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Examining the Relationship between Head Trauma and Neurodegenerative Disease: A Review of Epidemiology, Pathology and Neuroimaging Techniques

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Abstract

Traumatic brain injuries (TBI) are induced by sudden acceleration-deceleration and/or rotational forces acting on the brain. Diffuse axonal injury (DAI) has been identified as one of the chief underlying causes of morbidity and mortality in head trauma incidents. DAIs refers to microscopic white matter (WM) injuries as a result of shearing forces that induce pathological and anatomical changes within the brain, which potentially contribute to significant impairments later in life. These microscopic injuries are often unidentifiable by the conventional computed tomography (CT) and magnetic resonance (MR) scans employed by emergency departments to initially assess head trauma patients and, as a result, TBIs are incredibly difficult to diagnose. The impairments associated with TBI may be caused by secondary mechanisms that are initiated at the moment of injury, but often have delayed clinical presentations that are difficult to assess due to the initial misdiagnosis. As a result, the true consequences of these head injuries may go unnoticed at the time of injury and for many years thereafter. The purpose of this review is to investigate these consequences of TBI and their potential link to neurodegenerative disease (ND). This review will summarize the current epidemiological findings, the pathological similarities, and new neuroimaging techniques that may help delineate the relationship between TBI and ND. Lastly, this review will discuss future directions and propose new methods to overcome the limitations that are currently impeding research progress. It is imperative that improved techniques are developed to adequately and retrospectively assess TBI history in patients that may have been previously undiagnosed in order to increase the validity and reliability across future epidemiological studies. The authors introduce a new surveillance tool ((Retrospective Screening of Traumatic Brain Injury Questionnaire, RESTBI) to address this concern.

Keywords: TBI; Head trauma; Neurodegenerative disease; Amyotrophic Lateral Sclerosis (ALS); Chronic Traumatic Encephalopathy (CTE); Magnetic resonance imaging; Diffusion tensor imaging; Resting state functional connectivity; Positron Emission Tomography (PET); Retrospective TBI screening

Abbreviations: TBI: Traumatic Brain Injury; ROI: Region of Interest; DAI: Diffuse Axonal Injury; DTI: Diffusion Tensor Imaging; WM: White Matter; FA: Fractional Anisotropy; MR: Magnetic Resonance; MD: Mean Diffusivity; CT: Computed Tomography; SLF: Superior Longitudinal Fasciculus; mTBI: Mild TBI; ILF: Inferior Longitudinal Fasciculus; ND: Neurodegenerative Disease; CC: Corpus Collosum; AD: Alzheimer's Disease; fMRI: Function Magnetic Resonance Imaging; PD: Parkinson's Disease; ICN: Intrinsic Connectivity Network; ALS: Amyotrophic Lateral Sclerosis; RSN: Resting State Network; CTE: Chronic Traumatic Encephalopathy; fcMRI: Resting State Function Connectivity fMRI; APOE: Apolipoprotein E; DMN: Default Mode Network; Aβ: Amyloid-beta; PCC: Posterior Cingulate Cortex; NFL: Neurofibrillary Tangles; PET: Positron Emission Tomography; NFL: National Football League; SPECT: Single Photon Emission Computed Tomography; VBM: Voxel-Based Morphometry; FDG: 18F-2-fluro-2-deoxyglucose; VBR: Ventricle to Brain Ratio; CMRgl: Cerebral Metabolic Rate for glucose; TBV: Total Brain Volume; PiB: Pittsburgh Compound-B; LOC: Loss of Consciousness; PK: [11C](R)PK11195

Introduction

Even with its rising prevalence, there is a problematic lack of rigor in defining head trauma resulting in ambiguous and heterogeneous definitions throughout medical literature. However, TBI is generally defined as a closed head injury as a result of acceleration/deceleration forces and is separated into three categories: severe, moderate and mild. Severe TBI denotes head injuries that result in either permanent or an extended period of unconsciousness, amnesia, or death following a head injury and is quantitatively classified by a Glasgow Coma Score (GCS) of 3-8. In the middle of the spectrum, moderate TBI consists of a period of unconsciousness or amnesia ranging from 30 minutes to 24 hours with a GCS of 9-12. Mild TBI (mTBI) are generally recognized as head injuries that cause a brief state of altered consciousness that may result in up to 30 minutes of unconsciousness, but it is important to note that the majority of mTBIs do not result in loss of consciousness (LOC) [1,2]. The transient and heterogeneous nature of mTBI symptoms makes it exceedingly difficult to diagnose and, as a result, a large portion of these injuries go unrecognized. This is troubling considering that 80-90% of all head injuries are cases of mTBI [1,2]. This most common form of TBI, mTBI, is often referred to as a concussion and these two terms will be used interchangeably throughout this review.

As it currently stands, TBI represents the leading cause of morbidity and mortality worldwide in individuals under the age of

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45 [3] and it is still considered a growing epidemic with mounting evidence pointing towards increasingly dire consequences. The World Health Organization (WHO) reports an estimated 10 million people are affected annually by head injuries and predicts that TBIs will be the third largest contributor to the global burden of disease and mortality by 2020 [4]. The WHO suspects that this increase in TBI prevalence is due to a growing number of automobile accidents, but there are many other potential exposures to TBI [4]. For example, the number of sports-related TBIs is increasing at a rapid pace with the most recent study estimating that 1.6-3.8 million occur each year in the United States alone [5]. This number is up from the previously reported estimate of 306,000 sport-related concussions in 1991 [6], which is a trend that is at least partly attributable to growing awareness of head injuries.

In addition to the human toll of these injuries, TBIs are affixed with a substantial economic burden. Without accounting for NDs later in life, the Center for Disease and Control (CDC) reports that mTBIs alone cost the USA $17 billion annually, and that number jumps to $57 billion when all TBIs are included [7]. Strikingly, this only accounts for hospitalized cases of TBI and does not recognize patients treated only in the ER, outpatient facilities, or those who omit medical care all together. These omissions are significant, especially when considering the mTBI frequently occurring in sports. According to one study, sports related concussions accounted for 20% (306,000) of the 1.5 million TBIs in the US [5]. Of those 306,000 patients, 55% received outpatient care and 34% received no medical attention [5,8]. This means only 12% of these patients were hospitalized and, therefore, only 12% would be accounted for in the CDCs $57 billion estimate for the economic toll for TBIs. The CDC also acknowledges that their incidence figures fail to illustrate the true extent of the prevalence of TBIs and the consequences associated with head injuries. They suggest that these numbers underestimate the amount of TBIs primarily due to the fact that there is still no standard definition for a concussion and this lack of awareness contributes to a significant portion of TBIs going unreported [6,7].

A better understanding of the biomechanical forces causing TBIs may lead to a better understanding of their effects, enhanced protection, and potentially even aide in the diagnosis of head injuries. As such, researchers have increasingly focused on the biomechanical forces contributing to TBI. Both linear and angular/rotational acceleration forces contribute to TBIs, and they are classified as either focal or diffuse injuries depending on the mechanism of the injury. They are designated as focal injuries when the acceleration/deceleration forces cause impact between the brain and inner protrusions of the skull. Diffuse injuries, on the other hand, occur when the differential motion of the brain causes shearing and tearing of the axons, which results in diffuse axonal injuries (DAIs) [9]. Researchers are currently employing accelerometers in the helmets of athletes to obtain measurements for the various biomechanical forces that contribute to TBI *in vivo*. The Head Impact Telemetry System (HITS) is perhaps the most promising technology for this type of analysis and it incorporates multiple accelerometers within a standard football helmet that wirelessly communicate with a sideline computer in real time [10]. There are comparable findings for both college and high school (HS) athletes that have been examined using HITS. Diagnosed concussions in HS athletes resulted from impact forces with linear accelerations ranging from 74g-146g and angular accelerations from 5582-9515 rad/s/s [11]. In college athletes, diagnosed concussions resulted from impact magnitudes of 60.5-168.7 g [12]. The measurements of impact forces resulting in concussions showed no correlation with symptom severity, postural stability, or neurocognitive performance following the injury [12]. These findings have increased our understanding of the biomechanical properties behind TBIs, but the systems employed are currently unable to identify a "concussion threshold" that can be used to predict and diagnose TBIs.

In addition to investigating the causative biomechanical mechanisms of TBIs, a great deal of research is focused on the neuropathogenesis contributing to impairments following TBIs. As more is learned about the underlying pathophysiology of head injuries, there is greater evidence linking TBI with NDs including Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and chronic traumatic encephalopathy (CTE). Recent estimates suggest that there are more than 25 million people suffering from dementia and NDs worldwide [13,14]; a number that is sure to increase along with the demographic of our aging population. Worldwide, the proportion of people older than 60 is growing faster than any other age group. According to the WHO, this demographic of the population is expected to grow 223% between 1970 and 2025 totaling 1.2 billion people over the age of 60, which is expected to continue escalating to 2 billion people over 60 by the year 2050 [15]. As a result of this growing demographic, it has been reported that the number of individuals affected by neurodegenerative diseases in the United States and Europe is expected to triple by the year 2050 [16] and it is reasonable to expect this trend to extend to the global population. In order to prevent the unprecedented financial, societal and emotional costs of these age related brain disorders, a better understanding of their risk factors is compulsory to limit their prevalence.

These neurodegenerative disorders are all multifactorial diseases with unknown etiologies, but it is hypothesized that TBIs are a primary risk factor for each due to the similar nature of their pathologies [17-20]. There have been a number of epidemiological studies done attempting to quantify the relationship between TBI and these neurodegenerative diseases, but they yield conflicting and inconclusive results.

Dementia and Alzheimer's Disease

Epidemiology

Every 70 seconds, somebody in America develops dementia, which results in 450,000 new cases each year [21]. Dementia is an overarching term involved in a number of disease processes, but AD represents the most common form of dementia in the elderly. It is a disease characterized by the progressive loss of memory and cognitive capacity significant enough to interfere with quality of life. Mild cognitive impairment (MCI) often precedes full-blown AD and can be conceptualized as a transitional state between normal cognitive aging and dementia. Previous research indicates individuals with MCI progress to AD at a rate of 10-15% per year compared to just 1-2% of the general population [22,23]. Therefore, MCI can be used to identify populations who are at risk of developing AD. One compelling study that utilized questionnaires from 2552 retired professional football players suggests that head trauma may be associated with impaired cognition, thus increasing the risk for dementia. These athletes, who have had extensive exposure to repetitive head injuries, displayed a progressive decline in mental health functioning and higher rates of memory impairments and cognitive decline that is representative of MCI. Findings from this study also demonstrate a dose-response relationship between diagnosed concussions and an increased lifetime burden, as players reporting three or more concussions had a five-fold increase in prevalence of MCI [23]. However, no correlation was observed between concussion history and AD [23]. Studies like this have prompted researchers to further examine the relationship between TBIs and neurodegenerative disease.

Of the various neurodegenerative diseases, there is the strongest evidence suggesting a link between head trauma and AD. A meta-analysis of 15 case-control studies found that individuals with a history of TBI were 60% more likely to develop AD compared with others [24]. Within a population of AD patients, it has also been reported that history of TBI accelerates the onset of AD [25,26]. However, there are also studies that refute this relationship reporting no increased risk of AD for those who have sustained head trauma at some point in their lifetime [27,28]. It is also likely that the effects of TBI may vary between individuals as some research indicates that head trauma is only a risk factor for AD when the individual is a carrier of certain alleles, most notably the e4 allele of Apolipoprotein E (APOE) [29,30]. It is worth noting that APOE is a plasma lipoprotein primarily responsible for transporting lipids through the CNS that plays a vital role in synaptogenesis along with the maintaining, repairing, and remodeling of neuronal tissue [31]. One study in particular reports that carriers of this APOE e4 allele with history of TBI have a 10-fold increased risk of AD while non-carriers of this allele with TBI history had no increased risk of dementia [30]. In comparison, possessing the APOE e4 allele with no history of head trauma indicated a two fold increase risk of AD [30]. Perhaps the most telling finding comes from one of the few prospective studies that examined a population of World War II veterans and reports that TBIs significantly increase the risk of developing AD later in life [32].

Pathology

The major pathological hallmarks in the brain of AD patients are neuronal loss, synaptic dysfunction [33], and plaque deposition, which primarily consists of Amyloid-β (Aβ) peptide and neurofibrillary tangles (NFT's) composed of phosphorylated tau protein [21]. Aβ aggregation is widely regarded as the chief component in the pathogenesis of AD [34]. Aβ deposition primarily occurs in cortical regions responsible for memory and learning as well as in the small blood vessels of the meninges and cerebral cortex [21]. Oxidative stress and mitochondrial dysfunction are also key contributors to the pathological cascade leading to AD [35].

The first major indication of similar underlying pathologies between TBI and neurodegenerative disease was observed when researchers discovered Aβ plaque in the brains of up to 30% of patients who died acutely following TBI [36]. Notably, these Aβ plaques were also found in children following fatal TBI indicating that the plaque was not present due to standard AD progression in undiagnosed individuals before the TBI occurred. Tau pathology of NFTs, another key component of AD's pathogenic cascade, has also been observed following head trauma. Though it is more commonly observed in cases of repetitive head trauma, it has been observed as a chronic effect following a single TBI [37]. Increases in neuronal tau accumulation following exposure to head trauma was initially observed in rats [38], but this finding was later observed in humans as well. This increase of intraneuronal tau pathology is also observed in younger patients following acute head injury, suggesting it is not solely attributable to aging [39].

Researchers have attempted to delineate the biological processes by which the neuropathology following TBI may elicit a pathogenic cascade contributing to the progression of AD and other NDs. The chief event suspected of triggering this cascade appears to be the microstructural white matter injuries, known as DAIs, that often occur in head trauma. DAIs cause damage and swelling to the axonal cytoskeleton, which results in impaired axoplasmic transport [40]. This impaired axonal transport leads to the abnormal production and accumulation of toxic proteins, peptides, and their aggregates immediately following the trauma [40,41]. In relation to AD, amyloid precursor protein (APP) is one of the key proteins affected by this impaired axonal transport, leading to a rapid and considerable accumulation of APP in the damaged axons [42]. APP is the substrate that is later cleaved to form Aβ, so this event yields ample substrate readily available for intraaxonal Aβ production [40,42]. This axonal Aβ accumulation is then released and deposited in the tissue parenchyma as Aβ plaques that are characteristic of AD pathology. It appears that this process occurs spontaneously in aging adults as part of the normal progression of AD, but these DAIs significantly accelerate the process thus predisposing individuals to greater risk of neurodegenerative disease [40,41]. Notably, this axonal degeneration and Aβ accumulation via increased APP has been identified as a progressive long term effect that persists years following the initial head injury [43]. This process is likely influenced by various metabolic and genetic factors.

Intraaxonal production of NFTs, another hallmark of AD and other neurodegenerative diseases, has also been identified as a consequence of TBI. As observed with Aβ accumulation, the primary mechanism of post-traumatic NFT aggregation is impaired axonal transport following DAI [40]. The accumulation of NFT following head trauma is well established in both animal and human models, and it has been shown to accumulate at a relatively slower rate than APP with the first signs of NFT detected at 6 hours after the injury [40,44]. While Aβ accumulation has been observed as an acute effect following TBI in humans suffering fatal injuries, the accumulation of NFT has yet to be reported as acute response to a single head injury in humans. However, greater aggregate levels of NFT has been observed as a long term effect in TBI patients surviving at least one year following a single head injury compared to age matched controls [37]. This increase in intraaxonal NFT accumulation, even in individuals with history of only a single traumatic event, may be a significant risk factor for developing neurodegenerative disease later in life.

Similarly, this impaired axonal transport following DAI can also result in abnormal α-synuclein accumulation. The intraaxonal α-synuclein accumulation resulting from DAIs is typically the nitrated and conformationally modified forms that are representative of synucleinopathies [40]. Additionally, the oxidative stress following TBI may augment the accumulation of α-synuclein or play a role in stabilizing the aggregated forms of α-synuclein [40,41,45]. This augmented α-synuclein accumulation may contribute to dementia with Lewy bodies, which is a form of dementia distinct from AD [41].

Neuroimaging

Previous studies have employed conventional MR techniques utilizing T_1 and T_2 weighted imaging to obtain structural and anatomical images of the brain. These studies aim to use volumetric and voxel-based morphometry (VBM), which is well established as a tool to observe cerebral atrophy at a macroscopic level, specifically by measuring the changes in gray matter density across disease states [46]. Cortical atrophy has been observed in AD patients by studies reporting significantly reduced gray matter densities across various regions of the brain, specifically in the medial temporal lobe structures including the hippocampus, amygdala, and uncus [47,48]. In addition to whole brain atrophy, ventricle to brain ratio (VBR) is a well established global measure of brain integrity [49,50]. When cerebral atrophy occurs, the loss in total brain volume (TBV) is accompanied by increased ventricular volume, thus increasing the VBR, which is indicative of neurodegeneration and AD [51]. These findings compelled researchers to develop a hypothesis regarding the pathogenesis of NDs centered on initial brain reserve [52]. This hypothesis proposes that the greater

one's brain reserve is, the more they will be able to compensate for the normal pathological changes of aging to resist the clinical symptoms and functional impairments of ND. Thus, this theory postulates that populations with decreased brain volumes and gray matter density will be at greater risk of developing NDs later in life. In addition to the findings above which seem to support this hypothesis, a study specifically investigating the initial brain reserve hypothesis indicated that those with less brain volume are at greater risk for developing dementia later in life [53].

Parallel findings are observed in studies investigating the cortical atrophy that occurs following TBI [54]. One study found that significant brain atrophy is already observed just 11 months after a mild/moderate TBI and they report that the atrophy was even more pronounced in patients who experienced loss of consciousness (LOC) at time of injury [55]. The evidence of cerebral atrophy in TBI patients using VBM is further supported by a post-mortem study examining the brain matter of moderate-severe TBI patients who survived several months to years in a severely disabled or vegetative state [56]. This study reports a significant reduction in both the brain mass and volume compared to controls in relatively young patients, who were an average of 44 years of age at the time of injury [56]. A longitudinal study using VBR measurements to assess the global cerebral atrophy of mild/moderate TBI patients at different time points following their injury indicates progressive and chronic cortical damage that is comparable to AD patients [57]. The findings indicate that the most rapid increase in VBR occurs approximately 3 weeks after injury, but perhaps more importantly, they found that VBR continues to progressively increase beyond two years after the injury occurred [57]. In addition to the parallel findings of global brain atrophy, it is also reported that regional atrophy occurs in both AD and TBI that is specific to the same regions and structures of the brain such as the hippocampus [58]. It is possible that these alterations in VBM and gray matter density cause deleterious effects, especially when considering the aforementioned initial brain reserve hypothesis. It appears that head injuries deplete this initial brain reserve, which in turn could significantly predispose TBI patients to future risk of neurodegenerative disease as they lack the same capacity to overcome the neurological impairments experienced in normal aging.

In recent years, tremendous advancements have been made in developing new neuroimaging modalities that allow a more detailed look at the microstructural connectivity of the brain. This may provide key insights to understanding and quantifying pathology resulting from DAIs in specific regions of interest (ROIs) that are not able to be assessed using conventional MR and CT methods. Diffusion Tensor Imaging (DTI) is a non-invasive MRI method that is sensitive to the microscopic alterations of neuronal tissue, specifically occurring in the WM of the brain. DTI is able to provide this detailed information regarding the microstructure of the brain by measuring the diffusivity properties of water. For example, movement of water in CSF is unrestricted and, therefore, it is free to diffuse in all directions (isotropic). WM, however, is encapsulated by myelin sheaths, neurofilaments, microtubules, and axonal membranes that restrict diffusion to the direction that the axons are lying (anisotropic). The two primary indexes of DTI measure the directionality and magnitude of the diffusion properties; Fractional Anisotropy (FA) measures the directionality and Mean Diffusivity (MD) measures the magnitude of diffusion. Reduced FA and increased MD values are indicative of structural impairments within the white matter as it reflects myelin/axonal damage.

Studies using DTI to investigate WM structural integrity in AD patients yield compelling results. Many have found white matter abnormalities, as marked by a reduction in FA values, in multiple fiber tracts involving the uncinate, superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), fornix, cingulum, hippocampus, and corpus collosum (CC) [59-65]. Though there are also a handful of studies that fail to observe a significant reduction in FA values [66], recent meta-analyses of 41 studies on DTI in AD patients reports significant reduction of FA values for 11 of 13 ROIs compared to healthy controls [67]. This same meta-analysis also reports increased MD values indicative of microstructural damage in all 9 of the ROIs including the CC, posterior cingulum, uncinate fasciculus, and the hippocampus.

This same DTI modality has also been applied to TBI populations to observe the acute and chronic microstructural abnormalities resulting from head trauma. According to the findings of abnormal FA and MD values, the overwhelming trend indicates that chronic impairments to WM structural integrity occur as a result of TBI in areas comparable to the abnormalities reported in AD patients [68-77]. It is also worth noting that several studies report a significant trend between severity of the TBI [78] and the number of TBIs [72] with the extent of WM structural damage. Of particular interest, some of these DTI studies reporting significant WM impairments also note that the conventional CT and MR scans at time of injury were normal [69]. This indicates that there is often structural damage occurring as a direct result of head trauma that is undetected at the time of injury by conventional measures. Several studies also report that WM integrity is correlated with measures of executive function and reaction time [75,76] and microstructural WM abnormalities can be predictive of negative outcomes following TBI [79]. The findings are less consistent in studies that assess the acute changes in WM integrity following TBI (within 1 month). Several of these acute studies also observed WM abnormalities in key regions like the CC and fornix [78,80-82], but others found no difference compared to controls [83,84]. Interestingly, and perhaps surprisingly, several acute studies have found that FA values are increased and MD values are reduced in acute TBI patients that are still symptomatic [85,86]. These findings raise new questions regarding the recovery mechanisms and progressive changes in the brain as a result of head trauma. It is possible that this unexpected finding is the result of an immediate response mechanism that is later followed by decreasing FA values as the brain recovers, but a longitudinal study examining microstructural alterations following TBI is necessary to better understand these findings.

Another new, non-invasive imaging modality utilizes the blood oxygen level dependent (BOLD) measures that are typically used to obtain task based functional MRI (fMRI) data. Researchers are beginning to measure these BOLD fluctuations in the brain during its resting state, which represent the amount of intrinsic activity synchronization across the entire brain. These resting state fMRI measures are thought to represent what has been termed functional connectivity [87,88]. This may provide a valuable data resource for delineating the neural functional architecture of humans, and, coupled with DTI, may provide insight to the intrinsic connectivity networks (ICN) of the brain [89]. The majority of the brain's resources are expended during rest to maintain homeostasis, so measures of resting state networks (RSN) can provide key insight into the overall health of the brain at rest [90]. Another benefit of using resting state values is the fact that it does not involve the subject's engagement in cognitive tasks so it can be widely applied to different patient populations, even anesthetized individuals [90,91]. However, attempting to define a baseline state in the brain, arguably our most complex system, poses

a difficult challenge [92]. As researchers are attempting to optimize results from resting state functional connectivity fMRI (fcMRI) studies, they are using different methods (i.e., Seed-Based Correlation Analysis, Independent Component Analysis, Frequency Domain Analysis, and various group level analysis approaches) to analyze the data leading to increased heterogeneity between labs [89]. Additionally, there are a number of other factors such as compensatory effects and effects of medications that may influence functional connectivity in ways that are not entirely understood [93]. These varying methods of analysis and relatively unknown effects make the findings from these studies difficult to interpret and compare, but they still yield compelling results.

fcMRI techniques have been applied to AD populations in an attempt to identify ICNs involved in the progression of the disease. The network receiving the most attention in these fcMRI studies is the default mode network (DMN), which is a network of brain regions that is active during rest and typically deactivates during performance of a task [92]. The primary regions of the DMN include the medial prefrontal cortex, posterior cingulate cortex (PCC), lateral temporal cortex, angular gyrus, and parahippocampal gyrus [94,95]. fcMRI studies examining AD patients reveal disruptions to the DMN through several different methods of analysis [96-100]. The link between DMN disruptions and AD is strong enough to compel some researchers to believe that activation patterns within the DMN directly explain, or potentially even cause, the pathology of AD [94]. This finding has led researchers to develop what they call the "metabolism hypothesis". This hypothesis postulates that the continuous activity of the DMN augments a metabolism dependent cascade that is conducive to the formation of AD pathology, primarily Aβ deposition [94]. Mappings of Aβ plaques show a distribution that is strikingly similar to the anatomical regions comprising the DMN [101,102], indicating that hyperactivity of the DMN may increase risk of AD.

A longitudinal fcMRI study investigating the progression of AD supports this metabolism hypothesis. It reports increased DMN activity in the early stages of AD and in healthy controls, but the DMN quickly deteriorates in AD patients and continues to diminish as the disease progresses [103]. This could support the metabolism hypothesis because the increased metabolism, indicated by hyperactive DMN, leading up to AD results in increased deposition of Aβ plaques, which in turn intensifies the pathogenic cascade of AD. Another possible explanation for this finding is that the increased DMN in early cases of AD and healthy controls could be a result of healthy aging successfully compensating for diminished cognitive capacity, but their AD symptoms rapidly progress once patients are no longer able to maintain these compensatory effects [103].

fcMRI studies investigating the effects of TBI examine a number of different ICNs, but for the sake of comparison to these AD findings this section will focus on the DMN. Two studies investigating the chronic effects of TBI on the DMN (>6 months) report an overall increase in DMN as a result of TBIs [103,104]. It is also reported that this increased DMN activity is correlated with impairments of sustained attention, which is further supported by the finding of increased deactivation of DMN during tasks [104]. Other studies report diminished functional connectivity in the DMN within 6 months of sustaining a mild TBI [105-107]. More longitudinal work needs to be done, but it is possible that the functional connectivity of the DMN decreases immediately following TBI and increases during later stages of recovery as a compensatory effect. This is supported by research incorporating DTI to investigate ICNs, which reports reduced signaling efficiency in defective axonal bundles [108]. These defective axonal bundles, which are present in TBI patients as a result of DAI, eventually lead to inefficient networks that are required to work harder and overcompensate for the structural impairments in order to complete the same tasks [108]. This finding could potentially explain the heightened risk factor for neurodegenerative diseases later in life according to the metabolism hypothesis proposed by Buckner et al. [94].

Positron Emission Tomography (PET) and single positron emission computed-tomography (SPECT) provide unique insight to alterations of the brain`s metabolism across different disease states. PET assesses cerebral metabolic activity, most commonly the metabolism of glucose by using the tracer ^{18}F-2-fluro-2-deoxyglucose (FDG) [109]. Uptake of FDG in the brain indicates local glucose consumption providing energy to maintain ion gradients and synthesize neurotransmitters, which closely corresponds to levels of neuronal function [110]. Accordingly, a decline in glucose consumption is indicative of synaptic dysfunction and neuronal degeneration, which is commonly observed in neurodegenerative diseases [109]. SPECT also employs tracers to assess biological activity in specific regions of the brain, but does so through measuring levels of perfusion. PET exhibits significantly greater sensitivity and spatial accuracy, but SPECT offers extended time windows to observe biological processes over the course of hours or days [111].

When these neuroenergetic modalities are applied to AD patients, the most consistently reported findings are resting-state temporo-parietal hypometabolism in PET scans and temporo-parietal hypoperfusion in SPECT imaging [112-118]. Significantly reduced metabolism in the temporo-parietal cortex has also been observed longitudinally as AD progresses, which was further supported by one study that post-mortemly confirmed groupings for cognitively healthy and AD patients [114,115]. Reduced cerebral metabolic rates for glucose (CMRgl) in AD patients are also commonly observed in the PCC, precuneus, thalamus, mammillary bodies, hippocampus and frontal cortex [114,116,118-120]. The implication of suppressed CMRgl in the PCC relates to the fcMRI studies mentioned above since the PCC is a central node of the DMN. Other PET scans employ compounds capable of penetrating the blood-brain barrier such as the Pittsburgh Compound-B (PiB) with a high affinity for amyloid-B, which can effectively track Aβ aggregation in vivo [101]. Utilizing the PiB compound to map Aβ pathology via PET has been supported by strong correlations to post-mortem Aβ pathology findings [121]. In both controls and AD patients, research has shown a distinct relationship with higher levels of metabolism correlated with greater levels of Aβ pathology, specifically in the DMN [101,122]. This also supports Buckner's metabolism hypothesis indicating that hyperactivation of DMN may be a risk factor for AD later in life [94].

There is surprisingly limited data available to examine PET measures of CMRgl following TBI considering PET lends itself well to the many clinical issues emerging following incidents of head trauma. Additionally, the variable nature of TBIs makes this a difficult disease population to study because factors like severity, frequency, and time since injury are likely to influence CMRgl results. From the limited data available, it appears that there is an initial phase of increased CRMgl [123,124] followed by a period of reduced CMRgl and hypoglycolysis following TBI [124-126]. One study provided additional longitudinal insight by scanning patients three times during hyperacute (<5 days), acute (5-28 days), and chronic (1-6 month) recovery. They report a triphasic pattern with initial hyperglycolosis, followed by reduced CMRgl that later increases and recovers to normal levels by 6 months [123]. For the most part, these FDG PET studies only report findings of

global CMRgl. One study reported regional measures, which indicated reduced CMRgl in bilateral frontal lobes, temporal lobes, thalamus, and right cerebellum up to 6 months following TBI. Additional studies are needed to gain insight into the true chronic consequences of TBI on CMRgl. The observation of a triphasic pattern for metabolic response following TBI relates well to observations in the aforementioned fcMRI studies. However, these PET studies only report CMRgl up to six months post-injury, but the trend at this time point is an increase in CMRgl from previously reduced levels [123]. If the CMRgl continues to increase in the years following TBI, there may be serious implications involving the DMN and altered resting state functional connectivity that may implicate Buckner's metabolism hypothesis.

Another interesting PET study investigated the neuroinflammatory effects of TBI in a group of patients suffering from chronic symptoms from TBI. This PET study was able to measure inflammation by utilizing a different tracer, ligand [11C](R)PK11195 (PK), which is previously known to indicate activated microglia and, thus, is a sign of inflammation [127]. Within this study's population, the mean time since injury was 6.2 years with the most remote TBI occurring 17 years earlier. The PET scan indicated that all TBI patients had increased levels of persistent inflammation in subcortical regions like the thalamus and putamen and, though there is no correlation between time since injury and inflammation, the greatest PK uptake indicating greatest inflammation was observed for the participant whose injury was the most remote in time at 17 years [127]. This finding of perpetual neuroinflammatory mechanisms in the brain following TBI is substantiated by an immunohistochemistry study reporting increases in activated microglia and phagocytic macrophages in TBI patients for up to 18 years following a single head injury [128]. Neuroinflammatory responses like this are increasingly acknowledged as a chronic feature of multiple neurodegenerative diseases [129-134].

PET scans may also have the potential to examine the level of tau pathology developing in the brain following TBI by utilizing 2-(1-{6-[(2-[F-18] fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene) malononitrile (FDDNP). One recent study employed FDDNP PET scans on retired NFL players who have a history of repetitive exposure to TBI to see if there were any significant differences in tau compared to the general population [135]. The research indicates that the group of retired NFL players had significantly greater levels of tau pathology than healthy controls in the amygdala and all subcortical ROIs including caudate, putamen, thalamus, subthalamus, midbrain and cerebellar white matter [135]. Previously, tau pathology, a hallmark of AD, was found to exist in the brains of athletes with CTE as discovered post-mortemly by McKee et al., but this offers an approach to investigate this facet of the pathogenesis *in vivo* [136]. This is yet another pathway and neuroimaging modality that has the potential to be investigated as a means of in vivo identification of neurodegeneration in at risk populations.

Parkinson's Disease

Epidemiology

PD is the second most common neurodegenerative disorder. The clinical manifestation of PD is characterized by resting tremor, rigidity, bradykinesia, and postural/balance impairments. In addition to these motor impairments, a wide variety of non-motor comorbidity symptoms are observed in PD patients including depression, cognitive impairments and olfaction dysfunction [137]. Depression is perhaps the most common non-motor symptom in PD patients with prevalence rate reported to be as high as 90% [138].

Head trauma was first identified as a potential risk factor for PD by Martland in 1928 when repeated head injuries in boxers resulted in Parkinsonian symptoms along with cognitive decline, which he dubbed "punch drunk" [139]. Head injury as a potential risk factor for idiopathic PD gained more attention in 1984 when Muhammad Ali was diagnosed with PD at the age of 42. Since Ali's diagnosis, there have been many epidemiological studies investigating the role of TBI history in PD predisposition and pathology. The results of these studies have been conflicting with roughly half reporting that a history of TBI increases the risk of PD [140-149] while other studies report no such relationship [150-162]. Of the studies reporting a significant relationship between TBI and PD, the odds ratio for risk of PD following head trauma ranged from 1.4-11.7 [163].

One compelling study investigated the prevalence of PD among sets of twins. This is a strong way to control many of the extraneous variables contributing to the multifactorial etiology of PD like genetics, environmental exposures, etc. This study found a 3-4 fold increase in risk of PD if there was a history of TBI in one twin even when the average occurrence of TBI was 30 years prior to the onset PD [143]. Interestingly, the researchers report a dose-response relationship as the risk for PD increased with multiple TBI [143]. However, a recent review of 20+ epidemiological studies does little to support or refute this relationship between TBI history and PD [163].

Pathology

The main pathological finding of PD is the degeneration of dopaminergic neurons in the pars compacta of the substantia nigra, which leads to loss of dopamine in the striatum. Manifestation of clinical symptoms does not typically occur until roughly 80% of these dopaminergic neurons are depleted [163]. Additionally, PD is characterized by mitochondrial dysfunction [35], oxidative stress [35], defective handling of proteins [164], inflammation [165], and presence of α-synuclein Lewy body pathology in the surviving dopaminergic neurons [166]. α-Synuclein is a protein that has been described as one of the key neurodegenerative biomarkers in both familial and sporadic PD [167,168]. Interestingly, the presence of Lewy body pathology and α-synuclein aggregation has been observed in the olfactory tracts prior to any other regions of the brain, which points to olfaction dysfunction as one of the first signs of PD [169]. In addition to pathological changes observed in the cerebral cortex, immunohistochemistry studies have indicated increased α-synuclein in the cerebellum of PD patients, which contributes to the demyelination of neuronal tissue [170,171].

The pathophysiological changes associated with TBI are also well aligned with our current understanding of PD pathology. A common link between the two pathologies is the presence of α-synuclein. Recalling the previous discussion on the effects of DAIs, it is well established that the impaired axonal transport following microstructural white matter injuries leads to augmented accumulation of α-synuclein. As a universal component of Lewy body pathology, it is clearly implicated in the etiology of PD and TBIs have been found to increase and modify α-synuclein in both animals and humans [40,41,172]. The gene coding for expression of α-synuclein, SCNA, has also been linked to PD and TBI. Specifically, the expansion of Rep1, a polymorphic mixed-dinucleotide repeat in the SCNA promoter region increases expression of this protein in both humans and animals, which consequently elevates risk of PD [167]. One study investigating the effects of both SCNA and TBI history found that SCNA Long Rep1 carriers with a history of TBI were 6 times more likely to develop PD than non carriers of the at risk gene and no history of head trauma [167].

Neuroimaging

Conventional MRI studies using VBM to examine gray matter cerebral atrophy have been less conclusive for PD studies than the AD studies previously mentioned [173]. The inconsistency of conventional MRI modalities may be derived from the motion artifacts and image ghosting caused by the motor impairments and tremor associated with PD. Several studies found no difference in whole brain volumetric measurements in PD patients when compared to age matched healthy controls [174-176]. Two longitudinal studies, however, report an increased rate of annual brain volume loss and increased cerebral gray matter atrophy in PD patients [177,178]. ROI studies examining the gray matter density and volume in specific regions of the brain have yielded more agreeable results. This ROI analysis indicates that PD patients experience significant atrophy in structures like the hippocampus, amygdala, orbitofrontal cortex, substantia nigra, primary olfactory cortex, and anterior cingulated [179-184]. Increased global cerebral atrophy, similar to that observed in AD patients, is generally only observed in Parkinson's patients with dementia [180,181]. Recalling the aforementioned VBM studies on TBI patients, it appears that one unifying regional finding between TBI and PD patients is significant hippocampal atrophy [58].

Researchers have also utilized diffusion tensor imaging to investigate the microstructural WM abnormalities contributing to PD. Due to the known degeneration occurring in the substantia nigra of PD patients, initial focus was placed on imaging this structure in the brain using DTI. A number of early studies found no WM differences between PD patients and healthy controls in the substantia nigra [185-189]. More recent studies, however, have observed microstructural abnormalities in the substantia nigra indicated by reduced FA values and increased MD measures in PD patients [190-196]. One team of researchers was able to successfully distinguish PD patients from age matched healthy controls using only DTI measures from the caudal portion of the substantia nigra [191]. DTI studies also highlight widespread WM abnormalities in PD patients in regions of the brain outside the substantia nigra. Researchers have found decreased FA values and increased MD values indicating microstructural damage in the CC, hippocampus, SLF, ILF, uncinate, cingulum, external capsule, corticospinal tract, regions of the frontal lobe, and bilaterally in the cerebellum [192,193,197-199]. Additionally, DTI studies have revealed significant damage to the olfactory tracts in PD patients, which elucidates olfaction dysfunction as a common symptom [199-202]. Another interesting DTI finding in PD patients is damage to the orbitofrontal cortex [201]. This is a commonly observed feature in depression patients [203], so this finding may be responsible for the high rate of comorbid depression in the PD population [138].

When re-examining the DTI studies performed on TBI patients, there are several commonalities that crossover to the PD population. Most notably, researchers observed chronic global increases in MD values and decreases in FA values in TBI patients indicating widespread WM structural abnormalities similar to that of PD patients [72,77]. Additionally, researchers have found microstructural damage specific to the same individual ROIs in both groups of patients. In harmony with PD findings, WM structural abnormalities in TBI patients are observed in the CC, hippocampus, SLF, ILF, uncinate fasciculus, and the corticospinal tract [68,79,82,204-206].

fcMRI studies are also being applied to PD patients in order to delineate the abnormalities of ICNs that are contributing to the progression of their disease. Re-examining the unique pathophysiology of PD, it is evident that examining this disease from a network perspective is essential to properly understand it [207]. Degeneration of dopaminergic cells in the midbrain leads to dopamine depletion throughout the striatum [208]. This creates a neurochemical imbalance that impairs neuronal processing in the basal ganglia and propagates through dense corticostriatal connections to alter activity in other brain regions [209,210]. With this in mind, it is clear that impairments within the functional architecture of the brain are highly relevant to the pathology of PD and fcMRI studies can yield key insight on this matter. fcMRI studies investigating PD have tried to focus on mapping the functional architecture of corticostriatal connectivity since the pathology of PD is known to affect these structures. Multiple studies have reported disrupted functional connectivity within corticostriatal loops [207,211-214]. Interestingly, two of these studies observed an anterior shift in functional connectivity resulting in increased connectivity between the anterior putamen and cortical regions [207,212]. This is most likely a compensatory effect as the anterior putamen is known to be less affected by neurochemical alterations than the posterior putamen [207]. It could also be due the dopaminergic medication taken by PD patients since de novo patients displayed no increased FC in the anterior putamen [214]. The effects of L-DOPA on the fcMRI results are still not entirely known, but multiple studies have reported that dopaminergic medication will at least partially restore the functional ICNs of PD patients [215-218]. The increase in functional connectivity for patients receiving dopamine could also be a natural compensatory effect since patients receiving medications have generally had PD for significantly longer than de novo patients [214]. Other fcMRI studies investigating ICNs of PD patients have reported increased functional connectivity in the cortical motor areas [211,219]. One study reporting hyperconnectivity between the subthalamic nucleus and the motor cortex suggests that this abnormal coupling is responsible for PD rigor and tremor [219].

There are fewer fcMRI studies on TBI patients that have examined the corticostriatal ICNs with the same specificity as the PD studies above. However, there have been several interesting findings that may be related to the functional connectivity impairments reported in PD patients. One study investigating the sub-acute effects (mean time since injury: 60 days) reports significant functional connectivity impairments in the basal ganglia, motor network, sensorimotor cortex and the caudate [107]. Another study reports reduced inter-hemispheric functional connectivity among motor regions in TBI patients [220]. Further investigation on the chronic and acute effects of TBI on the corticostriatal ICNs is necessary to delineate their influence on the development and progression of PD.

A significant portion of the PET research in the realm of PD is focused on using ^{18}F-DOPA as a tracer to study dopaminergic metabolic activity rather than employing FDG to study CMRgl. These findings yield interesting results with the majority indicating decreased ^{18}F-DOPA uptake in key nigrostriatal structures, primarily the posterior putamen [221]. These are significant findings, but this review will primarily focus on FDG PET to investigate the effects of PD on CMRgl. The change in CMRgl resulting from PD is highly variable depending on the region of the brain [221]. Significant increases in CMRgl are reported in bilateral lentiform nucleus, PCC, and parahippocampus [222], whereas significant reductions in CMRgl are observed in the temporal, parietal, frontal, occipital cortices and caudate of PD patients [223,224]. Additionally, a longitudinal study examining PD patients at three time points spanning 4 years reports that disease progression is associated with increased CMRgl in the subthalamic nucleus, globus pallidus, dorsal pons, and primary cortex with declining CMRgl in the prefrontal and inferior parietal regions [224].

As previously discussed, FDG PET studies investigating the effects of head trauma on CMRgl are highly variable depending on the time since injury. Future FDG PET studies on TBI patients are necessary to adequately compare these acute and chronic findings to those observed in PD patients.

Amyotrophic Lateral Sclerosis

Epidemiology

ALS is less prevalent than AD and PD with an incidence rate of roughly 5 per 100,000 people when considering the general population, but it is still regarded as the most common Motor Neuron Disease (MND) [225]. It is a disease that progresses much quicker than other neurodegenerative diseases with 50% of ALS patients dying within three years of onset [14]. It is characterized clinically by progressive weakness, atrophy and spasticity of muscle tissue. These clinical manifestations are caused by degeneration of upper and lower motor neurons in the cortex, brainstem and spinal cord [226]. The underlying pathological mechanisms of ALS are less understood, but it is suspected that the some of the characteristics of ALS are comparable to those of other NDs [19].

As with AD and PD, it is not confirmed, but it is hypothesized that history of head trauma may be the main environmental risk factor for developing ALS later in life. Identification of a significantly higher incidence rate of ALS in professional athletes in sports like American football and soccer have led researchers to believe head injuries are a risk factor for ALS [20,227-229]. A study of retired NFL players found that neurodegenerative mortality for ALS was four times higher than that of the general population [20]. Another study indicates that professional Italian soccer players are 6.5 times more likely to develop ALS with a dose-response relationship between length of career and likelihood of disease [228]. These findings suggest that a history of TBI predisposes individuals to ALS, a notion that was first proposed back in 1911 [220]. However, once again, the epidemiological studies yield conflicting results as several found a significant relationship between previous TBI history and ALS [19,229-232] while several provide evidence to refute this claim [233-235].

Pathology

There are still many unknown features contributing to the pathogenesis and progression of familial (10%) and sporadic (90%) ALS. Structurally, the motor components targeted by neuropathology of ALS are the upper motor neurons of the corticospinal tract and the functionally linked lower motor neurons of the brainstem and anterior horns of the spinal cord [236]. One consistent finding regarding the molecular pathology of ALS that is now a hallmark for the disease is the deposition of ubiquitin positive proteins throughout the central nervous system (CNS) [237,238]. In recent years, researchers have further specified this hallmark of ALS to be a specific subset of ubiquitinated pathology known as TAR DNA-binding Protein 43 (TDP-43) [226]. As such, ALS is now classified as a TDP-43 proteinopathy. Another common feature of ALS pathology is a significant increase in microglial activity through the CNS, indicating widespread neuroinflammatory disease progression [35,133,134]. Post-mortem studies indicate that levels of microglial inflammatory activity correlate with the rate at which ALS progresses [133,134].

There are similar pathological findings between ALS and TBI patients as well. Notably, the characteristic protein contributing to the neuropathology of ALS, TDP-43, is reportedly also found in TBI patients. One post-mortem study examined the brains of 12 patients with CTE, a disease that develops as the result of extensive and repetitive head trauma. Of these 12 cases, 10 displayed abundant TDP-43 proteinopathy widespread throughout the CNS and motor neurons [239]. Additionally, the increased microglial inflammatory activity related to the progression of ALS is also observed in TBI patients [127]. This neuroinflammatory response following head trauma is chronic and progressive for up to 18 years following the injury, which may lead to greater risk of developing ALS [127,128]. This perpetual neuroinflammatory response, triggered by DAIs, is likely a key contributor to much of the cellular damage and pathology that has been previously discussed [240,241]. After a prolonged inflammatory response, the microglia become over-activated and induces detrimental neurotoxic effects by releasing multiple cytoxic substances and oxidative metabolites [242]. Additionally, the release of these neurotoxic substances can influence the activation of astrocytes and, subsequently, produce glial scar formation. Though astrocytes can provide neurotrophic support and guidance for axonal growth following CNS injury, the prolonged astrogliosis stemming from hyperactive inflammatory responses may inhibit axonal regeneration and impede functional recovery [242]. The perpetual nature of neuroinflammatory responses following TBI may contribute to a number of different biological processes that predispose individuals to a greater risk of neurodegenerative disease.

Neuroimaging

Several studies utilizing conventional MRI to obtain VBM measures for ALS patients yield comparable results to those observed in TBI, AD and PD populations with an overall trend of global brain atrophy [243-245]. In recent years, many studies have turned to DTI to assess the WM structural connectivity in the motor systems of ALS patients. The focal point of many of these studies has been the corticospinal tract, which can be visualized as the white matter "highway" connecting the upper and lower motor neurons [246]. Not surprisingly, these studies report significant WM impairments in the corticospinal tract of ALS patients [247-251]. Further investigation into the motor connectome of ALS patients reveals widespread WM structural impairments in primary motor regions (precentral gyrus and paracentral lobule), supplementary motor areas (caudal middle frontal gyrus), parts of the basal ganglia, PCC, and the precuneus [246]. The corpus collosum is another region that is consistently shown to have microstructural impairments in ALS patients [252].

fcMRI studies also indicate impairments of the functional architecture in brains of ALS patients, that often correlate with the level of WM damage determined via DTI. Specifically, increased levels of functional connectivity, indicative of inefficient networks, is observed in sensorimotor, premotor, prefrontal and thalamic regions of ALS patients [236]. Another fcMRI study found decreased functional connectivity between the left and right primary motor cortices, indicating a functional disconnect between hemispheres in ALS patients [253]. fcMRI findings regarding the DMN in ALS patients indicate decreased activity in the DMN as is observed in other neurodegenerative diseases [254].

PET is another modality that has been employed to study ALS patients. One study using PK PET to evaluate neuroinflammation reports that there is a significant increase in inflammation in the motor cortex, dorsolateral prefrontal cortex, and thalamus of ALS patients [255]. Similar findings were found as a chronic response to TBI, specifically an increase in inflammation of the thalamus, as indicated by greater uptake of PK, for up to 18 years following a single head injury [127]. Additionally, the FDDNP PET scans that were designed

to examine tau pathology in vivo displayed significant increases in tau in retired NFL players [135]. Tau pathology is a contributor to the pathogenesis of ALS so the elevated levels of tau following repetitive head injuries may be predisposing these individuals to a higher risk of ALS. There is a strong link between ALS and TBI patients regarding the PET findings, but additional neuroimaging studies investigating the chronic effects of TBI are required to delineate the functional and structural changes that may contribute to the pathogenesis of ALS.

Chronic Traumatic Encephalopathy

Epidemiology

The incidence rate of CTE and the overall epidemiological statistics pertaining to the condition are still primitive. The clinical spectrum of disease that is now identified as CTE was first postulated as a disorder in 1928 by Harrison Martland who termed this disorder "punch drunk" since it was largely found in boxers following multiple hits to the head either in competition or training [139]. This condition was further expounded and termed dementia pugilistic by Millspaugh in 1937 lending further medical validity to the disease [256]. Although it is nueropathologically similar to other NDs, dementia pugilistica was identified as a distinct neuropathological disorder in 1973 by Corsellis and it is now most commonly recognized as CTE [257].

Not surprisingly, much of the work today surrounding CTE and its incidence rate still revolves around athletes and other populations with frequent exposure to head injuries. Omalu et al. made significant contributions to the field by expanding the scope of CTE from focusing solely on boxers to athletes in a number of other contact sports (i.e., American football, hockey, wrestling, etc.) as well as military veterans [258-260]. An older study that is still frequently cited indicates that among ex-professional boxers the incidence rate of CTE is 17% [261]. In a more current and comprehensive review, McKee et al. indicate that the incidence of CTE in populations with frequent exposure to head injuries is at least 17%, but they speculate that the incidence rate is actually much higher [136]. After post-mortemly analyzing the brains of 85 individuals (all of which were either contact sport athletes or military veterans) with a history of repetitive mTBI and subconcussive head trauma, evidence of CTE was observed in 80% of the brains [262]. However, it is worth noting that this is a biased sample that over represents the actual incidence of CTE because families are far more likely to consider neuropathologic examination if they noticed symptoms representative of ND in their loved ones before their passing. It is also important to note when examining the epidemiology of CTE that the sample size is extremely small due to relatively the rare opportunity for post-mortem examination required to make definitive diagnoses.

Another key limitation in obtaining valid epidemiological statistics for CTE is the unreliable nature of the differential diagnosis for CTE versus other NDs. Individuals with CTE may present with symptoms that mimic those of AD, PD, or ALS and are subsequently misdiagnosed with one of these more well known conditions. This is why most individuals with CTE do not receive a proper diagnosis until post-mortem examination of their brains. In fact, one large review observed that when examining 68 post-mortemly confirmed cases of CTE, 37% had co-morbid neurodegenerative disease, the most common being a motor neuron disease like ALS [262]. These limitations are further amplified by the work of Hazrati et al. after examining the brains of 6 individuals with repetitive exposure to head trauma. They report that all six cases had evidence of ND, but not a single case was purely CTE and the three individuals with CTE pathology also had concomitant pathology of other NDs [261,263]. Additional research is required to create improved diagnostic criteria, discover objective biomarkers, and enhance our understanding of the progressive neuropathology of CTE in order to properly diagnose this disease in vivo.

CTE is also uniquely difficult to study because all clinical examinations must be done retrospectively through interviews conducted with family members of the deceased. This adds a challenging element when attempting to delineate the clinical progression of CTE. However, it is generally understood that the neuropathology of this condition leads to emotional, cognitive, and motor control impairments. Corsellis proposed three clinical stages of CTE in 1973 that are still supported today. The first stage typically features affective disturbances and psychotic symptoms relating to irritability, aggression and depression. As the disease progresses, individuals with CTE are affected by social instability, erratic behavior, memory loss and early signs of Parkinsonism during the second stage. The third stage is characterized by worsening dementia and severely impaired motor control either in the form of Parkinsonism or motor neuron disease [136,257,264,265]. Additionally, clinical presentation generally occurs at a younger age than other NDs with a recent review indicating that the average age of onset for CTE is 42 [136]. However, it can present much earlier life and the earliest known case of CTE was found in a 21 year old athlete following an abrupt suicide.

CTE is an apt representation of the insidious nature of head injuries as the neurological damage slowly accumulates and continues to progress many years after the exposure(s) to head trauma. It is distinct from the acute sequelae of a single concussive event and it is evident that this condition is not merely a severe case of prolonged concussive syndrome [266]. In fact, several of the post-mortemly confirmed cases of CTE had no medical history of any TBI, including mild concussions [136,266,267]. As such, many researchers are currently investigating the aggregate effects of repetitive subconcussive hits to the head that may exist without any medical record. This is a cause for concern considering that high school and collegiate athletes playing contact sports like football can be exposed to well over one thousand subconcussive hits to the head in a single season [268,269].

Pathology

Though CTE is still a nascent field of research compared to the aforementioned NDs, there are many recognizable gross neuropathological features. CTE is characterized by extensive atrophy in both cerebral hemispheres (particularly in the frontal, temporal and parietal lobes) as well as subcortical structures including the olfactory bulbs, thalamus, mammillary bodies, brainstem, and cerebellum [136,257,267]. This atrophy results in a significant reduction in brain mass [136]. Additional gross features indicative of CTE are cavum septum pellucidum, septal fenestrations, pallor of the locus coeruleus & substantia nigra, enlargement of the third & lateral ventricles, and thinning of the corpus collosum [136,257,267].

Additionally, there are extensive findings elucidating the microscopic alterations that contribute to the pathology of CTE. Like other NDs, abnormalities in protein deposition are a hallmark of CTE. The primary protein of interest is Tau, which is present in the form of NFTs, neuropil threads and glial tangles. Tau is also a feature of AD, but there are distinct differences in the presentation of Tau in CTE. Unlike AD, NFT clusters are generally denser in CTE and they form at the depths of the sulci, around small blood vessels and are preferentially distributed to superficial cortical layers [136,267]. This tau pathology is randomly distributed in the brains of CTE individuals while it has been observed to be more uniformly distributed in cases of AD. In CTE,

NFTs are most commonly observed in the dorsolateral, subcollosal, insular, temporal, dorsolateral parietal, and inferior occipital cortices as well as the olfactory bulbs, hippocampus, amygdala and subcortical white matter including the external capsule, anterior & posterior commissures, thalamic fasciculus and fornix [136].

Increased Aβ deposition is less common in individuals with CTE compared to what has been reported in AD patients. Abnormal Aβ deposits are found in 40-45% of individuals in CTE compared to nearly all cases of AD [266], and some studies show no presence of Aβ in their cases of CTE [260]. The role of Lewy body pathology, specifically α-Synuclein, in the development of CTE has also been investigated. In McKee's most recent review, 22% of the 85 confirmed cases of CTE also possessed abnormal levels of -Synuclein. However, these individuals with Lewy bodies were significantly older than the CTE cases without Lewy body pathology [262]. Another feature of CTE is the presence of TDP-43, which is a protein that was previously discussed for its role in ALS pathology. McKee et al. observed widespread TDP-43 in 80% of their 12 CTE cases, many of which were experiencing symptoms indicative of motor neuron disease [237,239]. A larger review indicates that of the 71 individuals with repetitive head injuries examined for TDP-43, 61 of them had TDP-43 proteinopathy in multiple brain regions [270].

Neuroimaging

Considering a conclusive diagnosis CTE cannot be made until post-mortem examination of the brain, there is very little research available that utilizes neuroimaging modalities to study the brains of living individuals who are afflicted with this progressive disease. From the current understanding of the neuropathology associated with CTE, there are several neuroimaging techniques that may be able useful in the diagnosis of CTE.

Structural MRI may be used to identify cerebral atrophy in vivo, which is a hallmark of CTE currently measured by weighing the brain during post-mortem examination. A recent review examined the structural MRI results of 100 "unarmed combatants" with extensive exposure to head trauma. There were several findings within this population of 100 individuals that are suggestive of CTE including 59% hippocampal atrophy, 43% cavum septum pellucidum, 24% cerebral atrophy, and 19% with enlarged lateral ventricles [271].

DTI is another neuroimaging modality that will be essential as researchers attempt to delineate the etiology of CTE. As the aforementioned articles clearly indicate, TBIs lead to microstructural damage in the WM of the brain that can be examined through DTI. A recent review indicates that these studies consistently report microstructural abnormalities following head trauma, but the exact nature of these abnormalities varies due to the heterogeneity of brain injuries [54]. These varying results are also attributable to the cross-sectional design of the studies performed. Brain damage following single or multiple head injuries has been shown to be progressive, so it is reasonable to expect that these neuroimaging findings will vary depending on the time elapsed since the injury. Longitudinal studies are required to understand the dynamic nature of TBIs and to delineate these alterations to the brains microstructural integrity during recovery. There are several DTI studies examining the chronic effects of not only TBIs, but also repetitive subconcussive events that may provide further insight to the progression of CTE. One such study utilizing DTI to compare the brains of veterans with blast exposure to those without blast exposure found global patterns of reduced FA in the WM of the blast exposure group [272]. Another study investigating the effects of multiple subconcussive hits to the head in HS athletes reports abnormal MD and FA values even in athletes with no previously diagnosed TBI [273].

	AD	PD	ALS	CTE
Clinical signs & symptoms	Dementia; progressive cognitive impairments memory loss	-Motor symptoms resting tremor, rigidity, bradykinesia, impaired balance -Comorbid symptoms: depression, MCI, olfaction dysfunction	-Progressive weakness, atrophy, and spasticity of muscle caused by motor neuron death	-Affective disturbances; irritability, depression, aggression -Social instability, memory loss, cognitive decline -Motor impairments
Pathology/ Abnormal proteins	-Aβ -Tau NFTs (uniformly distributed, less dense than CTE)	-Dopaminergic lesions in substantia nigra (SN) -Lewy body accumulation, specifically a-synuclein	-TDP 43 -Increased microglial activation	- Aβ (less consistent that AD) -Tau NFTs (randomly distributed dense clusters, depths of sulci, superficial layers) -a-synuclein and TDP-43
Gross structural findings	-Global atrophy -Increased VBR -Atrophy to hippocampus, amygdala, & uncus	-Regional atrophy in hippocampus, amygdala, orbitofrontal cortex, SN, & anterior cingulate	-Trend of global cerebral atrophy	-Global cerebral atrophy and various subcortical structures -Increased VBR -cavum septum pellucidum -septal fenestrations -thinning of CC -pallor of SN
Microstructural WM injuries	-Global WM abnormalities. Specifically uncinate, ILF, SLF, fornix, cingulum, hippocampus & CC	-WM impairments in SN, CC, hippocampus, SLF, ILF, uncinate, cingulum, external capsule, corticospinal tract, & cerebellum	-Marked damage to corticospinal tract -WM impairments in primary motor cortex, SMA, basal ganglia, precuneus, and CC	-Unknown -Populations with frequent exposure to head trauma generally have damaged microstructural WM as a result of DAI
Functional abnormalities	-Hyperactive DMN in early AD, but quickly diminishes as AD progresses -Hypometabolism throughout temporo-parietal cortex. Specifically in the PCC, thalamus, hippocampus & frontal cortex	-Neurochemical imbalance -disrupted connectivity in corticostriatal loops -increased FC in motor cortex and STN -increased CMRgl in STN, GP, motor cortex -Decreased CMRgl in prefrontal and inferior parietal regions	-Impaired FC in sensorimotor, premotor, prefontral, and thalamic regions -Decreased FC between left and right primary motor cortices -Decreased DMN	-Unknown -Populations with frequent exposure to head trauma reportedly exhibit decreased CMRgl in PCC, parieto-occipito lobes and cerebellum. Altered FC in the DLPFC and frontal gyri are also reported in this population

Table 1: Features of NDs

fMRI and PET studies examining the functional and neuroenergetic abnormalities in individuals with repetitive exposure to head trauma are also essential to better understand CTE. A FDG-PET study of boxers found hypometabolism in PCC, parieto-occipito frontal lobes, and the cerebellum following chronic exposure to subconcussive events [274]. Another study revealed that soldiers with multiple blast exposures (mean of 12) revealed decreased metabolism in cerebellum, vermis, pons, and medial temporal lobe [275]. A comparable study using resting state fMRI reports that retired NFL players exhibit decreased functional connectivity within the dorsal fronto-parietal network [276]. Additionally, they exhibited hyperfrontality and required increased activation in the frontal lobe during tasks of executive function [276]. Another study employing fMRI to examine the functional activity of HS athletes who were equipped with accelerometers in their helmets to track head impacts over the course of the season indicates that the effects of these repetitive head injuries can materialize quickly. The athletes were tested both before and after the season and the fMRI results indicate that even players without diagnosed concussions experienced neurophysiological impairments with significant alterations to the dorsolateral prefrontal cortex (DLPFC), the superior frontal gyri, and left middle frontal gyri [277]. It is worth noting that these neurophysiological abnormalities exhibited in the fMRI are strongly correlated with neurocognitive deficits and impaired verbal memory. Additionally, a correlation was observed between impaired fMRI activity and the number of subconcussive hits to the head tracked by the accelerometer over the course of the season [277-281].

These studies highlight the need for improved surveillance of head injuries since many of these results occur in the absence of a diagnosed TBI, especially in individuals with frequent exposure to subconcussive events. Properly identifying these at risk populations is essential to delineate the link between head injuries and all forms neurodegenerative disease. Additionally, these findings point to the marked absence of longitudinal data. Though these neuroimaging findings are compelling, they are inherently ambiguous in nature given the fact that CTE cannot be diagnosed until after the individual is deceased. Prospective MRI studies examining at risk populations, both before and after signs of ND, are required to fill this knowledge gap. Though it is a fairly morbid proposition, it would be beneficial to perform a study tracking these cases longitudinally for an eventual post-mortem assessment of CTE, which can then be compared against previously acquired *in vivo* neuroimaging data. To account for the vast heterogeneity and the multifaceted nature of the progressive effects of head injuries, future studies should employ multimodal neuroimaging techniques in order to comprehensively scan the brain for subtle abnormalities.

Discussion and Future Directions

In order to more effectively develop therapeutic targets to treat, and perhaps prevent the development of neurodegenerative disease, it is essential to identify the key steps responsible for the pathological cascade progressing from TBI to neurodegenerative disease. Between the initial brain reserve hypothesis, the metabolism hypothesis, and the overall intertwined natures of their pathologies, it is evident that TBI and neurodegenerative disease are not mutually exclusive. So why have the results of these large epidemiological studies been so conflicting? It is possible that the relationship simply does not exist or it is not strong enough as indicated by previous epidemiological studies. However, an overwhelming trend in the neuroimaging and pathological findings suggests otherwise.

Upon examining the existing epidemiological case studies, it is apparent that there is a fundamental problem in the way this topic is being investigated. There is no consistent definition of TBI used across these studies, and therefore, each epidemiological study classifies participants with history of TBI under a different set of criteria (Table 2). It is unreasonable to expect the findings to be consistent and valid across multiple studies while using different criteria to identify one of the two variables that are being compared. It is imperative to work towards a more uniform approach to investigate this relationship by introducing an improved retrospective head trauma screening tool based off current CDC guidelines for TBI. Settling on a gold standard that can be used to effectively identify TBI history in a retrospective fashion will improve the homogeneity of findings in future studies.

In addition to their inconsistencies, many of the existing epidemiological studies use dated definitions and guidelines for retrospectively identifying head trauma. This, of course, is understandable considering the pace at which our understanding of head injuries is growing. In the last 11 years alone, the operational definition of concussions has been altered each of the four times a consensus statement has been released by a team of experts meeting at the International Conference for Concussion in Sport [282-285]. The most current definition released by this panel reads: "Concussion is a brain injury and is defined as a complex pathophysiological process affecting the brain, induced by biomechanical forces. Several common features that incorporate clinical, pathologic and biomechanical injury constructs that may be utilized in defining the nature of a concussive head injury include:

1. Concussion may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an "impulsive" force transmitted to the head.
2. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, symptoms and signs may evolve over a number of minutes to hours.
3. Concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies.
4. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course. However, it is important to note that in some cases symptoms may be prolonged [282].

In essence, the sensitivity in nearly all of these previous epidemiological studies is too low to adequately assess TBI history in a retrospective fashion. The vast majority of these studies classify subjects as having a history of TBI only when they report a blow to the head resulting in loss of consciousness (LOC) or requiring medical attention. Both of these approaches are fundamentally flawed when considering current CDC guidelines for head trauma. It is now well established that TBIs can occur in the absence of LOC and, in fact, the majority of TBIs occur without LOC [286,287]. Furthermore, many people are unaware of their sustained injuries, which lead to a substantial portion of TBIs going unreported [7].

In addition to the distinct lack of a common definition for what constitutes a TBI, many studies use dissimilar and vague approaches to acquire this key piece of medical history (Table 2). Some large epidemiological studies use medical databases and rely on medical

records to link TBI history with neurodegenerative diseases. Recalling the aforementioned findings in the CDC's 2003 Report to Congress, it is clear that this is not sufficient since this method may only account for the 12% of mTBI patients that are hospitalized. Some studies rely on phone interviews, others employ "standardized" interviews with trained clinicians, and a large number of them utilize "standardized" medical history questionnaires. A key flaw, however, is that these questionnaires and interview methods are only standardized within that individual study's patient population. There is no transcript of the interview format or name of the questionnaire provided, which leads to these studies using dissimilar and undisclosed methodologies resulting in a lack of standardization across the field. Additionally, many times these standardized questionnaires and interviews only offer a quick "Yes/No" question to head trauma that is buried in a long list of other previous ailments.

In their 2003 Report to Congress, the CDC tangentially addressed this issue by pointing out the inadequacies of current head trauma screening tools and calling for improved methods to obtain more accurate TBI surveillance data [7]. Ten years later, the Institute of Medicine still felt the need to echo this sentiment by listing improved concussion surveillance as one of their top priorities in their 2013 report [288]. Robust head trauma surveillance tools have been developed for specific populations like military personnel (Brief Traumatic Brain Injury Screen, BTBIS) [289] and athletes (Sports Concussion Assessment Tool 3, SCAT-3) [282], but these are often incompatible with the general population. Furthermore, many of these TBI screening tools focus on events occurring in the more immediate past rather than focusing retrospectively on events spanning one's lifetime.

In addition to creating a retrospective TBI screening tool that is all-

Reference	Disease	Case Definition for TBI	Methodology	OR	Relevant Findings
Fratiglioni et al 1993[27]	AD	LOC	Interview an "informant" of the patient	.4	
Mayeux et al 1995[30]	AD	LOC	Interview	1.5	OR: 10.5 for e4 carriers
Guo et al 2000[278]	AD	LOC or medical attention	Structured questionnaire	4.6	OR: 9.9 for TBI with LOC
Plassman et al 2000[32]	AD	Medical record of LOC, post-traumatic amnesia or skull fracture occurring during military service	Military health records	2.16	
Chen et al 2007[19]	ALS	Injury requiring medical attention	Interview	1.4	OR:3.1 for head injury in 10 years leading up to onset of ALS
Schmidt et al 2010[231]	ALS	LOC or medical care	Telephone interview	1.26	OR: 1.88 for TBI occurring at older age (>29)
Turner et al 2010[233]	ALS	N/A	Reviewed data from Oxford Record Linkage Data	1.5	
Stern et al 1991[146]	PD	Head trauma severe enough to cause vertigo, dizziness, blurred vision, seizure or convulsion, transient memory loss, personality change or paralysis	Structured interview	2.9	
Martyn and Osmond 1995[155]	PD	LOC or hospital admission	Standardized questionnaire	.6	
Kuopio et al 1999[154]	PD	N/A	Interview	.89	OR:1.99 for multiple TBI OR:1.37 for TBI with LOC
Taylor et al 1999[147]	PD	Head trauma severe enough to cause LOC, blurred/double vision, dizziness, seizures, or memory loss	Structured interview	5.09	
Tsai et al 2002[148]	PD	Head trauma severe enough to cause vertigo or dizziness, LOC, post-traumatic amnesia, personality changes, seizures or paralysis	Structured Questionnaire	9.27	OR: 4.5 for young onset PD (< 40 years of age) compared to normal PD patients
Zorzon et al 2002[162]	PD	LOC	Structured interview	1.6	
Baldereschi et al 2003 [150]	PD	LOC	Standardized questionnaire interview	.85	
Bower et al 2003[140]	PD	LOC, posttraumatic amnesia, neurologic signs of Brain Injury, or Skull fracture with documented medical record	Medical history screened by nurse and confirmed by neurologist	4.3	OR:11 for TBI with LOC TBI with Hospitalization: 8
Goldman et al 2006[143]	PD	Amnesia or LOC following head injury	Phone interview	3.6	OR:4.3 for multiple TBI OR:4.1 for TBI resulting in hospitalization
Dick et al 2007[141]	PD	"Ever being knocked unconscious"	Standardized questionnaire interview	1.35	OR: 2.53 for multiple TBIs with LOC
Fang et al 2012[279]	PD	Hospitalization	Medical records	1.94	
Lee et al 2012[280]	PD	LOC > 5 minutes in duration	Interview	2	
Goldman et al 2012[167]	PD	Affirmative response to "Have you ever had a head injury where you lost consciousness or were diagnosed with a concussion by a doctor?"	Computer assisted phone interview	1.3	OR: 3.5 for Long Rep1 allele carries with TBI history
Harris et al 2013[281]	PD	Injury requiring physician attention	Standardized questionnaire interview	2.08	OR: 2.64 for TBI with LOC

Table 2: Methods and Findings of Epidemiological Studies

encompassing, it also needs to be composed with special consideration pertaining to its language and terminology. An important study investigating the incidence of TBI in university athletes highlights the immense variability that is derived from the language used in head trauma questionnaires [290]. Immediately following the season, football and soccer players were asked whether or not they experienced a blow to the head resulting in a concussion with 16.5% and 12.4% of players, respectively, reporting a concussion. This same group was then given a questionnaire with altered language that focused on whether they experienced the common symptoms of concussions following a hit to the head. Suddenly, the self-reported rate of players experiencing concussion symptoms following a blow to the head jumped to 70.4% and 62.7% of all football and soccer players [290]. Of the 70.4% of football players experiencing symptoms of a concussion, only 23% of them realized they had suffered a concussion compared with only 19% of soccer players recognizing their symptoms as a concussion [290]. This study perfectly illustrates the significant limitation of underreported TBIs even as our awareness of head injuries has grown. Essentially, 80% of these athletes never even knew they suffered a concussion so they would not have sought medical attention for their head injuries and would have falsely responded "no" when asked if they had a history of head trauma, which highlights the problem with current methodologies employed by large epidemiological studies.

Even with the heightened TBI awareness in recent years, athletes still frequently omit reporting head injuries for a myriad of reasons. One study used a detailed questionnaire immediately following the season asking high school football players (n=1532) if they had suffered a concussion during that previous season. Of the 15% who responded yes, indicating they knowingly suffered a concussion, 53% of them indicated that they never reported the injury with the top two reasons being they "did not think it was serious enough" or they did not want to leave the game. This is dangerous on many levels. Not only are these athletes at risk of second impact syndrome and further damage if they continue playing, but these injuries are likely to perpetually go unaccounted for. In addition to there being no medical record of these injuries, many of these athletes will write-off these childhood incidents as noninjurious events after living asymptomatically for a number of years and fail to retrospectively report them if presented with a simple "yes/no" questionnaire later in life. This is likely contributing to the overwhelming variability and inadequacy in responses to current questionnaires used to assess TBI history.

Additionally, it is reasonable to expect that the number of unreported mTBIs is even higher when examining the target populations of epidemiological studies investigating neurodegenerative diseases. Naturally, it will be more difficult to recall individual events that may have occurred decades earlier. Furthermore, others must take into account how incredibly low our awareness of head traumas was several decades ago. An accurate answer cannot be expected from a ~60 year old participant if they are simply asked if they have ever suffered a concussion or rely on medical data for head traumas. It is highly likely that they might have suffered a concussion forty years earlier either as an athlete or in an accident, but they were never properly aware of it. A review of NCAA data for 15 sports showed that the overall reported concussion rate doubled from 1.7 to 3.4 concussions per 1,000 athletic exposures from 1988 to 2003. Helmet technology has unquestionably improved during this same time span, which suggests that in recent years concussion rates have increased as a result of our increased awareness of head injuries. A new and improved retrospective screening tool is required to make advancements in addressing this knowledge gap from previous decades.

With this information, it is evident that there are three essential components to an effective TBI screening tool for this population: 1) terminology focusing on the symptoms of head injuries rather than simply the incidence, 2) questions geared towards potential exposures for the general population as opposed to focusing on specific factions (i.e., sports), and 3) questions that are all-encompassing in nature rather than focusing on shorter time frames. After an extensive literature review, there is no evidence of a questionnaire that accounts for all three of these components. Existing epidemiological studies that attempt to retrospectively assess TBI history do so ambiguously and inconsistently across studies (Table 2). Some rely on medical histories, which can miss up to 88% of TBIs if they only account for hospitalizations [3,8]. Other epidemiological studies only include head injuries that resulted in LOC, which does not account for up to 90% of mTBIs [7]. Another common approach to assess TBI history in these studies is through an interview with a trained clinician, but these interviews vary for each study and add an additional heterogeneous element to what is already an ambiguous task.

In an attempt to fill this void, the authors developed the Retrospective Screening of Traumatic Brain Injury (RESTBI) Questionnaire (see sites.duke.edu/restbi). This retrospective surveillance tool was designed with the goal of increasing the sensitivity to head injuries in order to recognize and identify the many TBIs that are currently unaccounted for. Additionally, the intent was to make a head trauma screening tool that can be used across various populations in order to increase consistency between different studies. With that in mind, the RESTBI was created so it could be handed out to collegiate athletes with the same effectiveness and accuracy that would be achieved if it was given to their grandparents. In order to do so, the RESTBI uses a framework for each question that will help elderly populations recall specific incidences where they may have been exposed to a potential head injury decades earlier that they are otherwise likely to forget. Additionally, the language and terminology found in the RESTBI focuses on the symptoms following TBIs due to the findings from Delaney et al. [287]. This should work towards addressing the knowledge gap from older populations who are less aware of what constitutes a head injury and may be unaware of previous injuries sustained. Finally, the fact that this is a questionnaire, rather than an interview form, will help yield increased reproducibility from different groups of researchers. It is important to note that, at this time, the authors are in process of validating the RESTBI. However, for the reasons listed above, the RESTBI has strong potential to increase the sensitivity for the retrospective surveillance of TBIs.

In addition to its function in epidemiological studies, the RESTBI could serve a vital role for nearly every neuroimaging study. It is indicated by the studies investigating TBI populations listed above that head traumas significantly alter the brain's anatomy, metabolism, and connectivity, both functionally and structurally. This is significant in terms of investigating the effects of TBI on the aging brain, but the scope of this problem may be much larger. How many neuroimaging studies might have inaccurate findings because they did not properly account for history of head trauma? This is a significant variable that is currently being inadequately assessed. All studies should consider utilizing a comprehensive and retrospective screening tool like the RESTBI to provide an extra data point to reference throughout the study. It may be the key piece in understanding the results for a study investigating ICNs (or some other topic where TBIs are not the focal point of the study) and it could potentially explain anomalies found in the data set.

This review also highlights the necessity for additional longitudinal neuroimaging studies that focus on the brain at different time points following head trauma. There are many significant findings for the

brains acute and sub-acute responses to head injury, but the current neuroimaging data available fails to investigate the chronic effects of remote TBI (~10 years post injury). Previous neuroimaging studies are all either focused on the immediate days and months following a head injury or the disease state that is occurring sometimes decades later. There is a massive and literal gap in the data. There are no studies providing data from asymptomatic, and otherwise healthy, adults that investigate the chronic and progressive effects of TBI history. Studying this population may provide vital information regarding pathogenic cascade following TBI. There needs to be a paradigm shift from the traditional view that TBIs are an acute, static injury towards treating them as complex events with progressive damage to the brain. Studies have shown perpetual damage in TBI patients progressing up to 18 years following TBI [127,128], so it is imperative to track these ongoing impairments longitudinally through multimodal neuroimaging studies in order properly treat and prevent further damage.

There are likely tens of millions of people who are living with a previously sustained head injury, many of which are undiagnosed. Since TBI awareness has only grown in recent years, many of these individuals who may have hit their head decades ago are likely to have shrugged off a brief state of altered consciousness and disregard these instances as noninjurious events after years of living symptom free. However, as a result of these undiagnosed head injuries, it is reasonable to hypothesize that these individuals may be experiencing a number of progressive structural and functional abnormalities within their brain that are currently unnoticed. In addition to the perpetual neuroinflammatory response that is potentially still ongoing from the initial injury, they could have progressively increasing CMRgl levels and hyperactivity in the DMN to compensate for the worsening FA and MD in the axons that structurally connect their brain, all of which may contribute to abnormal protein deposition and predispose them to neurodegenerative disease. There are an overwhelming number people who fit this description; these adults are otherwise healthy until it is too late and they reach a point where their brain's compensatory mechanisms eventually fail leading to neurodegenerative disease. In the CDC's most recent report, TBI is referred to as the "silent epidemic" because many of the lasting complications from head injuries may not be readily apparent as is the case in many of these purportedly asymptomatic adults [6]. The neuroimaging technology is rapidly evolving to properly examine these mechanisms so the next step is achieving improved methods to properly identify otherwise healthy adults with a history of TBI, even mTBIs that may have been previously undiagnosed. The RESTBI offers a potential solution and avenue to adequately address this growing "silent epidemic". It is evident that these neurodegenerative diseases are pathologically complex with multifaceted etiologies, but there is strong evidence suggesting TBIs may play prominent role. As more of these studies are completed and the mechanisms connecting TBI with neurodegenerative disease are identified, it will open the door for improved therapeutics that may have the potential to stop the pathogenic cascade and limit the prevalence of these devastating diseases.

Conclusion

Traumatic Brain Injuries are a growing epidemic affecting all demographics of our population on a global scale. As our understanding of these head injuries increases, we are made increasingly aware of their calamitous consequences that may lead to lifelong disability and disease. Pathological and neuroimaging studies have presented a framework that displays the extensive overlap between TBIs and neurodegenerative disease. In order to adequately assess the relationship between head injuries and the predisposition of these neurodegenerative diseases, we must improve our ability to retrospectively assess past exposure to TBIs. The RESTBI is a potential solution to this problem that will hopefully be adapted by future studies in order to increase the validity and reliability of future epidemiological findings.

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