

---

# Assessing Mild Traumatic Brain Injury Associated Blood Brain Barrier (BBB) Damage and Restoration Using Late Phase Perfusion Analysis by 3D ASL MRI- Implications for Predicting Progressive Brain Injury

---

[Charles R Joseph](#)\*

Posted Date: 4 October 2024

doi: 10.20944/preprints202410.0282.v1

Keywords: Mild traumatic brain injury; Chronic traumatic encephalopathy; Blood brain barrier dysfunction; Shear white matter injury; Arterial spin labeling MRI; Diffusion tensor imaging MRI; 18-fluorodeoxyglucose positron emission tomography; Dynamic contrast-enhanced (DCE) MR perfusion



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Review

# Assessing Mild Traumatic Brain Injury Associated Blood Brain Barrier (BBB) Damage and Restoration Using Late Phase Perfusion Analysis by 3D ASL MRI- Implications for Predicting Progressive Brain Injury- Focused Review

Charles R Joseph \*

Neurology and Internal Medicine, College of Osteopathic Medicine, Liberty University, Lynchburg, VA 24502, USA; crjoseph@liberty.edu

**Abstract:** Mild traumatic brain injury mTBI is a common occurrence around the world, associated with a variety of blunt force and torsion injuries affecting all age groups. Most never reach medical attention, and identification of acute injury and later clearance to return to usual activities is relegated to clinical evaluation, particularly in sports injuries. Advanced structural imaging is rarely performed due to the usual absence of associated acute anatomic/hemorrhagic changes. This review targets physiologic imaging techniques available to identify subtle blood brain barrier dysfunction and white matter tract shear injury, and their association with chronic traumatic encephalopathy. These techniques provide needed objective measures to assure recovery from injury in those patients with persistent cognitive/emotional symptoms and in the face of repetitive mTBI.

**Keywords:** Mild traumatic brain injury; Chronic traumatic encephalopathy; Blood brain barrier dysfunction; Shear white matter injury; Arterial spin labeling MRI; Diffusion tensor imaging MRI; 18-fluorodeoxyglucose positron emission tomography; Dynamic contrast-enhanced (DCE) MR perfusion

---

## 1. Introduction

Mild traumatic brain injury (mTBI) is a pervasive problem worldwide and typically managed without hospitalization thus unreported. The estimated prevalence rate of 369 per 100,000 individuals underestimates the scope of the problem as a result [1–3]. Most head injuries are mild (90%) defined by clinical functionality scales such as the Glasgow Coma scale where a score of 13–15/15 is defined as mild [4]. The scale includes basic tests of level of consciousness as defined by verbal, eye opening and motor responses to commands or noxious stimuli. It is an invaluable tool for assessing aTBI and follow up of moderate or severe TBI. More subtle brain injury however is not captured by this scale, as it is meant as a simple stratification tool for rapid assessment and prognosis of more serious head trauma [4].

The assessment of mTBI is currently the sole prevue of clinical assessment to categorize acute cognitive or other subtle neurologic deficit, along with behavioral/emotional effects [5]. Likewise, return to normal learning or sport activities are based on these measures [6]. Since anatomic imaging studies in mTBI are almost invariable normal, they are often not employed [9,10]. However, developing a noninvasive physiologic measure of acute injury and subsequent recovery would provide a critical objective assessment of safe return to sport/usual activities.

## 1.1. Background

### 1.1.1. Minor Closed Head Injury

Mild traumatic brain injury (mTBI) is defined as traumatic brain injury resulting in brief if any loss of consciousness with associated transient cognitive (thinking, memory, general confusion), neurologic (vertigo, delayed reaction times), and/or behavioral (depression, aggression) dysfunctions, and often headache [11]. Most frequent causes include contact sport, blast, and acceleration-deceleration injuries. Sports injuries are acutely assessed on the field acutely or within 72 hours using validated clinical testing instruments such as Sport concussion Assessment Tool (SKAT 6), Glasgow coma scale, Vestibular Ocular Motor Screening (VOMS) [5,12,13]. Along with inclusion of the testing measures cognitive function (orientation, immediate and delayed memory recall, concentration, emotionality, depression, anxiety, speech, and task specific processing, as well as coordination, balance, eye movements, and headache [14]. A more comprehensive version for office use, SCOAT 6, has also been validated for use within 72 hours of injury. In addition to testing SKAT 6 items, it catalogues prior head injuries, cognitive and emotional history, current medications, and a detailed neurologic examination. Further it includes recommended strategies for return to learning and return to sport activities [15,16]. Currently corroborating physiologic testing is not commonly employed.

To that end, the physiologic consequences of mTBI will be reviewed, and methods to identify those changes using imaging modalities will be discussed. The potential combined use of both clinical and physiologic testing may improve the accuracy of diagnosis and readiness to return to usual activities and predict persistent physiologic dysfunction. The latter when associated with prior mTBIs may potentially lead to chronic progressive disease -chronic traumatic encephalopathy (CTE) years later, as seen in professional contact sports athletes.

### 1.1.2. Pathophysiology

Given the brain is a soft delicate organ contained within a closed box, sudden applied blunt trauma and inertial forces of acceleration, deceleration, or rotational trauma, dictates the severity and location of cortical, white matter tract, and vasculature injury. Unlike moderate or severe TBI, mTBI injury is associated with minimal or no disruption of these structures in most cases, but not all [17,18]. That said physiologic consequences of disrupted electrolyte pumps and blood flow acutely post head injury have been well delineated with acute impairment of electrolyte (sodium potassium, calcium, and magnesium) distribution notably mitochondrial calcium sequestration with altered metabolism in neurons and astroglia and reduced local blood flow [19–21]. This results in an acute glycolysis hypermetabolism to restore normal electrolyte balance [21]. Disruption of the blood brain barrier (BBB) even in mild Traumatic Brain injury (mTBI) is reflective of this acute phase of injury [22,23]. The duration of this varies, dependent upon location and severity of injury leading to hypometabolism in the affected regions which can persist for weeks or longer [22]. The chronic phase of injury is largely thought to be related to persistent physiologic alterations from persistent activated microglia and its effect on the neurovascular unit [24,25]. The focus of this article principally addresses the BBB dysfunction and identifying imaging techniques. Additionally, techniques demonstrating shear force white matter tract injury will be discussed.

### 1.1.3. Shear Injury in TBI

The most troublesome and unfortunately permanent sequelae of TBI is the result of shear injury to white matter tracts [18,26,27]. The extent and severity of damage escalates proportional to force and location of impact with compiled additional effects from edema mass effect and inflammatory upregulation. In mTBI, the general assumption is absence of substantive anatomic injury [17,18]. This however belies subtle changes in personality, and emotionality, particularly in adolescence, from damage to developing limbic connections [26–29].

The underpinnings of shear injury are quite understandable with sudden mechanical deformation of the brain tearing apart connections [26,30,31]. The longer-term damage though is caused by subsequent mass effect from edema, hemorrhage, or later from inflammation [22,32–34]. To understand the latter influences, animal models have been employed using a variety of species, most commonly rodents and rarely large animals [35]. Translatability from rodent to human physiology is problematic given vast differences in brain structure and physiologic responses to injury [36,37].

Current medical state of the art possesses no means of restoring shear tract injury. Prevention of delayed injury by reducing mass effect and swelling preserve life and may reduce secondary shear injury [27,29–32]. But knowledge of how to best limit the secondary tract damage will require additional mechanistic study in higher animals (swine or primates) with closer anatomic affiliation to the human brain [36,37].

Too often the die is cast for potential clinical recovery based on the initial extent of shear force injury. That said identifying the severity of tract injury has potential importance in prognostic discussions with the patient and family.

#### 1.1.4. Blood Brain Barrier Dysfunction in TBI Acute And Chronic

In mTBI, the microcirculation (capillary system) BBB is disrupted acutely causing reduced mean capillary transit time (cMTT) and reduced glymphatic flow (GF) in the region(s) of impact both coup and contrecoup with limited or no white matter tract injury [39,40]. The effect of this disruption is leak and trapping of normally restricted substances into the brain and thus reduced clearance out of the brain. This results in measurable reduction in clearance rate of intraparenchymal fluid which can be identified by imaging techniques (see below). In animal studies, BBB disruption and leak of IGG locally persisted for up to a month following moderate TBI with associated delayed microhemorrhages at those sites [18,32].

A brief summary of the complexity of BBB structure and function is presented here. Details of the cellular interactions, signaling mechanisms, and what is known of the basic biology are beyond the scope of this review but referenced [40–45].

The blood brain barrier is dependent on a complex interplay of cells within the neurovascular unit (NVU), including the endothelial cells, pericytes, and astrocyte end feet [33,46,47]. Signalling within this triad in homeostasis allows for transport of needed electrolyte, glucose, and specific lipids and proteins while excluding common blood constituents that are toxic to the complex interstitial environment [48–54]. The interaction and communication among elements of the NVU, extracellular matrix (ECM) and microglia dictate the presence, expression, and integrity of the various tight junction (TJ) proteins [45,55–57]. Presence of specific inflammatory cytokines may result in either a proinflammatory milieu or counterintuitively, a restorative one [24,37,44,45]. For example, Endothelial cell derived IL1  $\beta$  acutely downregulates TJ protein ZO-1/occludin thus increasing BBB permeability, but by promoting expression of Pentraxin 3 later enhances its restoration [58]. The relative balance of local microglial proinflammatory versus homeostatic regulatory influences also determines the BBB integrity [59–61]. That balance is dictated by neuronal and astrocyte signaling which is influenced by presence of cell injury and local inflammation [61].

Fundamental questions remain regarding defining the restorative pathways post injury, and long-term consequences of persistent leak [62,63]. In TBI BBB leak is caused by proinflammatory microglial-endothelial signaling and to shear forces disrupting endothelial glycocalyx, the latter allowing leak of IGG and upregulation of inflammatory cytokines causing local conversion of microglia to proinflammatory state [58–61]. Activated microglia express complement (C3a) fragment which in turn upregulates C3aR in capillary endothelial cells altering its phenotype to a proinflammatory/immune cell attractant state with associated disruption of intercellular tight junctions thus triggering additional BBB leak [64]. In the chronic phase of injury presence of activated microglia induces BBB dysfunction, local chronic inflammatory changes, and neuronal dysfunction [23,39,65]. The persistence of this especially with multiple mTBI result in perivascular accumulation of pTau within astroglia and neurons in the sulcal depths, the hallmark of CTE [65–68].

Restoration of normal BBB integrity following mTBI generally occurs quickly in youth, however in some persistence of activated microglia can persist for months or longer resulting in reduction in threshold for additional mTBI related pathology with clinical accompaniment [67–69]. With advancing age, recovery is less complete and progression of both inflammation with BBB leak with cognitive decline following TBI is more likely [70]. Further, the lower threshold and persistence of mTBI in young women is well recognized and postulated to be influenced by sex hormones, and reduced muscle mass compared to their male counterparts [71]. The mechanisms of the BBB repair process in humans remain incompletely delineated, and in particular the specifics of the pathways active in youth but lost in the circumstances of repetitive TBI or in the normal aging process [72].

The cumulative effects of multiple mTBI events causes ongoing inflammatory upregulation resulting in both permanent microvascular changes and persistent upregulation of inflammation within the neuropil [67]. This induces altered synthesis, degradation, accumulation and transsynaptic spread of toxic misfolded proteins predominantly hyperphosphorylated Tau (pTau), but also Lewey body proteins, TDP-43 and to a delayed and minor degree  $\beta$  amyloid [69,74]. The consequence is the well described high incidence of chronic traumatic encephalopathy (CTE) in professional contact sport athletes [75]. The clinical correlates include aggression, depression, suicide ideation, impulsivity, cognitive decline, parkinsonian features [66,75,76]. To reduce the likelihood of progressive dementia from cumulative brain injury, the addition of objective physiologic testing in mTBI should prove invaluable in conjunction with clinical assessment to identify the early chronic inflammatory conversion.

Given the importance of maintaining BBB integrity, there is likely more than one pathway regulating restoration post injury [62,63]. That said, duration and speed of clinical recovery are correlated with patient's age, location and magnitude of force, and prior head injuries [60,61]. The inverse correlation of severity of head injury and restoration of BBB integrity are understandable related to anatomic and vascular disruption [77]. The caveat to this general rule in adolescence has shown clinical evidence of emotional dysfunction even in mTBI which can be persistent suggesting limbic system tract injury [66].

Of particular interest is why do these mechanisms rapidly repair the BBB leaks in youth with a single mTBI but flags in the aging brain even without injury? The answer may lie in the long-term presence of proinflammatory microglia and ECM constituent protein alterations which increase local BBB permeability [78]. Alternatively, upregulation of inflammatory cytokines related to other unrelated health issues may contribute [79–82]. Conversely, is it a failure of normal restorative signaling pathways lost in the aging process that are root cause? Or perhaps a combination all three mechanisms? This question has profound implications for treatment of the underpinnings of other diseases such as neurodegenerative diseases where loss of BBB integrity is the nexus of their development [63,79–82]. Further, of the two pathologic features of traumatic brain injury, restoration of BBB integrity as opposed to shear injury appears to be the most amenable to intervention.

To assess presence of BBB leak, physiologic imaging methods are required. Likewise, assessment of future treatment modalities to monitor outcomes of clinical treatment trials addressing BBB repair requires the same [63,83]. In the next sections, current most usable and clinically available methods of anatomic and physiologic imaging will be discussed and their roles in identifying specific pathologic features of head injury.

### *1.2. Structural Imaging in mTBI*

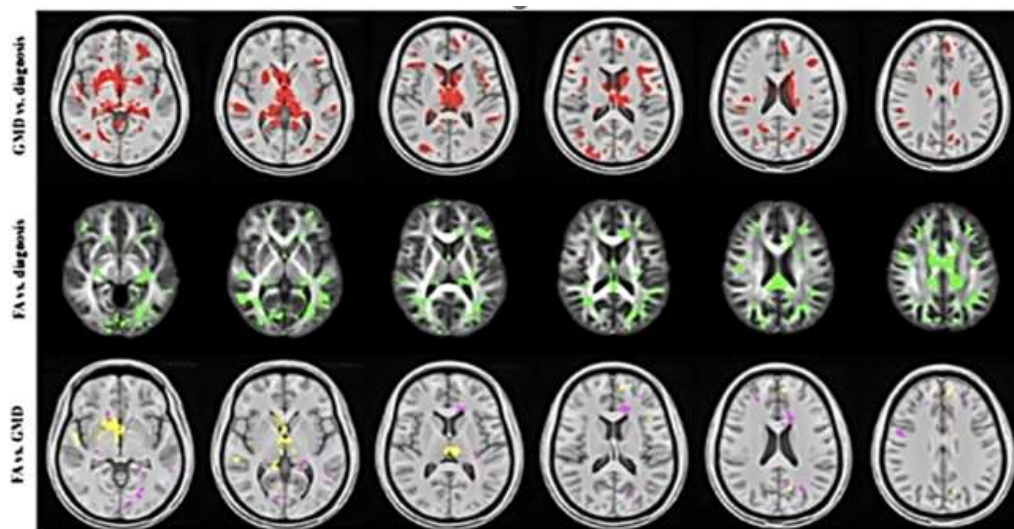
Although anatomic imaging in singular mTBI is infrequently done and if performed is almost invariably normal. It clearly has a place in evaluation of patients with multiple mTBI and of course more severe injury. In moderate or severe acute brain injury, CT head is the study of choice for evaluation of bleeding or mass effect [18,83,84]. Evaluating subacute or chronic injury the benefit of MRI capabilities for defining atrophy with T1 sequences, white matter lesions with fluid attenuated inversion recovery (FLAIR), and prior micro or macro hemorrhages with Susceptibility Weighted Images (SWI) are the gold standards [83,84].

### 1.3. Physiologic Imaging

Assessment of TBI potentially takes three forms: anatomic, clinical cognitive/neurologic examination, and physiologic testing. In mTBI, structural evaluation with CT or MRI is nearly always normal, whereas the clinical cognitive assessments are far more revealing. However subtle changes in processing, memory, personality, and emotional stability may miss subclinical physiologic injuries. Current clinically available methodologies for assessing the physiologic change in BBB function include Dynamic Contrast Enhanced MRI (DCE-MRI) and arterial spin labeling (ASL) MRI [85]. Evaluation of WM tract shear injury can be assessed directly with MRI tractography- Diffusion Tensor Imaging (DTI), Positron Emission Tomography (PET), assesses reduction in glucose utilization reflective of regional loss of normal metabolic function [85]. Indirect means include Functional MRI imaging (not discussed further as it is not commonly used clinically). Pros and cons of each method will be discussed below.

#### 1.3.1. Diffusion Tensor Imaging

Diffusion Tensor Imaging is a non-invasive method of investigating white matter tract integrity, which leverages imaging of water movement within the brain [86,87]. Water in the absence of obstruction will move randomly in all directions (isotropy). In normal brain however water is forced to move parallel to white matter tract obstructions (anisotropy). With shearing force injury these neat pathways are interrupted and hence water present in those locations moves more isotropically. Diffusion imaging techniques can identify that disruption (Figure 1). Technical improvement to this methodology is under development. Current methods available lack sensitivity and are hampered by long scan times [85]. Nonetheless, as methods ameliorating persistent BBB leak develop, knowledge of the extent of untreatable shear injury is of value in prognosticating ultimate neurologic recovery.



**Figure 1.** Sparse canonical correlation analysis (SCCA) of T1-weighted MP-RAGE and 30-direction diffusion tensor images (DTI) datasets are used to quantify traumatically induced disruption of WM and cortical networks. The cohort includes 17 controls and 16 patients with TBI (age and gender matched). Each patient had a history of non-penetrating TBI of at least moderate severity. White matter integrity is assessed by DTI and fractional anisotropy (FA) maps are generated. Separately, probabilistic segmentation of the T1-weighted imaging is performed to assess gray matter integrity. Variation in brain shape across subjects is normalized by diffeomorphically mapping these data into a population-specific template space. Image processing steps rely on the Camino and ANTs (Advanced Normalization Tools) neuroimage analysis open-source toolkits. SCCA demonstrates significant differences between the control and patient groups in both the FA ( $p < 0.002$ ) and gray matter ( $p < 0.01$ ) that are widespread but largely focus on thalamocortical networks related to the

limbic system. Using SCCA identified regions, a strong correlation is identified between degree of injury in WM and GM within the patient group. Figure courtesy of James R. Stone, Gandy, Sam, Milos D. Ikonovic, Effie Mitsis, Gregory Elder, Stephen T. Ahlers, Jeffrey Barth, James R. Stone, and Steven T. DeKosky. "Chronic traumatic encephalopathy: clinical biomarker correlations and current concepts in pathogenesis." *Molecular neurodegeneration* 9 (2014): 1-22. [122].

### 1.3.2. Dynamic Contrast Enhanced (DCE) MRI

Dynamic Contrast Enhanced (DCE) MRI directly measures leak of contrast agent into the neuropil in excess of its natural infusibility. Given gadolinium contrast agents are mostly excluded from passage through the BBB normally, their passage increases with its disruption. The technique assesses plasma volume, interstitial space and can calculate a volumetric transfer constant from vascular to interstitial space [88–90]. Excess accumulation of contrast in the interstitial space beyond the calculated diffusion amount is indicative of BBB leak. This method allows direct visualization of BBB leak but is invasive (requires gadolinium contrast injection) and thus is not suitable for serial measurements over time, given the concern of retained gadolinium contrast within the CNS [91–93] (Figure 2). Specific software to sort out normal contrast diffusion through the BBB from that related to excess leak is also required [89]. Depending on patient circumstances though its use as a diagnostic one-off study when coupled with DTI may prove helpful in prognosticating recovery in those slow to do so. The combination would reveal the extent of BBB leak and white matter tract injury.

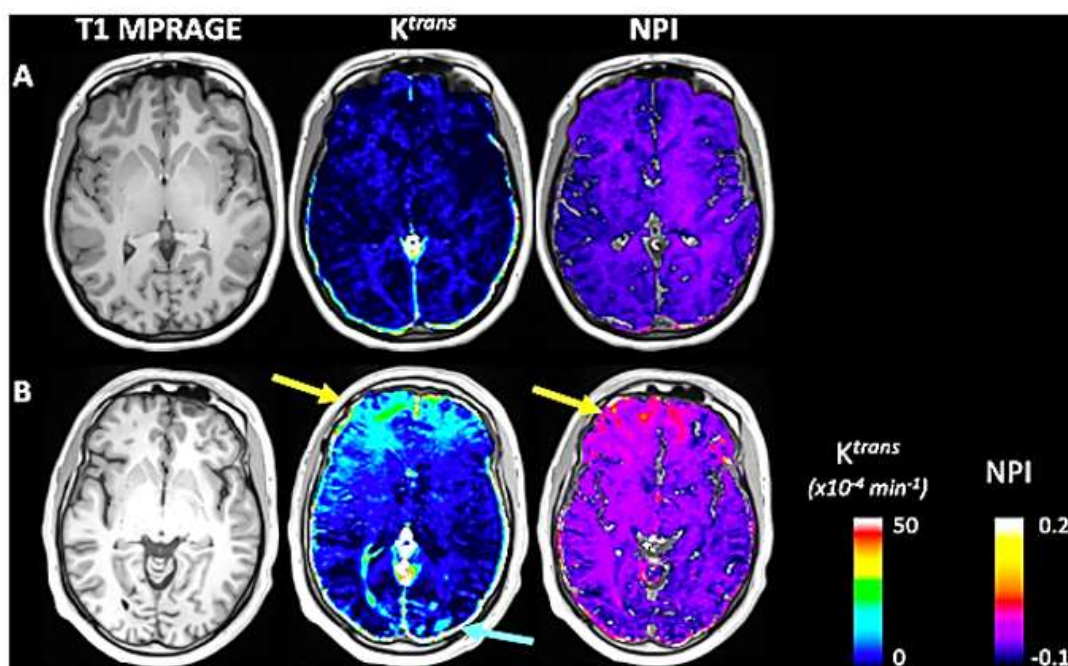


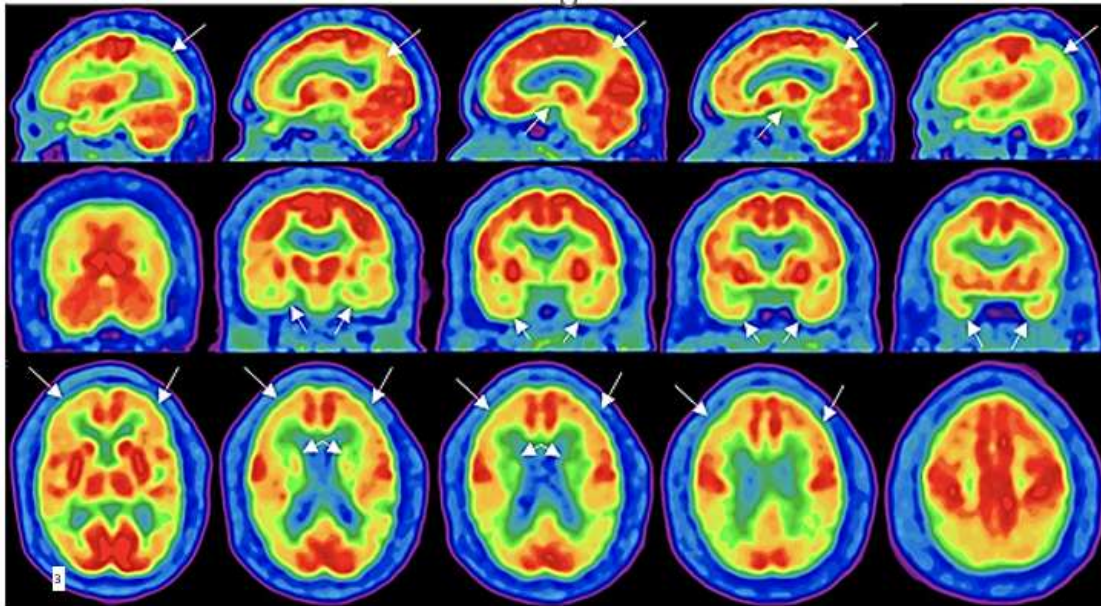
Fig. 2. Individual subject examples from a representative control (A) and subacute TBI subject (B). The TBI nonlesional patient shows similar mild elevations in  $K^{trans}$  and NPI in the anterior frontal white matter (yellow arrows), and additional small areas of  $K^{trans}$  elevation in the occipital lobes (blue arrow).

Ware, Jeffrey B., Saurabh Sinha, Justin Morrison, Alexa E. Walter, James J. Gugger, Andrea LC Schneider, Cian Dabrowski et al. "Dynamic contrast enhanced MRI for characterization of blood-brain-barrier dysfunction after traumatic brain injury." *NeuroImage: Clinical* 36 (2022): 103236. [123]

2213-1582/©2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/bync-nd/4.0/>).

### 1.3.3 18-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

Utilizing radioactively labeled fluorodeoxyglucose ( $^{18}\text{F}$ FDG) and measuring cellular uptake thereof via positron emission tomography (PET) indirectly measures metabolic activity [94,95]. With less metabolic activity there is reduced uptake of labeled glucose as occurs in acute mTBI [96,97]. In the acute phase of severe injury there is increased uptake of  $^{18}\text{F}$ FDG corresponding to the increased glycolysis required to reestablish electrolyte balance [98,99]. In the chronic phase of injury, there is reduced uptake of glucose corresponding to reduced local activity [99–103]. When overlaid on CT or MRI brain images localization of abnormalities is enhanced (Figure 3). Sensitivity, specificity, cost, and scan times limit its utility.



**Figure 3.** FDG-PET scan of the brain. (Top) Sagittal views (Left to right) illustrate hypometabolism in the bilateral posterior parietotemporal regions, posterior\_cingulate and precuneus (Middle) Coronal views (Posterior to anterior) show decreased uptake in the medial\_temporal\_lobes (Bottom) Axial views (Inferior to superior) demonstrate hypometabolism in the frontal\_lobe and anterior temporal poles.

Morgan, Richard, Jordon Prosapio, Sam Kara, Sreepadma Sonty, Pamela Youssef, and Kester Nedd. "Preliminary clinical diagnostic criteria for chronic traumatic encephalopathy: A case report and literature review." *Interdisciplinary Neurosurgery* 26 (2021): 101290. [124]

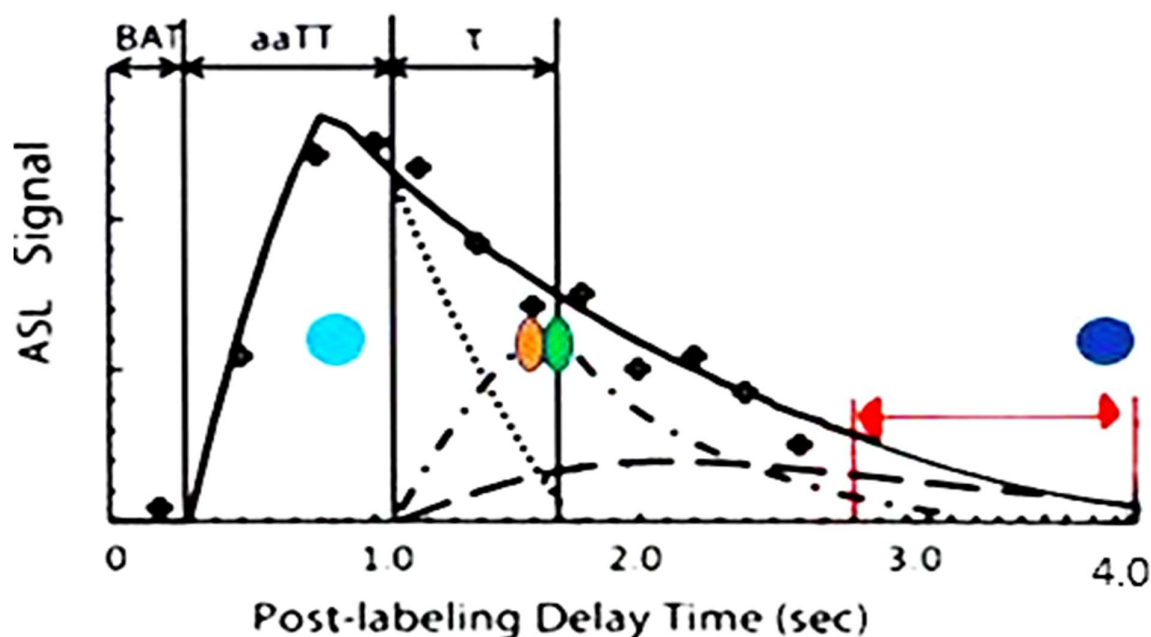
Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

Application of tau PET scan will not be discussed here as they would not be employed in mTBI but in cases of repetitive TBI when the question of CTE arises. The reader is referred to excellent reviews of these techniques [94,104–114].

### 1.3.4. Arterial Spin Labeling MRI

Another method to indirectly determine BBB leak utilizes the clearance rate of magnetically labelled protons using 3D ASL MRI technology. This technique leverages the physiologic effects of altered perfusion with delayed capillary mean transit time (cMTT) and reduced glymphatic outflow in the late phase of the perfusion cycle, correlating with the location of BBB leak [115] (Figure 4). It is

a non-invasive method using blood protons magnetically spin labeled in the neck and after specified post labeling delay (PLD), residual signal averages are sampled in desired cortical regions.



**Figure 4.** Composition of the ASL signal/time into its various components: arterial (dotted line), capillary (dot and dash line, and extra capillary (dashed line) spaces. TI (acquisition) times utilized in this study are between the red arrow limits. Note the signal composition is nearly completely extravascular (interstitial) water, which is normally cleared by the glymphatic system. Red bars and arrows = our post labeling delay acquisition times; Lt blue dot = 800-850 msec T1 of white matter; Orange dot = 1700ms T1 of gray matter (all values are for 3T); Green dot = 1650 msec T1 (63% signal decay) of blood; Dk Blue dot = 3800ms T1 of water (CSF fluid)

T1 times (63% signal decay) of major signal contributors indicated by the colored dots.

Magenta dot = 800-850 msec T1 of white matter.

Orange dot = 1650 msec T1 of blood.

Green dot = 1700 msec T1 of gray matter (all values are for 3T)

Dk blue dot = 3800 msec T1 of water (CSF fluid); (all values are for 3T)

BAT = bolus arrival time; aaTT =artery-artery arrival time;  $\tau$  = peak capillary arrival time

Adapted with publisher permission (Wiley) from reference [125].

By using multiple sequential PLD's in the late phase of the perfusion cycle linear analysis can be employed to determine rate of clearance (slope of the line) [115,116]. In regions of BBB leak there are localized changes in blood flow that correlate with diminished clearance rates. Since the signal measured is largely from trapped labeled water protons in the late phase of perfusion, it is much more sensitive determining minor BBB leaks than gadolinium (large molecule) based DCE [117].

Since this is a non-invasive technique, it is suitable for sequential studies without risk of exogenous contrast. Currently when combined with FLAIR and Susceptibility Weighted Images (SWI), scan time is about 18 <sup>1/2</sup> minutes [116]. ASL MRI requires a 3 Tesla magnet and is limited reduced S/N. The latter can be circumvented by measuring a large field of view and obtaining multiple PLDs. Using 3D data acquisition allows for multiple regions of the brain to be investigated in one study. For example, our usage in mTBI acquired clearance rates from 6 brain regions, homologous temporal, frontal, and parietal regions [115]. Newer ASL MRI sequences allow for acquiring multiple PLDs in one sequence, reducing scan times to under 5 minutes [118]. This technique has significant potential in following the progress of BBB repair or alternatively persistent

leak. In our pilot study of mTBI in college age athletes, both reduced glymphatic clearance post-acute injury and restoration of BBB integrity as measured by this technique correlated with high sensitivity with clinical recovery [116]. Future studies evaluating more serious head injury sequentially may shed light on those patients with persistent dysfunction which sets the stage for progressive dementia (CTE). In addition, this objective measure could help determine when and if an injured athlete or soldier could safely return to their sport or active duty. Limitations of this technique include the indirect method of determination (results are graphic in nature post analysis as opposed specific images of leak) and low S/N ratio. The latter is compensated for by analyzing multiple data points and acquiring signal from a large FOV. Given the test is noninvasive as well as, time and cost efficient, this method is suitable for serial studies post TBI in the assessment of BBB dysfunction [63,119].

### 1.3.6 Summary of techniques

Table 1 below summarizes the imaging target, relative advantages, and disadvantages of the four physiologic imaging techniques presented in evaluating mTBI. They provide objective information regarding the state of brain and vascular function at the time they are employed post head injury. The techniques will continue to improve and become more widely available providing both prognostic information. They also will be essential as outcome measures of future treatment trials.

**Table 1.** Methods of BBB and shear injury imaging modalities and limitations.

Imaging procedure.	Target	Sensitivity	Limitations
Diffusion Tensor Imaging (DTI) MRI	Diffusion of water - white matter tracts	Not clear, older techniques problematic. New techniques in development	Technique specific sensitivity, scan time
Dynamic Contrast Enhanced (DCE) MRI	BBB leak of contrast	Sensitive for BBB leak	Requires gadolinium contrast, long scan times, not suitable for serial studies due to cerebral accumulation of GD <sup>+</sup>
<sup>18</sup> FDG-PET	Glucose utilization metabolic activity	Can identify the brief hypermetabolism acutely (animal studies) and chronic hypometabolism (human) chronically across severity spectrum	Cost, long scan times, availability of technology,
3D ASL MRI	Perfusion/Diffusion of labeled protons	Highly sensitive in a small clinical trial in mTBI determining altered cMTT/BBB leak with delayed BBB clearance/recovery	Requires a 3T or greater field strength, Low signal, hand drawn ROI, requires a larger series for confirmation of sensitivity.

Table 1 summarizes the DTI in identifying shear tract injury, which if present, correlates with persistence of neurologic deficit and recovery depending on its extent. DCE, and ASL MRI identify loss of BBB integrity the former directly and the latter indirectly. <sup>18</sup>FDG-PET measures metabolic activity and thus could be negatively influenced by either shear tract injury or BBB leak.

## 2. Conclusion

With the mounting evidence of severe late life repercussions (CTE) related to repetitive mTBI among professional athletes in contact sports, there is a need to evaluate the physiology leveraging the loss of BBB integrity post injury, that if persistent, correlates with the progressive changes in CTE [39,60,79,85,120,121]. By adopting physiologic testing measures, safe return to the sport could be more accurately predicted in mTBI. Since the potential of both subtle white matter tract shear injury and persistent BBB leak occur simultaneously assessment of damage requires attention to both which

translates into white matter tract imaging as well as evaluation of BBB integrity. Further as we uncover the mechanisms of BBB repair going forward and can leverage that knowledge therapeutically, identifying and assessing outcomes of future treatments will be possible. The benefits of identifying BBB dysfunction spill over from TBI to preclinical stages of neurodegenerative disease (NG), where loss of its integrity is at the nexus of development and prime target for early intervention.

**Acknowledgments:** The author wants to thank Liberty University for funding this publication, in addition to students and faculty colleagues who were instrumental in the ASL MRI clinical research projects referred to in this article.

**Conflicts of Interest:** The author has no competing issues or conflicts of interest in the writing of this manuscript. The author is solely responsible for the content of this article.

### Acronyms Dictionary

**TBI**- mild traumatic brain injury  
**TJ protein ZO-1**-tight junction protein Zona Occludens 1  
**C3a**- complement C3a protein  
**C3aR**- complement C3a receptor protein  
**pTau**- hyperphosphorylated Tau  
**TDP-43**- Transactive response DNA binding protein- 43  
**FLAIR**- fluid attenuated inversion recovery  
**SWI**- Susceptibility Weighted Images  
**ASL MRI**-Arterial Spin Labeling MRI  
**PLD**- Post labeling delay  
**DTI MRI**- Diffusion Tensor Imaging  
**DCE MRI**- Dynamic Contrast Enhanced MRI  
**PET**- Positron Emission Tomography  
**S/N**- Signal to Noise  
**SKAT 6**- Sport concussion Assessment Tool  
**VOMS**- Vestibular Ocular Motor Screening  
**SCOAT 6**- Sports *Concussion* Office Assessment Tool  
**CTE**- chronic traumatic encephalopathy  
**cMTT**- mean capillary transit time  
**GF**- glymphatic flow  
**BBB**- Blood brain barrier  
**IGG**- Immunoglobulin G  
**NVU**- the neurovascular unit  
**ECM**- extracellular matrix  
**IL1  $\beta$** - interleukin 1 beta

## References

1. Maas AIR, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. *The Lancet Neurology*. 2022 Sep;21(11).
2. Forrest RHJ, Henry JD, McGarry PJ, Marshall RN. Mild traumatic brain injury in New Zealand: factors influencing post-concussion symptom recovery time in a specialised concussion service. *Journal of Primary Health Care [Internet]*. 2018;10(2):159. Available from: <https://www.publish.csiro.au/hc/pdf/HC17071>
3. Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. CDC NIH Rep to Congr 1–74.
4. Reith, Florence CM, Hester F. Lingams, Belinda J. Gabe, Fiona E. Lecky, Ian Roberts, and Andrew IR Maas. "Differential effects of the Glasgow Coma Scale Score and its Components: An analysis of 54,069 patients with traumatic brain injury." *Injury* 48, no. 9 (2017): 1932-1943.
5. Dessy AM, Yuk FJ, Maniya AY, Gometz A, Rasouli JJ, Lovell MR, et al. Review of Assessment Scales for Diagnosing and Monitoring Sports-related Concussion. *Cureus [Internet]*. 2017 Dec 7;9(12). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5802754/5>.
6. Polinder S, Cnossen MC, Real RGL, Covic A, Gorbunova A, Voormolen DC, et al. A Multidimensional Approach to Post-concussion Symptoms in Mild Traumatic Brain Injury. *Frontiers in Neurology [Internet]*. 2018 Dec 19;9. Available from: <https://www.frontiersin.org/articles/10.3389/fneur.2018.01113/full>
7. Williams RM, Puetz TW, Giza CC, Broglio SP. Concussion Recovery Time Among High School and Collegiate Athletes: A Systematic Review and Meta-Analysis. *Sports Medicine [Internet]*. 2015 Mar 28 [cited 2019 Nov 26];45(6):893–903. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4441834/>
8. Williams RM, Puetz TW, Giza CC, Broglio SP. Concussion Recovery Time Among High School and Collegiate Athletes: A Systematic Review and Meta-Analysis. *Sports Medicine [Internet]*. 2015 Mar 28 [cited 2019 Nov 26];45(6):893–903. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4441834/>
9. Wintermark M, Sanelli PC, Anzai Y, Tsiouris AJ, Whitlow CT, Druzgal TJ, et al. Imaging Evidence and Recommendations for Traumatic Brain Injury: Conventional Neuroimaging Techniques. *Journal of the American College of Radiology*. 2015 Feb;12(2): e1–14.
10. Eierud C, Craddock RC, Fletcher S, Aulakh M, King-Casas B, Kuehl D, et al. Neuroimaging after mild traumatic brain injury: Review and meta-analysis. *NeuroImage: Clinical*. 2014; 4:283–94.
11. Roberts MA, Manshadi F, Bushnell D, Hines M. Neurobehavioural dysfunction following mild traumatic brain injury in childhood: a case report with positive findings on positron emission tomography (PET). *Brain Inj*. 1995; 9:427–36.
12. Echemendia, Ruben J., Benjamin L. Brett, Steven Broglio, Gavin A. Davis, Christopher C. Giza, Kevin M. Guskiewicz, Kimberly G. Harmon et al. "Introducing the sport concussion assessment tool 6 (SCAT6)." *British Journal of Sports Medicine* 57, no. 11 (2023): 619-621.
13. Patricios, Jon, Geoff M. Schneider, Jacqueline van Ierssel, Laura K. Purcell, Gavin A. Davis, Ruben J. Echemendia, Pierre Frémont et al. "Sport concussion office assessment tool 6." *British journal of sports medicine* 57, no. 11 (2023): 651-667.
14. Polinder S, Cnossen MC, Real RGL, Covic A, Gorbunova A, Voormolen DC, et al. A Multidimensional Approach to Post-concussion Symptoms in Mild Traumatic Brain Injury. *Frontiers in Neurology [Internet]*. 2018 Dec 19;9. Available from: <https://www.frontiersin.org/articles/10.3389/fneur.2018.01113/full>
15. Meier TB, Bellgowan PS, Singh R, Kuplicki R, Polanski DW, Mayer AR. Recovery of cerebral blood flow following sports related concussion. *JAMA Neurol*. 2015; 72:530–8.
16. Roberts MA, Manshadi F, Bushnell D, Hines M. Neurobehavioural dysfunction following mild traumatic brain injury in childhood: a case report with positive findings on positron emission tomography (PET). *Brain Inj*. 1995; 9:427–36.
17. Ilvesmäki T, Luoto TM, Hakulinen U, Brander A, Ryymin P, Eskola H, et al. Acute mild traumatic brain injury is not associated with white matter change on diffusion tensor imaging. *Brain*. 2014; 137:1876–82.
18. Lee H, Wintermark M, Gean AD, Ghajar J, Manley GT, Mukherjee P. Focal lesions in acute mild traumatic brain injury and neurocognitive outcome: CT versus 3T MRI. *J Neurotrauma*. 2008; 25:1049–56.
19. Hiebert, John B., Qihua Shen, Amanda R. Thimmesch, and Janet D. Pierce. "Traumatic brain injury and mitochondrial dysfunction." *The American journal of the medical sciences* 350, no. 2 (2015): 132-138.
20. Vagnozzi R, Tavazzi B, Signoretti S, Amorini AM, Belli A, Cimatti M, et al. Temporal window of metabolic brain vulnerability to concussions: mitochondrial-related impairment part I. *Neurosurgery*. 2007; 61:379–89.
21. Bergsneider M, Hovda DA, Shalmon E, Kelly DF, Vespa PM, Martin NA, et al. Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. *J Neurosurg*. 1997; 86:241–51.
22. Hay, Jennifer R., Victoria E. Johnson, Adam MH Young, Douglas H. Smith, and William Stewart. "Blood-brain barrier disruption is an early event that may persist for many years after traumatic brain injury in humans." *Journal of neuropathology and experimental neurology* 74, no. 12 (2015): 1147-1157

23. Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain*. 2013; 136:28–42.
24. Thurgur, Hannah, and Emmanuel Pinteaux. "Microglia in the neurovascular unit: blood–brain barrier–microglia interactions after central nervous system disorders." *Neuroscience* 405 (2019): 55–67
25. Christman CW, Grady MS, Walker SA, Holloway KL, Povlishock JT. Ultrastructural studies of diffuse axonal injury in humans. *J Neurotrauma*. 1994; 11:173–86.
26. El Sayed, Tamer, Alejandro Mota, Fernando Fraternali, and Michael Ortiz. "Biomechanics of traumatic brain injury." *Computer Methods in Applied Mechanics and Engineering* 197, no. 51–52 (2008): 4692–4701.
27. Meier TB, Bellgowan PS, Singh R, Kuplicki R, Polanski DW, Mayer AR. Recovery of cerebral blood flow following sports related concussion. *JAMA Neurol*. 2015; 72:530–8.
28. Roberts MA, Manshadi F, Bushnell D, Hines M. Neurobehavioural dysfunction following mild traumatic brain injury in childhood: a case report with positive findings on positron emission tomography (PET). *Brain Inj*. 1995; 9:427–36.
29. Meaney DF, Smith DH. Biomechanics of concussion. *Clin Sports Med*. 2011; 30:19–31
30. Donat, Cornelius K., Maria Yanez Lopez, Magdalena Sastre, Nicoleta Baxan, Marc Goldfinger, Reneira Seeamber, Franziska Müller et al. "From biomechanics to pathology: predicting axonal injury from patterns of strain after traumatic brain injury." *Brain* 144, no. 1 (2021): 70–91.
31. Glushakova, Olena Y., Danny Johnson, and Ronald L. Hayes. "Delayed increases in microvascular pathology after experimental traumatic brain injury are associated with prolonged inflammation, blood–brain barrier disruption, and progressive white matter damage." *Journal of neurotrauma* 31, no. 13 (2014): 1180–1193.
32. Thurgur, Hannah, and Emmanuel Pinteaux. "Microglia in the neurovascular unit: blood–brain barrier–microglia interactions after central nervous system disorders." *Neuroscience* 405 (2019): 55–67.
33. Haider MN, Leddy JJ, Hinds AL, Aronoff N, Rein D, Poulsen D, et al. Intracranial pressure changes after mild traumatic brain injury: a systematic review. *Brain Inj*. 2018; 32:809–15.
34. Barzó, Pál, Anthony Marmarou, Panos Fatouros, Frank Corwin, and Jana Dunbar. "Magnetic resonance imaging—monitored acute blood-brain barrier changes in experimental traumatic brain injury." *Journal of neurosurgery* 85, no. 6 (1996): 1113–1121.
35. Morganti-Kossmann, Maria Cristina, E. Yan, and Nicole Bye. "Animal models of traumatic brain injury: is there an optimal model to reproduce human brain injury in the laboratory?" *Injury* 41 (2010): S10–S13.
36. Johnson, Victoria E., David F. Meaney, D. Kacy Cullen, and Douglas H. Smith. "Animal models of traumatic brain injury." *Handbook of clinical neurology* 127 (2015): 115–128.
37. Morganti-Kossmann MC, Rancan M, Otto VI, Stahel PF, Kossmann T. Role of cerebral inflammation after traumatic brain injury: a revisited concept. *Shock (Augusta, Ga)*. 2001; 16:165–77.
39. Doherty CP, O'Keefe E, Wallace E, Loftus T, Keaney J, Kealy J, et al. Blood–brain barrier dysfunction as a hallmark pathology in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. 2016; 75:656–62.
40. Hattori N, Huang S-C, Wu H-M, Liao W, Glenn TC, Vespa PM, et al. Acute changes in regional cerebral 18F-FDG kinetics in patients with traumatic brain injury. *J Nucl Med*. 2004; 45:775–83
41. Ziebell JM, Morganti-Kossmann MC. Involvement of pro-and anti-inflammatory cytokines and chemokines in the pathophysiology of traumatic brain injury. *Neurotherapeutics*. 2010; 7:22–30.
42. Woodcock T, Morganti-Kossmann C. The role of markers of inflammation in traumatic brain injury. *Front Neurol*. 2013; 4:18.
43. Ziebell JM, Morganti-Kossmann MC. Involvement of pro-and anti-inflammatory cytokines and chemokines in the pathophysiology of traumatic brain injury. *Neurotherapeutics*. 2010; 7:22–30.
44. Woodcock T, Morganti-Kossmann C. The role of markers of inflammation in traumatic brain injury. *Front Neurol*. 2013; 4:18.
45. Engelhardt, Britta, and Stefan Liebner. "Novel insights into the development and maintenance of the blood–brain barrier." *Cell and tissue research* 355.3 (2014): 687–699.
46. Iadecola, Costantino. "The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease." *Neuron* 96.1 (2017): 17–42.
47. Bhowmick, Saurav, et al. "Impairment of pericyte-endothelium crosstalk leads to blood-brain barrier dysfunction following traumatic brain injury." *Experimental neurology* 317 (2019): 260–270.
48. Sweeney, Melanie D., et al. "The role of brain vasculature in neurodegenerative disorders." *Nature neuroscience* 21.10 (2018): 1318–1331.
49. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Bloodbrain barrier: from physiology to disease and back. *Physiol Rev*. 2019; 99:21–78. doi: 10.1152/physrev.00050.2017
50. Andjelkovic, Anuska V., et al. "Blood-brain barrier dysfunction in normal aging and neurodegeneration: mechanisms, impact, and treatments." *Stroke* 54.3 (2023): 661–672.

51. Kadry, Hossam, Behnam Noorani, and Luca Cucullo. "A blood–brain barrier overview on structure, function, impairment, and biomarkers of integrity." *Fluids and Barriers of the CNS* 17.1 (2020): 1-24
52. Zhao, Lucy, et al. "Physiology of glymphatic solute transport and waste clearance from the brain." *Physiology* 37.6 (2022): 349-362
53. Preston, Jane E., N. Joan Abbott, and David J. Begley. "Transcytosis of macromolecules at the blood–brain barrier." *Advances in pharmacology* 71 (2014): 147-163.
54. van Leeuwen, E., Hampton, M. B., and Smyth, L. C. D. (2020). Redox signaling and regulation of the blood-brain barrier. *Int. J. Biochem. Cell Biol.* 125:105794. doi: 10.1016/j.biocel.2020.105794
55. Baeten KM, Akassoglou K (2011) Extracellular matrix and matrix receptors in blood–brain barrier formation and stroke. *Dev Neurobiol* 71:1018–1039.
56. Lochhead, Jeffrey J., et al. "Structure, function, and regulation of the blood-brain barrier tight junction in central nervous system disorders." *Frontiers in physiology* 11 (2020): 914.
57. Hudson, Natalie, and Matthew Campbell. "Tight junctions of the neurovascular unit." *Frontiers in Molecular Neuroscience* 14 (2021): 752781
58. Zhou, Chao, Hong Chen, Jian-Feng Zheng, Zong-Duo Guo, Zhi-Jian Huang, Yue Wu, Jian-Jun Zhong, Xiao-Chuan Sun, and Chong-Jie Cheng. "Pentraxin 3 contributes to neurogenesis after traumatic brain injury in mice." *Neural Regeneration Research* 15, no. 12 (2020): 2318-2326.
59. Shabab T, Khanabdali R, Moghadamtousi SZ, Kadir HA, Mohan G. Neuroinflammation pathways: a general review. *Int J Neurosci.* 2017; 127:624–33.
60. Zhang J, Puvenna V, Janigro D. Biomarkers of traumatic brain injury and their relationship to pathology. *Translational research in traumatic brain injury: CRC Press/Taylor and Francis Group*; 2016.
61. Ramlackhansingh AF, Brooks DJ, Greenwood RJ, Bose SK, Turkheimer FE, Kinnunen KM, et al. Inflammation after trauma: microglial activation and traumatic brain injury. *Ann Neurol.* 2011; 70:374–83.
62. Profaci, Caterina P., et al. "The blood–brain barrier in health and disease: Important unanswered questions." *Journal of Experimental Medicine* 217.4 (2020).
63. Joseph, Charles R. "Progressive Age-Associated Blood–Brain Barrier Leak/Dysfunction-Nexus of Neurodegenerative Disease Using MRI Markers to Identify Preclinical Disease and Potential New Targets for Future Treatments." *Diagnostics* 14, no. 7 (2024): 726.
64. Propson, N. E., Roy, E. R., Litvinchuk, A., Köhl, J., & Zheng, H. (2021). Endothelial C3a receptor mediates vascular inflammation and blood-brain barrier permeability during aging. *The Journal of Clinical Investigation*, 131(1). <https://doi.org/10.1172/JCI140966>
65. Nakajima Y, Horiuchi Y, Kamata H, Yukawa M, Kuwabara M, Tsubokawa T. Distinct time courses of secondary brain damage in the hippocampus following brain concussion and contusion in rats. *Tohoku J Exp Med.* 2010; 221:229–35.
66. Ryan LM, Warden DL. Post concussion syndrome. *Int Rev Psychiatry.* 2003; 15:310–6.
67. Prins ML, Alexander D, Giza CC, Hovda DA. Repeated mild traumatic brain injury: mechanisms of cerebral vulnerability. *J Neurotrauma.* 2013; 30:30–8.
68. Laurer HL, Bareyre FM, Lee VM, Trojanowski JQ, Longhi L, Hoover R, et al. Mild head injury increasing the brain's vulnerability to a second concussive impact. *J Neurosurg.* 2001; 95:859–70.
69. Sorby-Adams A, Marcoionni A, Dempsey E, Woenig J, Turner R. The role of neurogenic inflammation in blood-brain barrier disruption and development of cerebral oedema following acute central nervous system (CNS) injury. *Int J Mol Sci.* 2017; 18:1788.
70. Andjelkovic, Anuska V., et al. "Blood-brain barrier dysfunction in normal aging and neurodegeneration: mechanisms, impact, and treatments." *Stroke* 54.3 (2023): 661-672.
71. Farace E, Alves WM. Do women fare worse? A metanalysis of gender differences in outcome after traumatic brain injury. *Neurosurg Focus.* 2000; 8:1–8.
72. Bennett ER, Reuter-Rice K, Laskowitz DT. Genetic influences in traumatic brain injury. *Transl Res Traumatic Brain Inj.* 2016
73. McKee AC, Stein TD, Nowinski CJ, Stern RA, Daneshvar DH, Alvarez VE, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain.* 2013; 136:43–64.
74. Ayubcha, Cyrus, Mona-Elisabeth Revheim, Andrew Newberg, Mateen Moghbel, Chaitanya Rojulpote, Thomas J. Werner, and Abass Alavi. "A critical review of radiotracers in the positron emission tomography imaging of traumatic brain injury: FDG, tau, and amyloid imaging in mild traumatic brain injury and chronic traumatic encephalopathy." *European Journal of Nuclear Medicine and Molecular Imaging* 48 (2021): 623-641.
75. Mez J, Daneshvar DH, Kiernan PT, Abdolmohammadi B, Alvarez VE, Huber BR, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA.* 2017; 318:360–70.
76. Lenihan MW, Jordan BD. The clinical presentation of chronic traumatic encephalopathy. *Curr Neurol Neurosci Rep.* 2015; 15:23.

77. Karton, Clara, and T. Blaine Hoshizaki. "Concussive and subconcussive brain trauma: the complexity of impact biomechanics and injury risk in contact sport." *Handbook of clinical neurology* 158 (2018): 39-49.78. Bang SA, Song YS, Moon BS, Lee BC, Lee H-y, Kim J-M, et al. Neuropsychological, metabolic, and GABAA receptor studies in subjects with repetitive traumatic brain injury. *J Neurotrauma*. 2016; 33:1005–14.
79. Wooten DW, Ortiz-Teran L, Zubcevik N, Zhang X, Huang C, Sepulcre J, et al. Multi-modal signatures of tau pathology, neuronal fiber integrity, and functional connectivity in traumatic brain injury. *J Neurotrauma*. 2019; 36:3233–43.
80. Knox, Emily G., et al. "The blood-brain barrier in aging and neurodegeneration." *Molecular psychiatry* 27.6 (2022): 2659-2673.
81. Lendahl, Urban, Per Nilsson, and Christer Betsholtz. "Emerging links between cerebrovascular and neurodegenerative diseases—a special role for pericytes." *EMBO reports* 20.11 (2019): e48070.
82. Searson, Peter Charles, et al. "The influence of physiological and pathological perturbations on blood-brain barrier function." *Frontiers in Neuroscience* 17 (2023): 1289894.
83. Elschot, Elles P., et al. "A comprehensive view on MRI techniques for imaging blood-brain barrier integrity." *Investigative Radiology* 56.1 (2021): 10-19.
84. Eierud, C. et al. Neuroimaging after mild traumatic brain injury: Review and meta-analysis. *NeuroImage Clin.* 4, 283–294 (2014).
85. Sparks P, Lawrence T, Hinze S. Neuroimaging in the diagnosis of chronic traumatic encephalopathy: a systematic review. *Clin J Sport Med.* 2020;30: S1–S10.
86. Ranzenberger LR, Das JM, Snyder T. Diffusion Tensor Imaging. 2023 Nov 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. PMID: 30726046. DTI
87. Kim, E. et al. A systematic review and data synthesis of longitudinal changes in white matter integrity after mild traumatic brain injury assessed by diffusion tensor imaging in adults. *Eur. J. Radiol.* 147, 110117 (2022).
88. Yoен, Heera, Roh-Eul Yoo, Seung Hong Choi, Eunkyung Kim, Byung-Mo Oh, Dongjin Yang, Inpyeong Hwang et al. "Blood-brain barrier disruption in mild traumatic brain injury patients with post-concussion syndrome: evaluation with region-based quantification of dynamic contrast-enhanced MR imaging parameters using automatic whole-brain segmentation." *Korean journal of radiology* 22, no. 1 (2021): 118.
89. Ware, Jeffrey B., Saurabh Sinha, Justin Morrison, Alexa E. Walter, James J. Gugger, Andrea LC Schneider, Cian Dabrowski et al. "Dynamic contrast enhanced MRI for characterization of blood-brain-barrier dysfunction after traumatic brain injury." *NeuroImage: Clinical* 36 (2022): 103236.
90. Oh, Sung Suk, Eun-Hee Lee, Jong-Hoon Kim, Young Beom Seo, Yoo Jin Choo, Juyoung Park, and Min Cheol Chang. "The use of dynamic contrast-enhanced magnetic resonance imaging for the evaluation of blood-brain barrier disruption in traumatic brain injury: what is the evidence?" *Brain Sciences* 11, no. 6 (2021): 775.
91. Iyad, Nebal, Muntaser S. Ahmad, Sanaa G. Alkhatib, and Mohammad Hjouj. "Gadolinium contrast agents-challenges and opportunities of a multidisciplinary approach: Literature review." *European Journal of Radiology Open* 11 (2023): 100503.
92. Rasschaert, Marlène, Roy O. Weller, Josef A. Schroeder, Christoph Brochhausen, and Jean-Marc Idée. "Retention of gadolinium in brain parenchyma: pathways for speciation, access, and distribution. A critical review." *Journal of Magnetic Resonance Imaging* 52, no. 5 (2020): 1293-1305.
93. Stanescu, A. Luana, Dennis W. Shaw, Nozomu Murata, Kiyoko Murata, Joe C. Rutledge, Ezekiel Maloney, and Kenneth R. Maravilla. "Brain tissue gadolinium retention in pediatric patients after contrast-enhanced magnetic resonance exams: pathological confirmation." *Pediatric radiology* 50 (2020): 388-396.
94. Byrnes, Kimberly R., Colin M. Wilson, Fiona Brabazon, Ramona Von Leden, Jennifer S. Jurgens, Terrence R. Oakes, and Reed G. Selwyn. "FDG-PET imaging in mild traumatic brain injury: a critical review." *Frontiers in neuroenergetics* 5 (2014): 13.
95. Gandy S, DeKosky ST. [18F]-T807 tauopathy PET imaging in chronic traumatic encephalopathy. F1000Research. 2014;3.
96. Selwyn R, Hockenbury N, Jaiswal S, Mathur S, Armstrong RC,Byrnes KR. Mild traumatic brain injury results in depressed cerebral glucose uptake: an 18FDG PET Study. *J Neurotrauma*. 2013; 30:1943–53.
97. Wu H-M, Huang S-C, Hattori N, Glenn TC, Vespa PM, Yu C-L, et al. Selective metabolic reduction in gray matter acutely following human traumatic brain injury. *J Neurotrauma*. 2004; 21:149–61.
98. Hattori N, Huang S-C, Wu H-M, Liao W, Glenn TC, Vespa PM, et al. Acute changes in regional cerebral 18F-FDG kinetics in patients with traumatic brain injury. *J Nucl Med*. 2004; 45:775–83
99. Bergsneider M, Hovda DA, Shalmon E, Kelly DF, Vespa PM, Martin NA, et al. Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. *J Neurosurg*. 1997; 86:241–51.
100. Worley, Gordon, John M. Hoffman, Susan S. Paine, Sophia L. Kalman, Susan J. Claerhout, Orest B. Boyko, Raymond S. Kandt et al. "18-Fluorodeoxyglucose positron emission tomography in children and adolescents with traumatic brain injury." *Developmental Medicine & Child Neurology* 37, no. 3 (1995): 213-220.

101. Bergsneider M, Hovda DA, Lee SM, Kelly DF, McArthur DL, Vespa PM, et al. Dissociation of cerebral glucose metabolism and level of consciousness during the period of metabolic depression following human traumatic brain injury. *J Neurotrauma*. 2000; 17:389–401.
102. Buchsbaum MS, Simmons AN, DeCastro A, Farid N, Matthews SC. Clusters of low 18F-fluorodeoxyglucose uptake voxels in combat veterans with traumatic brain injury and post-traumatic stress disorder. *J Neurotrauma*. 2015; 32:1736–50.
103. Komura A, Kawasaki T, Yamada Y, Uzuyama S, Asano Y, Shinoda J. Cerebral glucose metabolism in patients with chronic mental and cognitive sequelae after a single blunt mild traumatic brain injury without visible brain lesions. *J Neurotrauma*. 2019; 36:641–9.
104. Leuzy A, Chiotis K, Lemoine L, Gillberg P-G, Almkvist O, Rodriguez-Vieitez E, et al. Tau PET imaging in neurodegenerative tauopathies—still a challenge. *Mol Psychiatry*. 2019;1.
105. Shivamurthy VK, Tahari AK, Marcus C, Subramaniam RM. Brain FDG PET and the diagnosis of dementia. *Am J Roentgenol*. 2015; 204: W76–85.
106. Moghbel MG, Saboury B, Basu S, Metzler SD, Torigian DA, Långström B, et al. Amyloid- $\beta$  imaging with PET in Alzheimer's disease: is it feasible with current radiotracers and technologies? Springer; 2012.
107. Leuzy A, Chiotis K, Lemoine L, Gillberg P-G, Almkvist O, Rodriguez-Vieitez E, et al. Tau PET imaging in neurodegenerative tauopathies—still a challenge. *Mol Psychiatry*. 2019;1.
108. Barrio JR, Small GW, Wong K-P, Huang S-C, Liu J, Merrill DA, et al. In vivo characterization of chronic traumatic encephalopathy using [F-18] FDDNP PET brain imaging. *Proc Natl Acad Sci*. 2015; 112: E2039–E47.
109. Harada R, Okamura N, Furumoto S, Tago T, Yanai K, Arai H, et al. Characteristics of tau and its ligands in PET imaging. *Biomolecules*. 2016; 6:7.
110. Choi SR, Schneider JA, Bennett DA, Beach TG, Bedell BJ, Zehntner SP, et al. Correlation of amyloid PET ligand florbetapir F 18 binding with A $\beta$  aggregation and neuritic plaque deposition in postmortem brain tissue. *Alzheimer Dis Assoc Disord*. 2012; 26:8–16.
111. Lister-James J, Pontecorvo MJ, Clark C, Joshi AD, Mintun MA, Zhang W, et al. Florbetapir f-18: a histopathologically validated Beta-amyloid positron emission tomography imaging agent. In: *Seminars in nuclear medicine*: Elsevier; 2011. p. 300–4.
112. Baker SL, Harrison TM, Maass A, La Joie R, Jagust WJ. Effect of off-target binding on 18F-flortaucipir variability in healthy controls across the life span. *J Nucl Med*. 2019; 60:1444–51.
113. Dani M, Brooks D, Edison P. Tau imaging in neurodegenerative diseases. *Eur J Nucl Med Mol Imaging*. 2016; 43:1139–50.
114. Kantarci K, Lowe VJ, Boeve BF, Senjem ML, Tosakulwong N, Lesnick TG, et al. AV-1451 tau and  $\beta$ -amyloid positron emission tomography imaging in dementia with Lewy bodies. *Ann Neurol*. 2017; 81:58–67.
115. Joseph, Charles R., Christopher M. Benhatzel, Logan J. Stern, Olivia M. Hopper, and Michael D. Lockwood. "Pilot study utilizing MRI 3D TGSE PASL (arterial spin labeling) differentiating clearance rates of labeled protons in the CNS of patients with early Alzheimer disease from normal subjects." *Magnetic Resonance Materials in Physics, Biology and Medicine* 33 (2020): 559-568.
116. Joseph, Charles R., Jubin Kang Lim, Bryce N. Grohol, Marija Zivcevska, Joshua Lencke, Ethan Dean Rich, Connor James Arrasmith et al. "Identifying delay in glymphatic clearance of labeled protons post-acute head trauma utilizing 3D ASL MRI (arterial spin labeling): A pilot study." *Scientific Reports* 14, no. 1 (2024): 6188.
117. Zhao, Moss Y., Audrey P. Fan, David Yen-Ting Chen, Magdalena J. Sokolska, Jia Guo, Yosuke Ishii, David D. Shin et al. "Cerebrovascular reactivity measurements using simultaneous 15O-water PET and ASL MRI: Impacts of arterial transit time, labeling efficiency, and hematocrit." *Neuroimage* 233 (2021): 117955.
118. Elschot, Elles P., Walter H. Backes, Alida A. Postma, Robert J. van Oostenbrugge, Julie Staals, Rob PW Rouhl, and Jacobus FA Jansen. "A comprehensive view on MRI techniques for imaging blood-brain barrier integrity." *Investigative Radiology* 56, no. 1 (2021): 10-19.
119. Joseph, Charles R., Alec Kreilach, Victoria Ashley Reyna, Thomas Ashton Kepler, Brittany Viola Taylor, Jubin Kang, Dallas McCorkle, and Nicholas L. Rider. "Utilizing Reduced Labeled Proton Clearance to Identify Preclinical Alzheimer Disease with 3D ASL MRI." *Case Reports in Neurology* 15, no. 1 (2023): 177.
120. Takahata K, Kimura Y, Sahara N, Koga S, Shimada H, Ichise M, et al. PET-detectable tau pathology correlates with long-term neuropsychiatric outcomes in patients with traumatic brain injury. *Brain*. 2019; 142:3265–79.
121. Gorgoraptis N, Li LM, Whittington A, Zimmerman KA, Maclean LM, McLeod C, et al. In vivo detection of cerebral tau pathology in long-term survivors of traumatic brain injury. *Sci Transl Med*. 2019; 11: eaaw1993.

122. Gandy, Sam, Milos D. Ikonovic, Effie Mitsis, Gregory Elder, Stephen T. Ahlers, Jeffrey Barth, James R. Stone, and Steven T.DeKosky. "Chronic traumatic encephalopathy: clinical biomarker correlations and current concepts in pathogenesis." *Molecular neurodegeneration* 9 (2014): 1-22.
123. Ware, Jeffrey B., Saurabh Sinha, Justin Morrison, Alexa E. Walter, James J. Gugger, Andrea LC Schneider, Cian Dabrowski et al. "Dynamic contrast enhanced MRI for characterization of blood-brain-barrier dysfunction after traumatic brain injury." *NeuroImage: Clinical* 36 (2022): 103236.
124. Morgan, Richard, Jordon Prosapio, Sam Kara, Sreepadma Sonty, Pamela Youssef, and Kester Nedd. "Preliminary clinical diagnostic criteria for chronic traumatic encephalopathy: A case report and literature review." *Interdisciplinary Neurosurgery* 26 (2021): 101290.
125. Li, Ka-loh, Xiaoping Zhu, Nola Hylton, Geon-Ho Jahng, Michael W. Weiner, and Norbert Schuff. "Four-phase single-capillary stepwise model for kinetics in arterial spin labeling MRI." *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine* 53, no. 3 (2005): 511-518.

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.