Neuroscience and Biobehavioral Reviews 84 (2018) 316–324

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Glymphatic system disruption as a mediator of brain trauma and chronic traumatic encephalopathy

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ARTICLE INFO

Keywords:
Traumatic brain injury
Sleep
Insomnia
Glymphatic system
Chronic traumatic encephalopathy
Aquaporin 4

ABSTRACT

Traumatic brain injury (TBI) is an increasingly important issue among veterans, athletes and the general public. Difficulties with sleep onset and maintenance are among the most commonly reported symptoms following injury, and sleep debt is associated with increased accumulation of beta amyloid (Aβ) and phosphorylated tau (*p*-tau) in the interstitial space. Recent research into the glymphatic system, a lymphatic-like metabolic clearance mechanism in the central nervous system (CNS) which relies on cerebrospinal fluid (CSF), interstitial fluid (ISF), and astrocytic processes, shows that clearance is potentiated during sleep. This system is damaged in the acute phase following mTBI, in part due to re-localization of aquaporin-4 channels away from astrocytic end feet, resulting in reduced potential for waste removal. Long-term consequences of chronic dysfunction within this system in the context of repetitive brain trauma and insomnia have not been established, but potentially provide one link in the explanatory chain connecting repetitive TBI with later neurodegeneration. Current research has shown *p*-tau deposition in perivascular spaces and along interstitial pathways in chronic traumatic encephalopathy (CTE), pathways related to glymphatic flow; these are the main channels by which metabolic waste is cleared. This review addresses possible links between mTBI-related damage to glymphatic functioning and physiological changes found in CTE, and proposes a model for the mediating role of sleep disruption in increasing the risk for developing CTE-related pathology and subsequent clinical symptoms following repetitive brain trauma.

1. Introduction

Traumatic brain injury (TBI) is an increasingly important issue among the general public, owing in part to the focus of the effects of TBI and concussion on professional and combat veterans. Sleep disturbances are a common symptom post-injury (Ayalon et al., 2007; Orff et al., 2009; Ouellet and Morin, 2006), with up to 80% of mild TBI (mTBI) patients reporting new-onset sleep difficulties (Orff et al., 2009). These disturbances commonly include abnormal sleep architecture, such as greater sleep onset latency and shorter time in rapid eye movement (REM) sleep (Orff et al., 2009), with symptoms often meeting diagnostic criteria for sleep disorders, such as sleep apnea (both obstructive and central), and insomnia (Castriotta and Murthy, 2011; Ouellet and Morin, 2006). Sleep deprivation is associated with a lower threshold for managing stress in relatively low stress environments (Minkel et al., 2012), the development of neuropsychological symptoms (Rao et al., 2014), and a decreased subjective quality of life (Baumann et al., 2007). One study showed that new-onset sleep difficulties following mTBI predicted the future symptoms associated with neuropsychiatric disorders, such as depression (Rao et al., 2014).

Physiologically, mTBI is associated with an acute "metabolic cascade" of cellular injury due to toxic effects of a glutamate surge from ruptured cell membranes, and diffuse axonal injury (DAI), which can result in signal disruption and accumulation of extracellular proteinaceous waste products. For example, glutamate and phosphorylated tau (*p*-tau) are released as byproducts of mechanical deformation and excitatory neuronal activity, resulting in acidosis and edema (Barkhoudarian et al., 2011; Giza and Hovda, 2014; Tang-Schomer et al., 2010). Inflammation and reactive astro- and micro-gliosis appear around the site of the injury (Giza and Hovda, 2014) – processes that may be exacerbated by further injury in both the acute and long-term phases.

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http://dx.doi.org/10.1016/j.neubiorev.2017.08.016
Received 17 March 2017; Received in revised form 17 August 2017; Accepted 21 August 2017
Available online 30 August 2017

Recent literature has suggested that sleep disturbances are associated with reduced clearance of metabolic waste products from the brain (Xie et al., 2013) via the "glymphatic" system (GS) (Iliff et al., 2013). During sleep, interstitial space expands, allowing increased convection of cerebrospinal and interstitial fluids (CSF and ISF) through the parenchyma, promoting the removal of metabolic waste products that accumulate naturally (i.e., even in the absence of traumatic forces) during normal neural activity (Xie et al., 2013). This process has particular implications in TBI, given the acute influx of metabolic waste and widespread metabolic disequilibrium. In TBI patients, astroglial scars, inflammation, the buildup of proteinaceous waste products (cleaved tau [C-tau], *p*-tau and beta-amyloid [Aβ]), and astrocytic proteins (glial fibrillary acidic protein (GFAP) and S100 calcium binding protein B [S100-B]), are thought to contribute to GS dysfunction (Jessen et al., 2015). Following this accumulation of protein and reduction in clearance potential, neurotoxins such as beta-amyloid and tau byproducts begin accruing in extracellular spaces (Iliff et al., 2014; Ren et al., 2013). Persistent abnormal accumulation of these waste products may then contribute to the potentiation of neurodegenerative processes like Alzheimer's disease (AD) (Tarasoff-Conway et al., 2015) and chronic traumatic encephalopathy (CTE) (Kanaan et al., 2015).

CTE is now regarded as a tauopathy, with the abnormal accumulation of *p*-tau in the depths of cortical sulci as a signature of the diagnosis and a potential marker of disease progression (McKee et al., 2016). Our knowledge of CTE in American football players relies on cross-sectional, posthumous evidence from autopsy samples, predominantly from symptomatic subjects; this limits our understanding of CTE risk and prevalence as well as the role that factors other than repetitive brain trauma have in CTE onset and progression (Asken et al., 2016). However, the current CTE literature provides evidence for the role of GS dysfunction due to the overlap between the neural structures commonly associated with CTE pathology and those involved in the GS. For instance, neurofibrillary tangle (NFT) accumulation patterns tend to co-localize with regions of maximal glymphatic flow, such as perivascular spaces, around astrocytes, and the glia limitans (the border between the pia mater and the astrocytic end feet lining the cortex).

This review will discuss the implications of GS disruption in TBI patients and its potential mechanistic contribution to neurodegenerative processes such as CTE. We also propose a model of the mediating effect that sleep disturbances may play in increasing the risk for the development of CTE pathology by virtue of chronic GS disruption following TBI. In this way, we hope to set a foundation and course for future research. We will review (1) pathognomonic signs and supportive neuropathological features associated with CTE; (2) recent findings in the GS literature; (3) proposed links among the GS, sleep disturbance, and CTE, and (4) implications for future research. In conducting this review, we evaluated data collected across all severity levels of TBI, but focused primarily on implications of mTBI and exposure to repetitive trauma (both clinically diagnosable and subclinical impacts). In considering TBI-related sleep outcomes, we focused specifically on insomnia, due to the relatively high frequency of insomnia-related symptoms reported in mTBI populations.

2. Chronic traumatic encephalopathy (CTE)

2.1. Background

The term "chronic traumatic encephalopathy" has appeared in the literature since the 1940's (Bowman and Blau, 1940). However, understanding of the clinical presentation and pathological findings expected in this condition have evolved over the past ten years, stimulated by the initial reports of CTE in American football players (Omalu et al., 2005), which because of the popularity of the sport engendered widespread interest. The neurological consequences of repetitive brain trauma were first described decades ago (Martland, 1928) and subsequent studies identified neuropathological changes such as cerebral atrophy, chronic perivascular hemorrhage, NFT deposition, ventricular enlargement, and cavum septum pellucidum (Adams and Bruton, 1989; Corsellis et al., 1973). The "modern" conception of CTE is primarily as a tauopathy, which could not be identified until antibodies to tau were developed. Abnormal accumulations of other peptides and proteins such as Aβ and TAR DNA-binding protein 43 (TDP-43) (McKee et al., 2016; McKee et al., 2013; Stein et al., 2015) were seen particularly when subjects were older and with more severe forms of the disease. Diagnosis of CTE currently requires postmortem evaluation, and neuropathological criteria have only recently been developed. Validated in vivo diagnostics are not available, however, positron emission tomography (PET) ligands for studying protein deposition burden in patients with a history of multiple mTBI and repetitive subclinical brain trauma are underway (Dickstein et al., 2016; Gandy and DeKosky, 2014; Provenzano et al., 2010), and MRI studies looking for characteristic, potentially diagnostic change, are also in development. Validating an in vivo mechanism to identify CTE presence and progression will be integral to determining incidence and prevalence of this disease, and for developing treatment interventions. Consensus criteria for pathological diagnosis of CTE are evolving, but a full review of current criteria may be found in McKee et al. (2016).

The precise etiology of *p*-tau accumulations at the depths of cortical sulci in CTE is unclear. Past literature has described shearing forces from brain trauma localized to these areas, including axonal shearing and microtubular disruption and, thus, deposits of tau appear in the injured areas (McKee et al., 2016). A recent study used mathematical modeling of three different types of TBI, including a helmet-to-helmet American football collision, fall from ground level to a marble floor, and a motor vehicle accident between a motorcycle and a car (Ghajari et al., 2017). Results from the 3D modeling indicated high strain and strain rates localized to the base of sulci across all injury types. This finding was validated further using MRI data from TBI patients of all severity levels (84% moderate-severe) with varying injury mechanisms compared to healthy controls. The authors found decreased fractional anisotropy within cortical sulci at the gray-white matter boundary in TBI patients compared to controls, which was not significant within the gyri (Ghajari et al., 2017), indicating that strain and strain rates at the base of cortical sulci is an important feature of TBI.

2.2. Neuropathological diagnostic criteria for CTE

The recently established criteria for CTE were based on blinded diagnoses by seven neuropathologists evaluating 25 cases of neurodegenerative disease with tauopathy. They concluded "the pathognomonic lesion of CTE consists of [phosphorylated] tau (*p*-tau) aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci" (McKee et al., 2016), which represents the sole *required* criterion for diagnosis. Consistent with previous pathological descriptions of patients exposed to repetitive brain trauma, they also noted frequent TDP-43-immunoreactive neuronal cytoplasmic inclusions and Aβ plaques.

3. Glymphatic system (GS)

3.1. Background

Traditional views of metabolite clearance held that the majority of metabolites, such as Aβ, were cleared from the brain by diffusion across the BBB (Fenstermacher and Parlak, 1975) and bulk flow of ISF into the CSF "sink" (Cserr, 1971). However, recent findings by Iliff et al. (2012), and Weller et al. (2010) suggested a more complex clearance process, noting that diffusion alone would not move rapidly enough to clear sufficiently the amount of waste products created by the brain's highly metabolic processes (Iliff et al., 2012; Tarasoff-Conway et al., 2015; Weller et al., 2010). Tracking CSF and ISF movement throughout the brain, Iliff et al. (2013) showed that clearance of particles such as Aβ

occurred not only through a slower process of diffusion, but also by way of the "glymphatic system" (GS). Although the "glymphatic system" is a relatively new concept, the idea that CSF plays a role in waste accumulation and disposal was proposed as early as 1664 by Thomas Willis in his classic treatise "Cerebri Anatome".

Iliff et al. (2013) describe the GS as an interchange between CSF and ISF, where CSF is recirculated into the parenchyma via the perivascular spaces [also called Virchow-Robin spaces (VRS)] within the subarachnoid space to subsequently interchange with ISF (Iliff et al., 2013). Aquaporin-4 (AQP4) channels, densely localized to astrocytic end feet, serve as conduits through which fluid moves and helps propagate a convective flow by decreasing resistance to CSF and ISF as it moves across the parenchyma (Iliff et al., 2013; Iliff et al., 2012). This movement is thought to be driven by a number of forces, but one of the most well-established of these movement mechanisms is arterial pulsatility. As VRS become continuous with the basal lamina (a loose extracellular matrix comprised of endothelial cells, pericytes and astrocytes), CSF moves out of the perivascular space and into the parenchyma, aided by arterial pulsatility, where it interchanges with ISF. As CSF and ISF move across the parenchyma, waste products secreted into interstitial space are carried out to a variety of pathways, including venous basement membranes. This clearance network was named the "glymphatic" system because of its similarity in function to peripheral lymphatic processes and its reliance on glial cells (Iliff et al., 2012). For a more thorough description of GS cellular dynamics, see Jessen et al. (2015).

Following their work outlining the GS, Iliff et al. (2014) tested whether *p*-tau followed a similar clearance pathway to that of Aβ (Iliff et al., 2014). They first tested the movement of recombinant human tau protein (Abcam) in transgenic Tie2-GFP:NG2-DsRed (a mutation allowing for easy identification of arteries, veins, and capillaries) mice to determine the normal pathway by which tau is cleared from interstitial space (Iliff et al., 2012). They found that tau accumulated in the caudal rhinal vein (draining from subcortical WM tracts), internal cerebral veins, and the inferior sagittal sinus. This drainage mechanism is similar to that used by Aβ and other interstitial tracers, suggesting that tau is cleared in a homologous way to previously traced metabolites (Iliff et al., 2014). This study has important implications for degenerative tauopathies such as CTE, as the clearance of *p*-tau in humans is not yet well-understood.

In addition to its role in waste removal, the GS has a role in the transport and distribution of molecules between different areas of the brain (Jessen et al., 2015). Jessen et al. discussed the importance of the GS for distributing lipids and glucose molecules throughout the brain, noting that one site of apoE production is within the walls of the third ventricle, and significant concentrations of apoE have been identified in pial astrocytic processes and around blood vessels (Jessen et al., 2015; Thrane et al., 2013). Additionally, lipid carrier proteins are released by astrocytes, assisting with the distribution of lipids throughout the brain. As Jessen et al. (2015) point out, this relationship among apoE, astrocytic processes, and lipid distribution signifies the importance of the GS in the widespread distribution of molecules needed for normal brain functioning.

Other studies have shown differing distribution and pathways of molecules based on the specific isoform or type of molecule. These differences are often attributable to varying molecular size (Morris et al., 2016) or differential rate of uptake of particular molecules as they move through the parenchyma (Achariyar et al., 2016). Achariyar et al. (2016) analyzed radial flow of third ventricle choroid plexus-derived apolipoprotein E (apoE2, apoE3, or apoE4) from periarterial spaces. The authors identified radial flow of apoE around arterial spaces, with the specific rates of radial distribution dependent on apoE isoform (apoE2 > apoE3 > apoE4). They concluded that the brain likely has a higher rate of retention of apoE4 than of apoE2 or 3, thus restricting bulk flow of apoE4 through the parenchyma (Achariyar et al., 2016). More research is needed to better understand the importance of cerebrovascular disease on GS functioning and differential distribution of molecules needed for neurological functioning within varying points of the GS.

Ries and Sastre (2016) review the importance of glial cells in Aβ accumulation, and emphasize how damage to microglia and astrocytes can affect Aβ clearance. Microglia and astrocytes produce proteases involved in Aβ degradation, such as insulin degrading enzyme, endothelian-converting enzymes and neprilysin (Ries and Sastre, 2016). These glial cells are also important in releasing molecules that aid in Aβ clearance, such as plasminogen activators and extracellular chaperones, including apilopoproteins, α2macroglobulin, and α1-antichymotrypsin (Ries and Sastre, 2016). Thus, damage to these glial cells in the context of chronic GS dysfunction would likely contribute to reduced clearance potential, and increased Aβ burden over time.

Ascertaining both the direction and mechanism of CSF and ISF circulation through the GS have been difficult, due largely to the complexity in studying the micro-mechanics of this system in vivo. Findings by Iliff et al. (2013) suggested that tracer movement was highly influenced by arterial pulsatility. However, the effect of alterations in cerebral blood flow into the parenchyma on glymphatic functioning is not entirely clear. Gaberel et al. (2014) evaluated the effects of four types of cerebral strokes on the glymphatic system in a mouse model, including subarachnoid hemorrhage (SAH), intracerebral hemorrhage, carotid ligature, and embolic ischemic stroke. They used an in vivo modified contrast-enhanced MRI model, and found that SAH and ischemic stroke were associated with impaired CSF circulation, but the other stroke types did not significantly affect this system (Gaberel et al., 2014). These results suggest that there are mechanisms to overcome certain changes in CBF within the GS, with more severe impairment to CSF movement at the level of subarachnoid space.

3.2. Sleep and GS functioning

In a follow-up study to the initial Iliff et al. (2012) GS findings, Xie et al. (2013) analyzed whether GS functioning was state-dependent. They demonstrated high potentiation of the GS during the sleep state, evidenced by the dilation of interstitial spaces by up to 60% of their wake-state diameter, a process dependent on inhibition of noradrenergic (NA) projections from the locus coeruleus (LC). These NA pathways are inhibited during sleep, allowing interstitial spaces to dilate and potentiating a more rapid rate of molecule movement throughout the parenchyma.

Xie et al. measured the effect of state-dependent alterations in interstitial space on GS flow in vivo using two-photon imaging to measure changes in fluorescent tracer injected into subarachnoid CSF. They showed major (~95%) reduction in tracer flow rates within periarterial and interstitial spaces in awake versus sleeping mice, which they attributed to the dilatation of interstitial spaces by 60% of their wake-state during sleep. With larger passage spaces, increased levels of CSF and ISF are allowed to flow through the parenchyma, carrying with them higher levels of injected tracer. In the wake state, reduced passage space decreases the potential for tracer to filter through interstitial spaces and thus reduces the flow of these molecules.

Importantly, anesthetized mice exhibited the same dilation of spaces as naturally sleeping mice, suggesting that the sleep state alone, and not circadian rhythms, was responsible for potentiating interstitial dilation (Xie et al., 2013). To our knowledge, this remains the only study focusing specifically on the impact of sleep on the GS, but recent work has used sleep deprivation as a means of reducing GS clearance efficiency, underscoring the importance of the sleep state on normal GS functioning (Achariyar et al., 2016; Plog and Nedergaard, 2015).

Reiter et al. (2014) reviewed the importance of pineal-secreted melatonin in the third ventricle for maintaining circadian sleep–wake patterns, and suggested that melatonin is circulated in the CSF via diffusion from the pineal gland into the third ventricle. The rapid removal of free radicals produced by melatonin is necessary for

maintaining homeostasis because it is a highly oxidative molecule. Melatonin circulates through the ventricles into the subarachnoid space, then through perivascular channels into the deep parenchyma of the brain before being carried back out through CSF and ISF channels (Reiter et al., 2014). Due to the key role of the perivascular spaces, as well as overall convective flow of the CSF-ISF system, in circulating sleep-inducing melatonin, injury to the GS may inhibit the normal process of melatonin circulation and may contribute to the disruption of normal sleep. A potentially damaging cycle is then established: without sleep, molecules continually accumulate, and over time, the movement of melatonin throughout the perivascular channels becomes less efficient.

The relationship between sleep and the GS suggests potentially important interactions, given previous findings of sleep disturbances associated with both TBI and neurodegenerative disease (Berezuk et al., 2015; Liguori et al., 2014; Ouellet, 2006; Porter et al., 2015; Reiter et al., 2014; Sullan et al., 2014; Tarasoff-Conway et al., 2015; Xie et al., 2013). The prevalence of sleep disturbances in populations with comorbid neurological insult or neurodegenerative disease suggests that changes in sleep impair its important role in maintaining a healthy and homeostatically intact neuronal environment, and/or that there is a common physiological mechanism that is disrupted by these neurologic conditions. Alternatively, repetitive brain trauma and/or neurodegenerative processes may affect the ability of the brain to achieve and maintain a sleep state, thus compounding the overall problem.

4. GS and TBI

4.1. Evidence for GS damage after TBI

Ren et al. (2013) developed a closed head injury (CHI) model (the "Hit and Run" Model) of TBI in mice where they induced TBI of varying severity while maintaining the integrity of the cranial cavity, and then measured the effects on GS functioning (Ren et al., 2013). They found that mild to moderate TBI altered AQP4 channel distribution in WT mice, resulting in reduced polarization of these channels at astrocytic end feet. This reduction in polarization was due largely to a differential distribution in AQP4 away from the end feet toward the soma of perivascular astrocytes; this alteration appears to begin 3 days post-injury in both mild and moderate models of injury. In mTBI, perivascular AQP4 channels re-localized to astrocytic end feet, thus normalizing polarization, within 14–28 days, whereas in moderate TBI normalization in AQP4 distribution had not occurred by 28 days (Ren et al., 2013). These results suggest protracted physiological recovery and delayed normalization of AQP4 distribution is a function of injury severity. Additionally, alterations in AQP4 expression following TBI were associated with the degree of astrogliosis (accumulation of astrocytes around the injury site) in moderate TBI. Shifts in AQP4 polarization at the end feet of astrocytes appeared to be more closely related to the progression of reactive astrogliosis than altered protein expression (e.g., GFAP) following injury (Ren et al., 2013).

The roles of astrocytic AQP4 channels in maintaining ionic homeostasis and directing astroglial proliferation and scar formation following injury are important features of both normal functioning and in recovery from TBI (Saadoun et al., 2005). Exogenous Aβ clearance was reduced by 65% in an AQP4 knockout study, further corroborating the importance of AQP4 channels in the flow of ISF and metabolites throughout the parenchyma (Iliff et al., 2012). In AQP4-knockout mice, severity of acute edema was reduced following concussion (which they term "micro TBI") (Liang et al., 2015). Altered AQP4 expression may be a compensatory mechanism to reduce cerebral edema; therefore, chronically reduced polarization in astrocytic end feet may result in reduced fluid movement across perivascular channels that could persist until AQP4 polarization resolves (Ren et al., 2013).

Iliff et al. (2014) further tested the effect of moderate to severe TBI on glymphatic functioning in mice and found significantly reduced movement of tracers injected into the cortex within perivascular spaces in WT mice following injury, primarily on the side ipsilateral to the experimental impact. Reduced tracer movement persisted 28 days post-TBI, along with an associated 25% decrease in solute clearance in brain-injured WT mice compared to uninjured WT controls. They also analyzed AQP4-knockout mice with and without TBI and WT mice with and without TBI to determine differences in clearance mechanics and recovery trajectories in the presence and absence of intact GS functioning. There was significantly more impairment following TBI in AQP4-knockout mice than WT mice, including increased axonal degradation and GFAP expression (indicating reactive astrogliosis), and decreased performance on motor and cognitive tasks (Iliff et al., 2014). This study illustrates the importance of AQP4 channels for reactive processes occurring following injury as well as the impact of TBI on the GS as a whole.

These findings provided foundational evidence to support the hypothesis that TBI of all severity levels can affect normal GS functioning. Reduced polarization of AQP4 channels localized to astrocytic end feet around the site of the injury, astrocytic scar formation, and inflammation occur after TBI of all severity levels in animal models. The changes appear to normalize after 14–28 days in mTBI; however, in moderate to severe TBI, normalization was not seen at 28 days post-injury. If astrocytic processes around areas susceptible to TBI-related shear-strain forces never fully normalize, which seems plausible in cases of repetitive brain trauma and a predilection for pathology at the depths of cortical sulci, it is likely that GS functioning may become chronically dysfunctional. To our knowledge, this hypothesis has not yet been tested, but incorporating this idea into future research may help to explain longer-term effects of multiple mTBI and/or repetitive subclinical brain trauma on GS functioning and *p*-tau deposition over time.

4.2. Linking CTE to the glymphatic system

Studying the abnormal accumulation and distribution of *p*-tau associated with CTE is difficult in lissencephalic animal models, such as rats or mice, which do not have cortical gyri and sulci. However, the specific propensity for *p*-tau accumulation in perivascular spaces and within astrocytes suggests shared mechanisms of action between development of CTE pathology and GS functioning. NFTs have also been identified in the LC in mild cases of CTE (McKee et al., 2016), a region both susceptible to TBI forces (Fujinaka et al., 2003; Sullan et al., 2014) and important in sleep-wake maintenance (Samuels and Szabadi, 2008). Establishing the effects of repetitive TBI (either subclinical, clinical, or a combination) on GS functioning over time is critical. It would enable identification of possible therapeutic interventions that could mitigate poor clinical outcomes associated with chronic sleep disturbance and GS dysfunction, and/or abnormal protein accumulation as is seen in CTE.

No studies have linked CTE pathology to GS dysfunction directly, but the literature suggests common pathways (Nedergaard, 2013). The predilection for NFT and astrocytic tangle aggregation in perivascular spaces and around small vessels in the superficial cortex is a consistent finding in patients with exposure to repetitive brain trauma and differentiates CTE from other neurodegenerative conditions. Given the importance of these regions for normal GS functioning, it is conceivable that the perivascular accumulation of *p*-tau is initiated by repetitive brain trauma mechanisms and then potentiated by reduced protein clearance associated with chronic GS dysfunction. Other structures implicated in CTE often discussed in relation to the GS include the LC, astrocytic end feet, and "high metabolism" subcortical structures such as the hippocampus, amygdala, and hypothalamus (Ratner et al., 2016).

Abnormalities seen in the LC associated with "mild" forms of CTE are particularly interesting, as the inhibition of this structure allows for dilation of interstitial spaces and thus increased protein clearance potential. Corsellis et al. (1973) described pallor of the LC in dementia pugilistica and reports from McKee et al. (2016) as well as Omalu et al.

(2006) showed microscopic evidence of LC involvement. Specifically, NFT deposition and neurites were seen in the LC during the earliest stages of CTE when gross pathological features were absent and *p*-tau was commonly restricted to the cortex (McKee et al., 2015; Omalu et al., 2006). NFT deposition and LC pallor appear to be more prevalent in more severe CTE cases (McKee et al., 2016). Thus, LC functionality is reduced even further in later stages of CTE, which has implications for GS efficiency and the brain's ability to clear metabolic waste. However, distinct pathological staging and a definitive understanding of CTE progression requires longitudinal studies with in vivo diagnostics and have yet to be established (McKee et al., 2016).

The involvement of the LC in both CTE and GS functioning provides support for a common mechanistic link between these two processes. The hypothesis that LC degradation is related to reduced GS functioning has raised questions due to the constricting effect of NA projections from the LC on interstitial space. Thus, it could be hypothesized that loss of neurons in the LC would increase GS flow from the resulting loss of NA tonic activity, providing a protective factor against abnormal accumulation of metabolic waste, such as *p*-tau.

However, prior studies suggest a more complex, network-based pattern of neural inhibition and excitation within the LC-NA system following the *loss* of neurons in the LC. For instance, the ventrolateral preoptic nucleus (VLPO) of the hypothalamus has inhibitory projections to the LC, which promote the sleep state (Chou et al., 2002; Kryger et al., 2011). Damage to white matter tracts between the LC and VLPO, and/or to the inhibitory interneurons within the LC responsible for communication with the VLPO, may increase tonic activity of the LC and reduce sleep time (time spent with dilated interstitial spaces) needed for efficient GS activity for a period of time after the injury. Thus, damage to the LC does not necessarily imply increased dilation within the parenchyma, and may in fact suggest reduced perfusion potential of the GS following damage to inhibitory interneurons within the LC.

In addition to NFTs in CTE pathology, a case series reported by McKee et al. described astrocytic tangles clustered at the depths of cortical sulci in subjects considered to have the mildest form of CTE (McKee et al., 2013). Kanaan et al. recently found "clear co-localization" of glial tau pathology within the cell bodies of astrocytes (as opposed to microglia), and concluded that astrocytic, not microglial, involvment characterized CTE glial tau pathology. Using immunohistological analyses, they additionally described prominent astrocytic tau pathology present in perivascular areas clustered in a dot-like pattern around small vessels (Kanaan et al., 2015).

Subpial *p*-tau positive astrocytes found at the glial limitans are not specific to CTE, and are also often present in the crests of frontal and temporal white matter in normal aging. However, when found with *perivascular* foci of *p*-tau positive neurons and thorn-shaped astrocytes within the sulcal depths and accompanied by a history of repetitive TBI, the *p*-tau positive astrocytes are considered uniquely diagnostic of CTE (McKee et al., 2016). The involvement of astrocytes and perivascular accumulation of *p*-tau is also an important finding in consideration of GS function. Due to the reliance of the GS on intact astrocytic processes as well as the movement of CSF and particles through perivascular space, the accumulation of proteins in these spaces puts normal GS function at significant risk and suggests chronic GS dysfunction likely either accompanies or precedes deposition of CTE pathology.

Repetitive brain trauma may also negatively affect subcortical structures with high metabolic output such as the hippocampus, amygdala, and hypothalamus. McKee's case series proposing CTE staging criteria noted that later stages were associated with NFT deposition in these regions, with evidence of atrophy in more severe cases (McKee et al., 2015). Turner et al. put forth four distinct phenotypes of CTE, proposing that phenotypes 1 and 2 are characterized by NFTs in the cerebral cortex and brainstem, with or without subcortical and basal ganglia involvement (Turner et al., 2013). However, they do not propose staging criteria associated with these different phenotypes, and thus later stages of the disease may account for the appearance of *p*-tau in subcortical regions. P-tau preferentially affects hippocampal area CA2 and the dendritic swellings of area CA4 in CTE, which differs from characteristic AD distribution patterns in area CA1 and the subiculum. Both *p*-tau positive NFTs and astrocytic aggregates are found in the amygdala, mammillary bodies, and other hypothalamic nuclei (which have projections from the LC). If there is a functional limitation in the ability to clear metabolic waste from interstitial space, such as following brain injury, highly metabolic areas would likely show significantly higher accumulation of proteinaceous waste in chronic stages of the disease. Thus, the accumulation of *p*-tau in these areas is a predictable finding in the context of chronic GS dysfunction.

Subcortical tau pathology grows more pronounced in more severe CTE cases, with increased abnormal protein accumulations becoming widespread throughout the brain. TDP-43 immunoreactive neuronal cytoplasmic inclusions were observed in dot-like patterns throughout the hippocampus and amygdala (McKee et al., 2016). However, the 1) involvement of the LC and highly metabolic structures, 2) irregular but specific protein accumulation patterns in perivascular regions of small vessels, and 3) unifying relationship that many of these structures have with GS physiology and functioning may elucidate our currently poor mechanistic understanding of CTE neuropathology initiation and progression.

5. Sleep as a moderating factor of GS function following brain injury

The time course between sustaining brain trauma to *p*-tau accumulation and possible degeneration throughout various areas of the brain remains poorly understood. There is currently very little information about the timing or manner in which CTE pathology and/or clinical symptomatology develop, due to the paucity of longitudinal studies and absence of validated in vivo biomarkers. In addition to determining the degree to which GS dysfunction moderates development of CTE pathology following repetitive TBI, identifying and treating other factors that exacerbate GS disruption may prevent, delay, or slow pathological progression.

Sleep disorders involving difficulty falling or remaining asleep are prevalent in TBI populations (Orff et al., 2009) and the sleep state is essential for optimal GS functioning (Xie et al., 2013). Therefore, we hypothesize that chronic sleep disruption may exacerbate GS dysfunction associated with repetitive brain trauma and increase the rate of protein accumulation contributing to neurodegenerative processes like CTE. The importance of sleep in both CTE pathology development and GS functioning provides interesting evidence for possible mechanistic links.

5.1. Proposed model of sleep as a mediator of chronic GS dysfunction and increased risk for CTE pathology

Normal GS clearance is highly potentiated during sleep (Xie et al., 2013), suggesting that normal sleep–wake cycles are key in maintaining adequate waste removal. Studies have revealed a diurnal pattern of Aβ deposition, whereby deposition increases during waking relative to sleeping (Lucey and Bateman, 2014). Mander et al. (2013) suggest there is a relationship between toxic amyloid accumulation and disruptions of non-REM (NREM) sleep cycles, contributing to changes in sleep architecture and further increased amyloid deposition. Additionally, Aβ concentrations in both humans and mouse models rise during wakefulness and fall during sleep, exhibiting a diurnal pattern of Aβ deposition (Lucey and Bateman, 2014). Preclinical studies with the TgCRND8 mouse model of AD (which overexpresses a mutant form of amyloid precursor protein resulting in high levels of beta amyloid and plaque formation beginning at an early age) have revealed the presence of increased wakefulness, hyperarousal, and reduced NREM sleep in association with amyloidosis (Colby-Milley et al., 2015). In the APP-PS1

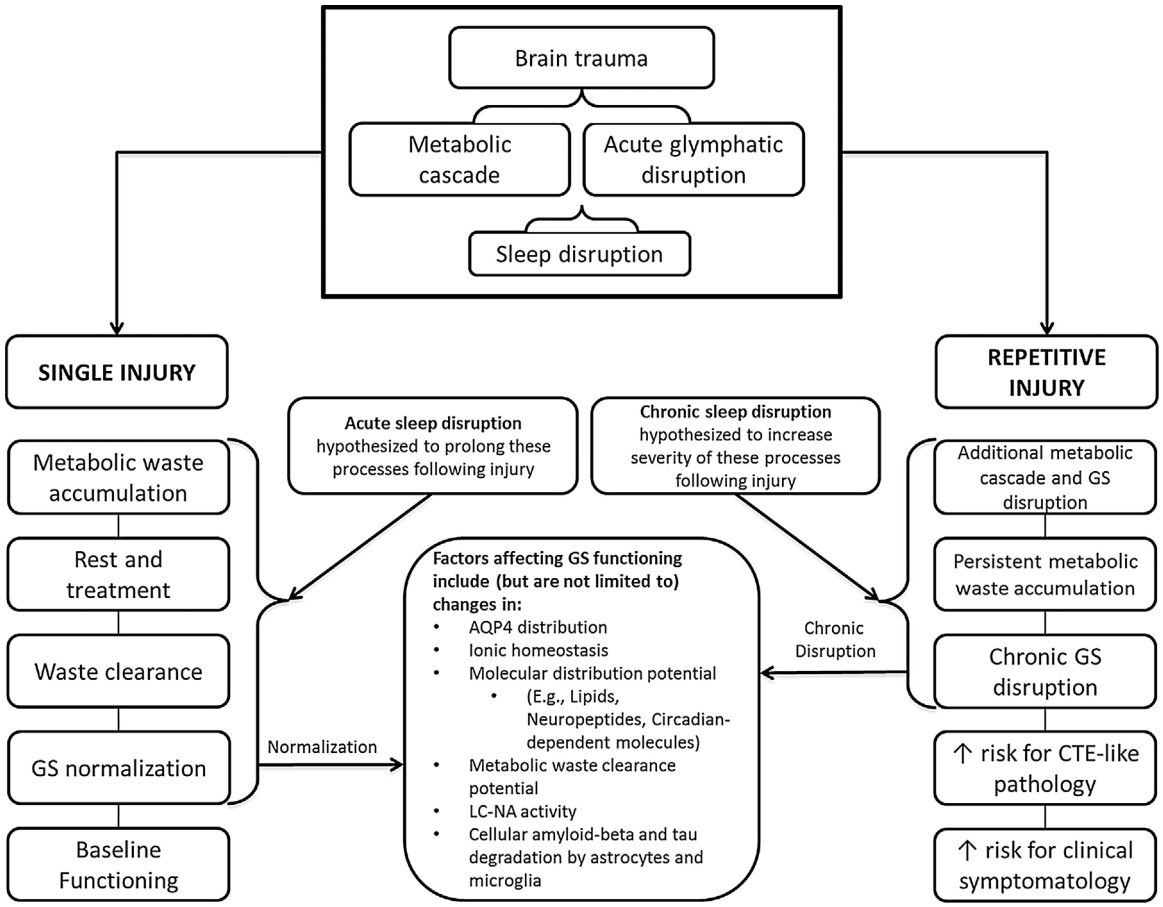

Fig. 1. In the acute phase following injury, sleep disruption is proposed to increase the severity of acute GS disruption. In the case of a single injury, disturbance to sleep in the course of a normal recovery cycle likely contributes to increased recovery time due in part to decreased potential for waste clearance following an influx of waste in the course of an acute metabolic cascade after injury. Decreased sleep, in this scenario, is hypothesized to contribute to a longer recovery time. Conversely, the "Repetitive Injury" pathway represents the proposed model of persistent accumulation of metabolic waste. "Repetitive Injury" refers to the exposure to multiple mTBI and/or repetitive subclinical trauma common in collision sports and certain military personnel. In this case, chronic sleep disruption may increase the severity of GS disruption. For instance, chronic toxin accumulation can directly interfere with NREM sleep (Mander et al., 2013), thus creating a cycle of increased toxin accumulation and disrupted ability to maintain normal sleep cycles (in both single and repetitive injury). In repetitive injury, the brain may be in a state of chronic disequilibrium, resulting in persistent waste accumulation. As this occurs in conjunction with chronic loss of sleep, we hypothesize the risk for the development of CTE-like pathology and symptomatology increases. AQP4: aquaporin 4; CTE: chronic traumatic encephalopathy; GS: glymphatic system; LC: locus coeruleus; NA: noradrenaline.

mouse model, sleep disturbance emerged after Aβ accumulation began in the hippocampus and was reversed by Aβ42 immunization (Roh et al., 2012). Taken together, these studies suggest that concomitant insomnia in addition to glymphatic disruption following TBI may increase proteinaceous waste buildup and heighten risk for negative functional outcomes. To the extent that βamyloid stimulates tau pathology, this may also be a factor in the tau pathology that emerges in CTE.

Based on these considerations, we offer a conceptual model of the relationship between repetitive brain trauma and CTE, mediated by GS dysfunction and moderated by time spent asleep, that might serve as a basic model for future research (Fig. 1). However, this model serves only as a basic outline of the relationship between these factors, and each section of this model requires extensive review.

6. Conclusion

The pathognomonic signs of CTE include an accumulation of NFTs around perivascular spaces and small vessels in dot-like distributions at the depths of cortical sulci, as well as tangles within the glia limitans and surrounding astrocytes. Pallor and NFT deposits are seen in the LC, even in cases considered "mild" or early stage. The importance of perivascular pathways, astrocytic processes, and noradrenergic input (from the LC) for maintaining proper GS functioning, combined with the functional disruption of the GS following single-event TBI, leads us to propose that the development and progressive nature of CTE pathology is at least partially attributable to, or potentiated by, chronic dysfunction of the GS, which is exacerbated by chronic sleep disruption. This also lends mechanistic support to the almost exclusive finding of CTE pathology in individuals with a history of repetitive brain trauma (Koga et al., 2016; Noy et al., 2016).

7. Limitations

The GS findings provide important insights into the mechanisms which drive metabolic waste clearance from the brain; however, translational factors must be considered when applying animal models of CSF and ISF movement to human brains. For example, there are important differences in the anatomical drainage pathways in animal versus humans. Rats, mice, and sheep, which have been used to study ISF-CSF movement, do not develop the intricate arachnoid villi seen in human meninges, and up to 50% of CSF in animal models drains through the cribriform plate to nasal and cervical lymph nodes (Weller et al., 2008). In humans, the majority of CSF is thought to drain through arachnoid villi to the venous sinuses (Weller et al., 2008). As such, conclusions regarding fluid movement within the GS must take into account these anatomical differences. Translation to human disorders has not yet been firmly established.

Additionally, other factors affecting GS functioning are not considered in this model of TBI and sleep-related GS dysfunction. While the GS has only recently been studied in vivo, a number of studies suggested roles that other factors (e.g., cardiovascular risk factors, Gaberel et al., 2014; diabetes, Jiang et al., 2017; neurodegenerative processes, Tarasoff-Conway et al., 2015; migraines, Schain et al., 2017; and body posture, Lee et al., 2015) play in modifying GS function. Future studies should aid our understanding of how these factors modify aspects of the proposed model.

Given the focused work by Iliff et al. on the study of tau and beta-amyloid pathways, we focused primarily on these molecules. However, many other molecules are likely transported through this system, and likely have an impact on long-term outcomes in TBI patients. Thus, molecules other than tau and beta-amyloid should be considered in future studies. Current research in TBI suggests that there are differential outcome trajectories based on injury type (e.g., blunt versus blast-related injuries). However, given the limited research in this field thus far, we have discussed only blunt trauma models as they relate to GS functioning. Future studies should also work to identify specific differences between injury type on changes to GS functioning.

8. Future directions

There have been significant advances in the technologies available for measuring glymphatic flow in animals. Translating this ability to measuring interstitial flow in humans remains undeveloped, and is a critical task for the future. Such research must address inter-species differences in the GS resulting from the differential anatomy of drainage pathways. To our knowledge, the study by Xie et al. (2013) remains the only investigation focusing specifically on the impact of sleep on the GS, and these findings should be replicated in humans. Due to the difficulty in studying the micromechanics of the GS via in vivo human studies, past research has used positron emission tomography (PET) and magnetic resonance imaging (MRI) to determine biomarkers of disease within perivascular spaces. For instance, Berezuk et al. (2015) and Inglese et al. (2006) used enlarged Virchow–Robin spaces (VRS) seen on MRI as a proxy for estimating neurological changes in symptomatic versus non-symptomatic patients (Berezuk et al., 2015; Inglese et al., 2006).

In theory, VRS size could be used as an estimate of GS functioning in humans. For instance, VRS may be used to measure dysfunction in the brain's ability to clear large molecules associated with immunological reactions, as these molecules may concentrate in perivascular spaces and appear as hyperintense regions visible on an MRI (Berezuk et al., 2015; Inglese et al., 2006). Generally, enlarged VRS are attributed to underlying small vessel pathology because they typically appear in highly vascularized areas like the basal ganglia and throughout the white matter. However, the relationship between VRS size and GS functioning has not been directly established and alternatively might indicate *increased* flow through these spaces rather than a "blockade" to normal GS functioning. Thus, these studies provide only a theory for a possible association between VRS and GS functioning. Future research should target understanding this relationship.

Studies have also utilized PET scans to examine in vivo Aβ and tau accumulation in patients with a history of multiple head injuries, such as boxers (Provenzano et al., 2010) or retired NFL players (Dickstein et al., 2016; Gandy and DeKosky, 2014). Tau-binding PET tracers are still early in development, and have not yet been validated by post-mortem studies. A PET ligand has also been developed and tested in a human patient to track AQP4 changes (Suzuki et al., 2013). While the use of these tracers to determine GS damage or in vivo CTE diagnoses requires validation, they provide tools for future research, with substantial implications for longitudinal changes as well as improved mechanistic understanding and development of therapeutic interventions.

There are many unanswered questions regarding CSF-ISF flow patterns into and out of the parenchyma. However, the GS concept opens many avenues for new research questions. For example, studies have modeled altered potential for CSF-ISF exchange in normal aging (Simon and Iliff, 2016), AD (Kyrtsos and Baras, 2015), glaucoma research (Wostyn et al., 2015), diabetes (Jiang et al., 2017), and the influence of body posture on glymphatic processes (Lee et al., 2015). In the case of AD, mathematical models utilizing findings from GS literature propose that arterial stiffness and heart rate changes alter the clearance potential of Aβ in older adults, thus increasing the risk for additional amyloid plaque burden (Kyrtsos and Baras, 2015). Such studies bring significant opportunities to study mechanisms of movement of fluids and potential breakdowns in the system; subsequent studies may answer questions related to neurological disease onset and progression (Iliff et al., 2013; Iliff et al., 2012).

The effect of brain trauma on the interstitial space, including inflammation and edema, supports the findings from Iliff et al. and Ren et al. that TBI affects molecular movement through interstitial spaces. For instance, in the case of ischemic stroke, significant changes were identified in the geometry of interstitial spaces (ISS), resulting in prolonged edema and the accumulation of harmful substrates (Arbel-Ornath et al., 2013). Thus, it is likely that in TBI models, similar changes in ISS architecture result and directly affect GS functioning. How ISS architecture is altered in the course of a TBI and how this changed architecture impacts GS flow is a key area for new studies. For further review on ISS architecture, refer to Lei et al. (2016).

Studying other effects of GS dysfunction, such as overall lipid distribution, glucose levels, state-dependent hormone levels (e.g., circadian-dependent processes versus waking processes), and astrocytic functioning, would provide significant insight into the extent to which localized damage effects the system as a whole. In addition, astrocytes and microglia have an important role in the production of molecules contributing to Aβ degradation and clearance, such as through autophagic and proteasomal degradation (e.g., the ubiquitin proteasome system) (reviewed in Ries and Sastre, 2016). Future studies should work to determine the role of damage to these processes in overall GS dysfunction and their contribution to the accumulation of Aβ over time in patients with a history of brain trauma.

While past studies have evaluated models of GS flow potential in vivo (Ratner et al., 2016, 2015), the impact of mTBI, or repetitive subconcussive brain trauma on system-wide movement of molecules is unclear. Also, the effect of changes within ISS geometry and structure as they relate to fluid movement, cellular death, and their effect on pharmacokinetics would be an important area of future work (reviewed in Lei et al., 2016).

Past research suggests an important role of the LC-NA system in state-dependent changes in GS functioning. However, this system is only one piece of the complex sleep–wake circuit. Orexinergic projections, for instance, have important implications for sleep-wake cycles (Davies et al., 2015). Orexin/hypocretin systems are discussed in the context of AD as well, given the relationship found between orexin receptor down-regulation and greater AB and *p*-tau load (Davies et al., 2015). Thus, considering the role of other neuropeptides, such as orexinergic projections, in GS functioning is also important. Based on the previously-discussed relationship between TBI, GS functioning, CTE, and *p*-tau load, other molecules known to be associated with neurodegenerative processes in the context of protein-related waste accumulation also should be an area of rigorous future study.

In the case of repetitive TBI, the effects of inflammation, edema, and alterations in AQP4 expression are likely different and/or more pronounced than in the case of a single head injury, with reduced AQP4 polarization at astrocytic end feet and reduced convective flow of ISF. Future research should investigate whether protein deposition at the base of cortical sulci in patients with CTE are related mechanistically to the role of CSF/ISF in the clearance of Aβ and *p*-tau from the animal brain. Explaining long-term outcome heterogeneity following repetitive brain trauma, and potential concomitant disruption of glymphatic functioning, will require prospective, longitudinal studies utilizing

biomarkers, genetic factors, and the influence of many neuro-biopsychosocial factors. Many of these factors are reviewed in Asken et al. (2016); the influence of sleep disruption is perhaps most relevant to the interaction of brain trauma and GS dysfunction.

Longitudinal study of the relationship between tau accumulation at the base of cortical sulci and GS functioning should provide insight into the downstream effects that shear and strain forces within these regions have over time. The AD literature describes trans-endothelial clearance of Aβ—meaning movement across the blood–brain barrier (Zlokovic, 2005). Iliff and colleagues propose that this trans-endothelial diffusion occurs as molecules are dispersed along perivascular pathways to be cleared through perivascular channels (Iliff et al., 2014). Thus, the GS functions to distribute these molecules in a manner allowing clearance by way of the GS as well as across the BBB. While this theory has not been tested in the case of CTE, the pathway for molecular movement along the subarachnoid space closely follows cortical sulci and gyri. In an environment with decreased movement within the GS, whether related to changes in arterial pulsatility, overall dysfunction in the convective flow of molecules, or a buildup of protein waste following injury, the inability of the brain to clear metabolic waste both along the GS or across the BBB may help to further explain the specific early accumulation of *p*-tau at the base of cortical sulci.

Attaining mechanistic insights into the contribution of repetitive brain trauma to chronic dysfunction of the GS, and the relation of such dysfunction to neurodegenerative pathology such as CTE, would provide a basis for developing treatments targeting delaying, slowing, or preventing degenerative processes. However, while there are difficulties in studying this system in vivo, and unanswered questions regarding similarities between human and animal glymphatic function, behavioral studies could assess the effects of early intervention for sleep disturbances on outcome trajectories in at-risk populations. For instance, Jaffee and colleagues reviewed the effect of monitoring sleep patterns in athletes following single-event mTBI, finding that intervention may alleviate detrimental effects of mTBI and sleep dysfunction on athletic performance (Jaffee et al., 2015). Given the relative success of therapies such as cognitive behavioral therapy for insomnia (CBT-I), the longitudinal effects of early sleep intervention in populations at risk of sustaining repetitive brain trauma, such as athletes or soldiers exposed to combat, should be a major focus of future investigations. While not a cure, reducing the severity of glymphatic dysfunction coincident with brain trauma and sleep disturbance via the delivery of simple and inexpensive sleep treatments may mitigate pathological burden and associated negative outcomes.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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