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REVIEW ARTICLE

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Noninvasive magnetic resonance imaging techniques in mild traumatic brain injury research and diagnosis

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Abstract

Mild traumatic brain injury (mTBI), frequently referred to as concussion, is one of the most common neurological disorders. The underlying neural mechanisms of functional disturbances in the brains of concussed individuals remain elusive. Novel forms of brain imaging have been developed to assess patients postconcussion, including functional magnetic resonance imaging (fMRI), susceptibility-weighted imaging (SWI), diffusion MRI (dMRI), and perfusion MRI [arterial spin labeling (ASL)], but results have been mixed with a more common utilization in the research environment and a slower integration into the clinical setting. In this review, the benefits and drawbacks of the methods are described: fMRI is an effective method in the diagnosis of concussion but it is expensive and time-consuming making it difficult for regular use in everyday practice; SWI allows detection of microhemorrhages in acute and chronic phases of concussion; dMRI is primarily used for the detection of white matter abnormalities, especially axonal injury, specific for mTBI; and ASL is an alternative to the BOLD method with its ability to track cerebral blood flow alterations. Thus, the absence of a universal diagnostic neuroimaging method suggests a need for the adoption of a multimodal approach to the neuroimaging of mTBI. Taken together, these methods, with their underlying functional and structural features, can contribute from different angles to a deeper understanding of mTBI mechanisms such that a comprehensive diagnosis of mTBI becomes feasible for the clinician.

KEYWORDS
ASL, concussion, DWI, fMRI, mTBI, neuroimaging, SWI

1 | INTRODUCTION

Mild traumatic brain injury (mTBI), frequently used synonymously with concussion, is one of the most common neurological disorders with an incidence rate of up to 600/100,000 in North America and Europe, occurring in males in two-thirds of cases (Li, Zhao, Yu, & Zhang, 2016). The mTBI is a serious challenge for society and economics as it can be a risk-factor for such consequences as a decline in cognitive functions, early dementia and mental illness (McInnes, Friesen, MacKenzie, Westwood, & Boe, 2017). The mechanism of injury in mTBI is usually described

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as a result of a transfer of mechanical energy into the brain from a traumatic event such as rapid acceleration/deceleration or a direct impact to the head (Jeter et al., 2013). The other type is a blast-related mTBI, caused by an explosive blast, which may result in brain damage due to tissue-transmitted shock waves within the vascular system traveling to the brain (Cernak, 2015).

According to The American Congress of Rehabilitation Medicine (ACRM), mTBI is a traumatically induced physiological disruption of brain function in the presence of one or more of the following symptoms: period of loss of consciousness (LOC), posttraumatic amnesia (PTA), alteration in mental state, and focal neurological deficit(s). Furthermore, the ACRM has underlined that standard neuroimaging tools [computed tomography (CT), MRI, electroencephalography (EEG), etc.] may show normal results (Head, 1993).

The World Health Organization (WHO) has modified the definition of mTBI to specify that manifestations of mTBI must not be due to drugs, alcohol, medications, other injuries or treatment for other injuries, or penetrating craniocerebral injury (Carroll et al., 2004). Additionally, the WHO suggested to substitute the term "concussion" for "mTBI," even though both terms are still used interchangeably. The term "concussion" is more commonly used in sports contexts and is often referred to as Sport Related Concussion (SRC); in turn, "mTBI" is mostly seen in the medical environment (Greenwald, Ambrose, & Armstrong, 2012; McCrory, Meeuwisse, & Johnston, 2009; Ruff et al., 2009).

From the perspective of diagnosis, the assessment of concussion currently relies heavily on subjective clinical symptoms reports that are often unreliable and/or nonspecific. MTBI is distinct from moderate and severe TBI on the basis of the Glasgow Coma Scale (GCS); this scale is used for assessing consciousness level, ranging from 3/15 (deep coma or death) to 15/15 (fully awake; Sternbach, 2000). MTBI patients in the acute phase have GCS scores ranging from 13 to 15/15 (Mena et al., 2011). As defined by the WHO and ACRM, LOC in mTBI is to be less than 30 min and PTA duration less than 24 hr. However, it was shown that concussions can also occur without LOC (Kelly & Rosenberg, 1997). Physicians also look for somatic symptoms such as dizziness, fatigue, headache, and so on. In addition, a neuropsychological assessment used in the acute phase may show deficits that become less apparent in the chronic phase (Echemendia, Putukian, Mackin, Julian, & Shoss, 2001). Thus, in the field of mTBI, the data are controversial and seemingly involve more diverse aspects than initially thought. Reports of subjective symptoms and results of neuropsychological assessment vary broadly, while LOC and PTA are not always present in mTBI patients. There is therefore a dire need to develop an objective assessment tool of mTBI. New neuroimaging approaches offer this opportunity.

Neuroimaging data on mTBI have, however, been controversial. Structural imaging such as computer tomography (CT) and conventional MRI (T1-weighted and T2-weighted) have essentially been inefficient to help with the diagnosis of mTBI. Other neuroimaging methods such as functional MRI (task-based MRI and resting state MRI; e.g., Chen, Johnston, Collie, McCrory, & Ptito, 2007; Mayer et al., 2015), diffusion weighted imaging (DWI) (Shenton, Price, Levin, & Edersheim, 2018), susceptibility weighted imaging (SWI; Lu, Cao, Wei, Li, & Li, 2015; Studerus-Germann, Thiran, Daducci, & Gautschi, 2016), perfusion weighted imaging (PWI; Andre, 2015; Hamer, Churchill, Hutchison, Graham, & Schweizer, 2020; Clark et al., 2020), positron emission tomography (PET) (Jensen & Lauritzen, 2019; Raji & Henderson, 2018), and single photon emission computed tomography (SPECT) (Amen et al., 2016; Romero, Lobaugh, Black, Ehrlich, & Feinstein, 2015) have shown promise, but even then the results have been mixed with a more common utilization in the research environment and a slower integration in the clinical setting due to cost and a lack of a standardization of the procedures.

With time, recovery after a single concussion tends to be complete in about 80% of cases (McCrory et al., 2009) while in the rest, individual characteristics and specifics of injury will come into play. In the latter group, many patients remain with postconcussive symptoms (PCS) months or even years post injury, with various contributing factors needing to be identified. Timely and accurate diagnosis of mTBI, with the purpose of developing more effective personalized rehabilitation strategies, along with the time course of recovery and eventual return to activity are needed. This also will contribute to a more short-term goal in the diagnosis, such as determination if a concussed subject can take an important exam or participate in a competition right after the incidence of the trauma to the best of their abilities, and if any special accommodations are needed to be provided (extensions, etc.).

Given the high incidence of this type of injury and the significant medico-legal implications of an accurate diagnosis, particularly in the realm of professional sports and insurance claims, there is a tremendous requirement for objective, clinically useful tools for the assessment of concussed patients. To date, the only objective approach that has shown consistent and reproducible results in the diagnosis of concussion is functional MRI (Chen et al., 2007; Holmes, Singh-Saluja, Chen, Gagnon, & Ptito, 2019; Saluja, Chen, Gagnon, Keightley, & Ptito, 2015). It is, however, a technique that is not widely available outside research centers while most other imaging techniques such as those mentioned above have proven more or less contributory. In essence, a multimodal approach combining multiple imaging modalities may prove to be more powerful for diagnosis than each of the modalities individually.

It is particularly relevant as mTBI can be accompanied by various underlying neuropathological alterations, such as metabolic deviations (Giza & Hovda, 2014), diffuse axonal injury and myelin loss (Johnson, Stewart, & Smith, 2013), cerebral microhemorrhages (Park et al., 2009), and changes in the cerebral blood flow (Wang et al., 2016). The presence and extent of these alterations can be discovered using different MRI sequences such as fMRI (both task-based and resting state), dMRI and myelin imaging, SWI, and ASL, respectively. Thus, only complex use of these techniques can give an extensive and comprehensive diagnosis.

In this review, we aim to describe the advantages and drawbacks of the aforementioned noninvasive MRI sequences available on a conventional MRI scanner, that may prove helpful in mTBI diagnosis. We will review articles on the topic of mTBI and concussion, published mostly throughout the past decade, to evaluate the neuroimaging

findings of fMRI, SWI, ASL, and dMRI in the different stages of mTBI, and to analyze the potential predictive ability of these neuroimaging techniques as they relate to the appearance and dynamics of PCS after a mTBI.

2 | METHODS

The studies were searched using the PubMed resource, with the filters set to the time period of the past 6 years from the moment when the paper was written (2015–2020) for task-based fMRI and rs-fMRI, and for the past 12 years (2009–2020) for ASL and SWI due to a significantly less volume of studies on the topic. The following key words were used in the search: "mTBI," "concussion," "fMRI," "resting state fMRI," "task-based fMRI," "SWI," "ASL," and "perfusion MRI." To provide a complete description of all available methods, we also included a brief overview of diffusion MRI and myelin-based imaging. Given that the scope of literature on the topic is too broad to fully review within this paper, this section was not performed using a systematic review approach.

2.1 | Task-based fMRI

Task-based fMRI has proven to be an effective tool in the diagnosis of concussion. This technique is based on blood-oxygen-level-dependent imaging (BOLD) methodology where the difference in the MR signal between deoxyhemoglobin and oxyhemoglobin are picked up and monitored using gradient echo sequences. The main processes examined by fMRI can be described as an activation of the neurons in response to the action of the stimulus and an increase in their metabolic needs which leads to local alterations in blood flow. Thus, these alterations are recorded during scanning as a BOLD signal, which measures the hemodynamic response of the brain in relation to the neural activities (Buchbinder, 2016; Buxton, 2013).

Multiple studies have demonstrated altered BOLD signal during performance of cognitive tasks in patients with concussions compared with healthy controls (HCs). Most of the recent studies have used working memory tasks (N-back) for their ease of presentation in the scanner as well as for their sensitivity to alterations in brain activity. Other tasks proven to be useful in studies on the role of fMRI in the diagnosis of mTBI are, among others, the spatial navigation task (Holmes et al., 2019; Saluja et al., 2015), the Flanker task (Sullivan, Hayes, Lafleche, Salat, & Verfaellie, 2018), the Shifted-attention Emotion Appraisal Task (SEAT; Wang et al., 2017) and the visual tracking eye movement tests (Astafiev et al., 2015).

Regarding alterations in brain activity after mTBI, the findings vary and are often controversial (Table 1). The majority of the latest studies on the topic have yielded mixed activity patterns during task performance, with an elevation of the activity in some areas and deactivation in others. These results appear in keeping with the suggested earlier explanation that higher activity in certain brain areas reflects a compensation strategy for damaged areas that show diminished activation (McAllister et al., 1999). However, there are studies demonstrating either increased or decreased activity during task-performance by mTBI patients, possibly also due to cognitive requirements of the task. The main regions showing increased fMRI activation in mTBI patients during task performance are parietal (Chen et al., 2016; Hsu et al., 2015; Mayer et al., 2015; Sullivan et al., 2018), occipital (Holmes et al., 2019; Mayer et al., 2015; Sullivan et al., 2018), and frontal lobe (Holmes et al., 2019; Hsu et al., 2015; Westfall et al., 2015) areas as well as the middle temporal gyrus (Saluja et al., 2015; Westfall et al., 2015) and cingulate cortex (Sullivan et al., 2018; Wylie et al., 2015). Decreased activation has been reported, particularly in the components of the default mode network (DMN). These involve the left (Saluja et al., 2015; Sullivan et al., 2018) and right (Chen et al., 2016) precuneus and the right dorsolateral (Saluja et al., 2015), left dorsomedial (Sullivan et al., 2018), and medial (Van der Horn et al., 2016) regions. It should be noted as well that most of the aforementioned studies were conducted in patients in the subacute phase of mTBI (<1 year postinjury).

First, in patients with mTBI compared with HCs, performance on the N-back task has been associated with altered activation in the dorsolateral prefrontal cortex (DLPFC), which has proven to be one of the major components in the working memory network in numerous studies (Barch, Sheline, Csernansky, & Snyder, 2003; Kim, Kroger, Calhoun, & Clark, 2015; Mansouri, Tanaka, & Buckley, 2009). Likewise, alterations in DLPFC activation with additional para-hippocampal involvement have been reported in two studies using the spatial navigation task (Holmes et al., 2019; Saluja et al., 2015). These findings, validated in studies using animal models, have established an involvement of direct hippocampal–prefrontal afferent pathways in the continuous updating of the task-related spatial information during spatial working memory performance. Thus, direct hippocampal–prefrontal afferents appear essential for successful encoding of task-related cues (Spellman et al., 2015).

Furthermore, the studies described above have shown in patients with mTBI abnormal activity patterns involving the precuneus (superior parietal lobule) in the execution of both the working memory (N-back) and spatial navigation tasks. These results are consistent with indications that the precuneus is associated with executive aspects of working memory (Koenigs, Barbey, Postle, & Grafman, 2009) as well as with working memory capacity (activation increases with an increase in task load; Vogel & Machizawa, 2004). Interestingly, patients with right parietal cortex lesions show a decline in spatial working memory (Koenigs et al., 2009).

Even though behavioral performance in most of the studies have not discerned between mTBI patients and HCs, some did show a correlation between brain activation and task performance. In an fMRI study using the spatial navigation task with pediatric mTBI patients, Holmes et al. (2019) revealed a difference in task performance between low-symptom and high-symptom groups and HCs: only performance of the low-symptom group was different from HCs with higher total trial times, while there was no difference between HCs and the high-symptom group. Concurrently, brain activation in the high-symptom group had greater elevation in frontal and occipital cortices compared with the low-symptom group, with additional activity in the cerebellum. These results led to the suggestion by the authors that unique

TABLE 1 Summary of mTBI studies using task-based fMRI

Author	Participants	Task	Major findings (activity alterations in mTBI patients)
Saluja et al. (2015)	15 mTBI pediatric patients, up to 3 months postinjury	Spatial navigation task	Diminished activation in the retrosplenial, thalamic, and parahippocampal areas bilaterally, along with the right dorsolateral prefrontal cortex and left precuneus; increased activation in the left hippocampus and right middle temporal gyrus.
Astafiev et al. (2015)	45 mTBI patients, 3 months to 5 years postinjury	Visual tracking tasks	Decrease in the right anterior internal capsule and right superior longitudinal fasciculus.
Hsu et al. (2015)	30 mTBI patients 1. Within 1 month postinjury 2. 6 weeks after (1)	The N-back	Increased activation of the bilateral frontal and parietal regions: In mTBI patients, decreased activation in 2-back, 1-back conditions were observed in female patients compared with female control subjects at the initial imaging study; increased activation in 2-back, 1-back conditions was observed in male patients compared with male control subjects. At the 6-week follow-up study, female patients showed persistent hypoactivation, male patients showed a regression of hyperactivation to the level of activation similar to control subjects.
Wylie et al. (2015)	27 mTBI patients 1. <72 hr post-injury 2. 1 week later	The N-back task	Changes from time 1 to time 2 showed an increase in posterior cingulate activation; activation was increased greater in those mTBI subjects without cognitive recovery; in increased workload, activation increased in cortical regions in the right hemisphere.
Mayer et al. (2015)	46 mTBI patients within 3 weeks of injury; follow-up examination 4 months postinjury	Multisensory (audiovisual) cognitive control task	Abnormal activation within different regions of visual cortex that depended on whether attention was focused on auditory or visual information streams: Increased activation within bilateral inferior parietal lobules during higher cognitive/perceptual loads. Functional abnormalities within the visual cortex and inferior parietal lobules were only partially resolved at 4 months postinjury.
Westfall et al. (2015)	19 adolescents with mTBI, 3–12 months postinjury	Auditory–verbal N-back task	Increased activation during the most difficult part of the task was observed in cluster 1 (left sublobar insula, left middle temporal gyrus, and left superior temporal gyrus), cluster 2 (left precentral gyrus and left sublobar insula), and cluster 3 (right frontal lobe subgyral region and right medial frontal gyrus).
Van der Horn et al. (2016)	55 mTBI patients, 4 weeks postinjury	The N-back task	Reduced activation within the medial prefrontal cortex; postconcussive complaints (PCC)-absent patients showed stronger deactivation of the DMN compared with PCC-present patients and HCs, especially during difficult task conditions; functional connectivity between the DMN and FEN was lower in PCC-absent patients compared with PCC-present patients.
Chen et al. (2016)	13 younger (21–30 years) and 13 older (51–68 years) mTBI patients 1. Within 1 month postinjury 2. 6 weeks after	The N-back task	Younger patients: Initial hyperactivation in the right precuneus and right inferior parietal gyrus in 2-back > 1-back conditions compared with younger HCs. Older patients: Hypoactivation in the right precuneus and right inferior frontal gyrus compared with older HCs.
Wang et al. (2017)	44 mTBI patients, within 2 weeks postinjury	Shifted-attention emotion appraisal task (SEAT)	Decreased activation in the response to fearful faces in clusters in the left superior parietal gyrus and left medial orbitofrontal gyrus, and bilaterally in the lateral orbitofrontal gyri.
Sullivan et al. (2018)	17 individuals with blast-related mTBI	Flanker task	Incongruent trials: Increased activation in the left superior parietal lobe, left dorsal anterior cingulate cortex, right supramarginal gyrus, and right lateral occipital cortex. Error trials: Greater deactivation in the areas of the default mode network including the left dorsomedial prefrontal cortex (DLPFC) and left posterior cingulate cortex, precuneus.

TABLE 1 (Continued)

Author	Participants	Task	Major findings (activity alterations in mTBI patients)
Sours, Kinnison, Padmala, Gullapalli, and Pessoa (2018)	30 mTBI patients during chronic phase	The N-back task	Decreased segregation between the DMN and task-positive networks, elevation in functional connectivity within the DMN regions.
Holmes et al. (2019)	27 mTBI pediatric patients, high-symptom and low-symptom groups	Spatial navigation task	Low-symptom group had an elevated activity in the frontal and occipital cortices; high-symptom group had broader increased activity in the frontal region and in the cerebellum.
Khetani, Rohr, Sojoudi, Bray, and Barlow (2019)	60 individuals with PPCS and 30 recovered after mTBI, ~14 years old, 38 days after mTBI	Visuospatial N-back task	Children with persistent postconcussive symptoms (PPCS) had decreased activation relative to the children with typical recovery in the posterior cingulate and precuneus during the one-back working memory condition, despite similar task performance.
Ramage, Tate, New, Lewis, and Robin (2019)	60 individuals, 3–24 months postconcussion	Constant effort task (CE)	Hyper-connectivity increased with an effort level but diminished quickly when maintaining the effort; connectivity between the left anterior insula, rostral anterior cingulate cortex, and right-sided inferior frontal regions, correlated with effort-level and state fatigue in mTBI participants.
Cook et al. (2020)	Meta-analysis of 7 studies: 174 patients, acute to subacute phase	Memory and attention tasks	Reduced activation within the right middle frontal gyrus (MFG).

symptom-dependent patterns of altered task-related brain activity occur in mTBI patients (Holmes et al., 2019). Consequently, it can be hypothesized that there is an optimal level of activation that reflects an application of compensatory strategies associated with better performance, at least in the pediatric population. In fact, previous studies have demonstrated different activation patterns in youth with mTBI. For example, Keightley et al. (2014) showed lower task-related activity in adolescents with mTBI due to an inability to involve compensatory strategies.

Overall, there is a great number of studies in mTBI patients that use task-based fMRI with a broad variety of findings. The general idea among all of them is the variability of the alterations in the BOLD signal during task performance throughout the recovery process. Thus, elevation in activity postinjury can be perceived as an involvement of compensatory mechanisms to overcome the functional deficit of affected areas until they gradually return to normal.

The fMRI has proven to be an effective tool in the diagnosis of concussion, although it has its limitations. Task-based fMRI is still more commonly in research than in clinical practice due to its complex procedures and time-consuming factors such as task development, personnel required to teach the task to the patient, time inside the scanner, and cost as well as additional equipment (screen, joy-stick, etc.). All the above have encouraged researchers to develop more accessible and simple diagnostic neuroimaging method for the mTBI population.

2.2 | Resting state fMRI

Another type of functional MRI which is broadly used in mTBI research is resting state fMRI (rs-fMRI). In recent years, studies using rs-fMRI in mTBI subjects are exceeding task-based fMRI studies, and is one of the most perspective methods for use in the diagnosis of concussion. Compared with task-based fMRI, rs-fMRI does not require special assistance during scanning, that is, a subject does not perform any tasks which they should learn prior to the procedure and no additional equipment is needed. However, significant drawback of this method for clinical use is a complexity of data processing following the scan.

Similarly to task-based fMRI, rs-fMRI is based on measuring of BOLD signal fluctuations. The rs-fMRI examines synchronous activations between spatially distinct regions to identify resting state networks (RSNs). In contrast to task-based fMRI, this method is focused on activations which are occurring in the absence of a task or stimulus (Lee, Smyser & Shimony, 2013).

A great majority of studies elucidated alterations in RSNs following concussion (Table 2). One of the main RSNs investigated in mTBI research is the default mode network (DMN). DMN is potentially associated with the consolidation of memory, working memory, processing of emotionally salient stimuli, and the interplay between emotional processing and cognitive functions (Mohan et al., 2016). Most of the recent studies showed an increase in DMN connectivity in concussed patients (Churchill, Hutchison, Graham, & Schweizer, 2018; Madhavan et al., 2019; Meier et al., 2020; Van der Horn et al., 2017), although a decreased connectivity was also noted by several authors (D'Souza et al., 2020; Iyer et al., 2019).

Additionally, task-related network (TRN), related to attention activation throughout the task performance, is studied in parallel with DMN, as one of the consequences following mTBI appears to be a disruption between DMN and TRN (Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011). Alterations in the interaction between DMN and TRN may result in poor long-term memory consolidation (Lefebvre & D'Angiulli, 2019).

Similarly, it was demonstrated that the salience network (SN) which plays a role in mediation of the balance between DMN

TABLE 2 Summary of mTBI studies using rs-fMRI

Author	Participants, time after injury	Major findings
Meier et al. (2020)	93 concussed athletes, within 24 hr postinjury	Acute increase in local connectivity was observed in a region in the right middle and superior frontal gyri (DMN).
Shafi et al. (2020)	80 individuals with postconcussion syndrome, at least 1 month postinjury	Distinct subnetwork components with hyperconnected frontal nodes and hypoconnected posterior nodes across both the salience and fronto-parietal networks were observed.
Palacios et al. (2017)	75 adult mTBI patients within 24 hr postinjury	Alterations in the connectivity of the most representative RSNs that are associated with cognitive performance at 6 months after injury.
Churchill et al. (2018)	35 athletes with acute concussion (<7 days postinjury)	A network of frontal, temporal and insular regions: Connectivity was negatively correlated with symptom severity. A network with anticorrelated elements of the default-mode network and sensorimotor system: Connectivity was positively correlated with symptom severity.
Madhavan et al. (2019)	91 adult mTBI patients (with first scanning at >3 days postinjury)	Functional connectivity was correlated with symptom severity in several regions of specific networks, including the dorsal attention, default mode, executive control, motor, visual, and salience networks. Motor, visual networks, and DMN were found to be associated strongly with symptom severity.
D'Souza et al. (2020)	65 mTBI patients within 7 days postinjury	Reduced functional connectivity in the anterior default mode network, central executive network, somato-motor and auditory network; a negative correlation between network connectivity and severity of post-concussive symptoms was observed.
Lu et al. (2019)	58 mTBI patients, >10 days postinjury	Reduced left substantia nigra (SN)-based functional connectivity with right insula and caudate and increased left SN-based functional connectivity with left precuneus and left middle occipital gyrus, and reduced right SN-based functional connectivity with left insula; abnormal functional connectivity significantly correlated with cognitive function.
Hou et al., 2019	47 mTBI patients, within 10 days postinjury	Alterations in the auditory and visual sub-networks in patients with PCS.
Iyer et al. (2019)	110 pediatric mTBI patients, 4-weeks postinjury	Decrease in connectivity within DMN, visual, and somatosensory networks, correlated with cognitive and emotional problems; increased connectivity within the limbic network, correlated with poorer sleep quality and higher fatigue.
Li et al. (2019)	55 mTBI patients within 7 days postinjury	Significantly decreased network centrality in the left middle frontal gyrus (MFG); decreased inflows from the left MFG to bilateral middle temporal gyrus, left medial superior frontal gyrus, and left anterior cingulate cortex; changes in network centrality and causal connectivity were associated with deficits in cognitive performance.
Van der Horn et al. (2017)	30 mTBI patients, 2 weeks postinjury	Minor longitudinal changes in functional connectivity within the precuneus component of DMN.

and the executive network, may be damaged as a result of concussion (Sharp et al., 2014; Sours et al., 2018). The impairment of SN leading to functional imbalances within the network appear to affect cognitive control, and particularly may diminish self-regulation of cognition, behavior and emotion (Peters, Dunlop, & Downar, 2016). Alterations in salience and fronto-parietal networks connectivity in mTBI patients were highlighted in a study by Shafi et al. (2020).

Together with this, alterations in the following other RS networks came to the attention of mTBI researchers: motor, visual, and auditory networks (D'Souza et al., 2020; Hou et al., 2019; Madhavan et al., 2019). Changes in these networks also were considered to be associated with such PCS as sensitivity to light and noise (visual and auditory networks, respectively) (Madhavan et al., 2019). In addition, it is noteworthy that most of the recent mTBI studies using rs-fMRI showed positive correlations between connectivity alterations and various PCS, including cognitive and emotional symptoms. Moreover, deviations in connectivity in the acute stage postinjury were considered as a predictive indicator of subsequent difficulties in cognitive performance (Churchill et al., 2018; Iyer et al., 2019; Li et al., 2019; Lu et al., 2019; Palacios et al., 2017).

Thus, rs-fMRI shows promising results in mTBI research, demonstrating functional changes in the brain following concussion, and having a potential for a predictive ability of later cognitive decline. Nevertheless, the complex postprocessing procedure and contradictions in findings is a major factor for this sequence not to be yet included in the clinical practice. Together with this, another significant limitation of the method which should be addressed, is an insufficient level of specificity of results the rsMRI presents. It is highly sensitive tool to detect functional alterations following concussion, however, those alterations are unspecific for mTBI. It also should be taken in consideration that studies using rsfMRI and task-based fMRI both are primarily showing the results at the group level as opposed to the individual. Even though there is a popular suggestion to use these techniques as a biomarker of concussion it is not used at the individual level and for a potential development in this direction it requires larger scope of normative data.

2.3 | Perfusion MRI

Perfusion MRI or PWI is performed by other types of MRI methods: dynamic susceptibility contrast (DSC), dynamic contrast-enhanced imaging (DCE), and arterial spin-labeling (ASL). DSC and DCE are invasive, and a gadolinium-based contrast is used in these sequences. However, in this review we only consider ASL, a noninvasive perfusion MRI sequence which has been used to measure cerebral blood flow (CBF) in mTBI patients and to demonstrate significant alterations related to symptoms in the acute phase (Wang et al., 2016).

One of the major features of ASL is the possibility of broader use given its safety and noninvasive nature. The main mechanism of ASL is magnetic labeling of the arterial blood water protons with the purpose of exploiting it as an endogenous tracer. Cerebral blood flow (CBF) is the variable most typically evaluated in ASL (De Havenon et al., 2017).

CBF alterations during the acute and subacute phases of mTBI were detected in numerous studies using SPECT (Gowda et al., 2006) and perfusion computed tomography (PCT) (Metting, Spikman, Rödiger, & van der Naalt, 2014). Nevertheless, the main benefit of ASL in comparison to SPECT to PCT is the absence of ionizing radiation and the possibility it offers for repeating scanning and tapping recovery.

ASL measurements can be divided into two groups of resulting values: absolute (aCBF) and relative CBF (rCBF). The aCBF values correspond to the perfusion level of the region of interest (ROI) independently of other regions, while rCBF values show the changes in the ROI relative to other brain regions. Consequently, rCBF is more sensitive to focal CBF abnormalities whereas aCBF values address the brain as a whole (Aracki-Trenkic et al., 2020).

Several studies (Table 3) showed contentious results regarding alterations of CBF in mTBI, questioned CBF as a valid biomarker in concussions and called for further investigation. Most of the studies using ASL demonstrated a decrease in blood flow up to 1 month after concussion (Lin et al., 2016; Meier et al., 2015; Peng et al., 2016; Wang et al., 2015) with a global decrease in aCBF particularly in the bilateral frontal and left occipital cortices (Lin et al., 2016) and in the bilateral frontotemporal lobes (Wang et al., 2015). Decrease in rCBF was demonstrated in the right insular and superior temporal cortex (Meier et al., 2015) and in the bilateral thalami (Bartnik-Olson et al., 2014). Hamer et al. (2020) also showed diminished CBF bilaterally in temporal areas only in males with chronic mTBI (Hamer et al., 2020). The earlier study by Ge et al. (2009) showed decreased CBF within the thalamus in mTBI patients (Ge et al., 2009). The most recent article on the effect of multiple mTBIs using ASL showed that history of more than three concussions causes a decrease in aCBF throughout a life span and can lead to an increased risk factor for Alzheimer's disease (Clark et al., 2020).

In addition, various studies showed a correlation between CBF alterations and cognitive decline. Bai et al. (2019) demonstrated that concussed males had a decrease in aCBF in the subacute phase of mTBI compared with healthy males; at the same time, lower aCBF in the posterior parietal cortex was associated with worse cognitive performance (Bai et al., 2019). Also, a decrease in CBF correlated with lower cognitive assessment scores in athletes with sport-related concussion (SRC) 24–48 hr postinjury (Wang et al., 2019).

In contrast, other findings showed an increase in CBF in mTBI (Doshi et al., 2015; Liu et al., 2016; Stephens, Liu, Lu, & Suskauer, 2018) as well as an absence of alterations (Militana et al., 2016). Doshi et al. (2015) revealed an increase in rCBF up to 10 days after mTBI in the frontal lobes, occipital lobes, and left striatum, in contradiction with the studies described above. The study by Stephens et al. (2018) examined teenage athletes 2–6 weeks postinjury. Compared with controls, rCBF was increased after 2 weeks in the left dorsal anterior cingulate cortex (ACC) and left insula than controls. After 6 weeks, higher rCBF persisted only in the left dorsal ACC. Elevation of rCBF in the left dorsal ACC was higher in athletes with physical symptoms 6 weeks postinjury compared with asymptomatic athletes and HCs (Stephens et al., 2018). Interestingly, Stephens et al. (2018) and Brooks et al. (2019) showed elevation of rCBF in the cingulate cortex in concussed youths. It was suggested that an increase in CBF in mTBI patients can represent "a neuroprotective response in an effort to meet the metabolic demands of the tissue during a time of injury" (Williams & Danan, 2016).

In addition, an ASL-fMRI study of mental fatigue during performance of a psychomotor vigilance test by patients in the acute and chronic phases of mTBI showed that those in the acute phase (within 2 weeks after injury) showed greater CBF in "bottom-up" and "top-down" attention areas (PFC, right inferior parietal lobe, anterior cingulate cortex, bilateral basal ganglia, and thalamus) than the HCs, even though the behavioral performances did not differ significantly; at the same time, there was lower CBF in the DMN. A comparison of the acute and chronic phases showed that patients in the chronic phase (12 months postinjury) had higher CBF in the anterior cingulate, middle frontal gyrus, and inferior frontal gyrus, and lower CBF in the precuneus, extending to PCC, paracentral lobule, and inferior parietal lobule, a result consistent with partial recovery (Liu et al., 2016).

Interesting recent findings were presented by Churchill, Hutchison, Graham, and Schweizer (2017) and Barlow et al. (2017). In the first study, increased aCBF was initially seen in the first 3 days

TABLE 3 Summary of mTBI studies using perfusion MRI (ASL)

Author	Method of CBF detection	Time after injury (acute vs. subacute vs. chronic phase)	Type of alterations in CBF	Major findings (CBF alterations in mTBI patients)
Ge et al. (2009)	ASL-MRI 3T	Chronic (∼24 months)	Decrease	Reduced CBF in the bilateral thalami.
Bartnik-Olson et al. (2014)	PWI	3–12 months[a]	Decrease	Reduced rCBF in the bilateral thalami.
Doshi et al. (2015)	ASL	3 hr to 10 days	Increase	Increase in the left striatum, frontal, and occipital lobes.
Meier et al. (2015)	ASL-MRI	1 day, 1 week, and 1 month	Decrease	Decrease in the right insula and superior temporal cortex resolved by 1 month, decrease in the dorsal midinsular cortex persisted at 1 month postconcussion.
Liu et al. (2016)	ASL-fMRI	Subacute (within 2 weeks) and chronic (>12 months)	Increase/ decrease	Acute phase: Increase in the right middle frontal gyrus and inferior frontal cortex, right inferior parietal lobe, anterior cingulate cortex, left superior frontal gyrus, bilateral basal ganglia, and thalamus. Chronic phase: Increase in the anterior cingulate, middle frontal gyrus, and inferior frontal gyrus, and lower CBF in precuneus, extending to PCC, paracentral lobule, and inferior parietal lobule; decrease in DMN in both phases.
Wang et al. (2016)	ASL-MRI	Acute (within 24 hr)/ subacute(after 8 days)	Decrease	Decrease in the bilateral frontal and temporal area within 24 hr and greater decrease after 8 days.
Lin et al. (2016)	3D pulse continuous ASL-MRI	Within 1 month	Increase/ decrease	Decrease in the bilateral frontal and left occipital cortex, in more severe symptoms—higher CBF in the bilateral frontal and left occipital lobes.
Barlow et al. (2017)	Pseudo continuous ASL-MRI	40 days	Increase/ decrease	Global CBF was higher in the bilateral inferior frontal and occipital regions in the symptomatic group and lower in the inferior temporal and parietal regions asymptomatic group compared with controls.
Churchill et al. (2017)	2D pulsed ASL-MRI	7 days	Increase/ decrease	Greater total symptom severity—elevated posterior cortical CBF; greater cognitive symptoms—lower frontal and subcortical CBF.
Stephens et al. (2018)	Pseudo-continuous ASL	2 and 6 weeks[a]	Increase	2 weeks: Increased rCBF in the left dorsal anterior cingulate cortex (ACC) and left insula than controls. 6 weeks: Higher rCBF persisted in the left dorsal ACC. Elevation of rCBF in the left dorsal ACC was higher in athletes with physical symptoms 6 weeks postinjury compared with asymptomatic athletes and HCs.
Bai et al. (2019)	3-D ASL-MRI	>1 month	Increase	Increased CBF in the posterior parietal cortex, only in males.
Hamer et al. (2020)	2D pulsed ASL-MRI	Chronic (and multiple)	Decrease	Lower CBF bilaterally in temporal area, only in males.
Wang et al. (2019)	ASL-MRI	Within 24–48 hr	Decrease	Decrease in the left inferior parietal lobule (IPL), right supramarginal gyrus (SMG), right middle frontal gyrus (MFG), posterior cingulate cortex, left occipital gyrus, and thalamus.
Brooks et al. (2019)	3D pseudo-continuous ASL	Chronic (>6 months)[a]	Increase/ decrease	Increase in anterior frontal/temporal regions, decrease in posterior and inferior regions.

[a]Youth and pediatric groups.

posttrauma followed by a decrease on days 5–7 (Churchill et al., 2017). The second study showed higher aCBF in symptomatic concussed children and lower aCBF in asymptomatic concussed children (scanning of both groups was made about a month after concussion; Barlow et al., 2017). A mixed pattern of alterations in rCBF was also demonstrated in the study by Brooks et al. (2019) in concussed youths. The study showed elevation in the anterior frontal and temporal regions, whereas the posterior and inferior regions had diminished rCBF (Brooks et al., 2019).

Even though the findings are conflicting, and no consensus is reached so far, study involving another method of perfusion MRI, such as dynamic susceptibility contrast-enhanced perfusion-weighted imaging (DSC PWI), showed the results in favor of the decrease in CBF following concussion (Liu et al., 2013). Additionally, a review on various perfusion imaging methods (CT perfusion, MR perfusion, and SPECT) concluded that blood flow and blood volume postconcussion tend to be reduced, mostly in frontal and temporal lobes (Yuh, Hawryluk, & Manley, 2014).

Overall, the application of ASL has been growing for the past years yielding encouraging results, but its drawbacks remain: lower signal difference (compared, e.g., to BOLD) (Detre & Wang, 2002), poor temporal resolution (Liu & Brown, 2007), and necessity of the complex subtraction procedure (Golay, Hendrikse, & Lim, 2004). Still, these disadvantages can be partially resolved using parallel imaging (Deshmane et al., 2012) and pseudocontinuous labeling (Dai, Garcia, De Bazelaire, & Alsop, 2008; Haller et al., 2016). The ASL method offers advantages such as stability over time and less variability across subjects (compared with BOLD), making it particularly useful for longitudinal studies in mTBI and other neurological disorders (Brown, Clark, & Liu, 2007). Considering the numerous mTBI studies with perfusion MRI, ASL used together with other MRI modalities, carries a high potential and may be part of novel methods of diagnosing concussion in the clinical setting.

2.4 | Susceptibility weighted imaging

Along with ASL, SWI is getting increasingly recognized in the diagnosis of mTBI. SWI, being a fully flow-compensated three-dimensional (3D) gradient echo (GRE) sequence, is particularly sensitive to microhemorrhages, venous blood and iron levels. Currently, SWI is considered the most promising technique for microbleeds identification, showing up to five times more precise results than such methods as GRE or echo-planar imaging (EPI) (Benedictus et al., 2013; Sepehry, Lang, Hsiung, & Rauscher, 2016). Thus, SWI may be useful in showing cerebral microbleeds following concussion.

The SWI sequence is especially focused on the detection of the intravascular venous deoxygenated blood and extravascular blood products (Haacke, Mittal, Wu, Neelavalli, & Cheng, 2009; Reichenbach, Venkatesan, Schillinger, Kido, & Haacke, 1997). The main principle of this technique is an exploitation of the magnetic property of iron, particularly within different states of hemoglobin, which causes magnetic field distortion affecting both T2* relaxation times and phase data (Toth, 2015). Both magnitude and phase information are necessary to generate proper tissue characterization, and they are merged together to create an SWI image (Haacke, Xu, Cheng, & Reichenbach, 2004). Hemorrhages are detected by dephasing of the signal caused by paramagnetic blood products, for example, deoxyhemoglobin in acute hematomas has a strong paramagnetic effect and leads to a significant signal loss on SWI (Kirov, Whitlow, & Zamora, 2018).

Despite being less effective for delineating anatomical structures because of its low contrast (Toth, 2015), SWI appears to be the most precise for detection of hemorrhages among other MRI modalities (CT, etc.). However, there are posttrauma time limitations for SWI diagnosis to be accurate. Hyperacute hemorrhages (<12 hr after the incident) cannot be spotted by SWI as at this time period the oxyhemoglobin lacks unpaired electrons, which yields to weak diamagnetic characteristics which results in unaffected SWI dephasing. Nonetheless, in the acute phase, the oxyhemoglobin is transformed into deoxyhemoglobin when oxygen molecules are released from blood particles, thus causing the paramagnetic effect that affects signal loss (Ong & Stuckey, 2010).

Together with this, SWI is used for quantitative susceptibility mapping (QSM). QSM is an MRI technique for quantifying the spatial distribution of magnetic susceptibility within biological tissues (Liu, Ghimire, Pang, Wu, & Shi, 2015). Specifically, QSM is used to measure cerebral SVO_2 (mixed venous oxygen saturation) (Doshi et al. (2015)), as well as to assess deep gray matter iron (Koch et al., 2021) and the role of myelin in white matter after mTBI (Weber et al., 2018). In study by Chai et al. (2017), the decreased susceptibility of the straight sinus appeared to correlate with PCS, and with a recovery to normal levels of oxygenation over time. Moreover, increased global white-matter susceptibility and decreased in global subcortical gray matter susceptibility were observed in mTBI patients (Koch et al., 2021). In addition, prognostic ability of QSM method was underlined by several authors (Koch et al., 2021; Weber et al., 2018).

We are considering SWI in this review as it proved to be a valid method for detecting one of the signs of mTBI—microhemorrhages, in keeping with reports from multiple studies (Beauchamp & Anderson, 2013; Steenerson & Starling, 2017). Detection of microhemorrhages in the early stages of mTBI can contribute to outcome prediction in the presence of PCS (Beauchamp et al., 2011; Geurts, Andriessen, Goraj, & Vos, 2012). Furthermore, SWI can be performed on conventional scanners, which makes this method highly applicable within the clinical setting.

Microbleeds are a marker of a traumatic axonal injury (TAI), a specific sign of mTBI. TAI has been demonstrated in mTBI patients in postmortem autopsies (Bigler, 2004), and its extent is an important prognostic factor in the development of cognitive decline and neuropsychiatric disability (Medana & Esiri, 2003). Einarsen et al. (2019) also showed that signs of TAI lesions remain on SWI scans at 3 and 12 months postinjury (Einarsen et al., 2019).

In one recent trauma study, microbleeds in brain tissue detected by SWI in the acute phase predicted worse cognitive decline and persistent PCS in concussed patients (Studerus-Germann et al., 2018). The same study compared efficacy of SWI and DTI in prediction ability of worse outcome. It showed that exploitation of the SWI technique in

TABLE 4 Summary of mTBI studies using SWI

Author	Participants, acute vs. chronic phase	Major findings
Park et al. (2009)	21 mTBI patients without any parenchymal hemorrhage on conventional MRI, within a week after admission	Microbleeds were located more frequently in white matter than in deep nucleus. Lesions were observed in the frontal lobe, occipital lobe, and brain stem.
Hasiloglu et al. (2011)	21 amateur boxers	Microhemorrhages were detected only in 2 of 10 patients.
Wang et al. (2014)	200 mTBI patients, 2 hr to 3 days postinjury, with follow-up testing (on presence of depressive symptoms) 1 year after	Depressive group had greater the number and volume of microbleeds than nondepressive group, particularly in the frontal, parietal, and temporal lobes.
Liu et al. (2013)	63 MTBI patients at least 3 days after injury, and follow-up testing on PCS after 7–15 months	Significant correlation was found between PCS and number of intracranial microbleeds.
Lu et al. (2015)	39 patients with mTBI, 6 months after injury	Significantly higher angle radian values were observed in the head of the caudate nucleus, the lenticular nucleus, the hippocampus, the thalamus, the right substantia nigra, the red nucleus, and the splenium of the CC.
De Haan, de Groot, Jacobs, and van der Naalt (2017)	127 individuals with mTBI (63 with MRI abnormalities and 64 without), chronic phase	Microhemorrhages were predominantly present in the frontal and temporal lobes. Worse outcome was demonstrated in 67% of the group with MRI abnormalities with a significant association of the total number of microhemorrhages in the temporal cortical area.
Trifan, Gattu, Haacke, Kou, and Benson (2017)	180 subjects with persistent neurobehavioral symptoms following head trauma (83% classified as mTBI), chronic phase (~29 months postinjury)	28% of the 180 TBI cases revealed hemorrhages.
Studerus-Germann et al. (2018)	30 mTBI patients tested at the baseline and 12 months postinjury	Amount of microbleeds in the acute phase correlates positively with cognitive symptoms such as slowing, difficulty in memory and concentration.
Einarsen et al. (2019)	194 mTBI patients, 72 hr, 3 months, and 12 months postinjury	TAI lesions in the lobar WM, CC, brainstem, basal ganglia, and thalamus, in 19% of participants after 3 months and in 16% after 12 months.

the acute phase of mTBI is more effective while, in contrast, DTI would be more practical in later phases (considering that DTI did not reveal any alterations in structural integrity 1 week after injury, but demonstrated significant changes after 1 year). Another study (Liu et al., 2015) investigated residual iron deposition as a marker of prior microbleeds; patients with persistent PCS showed a higher rate of microhemorrhages than mTBI patients who completely recovered.

Various articles on SWI in mTBI (Table 4) demonstrated that several brain areas typically affected by microbleeds are associated with a negative outcome. Wang et al. showed that microhemorrhages in frontal, parietal and temporal lobes predicted the presence of depression 12 months after the trauma (Wang et al., 2014). De Haan et al. also revealed in their study of the chronic phase of mTBI the presence of microbleeds in frontal and temporal areas. However, the unfavorable functional outcome was correlated with the presence and extent of the microhemorrhages only in temporal cortical areas. The study also showed that no microhemorrhages were found in the thalamus and internal capsule (De Haan et al., 2017). The earlier study showed that microbleeds in mTBI were more frequently found in white matter than in deep nuclei (Park et al., 2009). Together with this, it was emphasized that traumatic cerebral microbleeds in general were associated with lower scores on the GCS (1 day after injury) and Glasgow Outcome Scale (GOS) (1 year after injury) (Park et al., 2009).

In contrast, the mTBI study in the chronic phase by Lu et al. showed alterations in angle radian values (which could indicate excessive iron deposition to some extent) predominantly in gray matter (Lu et al., 2015). Higher angle radian values were found in the head of the caudate nucleus, the lenticular nucleus, the hippocampus, the thalamus, the right substantia nigra, the red nucleus, and the splenium of the corpus callosum in patients with mTBI. Additionally, performance on the Mini-Mental State Examination (MMSE) by mTBI patients correlated negatively with the angle radian values in the right substantia nigra, suggesting that this area is related to persistent cognitive decline in patients with chronic mTBI (Lu et al., 2015).

SWI is an appealing method in mTBI research and it has a great number of benefits (some of them are mentioned above). Additionally, SWI is so far the only MRI method which has diagnostic potential, whereas the other techniques have so far only provided results at the group level. However, there is only a limited number of studies on the topic and findings have raised various questions with contradictory findings. Trifan et al. showed that SWI is not effective with mild TBI, although it shows increased sensitivity for moderate and severe TBI (Trifan et al., 2017). Study by Jarrett et al. (2016) also did not show presence of microhemorrhages in mTBI patients. In addition, SWI is not effective in the hyperacute phase of mTBI (Ong & Stuckey, 2010). Nevertheless, the studies mentioned above still demonstrate promising results. Thus, further investigation using SWI is required to reach a consensus and to identify the best way to apply this technique for diagnosing mTBI in the clinical setting.

2.5 | Diffusion MRI

In diffusion MRI (dMRI), the MRI signal is sensitized to the diffusion of water molecules by using field gradients (Mori & Zhang, 2006). These field gradients cause a signal loss from water molecules that travel along the respective gradient direction. In unobstructed environments, water molecules move around freely, resulting in strong signal loss in the presence of such diffusion gradient, relative to a reference scan that is acquired without a diffusion gradient. In tissue such as white matter, the displacement of water is larger along the axon direction than perpendicular to the axon. Therefore, the signal reduction is stronger in the presence of a diffusion gradient that is applied along the axon direction compared with a gradient perpendicular to the axon (Beaulieu, 2002). Acquiring multiple scans with diffusion gradients along different directions can therefore be used to probe the microstructure and overall architecture of biological tissues.

Once these measurements are obtained, the dMRI signal is modeled. The best-known approach is to model water diffusion through the use of a tensor. This approach, called diffusion tensor imaging (DTI), models water diffusion as a 3D Gaussian, described by three eigenvectors and their corresponding eigenvalues (Mori & Zhang, 2006). These parameters can then be used to build measures that describe water diffusion, such as fractional anisotropy (FA, defined as the normalized variance of eigenvalues, measures how elongated the tensor is), axial diffusivity (AD, defined as the largest eigenvalue), radial diffusivity (RD, defined as the average of the second and third eigenvalues), and mean diffusivity (MD, defined as the average of all three eigenvalues) (Mori & Zhang, 2006). Investigations using animal models have shown how certain microstructural alterations can influence these tensor measures (Budde, Janes, Gold, Turtzo, & Frank, 2011; Sun et al., 2006).

Given its relatively high accessibility and ease of use, DTI has been extensively used to study white matter neuropathologies in individuals with TBI (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013; Manning et al., 2017). A 2013 review of over 100 DTI studies of TBI found that an overwhelming majority reported decreased FA in the corpus callosum of participants with mTBI, demonstrating the high sensitivity of this measure for white matter damage (Hulkower et al., 2013). However, FA, and DTI in general, have important limitations. The classical tensor-based measures rely on the mathematical assumption of DTI that every voxel contains a single homogeneous orientation of water diffusion, which often implies a single predominant fiber orientation (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2013; Jones, Knösche, & Turner, 2013). In contrast, recent work suggests that over 90% of voxels in the white matter contain fibers that are heterogeneously oriented (Jeurissen et al., 2013). Any form of microstructural heterogeneity, whether it is from fiber configuration (e.g., crossing, kissing, fanning, or converging fibers), myelination, or pathology (loss of axons, edema, and microglial infiltration), will not be adequately discerned by a tensor. As a result, whereas FA can readily detect white matter damage in the context of mTBI (Hulkower et al., 2013), it cannot be used to discern between different forms of white matter neuropathology because of poor specificity (Dodd, Epstein, Ling, & Mayer, 2014; Guberman, Houde, Ptito, Gagnon, & Descoteaux, 2020). In a more recent review of DTI studies of mTBI, Dodd et al. (2014) focused on injuries in the subacute period of recovery, when multiple different pathologies (each with differing, sometimes contradictory impacts on the dMRI signal) overlap. They found that the trend of FA change was inconsistent, with an equal number of studies showing lower FA in participants with mTBI compared with healthy controls as studies showing higher FA in patient groups.

In recent years, novel modeling techniques have addressed this limitation. These techniques aim to bypass the assumptions of the tensor model to account for microstructural heterogeneity (Descoteaux, Deriche, Knosche, & Anwander, 2008; Tournier, Calamante, & Connelly, 2007; Wedeen et al., 2008; Zhang, Schneider, Wheeler-Kingshott, & Alexander, 2012). Of note, constrained spherical deconvolution (CSD) is particularly promising. This technique assumes that the measured diffusion signal can be estimated from a convolution between a true distribution of axonal fibers and a fiber response function, that is, a description of how the diffusion signal behaves in voxels containing homogeneous fibers. This fiber response function can be estimated by fitting a tensor in voxels that are known to contain homogeneous fibers, such as deep within the corpus callosum. By performing the opposite computation, that is, deconvolving the fiber response function from the measured diffusion signal, CSD estimates the underlying fiber orientations, giving rise to a fiber orientation distribution function (fODF). Compared with the tensor and other alternatives, the fODF can discern multiple fiber orientations, even at small angles of crossing (Descoteaux et al., 2008; Tournier et al., 2007). In addition, by representing fibers instead of water diffusion, the fODF gives rise to a measure called apparent fiber density (AFD), which has been shown to be more specific to axonal density. Further, because the fODF is orientation-specific, AFD can be computed for a specific fiber orientation, giving rise to a sub-voxel scale called the fiber element, or *fixel* (Raffelt et al., 2012). Raffelt et al. (2012) studied patients with amyotrophic lateral sclerosis (ALS) and found that FA in regions where the corticospinal tract crosses with the corpus callosum appeared to paradoxically increase in patients compared with healthy controls. Raffelt et al., however, found that AFD along fixels defined by the corticospinal tract was lower in ALS patients, more accurately reflecting their axonal loss (Raffelt et al., 2012).

Studies are increasingly applying novel dMRI approaches to study mTBIs. A prior study from our group applied CSD on a sample of concussed youth in the subacute stage of recovery. We found patterns suggestive of diverse neuropathologies in the concussed group, with one thalamo-prefrontal tract displaying a pattern of change in diffusion measures suggestive of myelin structure alterations, and a cingulo-prefrontal tract displaying a pattern of change in diffusion measures suggestive of axonal density loss (Guberman et al., 2020). Another recent study used neurite orientation dispersion and density imaging (NODDI), another novel modeling approach, to investigate white matter microstructure early after injury and later in recovery in a sample of concussed adults. They found early increases in free water fraction, thought to be reflective of edema, and later decreases in neurite density, thought to be reflective of axonal loss (Palacios et al., 2020) and myelin density decrease (Jespersen

et al., 2010). These studies reflect how novel dMRI techniques have the potential to disambiguate between different concurrent white matter neuropathologies.

3 | CONCLUSION

There are numerous neuroimaging methods in mTBI research which have been progressively developed over the last decade. However, these methods remain incomplete for application in the clinical environment and they require further research and standardization of the diagnostic procedure. With task-based fMRI, SWI, ASL, and dMRI, prevalent patterns of the affected areas can be identified after the trauma (see Table 5). Most of studies discuss white matter abnormalities, especially in PFC (DLPFC in particular) and in the corpus collosum while others also include changes in posterior cortical regions. At the same time, a series of papers have demonstrated gray matter alterations postconcussion, primarily in the thalami and hippocampi. From

TABLE 5 Summary of locations of detected neuropathological alterations in mTBI patients

Modality	Type of neuropathological alterations detected in mTBI patients	Location
Task-based fMRI	Abnormal cortical activity (alterations of a BOLD signal, which measures the hemodynamic response of the brain in relation to the neural activities)	*Spatial navigation task*: Right DL-PFC, left hippocampus, left precuneus, retrosplenial, thalamic, and parahippocampal areas bilaterally *Visual-tracking tasks*: Right anterior internal capsule and right superior longitudinal fasciculus (Astafiev et al., 2015) *Multi-sensory cognitive control task*: Visual cortex and inferior parietal lobules (Mayer et al., 2015) *N-back*: Bilateral frontal and parietal regions, posterior cingulate activation, medial prefrontal cortex, left sublobar insula, left middle/superior temporal gyrus, and precuneus (Chen et al., 2016; Khetani et al., 2019; Sours et al., 2018; Van der Horn et al., 2016; Westfall et al., 2015; Wylie et al., 2015) *SEAT*: Left superior parietal gyrus and left medial orbitofrontal gyrus, and lateral orbitofrontal gyri bilaterally (Wang et al., 2017) *Flanker task*: Left superior parietal lobe, left dorsal anterior cingulate cortex, right supramarginal gyrus, and right lateral occipital cortex (Sullivan et al., 2018) *CE*: Left anterior insula, rostral anterior cingulate cortex, and right-sided inferior frontal regions (Ramage et al., 2019)
Resting-state fMRI	Abnormal cortical activity (alterations of a BOLD signal, which measures the hemodynamic response of the brain in relation to the neural activities)	DMN, SN, fronto-parietal (FPN) dorsal attention, executive control, motor, visual, somato-motor, somatosensory, auditory, and limbic networks (Churchill et al., 2018; D'Souza et al., 2020; Hou et al., 2019; Iyer et al., 2019; Li et al., 2019; Lu et al., 2019; Madhavan et al., 2019; Meier et al., 2020; Shafi et al., 2020)
ASL	Alterations in CBF	Frontal cortex, middle frontal gyrus, and inferior frontal gyri, thalamus, inferior parietal lobule, anterior cingulate cortex, temporal cortex bilaterally, and left occipital cortex (Bai et al., 2019; Barlow et al., 2017; Bartnik-Olson et al., 2014; Brooks et al., 2019; Churchill et al., 2017; Doshi et al., 2015; Hamer et al., 2020; Lin et al., 2016; Liu et al., 2016; Meier et al., 2015; Stephens et al., 2018; Wang et al., 2016; Wang et al., 2019)
SWI	Cerebral microbleeds	Frontal lobe, temporal lobe, brain stem, the thalamus, CC, occipital lobe, parietal lobe, head of the caudate nucleus, the lenticular nucleus, the hippocampus, the right substantia nigra, the red nucleus, and basal ganglia (De Haan et al., 2017; Einarsen et al., 2019; Hasiloglu et al., 2011; Liu et al., 2013; Lu et al., 2015; Park et al., 2009; Studerus-Germann et al., 2018; Trifan et al., 2017; Wang et al., 2014)
DWI	Damaged white matter pathways	CC (Hulkower et al., 2013)
Myelin-specific imaging	Alterations in myelin density and structure	CC, right posterior thalamic radiation, left superior corona radiata, left superior longitudinal fasciculus, and left posterior limb of the internal capsule, bilateral basal ganglia, left corticospinal tract, and left anterior and superior temporal lobe(Spader et al., 2018; Wright et al., 2016)

a cognitive perspective, mTBI is correlated with poorer executive functions and difficulties with memory, attention, and learning, all of which can be explained by the underlying functional decline in the affected brain areas.

The benefits and drawbacks of the methods enumerated in this review and the absence of a universal diagnostic neuroimaging method suggests a need for the adoption of a multimodal approach to the neuroimaging of mTBI. Multimodality does not only require the use of various imaging techniques, but also the adoption of more sophisticated statistical approaches, capable of combining these different modalities and extracting the most relevant information from them (Guberman et al., 2021; Manning et al., 2019). FMRI is an effective method in the diagnosis of concussion but it is expensive and time-consuming making it difficult for regular use in everyday practice. The dMRI is primarily used for the detection of white matter abnormalities, especially axonal injury, specific for mTBI; myelin imaging is focused on changes in myelin density and structure; SWI allows detection of microbleeds in the brain, and ASL is an alternative to the BOLD method with its ability to track cerebral blood flow alterations. Taken together, these methods with their underlying functional and structural features can contribute to a deeper understanding of mTBI mechanisms from different angles making a comprehensive diagnosis of mTBI feasible for the clinician.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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