al., 2012). Winocur and Moscovitch (1990) compared cognitive functioning in community-dwelling and institutionalized older adults. After controlling for variables such as IQ, age, and health, they

found that community-dwelling older adults had higher levels of cognitive functioning. They also identified a subgroup of high-functioning institutionalized older adults who performed similarly to the community-dwelling group. For this subgroup, they postulated that cognitive functioning may have been influenced by adjustment to institutional life, such that more social activity was correlated with better cognitive functioning, as was found in a prior study (Winocur et al., 1987). Winocur and Moscovitch suggested that lower cognitive functioning observed in the institutionalized group might be a result of an understimulating environment. This interpretation is also consistent with the position of Schooler and Mulatu (2001), who suggested that even if people have higher levels of education, it is the *continued practice* in complex activities that maintains their cognitive abilities—speaking directly to the thesis of this paper.

A number of studies have examined the benefits of continuous exposure (Blackerby, 1990; Spivack et al., 1992; Willer et al., 1999; De Weerdt et al., 2000; Shiel et al., 2001; Zhu et al., 2001; Cifu et al., 2003; De Wit et al., 2005), and interventions that incorporate many elements of EE, such as cognitive, social, and physical stimulation (Hayslip et al., 1995; Neely and Backman, 1995; Fasotti et al., 2000; Powell et al., 2002; Vance and Johns, 2002; Gunther et al., 2003; Rath et al., 2003; Noice and Noice, 2004; Van De Winckel et al., 2004; Green et al., 2006; Stine-Morrow et al., 2007; Spikman et al., 2009). These types of interventions can be contrasted with interventions involving manipulations over a discrete period of time that are designed to enhance a specific cognitive domain or skill. The former have broadly led to more generalizable gains, both cognitively and physically.

Brain-injured animals and environmental enrichment

Brain-injured animals show clear-cut benefits from exposure to EE. Studies comparing recovery in brain-injured animals reared in EEs to those reared in standard environments have demonstrated increased neurogenesis, upregulation of neurotrophic factors, increased neuronal survival, increased afferent innervation, as well as reductions in spontaneous apoptosis and infarct size (Van Praag et al., 2000; Dobrossy and Dunnett, 2001, 2004; Passineau et al., 2001; Gobbo and O'Mara, 2004; Will et al., 2004; Pereira et al., 2007; Hoffman et al., 2008; Sozda et al., 2010; Sun et al., 2010; Monaco et al., 2013; Shin et al., 2013). Superior performance on tasks of learning and memory, and spatial reference has also been found (Hamm et al., 1996; Johansson and Ohlsson, 1996; Passineau et al., 2001; Gobbo and O'Mara, 2004; Will et al., 2004; Lippert-Gruener et al., 2007; Pereira et al., 2007; Hoffman et al., 2008; Sozda et al., 2010; Monaco et al., 2013). Hamm et al. (1996) compared cognitive functioning in brain-injured and sham-brain-injured rats housed in EEs to those housed in standard environments. Rats housed in EEs were in social groups and had access to a variety of foods, novel toys, scented objects, and a running wheel. At 15 days post-injury, brain-injured rats exposed to EE performed significantly better than brain-injured rats in standard environments. Interestingly, they also found that brain-injured rats recovering in EE performed just as well as non-brain injured animals.

In an older but seminal study by Johansson and Ohlsson (1996), brain-injured rats recovering in comprehensive EE (i.e., cognitive, social, and physical enrichment) were compared to those recovering in either enriched social environments or enriched exercise environments. Rats in the EE group were placed in one cage with several other rats, and novel toys and objects that promoted exercise, whereas rats in the social-interaction group were caged with other rats without objects or toys, and rats in the exercise group were individually caged with access to a running wheel. The social-interaction group improved more than the exercise group; however, the EE group improved more than either group. More recently, Hoffman et al. (2008) demonstrated the importance of timing and duration of EE, comparing brain-injured rats exposed to continuous EE to those in early and temporary EE (immediately post-injury lasting 1 week), late EE (commencing 1 week post-injury) and no EE. The continuous EE group not only had significantly less hippocampal cell loss, but also performed better on motor and cognitive tests. Interestingly, they found an advantage of continuous and *early* EE for motor tasks, but an advantage of continuous and *delayed* EE for cognitive tasks. The benefits of increased EE-exposure in brain-injured rats have since been replicated (De Witt et al., 2011; Matter et al., 2010), and, moreover, shown to last for up to 6 months (Cheng et al., 2012).

These studies provide evidence that EE help animals to recover functions to levels that make them indistinguishable from healthy controls, and that *continual* EE is necessary to *maintain* both neural and cognitive improvements. The benefits of EE are substantial, but not permanent, thus highlighting the importance of ongoing stimulation. These findings are particularly relevant to the post-discharge environment, and the factors may contribute to decline.

Brain-injured humans and environmental enrichment

EE interventions for brain-injured humans can be grouped into two broad types: those that provide increased hours and duration of therapy (without prescription of specific content of therapies) and those that address discrete impairments and focus on improvement of a specific skill. Note that in clinical practice, the latter might be referred to as "training" rather than EE. However, we include them here as they entail increased cognitive stimulation.

While EE intervention designs have not been as comprehensive in human TBI studies, the effects of some of the classical properties of EE, such as novelty, intensity, and duration, have been examined. However, much like in healthy individuals, interventions for TBI survivors aimed at training specific skills have often resulted in poor generalization to everyday performance (Ruff et al., 1991; Cicerone et al., 2000, 2005; Sohlberg et al., 2000; Park and Ingles, 2001; Boman et al., 2004; Kennedy et al., 2008). In contrast to skills training, Cicerone et al. (2000) have suggested that cognitive rehabilitation should not focus exclusively on remediation of impairments, but should reduce disability and help restore social role functioning. In an earlier framework, Toglia (1991) proposed a "multi-context" treatment approach to enhance generalizability that contained hallmarks of what later became EE: namely, varied stimulation and environments that are meaningful to the person that thereby enhance engagement. Interventions that have incorporated such components

have demonstrated better generalizability, as well as improvements in community integration (Fasotti et al., 2000; Powell et al., 2002; Vance and Johns, 2002; Rath et al., 2003; Van De Winckel et al., 2004; Toglia et al., 2010; Leon-Carrion et al., 2012).

The second broad category of interventions that are more intensive have also resulted in significant functional gains (Willer et al., 1999; Cicerone et al., 2004). Cicerone et al. (2004) compared the effectiveness of an intensive cognitive rehabilitation program to standard neurorehabilitation for persons with TBI. Participants in the intensive program demonstrated greater improvement in cognitive function (composite score based on attention, speed of processing, memory and executive function test scores) as well as greater improvement in community integration. Increasing hours of therapy has also led to greater functional and cognitive gains and faster recoveries (Blackerby, 1990; Spivack et al., 1992; De Weerdt et al., 2000; Shiel et al., 2001; Zhu et al., 2001; Slade et al., 2002; Cifu et al., 2003; De Wit et al., 2005; Zhu et al., 2007). Turner-Stokes et al.'s (2005) review of multi-disciplinary rehabilitation for brain injury recommended that "intensive intervention appears to lead to earlier gains." Therefore, they concluded that "Patients discharged from in-patient rehabilitation should have access to out-patient or community-based services appropriate to their needs." Cernich et al. (2010) provided a similar recommendation in their review of cognitive rehabilitation following TBI. Recently, Hayden et al. (2013) provided support for this recommendation, demonstrating functional gains for TBI survivors receiving rehabilitation services in the post-acute phase after brain injury.

ABSENCE OR REDUCTION OF ENVIRONMENTAL ENRICHMENT

If exposure to EE is beneficial at both behavioral and neural levels, it logically follows that the absence or reduction of EE would lead to poorer behavioral and neural health. Experience-dependent plasticity refers to changes in the brain that result from behavioral experiences. While stimulation can enhance or maintain neural pathways, the absence of stimulation can depress or weaken them with associated loss of a function that was previously acquired or mastered (Rubinov et al., 2009; Warraich and Kleim, 2010). Overall, there appears to be a growing consensus that maintaining and increasing neuroplasticity of the brain depends on continual and intensive cognitive, physical, and social stimulation (Kleim and Jones, 2008). TBI survivors transitioning from a rehabilitation setting to a home setting are therefore vulnerable to reversal of those gains made in the early and intensive therapeutic setting.

This assertion is supported by the flipside of EE experiments: animals that are exposed to less stimulating or impoverished environments do not fare as well. As described above, mice with less EE exposure have lower performances on spatial memory tasks, as compared to continuously enriched mice (Bennett et al., 2006), and rats that received less EE exposure maintain benefits for a shorter period of time (Amaral et al., 2008). Similarly, brain injured rats recovering in impoverished environments show poorer recovery of cognitive and motor functioning (Hamm et al., 1996; Hoffman et al., 2008; Matter et al., 2010; De Witt et al., 2011) and do not maintain benefits gained from short-term EE (Matter et al., 2010; De Witt et al., 2011; Cheng et al., 2012).

Furthermore, there is evidence that effects of environmental conditions are reversible (Bernstein, 1972; Winocur, 1998). Winocur (1998) demonstrated that when he transferred rats from impoverished to enriched environments, they improved significantly, whereas rats transferred from enriched and standard environments to impoverished ones declined. Similarly, more sedentary lifestyles have been linked to disease and disability, and overall poorer health (Huppert, 1991; Pushkar et al., 1997; Mackinnor et al., 2003; Salthouse, 2006; Shors et al., 2012).

ENVIRONMENTAL ENRICHMENT, POST-ACUTE DECLINE AND SUB-ACUTE ATROPHY

As therapies diminish in frequency over time (e.g., when patients move from in-patient neurorehabilitation to the home or a chronic-care facility), the amount of EE may also lessen. In the context of chronic TBI, Turner and Green (2008) examined the principles of negative neuroplasticity (maladaptive morphological changes to the brain in response to environmental factors), as described by Mahncke et al. (2006a,b), in the context of normal aging. These are: (1) reduced schedules of activity, (2) noisy processing in peripheral and central sensory systems, (3) alterations in neuromodulary control, and (4) negative learning. They suggest that a similar downward spiral of negative neuroplastic change may undermine long-term outcome in TBI due to similar environmental changes (as well as physiological changes) that result in withdrawal from communities and social networks, resulting in reduced stimulation. Such changes are withdrawal from the workforce (or school), physical losses that preclude travel, and perceptual and cognitive decrements that compromise communication.

As previously noted, in the case where neural pathways are under-stimulated, it is possible to lose the function that was acquired or mastered (Rubinov et al., 2009; Warraich and Kleim, 2010). Findings of increased neural representation after training (Cirillo et al., 2011; Cardinali et al., 2012) and different brain activation when comparing exposure vs. deprivation of stimulation (Klinge et al., 2012) provide evidence for experience-dependent neuroplasticity. This raises the question whether under-stimulation of neural pathways, due to disuse, may be responsible for post-acute neural degeneration seen in TBI survivors. If so, EE exposure may play a role in minimizing, or averting, this problem.

With respect to neural degeneration, mechanisms of apoptosis have been modeled in animals to understand the cascade of events that takes place after TBI (Raghupathi et al., 2000; Keane et al., 2001; Raghupathi, 2004). Coulson et al. (2004) provided support for their hypothesis that synaptic input may be the key to regulating neuronal survival and death pathways following neurotrauma. Synaptic activity regulates expression levels of neurotrophins and facilitates growth factor signaling. There is evidence that EE exposure enhances nerve growth factor and brain-derived neurotropic factor in animals (Clarkson-Smith and Hartley, 1989; Blackerby, 1990; Bassuk et al., 1999; De Weerdt et al., 2000; Mahoney et al., 2000; Wang et al., 2002; Wilson et al., 2002; Cifu et al., 2003; Johansson, 2003; Rath et al., 2003; Spikman et al., 2009). As well, animal studies have demonstrated that EE can enhance neurogenesis and attenuate apoptosis in the injured

brain (Van Praag et al., 2000; Dobrossy and Dunnett, 2001, 2004; Passineau et al., 2001; Gobbo and O'Mara, 2004; Will et al., 2004; Pereira et al., 2007; Hoffman et al., 2008). Lastly, neurons deprived of synaptic input can be rescued from death by an increased supply of growth factors (Coulson et al., 2004). Taken together, these findings offer the possibility that EE can help to prevent neuronal death.

The relation between changes in brain structure and neuropsychological performance has also been recently explored (Farbota et al., 2012), providing further evidence that as we see declines at a neural levels, we also see parallel declines in cognitive functioning. Recent work from our laboratory has demonstrated that in TBI survivors, more engagement in EE, defined as participation in activities involving cognitive, physical, and social demands, is correlated with less hippocampal volume loss in the post-acute stages (Miller and Green, in press). While these findings are correlational, they provide preliminary evidence of the positive impact that an enriched environment can have in TBI survivors.

The research reviewed within this section of the scoping review supports that EE improves outcomes and that a dearth of EE results in poorer outcomes. Studies demonstrate continued and repeated EE exposure (Blackerby, 1990; Spivack et al., 1992; De Weerdt et al., 2000; Schooler and Mulatu, 2001; Shiel et al., 2001; Zhu et al., 2001, 2007; Cifu et al., 2003; De Wit et al., 2005; Amaral et al., 2008), which provides intensive cognitive, social, and physical stimulation is necessary to induce beneficial effects (Willer et al., 1999; Cicerone et al., 2004; Bennett et al., 2006). Furthermore, if this exposure is reduced or removed, the benefits will not be maintained and may diminish (Bernstein, 1972; Winocur, 1998; Cheng et al., 2012). Synaptic input may be necessary to maintain and strengthen neural pathways and connections, particularly those at risk after brain injury (Coulson et al., 2004; Turner and Green, 2008). Moreover, this research supports our contention that for the subset of people with moderate-severe TBI that show post-acute cognitive decline and neural deterioration in the post-acute phase, there may be some environmental variables that contribute to their negative outcomes.

POST-DISCHARGE EXPERIENCES AND ENVIRONMENTAL ENRICHMENT

In the first section, we discussed findings revealing that the brain atrophies and that cognitive abilities decline in the post-acute stages of brain injury. In the second section, we discussed findings that demonstrate that EE can alter the brain (both healthy and damaged), and perhaps most importantly that it has the potential to minimize atrophy after brain injury. Moreover, a mechanism of disuse-mediated atrophy has been proposed (i.e., synaptic input and neuronal survival) (Coulson et al., 2004).

A critical question, then, is to what extent do post-discharge factors reflect EE? This is important because it is possible that the post-discharge environment may be un-enriched, and this would in theory exacerbate/lead to post-acute cognitive and neural declines. Thus, it is of value to explore the factors that influence the environments in which people with brain injuries return with respect to level of enrichment, so that factors can be adjusted to provide *optimal levels of EE*. In the current section, we will discuss how post-discharge variables are conceptually related to EE and we will also discuss findings that show how these examples of EE (or lack thereof) correspond to human TBI outcomes.

WHAT IS ENVIRONMENTAL ENRICHMENT IN THE POST-DISCHARGE ENVIRONMENT?

Continued participation in environments that are challenging, yet at levels that allow people to participate and remain motivated to do so, is the crux of EE. In the section "Environmental Enrichment in Healthy Humans" we summarized findings demonstrating that people who (1) attend more social events, (2) are more physically active, and (3) engage in activities with continuous novelty (e.g., learning a new language, playing bridge) are mentally healthier. While demographic variables (i.e., age, premorbid intelligence, level of education) influence outcome after brain injury (Ruff et al., 1991; Green et al., 2008), environmental variables (e.g., access to insurance coverage) also play a vital role in recovery, as will be discussed. We contend that these variables map onto EE in that they provide cognitive, social, and physical stimulation through access to therapy, community resources, fostering return to meaningful occupations, and encouraging engagement in their environments.

POST-DISCHARGE ENVIRONMENTAL FACTORS THAT INFLUENCE MENTAL AND PHYSICAL STIMULATION

A number of factors influence the degree of cognitive, social, and physical stimulation TBI survivors experience either directly (e.g., presence of community resources such as a support groups or fitness centers) or indirectly (e.g., by influencing access to therapy). These include insurance, financial support, social support, and community resources.

Insurance

As recommended by Turner-Stokes et al. (2005), after discharge from in-patient rehabilitation, TBI survivors should have access to out-patient or community-based services appropriate to their needs to facilitate the recovery process. Till et al. (2008) demonstrated that post-acute cognitive decline was negatively correlated with hours of therapy, which was associated with insurance coverage. It has been widely demonstrated that individuals who have insurance coverage receive more access to therapy after discharge than those who do not (Pressman, 2007; Heffernan et al., 2011; Chen et al., 2012; Lundqvist and Samuelsson, 2012). Those that are insured have better access to post-acute medical care, which includes physical, occupational, and cognitive therapies, as well as home health and nursing needs, modification of living environment, vocational training, and job retraining (Shafi et al., 2007). In line with these findings, Shafi et al. (2007) found that ethnic minorities were less likely to be insured and more likely to have moderate to severe disability at follow-up.

Financial support

Diminished financial resources may reduce opportunities for accessing EEs. For example, Sander et al. (2009) reported that after controlling for age, education, injury severity, and race/ethnicity, income made a significant contribution to the variance in social integration, and in a more recent study, Sander et al. (2011) reported that TBI survivors perceived financial issues (e.g., home ownership, insufficient funds), as contributing to

decreased participation in the community. Similar to Shafi et al. (2007) discussed previously, Staudenmayer et al. (2007) examined ethnic disparities in long-term functional outcomes after TBI. They concluded that less social and financial resources were likely implicated as an explanation. Additionally, in a study examining perceived needs after brain injury, many TBI survivors reported still requiring help managing money 1 year post-injury (Corrigan et al., 2004), which may compound the challenges of diminished finances after TBI. Increased financial burden can mean less access to expensive resources (e.g., therapy, participating in social activities, transportation).

Social support

Logically, a supportive social network influences participation in therapy (Sander et al., 2009; Turner et al., 2009b; Keightley et al., 2011), for example by providing transportation, accompaniment to therapies, supervision for recommended regimens for which safety is of concern (e.g., a gym program). Turner et al. (2007) found that those who had more supportive and closer networks at home had better transitions from the hospital setting to the home environment, as this was related to more access to social activities and transportation outside the home.

POST-DISCHARGE FACTORS THAT INFLUENCE ENGAGEMENT

Without private insurance, and with less social and financial resources, TBI survivors may be less able to engage in stimulating activities to facilitate recovery. However, as we will discuss, there are also factors that are purported to influence the level of engagement in the post-discharge environment, such as the amount of family support and patient education provided, as well as the structure and routine present in their home environment.

Family support

In Freeman's (1997) review of community-based rehabilitation for TBI survivors, he suggested that the level of care in the home setting, with a strong support network, can play a major role in successful rehabilitation. The family environment may provide a wide variety of activities that are inclusive, stimulating, and meaningful to the individual. Importantly, these are all properties found to be critical for experience-dependent plasticity (Kleim and Jones, 2008) and generalization of relearnt skills (Toglia, 1991). In a case study by McCormack and Liddiard (2009), a TBI survivor receiving community rehabilitation was followed for 3 years. The authors concluded that the supportive and effective care system in his family facilitated his recovery following severe TBI. His progress was attributed to active familial involvement that fostered goal setting and carry-over between sessions. Furthermore, learning took place in his home environment, increasing his ability to generalize skills. The authors concluded that these findings "add further weight . . . to the thesis that, with the right support, there is no place like home."

Post-discharge information and education

Several studies have indicated that the most often-reported barrier is adequate preparation prior to discharge (Rotondi et al., 2007; Sander et al., 2009; Keightley et al., 2011; Sander et al., 2011; Turner et al., 2011b). Many TBI survivors and their caregivers report that they were not given enough information regarding brain injuries (e.g., behavioral sequelae), how to access community resources (e.g., rehabilitation, emotional support, respite services), or how to access or implement home therapies (Rotondi et al., 2007; Sander et al., 2009, 2011; Keightley et al., 2011; Turner et al., 2011b). Corrigan et al. (2004) reported that TBI survivors who initially reported requiring help participating in recreation still did not have their perceived needs (viewed as a measure of quality of life) met 1 year post-injury. Likewise, Sander et al. (2011) reported that for TBI survivors, feeling more integrated into the community was related to greater participation in their environments. Without receiving appropriate assistance and information/educational resources to facilitate the post-discharge process, successful community integration will continue to be a challenge.

Routine and schedules

Many studies document that TBI survivors report feeling ill-prepared for the transition from hospital to home (Rusconi and Turner-Stokes, 2003). Several qualitative studies have explored the transition home, and the barriers or difficulties that TBI survivors experience (Rittman et al., 2004; Turner et al., 2007, 2009b, 2011a). Rittman et al. (2004) found that, post-discharge, commonly reported problems were increased idle time, boredom, and little-to-no engagement in meaningful activities. Survivors often reported, ". . . finding something new every day that they couldn't do . . ." What appears to influence the above is routine, or lack thereof. When routines were not re-established, survivors and caregivers experienced more chaos and disruption in the transition home. Turner et al. (2011a) examined perspectives concerning recovery and adjustment during the transition phase from hospital to home, and found that the process of adjusting emotionally to life at home posed significant challenges for many brain-injury survivors during this phase.

Turner et al.'s (2007) qualitative study of brain injury survivors' experiences with the transition from hospital to home made similar observations in terms of difficulty re-engaging in meaningful activities and occupations. However, those who were able to create a routine or structure once at home had better transitions. Essentially, this facilitated participation in their environments by providing organization in their daily schedules, which had been previously often provided for them in the rehabilitation setting.

Turner et al. (2009b) extended their work by examining re-engagement in meaningful occupations during the transition from hospital to home in brain-injury survivors. Many survivors reported that recovery sped up at home, and caregivers frequently attributed this to key elements such as creating routines and schedules, which enabled participation in meaningful activities. However, for those that did not have such experiences, not being able to participate in desired occupations led to stress and frustration. Turner et al. (2009b) found that "for some participants, the impact of this change in environment, coupled with the reality of not being able to engage in their desired occupations, led to a relatively unproductive lifestyle in which the main activity of their day involved little more than watching television or playing computer games." In Hoogerdijk et al.'s (2011) study of identity after TBI, the authors suggested that the adaptation process is a necessary struggle to gain new identity and it is facilitated by

engagement in familiar occupations in familiar environments. In line with this finding, Nalder et al. (2012a,b) reported that TBI survivors that were able to reengage in meaningful occupations had greater perceived success of the transition from hospital to home. Reengagement in meaningful occupations was often experienced by individuals with higher levels of global functioning and psychosocial integration.

SUMMARY OF POST-DISCHARGE EXPERIENCES AND ENVIRONMENTAL ENRICHMMENT

The research presented in this section of the scoping review provides evidence that there are variables in the post-discharge environment that influence the amount stimulation and other variables that influence the level of engagement in EE. Largely, evidence suggests that those with better access and resources that map onto EE (i.e., insurance coverage, financial and social support) and those that are in environments that encourage participation (i.e., strong familial support, access to educational resources, more structure) have better functional outcomes.

DISCUSSION

The most direct (preliminary) evidence of the benefits of EE in the post-acute stages of recovery comes from work by Miller and Green (in press), where more engagement in enriched environments, defined as participation in activities involving cognitive, physical, and social demands, was correlated with less hippocampal volume loss. Further direct evidence of comes from Till et al.'s (2008) finding of a relationship between hours of therapy at 5 months post-injury and degree of cognitive decline, which the authors speculated was ay be due in part to lack of access to complex and enriched environments.

As we have discussed, a large corpus of studies have demonstrated the benefits of EE in healthy and brain-injured animals. There is evidence of neuroplastic change after EE exposure, with beneficial changes to neuroanatomy and neurochemistry (Kramer et al., 2004). These studies further support Coulson et al.'s (2004) hypothesis that synaptic input is critical to offset atrophy, in that increased input regulates neuronal survival, and prevents or attenuates apoptosis. This is of particular relevance to the neural decline observed in the post-acute stages after TBI. Turner and Green's (2008) re-formulation of the work of Mahncke et al. (2006a,b) in healthy older adults—that negative neuroplasticity (i.e., reduced activity schedules) may undermine long-term outcome in TBI—is also in accord with the hypothesis that EE may indeed play an important role in recovery.

In humans, engaging in cognitively, socially, and physically stimulating activities is related to better cognitive functioning in younger and older adults. Studies have also demonstrated that therapies for TBI survivors delivering continuous and intensified interventions result in better recovery at all levels of analysis, as well as better functional gains. These therapies have critical elements of EE, such as novelty, intensity, and prolonged periods of engagement in meaningful activities.

According to Schooler's (1987) model of environmental complexity, when cognitive efforts are reinforced and rewarded, people are motivated to continue engaging in complex environments, which in turn enhances cognitive functioning. However, TBI survivors may show reduced participation in complex environments, due to cognitive impairment, lack of psychological support/facilitation, or lack of resources, and thereby fail to obtain the emotional and neuromodulatory rewards for engaging. These conditions create a downward spiral of negative neuroplasticity (Turner and Green, 2008). Animal literature examining EE has provided critical evidence for the benefits of maintaining high levels of enrichment and stimulation post-discharge (Hamm et al., 1996; Bennett et al., 2006; Amaral et al., 2008; Hoffman et al., 2008). Findings that support the "Use it or Lose it" theory also suggest that continued engagement in mentally effortful activities is necessary to maintain cognitive functioning (Huppert, 1991; Pushkar et al., 1997; Mackinnor et al., 2003; Salthouse, 2006; Shors et al., 2012), and that an individual's environment (e.g., stressful or under-stimulating) can influence level of activity (Winocur and Moscovitch, 1990; Winocur, 1998). While TBI survivors may benefit from capacity-enhancing and intensified therapies provided in hospital, animal models have demonstrated that the effects of this enrichment will only continue to persist with longer exposure periods (Amaral et al., 2008). Furthermore, transitioning from a more stimulating/complex environment to a lesser one may result in a loss of benefits (Winocur, 1998).

The aim of this paper was to examine the question whether EE in the sub-acute and chronic stages of injury can influence progressive neural and cognitive decline. The aim of the first section was to establish the role of EE in long-term outcomes, and in particular, in offsetting decline; the aim of the second section was to illustrate that in the post-acute stages of injury, a number of factors influence the degree of EE. We have argued that post-discharge environments map onto conventional variables considered to create EE. Access to rehabilitative, social, and community resources, as well as strong support networks, provides essential cognitive, social, and physical stimulation. Moreover, these factors have shown to influence outcomes.

While there is strong evidence to suggest that TBI may be a progressive injury, more research needs to be conducted to further elucidate the role of EE in influencing this decline. It is important to note that the exact active ingredients of current interventions that incorporate multi-context environments and higher intensity therapies are still unclear, and how they compare to therapies that incorporate all elements of EE is still unknown. Furthermore, studies are needed that examine whether there is a correlation between post-acute brain changes and declines in function, as well as the type of environments that TBI survivors return to post-discharge. Turner et al. (2008) recommended that research is needed to explore the transition home after brain injury in order to "(1) Develop a comprehensive theoretical framework of the transition phase; and (2) facilitate both the validation of current intervention strategies and the development of innovative/tailored intervention approaches."

As reported by caregivers and TBI survivors, creating a routine and structure around daily activities facilitated engagement. Furthermore, activities that are meaningful and at an appropriate level (e.g., tailored to the individuals specific impairments) to facilitate participation are critical. Researchers that have

examined the needs of TBI survivors and their caregivers in the post-acute phase have recommended increased education provided by health care institutions would be beneficial to ease the transition from hospital to home (Turner et al., 2007, 2009a, 2011b; Arango-Lasprilla et al., 2011). Based on the results of our scoping review, we suggest that more resources and guidelines on how to create structure and daily routines, as well as information regarding self-administered therapies and activities for the individual and their caregiver, would be beneficial. Further rehabilitation support during the post-acute stages of recovery, such as home assessments or on-going therapy maintenance, would also be optimal. Gan et al. (2010) examined the support needs after brain injury and made several recommendations for support services. They suggested that family systems-based services should be accessible, life-long, individualized and flexible, as well as efficient, and that support system-based services should include proper diagnoses, incorporate a multi-component approach, provide brain-injury-specific services that are responsive to needs with proactive follow-ups, and importantly, provide continuous education. The benefits of social peer-mentoring programs as an intervention to enhance improvements in social integration for TBI survivors has also shown promise in recent studies and is currently being further investigated (Struchen et al., 2011; Hanks et al., 2012).

TBI survivors often fail to return to pre-injury levels of cognitive function, as well as employment and income, and these factors have been shown to be related with life satisfaction, perceived quality of life, depression and social isolation (Christensen et al., 2008; Eriksson et al., 2009; Hawthorne et al., 2009; Resch et al., 2009; Shigaki et al., 2009; Strandberg, 2009; Tsaousides et al., 2009). Assuming that post-acute atrophy contributes to the failure to return to pre-injury levels of cognitive function and thus successful community integration, then the clinical consequences are notable.

While the elements that comprise EE may be different from one person to another, it is evident that engagement in such environments is beneficial at both the cognitive and neural level, and thus it is plausible that EE can offset post-acute deterioration. Providing information and support to ease the transition home, information about the benefits of an enriched environment and guidelines on how to successfully participate in enriched settings, may be key elements in improving recovery. Most importantly, it may be a critical factor to facilitate successful community integration.

REFERENCES

Amaral, O. B., Vargas, R. S., Hansel, G., Izquierdo, I., and Souza, D. O. (2008). Duration of environmental enrichment influences the magnitude and persistence of its behavioral effects on mice. *Physiol. Behav.* 93, 388–394.

Arango-Lasprilla, J. C., Nicholls, E., Villasenor Cabrera, T., Drew, A., Jimenez-Maldonado, M., and Martinez-Cortes, M. L. (2011). Health-related quality of life in caregivers of individuals with traumatic brain injury from Guadalajara, Mexico. *J. Rehabil. Med.* 43, 983–986.

Arksey, H., and O'Malley, L. (2005). Scoping studies: towards a methodological framework. *Int. J. Soc. Res. Methodol.* 8, 19–32.

Basso, A. (1989). "Spontaneous recovery and language rehabilitation," in *Cognitive Approaches in Neuropsychological Rehabilitation,* eds X. Seron and G. Deloche (Hillsdale, NJ: Lawrence Erlbaum), 17–37.

Bassuk, S., Glass, T., and Berkman, L. (1999). Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Ann. Intern. Med.* 131, 165–173.

Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., et al. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *Neuroimage* 42, 503–514.

Bennett, E. L., Rosenzweig, M. R., Diamond, M. C., Morimoto, H., and Hebert, M. (1974). Effects of successive environments on brain measures. *Physiol. Behav.* 12, 621–631.

Bennett, J., McRae, P., Levy, L., and Frick, K. (2006). Long-term continuous, but not daily, environmental enrichment reduces spatial memory decline in aged male mice. *Neurobiol. Learn. Mem.* 85, 139–152.

Bernstein, L. (1972). The reversibility of learning deficits in early environmentally restricted rats as a function of amount of experience in later life. *J. Psychosom. Res.* 16, 71–73.

Bigler, E. D., Blatter, D. D., Anderson, C. V., Johnson, S. C., Gale, S. D., Hopkins, R. O., et al. (1997). Hippocampal volume in normal aging and traumatic brain injury. *AJNR Am. J. Neuroradiol.* 18, 11–23.

Blackerby, W. F. (1990). Intensity of rehabilitation and length of stay. *Brain Inj.* 4, 167–173.

Blatter, D. D., Bigler, E. D., Gale, S. D., Johnson, S. C., Anderson, C. V., Burnett, B. M., et al. (1997). MR-based brain and cerebrospinal fluid measurement after traumatic brain injury: correlation with neuropsychological outcome. *AJNR Am. J. Neuroradiol.* 18, 1–10.

Boman, I. L., Lindstedt, M., Hemmingsson, H., and Bartfai, A. (2004). Cognitive training in home environment. *Brain Inj.* 18, 985–995.

Bruns, J. Jr., and Hauser, W. A. (2003). The epidemiology of traumatic brain injury: a review. *Epilepsia* 44(Suppl. 10), 2–10.

Cardinali, L., Jacobs, S., Brozzoli, C., Frassinetti, F., Roy, A. C., and Farne, A. (2012). Grab an object with a tool and change your body: tool-use-dependent changes of body representation for action. *Exp. Brain Res.* 218, 259–271.

Cassidy, J. D., Carroll, L. J., Peloso, P. M., Borg, J., Von Holst, H., Holm, L., et al. (2004). Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO collaborating centre task force on mild traumatic brain injury. *J. Rehabil. Med.* 43(Suppl), 28–60.

Cernich, A. N., Kurtz, S. M., Mordecai, K. L., and Ryan, P. B. (2010). Cognitive rehabilitation in traumatic brain injury. *Curr. Treat. Options Neurol.* 12, 412–423.

Chen, A. Y., Zagorski, B., Parsons, D., Vander Laan, R., Chan, V., and Colantonio, A. (2012). Factors associated with discharge destination from acute care after acquired brain injury in Ontario, Canada. *BMC Neurol.* 12:16. doi: 10.1186/1471-2377-12-16

Cheng, J. P., Shaw, K. E., Monaco, C. M., Hoffman, A. N., Sozda, C. N., Olsen, A. S., et al. (2012). A relatively brief exposure to environmental enrichment after experimental traumatic brain injury confers long-term cognitive benefits. *J. Neurotrauma* 29, 2684–2688.

Christensen, B. K., Colella, B., Inness, E., Hebert, D., Monette, G., Bayley, M., et al. (2008). Recovery of cognitive function after traumatic brain injury: a multilevel modeling analysis of Canadian outcomes. *Arch. Phys. Med. Rehabil.* 89, S3–S15.

Christensen, H., and Mackinnon, A. (1993). The association between mental, social and physical activity and cognitive performance in young and old subjects. *Age Ageing* 22, 175–183.

Christodoulou, C., Deluca, J., Ricker, J. H., Madigan, N. K., Bly, B. M., Lange, G., et al. (2001). Functional magnetic resonance imaging of working memory impairment after traumatic brain injury. *J. Neurol. Neurosurg. Psychiatry* 71, 161–168.

Churchill, J. D., Galvez, R., Colcombe, S., Swain, R. A., Kramer, A. F., and Greenough, W. T. (2002). Exercise, experience and the aging brain. *Neurobiol. Aging* 23, 941–955.

Cicerone, K., Mott, T., Azulay, J., and Friel, J. (2004). Community integration and satisfaction with functioning after intensive cognitive rehabilitation for traumatic brain injury. *Arch. Phys. Med. Rehabil.* 85, 943–950.

Cicerone, K. D., Dahlberg, C., Kalmar, K., Langenbahn, D. M., Malec, J. F., Bergquist, T. F., et al. (2000).

Evidence-based cognitive rehabilitation: recommendations for clinical practice. *Arch. Phys. Med. Rehabil.* 81, 1596–1615.

Cicerone, K. D., Dahlberg, C., Malec, J. F., Langenbahn, D. M., Felicetti, T., Kneipp, S., et al. (2005). Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Arch. Phys. Med. Rehabil.* 86, 1681–19692.

Cifu, D. X., Kreutzer, J. S., Kolakowsky-Hayner, S. A., Marwitz, J. H., and Englander, J. (2003). The relationship between therapy intensity and rehabilitative outcomes after traumatic brain injury: a multicenter analysis. *Arch. Phys. Med. Rehabil.* 84, 1441–1448.

C.I.H.I. (2006). Head injuries in Canada: a decade of change (1994-1995 to 2003-2004). *National Trauma Regist. Anal. Brief*. Available online at: http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=bl_ntr_aug2006_e. [Accessed February 10, 2010].

Cirillo, J., Todd, G., and Semmler, J. G. (2011). Corticomotor excitability and plasticity following complex visuomotor training in young and old adults. *Eur. J. Neurosci.* 34, 1847–1856.

Clarkson-Smith, L., and Hartley, A. (1989). Relationships between physical exercise and cognitive abilities in older adults. *Psychol. Aging* 2, 183–189.

Corrigan, J. D., Whiteneck, G., and Mellick, D. (2004). Perceived needs following traumatic brain injury. *J. Head Trauma Rehabil.* 19, 205–216.

Coulson, E. J., Reid, K., Shipham, K. M., Morley, S., Kilpatrick, T. J., and Bartlett, P. F. (2004). The role of neurotransmission and the Chopper domain in p75 neurotrophin receptor death signaling. *Prog. Brain Res.* 146, 41–62.

Crowe, M., Andel, R., Pedersen, N., Johansson, B., and Gatz, M. (2003). Does participation in leisure activities lead to a reduced risk of Alzheimer's disease? A prospective study of Swedish twins. *J. Gerontol. Ser. B* 58B, 249–255.

Davidson, A., and Bar-Yam, Y. (2006). "Environmental complexity: information for human-environment well-being," in *Unifying Themes in Complex Systems*, eds A. Bar-Yam and Y. Minai (New England; Berlin; Heidelberg: Springer), 157–168.

De Weerdt, W., Selz, B., Nuyens, G., Staes, F., Swinnen, D., Van De Winckel, A., et al. (2000). Time use of stroke patients in an intensive rehabilitation unit: a comparison between a Belgian and a Swiss setting. *Disabil. Rehabil.* 22, 181–186.

De Wit, L., Putman, K., Dejaeger, E., Baert, I., Berman, P., Bogaerts, K., et al. (2005). Use of time by stroke patients: a comparison of four european rehabilitation centers. *Stroke* 36, 1977–1983.

De Witt, B. W., Ehrenberg, K. M., McAloon, R. L., Panos, A. H., Shaw, K. E., Raghavan, P. V., et al. (2011). Abbreviated environmental enrichment enhances neurobehavioral recovery comparably to continuous exposure after traumatic brain injury. *Neurorehabil. Neural Repair* 25, 343–350.

Diamond, M. (2001). Response of the brain to enrichment. *An. Acad. Bras. Cienc.* 73, 211–220.

Dikmen, S., Reitan, R. M., and Temkin, N. R. (1983). Neuropsychological recovery in head injury. *Arch. Neurol.* 40, 333–338.

Dikmen, S. S., Ross, B. L., Machamer, J. E., and Temkin, N. R. (1995). One year psychosocial outcome in head injury. *J. Int. Neuropsychol. Soc.* 1, 67–77.

Dobrossy, M. D., and Dunnett, S. B. (2001). The influence of environment and experience on neural grafts. *Nat. Rev. Neurosci.* 2, 871–879.

Dobrossy, M. D., and Dunnett, S. B. (2004). Environmental enrichment affects striatal graft morphology and functional recovery. *Eur. J. Neurosci.* 19, 159–168.

Eckert, M. J., and Abraham, W. C. (2012). "Effects of environmental enrichment exposure on synaptic transmission and plasticity in the hippocampus," in *Current Topics in Behavorial Neurosciences*, eds M. A. Geyer, B. A. Ellenbroek, and C. A. Marsden (Berlin; Heidelberg: Springer), 1–23.

Eriksson, G., Kottorp, A., Borg, J., and Tham, K. (2009). Relationship between occupational gaps in everyday life, depressive mood and life satisfaction after acquired brain injury. *J. Rehabil. Med.* 41, 187–194.

Farbota, K. D., Bendlin, B. B., Alexander, A. L., Rowley, H. A., Dempsey, R. J., and Johnson, S. C. (2012). Longitudinal diffusion tensor imaging and neuropsychological correlates in traumatic brain injury patients. *Front. Hum. Neurosci.* 6:160. doi: 10.3389/fnhum.2012.00160

Fares, R. P., Belmeguenai, A., Sanchez, P. E., Kouchi, H. Y., Bodennec, J., Morales, A., et al. (2013). Standardized environmental enrichment supports enhanced brain plasticity in healthy rats and prevents cognitive impairment in epileptic rats. *PLoS ONE* 8:e53888. doi: 10.1371/journal.pone.0053888

Farne, A., Buxbaum, L. J., Ferraro, M., Frassinetti, F., Whyte, J., Veramonti, T., et al. (2004). Patterns of spontaneous recovery of neglect and associated disorders in acute right brain-damaged patients. *J. Neurol. Neurosurg. Psychiatr.* 75, 1401–1410.

Fasotti, L., Kovacs, F., Eling, P., and Brouwer, W. (2000). Time pressure management as a compensatory strategy training after closed head injury. *Neuropsychol. Rehabil.* 10, 47–65.

Faul, M., Xu, L., Wald, M. M., and Coronado, V. G. (2010). Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

Fratiglioni, L., Wang, H., Ericsson, K., Maytan, M., and Winblad, B. (2000). Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet* 355, 1315–1319.

Freeman, E. A. (1997). Community-based rehabilitation of the person with a severe brain injury. *Brain Inj.* 11, 143–153.

Fujiwara, Y., Chaves, P. H., Yoshida, H., Amano, H., Fukaya, T., Watanabe, N., et al. (2009). Intellectual activity and likelihood of subsequently improving or maintaining instrumental activities of daily living functioning in community-dwelling older Japanese: a longitudinal study. *Int. J. Geriatr. Psychiatry* 24, 547–555.

Gabriel, A., Paoletti, G., Della Seta, D., Panelli, R., Marcus, M., Farabollini, F., et al. (2009a). Enriched environment and the recovery from inflammatory pain: social versus physical aspects and their interaction. *Behav. Brain Res.* 208, 90–95.

Gabriel, A. F., Marcus, M. A., Honig, W. M., Helgers, N., and Joosten, E. A. (2009b). Environmental housing affects the duration of mechanical allodynia and the spinal astroglial activation in a rat model of chronic inflammatory pain. *Brain Res.* 1276, 83–90.

Gan, C., Gargaro, J., Brandys, C., Gerber, G., and Boschen, K. (2010). Family caregivers' support needs after brain injury: a synthesis of perspectives from caregivers, programs, and researchers. *NeuroRehabilitation* 27, 5–18.

Gobbo, O. L., and O'Mara, S. M. (2004). Impact of enriched-environment housing on brain-derived neurotrophic factor and on cognitive performance after a transient global ischemia. *Behav. Brain Res.* 152, 231–241.

Green, R. E., Colella, B., Christensen, B., Johns, K., Frasca, D., Bayley, M., et al. (2008). Examining moderators of cognitive recovery trajectories after moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S16–S24.

Green, R. E., Melo, B., Christensen, B., Ngo, L., and Skene, C. (2006). Evidence of transient enhancement to cognitive functioning in healthy young adults through environmental enrichment: implications for rehabilitation after brain injury. *Brain Cogn.* 60, 201–203.

Greenberg, G., Mikulis, D. J., Ng, K., Desouza, D., and Green, R. E. (2008). Use of diffusion tensor imaging to examine subacute white matter injury progression in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S45–S50.

Gribbin, K., Schaie, K., and Parham, I. (1980). Complexity of life style and maintenance of intellectual abilities. *J. Soc. Issues* 36, 47–61.

Gunther, V. K., Schafer, P., Holzner, B. J., and Kemmler, G. W. (2003). Long-term improvements in cognitive performance through computer-assisted cognitive training: a pilot study in a residential home for older people. *Aging Ment. Health* 7, 200–206.

Hamm, R., Temple, M., O'Dell, D., Pike, B., and Lyeth, B. (1996). Exposure to environmental complexity promotes recovery of cognitive function after traumtic brain injury. *J. Neurotrauma* 13, 41–47.

Hanks, R. A., Rapport, L. J., Wertheimer, J., and Koviak, C. (2012). Randomized controlled trial of peer mentoring for individuals with traumatic brain injury and their significant others. *Arch. Phys. Med. Rehabil.* 93, 1297–1304.

Hawthorne, G., Gruen, R. L., and Kaye, A. H. (2009). Traumatic brain injury and long-term quality of life: findings from an Australian study. *J. Neurotrauma* 26, 1623–1633.

Hayden, M. E., Plenger, P., Bison, K., Kowalske, K., Masel, B., and Qualls, D. (2013). Treatment effect versus pretreatment recovery in persons with traumatic brain injury: a study regarding the effectiveness of postacute rehabilitation. *PM R.* doi: 10.1016/j.pmrj.2012.12.005. [Epub ahead of print].

Hayslip, B., Maloy, R. M., and Kohl, R. (1995). Long-term efficacy of fluid ability interventions with older

adults. *J. Gerontol. Ser. B Psychol. Sci. Soc. Sci.* 50, P141–P149.

Hebb, D. O. (1947). The effects of early experience on problem solving in maturity. *Am. Psychol.* 2, 306–307.

Heffernan, D. S., Vera, R. M., Monaghan, S. F., Thakkar, R. K., Kozloff, M. S., Connolly, M. D., et al. (2011). Impact of socioethnic factors on outcomes following traumatic brain injury. *J. Trauma* 70, 527–534.

Heinemann, A. W., Hamilton, B., Linacre, J. M., Wright, B. D., and Granger, C. (1995). Functional status and therapeutic intensity during inpatient rehabilitation. *Am. J. Phys. Med. Rehabil.* 74, 315–326.

Himanen, L., Portin, R., Isoniemi, H., Helenius, H., Kurki, T., and Tenovuo, O. (2006). Longitudinal cognitive changes in traumatic brain injury: a 30-year follow-up study. *Neurology* 66, 187–192.

Hoffman, A., Malena, R., Westergoma, B., Luthra, P., Chenga, J., Aslama, H., et al. (2008). Environmental enrichment-mediated functional improvement after experimental traumatic brain injury is contingent on task-specific neurobehavioral experience. *Neurosci. Lett.* 431, 226–230.

Holbrook, T. L., Anderson, J. P., Sieber, W. J., Browner, D., and Hoyt, D. B. (1999). Outcome after major trauma: 12-month and 18-month follow-up results from the Trauma Recovery Project. *J. Trauma* 46, 765–771. discussion: 771–763.

Hoogerdijk, B., Runge, U., and Haugboelle, J. (2011). The adaptation process after traumatic brain injury an individual and ongoing occupational struggle to gain a new identity. *Scand. J. Occup. Ther.* 18, 122–132.

Hudak, A., Warner, M., Marquez De La Plata, C., Moore, C., Harper, C., and Diaz-Arrastia, R. (2011). Brain morphometry changes and depressive symptoms after traumatic brain injury. *Psychiatry Res.* 191, 160–165.

Huppert, F. (1991). *Age-Related Changes in Memory: Learning and Remembering New Information.* Amsterdam: Elsevier Science Publishers.

Johansson, B. B. (2000). Brain plasticity and stroke rehabilitation: the Willis lecture. *Stroke* 31, 223–230.

Johansson, B. B. (2002). "Environmental effects on recovery after stroke," in *Cerebrovascular Disease, 22nd Princeton Conference*, ed P. H. Chan (New York, NY: Cambridge University Press), 328–336.

Johansson, B. B. (2003). Environmental influence on recovery after brain lesions - experimental and clinical data. *J. Rehabil. Med.* 35, 11–16.

Johansson, B. B., and Ohlsson, A. L. (1996). Environment, social interaction, and physical activity as determinants of functional outcome after cerebral infarction in the rat. *Exp. Neurol.* 139, 322–327.

Jung, C. K., and Herms, J. (2012). Structural dynamics of dendritic spines are influenced by an environmental enrichment: an *in vivo* imaging study. *Cereb. Cortex*. doi: 10.1093/cercor/bhs317. [Epub ahead of print].

Keane, R. W., Kraydieh, S., Lotocki, G., Alonso, O. F., Aldana, P., and Dietrich, W. D. (2001). Apoptotic and antiapoptotic mechanisms after traumatic brain injury. *J. Cereb. Blood Flow Metab.* 21, 1189–1198.

Keightley, M., Kendall, V., Jang, S. H., Parker, C., Agnihotri, S., Colantonio, A., et al. (2011). From health care to home community: an Aboriginal community-based ABI transition strategy. *Brain Inj.* 25, 142–152.

Kempermann, M., Gast, G., and Gage, F. (2002). Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogensis by long-term environmental enrichment. *Ann. Neurol.* 52, 135–143.

Kennedy, M., Coelho, C., Turkstra, L., Ylvisaker, M., Sohlberg, M., Yorkston, K., et al. (2008). Intervention for executive functions after traumatic brain injury: a systematic review, meta-analysis and clinical recommendations. *Neuropsychol. Rehabil.* 18, 257–299.

Kim, J., Whyte, J., Patel, S., Avants, B., Europa, E., Wang, J., et al. (2010). Resting cerebral blood flow alterations in chronic traumatic brain injury: an arterial spin labeling perfusion FMRI study. *J. Neurotrauma* 27, 1399–1411.

Kleim, J. A., and Jones, T. A. (2008). Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J. Speech Lang. Hear. Res.* 51, S225–S239.

Klinge, C., Roder, B., and Buchel, C. (2012). Does training or deprivation modulate amygdala activation? *Neuroimage* 59, 1765–1771.

Kobayashi, S., Ohashi, Y., and Ando, S. (2002). Effects of enriched environments with different durations and starting times on learning capacity during aging in rats assessed by a refined procedure of the Hebb-Williams maze task. *J. Neurosci. Res.* 70, 340–346.

Kolb, B., and Whishaw, I. (1998). Brain plasticity and behaviour. *Annu. Rev. Psychol.* 49, 43–64.

Kramer, A. F., Bherer, L., Colcombe, S. J., Dong, W., and Greenough, W. T. (2004). Environmental influences on cognitive and brain plasticity during aging. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* 59, M940–M957.

Latham, N., and Mason, G. (2010). Frustration and perseveration in stereotypic captive animals: is a taste of enrichment worse than none at all? *Behav. Brain Res.* 211, 96–104.

Leger, M., Quiedeville, A., Paizanis, E., Natkunarajah, S., Freret, T., Boulouard, M., et al. (2012). Environmental enrichment enhances episodic-like memory in association with a modified neuronal activation profile in adult mice. *PLoS ONE* 7:e48043. doi: 10.1371/journal.pone.0048043

Leon-Carrion, J., Dominguez-Morales, M. R., Barroso Y Martin, J. M., and Leon-Dominguez, U. (2012). Recovery of cognitive function during comprehensive rehabilitation after severe traumatic brain injury. *J. Rehabil. Med.* 44, 505–511.

Levine, B., Kovacevic, N., Nica, E. I., Cheung, G., Gao, F., Schwartz, M. L., et al. (2008). The Toronto traumatic brain injury study: injury severity and quantified MRI. *Neurology* 70, 771–778.

Lezak, M. (2004). "The neuropsychological examination: procedures," in *Neuropsychological Assessment*, ed M. Lezak (New York, NY: Oxford University Press), 110–143.

Lippert-Gruener, M., Maegele, M., Garbe, J., and Angelov, D. N. (2007). Late effects of enriched environment (EE) plus multimodal early onset stimulation (MEOS) after traumatic brain injury in rats: ongoing improvement of neuromotor function despite sustained volume of the CNS lesion. *Exp. Neurol.* 203, 82–94.

Lores-Arnaiz, S., Lores Arnaiz, M. R., Czerniczyniec, A., Cuello, M., and Bustamante, J. (2010). Mitochondrial function and nitric oxide production in hippocampus and cerebral cortex of rats exposed to enriched environment. *Brain Res.* 1319, 44–53.

Lundqvist, A., and Samuelsson, K. (2012). Return to work after acquired brain injury: a patient perspective. *Brain Inj.* 26, 13–14.

Mackenzie, J. D., Siddiqi, F., Babb, J. S., Bagley, L. J., Mannon, L. J., Sinson, G. P., et al. (2002). Brain atrophy in mild or moderate traumatic brain injury: a longitudinal quantitative analysis. *AJNR Am. J. Neuroradiol.* 23, 1509–1515.

Mackinnor, A., Christensen, H., Hofer, S., Korten, A., and Jorm, A. (2003). Use it and still lose it? The association between activity and cognitive performance established using latent growth techniques in a community sample. *Aging Neuropsychol. Cogn.* 10, 215–229.

Mahncke, H., Connor, B., Appelman, J., Ahsanuddin, O., Hardy, J., Wood, R., et al. (2006a). Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proc. Natl. Acad. Sci. U.S.A.* 103, 12523–12528.

Mahncke, H. W., Bronstone, A., and Merzenich, M. M. (2006b). Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. *Prog. Brain Res.* 157, 81–109.

Mahoney, J., Eisner, J., Havighurst, T., Gray, S., and Palta, M. (2000). Problems of older adults living alone after hospitalization. *J. Gen. Int. Med.* 15, 611–619.

Marioni, R. E., Valenzuela, M. J., Van Den Hout, A., Brayne, C., and Matthews, F. E. (2012a). Active cognitive lifestyle is associated with positive cognitive health transitions and compression of morbidity from age sixty-five. *PLoS ONE* 7:e50940. doi: 10.1371/journal.pone.0050940

Marioni, R. E., Van Den Hout, A., Valenzuela, M. J., Brayne, C., and Matthews, F. E. (2012b). Active cognitive lifestyle associates with cognitive recovery and a reduced risk of cognitive decline. *J. Alzheimers Dis.* 28, 223–230.

Matter, A. M., Folweiler, K. A., Curatolo, L. M., and Kline, A. E. (2010). Temporal effects of environmental enrichment-mediated functional improvement after experimental traumatic brain injury in rats. *Neurorehabil. Neural Repair* 25, 558–564.

McCormack, E., and Liddiard, H. (2009). Home or away? Community rehabilitation following traumatic brain injury: a case report. *Physiother. Res. Int.* 14, 66–71.

Meagher, R. K., and Mason, G. J. (2012). Environmental enrichment reduces signs of boredom in caged mink. *PLoS ONE* 7:e49180. doi: 10.1371/journal.pone.0049180

Milgram, N. (2003). Cognitive experience and its effect on age-dependent cognitive decline in beagle dogs. *Neurochem. Res.* 2, 1677–1682.

Miller, L., and Green, R. E. (in press). Can environmental enrichment serve as a protective intervention

for neurodegeneration in traumatic brain injury? *Front. Hum. Neurosci.*

Millis, S. R., Rosenthal, M., Novack, T. A., Sherer, M., Nick, T. G., Kreutzer, J. S., et al. (2001). Long-term neuropsychological outcome after traumatic brain injury. *J. Head Trauma Rehabil.* 16, 343–355.

Mohammed, A. K., Winblad, B., Ebendal, T., and Larkfors, L. (1990). Environmental influence on behaviour and nerve growth factor in the brain. *Brain Res.* 528, 62–72.

Monaco, C. M., Mattiola, V. V., Folweiler, K. A., Tay, J. K., Yelleswarapu, N. K., Curatolo, L. M., et al. (2013). Environmental enrichment promotes robust functional and histological benefits in female rats after controlled cortical impact injury. *Exp. Neurol.* doi: 10.1016/j.expneurol.2013.01.007. [Epub ahead of print].

Murray, C. J., and Lopez, A. D. (1997). Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 349, 1498–1504.

Nalder, E., Fleming, J., Cornwell, P., Foster, M., and Haines, T. (2012a). Factors associated with the occurrence of sentinel events during transition from hospital to home for individuals with traumatic brain injury. *J. Rehabil. Med.* 44, 837–844.

Nalder, E., Fleming, J., Foster, M., Cornwell, P., Shields, C., and Khan, A. (2012b). Identifying factors associated with perceived success in the transition from hospital to home after brain injury. *J. Head Trauma Rehabil.* 27, 143–153.

Narayan, R. K., Michel, M. E., Ansell, B., Baethmann, A., Biegon, A., Bracken, M. B., et al. (2002). Clinical trials in head injury. *J. Neurotrauma* 19, 503–557.

Neely, A. S., and Backman, L. (1995). Effects of multifactorial memory training in old age: generalizability across tasks and individuals. *J. Gerontol. Ser. B Psychol. Sci. Soc. Sci.* 50, P134–P140.

Newson, R., and Kemps, E. (2005). General lifestyle activities as a predictor of current cognition and cognitive change in older adults: a cross-sectional and longitudinal examination. *J. Gerontol.* 60B, P113.

Ng, K., Mikulis, D. J., Glazer, J., Kabani, N., Till, C., Greenberg, G., et al. (2008). Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S35–S44.

Nilsson, M., Perfilieva, E., Johansson, U., Orwar, O., and Eriksson, P. S. (1999). Enriched environment increases neurogenesis in the adult rat dentate gyrus and improves spatial memory. *J. Neurobiol.* 39, 569–578.

Noice, H., and Noice, T. (2004). A short term intervention to enhance cognitive and affective functioning in older adults. *J. Aging Health* 16, 562–585.

Paillard-Borg, S., Fratiglioni, L., Xu, W., Winblad, B., and Wang, H. X. (2012). An active lifestyle postpones dementia onset by more than one year in very old adults. *J. Alzheimers Dis.* 31, 835–842.

Park, N. W., and Ingles, J. L. (2001). Effectiveness of attention rehabilitation after an acquired brain injury: a meta-analysis. *Neuropsychology* 15, 199–210.

Passineau, M., Green, E., and Dalton, D. (2001). Therapeutic effects of environmental enrichment on cognitive function and tissue integrity following severe traumatic brain injury in rats. *Exp. Neurol.* 168, 373–384.

Pereira, L. O., Arteni, N. S., Petersen, R. C., Da Rocha, A. P., Achaval, M., and Netto, C. A. (2007). Effects of daily environmental enrichment on memory deficits and brain injury following neonatal hypoxia-ischemia in the rat. *Neurobiol. Learn. Mem.* 87, 101–108.

Pickett, W., Simpson, K., and Brison, R. J. (2004). Rates and external causes of blunt head trauma in Ontario: analysis and review of Ontario Trauma Registry datasets. *Chronic Dis. Can.* 25, 32–41.

Pietropaolo, S., Branchi, I., Cirulli, F., Chiarotti, F., Aloe, L., and Alleva, E. (2004). Long-term effects of the periadolescent environment on exploratory activity and aggressive behaviour in mice: social versus physical enrichment. *Physiol. Behav.* 81, 443–453.

Pignatti, F., Rozzini, R., and Trabucchi, M. (2002). Physical activity and cognitive decline in elderly persons. *Arch. Intern. Med.* 162, P361.

Powell, J., Heslin, J., and Greenwood, R. (2002). Community based rehabilitation after severe traumatic brain injury: a randomised controlled trial. *J. Neurol. Neurosurg. Psychiatr.* 72, 193–202.

Pressman, H. T. (2007). Traumatic brain injury rehabilitation: case management and insurance-related issues. *Phys. Med. Rehabil. Clin. N. Am.* 18, 165–174. viii.

Pushkar, D., Arbuckle, T., Conway, M., Chaikelson, J., and Maag, U. (1997). Everyday activity parameters and competence in older adults. *Psychol. Aging* 12, 600–609.

Qiu, X., Huang, C. X., Lu, W., Yang, S., Li, C., Shi, X. Y., et al. (2012). Effects of a 4 month enriched environment on the hippocampus and the myelinated fibers in the hippocampus of middle-aged rats. *Brain Res.* 1465, 26–33.

Qiu, X., Li, C., Jiang, R., Chen, L., Huang, C., Yang, S., et al. (2011). The effects of short-term enriched environment on capillaries of the middle-aged rat cortex. *Neurosci. Lett.* 505, 186–190.

Raghupathi, R. (2004). Cell death mechanisms following traumatic brain injury. *Brain Pathol.* 14, 215–222.

Raghupathi, R., Graham, D. I., and McIntosh, T. K. (2000). Apoptosis after traumatic brain injury. *J. Neurotrauma* 17, 927–938.

Rath, J., Simon, D., Langenbahn, D., Sherr, R., and Diller, L. (2003). Group treatment of problem-solving deficits in outpatients with traumatic brain injury: a randomised outcome study. *Neuropsychol. Rehabil.* 13, 461–488.

Resch, J. A., Villarreal, V., Johnson, C. L., Elliott, T. R., Kwok, O. M., Berry, J. W., et al. (2009). Trajectories of life satisfaction in the first 5 years following traumatic brain injury. *Rehabil. Psychol.* 54, 51–59.

Rittman, M., Faircloth, C., Boylstein, C., Gubrium, J. F., Williams, C., Van Puymbroeck, M., et al. (2004). The experience of time in the transition from hospital to home following stroke. *J. Rehabil. Res. Dev.* 41, 259–268.

Rosenzweig, M. (1966). Environmental complexity, cerebral change, and behavior. *Am. Psychol.* 21, 321–332.

Rosenzweig, M., and Bennett, E. (1996). Psychobiology of plasticity: effects of training and experience on brain and behaviour. *Behav. Brain Res.* 78, 57–65.

Rotondi, A. J., Sinkule, J., Balzer, K., Harris, J., and Moldovan, R. (2007). A qualitative needs assessment of persons who have experienced traumatic brain injury and their primary family caregivers. *J. Head Trauma Rehabil.* 22, 14–25.

Rubinov, M., McIntosh, A. R., Valenzuela, M. J., and Breakspear, M. (2009). Simulation of neuronal death and network recovery in a computational model of distributed cortical activity. *Am. J. Geriatr. Psychiatry* 17, 210–217.

Ruff, R., Barth, J., Kreutzer, J., Levin, H., and Foulkes, M. (1991). Verbal learning deficits following severe head injury: heterogeneity in recovery over 1 year. *J. Neurosurg.* 75, S50–S58.

Rumrill, P. D., Fitzgerald, S. M., and Merchant, W. R. (2010). Using scoping literature reviews as a means of understanding and interpreting existing literature. *Work* 35, 399–404.

Rusconi, S., and Turner-Stokes, L. (2003). An evaluation of aftercare following discharge from a specialist in-patient rehabilitation service. *Disabil. Rehabil.* 25, 1281–1288.

Salmond, C. H., Menon, D. K., Chatfield, D. A., Pickard, J. D., and Sahakian, B. J. (2006). Changes over time in cognitive and structural profiles of head injury survivors. *Neuropsychologia* 44, 1995–1998.

Salthouse, T. (2006). Mental exercise and mental aging: evaluating the validity of the "use it or lose it" hypothesis. *Perspect. Psychol. Sci.* 1, 68–87.

Sampson, E. L., Bulpitt, C. J., and Fletcher, A. E. (2009). Survival of community-dwelling older people: the effect of cognitive impairment and social engagement. *J. Am. Geriatr. Soc.* 57, 985–991.

Sander, A. M., Clark, A., and Pappadis, M. R. (2010). What is community integration anyway?: defining meaning following traumatic brain injury. *J. Head Trauma Rehabil.* 25, 121–127.

Sander, A. M., Pappadis, M. R., Clark, A. N., and Struchen, M. A. (2011). Perceptions of community integration in an ethnically diverse sample. *J. Head Trauma Rehabil.* 26, 158–169.

Sander, A. M., Pappadis, M. R., Davis, L. C., Clark, A. N., Evans, G., Struchen, M. A., et al. (2009). Relationship of race/ethnicity and income to community integration following traumatic brain injury: investigation in a non-rehabilitation trauma sample. *NeuroRehabilitation* 24, 15–27.

Sander, A. M., Roebuck, T. M., Struchen, M. A., Sherer, M., and High, W. M. (2001). Long-term maintenance of gains obtained in postacute rehabilitation by persons with traumatic brain injury. *J. Head Trauma Rehabil.* 16, 356–373.

Scarmeas, N., and Stern, Y. (2003). Cognitive reserve and lifestyle. *J. Clin. Exp. Neuropsychol.* 25, 625–633.

Schooler, C. (1987). "Psychological effects of complex environments during the life span: a review and theory," in *Cognitive Functioning and Social Structure Over the Life Course*, ed C. S. K. W. Schaie (Norwood, NJ: Ablex), 24–49.

Schooler, C., and Mulatu, M. (2001). The reciprocal effects of leisure time

activities and intellectual functioning in older people: a longitudinal analysis. *Psychol. Aging* 16, 466–482.

Schuit, A., Feskens, E., Launer, L., and Kromhout, D. (2001). Physical activity and cognitive decline, the role of apolipoprotein e4 allele. *Med. Sci. Sports Exerc.* 33, 772–777.

Seeman, T., Lusignolo, T., Albert, M., and Berkman, L. (2001). Social relationships, social support, and patterns of cognitive aging in healthy, high-functioning older adults: MacArthur studies of successful aging. *Health Psychol.* 20, 243–255.

Shafi, S., Marquez De La Plata, C., Diaz-Arrastia, R., Shipman, K., Carlile, M., Frankel, H., et al. (2007). Racial disparities in long-term functional outcome after traumatic brain injury. *J. Trauma* 63, 1263–1268. discussion: 1268–1270.

Shiel, A., Burn, J. P., Henry, D., Clark, J., Wilson, B. A., Burnett, M. E., et al. (2001). The effects of increased rehabilitation therapy after brain injury: results of a prospective controlled trial. *Clin. Rehabil.* 15, 501–514.

Shigaki, C. L., Johnstone, B., and Schopp, L. H. (2009). Financial and vocational outcomes 2 years after traumatic brain injury. *Disabil. Rehabil.* 31, 484–489.

Shin, S. S., Bales, J. W., Yan, H. Q., Kline, A. E., Wagner, A. K., Lyons-Weiler, J., et al. (2013). The effect of environmental enrichment on substantia nigra gene expression after traumatic brain injury in rats. *J. Neurotrauma* 30, 259–270.

Shors, T. J., Anderson, M. L., Curlik, D. M. 2nd., and Nokia, M. S. (2012). Use it or lose it: how neurogenesis keeps the brain fit for learning. *Behav. Brain Res.* 227, 450–458.

Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., et al. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain* 131, 559–572.

Sidaros, A., Skimminge, A., Liptrot, M. G., Sidaros, K., Engberg, A. W., Herning, M., et al. (2009). Long-term global and regional brain volume changes following severe traumatic brain injury: a longitudinal study with clinical correlates. *Neuroimage* 44, 1–8.

Simpson, J., and Kelly, J. P. (2011). The impact of environmental enrichment in laboratory rats–behavioural and neurochemical aspects. *Behav. Brain Res.* 222, 246–264.

Slade, A., Tennant, A., and Chamberlain, M. A. (2002). A randomised controlled trial to determine the effect of intensity of therapy upon length of stay in a neurological rehabilitation setting. *J. Rehabil. Med.* 34, 260–266.

SMARTRISK. (2006). *The Economic Burden of Injury*. Toronto, ON: SMARTRISK.

Sohlberg, M. M., McLaughlin, K. A., Pavese, A., Heidrich, A., and Posner, M. I. (2000). Evaluation of attention process training and brain injury education in persons with acquired brain injury. *J. Clin. Exp. Neuropsychol.* 22, 656–676.

Sozda, C. N., Hoffman, A. N., Olsen, A. S., Cheng, J. P., Zafonte, R. D., and Kline, A. E. (2010). Empirical comparison of typical and atypical environmental enrichment paradigms on functional and histological outcome after experimental traumatic brain injury. *J. Neurotrauma* 27, 1047–1057.

Speisman, R. B., Kumar, A., Rani, A., Pastoriza, J. M., Severance, J. E., Foster, T. C., et al. (2012). Environmental enrichment restores neurogenesis and rapid acquisition in aged rats. *Neurobiol. Aging* 34, 263–274.

Spikman, J. M., Boelen, D. H., Lamberts, K. F., Brouwer, W. H., and Fasotti, L. (2009). Effects of a multifaceted treatment program for executive dysfunction after acquired brain injury on indications of executive functioning in daily life. *J. Int. Neuropsychol. Soc.* 16, 118–129.

Spivack, G., Spettell, C. M., Ellis, D. W., and Ross, S. E. (1992). Effects of intensity of treatment and length of stay on rehabilitation outcomes. *Brain Inj.* 6, 419–434.

Staudenmayer, K. L., Diaz-Arrastia, R., De Oliveira, A., Gentilello, L. M., and Shafi, S. (2007). Ethnic disparities in long-term functional outcomes after traumatic brain injury. *J. Trauma* 63, 1364–1369.

Stine-Morrow, E., Parisi, J., Morrow, D., Greene, J., and Park, D. (2007). An engagement model of cognitive optimization through adulthood. *J. Gerontol. Ser. B* 62B, 62–69.

Strandberg, T. (2009). Adults with acquired traumatic brain injury: experiences of a changeover process and consequences in everyday life. *Soc. Work Health Care* 48, 276–297.

Struchen, M. A., Davis, L. C., Bogaards, J. A., Hudler-Hull, T., Clark, A. N., Mazzei, D. M., et al. (2011). Making connections after brain injury: development and evaluation of a social peer-mentoring program for persons with traumatic brain injury. *J. Head Trauma Rehabil.* 26, 4–19.

Sun, H., Zhang, J., Zhang, L., Liu, H., Zhu, H., and Yang, Y. (2010). Environmental enrichment influences BDNF and NR1 levels in the hippocampus and restores cognitive impairment in chronic cerebral hypoperfused rats. *Curr. Neurovasc. Res.* 7, 268–280.

Till, C., Colella, B., Verwegen, J., and Green, R. E. (2008). Postrecovery cognitive decline in adults with traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S25–S34.

Toglia, J., Johnston, M. V., Goverover, Y., and Dain, B. (2010). A multicontext approach to promoting transfer of strategy use and self regulation after brain injury: an exploratory study. *Brain Inj.* 24, 664–677.

Toglia, J. P. (1991). Generalization of treatment: a multicontext approach to cognitive perceptual impairment in adults with brain injury. *Am. J. Occup. Ther.* 45, 505–516.

Trivedi, M. A., Ward, M. A., Hess, T. M., Gale, S. D., Dempsey, R. J., Rowley, H. A., et al. (2007). Longitudinal changes in global brain volume between 79 and 409 days after traumatic brain injury: relationship with duration of coma. *J. Neurotrauma* 24, 766–771.

Tsaousides, T., Warshowsky, A., Ashman, T. A., Cantor, J. B., Spielman, L., and Gordon, W. A. (2009). The relationship between employment-related self-efficacy and quality of life following traumatic brain injury. *Rehabil. Psychol.* 54, 299–305.

Turner, B., Fleming, J., Cornwell, P., Worrall, L., Ownsworth, T., Haines, T., et al. (2007). A qualitative study of the transition from hospital to home for individuals with acquired brain injury and their family caregivers. *Brain Inj.* 21, 1119–1130.

Turner, B., Fleming, J., Cornwell, P., Haines, T., and Ownsworth, T. (2009a). Profiling early outcomes during the transition from hospital to home after brain injury. *Brain Inj.* 23, 51–60.

Turner, B., Ownsworth, T., Cornwell, P., and Fleming, J. (2009b). Reengagement in meaningful occupations during the transition from hospital to home for people with acquired brain injury and their family caregivers. *Am. J. Occup. Ther.* 63, 609–620.

Turner, B., Fleming, J., Ownsworth, T., and Cornwell, P. (2011a). Perceptions of recovery during the early transition phase from hospital to home following acquired brain injury: a journey of discovery. *Neuropsychol. Rehabil.* 21, 64–91.

Turner, B. J., Fleming, J., Ownsworth, T., and Cornwell, P. (2011b). Perceived service and support needs during transition from hospital to home following acquired brain injury. *Disabil. Rehabil.* 33, 818–829.

Turner, B. J., Fleming, J. M., Ownsworth, T. L., and Cornwell, P. L. (2008). The transition from hospital to home for individuals with acquired brain injury: a literature review and research recommendations. *Disabil. Rehabil.* 30, 1153–1176.

Turner, G. R., and Green, E. (2008). Cognitive remediation in aging and ABI: a question of negative plasticity? *Neuropsychol. Rehabil.* 18, 372–384.

Turner-Stokes, L., Disler, P. B., Nair, A., and Wade, D. T. (2005). Multidisciplinary rehabilitation for acquired brain injury in adults of working age. *Cochrane Database Syst. Rev.* 3:CD004170. doi: 10.1002/14651858.CD004170.pub2

Valero, J., Espana, J., Parra-Damas, A., Martin, E., Rodriguez-Alvarez, J., and Saura, C. A. (2011). Short-term environmental enrichment rescues adult neurogenesis and memory deficits in APP(Sw, Ind) transgenic mice. *PLoS ONE* 6:e16832. doi: 10.1371/journal.pone.0016832

Van De Winckel, A., Feys, H., De Weerdt, W., and Dom, R. (2004). Cognitive and behavioural effects of music-based exercises in patients with dementia. *Clin. Rehabil.* 18, 253–260.

Van Praag, H., Kempermann, G., and Gage, F. (2000). Neural consequences of environmental enrichment. *Neuroscience* 1, 191–198.

Vance, D., and Johns, R. (2002). Montessori improved cognitive domains in adults with Alzheimer's Disease. *Phys. Occup. Ther. Geriatr.* 20, 19–36.

Vazquez-Sanroman, D., Sanchis-Segura, C., Toledo, R., Hernandez, M. E., Manzo, J., and Miquel, M. (2013). The effects of enriched environment on BDNF expression in the mouse cerebellum depending on the length of exposure. *Behav. Brain Res.* 243C, 118–128.

Verghese, J., Lipton, R., Katz, M., Hall, C., Derby, C., Kuslansky, G., et al. (2003). Leisure activities and the risk of dementia in the elderly. *N. Engl. J. Med.* 348, 2508–2616.

Voss, M. W., Nagamatsu, L. S., Liu-Ambrose, T., and Kramer, A. F. (2011). Exercise, brain, and

cognition across the life span. *J. Appl. Physiol.* 111, 1505–1513.

Wang, H., Karp, A., Wonblad, B., and Fratiglioni, L. (2002). Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. *Am. J. Epidemiol.* 155, 1081–1087.

Warner, M. A., Marquez De La Plata, C., Spence, J., Wang, J. Y., Harper, C., Moore, C., et al. (2010). Assessing spatial relationships between axonal integrity, regional brain volumes, and neuropsychological outcomes after traumatic axonal injury. *J. Neurotrauma* 27, 2121–2130.

Warraich, Z., and Kleim, J. A. (2010). Neural plasticity: the biological substrate for neurorehabilitation. *PM R* 2, S208–S219.

West, R. W., and Greenough, W. T. (1972). Effect of environmental complexity on cortical synapses of rats: preliminary results. *Behav. Biol.* 7, 279–284.

Will, B., Galani, R., Kelche, C., and Rosenzweig, M. R. (2004). Recovery from brain injury in animals: relative efficacy of environmental enrichment, physical exercise or formal training (1990-2002). *Prog. Neurobiol.* 72, 167–182.

Willer, B., Button, J., and Rempel, R. (1999). Residential and home-based postacute rehabilitation of individuals with traumatic brain injury: a case control study. *Arch. Phys. Med. Rehabil.* 80, 399–406.

Williamson, L. L., Chao, A., and Bilbo, S. D. (2012). Environmental enrichment alters glial antigen expression and neuroimmune function in the adult rat hippocampus. *Brain Behav. Immun.* 26, 500–510.

Wilson, J. T., Wiedmann, K. D., Hadley, D. M., Condon, B., Teasdale, G., and Brooks, D. N. (1988). Early and late magnetic resonance imaging and neuropsychological outcome after head injury. *J. Neurol. Neurosurg. Psychiatr.* 51, 391–396.

Wilson, R., Barnes, L., and Bennett, D. (2003). Assessment of lifetime participation in cognitively stimulating activities. *J. Clin. Exp. Neuropsychol.* 25, 634–642.

Wilson, R. S., Mendes De Leon, C. F., Barnes, L. L., Schneider, J. A., Bienias, J. L., Evans, D. A., et al. (2002). Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *J. Am. Med. Assoc.* 287, 742–748.

Winocur, G., and Moscovitch, M. (1990). A comparison of cognitive function in community-dwelling and institutionalized old people of normal intelligence. *Can. J. Psychol.* 44, 435–444.

Winocur, G., Moscovitch, M., and Freedman, J. (1987). An investigation of cognitive function in relation to psychosocial variables in institutionalized old people. *Can. J. Psychol.* 41, 257–269.

Winocur, G. (1998). Environmental influences on cognitive decline in aged rats. *Neurobiol. Aging* 19, 589–597.

Xu, L., Jiang, C. Q., Lam, T. H., Zhang, W. S., Thomas, G. N., and Cheng, K. K. (2011). Dose-response relation between physical activity and cognitive function: guangzhou biobank cohort study. *Ann. Epidemiol.* 21, 857–863.

Yang, S., Li, C., Qiu, X., Zhang, L., Lu, W., Chen, L., et al. (2013). Effects of an enriched environment on myelin sheaths in the white matter of rats during normal aging: a stereological study. *Neuroscience* 234C, 13–21.

Zhu, X. L., Poon, W. S., Chan, C. H., and Chan, S. H. (2001). Does intensive rehabilitation improve the functional outcome of patients with traumatic brain injury? Interim result of a randomized controlled trial. *Br. J. Neurosurg.* 15, 464–473.

Zhu, X. L., Poon, W. S., Chan, C. C., and Chan, S. S. (2007). Does intensive rehabilitation improve the functional outcome of patients with traumatic brain injury (TBI)? A randomized controlled trial. *Brain Inj.* 21, 681–690.

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Chronic traumatic encephalopathy and other neurodegenerative proteinopathies

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"Chronic traumatic encephalopathy" (CTE) is described as a slowly progressive neurodegenerative disease believed to result from multiple concussions. Traditionally, concussions were considered benign events and although most people recover fully, about 10% develop a post-concussive syndrome with persisting neurological, cognitive and neuropsychiatric symptoms. CTE was once thought to be unique to boxers, but it has now been observed in many different athletes having suffered multiple concussions as well as in military personal after repeated blast injuries. Much remains unknown about the development of CTE but its pathological substrate is usually tau, similar to that seen in Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD). The aim of this "perspective" is to compare and contrast clinical and pathological CTE with the other neurodegenerative proteinopathies and highlight that there is an urgent need for understanding the relationship between concussion and the development of CTE as it may provide a window into the development of a proteinopathy and thus new avenues for treatment.

Keywords: concussions, chronic traumatic encephalopathy, neurodegenerative disease, Alzheimer's disease, frontotemporal lobar degeneration, tau

CONCUSSIONS: AN EVOLUTION IN OUR UNDERSTANDING

"Chronic traumatic encephalopathy" (CTE) is described as a slowly progressive neurodegenerative disease with pathological tau accumulation at the depths of the sulci in superficial layers of the cortex. Clinically CTE is believed to include neuropsychiatric, cognitive and motor deficits that manifest years after implicated concussive or subconcussive events (McKee et al., 2009). It is believed to be a consequence of repeated mild brain traumas also known as concussions. Although the majority of concussions are fully resolved within 3 months (Iverson, 2007), and conventional neuroimaging and neuropsychological testing are typically normal (Broglio and Puetz, 2008), the notion of concussion as a completely benign event (e.g., "bell-ringer") is outdated. Most people return to baseline after a single concussion but an estimated 10% of cases result in serious and persisting somatic, affective, cognitive, and/or movement sequelae (Wood, 2004). There is growing clinical and societal concern about the effects of multiple concussions (Jordan, 2013) although one meta-analyses revealed no significant effects after multiple concussions (Belanger et al., 2010). CTE was first described in Miller (1966) as a constellation of symptoms typical of neurodegenerative disease. Clinically and pathologically it bears resemblance to other neurodegenerative diseases, now thought of as proteinopathies, which includes Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD). Although widespread media attention has spawned a dogma on the *delayed* effects of multiple concussions (Corsellis and Brierley, 1959; Corsellis et al., 1973; Omalu et al., 2005, 2010a; Gavett et al., 2010; Costanza et al., 2011; Stern et al., 2011; Goldstein et al., 2012; McKee et al., 2013), there remains much to be known on the clinical and pathophysiology of CTE. A better understanding of the differences and similarities of CTE and the other proteinopathies may help guide future studies.

MULTIPLE CONCUSSIONS AND CHRONIC TRAUMATIC ENCEPHALOPATHY

PUNCH DRUNK SYNDROME, DEMENTIA PUGILISTICA, CHRONIC TRAUMATIC ENCEPHALOPATHY

In 1928, Martland introduced the term "punch-drunk" state (Martland, 1928) in reference to the chronic motor and psychiatric consequences of blows to the head in boxing. Millspaugh (1937) coined "dementia pugilistica" to describe similar cases. A few decades later, Critchley (1957) reported on 69 cases of progressive neurological disease in boxers and proposed "chronic progressive traumatic encephalopathy of boxers." He described an insidious and gradual development of mental and physical anomalies marked by a "euphoric dementia" with emotional lability, little insight, progressive bradyphrenia, and memory deficits, along with changes in behavior. Critchley added that many patients displayed mood-swings, intense irritability, and occasionally, uninhibited violent behavior. He noted "fatuous cheerfulness" as the commonest mood finding but also reported paranoid depression. Motor findings included pyramidal, extra-pyramidal, and cerebellar signs, with tremor and dysarthria the most frequently reported. Sensory perceptual findings included deafness and poor vision. His patients also complained of persistent dull headaches, postural dizziness, and unsteady gait, reminiscent of acute concussion and post-concussive syndrome. In 1969, Roberts reported on 224 former boxers and found that 17% suffered from significant memory loss, aggression, confusion, or depression and that there was direct correlation of incidence to number of fights and overall length of boxing career (Roberts, 1969). Many observational studies, some prospective, have also been undertaken, including a systematic review of 36 of an initial 943 studies on the chronic effects of amateur boxing (Loosemore et al., 2007).

The early literature on the chronic effects of multiple concussions focused on boxing, but multiple concussions sustained under different circumstances can also produce chronic effects. The term CTE has been coined to encompass progressive neurodegenerative effects observed after multiple concussions sustained in any context (Miller, 1966).

Clinical CTE cases overlap with punch-drunk syndrome. CTE is usually described as an evolving constellation of cognitive, psychiatric and motor symptoms (McKee et al., 2009). Cognitive findings may precede, co-occur or follow psychiatric findings, and can include impaired concentration, attention, and memory along with disorientation, confusion, and speech abnormalities later on McKee et al. (2009). Emotional lability, inappropriate behavior, paranoia, outbursts of aggressive behavior and explosivity, mood disturbance, disinhibition, psychosis, and dysexecutive symptoms are observed. Dizziness and headaches are frequent (McKee et al., 2009). Psychiatric symptoms are observable at all stages of CTE, with no clear dose response between extent of neuropathology and clinical symptoms (McKee et al., 2013). Parkinsonian symptoms of tremor, masked facies, wide based gait, poor speech, ocular abnormalities, bradykinesia, and dementia appear as the disease progresses (Omalu et al., 2011a; McKee et al., 2013).

WHO IS AT RISK?

The majority of cases of suspected CTE have been reported in athletes in contact sports, including boxing, hockey, wrestling, soccer, and North American football (Corsellis et al., 1973; Omalu et al., 2006, 2010b; McKee et al., 2009; Dekosky et al., 2010; Gavett et al., 2011; Neselius et al., 2012). CTE has also been associated with physical abuse and epilepsy (McKee et al., 2009). More recently, CTE was reported in a war veteran having suffered blast-injury without signs of overt concussion (Omalu et al., 2011b).

CTE requires post-mortem assessment and all post-mortem studies to date contain samples that are not representative of either the general population or even of multiply concussed populations. McKee et al. (2009) reported that 46/51 (90%) of neuropathologically confirmed CTE cases occurred in athletes who had played contact sports. However, in general, brains referred for autopsy are those of individuals who displayed overt neurological signs at the time of death and therefore were at elevated risk of underlying pathology compared to the large number of athletes who play contact sports but do not show neurological signs throughout their life.

McKee et al. (2013) recently published an expansion of her previous study with 85 brains from former athletes, veterans and civilians with a history of multiple concussions. Importantly, there was no evidence of CTE despite repetitive concussion in 17/85 (20%) of cases, and in 15/85 cases (37%) there was significant comorbid pathology of AD, Lewy body disease (LBD), motor neuron disease (MND), or FTLD. In advanced cases, a comorbid condition such as AD, LBD, or FTLD was present in almost half the cases (10/25) These findings converge with a recent study undertaken by our group, which showed that even with a history of multiple concussions from contact sport *and* a positive clinical presentation before death, a diagnosis of CTE is not inevitable on neuropathological examination. Our case series included the brains of six retired professional players of the Canadian Football League with a history of multiple concussions (Hazrati et al., 2013) and all clinically symptomatic before death. While each case displayed significant neuropathological changes on post-mortem examination, only three showed pathology consistent with CTE. In the other three cases, the neuropathological diagnoses were Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS), and AD. Even the cases with CTE had co-pathology, including AD, PD, or vasculopathy. This study demonstrates that there is not always a direct relationship between multiple concussions, clinical symptomology, and CTE.

In a recent retrospective analysis a higher incidence of mortality from neurodegenerative disease including AD- and ALS was reported among former National Football League players, compared to the general population (Lehman et al., 2012). Notably, however, players (vs. the rest of the general US population studied), and in particular players in speed positions, showed the *lowest* death rate for other causes of death including cardiovascular disease and cancer, the largest killers of the general US population. These data may thus inflate the apparent risk of neurodegenerative disease and argue for prospective research into the biological effects of multiple concussions.

AGE OF ONSET

Critchley (1957) reports age of onset on 11 cases of punch-drunk syndrome: two were still boxing, six were in their 20 s, two were in their 30 s, and one was 61 years old. McKee et al. (2009) reported CTE symptom onset at ages ranging from 25 to 76 years; one-third were symptomatic at retirement and half were symptomatic within 4 years of their retirement. Although Omalu et al. (2011a) proposed an asymptomatic period between playing of the sport and symptom onset, in his series of 10 cases, four were in their 30 s, three were in their 40 s, and three were in their 50 s. Thus, very few of the players had a prolonged asymptomatic or latent period. There has been no differentiation between the delayed onset of CTE-associated symptoms and the more immediate onset observed in boxers. Importantly, in the absence of serial, longitudinal evaluations in the above studies, we cannot rule out symptom onset prior to formal diagnosis.

Whether CTE and the punch-drunk syndrome are dissociable entities is still unclear. While both syndromes can be associated with the cumulative effects of concussion, it is conceivable that CTE reflects a delayed onset entity, while the punch-drunk syndrome represents a continuation and progression of symptoms from an acute concussive state (Gardner et al., 2014). Also uncertain is whether some players are in a prolonged or more severe postconcussive syndrome that may have a different pathophysiology than the players who develop symptoms decades after their last concussion.

CHRONIC TRAUMATIC ENCEPHALOPATHY vs. OTHER PROTEINOPATHIES

CLINICAL COMPARISONS

The clinical diagnosis of CTE is currently not feasible due to the overlap with other neurodegenerative conditions. AD is the most common neurodegenerative disease in those over age 65 (Prince et al., 2013) and most often presents with impaired learning and recall of recently learned information (McKhann et al., 2011). Neuropsychiatric symptoms including depression, apathy, agitation, and irritability, as in CTE, are not uncommon (Cummings, 1997).

FTLD is the most common neurodegenerative disease in those less than 65, and includes several clinical syndromes involving changes in behavior, language, and motor function. The main clinical phenotypes are: behavioral variant frontotemporal dementia (bvFTD), primary progressive aphasia, FTD-motor neuron disease (FTD-MND), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS). Although these syndromes strongly overlap in clinical, genetic, and pathological features their syndrome specific clinical expression differs markedly due to focal pathology (Brun, 1993) (**Figure 1A**). bvFTD, as its name implies, is primarily a behavioral syndrome characterized by dramatic personality and behavioral changes. The apathy, loss of social norms, and decreased empathy seen in bvFTD are frequent symptoms in traumatic brain injury (TBI) including moderate-severe TBI, concussion, and CTE and are attributed to frontal lobe degeneration (Damasio et al., 1991; Stuss et al., 2001; Jordan, 2013) in particular orbitofrontal and ventromedial prefrontal cortex, as well as insula (Rosen et al., 2005). The language variants, as well as CBS (a progressive, asymmetric, akinetic-rigid syndrome) and PSP (cognitive and behavioral deficits and prominent oculomotor and movement impairments) (Litvan et al., 1996) have less in common with CTE. bvFTD-like symptoms can co-occur in patients with MND (Lomen-Hoerth et al., 2003), and some patients with CTE have presented with MND phenotype and a TAR-DNA binding protein 43 (TDP-43) pathology (McKee et al., 2010). Parkinsonism and cognitive deficits as seen in LBD and PD are also seen in CTE and there are cases of LBD and PD subsequent to multiple concussions (Hazrati et al., 2013; McKee et al., 2013).

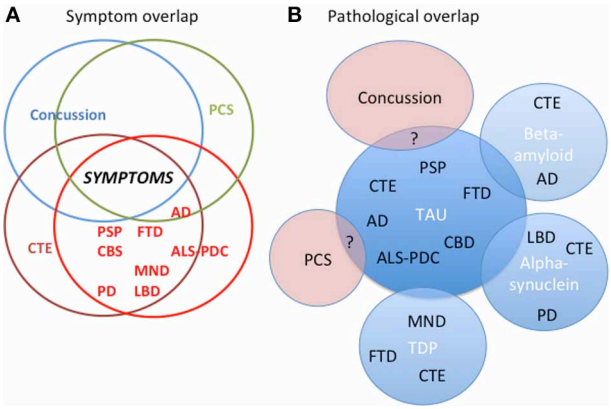

FIGURE 1 | The interrelationships between concussion, post-concussion syndrome (PCS), chronic traumatic encephalopathy (CTE), and all the neurodegenerative diseases. (A) There is considerable symptom overlap between concussion, PCS, CTE, and the neurodegenerative diseases. **(B)** Pathologically the relationship between concussion, PCS, CTE, and all the neurodegenerative diseases is unclear. In CTE there is substantial evidence for overlapping pathology of tau, TDP-43, amyloid, and alpha-synuclein with neurodegenerative diseases. In neurodegenerative diseases such as AD, PD, and LBD, there is also overlapping pathology. The pathology of concussion and PCS and their relationship to CTE remains to be explored. AD, Alzheimer's Disease; ALS-PDC, amyotrophic lateral sclerosis-parkinson's dementia complex (Guam); CBD, corticobasal degeneration; CBS, corticobasal syndrome; CTE, chronic traumatic encephalopathy; LBD, Lewy Body Disease; FTD, frontotemporal dementia; MND, motor neuron disease; PCS, Post-concussive syndrome; PSP, progressive supranuclear palsy; PD, Parkinson's disease. "?" indicates uncertainty about overlap.

The overlap in signs and symptoms of CTE and other neurodegenerative diseases, especially bvFTD, is likely a result of focal involvement of frontal networks that subserve numerous higher functions including personality/emotional life, executive function, and motivation (Stuss and Levine, 2002). A better understanding of the pathophysiology of any of the neurodegenerative diseases may shed light on the risk factors for developing CTE.

PATHOLOGICAL SIGNS OF CTE vs. OTHER NEURODEGENERATIVE DISEASE

Only a limited number of cases of suspected CTE have undergone pathological examination but post-mortem assessments show a distinct pattern from other proteinopathies including dilated ventricles, a fenestrated, and cavum septum pellucidum, significant atrophy of the medial temporal lobes, thalamus, and mammillary

bodies and occasionally pallor of the locus coeruleus and substantia nigra (McKee et al., 2009; Gavett et al., 2011; Stern et al., 2011). Hyperphosphorylated tau deposits in neurons of specific areas of the brains of boxers and professional football players, thus adding CTE to the list of known tauopathies that includes PSP, CBD, FTLD, Guam-Parkinson Dementia Complex, and AD. Tau is a protein that binds to and stabilizes microtubules required for maintaining neuronal shape and for transport of cellular cargo (Brunden et al., 2009). The distribution of these pathological changes is along the amygdalo-hippocampal-septo-hypothalamic-mesencephalic continuum, which is part of the emotional or visceral brain (McKee et al., 2009). The pathological changes are greatest in the depths of sulci, perivascularly around small vessels, and in the superficial cortical layers (II/III). This tau distribution pattern is distinct from other tauopathies. In AD, the neurofibrillary tangles (NFTs) are more regular, are primarily in layers III and V of the cortex, and are neither perivascular nor primarily at the depths of the sulci. In PSP, the NFTs are mainly in the basal ganglia and hindbrain structures. Other distinguishing patterns of tau deposition seen in CTE include irregular and patchy distributions and also prominence in the periventricular and subpial areas. Unlike AD, CTE usually lacks significant amounts of beta-amyloid plaque deposition (Braak and Braak, 1997; McKee et al., 2009; Gavett et al., 2011; Stern et al., 2011).

In select cases of CTE, widespread TDP-43 immunopositive inclusions have been observed (McKee et al., 2010). Lesions involving the corticospinal tracts and the anterior horns of the spinal cord are associated with clinical motor findings of spasticity, weakness, and fasciculations similar to those seen in ALS (McKee et al., 2010). The pathological accumulation of TDP-43 is also seen in FTLD and like tau can cause various FTLD syndromes (Whitwell and Josephs, 2011). Alpha-synuclein positive Lewy bodies as seen in PD and LBD and Alzheimer's beta-amyloid pathology has also occasionally been reported in CTE (McKee et al., 2013).

Similarities exist between CTE and the chronic effects of moderate and severe TBI, in which there can be neurodegeneration in the chronic phase months to years after TBI with sub-acute atrophy within the hippocampi (Ng et al., 2008) and elsewhere (Green et al., 2010). Interestingly, the corpus callosum (unmyelinated axons in particular) is vulnerable to protein deposition post-TBI, suggesting commonality with CTE (Reeves et al., 2005, 2012).

Recently Omalu et al. (2011a) proposed four histomorphologic phenotypes in CTE based on the distribution of NFTs and neuritic threads in the cortex, brainstem, subcortical nuclei, basal ganglia, and cerebellum, and they include amyloid plaques in one phenotype. In contrast, McKee et al. (2013) proposed a staging scheme for CTE severity based on tau distribution which would range from focal epicentres of phosphorylated tau (p-tau) usually in the frontal cortex and typically around small vessels at the depths of sulci to widespread p-tau pathology in a patchy irregular distribution in cortical areas and medial temporal lobe as well as in thalamus, hypothalamus, mammillary bodies, basal ganglia, brainstem and in white matter tracts. Currently, the clinical-pathological relationship is unknown and questions as to whether differences relate to different types of CTE, different types of injury and/or different clinical syndromes remain. There is some evidence for pathological and clinical differences between the classic CTE cases and the "modern" form described in the last few years (Gardner et al., 2014). These authors argue that the classic form of CTE does not appear to advance in a predictable and sequential series of stages, and progression of physical symptoms is only present in approximately one-third of cases. Clearly long-term, prospective clinical studies followed by detailed neuropathological examination are needed to help unravel this issue.

It has become increasingly apparent that CTE frequently coexists with other pathologies. In our series of six cases, the three patients with CTE also exhibited other neurodegenerative pathology as noted above (Hazrati et al., 2013). McKee's recent case series (McKee et al., 2013) found co-pathology of CTE with AD, LBD or both in 17 cases and CTE and MND in eight cases. The relative contribution of the different pathological substrates to the clinical symptoms is currently unknown and requires further study. A recent review of the contemporary cases in the literature found that over 50% had copathology with CTE and only 20% had pure CTE (Gardner et al., 2014).

In vivo diagnosis of the specific proteinopathy responsible for a neurodegenerative disease is now the goal. Currently, amyloid imaging and cerebrospinal fluid (CSF) biomarkers of amyloid and tau for the *in vivo* diagnosis of AD are available although not in clinical use (Sperling and Johnson, 2013). Regarding the other neurodegenerative diseases, neither imaging nor fluid biomarkers are available for their diagnosis although there are some experimental data coming out in PD (Parnetti et al., 2013; Schapira, 2013) and FTLD (Hu et al., 2010, 2013). In CTE, concussion, and post-concussion syndrome there are a few studies suggesting abnormalities including elevated levels of CSF tau (Neselius et al., 2012; Shenton et al., 2012; Zetterberg et al., 2013) but these lack pathological confirmation and haven't been reproduced. CTE is still in its infancy with regard to defining the clinical syndrome and determining *in vivo* biomarkers of the underlying pathology.

SUMMARY AND CONCLUSIONS: MUCH REMAINS TO BE KNOWN

Tau deposition and pathological changes in a particular distribution have been observed in cases of multiple concussions. The evidence to date concerning CTE, its association with multiple concussions, and its clinical signs and symptoms comes from case reports, cases series, and retrospective analyses (Graves et al., 1990; Schofield et al., 1997; Mehta et al., 1999; McKee et al., 2013). The symptoms described in CTE overlap with those described in concussion, PCS and the neurodegenerative diseases. **Figure 1A**. There is a selection bias for many of the reported cases, some died from violent deaths such as suicide or drug overdose and/or were otherwise clinically symptomatic with cognitive symptoms. There are now an increasing number of reports of cases with multiple concussions but no evidence of CTE at autopsy (Hazrati et al., 2013; McKee et al., 2013). The exact relationship between multiple concussions and CTE is ambiguous. Moreover, one must distinguish clinically and pathologically between static, non-progressive cumulative effects of multiple concussions vs. progressive findings of symptomatic neurodegenerative disease. Complicating the situation are cases of a single,

but more serious TBI associated with increased risk of dementia (Blennow et al., 2012; Sayed et al., 2013) as well as atrophy and loss of white matter integrity in the sub-acute and chronic stages of injury (Greenberg et al., 2008; Ng et al., 2008; Whitwell and Josephs, 2011; Adnan et al., 2013)

Prospective, longitudinal studies with neuropathological analysis that sample a broader cross section of individuals, including those with a history of multiple concussions but without positive clinical neurological findings prior to death are critically needed. Understanding the relationship of multiple concussions to CTE as well as possible modifiers is paramount for preventing or ameliorating this illness and for finding a cure. Furthermore, and most importantly, by evoking a diagnosis of CTE as a cause of the symptoms and signs and symptoms in multiple concussions, and failing to address treatable and potentially reversible causes of the suffering is a disservice to the patient and a lost opportunity to understand their sequelae (Wortzel et al., 2013).

CTE now joins the family of tauopathies that includes PSP, bvFTD, and AD but there a number of cases of associated TDP and amyloid pathology, which requires further study and clinical correlate (**Figure 1B**). As well, the pathological relationship of CTE with concussion and post-concussion syndrome remains to be explored. As we move toward protein specific treatments, *in vivo* diagnosis of CTE at an early stage will be imperative for implementing appropriate treatments and to delay, halt, or reverse its progression. In order to do this, good clinical-pathological studies will be required and appropriate biomarkers will have to be developed.

REFERENCES

Adnan, A., Crawley, A., Mikulis, D., Moscovitch, M., Colella, B., and Green, R. (2013). Moderate-severe traumatic brain injury causes delayed loss of white matter integrity: evidence of fornix deterioration in the chronic stage of injury. *Brain Inj.* 27, 1415–1422. doi: 10.3109/02699052.2013.823659

Belanger, H. G., Spiegel, E., and Vanderploeg, R. D. (2010). Neuropsychological performance following a history of multiple self-reported concussions: a meta-analysis. *J. Int. Neuropsychol. Soc.* 16, 262–267. doi: 10.1017/S1355617709991287

Blennow, K., Hardy, J., and Zetterberg, H. (2012). The neuropathology and neurobiology of traumatic brain injury. *Neuron* 76, 886–899. doi: 10.1016/j.neuron.2012.11.021

Braak, H., and Braak, E. (1997). Staging of Alzheimer-related cortical destruction. *Int. Psychogeriatr.* 9(Suppl. 1), 257–261. discussion: 269–272. doi: 10.1017/S1041610297004973

Broglio, S. P., and Puetz, T. W. (2008). The effect of sport concussion on neurocognitive function, self-report symptoms and postural control: a meta-analysis. *Sports Med.* 38, 53–67. doi: 10.2165/00007256-200838010-00005

Brun, A. (1993). Frontal lobe degeneration of non-Alzheimer type revisited. *Dementia* 4, 126–131. doi: 10.1159/000107311

Brunden, K. R., Ballatore, C., Crowe, A., Smith, A. B., 3rd, Lee, V. M., and Trojanowski, J. Q. (2009). Tau-directed drug discovery for Alzheimer's disease and related tauopathies: a focus on tau assembly inhibitors. *Exp. Neurol.* 223, 304–310. doi: 10.1016/j.expneurol.2009.08.031

Corsellis, J. A., and Brierley, J. B. (1959). Observations on the pathology of insidious dementia following head injury. *J. Ment. Sci.* 105, 714–720.

Corsellis, J. A., Bruton, C. J., and Freeman-Browne, D. (1973). The aftermath of boxing. *Psychol. Med.* 3, 270–303. doi: 10.1017/S0033291700049588

Costanza, A., Weber, K., Gandy, S., Bouras, C., Hof, P. R., Giannakopoulos, P., et al. (2011). Review: Contact sport-related chronic traumatic encephalopathy in the elderly: clinical expression and structural substrates. *Neuropathol. Appl. Neurobiol.* 37, 570–584. doi: 10.1111/j.1365-2990.2011.01186.x

Critchley, M. (1957). Medical Aspects of Boxing, Particularly from a neurological standpoint. *BMJ* 1, 357–362. doi: 10.1136/bmj.1.5015.357

Cummings, J. L. (1997). The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* 48, S10–S16. doi: 10.1212/WNL.48.5_Suppl_6.10S

Damasio, A. R., Tranel, D., and Damasio, H. C. (1991). "Somatic markers and guidance of behavior: theory and preliminary testing," in *Frontal Lobe Function and Dysfunction,* eds H.M.E. H. S. Levin and A. L. Benton. (New York, NY: Oxford University Press), 217–229.

Dekosky, S. T., Ikonomovic, M. D., and Gandy, S. (2010). Traumatic brain injury–football, warfare, and long-term effects. *N. Engl. J. Med.* 363, 1293–1296. doi: 10.1056/NEJMp1007051

Gardner, A., Iverson, G. L., and McCrory, P. (2014). Chronic traumatic encephalopathy in sport: a systematic review. *Br. J. Sports Med.* 48, 84–90. doi: 10.1136/bjsports-2013-092646

Gavett, B. E., Stern, R. A., Cantu, R. C., Nowinski, C. J., and McKee, A. C. (2010). Mild traumatic brain injury: a risk factor for neurodegeneration. *Alzheimers Res. Ther.* 2, 18. doi: 10.1186/alzrt42

Gavett, B. E., Stern, R. A., and McKee, A. C. (2011). Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. *Clin. Sports Med.* 30, 179–188, xi. doi: 10.1016/j.csm.2010.09.007

Goldstein, L. E., Fisher, A. M., Tagge, C. A., Zhang, X. L., Velisek, L., Sullivan, J. A., et al. (2012). Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci. Transl. Med.* 4, 134ra160. doi: 10.1126/scitranslmed.3003716

Graves, A. B., White, E., Koepsell, T. D., Reifler, B. V., Van Belle, G., Larson, E. B., et al. (1990). The association between head trauma and Alzheimer's disease. *Am. J. Epidemiol.* 131, 491–501.

Green, R., Koshimori, Y., and Turner, G. (2010). Research digest. Understanding the organic basis of persistent complaints in mTBI: findings from functional and structural neuroimaging. *Neuropsychol. Rehabil.* 20, 471–478. doi: 10.1080/09602011003693298

Greenberg, G., Mikulis, D. J., Ng, K., Desouza, D., and Green, R. E. (2008). Use of diffusion tensor imaging to examine subacute white matter injury progression in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S45–S50. doi: 10.1016/j.apmr.2008.08.211

Hazrati, L. N., Tartaglia, M. C., Diamandis, P., Davis, K. D., Green, R. E., Wennberg, R., et al. (2013). Absence of chronic traumatic encephalopathy in retired football players with multiple concussions and neurological symptomatology. *Front. Hum. Neurosci.* 7:222. doi: 10.3389/fnhum.2013.00222

Hu, W. T., Chen-Plotkin, A., Grossman, M., Arnold, S. E., Clark, C. M., Shaw, L. M., et al. (2010). Novel CSF biomarkers for frontotemporal lobar degenerations. *Neurology* 75, 2079–2086. doi: 10.1212/WNL.0b013e318200d78d

Hu, W. T., Watts, K., Grossman, M., Glass, J., Lah, J. J., Hales, C., et al. (2013). Reduced CSF p-Tau181 to Tau ratio is a biomarker for FTLD-TDP. *Neurology* 81, 1945–1952. doi: 10.1212/01.wnl.0000436625.63650.27

Iverson, G. (2007). Predicting slow recovery from sport-related concussion: the new simple-complex distinction. *Clin. J. Sport Med.* 17, 31–37. doi: 10.1097/JSM.0b013e3180305e4d

Jordan, B. D. (2013). The clinical spectrum of sport-related traumatic brain injury. *Nat. Rev. Neurol.* 9, 222–230. doi: 10.1038/nrneurol.2013.33

Lehman, E. J., Hein, M. J., Baron, S. L., and Gersic, C. M. (2012). Neurodegenerative causes of death among retired National Football League players. *Neurology* 79, 1970–1974. doi: 10.1212/WNL.0b013e31826daf50

Litvan, I., Agid, Y., Calne, D., Campbell, G., Dubois, B., Duvoisin, R. C., et al. (1996). Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* 47, 1–9. doi: 10.1212/WNL.47.1.1

Lomen-Hoerth, C., Murphy, J., Langmore, S., Kramer, J. H., Olney, R. K., and Miller, B. (2003). Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 60, 1094–1097. doi: 10.1212/01.WNL.0000055861.95202.8D

Loosemore, M., Knowles, C. H., and Whyte, G. P. (2007). Amateur boxing and risk of chronic traumatic brain injury: systematic review of observational studies. *BMJ* 335, 809. doi: 10.1136/bmj.39342.690220.55

Martland, H. (1928). Punch drunk. *JAMA* 91, 1103–1107. doi: 10.1001/jama.1928.02700150029009

McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, E. T., Gavett, B. E., Budson, A. E., et al. (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J. Neuropathol. Exp. Neurol.* 68, 709–735. doi: 10.1097/NEN.0b013e3181a9d503

McKee, A. C., Gavett, B. E., Stern, R. A., Nowinski, C. J., Cantu, R. C., Kowall, N. W., et al. (2010). TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J. Neuropathol. Exp. Neurol.* 69, 918–929. doi: 10.1097/NEN.0b013e3181ee7d85

McKee, A. C., Stern, R. A., Nowinski, C. J., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., et al. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136, 43–64. doi: 10.1093/brain/aws307

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 263–269. doi: 10.1016/j.jalz.2011.03.005

Mehta, K. M., Ott, A., Kalmijn, S., Slooter, A. J., Van Duijn, C. M., Hofman, A., et al. (1999). Head trauma and risk of dementia and Alzheimer's disease: the Rotterdam Study. *Neurology* 53, 1959–1962. doi: 10.1212/WNL.53.9.1959

Miller, H. (1966). Mental after-effects of head injury. *Proc. R. Soc. Med.* 59, 257–261.

Millspaugh, J. (1937). Dementia pugilistica. *U.S. Naval Med. Bull.* 35, 297–303.

Neselius, S., Brisby, H., Theodorsson, A., Blennow, K., Zetterberg, H., and Marcusson, J. (2012). CSF-biomarkers in Olympic boxing: diagnosis and effects of repetitive head trauma. *PLoS ONE* 7:e33606. doi: 10.1371/journal.pone.0033606

Ng, K., Mikulis, D. J., Glazer, J., Kabani, N., Till, C., Greenberg, G., et al. (2008). Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S35–S44. doi: 10.1016/j.apmr.2008.07.006

Omalu, B., Bailes, J., Hamilton, R. L., Kamboh, M. I., Hammers, J., Case, M., et al. (2011a). Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. *Neurosurgery* 69, 173–183. discussion: 183. doi: 10.1227/NEU.0b013e318212bc7b

Omalu, B., Hammers, J. L., Bailes, J., Hamilton, R. L., Kamboh, M. I., Webster, G., et al. (2011b). Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. *Neurosurg. Focus* 31, E3. doi: 10.3171/2011.9.FOCUS11178

Omalu, B. I., Bailes, J., Hammers, J. L., and Fitzsimmons, R. P. (2010a). Chronic traumatic encephalopathy, suicides and parasuicides in professional American athletes: the role of the forensic pathologist. *Am. J. Forensic Med. Pathol.* 31, 130–132. doi: 10.1097/PAF.0b013e3181ca7f35

Omalu, B. I., Hamilton, R. L., Kamboh, M. I., Dekosky, S. T., and Bailes, J. (2010b). Chronic traumatic encephalopathy (CTE) in a National Football League Player: Case report and emerging medicolegal practice questions. *J. Forensic Nurs.* 6, 40–46. doi: 10.1111/j.1939-3938.2009.01064.x

Omalu, B. I., Dekosky, S. T., Hamilton, R. L., Minster, R. L., Kamboh, M. I., Shakir, A. M., et al. (2006). Chronic traumatic encephalopathy in a national football league player: part II. *Neurosurgery* 59, 1086–1092. discussion: 1092–1083. doi: 10.1227/01.NEU.0000245601.69451.27

Omalu, B. I., Dekosky, S. T., Minster, R. L., Kamboh, M. I., Hamilton, R. L., and Wecht, C. H. (2005). Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery* 57, 128–134. discussion: 128–134. doi: 10.1227/01.NEU.0000163407.92769.ED

Parnetti, L., Castrioto, A., Chiasserini, D., Persichetti, E., Tambasco, N., El-Agnaf, O., et al. (2013). Cerebrospinal fluid biomarkers in Parkinson disease. *Nat. Rev. Neurol.* 9, 131–140. doi: 10.1038/nrneurol.2013.10

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., and Ferri, C. P. (2013). The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* 9, 63–75 e62. doi: 10.1016/j.jalz.2012.11.007

Reeves, T. M., Phillips, L. L., and Povlishock, J. T. (2005). Myelinated and unmyelinated axons of the corpus callosum differ in vulnerability and functional recovery following traumatic brain injury. *Exp. Neurol.* 196, 126–137. doi: 10.1016/j.expneurol.2005.07.014

Reeves, T. M., Smith, T. L., Williamson, J. C., and Phillips, L. L. (2012). Unmyelinated axons show selective rostrocaudal pathology in the corpus callosum after traumatic brain injury. *J. Neuropathol. Exp. Neurol.* 71, 198–210. doi: 10.1097/NEN.0b013e3182482590

Roberts, A. (1969). *Brain Damage in Boxers: a Study of the Prevalence of Traumatic Encephalopathy among Ex-Professional Boxers*. London: Pitman Medical and Scientific Publishing Co., Ltd.

Rosen, H. J., Allison, S. C., Schauer, G. F., Gorno-Tempini, M. L., Weiner, M. W., and Miller, B. L. (2005). Neuroanatomical correlates of behavioural disorders in dementia. *Brain* 128, 2612–2625. doi: 10.1093/brain/awh628

Sayed, N., Culver, C., Dams-O'Connor, K., Hammond, F., and Diaz-Arrastia, R. (2013). Clinical phenotype of dementia after traumatic brain injury. *J. Neurotrauma* 30, 1117–1122. doi: 10.1089/neu.2012.2638

Schapira, A. H. (2013). Recent developments in biomarkers in Parkinson disease. *Curr. Opin. Neurol.* 26, 395–400. doi: 10.1097/WCO.0b013e3283633741

Schofield, P. W., Tang, M., Marder, K., Bell, K., Dooneief, G., Chun, M., et al. (1997). Alzheimer's disease after remote head injury: an incidence study. *J. Neurol. Neurosurg. Psychiatr.* 62, 119–124. doi: 10.1136/jnnp.62.2.119

Shenton, M. E., Hamoda, H. M., Schneiderman, J. S., Bouix, S., Pasternak, O., Rathi, Y., et al. (2012). A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging Behav.* 6, 137–192. doi: 10.1007/s11682-012-9156-5

Sperling, R., and Johnson, K. (2013). Biomarkers of Alzheimer disease: current and future applications to diagnostic criteria. *Continuum (Minneap. Minn.).* 19, 325–338. doi: 10.1212/01.CON.0000429181.60095.99

Stern, R. A., Riley, D. O., Daneshvar, D. H., Nowinski, C. J., Cantu, R. C., and Mckee, A. C. (2011). Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy. *PMR* 3, S460–S467. doi: 10.1016/j.pmrj.2011.08.008

Stuss, D. T., Gallup, G. G., Jr., and Alexander, M. P. (2001). The frontal lobes are necessary for 'theory of mind.' *Brain* 124, 279–286. doi: 10.1093/brain/124.2.279

Stuss, D. T., and Levine, B. (2002). Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annu. Rev. Psychol.* 53, 401–433. doi: 10.1146/annurev.psych.53.100901.135220

Whitwell, J. L., and Josephs, K. A. (2011). Neuroimaging in frontotemporal lobar degeneration–predicting molecular pathology. *Nat. Rev. Neurol.* 8, 131–142. doi: 10.1038/nrneurol.2012.7

Wood, R. L. (2004). Understanding the 'miserable minority': a diasthesis-stress paradigm for post-concussional syndrome. *Brain Inj.* 18, 1135–1153. doi: 10.1080/02699050410001675906

Wortzel, H. S., Brenner, L. A., and Arciniegas, D. B. (2013). Traumatic brain injury and chronic traumatic encephalopathy: a forensic neuropsychiatric perspective. *Behav. Sci. Law*. doi: 10.1002/bsl.2079. [Epub ahead of print].

Zetterberg, H., Smith, D. H., and Blennow, K. (2013). Biomarkers of mild traumatic brain injury in cerebrospinal fluid and blood. *Nat. Rev. Neurol.* 9, 201–210. doi: 10.1038/nrneurol.2013.9

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Absence of chronic traumatic encephalopathy in retired football players with multiple concussions and neurological symptomatology

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Background: Chronic traumatic encephalopathy (CTE) is the term coined for the neurodegenerative disease often suspected in athletes with histories of repeated concussion and progressive dementia. Histologically, CTE is defined as a tauopathy with a distribution of tau-positive neurofibrillary tangles (NFTs) that is distinct from other tauopathies, and usually shows an absence of beta-amyloid deposits, in contrast to Alzheimer's disease (AD). Although the connection between repeated concussions and CTE-type neurodegeneration has been recently proposed, this causal relationship has not yet been firmly established. Also, the prevalence of CTE among athletes with multiple concussions is unknown.

Methods: We performed a consecutive case series brain autopsy study on six retired professional football players from the Canadian Football League (CFL) with histories of multiple concussions and significant neurological decline.

Results: All participants had progressive neurocognitive decline prior to death; however, only 3 cases had post-mortem neuropathological findings consistent with CTE. The other 3 participants had pathological diagnoses of AD, amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD). Moreover, the CTE cases showed co-morbid pathology of cancer, vascular disease, and AD.

Discussion: Our case studies highlight that not all athletes with history of repeated concussions and neurological symptomology present neuropathological changes of CTE. These preliminary findings support the need for further research into the link between concussion and CTE as well as the need to expand the research to other possible causes of taupathy in athletes. They point to a critical need for prospective studies with good sampling methods to allow us to understand the relationship between multiple concussions and the development of CTE.

Keywords: chronic traumatic encephalopathy, repetitive brain injury, professional athletes, dementia, neurodegenerative disease

INTRODUCTION

Sport-related concussions affect millions of people in North America annually (Pickett et al., 2004). Among Canadian university hockey players, concussion accounts for 13% of all injures, ranking as the second most common injury after sprains or strains (Rishiraj et al., 2009). Although concussions were previously considered reversible injuries with transient symptoms, a number of recent studies have emerged linking repeated concussions and possibly asymptomatic subconcussive impacts with long-term neurodegenerative changes (McKee et al., 2009, 2010; Omalu et al., 2011; Stern et al., 2011).

The clinical neurocognitive impact of repetitive head injury was described by Martland in 1928 in "poorly skilled boxers" who withstood multiple blows to the head in efforts to position themselves in close proximity to their opponents to land a punch; subsequent symptoms included ataxia, amnesia, dementia, dysarthria, parkinsonism, and other motor and coordination deficits (Martland, 1928; Parker, 1934). In addition, behavioral

and personality changes, aggression, jealousy, paranoia, and an increased incidence of physical domestic disputes and suicide were noted (Parker, 1934; Mendez, 1995; McKee et al., 2009; Omalu et al., 2010a).

Recently, the term chronic traumatic encephalopathy (CTE) was coined to refer to the clinical constellation of neurocognitive decline in conjunction with neuropathological findings of abnormal hyperphosphorylated-tau neuronal deposits in a pattern distinguishable from other tauopathies. CTE has been associated with many contact sports, including football, wrestling, hockey, and rugby (Corsellis et al., 1973; Omalu et al., 2005, 2006, 2010a,b,c, 2011; McKee et al., 2009, 2010; Gavett et al., 2011; Stern et al., 2011).

Because of the clinical and social ramifications of CTE and its putative relationship to concussion history, further research is critically needed to better understand the prevalence and risk factors for CTE. As well, the relationship between multiple concussions, positive clinical symptoms and the presence of CTE is also unclear. The current case series examines this relationship.

CTE can only be definitively diagnosed post-mortem. Given the relative rarity of cases of CTE, and the even rarer opportunity for post-mortem examination of individuals with a history of concussions at risk for CTE, it is important to provide a description of these clinical cases as they emerge.

On gross neuropathological examination, typical advanced CTE findings include dilated ventricles, fenestrated cavum septi pellucidi, and significant atrophy of the medial temporal lobes, thalamus, and mammillary bodies (McKee et al., 2009; Gavett et al., 2011; Stern et al., 2011). There can also be pallor of the locus coeruleus and substantia nigra (McKee et al., 2009; Gavett et al., 2011; Stern et al., 2011). Microscopically, CTE typically features tau-positive NFTs and astrocytic tangles, and neuropil neurites in a distribution distinctly different from other tauopathies such as Progressive Supranuclear Palsy, Corticobasal degeneration, and Alzheimers' Disease (AD) (McKee et al., 2009; Omalu et al., 2011). In CTE, these changes are patchy, localized to the depths of sulci, perivascularly around small vessels, in subpial areas and in the superficial cortical layers (II/III) (McKee et al., 2009; Omalu et al., 2011). In contrast to AD, CTE, as defined in recent literature (McKee et al., 2009; Omalu et al., 2011) lacks significant amounts of Alzheimer's-like beta-amyloid plaques (McKee et al., 2009; Gavett et al., 2011; Omalu et al., 2011; Stern et al., 2011). The neuropathology of CTE has been recently expanded to encompass in some cases the possible presence of widespread TDP-43-positive inclusions in the brainstem, basal ganglia, and cortex (McKee et al., 2010). In such cases, the presence of these lesions in the corticospinal tract and anterior horn of the spinal cord may be associated with clinical findings of spasticity, weakness, and fasciculations, similar to the clinical presentation ALS (McKee et al., 2010).

Here, we report on the clinical and pathological case histories for 6 retired Canadian Football League (CFL) athletes who underwent autopsies limited to the central nervous system. We address the question whether retired professional athletes with a history of multiple concussions and the presence of neurological findings will invariably manifest as CTE (alone or with co-morbid pathology) or whether this history can be associated with other diagnoses.

METHODS

This study was approved by the Ethics Review Board of the University Health Network. Informed consent to participate in this study was provided by each participant or the participant's designated next of kin.

PARTICIPANTS

The brains of six adults consecutively referred for autopsy were examined. Participants comprised a convenience sample of adults who played professional football (CFL) with a history of multiple concussions and medically- or family-member documented histories of progressive cognitive, psychiatric, and/or motor symptoms (see **Table 1**).

DESIGN

This was a retrospective, case series design of consecutively referred brains for autopsy. Analyses are descriptive, using the following possible primary outcomes: neuropathological diagnosis of (i) CTE alone, (ii) CTE plus other neurological disorder, (iii) other neurodegenerative disorder and (iv) no neurodegenerative disorder.

PROCEDURES

Clinical details were collected from next of kin, treating physicians, and medical records. The clinical data was obtained through structured interviews of the family members as well through clinical consult notes sent by treating physicians. The brain autopsy was authorized by next of kin.

Neuropathological analysis protocol

The post-mortem time varied from 4 to 72 h. At autopsy, the brains were immediately placed in neutral formalin and sectioned after two weeks. At the time of autopsy, a piece of frontal lobe was snap frozen for future proteomic/genetic studies. The brains were photographed and extensively sampled from several cortical, subcortical, cerebellar and brainstem areas. Tissue blocks were processed and embedded in paraffin. Six micron coronal sections were stained with Luxol fast blue and hematoxylin and eosin (H&E/LFB), Bielschowsky silver impregnation or Gallyas silver stain, and by immunohistochemistry with the following antibodies: hyperphosphorylated-tau (mouse monoclonal AT8; Pierce Endogen, Rockford IL; 1:2000), [alpha]-synuclein (rabbit polyclonal; Chemicon, Temecula, CA; 1:15,000), and A[beta] (mouse monoclonal, Dako North America Inc., Carpinteria, CA; 1:2000) (after formic acid pretreatment). Other antibodies used for immunostaining were: glial fibrillary acidic protein (GFAP-Chemicon; 1:2000), TDP-43 (rabbit polyclonal to TAR DNA-binding protein, 1:1000; Abcam, Cambridge, MA), and ubiquitin (rabbit polyclonal, 1:2000; Dako North America Inc., Carpinteria, CA). The neuropathological diagnoses were based on most recent neuropathological criteria provided by consensus studies for AD (Hyman et al., 2012), Parkinson's disease (PD) (Dickson, 2012) and fronto-temporal dementia (Cairns et al., 2007). CTE diagnosis was based on recent publications (McKee et al., 2009; Omalu et al., 2011).

Table 1 | Summary of clinical histories of professional football athletes in study cohort.

Case	Age at onset (yrs)	Initial symptoms	Progressive dementia	Behavioral changes	Language	Memory decline	Executive function	VSP	Motor impairment	Disease duration (yrs)	Concussions	Family history	Pathological diagnosis
1	70	Apathy, Memory deficits, decreased concentration, getting lost, language deficits	Yes	Apathy; rummaging through garbage, irritable, aggressive late	Severe expressive aphasia (nonfluent) 2005	STM	Decreased concentration	Getting lost	Very late (2010)	16	Multiple	Brother (late onset AD), Paternal aunt and Grandfather (dementia). Parents died young.	1. CTE 2. AD (Braak VI/VI)
2	56	Pseudobulbar affect	No	No	Mild word-finding deficits late	Mild STM (late onset)	Mild difficulty with planning/ organizing, problem-solving very late	No	Dysarthria/ dysphagia	5	Multiple	Nil	1. ALS
3	50	Personality-affect flatter; appeared depressed; STM; subtle changes in gait	Yes	1994 MDE, apathy, less empathy, dis-inhibited, agitation/ aggression, anxious, paranoid delusions, hallucinations	Later moderate expression/ comprehension deficits	STM	Decreased concentration late 90s	No	Slower gait, Instability, Tremor, Rigidity, Parkinsonian Gait and RBD, Lost sense of olfaction.	29	Multiple	Sister (PD) Mother & Father (depression)	1. DLBD 2. CTE
4	55	Memory deficits, apathetic, depressed	Yes	Apathetic, agitated, depressed Later paranoid delusions	Word-finding initially then loss of semantic meaning, word substitution	STM	Financial trouble 2009 because of poor judgment	Getting lost	Difficulty walking because of toe amputation	12	Multiple	Vascular dementia paternal grandfather	1. CTE 2. Multiple infarcts
5	64	Memory deficits, irritability	Yes	Aggressive, apathetic, hallucinations, delusions	Word-finding difficulty, increased speech output	STM	Poor judgment early on–let people leave with articles without paying	Getting lost	No	10	Multiple	Mother late onset AD, Father late onset dementia	1. AD
6	48	Motor-slowing; anxious, withdrawn	Yes	Hallucinations; delusions; throwing everything away	Decreased speech output	STM	Loss of judgment, loss of planning/ organizing	Getting lost (late onset)	Dysphagia, Dysarthria, Bradykinesia	15	Multiple	Nil	1. PD

Abbreviations: MDE, major depressive episode; STM, short-term memory; VSP, visuospatial function; PD, Parkinson's disease; AD, Alzheimer's disease; ALS, Amyotrophic Lateral Sclerosis; DLBD, Diffuse Lewy body disease. "Disease Duration" indicates number of years between initial symptoms and death.

RESULTS

OVERVIEW OF CASES

All six participants had been professional football athletes in the CFL, and had played multiple positions including offensive and defensive positions. All participants had histories of multiple concussions, but information about the exact frequency and intensity of head injury could not be determined. Their ages ranged from 61 to 87 years with disease durations of 3–17 years from the onset of first reported neurodegenerative symptoms to death. Additional details are provided in **Table 1**.

CASE FINDINGS

Case 1

Sport history. This patient played football from a young age, continued through university and played professionally in the CFL for 5 years. He played multiple positions, but was predominantly a halfback and kick returner. He had many concussions.

Clinical history. Around age 70, the patient first developed memory impairment, including getting lost, and difficulty concentrating. Apathy was also noted in his early 70s. His hygiene was not impaired, but he rummaged through the family's garbage and pulled out old items. His eating habits changed, as he became bothered by the texture of certain foods, especially meat. He was a restless sleeper, but did not display violent behavior during sleep. He also developed language deficits including word-finding difficulty and semantic paraphasias. By 85 he had developed significant expressive aphasia while his comprehension remained intact until a few weeks before his death. He also showed significant neuropsychiatric symptoms that included increased irritability and agitation. His motor function was preserved until late in his course of illness; he was still walking until age 86 when he became confined to a wheelchair due to unsteadiness. The patient died at age 86 years.

Family history. His family history was significant for a brother who developed AD in his 70's and dementia in his paternal aunt and grandfather. Both his parents died young from unrelated causes.

Neuropathological findings. Neuropathological examination showed a moderately atrophic brain (1290 g) with mild but preferential wasting of the frontal and temporal lobes (**Figure 1**). The ventricles (including the temporal horns of the lateral ventricles) were moderately enlarged. There was cavum septi pellucidi, thinning of the corpus callosum and atrophy of the amygdala and mamillary bodies. The hippocampi appeared normal in size. Examination of the midbrain revealed depigmentation of the substantia nigra (SN) (**Figure 1**).

Microscopically, the brain showed widespread tauopathy. More specifically, hyperphosphorylated-tau staining showed concentration of neurofibrillary tangles (NFTs) predominantly in the superficial layers in the gray matter and depths of sulci (**Figure 2**). There was continuous tau-positive glia in the subpial and patchy areas seen in the grey/white matter junction and around blood vessels. Numerous NFT were also noted in the deeper layers of the cortex as well. Tau distribution was diffuse throughout the brain involving the frontal, temporal (highest populations), and inferior parietal lobes, indusium griseum, and striate and cingulate cortices. There was heavy tau staining in the amygdala and throughout the hippocampus (CA1-4, subiculum and trans-enthorhinal cortex). There were patchy tau-positive inclusions seen throughout the brainstem, as well as in the nucleus basalis of Meynert, the thalamus, hypothalamus, and mammillary bodies. Numerous senile plaques were observed throughout the brain, most notably in the trans-entorhinal cortex. TDP-43 staining was not a feature of this case.

Neuropathological diagnosis. Overall, the pathological patterns of staining showed characteristics of both CTE and severe AD (Braak Stage VI/VI).

Case 2

Sport history. This participant played football, hockey, and rugby from a young age, including 12 years in the CFL playing defense. He had many concussions.

Clinical history. The patient first developed emotional lability and slurred speech at age 56 years, and was subsequently diagnosed with bulbar onset ALS. Over the next few years, he lost his speech and ability to swallow, requiring a feeding tube at age 59 and a tracheotomy at age 61. His limb movements, personality, and cognitive function remained relatively preserved, although there was a mild decline in short memory function at age 60. He died at age 61.

Family history. No family history of a neurodegenerative disease.

Neuropathological findings. Neuropathological examination showed normal brain weight (1540 g) and normal exterior appearance without atrophy (**Figure 1**). Ventricles were of normal size with no cavum septi pellucid. SN showed normal pigmentation.

Microscopic examination revealed loss of neurons in the motor nuclei of multiple cranial nerves—predominantly cranial nerves VII and XII—with TDP-43 positive intracytoplasmic inclusions (**Figure 2**). Some intracytoplasmic TDP-43-positive inclusions and neuronal loss was also noted in the cervical spinal cord involving the lower motor neurons. Inclusions were also noted in the primary motor cortex, and to a lesser extent, in the dentate gyrus. Pathological deposition of hyperphosphorylated tau was very scarce and limited to the trans-entorhinal cortex in the shape of NFTs in neurons. A few beta-amyloid plaques were also noted.

Neuropathological diagnosis. These neuropathological findings were consistent with the diagnosis of amyotrophic lateral sclerosis (ALS).

Case 3

Sport history. This participant retired after a12-year CFL career, playing both offense and defense positions. He had many concussions.

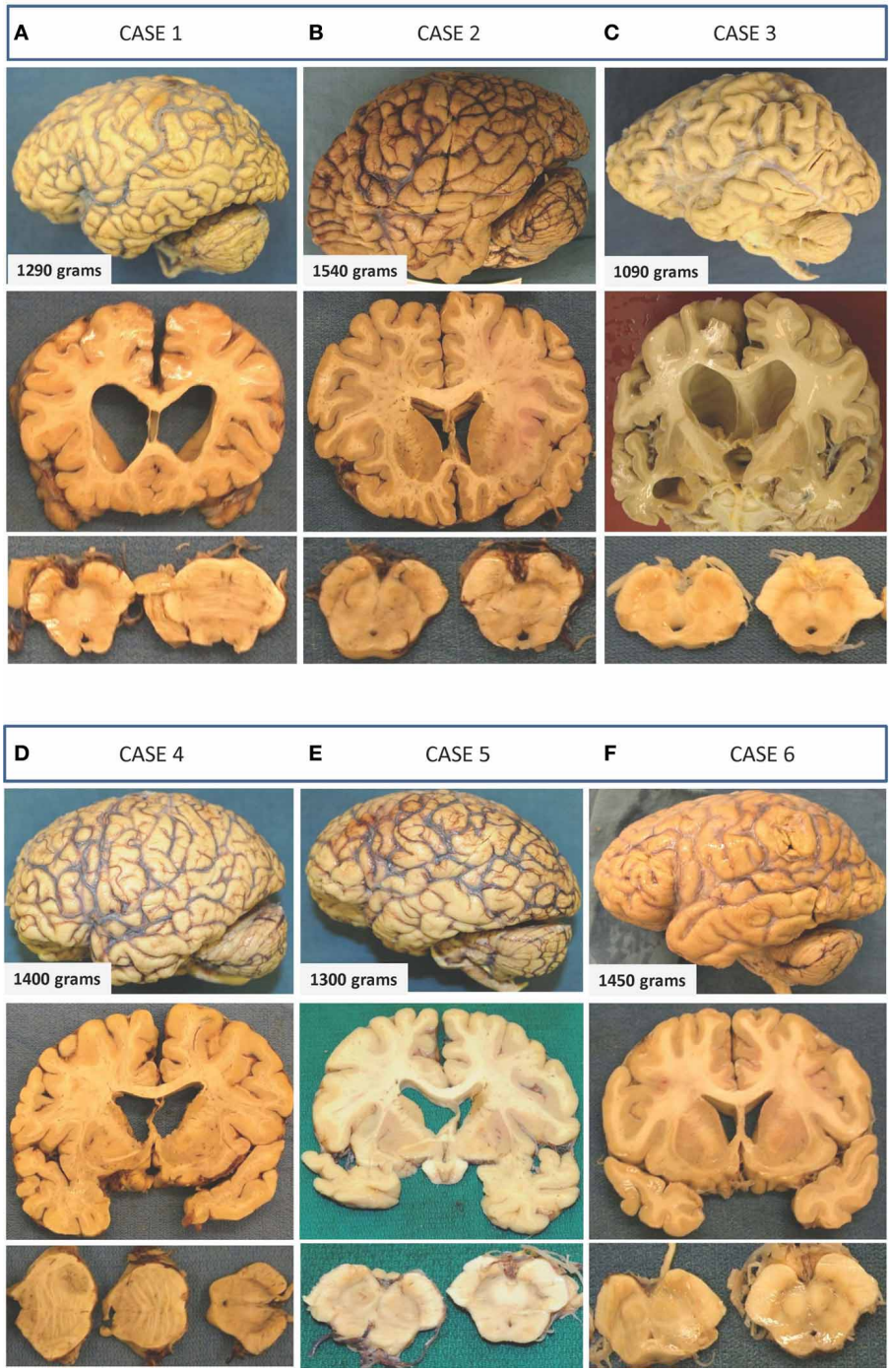

FIGURE 1 | Gross macroscopic findings on neuropathological examination. Selected examples from each case are presented as three vertical panels with lateral views of the unsectioned brain (upper panel), coronal sections through various parts of the cerebrum (middle panel), and axial sections through the brainstem (lower panel). **(A) Case 1:** There is mild-to-moderate atrophy with ventricular enlargement and cavum septi pellucidi. Thinning of the corpus callosum and mild depigmentation of the substantia nigra is also evident. **(B) Case 2:** Unsectioned brain, ventricles, and sections of the midbrain and substantia nigra appear within normal limits with no apparent evidence of neurodegeneration. **(C) Case 3**: Preferential mild-to-moderate atrophy of frontal and temporal lobes with significant enlargement of ventricles seen on coronal sections. A fenestrated septum pellucidum and atrophied amygdala and hippocampus are also seen on this section. The substantia nigra of this patient shows significant loss of pigmentation. **(D) Case 4:** There is mild frontal and temporal lobe atrophy with enlarged ventricles and cavum septi pellucidi. Axial sections of the brainstem show normal appearing substantia nigra and a metastatic lesion in the pons. **(E) Case 5:** Atrophic brain is seen with moderately enlarged ventricles and a normally pigmented substantia nigra. **(F) Case 6:** Minimal atrophy and ventricular enlargement are seen, and there is mild loss in the substantia nigra.

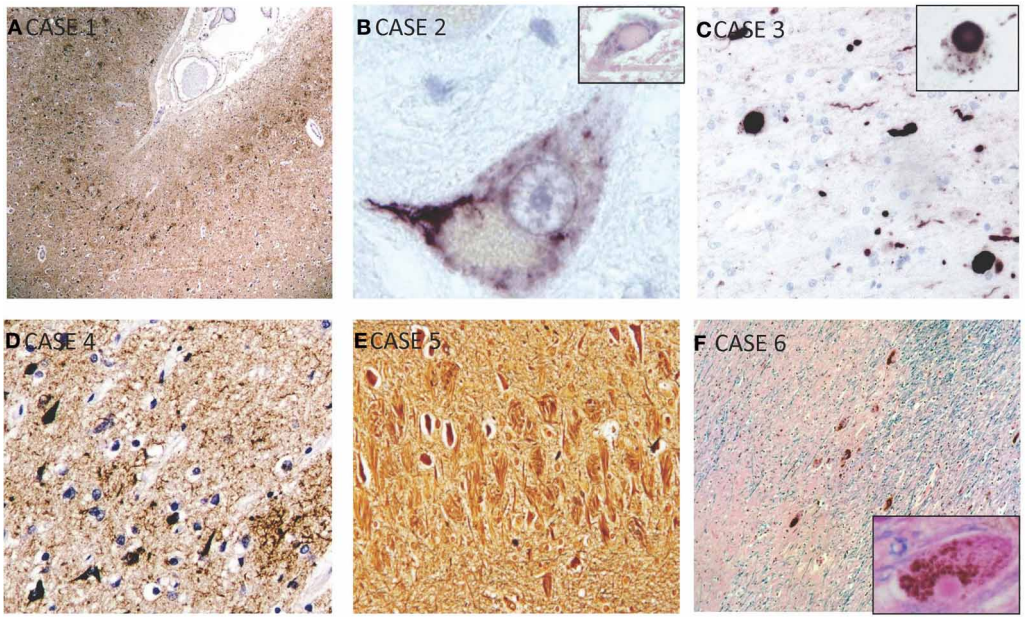

FIGURE 2 | Selected microscopic findings on neuropathological examination. (A) Case 1: High power view of sample of cerebral cortex stained for hyperphosphorylated-tau shows concentration of neurofibrillary tangles predominantly in the superficial layers of the gray matter and in the depths of sulci, which is characteristic of CTE. **(B) Case 2:** Magnified motor neuron in ventral horn of spinal cord shows a representative intracytoplasmic TDP-43 inclusion. Inset shows a hyalin inclusion. **(C) Case 3:** Alpha-synuclein staining showing Lewy bodies and neurites which are seen throughout the cortex, substantia nigra, and locus ceruleus. This patient also had features of CTE (not shown). Inset shows higher power view of cytoplasmic Lewy body. **(D) Case 4:** Immunohistochemisty showing widespread reactivity against tau-positive neurofibrillary and astrocytic tangles in multiple layers. **(E) Case 5:** Bielschowsky silver stain showing numerous neurofibrillary tombstones in the hippocampus. **(F) Case 6:** HandE/LFB and alpha-synuclein staining of representative cortical section showing diffuse Lewy bodies and Lewy neurites. Inset shows Lewy body.

Clinical findings. His wife noticed personality changes, including flat affect and depressed mood, when he was age 50. At age 55, he developed some short-term memory impairment. In his 60s, his family noticed executive deficits in that he could no longer manage his company. At the age of 62, she noticed some subtle changes in his gait. He walked more slowly, and less steadily. He also had a major depressive episode that year and underwent electroconvulsive therapy. He developed a tremor, rigidity, a parkinsonian gait, and rapid eye movement (REM) sleep behavior disorder, and also lost his sense of olfaction. His wife also noted apathy and reduced empathy. In his early 70s, he became disinhibited, had delusions, hallucinations, and episodes of agitation and aggression. He was diagnosed with PD, but the early cognitive changes at the onset of his disease and the subsequent hallucinations were more typical of dementia with Lewy bodies (DLB). The patient died at age 79.

Family history. His sister was reported to have PD. Both his parents suffered from depression.

Neuropathological findings. Neuropathological examination of the brain revealed a moderately atrophic brain with a weight of 1090 g after fixation (**Figure 1**). Moderate volume loss was noted in the frontal, temporal, and parietal lobes, and mild atrophy was noted in the occipital lobe. There was significant ventricular enlargement, thinning of the corpus callosum, and cavum septi pellucidi. Coronal sectioning of the brain revealed significant atrophy of the amygdala and hippocampus. The brainstem examination revealed pallor of the SN (**Figure 1**).

Microscopic examination revealed a widespread tauopathy in the form of neurofibrillary and astrocytic tangles clustering in patches in the superficial layers of most cortical areas in both the sulci and gyral crowns. The primary visual cortex was spared. Tau-immunopositive neurons were most pronounced in the amygdala and hippocampus. There were diffuse astrocytic tangles noted around blood vessels and throughout the parenchyma. Tau-positive inclusions and neurites also populated the subcortical structures including the striatum, globus pallidus, dentate nucleus of the cerebellum, thalamus, subthalamic nucleus, substantia nigra, hypothalamus, septal nuclei, nucleus basalis of Meynert, mammillary bodies, periventricular white matter, locus ceruleus, red nucleus and the nucleus of the third cranial nerve. Localized TDP-43 staining of the amygdala and hippocampus revealed numerous inclusions. Alpha-synuclein staining revealed numerous Lewy bodies and Lewy neurites throughout the cortex, substantia nigra and locus ceruleus suggested advanced Lewy body disease (**Figure 2**). There were senile plaques in the hippocampus and cortical areas that were tau-positive, and stained with Congo red and Gallyas silver. Luxol fast blue stain showed abnormal pallor of the white matter. There was also neuronal loss in the substantia nigra, locus ceruleus,

hippocampus, and nucleus basalis of Meynert. Given the extensive neuronal and astrocytic tauopathy, TDP-43 inclusions and synucleinopathy.

Neuropathological diagnosis. This case was diagnosed with combined CTE and diffuse Lewy body disease.

Case 4

Sport history. This participant played football in high school and in the CFL for 6 years. He had many concussions.

Clinical findings. When the patient was 55-years old, his sister noted that he had difficulty with short-term memory and that he was less able to formulate arguments. He subsequently developed visuospatial impairments and was reported to get lost in familiar environments. He developed apathy and agitation, and became very depressed. His loss of judgment led to bankruptcy and at the age of 66, he became a ward of the state. He developed language deficits and exhibited word substitution, and was incoherent at times. He became depressed and had paranoid delusions. His past medical history was unremarkable except for recurrent phlebitis. The patient developed lung cancer and died of its complications at age 67.

Family history. His paternal grandfather had vascular dementia.

Neuropathological findings. Neuropathological examination revealed a brain weight of 1400 g with mild atrophy of the frontal and temporal lobes (**Figure 1**). There were findings consistent with widespread metastatic disease from a lung carcinoma and severe vascular atherosclerotic disease with recent multifocal brain infarctions. There was also thinning of the olfactory tracts and hypothalamus. Coronal sections of the brain showed an enlarged ventricular system, corpus callosum atrophy, and cavum septi pellucidi. Pigmentation of the SN appeared within normal limits (**Figure 1**).

Microscopically, there was mild to moderate neuronal loss and gliosis in CA1, subiculum, entorhinal cortex, amygdala, mammillary bodies, and medial thalamic nuclei. There was granulovacuolar degeneration noted in the CA1 and subiculum area with pronounced subpial gliosis in the trans-entorhinal cortex. Immunohistochemically, there was widespread tau-positive neurofibrillary and astrocytic tangles in multiple layers (superficial > deep) of the cortex, especially in the depths of sulci (**Figure 2**). There were some inclusions noted in the gyral crowns. These inclusions were consistently found in all cortical areas with a predilection for the medial temporal, hippocampus, and amygdala areas. NFTs were also noted in thalamus, peri-ventricular hypothalamic areas extending into the mamillary bodies, the nucleus basalis of Meynert and clustering around blood vessels. Beta-amyloid staining revealed amyloid plaques. TDP-43 and alpha-synuclein staining were unremarkable.

Neuropathological diagnosis. Overall, neuropathological findings and the distribution of tauopathy were compatible with changes seen in CTE. Although there were multiple infarcts noted, they appeared to be relatively recent infarcts and could not fully account for the participant's longer-term dementia.

Case 5

Sport history. This patient played in the CFL for 8 years. He had many concussions.

Clinical findings. At age 64, he began to show behavioral changes, including anger, poor judgment, and irritability. Over the next few years his memory worsened and he began to get lost. He then began having hallucinations of strangers in his home and also developed some misidentification for others and himself. He seemed to no longer recognize himself as he would attack mirrors when he walked in front of them. He developed delusions that people were stealing from him and had episodes of aggression and agitation, as well as impaired motor function. The patient died at age 74.

Family history. His mother had late onset AD and his father had late onset dementia.

Neuropathological findings. His brain was atrophic with a weight of 1300 g after fixation with moderate ventricular enlargement (**Figure 1**). SN showed normal pigmentation.

Microscopic examination revealed numerous NFTs in neurons of the deep cortical layers (**Figure 2**). These were concentrated to the trans-entorhinal cortex, hippocampus, and isocortex with significant extension into the primary visual cortex. There was also significant presence of tangles in nucleus basalis of Meynert, amygdala, substantia nigra, and in the Edinger–Westphal nucleus. Supplementing the tangles were numerous dense-core, beta-amyloid positive plaques. No evident TDP-43 or alpha-synuclein staining was seen.

Neuropathological diagnosis. Overall, findings were consistent with severe AD (Braak Stage VI/VI) without any pathological evidence of CTE.

Case 6

Sport history. He began playing football in high school and played seven years in the CFL. He suffered multiple concussions.

Clinical findings. At age 48, his wife noted that he was becoming withdrawn and then he gradually changed from a confident, assertive, energetic person to an anxious, insecure, and more lethargic person. At age 50, he noted his handwriting had become messier, and also complained of some cramping and numbness in his feet and decreased ability for playing baseball. He also began exhibiting memory deficits, which became progressively worse over the subsequent years. A few years later, his wife noted his speech was slurred and hypophonic and the slowing of his movements became more apparent. He did not have a tremor. At age 54, his wife became concerned about his judgment based on poor business decisions. He became obsessive about bladder incontinence and went to the bathroom multiple times a day, yet seemed incongruously unperturbed when accidents did happen. By age 55, he was having repeated episodes of loss of bladder control. He had vivid dreams that he was convinced were real, but no REM sleep behavior disorder. His judgment continued to deteriorate, and he became less attentive to hygiene. He had delusions and hallucinations, but these stopped with discontinuation of Sinemet

therapy. He eventually had episodes of agitation and developed great difficulty ambulating. He had prosopagnosia at age 58. At that time, he began showing difficulty recalling the names of his children. His past medical history was unremarkable. The patient died at age 63.

Family history. No family history of a neurodegenerative disease.

Neuropathological findings. Neuropathological examination showed a brain of normal weight (1450 g) with mild diffuse cortical atrophy. Ventricles were mildly dilated (**Figure 1**).

On microscopic examination, there was diffuse Lewy body disease with Lewy bodies and Lewy neuritis in the cerebral cortex, olfactory bulbs, indusium griseum, SN and limbic system, including the CA2-4 subdivisions of the hippocampus (**Figure 2**). There was extensive neuronal loss in the SN pars compacta, locus ceruleus, dorsal nucleus of CN X and nucleus basalis of Meynert. There was very limited tau labeling in the hippocampus, the amygdala, and peri-amygdala cortex. There was, however, widespread distribution of diffuse amyloid plaques. TDP-43 staining in this case was unremarkable.

Neuropathological diagnosis. Overall, this case showed typical changes of long-term progressive PD. While the tau-deposits in the hippocampal area were age-appropriate Alzheimer-type changes (Braak Stage II/VI), there was no evidence of AD. There was also no pathological evidence consistent with CTE.

DISCUSSION

At present, the diagnosis of CTE requires post-mortem examination. In our case series, a history of participation in professional football and a history of multiple concussions, combined with positive clinical signs and symptoms of progressive neurodegenerative disease, were not inevitably associated in each of the 6 cases with a post-mortem diagnosis of CTE. The neuropathological diagnosis of our six cases comprised: CTE + AD, CTE + diffuse Lewy body disease, CTE + multiple infarcts, AD, ALS, and PD (see **Table 1**). In our case series of professional football athletes, we observed that the reported progressive neurological findings in some athletes participating in contact sports were associated with CTE, while other athletes had more common neurodegenerative conditions, namely AD, PD, and ALS. Moreover, those individuals with post-mortem diagnosis of CTE had co-morbid pathological findings that may also have contributed to the clinical signs and symptoms. Thus, our findings advocate caution in the clinical diagnosis of CTE in patients with histories of contact sports and neurocognitive decline, as other diagnoses of neurodegenerative diseases are also possible. Our findings are consistent with a literature review by Nowak et al. (2009), in which dementia in retired boxers could be explained by pathologies aside from dementia pugilistica (Nowak et al., 2009—see also McKee et al., 2013). In contrast, other previous studies either focused on describing CTE in professional athletes (Omalu et al., 2005, 2006, 2010b,c; McKee et al., 2009, 2010) or found that a majority of professional athletes had CTE (Omalu et al., 2011).

These findings raise questions regarding the relationship between multiple concussions in professional football alumni and CTE, the prevalence of CTE in this population and the risk factors. Previous post-mortem research with larger samples of professional athletes with multiple concussions has suggested a very high incidence rate; however, such studies have been limited by biased samples restricted to clinically symptomatic cases and a lack of medical post-mortem controls with co-morbidities consistent with the professional athlete histories, including comparable medication/substance histories as well as pain disorders, of potential relevance given increasing evidence for the role of neuroinflammatory processes in pain disorders (Davis and Moayedi, 2012).

Our findings cannot address these limitations, but suggest the testable hypothesis that the mapping between multiple concussion history in former professional athletes plus positive progressive clinical findings is not one-to-one with CTE, a hypothesis supported by the expectation that aging professional athletes should be as susceptible as the general aging population to neurodegenerative diseases such as AD, vascular dementia, PD or ALS.

A limitation of our retrospective clinical case series was that historical information was subject to recall bias. The participants' informants could not provide the actual number or severity of the concussions, although there was sufficient information to indicate that each player had sustained multiple concussions throughout their careers. When these players were active participants, concussions were not well recognized, and if recognized, were treated as a minor injury.

CONCLUSION

Our initial experience with this cohort of retired professional football athletes with multiple concussions and progressive neurocognitive decline demonstrates that these cases did not uniformly have neuropathological findings of CTE. Some cases with CTE pathology had concomitant pathologies that could also contribute to cognitive decline. Thus, it is difficult to establish a definitive link between a history of multiple concussions and CTE. Neuropathological examination remains essential for diagnosis of CTE, as other types of brain degeneration may be present in professional athletes with neurocognitive decline. Further research is needed to establish the relationship between multiple concussions and the development of CTE and to examine the prevalence and the risk factors that mediate the relationship between multiple concussions and development of CTE.

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REFERENCES

Cairns, N. J., Neumann, M., Bigio, E. H., Holm, I. E., Troost, D., Hatanpaa, K. J., et al. (2007). TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. *Am. J. Pathol.* 171, 227–240.

Corsellis, J. A., Bruton, C. J., and Freeman-Browne, D. (1973). The aftermath of boxing. *Psychol. Med.* 3, 270–303.

Davis, K. D., and Moayedi, M. (2012). Central mechanisms of pain revealed through functional and structural MRI. *J. Neuroimmune Pharmacol.* doi: 10.1007/s11481-012-9386-8. [Epub ahead of print].

Dickson, D. (2012). Parkinson's disease and parkinsonism: neuropathology. *Cold Spring Harb. Perspect. Med.* 2:pii: a009258. doi: 10.1101/cshperspect.a009258

Gavett, B. E., Stern, R. A., and McKee, A. C. (2011). Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. *Clin. Sports Med.* 30, 179–188, xi.

Hyman, B. T., Phelps, C. H., Beach, T. G., Bigio, E. H., Cairns, N. J., Carrillo, M. C., et al. (2012). National Institute on Aging – Alzheimer's Association guidelines for the neuorpathologic assessment of Alzheimer's disease. *Alzheimers Dement.* 8, 1–13.

Martland, H. S. (1928). Punch drunk. *J. Am. Med. Assoc.* 91, 1103–1107.

McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, E. T., Gavett, B. E., Budson, A. E., et al. (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J. Neuropathol. Exp. Neurol.* 68, 709–735.

McKee, A. C., Gavett, B. E., Stern, R. A., Nowinski, C. J., Cantu, R. C., Kowall, N. W., et al. (2010). TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J. Neuropathol. Exp. Neurol.* 69, 918–929.

McKee, A. C., Stein, T. D., Nowinski, C., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., et al. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136, 46–64.

Mendez, M. F. (1995). The neuropsychiatric aspects of boxing. *Int. J. Psychiatry Med.* 25, 249–262.

Nowak, L. A., Smith, G. G., and Reyes, P. F. (2009). Dementia in a retired world boxing champion: case report and literature review. *Clin. Neuropathol.* 28, 275–280.

Omalu, B., Bailes, J., Hamilton, R. L., Kamboh, M. I., Hammers, J., Case, M., et al. (2011). Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. *Neurosurgery* 69, 173–183. discussion: 183.

Omalu, B. I., Bailes, J., Hammers, J. L., and Fitzsimmons, R. P. (2010a). Chronic traumatic encephalopathy, suicides and parasuicides in professional American athletes: the role of the forensic pathologist. *Am. J. Forensic Med. Pathol.* 31, 130–132.

Omalu, B. I., Fitzsimmons, R. P., Hammers, J., and Bailes, J. (2010b). Chronic traumatic encephalopathy in a professional American wrestler. *J. Forensic Nurs.* 6, 130–136.

Omalu, B. I., Dekosky, S. T., Hamilton, R. L., Minster, R. L., Kamboh, M. I., Shakir, A. M., et al. (2006). Chronic traumatic encephalopathy in a national football league player: part II. *Neurosurgery* 59, 1086–1092. discussion: 1092–1093.

Omalu, B. I., Dekosky, S. T., Minster, R. L., Kamboh, M. I., Hamilton, R. L., and Wecht, C. H. (2005). Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery* 57, 128–134. discussion: 128–134.

Omalu, B. I., Hamilton, R. L., Kamboh, M. I., Dekosky, S. T., and Bailes, J. (2010c). Chronic traumatic encephalopathy (CTE) in a National Football League Player: case report and emerging medicolegal practice questions. *J. Forensic Nurs.* 6, 40–46.

Parker, H. L. (1934). Traumatic encephalopathy ('Punch Drunk') of professional pugilists. *J. Neurol. Psychopathol.* 15, 20–28.

Pickett, W., Simpson, K., and Brison, R. J. (2004). Rates and external causes of blunt head trauma in Ontario: analysis and review of Ontario Trauma Registry datasets. *Chronic Dis. Can.* 25, 32–41.

Rishiraj, N., Lloyd-Smith, R., Lorenz, T., Niven, B., and Michel, M. (2009). University men's ice hockey: rates and risk of injuries over 6-years. *J. Sports Med. Phys. Fitness* 49, 159–166.

Stern, R. A., Riley, D. O., Daneshvar, D. H., Nowinski, C. J., Cantu, R. C., and McKee, A. C. (2011). Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy. *PM R* 3, S460–S467.

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Methodological considerations in longitudinal morphometry of traumatic brain injury

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Traumatic brain injury (TBI) has recently been reconceptualized as a chronic, evolving disease process. This new view necessitates quantitative assessment of post-injury changes in brain structure that may allow more accurate monitoring and prediction of recovery. In particular, TBI is known to trigger neurodegenerative processes and therefore quantifying progression of diffuse atrophy over time is currently of utmost interest. However, there are various methodological issues inherent to longitudinal morphometry in TBI. In this paper, we first overview several of these methodological challenges: lesion evolution, neurosurgical procedures, power, bias, and non-linearity. We then introduce a sensitive, reliable, and unbiased longitudinal multivariate analysis protocol that combines dimensionality reduction and region of interest approaches. This analysis pipeline is demonstrated using a small dataset consisting of four chronic TBI survivors.

Keywords: longitudinal, power, bias, magnetic resonance imaging, sparse canonical correlation analysis

INTRODUCTION

Traumatic brain injury (TBI) triggers a cascade of events that lead to long-term neuropathological and behavioral consequences. Recently, more and more researchers have been conceptualizing TBI as a chronic disease with dynamic and evolving recovery and degeneration processes (e.g., Masel and Dewitt, 2010). Among the post-injury changes in moderate to severe TBI, widespread volume reduction in brain parenchyma, frequently called diffuse atrophy, is probably most prominent and significant (Bigler, 2005; Povlishock and Katz, 2005). An important mechanism of this diffuse change is Wallerian degeneration due to traumatic axonal injury, which may continue months and years after injury. Describing the spatial and temporal characteristics of these degenerative morphological changes may provide important clues for the mechanisms underlying individual differences in functional recovery or decline, ultimately contributing to development of better treatment. In mild TBI, due to limited sensitivity of conventional cross-sectional approach, objective evidence of brain injury has been difficult to obtain. Employing a within-subject longitudinal design, future morphometry studies in this group may reveal evidence of sutle brain changes over time. Ideally, the neural degeneration processes can be tracked longitudinally by conducting repeated assessments using sensitive and reliable *in vivo* non-invasive imaging methods such as structural magnetic resonance imaging (MRI). However, only a handful of studies with a limited number of assessment time points are available to date (e.g., Ross, 2011). Because an increasing number of longitudinal studies are expected in the future, it would be useful to review the methodological challenges inherent in analyzing longitudinal imaging data at the early stage of this area of research. The first goal of this paper is to briefly overview the following methodological considerations in longitudinal morphometry of TBI: lesion evolution (structural changes in lesion over time), neurosurgical procedures (surgery on central nervous system), power (probability to detect changes when they are truly present), bias (directional error in parameter estimation), and non-linearity (relationship that cannot be described by the first degree equations). Another purpose of this article is to introduce a novel method that combines dimensionality reduction and region of interest approaches (Avants et al., 2010a), which intends to serve as an example of sensitive, reliable, and unbiased longitudinal multivariate change detection protocols. This analysis pipeline will be demonstrated and validated using a pilot TBI dataset. We focus on structural MRI measures to quantify neurodegeneration such as volume change and cortical thickness indices. However, the principles and conclusions from this paper may be generalized to data using other imaging modalities and techniques such as diffusion tensor imaging and functional MRI. In addition, the same logic can be applied to quantify neural regeneration.

METHODOLOGICAL CHALLENGES IN LONGITUDINAL MORPHOMETRY OF TBI

LESION EVOLUTION

From the moment of injury, the brain goes through numerous structural changes, both focal and diffuse in nature (Gennarelli and Graham, 2005; Povlishock and Katz, 2005; Kubal, 2012). We here review two types of lesion characteristics that can confound progressive atrophy measurement in a longitudinal imaging study of TBI.

Edema

Posttraumatic edema is accumulation of water in the intracellular and/or extracellular spaces of the brain. The precise time course for human posttraumatic cerebral edema has yet to be determined. If this "brain swelling" is diffuse, it effectively leads to an overestimation of brain volume. Therefore, if the first assessment in a longitudinal study is in the acute phase, researchers must exercise great caution because the changes due to the initial stabilization of the brain are confounded with subsequent atrophy. This results in overestimation of the amount of atrophy over time. If one's primary interest is in the post-acute phase, the first measurement can be done after edema is completely resorbed, e.g., 1–2 months after the injury (e.g., Bendlin et al., 2008; Ng et al., 2008; Sidaros et al., 2009).

Focal encephalomalacia

If the brain suffers from various types of bleeding (hematoma and hemorrhage) or bruises (contusions), local tissue abnormalities appear in the imaging. The size of the lesion in the acute phase is known to evolve (increase or decrease) over time depending on various factors (e.g., Chang et al., 2006). In the post-acute phase, if the cells surviving the acute phase develop atrophy, the size of focal encephalomalacia is likely to grow slowly. Changes in focal lesions over time make it difficult to accurately quantify diffuse atrophy, especially in the perilesional areas. One way to deal with focal abnormalities is to exclude participants with focal injuries or conduct a subgroup analysis by dividing participants into two groups according to the presence of focal lesions. Typically, a lesion volume threshold is employed because it is practically infeasible to exclude the brains with focal lesions of any size. Using different thresholds for cortical and subcortical lesions may make sense considering that smaller lesions in the subcortical regions often have more detrimental functional consequences. However, excluding those with focal lesions will introduce a severity bias. Another way to control the effects of focal lesion is to restrict the analysis only to the areas where no focal lesions are found for all participants. To achieve this, lesion masks are built (typically manually) for each brain and then combined to form a "lesion frequency map" (e.g., Levine et al., 2008; Kim et al., 2010). Recent efforts to develop automatic lesion detection algorithms have shown some success in reducing the burden of manual lesion drawing (e.g., Hillary and Biswal, 2009; Ghosh et al., 2011).

NEUROSURGICAL PROCEDURES

Various neurosurgical procedures, performed to stabilize the injured brain (e.g., evacuation of hematomas/hemorrhages, controlling intra-cranial pressure, etc.), are invasive and cause temporary and/or permanent alterations of the brain. Edema and glial scarring from surgical procedures typically need weeks to months to stabilize, making it challenging to separate the unique effect of surgery and true neural degeneration on longitudinal imaging measures. If neurosurgery leaves focal alterations, they may be dealt with similar methods used for focal encephalomalacia (see section "Focal encephalomalacia"). However, research is lacking in this area. Most neurosurgeries are done during the acute phase. However, procedures such as cranioplasty can be done in the post-acute phase and require careful follow-up. For example, it was recently reported that a significant portion of patients who undergo cranioplasty develop fluid collection underneath the site of operation (Chang et al., 2010; Lee et al., 2011), which may distort brain volume measurement. Even more important is the issue of late cranioplasty and how having skull replaced part-way into a longitudinal study might affect the results.

POWER

Statistical power in structural neuroimaging depends on various factors including effect size, measurement error, method of multiple comparison correction, and sample size. Unfortunately, in longitudinal studies of patients with moderate to severe TBI, sample size is typically small due to participant attrition and numerous exclusion criteria including metal implants, lesion characteristics, and patient movement in the MRI scanner. In mild TBI, while fewer participants' data are lost, the effect size of longitudinal change is expected to be relatively small. Therefore, adopting a sensitive and reliable imaging analysis protocol becomes more crucial to achieve powerful longitudinal change detection. There are various ways to quantify longitudinal changes in the imaging data (e.g., Bosc et al., 2003; Holland et al., 2012). They can be classified into two broad categories: (1) regions-of-interest (ROI) or segmentation based approaches and (2) deformation or registration based methods. Here we briefly discuss these two change detection methods in the context of power.

One way to improve detection power in small imaging datasets is to use a limited number of a priori ROIs and measure longitudinal changes within those ROIs. Typically, ROIs are constructed at each time point for each individual by an "expert" human rater or an automatic segmentation algorithm. The majority of previous longitudinal imaging studies in TBI used this approach (e.g., Ng et al., 2008; Warner et al., 2010; Xu et al., 2010). Assuming that the size and location of the ROIs are on target, this approach is likely to increase statistical power. However, reliable a priori hypotheses are frequently unavailable due to the lack of existing research and thus potentially important changes in unselected regions can be missed. In addition, due to heterogeneous injury mechanisms and lesion characteristics in TBI, using the same set of a priori ROIs across different samples may not be ideal. An important limitation of manually defining ROI is that human raters do not reproduce the same results when measurement is repeated, introducing repeat measurement error. Maintaining high intra- and inter-rater reliability costs a substantial amount of time and effort. Automating ROI construction using computer algorithms is a potential solution. However, automatic segmentation of brain structures, especially when a lesion is present, still remains one of the most challenging tasks.

To overcome some of the limitations of the ROI or segmentation based approach, some researchers have adopted deformation based methods of change detection. These methods do not rely on the researcher to identify specific ROIs and are well-suited to exploratory studies. In deformation or tensor based morphometry (DBM/TBM; e.g., Ashburner et al., 1998; Ashburner and Friston, 2000), one image (e.g., a patient's) is directly warped to the other (e.g., a template) using non-linear deformable spatial registration and the resulting deformation fields are used for

quantification of volume differences between the two images. Reliability of this approach is, in general, much higher than manual drawing. Deformation based methods may be used for serial studies as well. To quantify longitudinal changes, a subject's brain at one time point may be directly warped to the same person's brain at later time point (e.g., Sidaros et al., 2009). Directly comparing images effectively bypasses the repeat measurement error issue, offering advantages in terms of statistical power. For TBI, large deformation registration schemes (for an introduction, see Ashburner, 2007) should be used to allow detection of a wide range of volume changes (Kim et al., 2008). Custom or population-specific templates can also help increase detection power (Lepore et al., 2007). Many large deformation algorithms, some of them using diffeomorphisms, are freely available and their performance was recently compared in a large-scale evaluation study (Klein et al., 2009).

More recently, multivariate pattern analysis (MVPA) has been employed to increase detection power over univariate approaches, particularly in fMRI studies (e.g., Haxby et al., 2001). In the last section, we will illustrate an image analysis pipeline that uses MVPA to interrogate longitudinal TBI effects.

BIAS

Bias, a directional error in parameter estimation, can arise in longitudinal morphometry when data from different time points are not treated equivalently. In that sense, avoiding bias in the ROI/segmentation based approach is relatively straightforward because the same system of measurement can be applied to the data at each time point. For example, one can keep the expert raters blinded to the order of measurements or even randomize the images from different time points. In DBM/TBM, however, due to the fact that the images from two or more time points are directly compared, there is a possibility that the images undergo systematically different processing steps.

The issue of bias in longitudinal DBM/TBM has recently become the focus of discussion among researchers investigating the trajectory of atrophy using the Alzheimer's disease Neuroimaging Initiative database (ADNI; www.loni.ucla.edu/ADNI). Partly due to this discussion, several nice summaries on this topic are available in the literature (Holland et al., 2012; Hua et al., 2011; Thompson and Holland, 2011) and they enumerate sources of bias and rules to follow to prevent those biases from affecting the estimate of longitudinal changes. One important issue is designating images at each time point as the source (i.e., image to be warped) or the target (i.e., image to be warped to). Symmetric or inverse-consistent registration methods should be used to avoid bias from asymmetric registration processes. An inverse-consistent or symmetric registration is an algorithm that yields the same correspondences between the images from two time points when the order of them is switched (e.g., Avants et al., 2008). If inverse-consistency cannot be guaranteed by the registration algorithm itself, symmetry may still be achieved by first measuring the changes in both directions independently and then averaging them (Thompson and Holland, 2011). In addition, all images from different time points should undergo the same number of interpolations. For example, Yushkevich and colleagues recently showed that distributing interpolation equally across all of a subject's images is critical for eliminating bias (Yushkevich et al., 2010).

NON-LINEARITY

To our knowledge, most existing longitudinal morphometry studies in TBI have had only two measurement points. As studies with multiple time points emerge, it would be important to consider the potential non-linear nature of the post-injury atrophy. First of all, true biological non-linearity needs to be distinguished from the spurious non-linearity caused by bias. A good example is a controversial study conducted by Hua and colleagues (2010), in which structural atrophy of AD patients was quantified between the baseline and four follow-up scans using TBM. Cumulative atrophy was determined by warping all of the follow-up images to the same baseline image. As a result, the authors found an unexpected non-linearity—i.e., a rapid jump of the atrophy rate between the baseline and the first follow-up point, with more linear increase thereafter. This jump was due to the fact that this study design confounded both interpolation effects and atrophy effects, which have a similar magnitude (approximately 1% change). Subsequent re-analysis studies showed that this trend was replicated even in healthy controls and that a large portion of the bias could be corrected by using inverse-consistent registration methods (Hua et al., 2011; Thompson and Holland, 2011) which interpolate every time point in the same way.

Allowing for the possibility of true biological non-linearity in the atrophy rate after TBI, the next question becomes the exact shape of non-linear degeneration and how much individual variability exists. Growth curve analysis, which is known to be capable of accommodating many mathematical functions, missing data points, variable time intervals, and individual differences, may be a fruitful approach to explore. Mixed effects models have similar advantages.

EXAMPLE OF LONGITUDINAL MULTIVARIATE MORPHOMETRY: A PILOT STUDY

RATIONALE

MVPA has gained acceptance for its ability to combine the benefits of both prior-constrained ROI studies and the exploratory nature of DBM/TBM. This multivariate approach reduces the multiple comparisons problems by clustering regions together in an automated way (known as dimensionality reduction in machine learning) and then allowing hypotheses to be tested on this reduced set of areas. We here hypothesize that, even in a small, heterogeneous TBI sample, there are common areas across individuals that undergo neurodegeneration and that can be detected as regions of correlated white matter (WM) and gray matter (GM) changes (Avants et al., 2010b).

METHOD

In this study, we used best-practice pre-processing to determine two quantitative measures (i.e., cortical thickness and WM volume change) throughout the whole brain in four survivors of diffuse TBI (average age at baseline = 38.3) serial T1 data (**Figure 1**). The average time post-injury at baseline was 6.6 months and the average assessment interval was 15.8 months. We then applied a dimensionality reduction technique, sparse canonical correlation

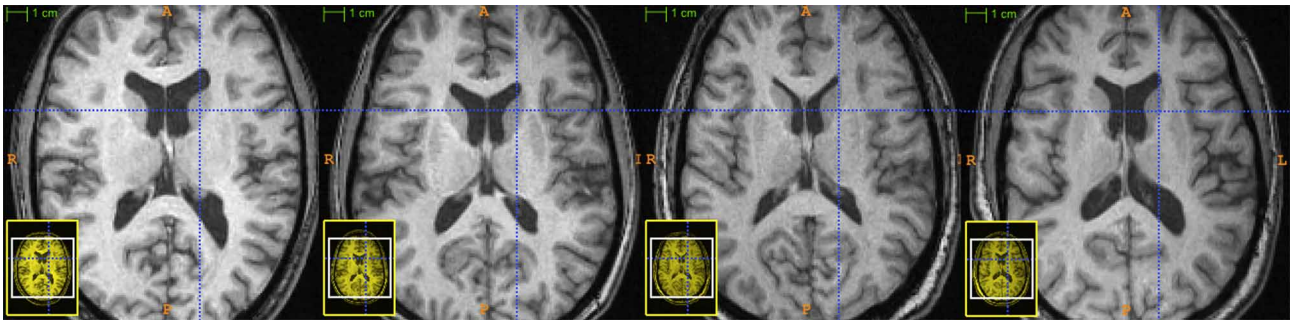

FIGURE 1 | Four TBI survivors' representative axial scans at the baseline.

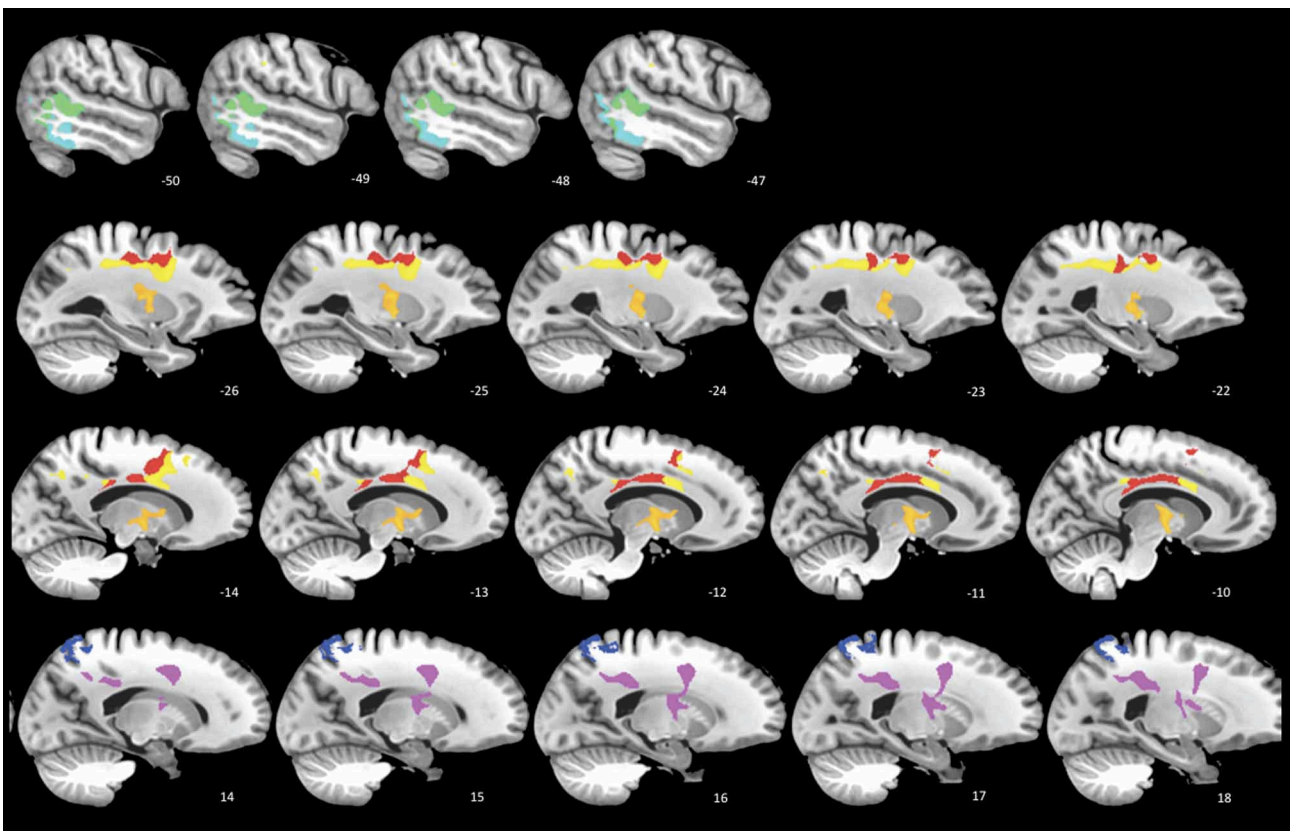

FIGURE 2 | SCCAN reveals multiple cortical and white matter regions of longitudinal atrophy. Cortical areas (cool colors) include posterior temporal lobes, posterior cingulate, and superior parietal lobe. The white matter and deep gray matter (warm colors) regions includes the thalamus (orange, second row), primary motor tract, and the mid- and posterior bodies of the corpus callosum.

analysis for neuroimaging (SCCAN), to obtain a limited number of ROIs that are sensitive and specific to longitudinal change that is related across tissues (Avants et al., 2010a,b). As reviewed above, quantitative longitudinal analyses must be conducted with unbiased techniques if the image-based measurements are to be interpreted physically (Yushkevich et al., 2010). Thus, we used Advanced Normalization Tools (ANTs) and a population-specific template (Avants et al., 2010c; Reuter et al., 2012) to compute the unbiased deformable mapping between each subject's baseline and follow-up image. The resulting diffeomorphic mapping quantifies longitudinal volume changes. We also employed prior-based spatiotemporal maximum a posteriori image segmentation to extract change in the cortical GM over time (Avants et al., 2011) and to identify cortical thickness alterations in each subject. This processing protocol leads to two complementary measures that may be used to assess atrophy—i.e., WM volume change via Jacobian determinant and GM cortical thickness. Thickness is, in general, more sensitive than volumetric measures

because it incorporates tissue-specific information (Hutton et al., 2009). Both measures were annualized.

We hypothesized that, in chronic TBI, spatially distinct but covarying atrophy would be observed in both WM and GW and that this atrophy rate would be greater than zero. In summary, the procedure was as follows: (1) Apply the unbiased longitudinal mapping methods (Avants et al., 2010a; Yushkevich et al., 2010); (2) Quantify the annualized volumetric change in WM and the annualized atrophy in GM; (3) Employ SCCAN to identify four localized regions of GM and four correlated and localized regions in WM to be tested for significant atrophy; (4) Use the one-sample *t*-test with false discovery rate correction (FDR) to determine if the atrophy in SCCAN-identified regions is significant. We arbitrarily limited the number of regions to 4 for WM and 4 for GM considering the small number of participants.

RESULTS AND DISCUSSION

Seven of eight regions (4 WM, 3 GM) were significant at the FDR-corrected $p < 0.1$ level (**Figure 2**). In line with previous TBM studies with larger samples (Kim et al., 2008; Sidaros et al., 2009), these regions included thalamus, corpus callosum, and posterior cingulate (see **Figure 2** legend for the complete list). In the most significant region ($p < 0.015$), the estimated atrophy rates for WM and GM were $7.3 \pm 3.9\%$ and $4.2 \pm 1.8\%$, respectively (mean $\pm$ SD of the amount of atrophy in percentage). FDR-corrected $p < 0.05$ is also achievable if only the most highly correlated regions are tested.

This preliminary study reveals significant longitudinal atrophy patterns after correction for multiple comparisons despite the very few subjects involved. Three main points emerge from this design: (1) significant and localized regions with atrophy may be identified by employing MVPA in longitudinal morphometry of TBI; (2) unbiased approaches are essential for identifying quantitative atrophy measures and retain enough power to be effective in small cohorts; (3) this paradigm is easily extended to include additional modalities and will be more reliable with additional subjects. In addition, future research comparing the current method with alternative approaches are warranted.

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REFERENCES

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage* 38, 95–113.

Ashburner, J., and Friston, K. J. (2000). Voxel-based morphometry– the methods. *Neuroimage* 11, 805–821.

Ashburner, J., Hutton, C., Frackowiak, R., Johnsrude, I., Price, C., and Friston, K. (1998). Identifying global anatomical differences: deformation-based morphometry. *Hum. Brain Mapp.* 6, 348–357.

Avants, B., Cook, P. A., McMillan, C., Grossman, M., Tustison, N. J., Zheng, Y., et al. (2010a). Sparse unbiased analysis of anatomical variance in longitudinal imaging. *Med. Image Comput. Comput. Assist. Interv.* 13, 324–331.

Avants, B. B., Cook, P. A., Ungar, L., Gee, J. C., and Grossman, M. (2010b). Dementia induces correlated reductions in white matter integrity and cortical thickness: a multivariate neuroimaging study with sparse canonical correlation analysis. *Neuroimage* 50, 1004–1016.

Avants, B. B., Yushkevich, P., Pluta, J., Minkoff, D., Korczykowski, M., Detre, J., et al. (2010c). The optimal template effect in hippocampus studies of diseased populations. *Neuroimage* 49, 2457–2466.

Avants, B., Epstein, C. L., Grossman, M., and Gee, J. C. (2008). Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med. Image Anal.* 12, 26–41.

Avants, B. B., Tustison, N. J., Wu, J., Cook, P. A., and Gee, J. C. (2011). An open source multivariate framework for n-tissue segmentation with evaluation on public data. *Neuroinformatics* 9, 381–400.

Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., et al. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *Neuroimage* 42, 503–514.

Bigler, E. D. (2005). "Structural imaging," in *Textbook of Traumatic Brain Injury,* eds J. M. Silver, T. W. McAllister, and S. C. Yudofsky (Washington, DC: American Psychiatric Publishing, Inc.), 79–105.

Bosc, M., Heitz, F., Armspach, J. P., Namer, I., Gounot, D., and Rumbach, L. (2003). Automatic change detection in multimodal serial MRI: application to multiple sclerosis lesion evolution. *Neuroimage* 20, 643–656.

Chang, E. F., Meeker, M., and Holland, M. C. (2006). Acute traumatic intraparenchymal hemorrhage: risk factors for progression in the early post-injury period. *Neurosurgery* 58, 647–655. discussion: 655–656.

Chang, V., Hartzfeld, P., Langlois, M., Mahmood, A., and Seyfried, D. (2010). Outcomes of cranial repair after craniectomy. *J. Neurosurg.* 112, 1120–1124.

Gennarelli, T. A., and Graham, D. I. (2005). "Neuropathology," in *Textbook of Traumatic Brain Injury,* eds J. M. Silver, T. W. McAllister, and S. C. Yudofsky (Washington, DC: American Psychiatric Publishing, Inc.), 27–50.

Ghosh, N., Recker, R., Shah, A., Bhanu, B., Ashwal, S., and Obenaus, A. (2011). Automated ischemic lesion detection in a neonatal model of hypoxic ischemic injury. *J. Magn. Reson. Imaging* 33, 772–781.

Haxby, J. V., Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., and Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science* 293, 2425–2430.

Hillary, F. G., and Biswal, B. B. (2009). Automated detection and quantification of brain lesions in acute traumatic brain injury using, M. R. I. *Brain Imaging Behav.* 3, 111–122.

Holland, D., McEvoy, L. K., and Dale, A. M. (2012). Unbiased comparison of sample size estimates from longitudinal structural measures in ADNI. *Hum. Brain Mapp.* 33, 2586–2602.

Hua, X., Gutman, B., Boyle, C. P., Rajagopalan, P., Leow, A. D., Yanovsky, I., et al. (2011). Accurate measurement of brain changes in longitudinal MRI scans using tensor-based morphometry. *Neuroimage* 57, 5–14.

Hua, X., Lee, S., Hibar, D. P., Yanovsky, I., Leow, A. D., Toga, A. W., et al. (2010). Mapping Alzheimer's disease progression in 1309 MRI scans: power estimates for different inter-scan intervals. *Neuroimage* 51, 63–75.

Hutton, C., Draganski, B., Ashburner, J., and Weiskopf, N. (2009). A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. *Neuroimage* 48, 371–380.

Kim, J., Avants, B., Patel, S., Whyte, J., Coslett, B. H., Pluta, J., et al. (2008). Structural consequences of diffuse traumatic brain injury: a large deformation tensor-based morphometry study. *Neuroimage* 39, 1014–1026.

Kim, J., Whyte, J., Patel, S., Avants, B., Europa, E., Wang, J., et al. (2010). Resting cerebral blood flow alterations in chronic traumatic brain injury: an arterial spin labeling perfusion fMRI study. *J. Neurotrauma* 27, 1399–1411.

Klein, A., Andersson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M. C., et al. (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage* 46, 786–802.

Kubal, W. S. (2012). Updated imaging of traumatic brain injury. *Radiol. Clin. North Am.* 50, 15–41.

Lee, J. W., Kim, J. H., Kang, H. I., Moon, B. G., Lee, S. J., and Kim, J. S. (2011). Epidural fluid collection after cranioplasty: fate and predictive factors. *J. Korean Neurosurg. Soc.* 50, 231–234.

Lepore, N., Brun, C., Pennec, X., Chou, Y. Y., Lopez, O. L., Aizenstein, H. J., et al. (2007). Mean template for

tensor-based morphometry using deformation tensors. *Med. Image Comput. Comput. Assist. Interv.* 10, 826–833.

Levine, B., Kovacevic, N., Nica, E. I., Cheung, G., Gao, F., Schwartz, M. L., et al. (2008). The Toronto traumatic brain injury study: injury severity and quantified MRI. *Neurology* 70, 771–778.

Masel, B. E., and Dewitt, D. S. (2010). Traumatic brain injury: a disease process, not an event. *J. Neurotrauma* 27, 1529–1540.

Ng, K., Mikulis, D. J., Glazer, J., Kabani, N., Till, C., Greenberg, G., et al. (2008). Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch. Phys. Med. Rehabil.* 89, S35–S44.

Povlishock, J. T., and Katz, D. I. (2005). Update of neuropathology and neurological recovery after traumatic brain injury. *J. Head Trauma Rehabil.* 20, 76–94.

Reuter, M., Schmansky, N. J., Rosas, H. D., and Fischl, B. (2012). Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage* 61, 1402–1418.

Ross, D. E. (2011). Review of longitudinal studies of MRI brain volumetry in patients with traumatic brain injury. *Brain Inj.* 25, 1271–1278.

Sidaros, A., Skimminge, A., Liptrot, M. G., Sidaros, K., Engberg, A. W., Herning, M., et al. (2009). Long-term global and regional brain volume changes following severe traumatic brain injury: a longitudinal study with clinical correlates. *Neuroimage* 44, 1–8.

Thompson, W. K., and Holland, D. (2011). Bias in tensor based morphometry Stat-ROI measures may result in unrealistic power estimates. *Neuroimage* 57, 1–4. discussion: 5–14.

Warner, M. A., Marquez De La Plata, C., Spence, J., Wang, J. Y., Harper, C., Moore, C., et al. (2010). Assessing spatial relationships between axonal integrity, regional brain volumes, and neuropsychological outcomes after traumatic axonal injury. *J. Neurotrauma* 27, 2121–2130.

Xu, Y., McArthur, D. L., Alger, J. R., Etchepare, M., Hovda, D. A., Glenn, T. C., et al. (2010). Early nonischemic oxidative metabolic dysfunction leads to chronic brain atrophy in traumatic brain injury. *J. Cereb. Blood Flow Metab.* 30, 883–894.

Yushkevich, P. A., Avants, B. B., Das, S. R., Pluta, J., Altinay, M., and Craige, C. (2010). Bias in estimation of hippocampal atrophy using deformation-based morphometry arises from asymmetric global normalization: an illustration in ADNI 3 T MRI data. *Neuroimage* 50, 434–445.

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