BOLD Alterations in Working Memory after Mild Traumatic Brain Injury versus Concussion: A fMRI Study

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Abstract

Mild traumatic brain injury (mTBI) and concussion are terms that are often used interchangeably. A lack of uniformity between their definitions, however, has created controversies across disciplines. With the concussion definition, developed by the Concussion in Sport Group (CISG), patients do not need to present with one of the objective clinical signs after head injury (e.g., loss of consciousness), but instead only post-concussive symptoms (PCS), whereas they are essential for the mTBI definition created by the World Health Organization (WHO). The discrepancy between the definitions has generated diagnostic challenges when PCS are present and patients lack the hallmark features of mTBI. Through use of task-based functional magnetic resonance imaging (fMRI), this study aimed to determine if mTBI and concussion are distinct diagnostic entities, or if they should be considered synonymous. We recruited patients who fit the WHO criteria of mTBI, patients who fit the CISG definition of concussion without the mTBI criteria, and healthy controls. Using a verbal working memory task, we compared task performance and fMRI blood-oxygen-level-dependent (BOLD) signal changes between groups. Whole-brain analysis of fMRI activations revealed differences in altered activations patterns between the concussion and mTBI groups, despite performing as well as the control group on the task. Specifically, the mTBI group showed significantly reduced BOLD signal changes in prefrontal, insular, and parietal brain regions when compared to the concussion and control groups. Furthermore, the concussion group had additional increases in activity outside the regions of interest, in the left medial frontal gyrus, left frontal eye fields, right globus pallidus, right caudate, and left fusiform gyrus, which was not seen in the control group. Both patient groups also presented with abnormal activations in our regions of interest, but these atypical activation patterns could not be attributed to post-concussion symptom scale

(PCSS) score. It seems that while there are functional abnormalities seen in concussion, these alterations differ from those seen in mTBI. We may therefore need to consider TBI on a spectrum, with concussion being less severe than mTBI. These results demonstrate that it may be inappropriate to combine mTBI and concussion under one banner, with important implications in both clinical and research settings.

Résumé

Les termes traumatisme craniocérébral léger (TCCL) et commotion cérébrale sont utilisés de façon interchangeable. Cependant, l'absence d'une définition uniforme entre les deux a créé des controverses interdisciplinaires. En ce qui concerne la définition de la commotion cérébrale, développée par le Concussion in Sport Group (CISG), les patients ne sont pas requis de présenter l'un des signes cliniques objectifs après un traumatisme crânien (par ex., une perte de conscience), mais uniquement des symptômes post-commotionnels; cependant, ceux-ci sont essentiels pour la définition du TCCL créée par l'Organisation mondiale de la santé (OMS). Cette différence entre les définitions a engendré des défis diagnostiques lorsque les symptômes post-commotionnels sont présents mais que les patients n'ont pas les caractéristiques du TCCL. Grâce à l'utilisation de l'imagerie par résonance magnétique fonctionnelle (IRMf), la présente étude vise à déterminer si le TCCL et la commotion cérébrale sont des entités diagnostiques distinctes, ou s'ils doivent être considérés uniformément. Nous avons recruté des patients qui rencontraient les critères de l'OMS pour le TCCL, des patients qui correspondaient à la définition de la commotion cérébrale sans les critères du TCCL du CISG et des sujets témoins. À l'aide d'une tâche de mémoire de travail, nous avons comparé les performances et les patrons d'activation IRMf entre les groupes. L'analyse des activations de l'IRMf a révélé des différences

dans les patrons d'activation entre les groupes commotion cérébrale et TCCL, malgré des performances comparables à celles du groupe témoin. Plus précisément, le groupe TCCL a montré des changements de signaux significativement réduits, dans les régions cérébrales préfrontale, insulaire et pariétale, par rapport aux groupes commotion cérébrale et témoins. De plus, le groupe commotion cérébrale montrait des augmentations supplémentaires d'activité en dehors des régions d'intérêt, dans le gyrus frontal médial gauche, les champs oculaires frontaux gauches, le pallidum droit, le caudé droit et le gyrus fusiforme gauche, non observées chez le groupe témoin. Les deux groupes de patients présentaient des activations anormales dans nos régions d'intérêt, mais ces patrons d'activation atypique ne pouvaient être mis en relation avec le score à l'échelle des symptômes post-commotionnels. Il semble que s'il existe des anomalies fonctionnelles observées à la suite d’une commotion cérébrale, celles-ci sont différentes de celles observées après un TCCL. Conséquemment, il serait plus approprié de placer les traumatismes cérébraux sur un spectre, la commotion cérébrale étant moins grave que le TCCL. Ces résultats démontrent donc qu'il est inapproprié de combiner le TCCL et la commotion cérébrale sous la même bannière de telle sorte que cela aura des implications importantes dans les contextes cliniques et de recherche.

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Contribution of Authors

This thesis includes one manuscript written to be submitted for publication. I am the first author, along with contributions from Dr. Jen-Kai Chen, Ekaterina Lunkova, Joelle Amir, Dr. Alain Ptito, and Dr. Rajeet Singh Saluja.

Sarah McCabe: study design, subject recruitment, subject testing, data compilation and analysis, manuscript preparation, manuscript revision

Jen-Kai Chen: study design, manuscript revision

Ekaterina Lunkova: subject recruitment, subject testing, manuscript revision

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Rajeet Singh Saluja: study design, supervision, funding, manuscript revision

Chapter 1: Introduction.

Traumatic brain injuries (TBIs) are among one the most common neurological conditions (Ontario Neurotrauma Foundation, 2018a), with 3-4 million new cases each year in the United States alone (Coronado et al., 2012), and over 50 million worldwide (Maas et al., 2017). While TBIs can vary in severity, mTBI accounts for upwards of 80% (Ruff et al., 2009). As many individuals consult community-based primary care providers days after the injury or seek no care at all (Greenwald et al., 2012; McCrory et al., 2017; Ruff et al., 2009), the 1998 National Institute of Health (NIH) Consensus statement concluded that mTBI is underdiagnosed (National Institutes of Health, 1998). We can thus deduce that mTBI is a vast, but insufficiently recognised, public health concern.

Previous studies have found that 15-25% of individuals with mTBI report persistent post-concussion symptoms (PCS), including cognitive, physical, and emotional sequelae that interfere with activities of daily living at least one-year post-injury (Bazarian et al., 1999; Heitger et al., 2007; Hiploylee et al., 2017; Sharp & Jenkins, 2015). This has created serious challenges not only for the affected individuals and their loved ones, but also the healthcare system.

To add to this challenge, the term concussion is often used synonymously with mTBI in both scientific literature and clinical settings, but their definitions are not fully in agreement with each other. This has given rise to numerous controversies surrounding the use of the terms and the correct diagnoses of patients with these injuries in the general population. From a clinical standpoint, obtaining the proper diagnosis is essential in treating these injuries, impacting symptom management strategies, evaluation for safe return to daily activities, and prevention of further injury. In the research context, discrepancies in the diagnostic criteria can result in the

enrolment of heterogenous patient populations, with the potential to confound true incidence rates of the injuries and clinical trial outcomes when assessing treatment strategies (Sussman et al., 2018).

The use of standard clinical imaging for mTBI and concussion has also proven difficult and has further complicated the diagnostic process, as structural abnormalities are not always visible and commonly reveal normal results (Misch & Raukar, 2020; Ontario Neurotrauma Foundation, 2018a; Ptito et al., 2007). We have instead shifted towards more advanced neuroimaging techniques that can detect functional injuries. Task-based functional magnetic resonance imaging (fMRI) is known to be an effective tool in the diagnosis of mTBI/concussion, with patients presenting with altered blood oxygen level-dependent (BOLD) signal changes during performance of cognitive tasks in comparison to healthy controls (e.g., (Chen et al., 2004, 2007)). This technique has shown potential to assist us with clinical decision making and may be used to establish which operational definitions of mTBI and concussion are appropriate.

The discrepancies in the diagnostic criteria for mTBI and concussion is a great barrier within the field of traumatic brain injury. As a result, the current body of work implements task-based fMRI to aid in determining if mTBI and concussion are distinct diagnostic entities or if they should be considered as one. This study aims to clarify and advance our empirical and clinical understanding of both mTBI and concussion, addressing this major heath concern.

Chapter 2: Definitions of Concussion and mTBI.

2.1. Operational Definitions of mTBI.

In current clinical practice, there are two operational definitions that are used to diagnose mTBI. The American Congress of Rehabilitation Medicine (ACRM) (Mild Traumatic Brain Injury Committee, 1993) was the first organized interdisciplinary group to promote specific diagnostic criteria for mTBI (Greenwald et al., 2012). A patient with mTBI was defined as "a person who has had a traumatically induced physiological disruption of brain function as manifested by at least one of the following" [criteria seen in Table 1] (Mild Traumatic Brain Injury Committee, 1993). While the ACRM definition has been widely used in the fields of rehabilitation and neuropsychology, the World Health Organization (WHO) has since derived a more advanced definition (Holm et al., 2005). During the years of 1998-2003, the WHO Collaborating Centre for Neurotrauma Task Force on mTBI performed a comprehensive literature search and critical review to assemble the best evidence of mild traumatic brain injury. After extensive evaluation of the methodological quality of the literature on this topic, 42% of the studies were accepted for review. The WHO then slightly modified the mTBI definition to comprise of: "an alteration in brain function, or other evidence of brain pathology, caused by an external force" as manifested by (i) one or more of the following: loss of consciousness (LOC) for 30 minutes or less; post-traumatic amnesia (PTA) for events immediately before or up to 24 hours after the accident; any alteration in mental state at the time of the incident; or transient neurological abnormalities; (ii) a Glasgow Coma Scale (GCS) score of 13-15 after 30 minutes post injury or later (Holm et al., 2005). Regardless of the definition used, we can confirm that

diagnosis of mTBI requires the presence of: (1) a direct or indirect injury to the brain, and (2) at least one operational criterion (see Table 1).

There are, however, some differences that exist between the ACRM and WHO definitions of mTBI, also apparent in Table 1. First, the WHO simplified the classification of altered mental status by removing "dazed" from the list of symptoms, and also changed the focal neurological deficit criteria of the ACRM to "other transient neurological abnormalities, such as focal signs, seizure, and intracranial lesion, which are not requiring surgery" (Carroll et al., 2004; Prince & Bruhns, 2017). The WHO definition also allows for the Glasgow Coma Scale (GCS) score of 13-15 to be assessed after a 30-minute time frame, recognizing potential delays in professional assessment (Holm et al., 2005; Prince & Bruhns, 2017). Finally, the WHO definition states that the manifestations of mTBI must not be due to drugs, alcohol, or medications, other pathologies, or penetrating craniocerebral injury (Carroll et al., 2004), while this was not mentioned in the ACRM criteria. The WHO criteria truly highlight the complex nature of these injuries and has become the most generally accepted mTBI definition in the field, replacing the ACRM criteria.

Nonetheless, it should be stressed that even with the strict criteria established by the WHO, there is a wide range of severity and symptoms within the diagnosis of mTBI that complicates assessment and treatment (Lefevre-Dognin et al., 2021; Shukla & Devi, 2010). Some patients present with very brief and seemingly minor symptoms, whereas others experience close to the maximum LOC and/or PTA. The stress from head trauma also has the potential to cause problems such as assuming oneself was unconscious during a period soon after the trauma in which they have no memory or denying LOC when it did occur (Ruff et al., 2009). PTA can also be complicated as it is easily mistaken as the individual's initial confusion post-

trauma and has few standardized measures available (Bodin et al., 2012). Finally, the WHO criteria do not set a minimum duration for the transient neurological abnormalities after mTBI. Thus, despite the increase in public awareness surrounding the acute and potential long-term effects of mTBI, our understanding of its definition and diagnostic criteria should be considered incomplete and must evolve.

	ACRM (1993)	**WHO (2004)**
Loss of consciousness (LOC)	< 30 min	< 30 min
Post-traumatic amnesia (PTA)	< 24 h	< 24 h
Alteration in mental state	Dazed, disoriented, or confused	Disoriented or confused
Neurological deficits/abnormalities	Focal neurological deficits that may or may not be transient	Other transient neurological abnormalities, such as focal signs, seizure, and intracranial lesion, which are not requiring surgery
Glasgow Coma Scale (GCS)	Initial GCS 13-15 (30 min post-injury)	GCS 13-15 (after 30 min post-injury)
Other		These manifestations of mTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries, or caused by penetrating craniocerebral injury.

Table 1. Operational criteria for mTBI created by the ACRM and WHO.

2.2. Operational Definitions of Concussion.

The term concussion has received increasing attention in the media in recent years primarily due to increased awareness and acknowledgement of concussion in sport. Despite many organizations attempting to offer a detailed definition for this injury, there continues to be a substantial gap in the literature regarding the definition and classification of concussion.

The most recent consensus statement published by the Concussion in Sport Group (CISG) in 2017, offers what may be the most accepted definition of concussion (Kazl & Torres, 2019). The CISG aimed to develop our conceptual understanding of sports related concussion (SRC), using an expert consensus-based approach. They define concussion as "a traumatic brain injury induced by biomechanical forces" (McCrory et al., 2017). As specified by the consensus statement, a concussion may result in neuropathological changes, but acute clinical signs and symptoms largely reflect functional disturbances rather than a structural injury (McCrory et al., 2017). These clinical signs and symptoms (presented in Table 2) may or may not involve LOC or PTA. If symptoms or signs in any one or more of the clinical domains are present, an SRC should be suspected, and the appropriate management strategy should be instituted (McCrory et al., 2017).

This definition of concussion is notably broad and inclusive. When these acute injury variables are excluded from the diagnostic criteria, the presence of concussion becomes defined by self-reported symptoms. It therefore becomes difficult to deduce how self-reported concussive symptoms are linked to biomechanical head trauma without evidence of structural brain injury (Gasquoine, 2019). As the signs and symptoms (see Table 2) are non-specific to concussion, the consensus states that their presence should simply prompt the inclusion of concussion in a

differential diagnosis for further evaluation, instead of the symptoms themselves being diagnostic of concussion (McCrory et al., 2017).

Difficulties have also occurred when the onset of symptoms are delayed, or when they are inaccurately reported by those who do not recognize the significance of their symptoms or who are reluctant to report them (McCrory, Meeuwisse, Echemendia, et al., 2013). The involvement of a compensation claim or disability insurance may also affect perpetuating symptoms (Cole & Bailie, 2016; King, 2019; Sharp & Jenkins, 2015). This may present as exaggerating symptom severity, fabricating symptoms, or reporting previously resolved symptoms as unresolved (Cole & Bailie, 2016). Contrarily, underreporting of post-concussive symptoms also occurs, especially in cases where individuals do not want to be withheld from play or work (Cole & Bailie, 2016).

Based on the CISG definition, concussion ultimately seems to be a benign phenomenon, with transient neurological dysfunctions resolving spontaneously with time. As concussions are a heterogenous clinical entity, investigators and physicians continue to characterise a diverse range of symptoms and functional impairments, which has given rise to a widespread collection of clinical profiles following these head injuries (Sussman et al., 2018). Appropriately, the CISG has recognized concussion to be among the most complex injuries in sports medicine to diagnose, assess, and manage (Kazl & Torres, 2019). Without a commonly agreed upon definition of concussion, and without a clear distinction from mTBI, it is imperative that we continue to investigate these injuries.

The suspected diagnosis of SRC can include **one or more** of the following clinical domains:

- Symptoms: somatic (e.g., headache), cognitive (e.g., feeling like in a fog) and/or emotional symptoms (e.g., lability)
- Physical signs (e.g., loss of consciousness, amnesia, neurological deficit)
- Balance impairment (e.g., gait unsteadiness)
- Behavioral changes (e.g., irritability)
- Cognitive impairment (e.g., slowed reaction times)
- Sleep/wake disturbance (e.g., somnolence, drowsiness)

If symptoms or signs in any one or more of the clinical domains are present, an SRC should be suspected, and the appropriate management strategy instituted. It is important to note, however, that these symptoms and signs also happen to be non-specific to concussion, so their presence simply prompts the inclusion of concussion in a differential diagnosis for further evaluation, but the symptom is not itself diagnostic of concussion.

Table 2. Clinical signs and symptoms of concussion designed by the Concussion in Sport Group (CISG) (McCrory et al., 2017).

2.3. Other Classifications of mTBI and Concussion.

While the CISG definition of concussion and the WHO definition of mTBI seem to be the most common operational criteria for these respective injuries, several other groups have also created their own guidelines for mild head injuries. The Department of Veterans Affairs and Department of Defence (VA/DoD) has created clinical practice guidelines for the management of concussion/mild traumatic brain injury (Department of Veterans Affairs, 2016) (see Table 3). Within these guidelines, the terms "mTBI" and "concussion" are used interchangeably. The VA/DoD add that alternations in consciousness or mental state can last up to 24 hours, and that structural imaging must be normal (Department of Veterans Affairs, 2016). They also recommend avoiding the use of the terms "brain damage" or "brain injury", as this may inadvertently reinforce the perception of long-term disability, and instead suggest using the terms "concussion" or "history of mild TBI" to imply transience of the condition when communicating with patients (Department of Veterans Affairs, 2016). Assuming transience of symptoms, however, may be problematic, as we know that many patients do not recover quickly, and that

apparent trivial injuries can have long-term effects. The VA/DoD guidelines ultimately imply that mTBI and concussion are equivalent, despite considerable differences in how the terms are defined elsewhere in the literature (Sussman et al., 2018).

The Ontario Neurotrauma Foundation (ONF) also initiated a project with the objective of creating a guideline for concussion/mTBI and the prolonged symptoms of these injuries (Ontario Neurotrauma Foundation, 2018b). The purpose of this guideline was to implement evidence-based, best-practice care for healthcare professionals treating mTBI. The ONF states that concussion/mTBI denotes the acute neurophysiological event related to blunt impact or other mechanical energy applied to the head, neck, or body (with transmitting forces to the brain), such as sudden acceleration, deceleration, or rotational forces (Ontario Neurotrauma Foundation, 2018b). They emphasize that all concussions should be considered a mTBI, however mTBI should be distinguished from concussion when there is evidence of intracranial injury on conventional neuroimaging or prolonged neurologic deficit (Ontario Neurotrauma Foundation, 2018b). This contradicts previous definitions that have stated that evidence on standard imaging is not required for mTBI diagnosis (Department of Veterans Affairs, 2016; Holm et al., 2005; Mild Traumatic Brain Injury Committee, 1993), and creates further complications when access to neuroimaging tools is limited. Moreover, with this definition, the initial diagnosis of 'concussion' may be inaccurate if no neurological abnormalities are first detected. As it takes ample time to recognize and diagnose persistent deficits post-injury, this may lead to ill-advised management plans.

An alternate perspective has also been presented by the "Agence de la santé et des services sociaux de Montréal", who have created a categorization for levels of risk associated with mTBI, based on clinical symptoms and the risk of medical and functional complications

(Lacaille et al., 2011). They suggest that we use the term "mild *trivial* TBI" in place of "concussion" to characterize injuries that are not accompanied by LOC or PTA (Lacaille et al., 2011; Whitman et al., 1984). By contrast, they use "mild *simple* TBI" to denote injuries with LOC or PTA, similar to the mTBI definition popular in clinical use today (Holm et al., 2005). While this is not a widely used classification system, it provides some clarity surrounding the definitional confusion of these terms and aims to create rehabilitation plans that are best suited to the needs of each individual patient (Lacaille et al., 2011).

	Mild	**Moderate**	**Severe**
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of Consciousness (LOC)	0-30 min	>30 min and <24 hours	>24 hours
Alteration of consciousness/ mental state (AOC)*	up to 24 hours	>24 hours; severity based on other criteria	
Posttraumatic amnesia (PTA)	0-1 day	>1 and <7 days	>7 days
Glasgow Coma Scale (GCS) (best available score in first 24 hours)	13-15	9-12	<9

Table 3. Classification of TBI Severity from the Department of Veterans Affairs and Department of Defence (Department of Veterans Affairs, 2016).
*Alteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be looking and feeling dazed and uncertain of what is happening, confusion, and difficulty thinking clearly or responding appropriately to mental status questions and being unable to describe events immediately before or after the trauma event.

2.4. Contrasting and comparing mTBI and concussion.

The WHO definition of mTBI (Holm et al., 2005) and the CISG definition of concussion (McCrory et al., 2017), while similar, have important differences and pose extremely difficult diagnostic dilemmas. In the CISG concussion definition, patients do not need to have one of the more objective clinical signs, particularly LOC or PTA, but instead only symptoms after the head injury, whereas in the WHO definition, they are essential. It can be challenging to diagnose individuals outside of the sports realm who present post-concussive symptoms but lack the hallmark features of mTBI from the WHO criteria. With negative findings on standard clinical imaging, we are unsure as to where these patients lie on the TBI spectrum and under which diagnostic category they truly fall.

Currently, the term concussion is more often used for head injuries that occur during sport, with mTBI being preferred in other medical specialities (Tator, 2009). Some have argued that the term concussion should be used to place emphasis on the impaired functional status following head trauma, while the term mild traumatic brain injury should be used to characterize the subsequent pathophysiology (Anderson et al., 2006). The 2012 Zurich Consensus Statement in Sport proposed that concussion and mTBI should be viewed as distinct entities (McCrory, Meeuwisse, Aubry, et al., 2013; Sharp & Jenkins, 2015), with use of the term concussion in reference to head injuries that result in transient neurological deficits only (Bodin et al., 2012). This statement is debatable because a percentage of patients who present with seemingly minor "concussion" injuries have been known to experience long-term symptoms instead of the assumed transient ones (Sharp & Jenkins, 2015). Despite the attempts to solve this on-going problem, a consensus has yet to be reached.

Further, some clinicians may find the term concussion preferable when communicating with patients, as it avoids the stigma associated with more severe brain injury and implies less serious health consequences (DeMatteo et al., 2010). This may also decrease the possibility of the patient developing self-perception of long-term disability (DeMatteo et al., 2010). However, this communication strategy has the potential to unintentionally communicate that a brain injury did not occur, resulting in less adequate healthcare follow-up and return to daily activities earlier than appropriate (DeMatteo et al., 2010).

As the assessment of these injuries currently relies heavily on subjective self-reported clinical symptoms, the need to develop objective measures for accurate diagnoses in both clinical and research settings is ever-present. A consensus of the diagnostic system and operational criteria would contribute to fully understanding the medical, psychosocial, and demographic factors that influence prognosis of these injuries, with the ability to reduce variability in reported outcomes (Mayer et al., 2017).

Chapter 3: Neuroimaging in Concussion and mTBI.

3.1. Functional magnetic resonance imaging.

As structural abnormalities are not essential in the classification of mTBI nor concussion, conventional structural neuroimaging, such as computed tomography (CT) and T1- and T2-weighted MRI, is not informative in the diagnostic process for most patients. Thus, advanced imaging techniques have been used to reveal both the pathophysiological and functional sequelae of injury and can give extensive and comprehensive diagnostic information (Keightley et al., 2014; Lunkova et al., 2021). These include both task-based and resting state fMRI (e.g., (Amir et al., 2021; Chen et al., 2004, 2008)), diffusion weighted imaging (e.g., (Guberman et al., 2020; Shenton et al., 2018; Tayebi et al., 2021)), susceptibility weighted imaging (e.g., (Liu et al., 2015)) and arterial spin labelling perfusion MRI (e.g.,(Andre, 2015; Lin et al., 2016)). Complex use of many of these techniques has shown promise in the literature, but the results are mixed, lack utilization in the research environment and have not yet reached common integration to clinical settings (Lunkova et al., 2021).

To date, the only advanced imaging technique that has shown consistent and reproducible results in the diagnosis of concussion and mTBI is fMRI (Lunkova et al., 2021). fMRI is helpful in characterizing the neurophysiological phenotypes of functional brain injuries that lack clear focal structural abnormalities. It has become increasingly popular due to its low invasiveness, absence of radiation exposure, good spatial resolution, and relatively wide availability (Gosselin et al., 2015). fMRI is a specialized MRI scan that allows the detection of differences in the magnetic properties of oxygenated versus deoxygenated hemoglobin (Huettel et al., 2004). When a portion of the cortex becomes activated, neuronal activity is expressed as a relative increase in

oxyhemoglobin compared to deoxyhemoglobin in the activated zones. The relative decrease in deoxyhemoglobin concentration, which has a paramagnetic effect, can be detected by MRI as a weak transient rise in the T2*-weighted signal (Huettel et al., 2004). This technique is known as blood-oxygen-level-dependent (BOLD) contrast. In task-based fMRI specifically, patterns of activations in brain regions associated with the specific task or stimulus are revealed, with MRI scans performed during alternating periods of performing or not performing the task (Yuh et al., 2014).

3.2. Previous task-based fMRI findings.

When imaging mTBI and concussion, previous studies using task-based fMRI have focused on frontal lobe/executive functioning tasks, with many employing tests of attention and memory (Yuh et al., 2014). As deficits in basic information processing are commonly observed after mTBI, the consequences of these injuries on working memory have been a prime focus in functional imaging literature (Bryer et al., 2013). Working memory involves the ability to temporarily store and manipulate information for the purpose of carrying out a complex cognitive task (Keightley et al., 2014). Working memory deficit is one of the most common cognitive impairments reported after mTBI and concussion (McAllister et al., 2006).

fMRI was first used in this context through use of an auditory n-back working memory task with a varying degree of processing load (McAllister et al., 1999, 2001). In these studies, healthy control subjects demonstrated progressively increasing brain activation with increasing working memory load, while subjects with mTBI presented with altered activation patterns with increasing load, despite similar task performance between the two groups (McAllister et al., 1999, 2001). Abnormal increases in activation were seen in the right dorsolateral prefrontal

cortex (DLPFC), which is known to play a large role in the working memory network (Barch et al., 2003; Kim et al., 2015; Mansouri et al., 2009). It is thought that the increases in activation may represent a compensation mechanism for damaged areas outside of the prefrontal region that show diminished activation (McAllister et al., 1999).

Soon after, our group began to use fMRI in the context of concussion and mTBI (Chen et al., 2004, 2007, 2008; Keightley et al., 2014) through use of a verbal and visual working memory task devised by Dr. Michael Petrides. This task is known to be an excellent measure of the function of the DLPFC (Petrides et al., 2001). In the first study by Chen and colleagues (2004), athletes with concussion showed decreased task-specific percent BOLD signal increases in the DLPFC, contrary to McAllister's group. They also found that concussed athletes had additional activation peaks outside those typically seen in the control group. Their performance on the task, however, was not impaired in comparison to that of healthy controls. The decreased activations observed in concussed athletes may thus be explained by functional deficits in the prefrontal regions post-injury, and the irregular activation peaks may represent cognitive resources that are acting as compensatory mechanisms (Chen et al., 2004). Chen and colleagues later demonstrated that these percent BOLD signal alterations also correlated with severity of symptoms after injury, represented by the post-concussion symptom (PCS) score, with increased PCS score correlating with diminished activation in the DLPFC (Chen et al., 2007).

While both the n-back task and the Petrides task evaluate working memory, the discrepancies in activation patterns may be at least partially explained by the task construct and the cognitive needs of the task. The n-back task is classified as a continuous task and is considered to have higher cognitive demand than the Petrides working memory task, which is classified as a discrete task (Bryer et al., 2013). Nonetheless, together these studies have proven

that task-based fMRI provides insight into the pathophysiology underlying mTBI and concussion, thereby acting as an effective tool in the diagnosis and assessment of the injuries.

Chapter 4: Summary and Study Objectives.

It is evident that we have an inadequate understanding of the appropriate use of mTBI and concussion, and whether the terms should be considered synonymous. This is especially true when diagnosing individuals outside of the sports setting who present with post-concussive symptoms but lack hallmark features of mTBI from the WHO criteria, including LOC or PTA. There have been increasing recommendations to investigate and differentiate between mTBI and concussion, with the goal of gaining insight into the underlying mechanisms of the impairments and implications of these injuries. The proper diagnosis and assessment of patients with these injuries have important and long-term consequences. Amidst decades of confusion, there is a dire need to create universal and concrete definitions of both mTBI and concussion. However, to our knowledge, no study thus far has compared mTBI and concussion in a neuroimaging study.

Of the advanced neuroimaging techniques currently available, fMRI has shown the most consistency and promise for assessment of mTBI and concussion. Thus, the objectives of this study were a) to discover whether patients who fit the CISG definition of concussion but lack the clinical criteria of mTBI as defined by the WHO (LOC, PTA) have similar fMRI activation patterns in a working memory task compared to mTBI patients and b) to determine if it is appropriate to consider these patient populations as one, or if the diagnostic criteria need to be revisited to be more inclusive of all patients.

We hypothesize that abnormal BOLD signal changes will be present in both the mTBI and concussion groups when compared to the control group. Building on this, we also hypothesize that those fitting the mTBI criteria will have lower percent BOLD signal changes than those who fit the concussion definition. This would indicate that TBI should be considered a

spectrum, with concussion being less severe than mTBI. These results have the potential to positively contribute to alleviating the public health concern of mTBI and concussion, as this is a critical first step in successful management of these injuries (Ontario Neurotrauma Foundation, 2018a).

Manuscript

Introduction

Mild traumatic brain injury (mTBI) has emerged as a significant public health concern, with an incidence rate above 600/100 000 (Cassidy et al., 2004). The impact of a mTBI can be significant, with an estimated 15-25% of individuals reporting persistent post-concussion symptoms (PCS) that interfere with quality of life and activities of daily living at least one-year post-injury (Bazarian et al., 1999; Heitger et al., 2007; Hiploylee et al., 2017; Sharp & Jenkins, 2015). Although at the mildest end of the TBI spectrum, mTBI creates serious challenges for not only affected individuals and their loved ones, but also the healthcare system. The term "concussion" is often used synonymously with mTBI in both scientific literature and clinical settings, despite a lack of agreement between their definitions. This has given rise to complications in diagnosis and controversies surrounding the correct use of the terms.

In current practice, mTBI has been defined by the World Health Organization (WHO) as "an acute brain injury resulting from mechanical energy to the head from external physical force", with operational criteria including (i) one or more of the following: loss of consciousness (LOC) for 30 minutes or less; post-traumatic amnesia (PTA) for events immediately before or up to 24 hours after the accident; any alteration in mental state at the time of the incident; or transient neurological abnormalities; (ii) a Glasgow Coma Scale (GCS) score of 13-15 after 30 minutes post injury or later (Holm et al., 2005). In contrast, the Concussion in Sport Group (CISG) published a consensus statement in 2016 defining sports-related concussion (SRC) as a traumatic brain injury induced by biomechanical forces with a range of clinical signs and symptoms that may or may not involve LOC or PTA (McCrory et al., 2017). The CISG specifies

that a concussion may result in neuropathological changes, but acute clinical signs and symptoms largely reflect functional disturbances rather than a structural injury (McCrory et al., 2017). These signs and symptoms (see Table 1) are non-specific to concussion, thus the consensus states that their presence should simply prompt the inclusion of concussion in a differential diagnosis for further evaluation, instead of the symptoms themselves being diagnostic of concussion (McCrory et al., 2017).

The WHO definition of mTBI (Holm et al., 2005) and the CISG definition of concussion (McCrory et al., 2017), while similar, have important differences which have been largely disregarded. With the CISG concussion definition, patients do not need one of the more objective clinical signs, particularly LOC or PTA, but instead only symptoms after the head injury, whereas in the WHO mTBI definition, they are essential. Challenges arise when diagnosing individuals who present with post-concussive symptoms after a head injury but lack these hallmark features of mTBI from the WHO criteria.

While assessment of concussion and mTBI has often been based on subjective self-reported clinical symptoms, this is often unreliable and/or nonspecific. Neuroimaging techniques have thus been increasingly used in attempts to further understand these injuries. As structural abnormalities are not always visible on standard clinical imaging, we have instead shifted towards more advanced neuroimaging techniques that can detect functional injuries (Misch & Raukar, 2020; Ontario Neurotrauma Foundation, 2018a; Ptito et al., 2007). The advanced imaging technique to date that has shown the most consistent and reproducible results in the diagnosis of concussion/mTBI is functional MRI (fMRI) (e.g., (Chen et al., 2004; Lunkova et al., 2021; Ptito et al., 2007)).

Specifically, multiple task-based fMRI studies have shown that patients with mTBI/concussion present with altered blood-oxygen-level-dependent (BOLD) signals during performance of working memory tasks compared to healthy controls (Chen et al., 2004, 2007; Christodoulou et al., 2001; McAllister et al., 1999, 2001).

We have therefore used task-based fMRI to determine if mTBI and concussion are distinct diagnostic entities, or if they should be considered as one. This study questioned whether patients who fit the CISG definition of concussion but lack the clinical criteria of mTBI as defined by the WHO (i.e., LOC, PTA) have similar fMRI activation patterns in a working memory task compared to patients who fit the mTBI definition. As discrepancies in the diagnostic criteria for mTBI and concussion are a great barrier within the field of traumatic brain injury, we expect for our results to positively contribute to the diagnostic process of mTBI and concussion and to aid in addressing this major public health concern.

The suspected diagnosis of SRC can include **one or more** of the following clinical domains: • Symptoms: somatic (e.g., headache), cognitive (e.g., feeling like in a fog) and/or emotional symptoms (e.g., lability) • Physical signs (e.g., loss of consciousness, amnesia, neurological deficit) • Balance impairment (e.g., gait unsteadiness) • Behavioral changes (e.g., irritability) • Cognitive impairment (e.g., slowed reaction times) • Sleep/wake disturbance (e.g., somnolence, drowsiness) If symptoms or signs in any one or more of the clinical domains are present, an SRC should be suspected, and the appropriate management strategy instituted. It is important to note, however, that these symptoms and signs also happen to be non-specific to concussion, so their presence simply prompts the inclusion of concussion in a differential diagnosis for further evaluation, but the symptom is not itself diagnostic of concussion.

Table 1. Concussion in Sport Group (CISG) clinical signs and symptoms of concussion (McCrory et al., 2017).

Methodology

Subject recruitment

A total of 53 participants were recruited for this study. This included 9 patients who fit the diagnostic criteria of mTBI as defined by the WHO (4 female, ages ranging from 19 to 42 years; mean=26.3 standard deviation=9.1, median=23), 13 patients who fit the CISG definition of concussion but lack the diagnostic criteria of mTBI as defined by the WHO (11 female, ages ranging from 18 to 54 years; mean=30.2, standard deviation=11.4, median=28), and 31 healthy controls (16 female, ages ranging from 19 to 54 years; mean=30.6, standard deviation=9.4, median=28). All brain-injured subjects were referred by the Traumatic Brain Injury Clinic at the Montreal General Hospital, a Level-1 trauma centre. Inclusion criteria for the mTBI and concussion groups were 1) a diagnosis of mTBI or concussion by a physician as per the operational criteria from the respective definitions for clinical identification; 2) within one month of injury and still symptomatic; and 3) functional knowledge of English or French. Healthy controls without a history of traumatic brain injury and/or any neurological disorder were recruited from the general population. Medical records were verified to ensure that each case was sufficiently detailed to support the diagnosis of mTBI or concussion. Subjects were excluded if they had 1) moderate/severe TBI, penetrating brain injury, hemorrhagic lesions on structural imaging, or any cranial surgical intervention; 2) prior head injury within the preceding year or continually suffering symptoms from a previous head injury at the time of testing; 3) history of ADHD, neurological disorders, neurodevelopmental disorders, or psychiatric disorders; 4) chronic use of psychiatric medication; or 5) contraindications to MRI (i.e., pregnancy, claustrophobia, metallic implants, etc.). Data regarding the age, gender, time since injury,

mechanism of injury, and degree of post-concussion symptoms present at the time of testing for each group are presented in Table 2.

Subject ID	**Group**	**Gender**	**Age**	**Time since injury (days)**	**Mechanism of injury**	**PCSS**
P01	Concussion	F	34	33	Recreational sport collision	52
P02	Concussion	F	42	31	Fall from height	75
P07	Concussion	F	47	32	Motor vehicle accident	41
P09	Concussion	M	23	35	Ball to head	23
P10	Concussion	F	18	35	Motor vehicle accident	59
P12	Concussion	F	30	32	Jiu jitsu injury	9
P13	Concussion	F	20	32	Martial arts injury	49
P14	Concussion	F	28	23	Cycling accident	19
P15	Concussion	F	33	23	Head hit by door	66
P17	Concussion	F	21	30	Snowboarding accident	54
P19	Concussion	M	23	34	Elbow to head	18
P22	Concussion	F	20	32	Hit head on ceiling	27
P03	mTBI	F	22	35	Fall down stairs	52
P04	mTBI	M	42	18	Skiing accident	59
P05	mTBI	F	19	28	Pedestrian versus car	38
P06	mTBI	M	42	28	Skateboard versus car	49
P11	mTBI	F	19	13	Motor vehicle accident	64
P16	mTBI	M	25	18	Snowboarding accident	63
P18	mTBI	M	23	7	Skiing accident	21
P20	mTBI	M	24	5	Skiing accident	66
P21	mTBI	F	20	36	Skiing accident	6
C1	Control	M	19	N/A		
C2	Control	F	20			
C3	Control	F	22			
C4	Control	F	22			
C5	Control	M	38			
C6	Control	M	26			
C7	Control	F	28			
C8	Control	F	23			
C9	Control	F	29			
C10	Control	F	33			
C11	Control	F	23			
C12	Control	M	35			
C13	Control	F	29			
C14	Control	M	27			
C15	Control	F	44			

C16	Control	M	35	
C17	Control	F	46	
C18	Control	F	35	
C19	Control	M	30	
C20	Control	F	24	
C21	Control	M	22	
C22	Control	M	28	
C23	Control	M	23	
C24	Control	M	54	
C25	Control	F	31	
C26	Control	M	34	
C27	Control	M	49	
C28	Control	M	26	
C29	Control	M	23	
C30	Control	F	22	
C31	Control	F	49	

Table 2. Demographic, medical, and injury information for all participants. Note: PCSS=post-concussion symptom scale score (as assessed using the Post-concussion Symptom Scale-Revised).

Neuropsychological testing

Participants with mTBI or concussion completed a comprehensive neuropsychological test battery using tests that have consistently shown sensitivity to the effects of mTBI and concussion. Tests included the Purdue Pegboard Test (Tiffin & Asher, 1948), Tower of London Test (Shallice, 1982), Rey Auditory Verbal Learning Test (RAVLT) (Lezak et al., 2004), Symbol Digit Modalities Test (SDMT) (Smith, 1973), Wechsler Adult Intelligence Scale (WAIS-IV) (Wechsler, 2008), and the Trail Making Test (Tombaugh, 2004). Participants' self-perceived levels of anxiety and depression were assessed via the Beck Inventories (Beck et al., 1961, 1988), and difficulties experienced from dizziness were evaluated with the Dizziness Handicap Inventory (Jacobson & Newman, 1990). Each brain-injured subject also filled out the Post-Concussion Symptom Scale (PCSS; (Lovell et al., 2006)), a questionnaire in which 22 symptoms associated with concussion are scored from zero to six. All testing was administered in a standardized order and was completed in a single session.

fMRI Experimental Task

The experimental task used during the fMRI scanning sessions was adapted from the externally ordered working memory task devised by Petrides and validated in patients with lateral frontal lesions (Petrides, 2000a), monkeys with dorsolateral prefrontal cortex (DLPFC) lesions (Petrides, 1991, 1995, 2000b), and functional neuroimaging work (Petrides et al., 1993; Stern et al., 2000).

The verbal version of the task was used for this study. The subjects were first familiarized with a set of five pseudo words that were used throughout the test, such that visual imagery was minimal. During each trial, four of the five words were presented successively in random order at the centre of a projector screen. The subjects were required to monitor the four words presented on each trial. After the presentation of the fourth word, there was a one second delay. Immediately after this delay, a test item was presented that was either one of the four stimuli already presented, or the item that had not been presented on that trial. The subject had to decide and indicate within 1.5 seconds whether this test item was one of the four words presented prior to the delay (yes), or whether it was the word from the set of five that was not presented (no) by pressing a mouse button (yes = left button, no = right button). Each trial was delivered in this same manner. The responses were recorded for all subjects and accuracy and response times were calculated.

A baseline control condition was used to "subtract out" any activation related to motor and perceptual components of the working memory task. In this control condition, the format and type of stimulus presented, mode of response, and timing of events were identical to those in the experimental working memory task. A similar, but unrelated and novel pseudo word was

successively presented four times in a row, followed by the delay of one second. After the delay, one of two words associated with either a left or right mouse button press was displayed, and, as in the experimental condition, the subject had to respond. The subject learned prior to scanning which of these two words is associated with a left mouse button press, and which with a right button press. The subjects made identical responses in both conditions (i.e., pressing the mouse button), however the working memory condition required constant monitoring of the presented words, whereas the control condition did not require such an executive function and the decision during the test was made based on pre-instructed knowledge and learned associations. A schematic representation of this task can be found in Figure 1.

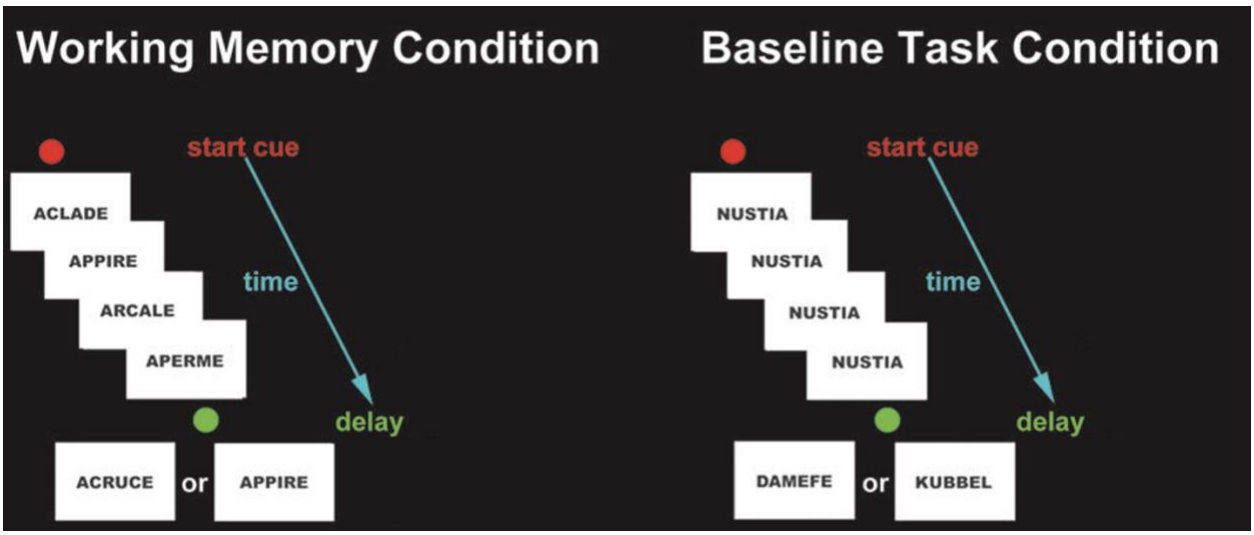


Figure 1. Schematic diagram of the externally ordered working memory task.

Image Acquisition

The fMRI scanning was performed at the Montreal Neurological Institute on a Siemens 3-Tesla MAGNETOM Prisma Fit MRI system equipped with a 64-channel head coil. Each session began with the acquisition of high-resolution T1-weighted 3D anatomical image for

anatomical reference (voxel size $1mm^3$), using 3D magnetization prepared rapid gradient echo (3D-MP-RAGE) sequence (time of repetition [TR] = 2300ms; echo time [TE] = 2.98ms; slice thickness = 1mm; field of view [FOV] = 256mm; image matrix = 256x256; flip angle = 9 degrees; interleaved excitation). Acquisition of T2*-weighted gradient echo (GE) echo-planer images (EPIs) for BOLD fMRI (TR = 3000ms; TE = 30ms; 38 slices; slice thickness = 4mm; FOV = 300mm; 128x128 image matrix; flip angle = 90 degrees; interleaved excitation) followed.

Two functional scans for the working memory and control conditions were acquired in a single scanning session. Each functional scan lasted six minutes, with working memory and baseline conditions alternating every eight trails. A total volume of 120 acquisitions were obtained during each functional scan. All stimuli were presented via a projector to a screen placed at the back of the scanner. Prior to the scanning session, the subjects were introduced to the tasks outside the scanner and given at least 48 practice trials (i.e., two runs) to ensure familiarity before entering the scanner.

fMRI Experimental Task Data

All behavioural data analyses were completed using the IBM Statistical Package for the Social Sciences (SPSS) version 28.0. We compared the working memory performance measures (control condition accuracy, control condition reaction time (RT), working memory condition accuracy, and working memory condition RT) between the mTBI, concussion, and healthy control groups using one-way ANOVA.

Imaging Analysis

All MRI images were preprocessed and analyzed using Statistical Parameter Mapping (SPM) version 12 (Wellcome Department of Cognitive Neurology, London UK) running in MATLAB (version R2022b). The raw fMRI data was realigned and unwrapped; slice-time corrected; co-registered to the corresponding T1-weighted anatomical image; segmented into gray matter, white matter, and cerebrospinal fluid tissue; normalized to standardized space; and smoothed using a 6mm Gaussian kernel.

For first-level analysis, a working memory minus baseline control task subtraction was performed for each participant's scan. Mean parametric t-maps were constructed on a voxel-by-voxel basis by averaging functional data across scans using a general linear model (GLM) approach (Friston et al., 1994). Within group averages across participants for each subject group were obtained by performing a t-test over the mean parameter estimates from each subject using a summary statistic. The resulting T-statistic images were corrected for multiple comparisons using topological FDR ((Benjamini & Hochberg, 1995). A SPM viewer toolbox, xjView (http://www.alivelearn.net-/xjview/), was used to view and generate sectional images.

A one-way analysis of variance (ANOVA) was used to address whole-brain fMRI activation differences between the mTBI group, the concussion group, and the control group. Region of interest (ROI) analyses were completed using the SPM toolbox MarsBaR (Brett et al., 2002). The ROIs were defined using a 5mm radius spheres centering the peak of each region and the mean percent BOLD signal change was extracted from each subject for each group respectively. Finally, we calculated, for the healthy control group, a 95% confidence interval of the percent BOLD signal change in each ROI to establish a 'normal' range of task-related signal variation. This range was used to determine if the BOLD response of each brain injured subject was in the normal range of the control group.

Standard Protocol Approvals, Registrations, and Patient Consents

Approval was obtained from the McGill University Health Centre review board before commencement of the study, and all participants were provided with and signed written consent forms prior to participation.

Results

Demographic and clinical characteristics

Table 2 reveals demographic and clinical data at the time of testing for each group. ANOVA showed no significant age differences found between the control, concussion, and mTBI groups. Total scores for the Post-concussion Symptom Scale-Revised were not significantly different between mTBI and concussion groups (p=0.819). Further, Table 3 depicts self-reported psychometric testing of anxiety, depression, and dizziness, using the Beck Anxiety Inventory, Beck Depression Inventory, and Dizziness Handicap Inventory respectively, which were not significantly different between the mTBI and concussion groups. While sex differences were present between and within groups, analyses showed no significant differences in fMRI activations between males and females.

Variables	***Controls***	***Concussion***	***mTBI***	**P-value**
Demographic characteristics, mean (SD)				
Sex	16F, 15M	11F, 2M	4F, 5M	
Age (years)	30.6 (9.4)	30.2 (11.4)	26.3 (9.1)	0.516
Clinical characteristics				
PCSS Score		43.7 (22.8)	46.0 (9.7)	0.819
BDI-2 Score		13.8 (7.6)	9.9 (7.9)	0.252
BAI Score		14.6 (10.0)	13.6 (12.4)	0.844

DHI Score	32.4 (16.6)	26.9 (22.0)	0.505

Table 3. Demographic and clinical data for all participants.
PCSS, Post-concussion symptom scale score (as assessed using the Post-concussion Symptom Scale-Revised); BAI: Beck Anxiety Inventory; BDI-2: Beck Depression Inventory; DHI Dizziness Handicap Inventory.

Neuropsychological testing

Scores of the Processing Speed Index of Weschler's Adult Intelligence Scale and the Tower of London Test were standardized to account for age and sex variables. T-tests were then performed to determine if any group differences existed between the mTBI and concussion groups. The results of the Symbol Search test of the Processing Speed Index of Weschler's Adult Intelligence Scale showed that those in the mTBI group had significantly reduced standardized scores compared to those in the concussion group. There were no significant differences on the Tower of London test results between groups, however the mTBI group had lower total correct and higher total moves, as well as a shorter first move time and longer total time.

The Trail Making Test, Symbol Digit Modalities Test, Rey Auditory Verbal Learning Test, and Purdue Pegboard Test cannot be standardized, thus raw scores were compared to normative data, and the percentage of participants that had scores outside of the normal range was calculated. In all tests, except for the Symbol Digit Modalities Test and a subtest of the Purdue Pegboard Test, the mTBI group presented with higher percentage of participants with scores outside of the normal range in comparison to the concussion group. These results are summarized in Table 4.

Test	**Sub-test**	**Concussion**	**mTBI**	**P-value**
		Mean of Standardized Scores		
WAIS-IV Processing	Symbol Search	11.23	8.44	0.040*
Speed Index	Coding	10.62	9.11	0.211
Tower of London	Total Correct	100.46	98.67	0.808

	Total Moves	99.23	104.22	0.543
	First Move	101.23	95.11	0.154
	Execution Time	102.15	105.33	0.527
	Total Time	101.54	107.33	0.231
		% with Scores Outside of Normalized Data Range		
Trail Making Test	Part A	15.38	33.33	
	Part B	38.46	55.56	
	Difference score (B-A)	15.38	44.44	
SDMT		46.15	22.22	
RAVLT	Learning	23.08	55.56	
	Immediate Recall	15.38	22.22	
	Delayed Recall	7.69	33.33	
	Recognition	23.08	33.33	
Purdue Pegboard Test	Right	0	0	
	Left	15.38	11.11	
	Right & Left	0	22.22	

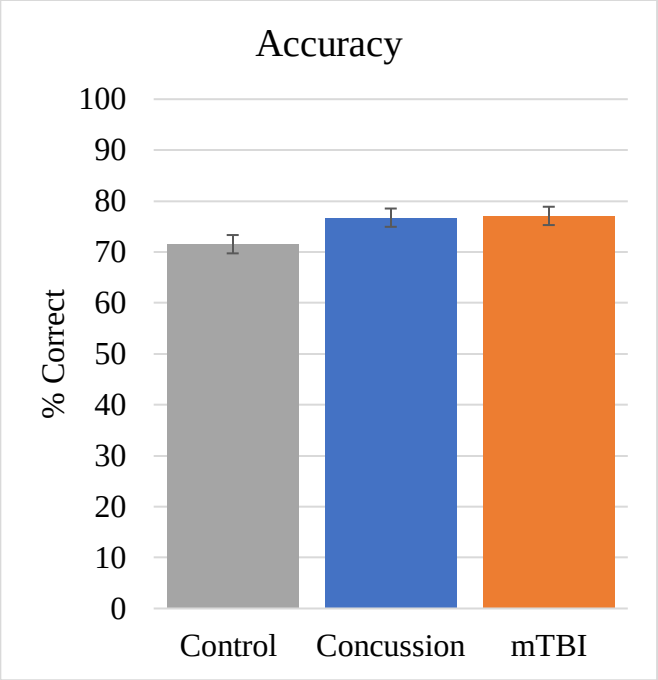
Table 4. Summary of neuropsychological testing for the mTBI and concussion groups. WAIS-IV, Weschler's Adult Intelligence Scale; SDMT, Symbol Digit Modalities Test; RAVLT, Rey Auditory Verbal Learning Test.
* Significantly lower than the concussion group ($p<0.05$).

Working memory task data

Table 5 and Figure 2 depict accuracy and reaction times of the control, concussion, and mTBI groups for the verbal working memory task. ANOVA results revealed that there were no significant differences in mean percent correct between groups. The same analysis indicated that reaction time was also not significantly different between groups.

	Control	***Concussion***	***mTBI***	***F statistic***	***P-value***
WM ACC (%)	71.5 (8.2)	76.7 (11.4)	77.1 (9.1)	2.74	0.074
WM RT (ms)	1132.7 (189.1)	1118.0 (175.3)	1141.6 (173.0)	0.038	0.962

Table 5. Working memory task data: Group mean response accuracy and mean reaction time. Values are mean (SD). ACC, accuracy as % correct; RT, reaction time in milliseconds.



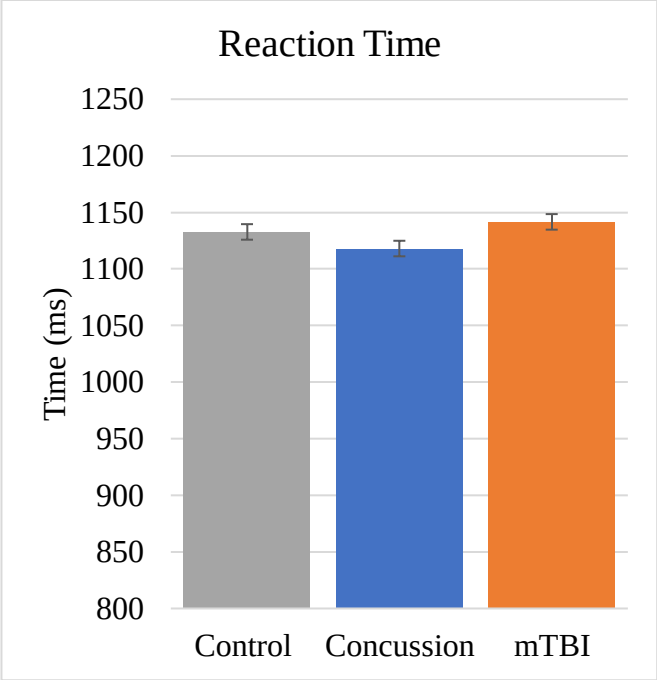


Figure 4. Performance on the working memory task for the control, concussion and mTBI groups. There were no significant differences in reaction time or accuracy between these groups.

fMRI data

Whole brain analysis was completed to examine differences in mean percent BOLD signal change for the verbal working memory condition compared to the control condition for each group. The anatomical location of significant peak activations (i.e., $P < 0.05$ (FDR-corrected) and their t-values are summarized in Table 6, 7, and 8 for the control, concussion, and mTBI groups respectively. A clear difference between the groups can be seen by comparing the brain activation maps as shown in Figure 5.

Regions of greater activation for the verbal working memory condition in the control group were found bilaterally in the dorsolateral prefrontal cortex (DLPFC) (Brodmann area (BA) 9/46), rostral insula (BA13), pars orbitalis (BA47), premotor cortex (BA 6), superior parietal lobes (BA 7), and middle occipital gyri (BA18). Additionally, greater activations were found in

the left anterior prefrontal cortex (BA 10), supplementary motor area, right dorsal anterior cingulate cortex (dACC) (BA 32), right putamen, left inferior occipital gyrus (BA 19), and right cerebellum.

Patients in the concussion group, by contrast, showed significant activity in some, but not all these regions. Specifically, no significant activation was found in the left anterior prefrontal cortex, the right DLPFC, the bilateral pars orbitalis, the right dACC, or the left inferior occipital gyrus. Whole-brain analysis also revealed that the concussion group had additional activation peaks in the left medial frontal gyrus, left frontal eye fields, right globus pallidus, right caudate, and left fusiform gyrus. These regions were not detected in the control group.

Finally, patients in the mTBI group, did not show significantly increased activity in most of the regions observed in the control group. Significant activation was only found in the supplementary motor area and left middle occipital gyrus.

Region	BA	x	y	z	T
Left anterior prefrontal cortex	10	-34	48	16	7.29
Left dorsolateral prefrontal cortex	46	-38	28	18	6.12
Right dorsolateral prefrontal cortex	9	44	36	28	8
Left pars orbitalis	47	-48	18	-4	6.11
Right pars orbitalis	47	34	26	-8	6.19
Left rostral insula	13	-30	22	2	8.07
Right rostral insula	13	34	20	2	9.44
Right dorsal anterior cingulate cortex	32	10	20	36	7.79
Supplementary motor area	6	8	14	50	7.32
Supplementary motor area	6	-2	10	58	9.31
Right putamen		12	10	-2	7.35
Left premotor	6	-42	2	32	7.55
Right premotor	6	36	6	30	6.1
Left thalamus		-6	-2	6	6.02
Right thalamus		4	-4	6	5.81
Left superior parietal lobule	7	-26	-50	42	8.32
Right superior parietal lobe	7	24	-56	54	7.3
Right cerebellum		26	-64	-24	6.54
Left inferior occipital gyrus	19	-36	-76	-12	6.61
Left middle occipital gyrus	18	-30	-90	-2	7.26
Right middle occipital gyrus	18	38	-86	0	7.01

Table 6. Significant task-related activation peaks of the control group ($P < 0.05$ (FDR-corrected)).

Region	BA	x	y	z	T
Left dorsolateral prefrontal cortex	46	-42	42	6	5.13
Left insula	13	-32	20	-4	8.19
Right insula	13	32	24	2	7.59
Left putamen		-24	18	14	8.22
Left medial frontal gyrus		-12	16	48	7.42
Left frontal eye fields	8	-2	16	46	6.6
Supplementary motor area	6	0	6	64	6.49
Left premotor	6	-50	6	40	6.51
Left middle frontal gyrus		-26	0	58	6.85
Right globus pallidus		12	-4	-2	7.24
Right caudate		24	-28	18	5.83
Left inferior parietal lobe		-20	-50	44	6.18
Right inferior parietal lobe	40	40	-36	34	6.12
Left fusiform gyrus	37	-40	-56	-16	7.41
Left superior parietal lobule	7	-24	-64	46	6.25
Right superior parietal lobe	39	30	-58	44	5.61
Right cerebellum		34	-64	-28	5.34
Left middle occipital gyrus	18	-36	-90	6	7.86
Right middle occipital gyrus	18	32	-86	0	7.88

Table 7. Significant task-related activation peaks of the concussion group ($P < 0.05$ (FDR-corrected)).

Region	BA	x	y	z	T
Supplementary motor area	6	2	10	54	5.27
Supplementary motor area	6	-2	4	60	11.04
Left middle occipital gyrus	18	-26	-88	-12	6.77

Table 8. Significant task-related activation peaks of the mTBI group ($P < 0.05$ (FDR-corrected)).

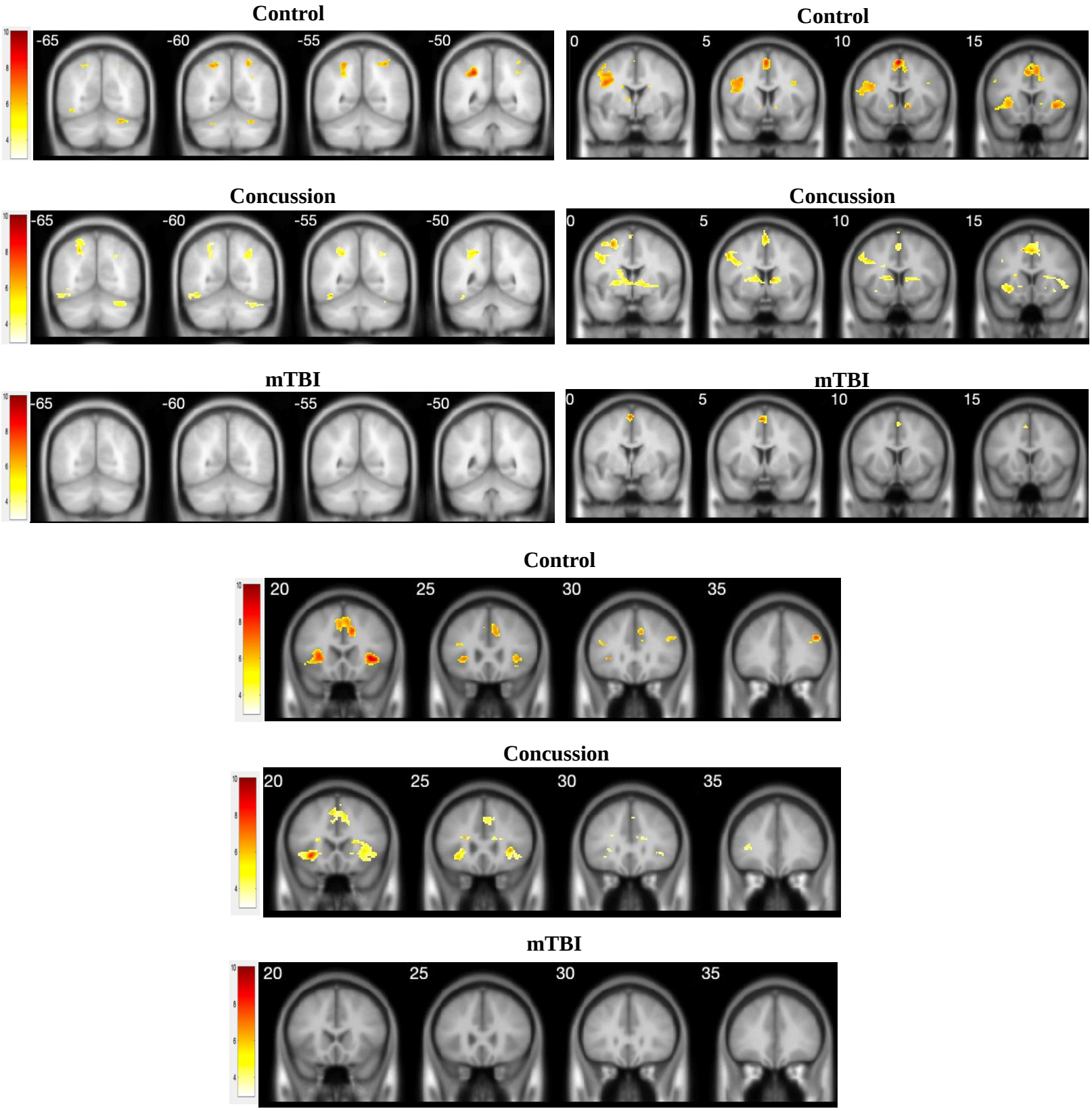


Figure 5. BOLD activation patterns for the working memory condition against the control condition for each respective group. Numbers correspond to y coordinate.

ANOVA Results

To analyze whole-brain differences between the three groups, ANOVA was carried out and revealed significant group effects (see Table 9). Post hoc tests indicated that the mTBI group had significantly less activation than the control and concussion groups in the left and the right cerebellum, the right middle temporal gyrus, and the left superior parietal lobe. Meanwhile, the concussion group had significantly decreased activation in the left insula when compared to the control group.

Region	**BA**	**Anatomical Location (x y z)**	**Mean BOLD Change (%)**			**F statistic**
			Control	*Concussion*	*mTBI*	
Left cerebellum		-2 -52 -26	0.111	0.120	-0.088*†	7.82
Right cerebellum		6 -52 -26	0.088	0.188	-0.109*†	7.39
Right middle temporal gyrus	21	44 -26 -14	0.002	0.024	-0.110*†	7.33
Left superior parietal lobule	7	-16 -50 58	0.036	-0.048	-0.242*†	7.18
Left insula	13	-32 22 10	0.341	0.067*	0.248	7.17

Table 9. Percent BOLD signal change and F statistic results in the ANOVA-identified regions in the verbal working memory task.
* Significantly lower than control group ($p<0.05$).
† Significantly lower than concussion group ($p<0.05$).

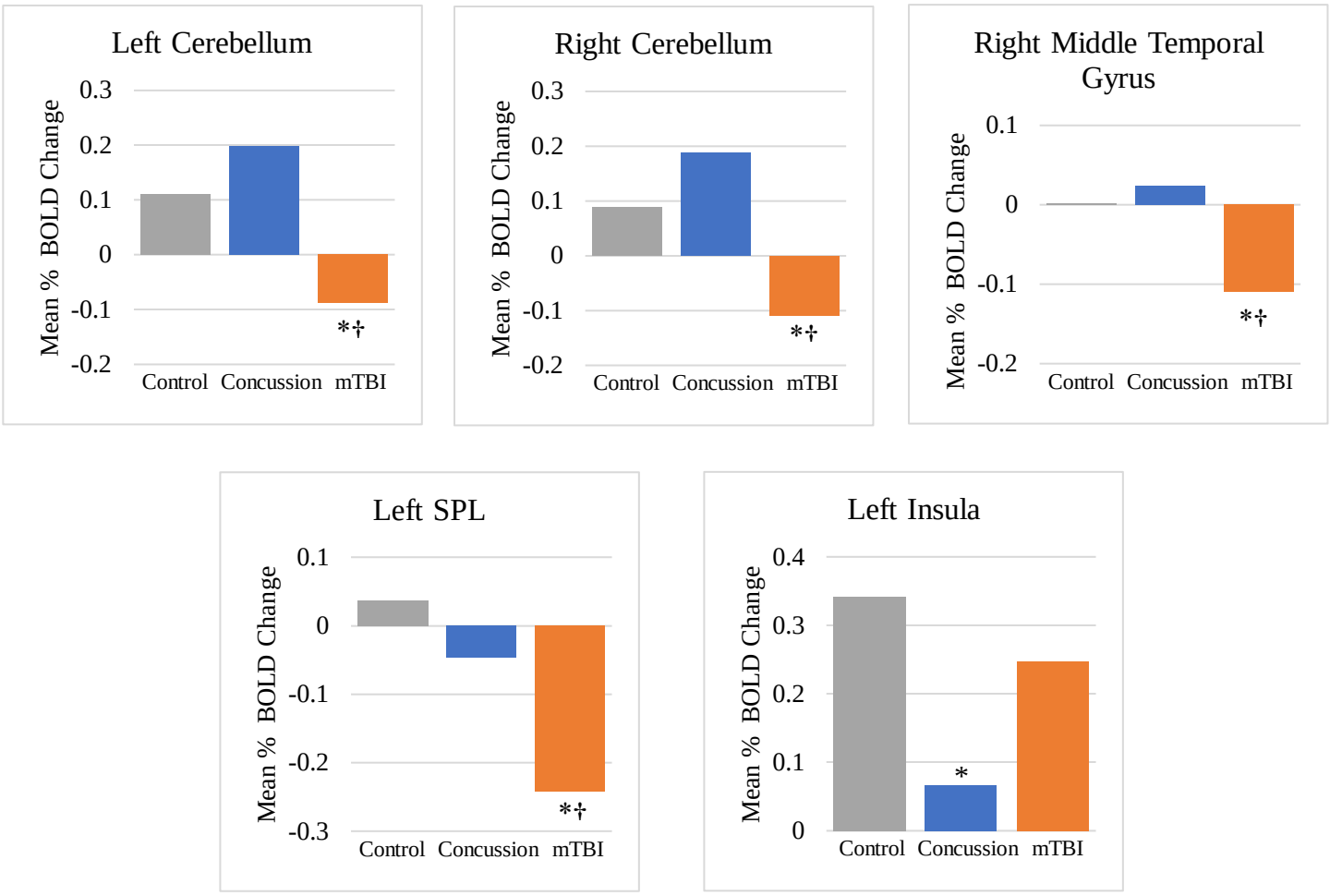


Figure 6. ANOVA results showing differences in BOLD signal change between the control (grey), concussion (blue), and mTBI (orange) groups.
* Significantly lower than control group ($p<0.05$).
† Significantly lower than concussion group ($p<0.05$).
SPL, superior parietal lobule.

ROI Analyses

Region of interest analyses were carried out to further quantify the observed differences in activation patterns. Specifically, ROIs were identified using the average activation map of the control group, where significant peaks were detected. The corresponding mean activations were extracted for each group. Out of all activation peaks for the control group, post hoc analyses indicated that the mTBI group had decreased activation in the right DLPFC, left pars orbitalis, bilateral premotor cortices, right superior parietal lobule, and right cerebellum, followed by the concussion group that had less BOLD signal change than the controls in these regions, but higher activation than the mTBI group (see Figure 7).

Individual Analyses

To determine whether BOLD responses of each brain injured individual was within the range of the control group, we calculated a 95% confidence interval of the percent BOLD signal change of the control group in the right DLPFC, as this is a region that is highly identified within the literature using this working memory task. The confidence interval was used to establish a range of 'normal' task-related signal variation. As seen in Figure 8, in the right DLPFC all but two of the patients in the mTBI group presented with BOLD responses outside of the 95% confidence range of the control group, whereas nine of those in the concussion group had BOLD responses outside of the 95% confidence range of the control group.

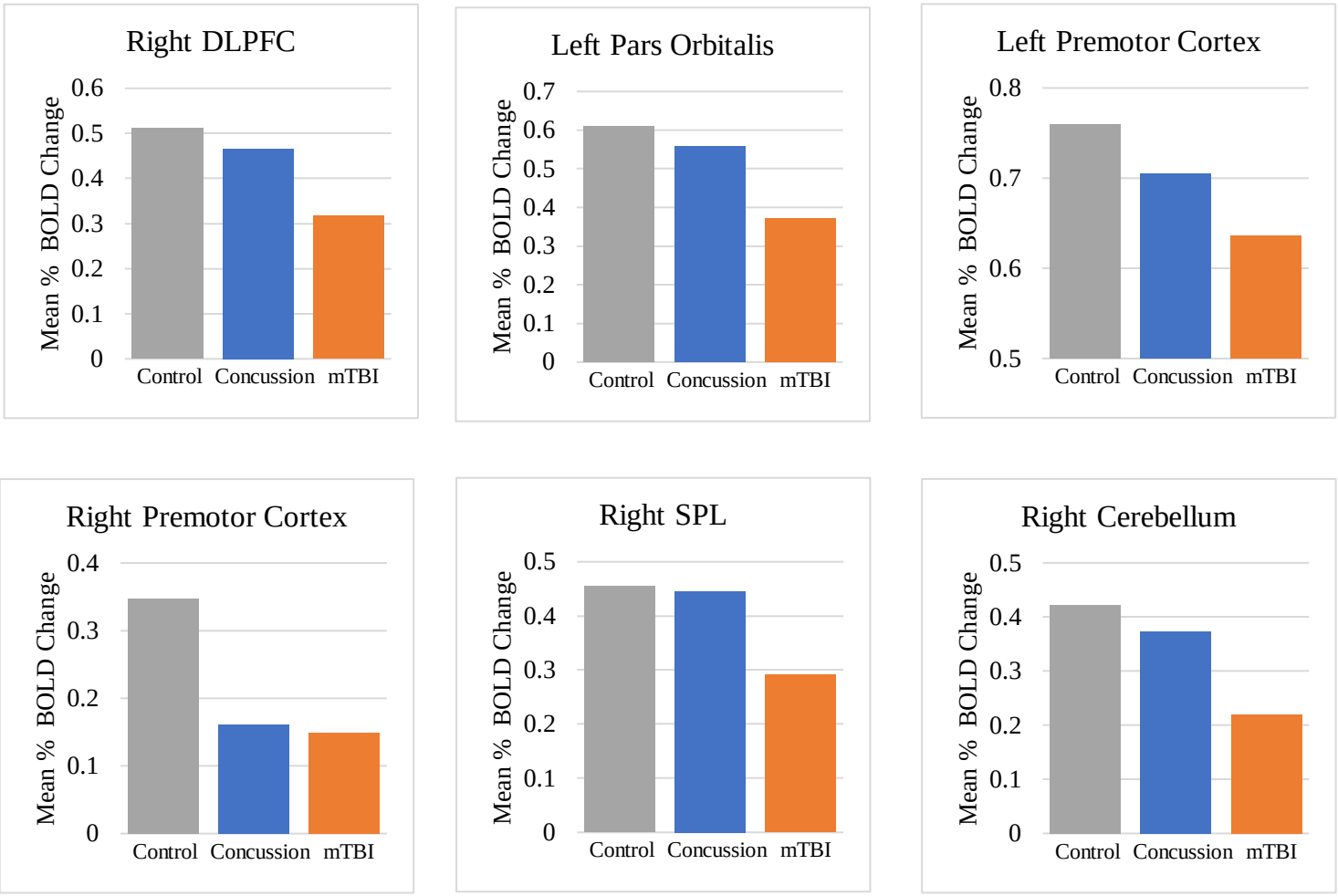


Figure 7. Results from ROI Analyses showing the most activation in the control group, followed by the concussion group, and the least activation in the mTBI group during the verbal working memory task.
DLPFC, dorsolateral prefrontal cortex; SPL, superior parietal lobule.

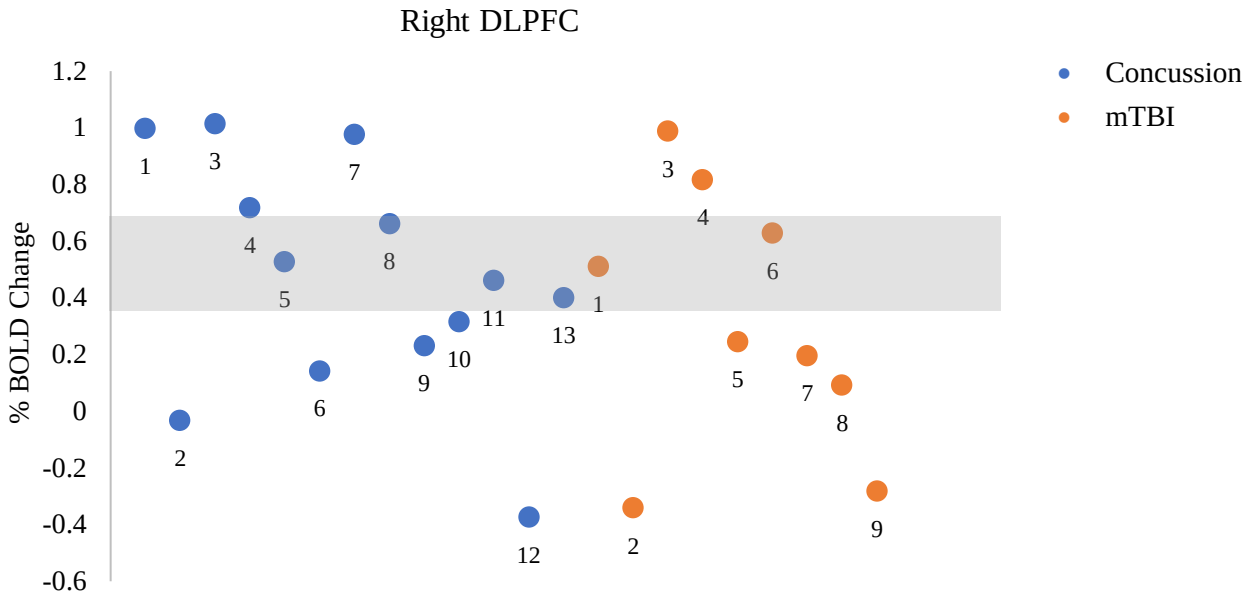


Figure 8. Individual % BOLD signal change in right DLPFC during the task. Both groups showed responses outside of the 95% confidence range of the control group (shaded area, 95% CI [0.381-0.641]).

Linear regression

Finally, to further examine the relationship between post-concussion symptoms and fMRI activation patterns, we analyzed the relationship between post-concussion symptom scale scores and the % BOLD change in the bilateral DLPFC using a linear regression approach. Linear regressions did not show significant correlations between BOLD signal changes in the DLPFC and PCSS in the mTBI or the concussion group, meaning that patient symptomatology did not correlate with our fMRI results.

Discussion

We used an externally ordered working memory task with fMRI to investigate whether patients who fit the CISG definition of concussion but lack the clinical criteria of mTBI as

defined by the WHO (i.e., LOC, PTA) have similar activation patterns compared to mTBI patients. In doing so, we aimed to clarify the appropriate use of the terms mTBI and concussion. The findings from this study revealed that, despite performing equally on the working memory task, altered fMRI activation patterns were different between the concussion and mTBI groups. The mTBI group generally showed significantly reduced BOLD signal changes when compared to concussion and control groups. In contrast, the concussion group showed some reduced and some increased activations compared to the control and mTBI groups.

fMRI findings of peak activations in our control group are in correspondence with previous studies that have used the same working memory task (Chen et al., 2004, 2007, 2008; Gosselin et al., 2015) and confirm that this is a reliable task, providing consistent results across studies. This study is unique and the first of its kind to use this task to examine the differences in fMRI activation patterns between mTBI and concussion.

Both the concussion and mTBI groups showed differences in activations when compared to the control group, yet these alterations were different between the two groups. In the concussion group, atypical activation patterns were found outside of the regions of interest of the control group. This may be explained as the recruitment of additional brain regions acting a compensatory mechanism after head injury to maintain the same level of working memory performance. Findings from other task-based fMRI studies (Forcione et al., 2018; Holmes et al., 2018), as well as studies from our group using the same task (Chen et al., 2004), have supported this ideology. The mTBI group, however, did not present with activations outside of those of the control group, instead presenting with significantly decreased activations in most ROIs. The lower activations in the mTBI group may reflect greater functional abnormalities. It is possible that individuals in the mTBI group are less likely to engage in these compensatory mechanisms

after head injury. Taken together, it truly seems that these two diagnostic groups respond differently to the head injuries at the functional level.

While the goal of this study was to investigate functional imaging differences between concussion and mTBI groups, findings from neuropsychological tests also showed differences in performance between the groups, suggesting more cognitive challenges in the mTBI group. Significantly lower scores were found in the mTBI group in subtests of the processing speed index of the Weschler's Adult Intelligence Scale-IV, meaning increased difficulty with sustained attention, problems with visual discrimination, and slower mental processing. While Tower of London test scores were not significantly different between groups, the mTBI group presented with lower total correct, indicating impairments in aspects of problem solving; higher total moves and shorter first move time, proving increased impulsivity and decreased planning ability; and longer total time to complete the task when compared to the concussion group. As the mTBI group also presented with a generally greater percentage of participants with scores outside of the normalized range on the remaining tests, we may conclude that, after a head injury, those who fit the mTBI criteria seem to be more vulnerable to reduced cognitive functioning than those who fit the concussion criteria.

Further, ANOVA for whole-brain analysis resulted in significant group effects. The mTBI group had significantly less activation than the control and concussion groups in many identified regions. This was expected, as these injuries include more objective signs of head injury (e.g., LOC/PTA). It is possible that task-related brain activity correlates with the injury specific factors after brain injury, as mTBI patients presented with decreased cerebral activation during the working memory task.

ROI analyses from regions of the average activation map for the control group showed a trend of the control group presenting with the highest activations, followed by the concussion group, and finally the mTBI group presenting with the lowest activation. These findings provide support of a linear spectrum of injury severity.

We also analyzed individual activations to determine whether the BOLD response of each participant in the mTBI and concussion groups was within the range of the control group in our ROIs. Seven of nine of the mTBI patients presented with BOLD responses outside of the 95% confidence range of the control group (77.8% of patients), whereas nine of 13 of those with concussion were outside of the confidence interval (69.2% of patients). It seems that those with concussion are more likely to have activations that are within the normal range, whereas those with mTBI have more altered activation patterns relative to the control group.

Finally, linear regression analysis did not yield significant relationships between PCSS score reported by the patient and the degree of BOLD signal change in the DLPFC. This may be because PCSS is a self-reported measurement, and thus ulterior motives, such as high stakes to return to activities of daily living or work, or the involvement of insurance claims, has the potential to introduce bias of the self-reported symptoms. There were also no significant differences between reported PCSS scores in the mTBI and concussion groups. These findings may suggest that PCSS does not contribute as a diagnostic indicator that can aid in differentiating between these two head injuries in the future.

Although the terms concussion and mTBI have traditionally been used interchangeably across disciplines, it seems that it may not be appropriate to combine mTBI and concussion under one diagnostic banner. The BOLD signal changes seen in this study are reflective of this, as the concussion group generally showed greater activations than the mTBI group on the task.

We recognize that mTBI patients present with greater functional changes post-injury. Based on our findings, TBI should be treated as a spectrum, classifying mTBI and concussion as distinct diagnostic entities, with concussion at the least severe end of the spectrum. This ideology can be visualized in Figure 9.

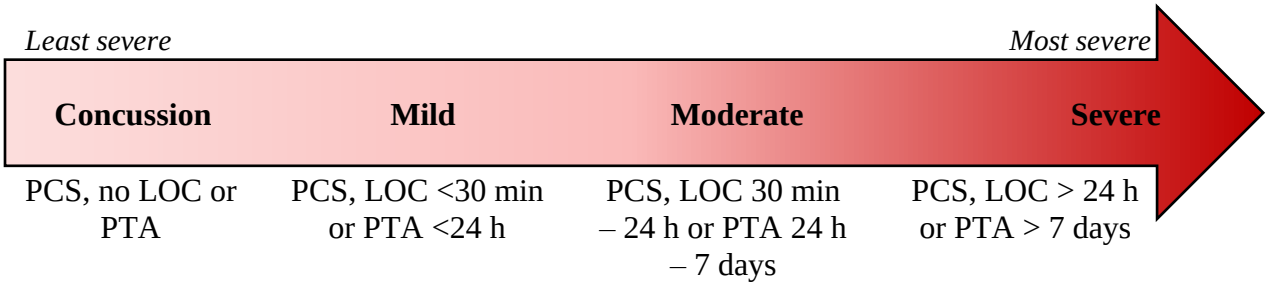


Figure 9. Ideology of TBI as a spectrum.
PCS, post-concussive symptoms; LOC, loss of consciousness; PTA, post-traumatic amnesia.

There is great potential for knowledge translation of the findings to clinical settings. Accurate diagnoses of concussion and mTBI are necessary to effectively communicate with patients and guide subsequent management decisions. If mTBI and concussion are to be treated as distinct entities, access to services and treatment plans may differ based on the diagnosis given. Additionally, this study allows us to be more inclusive of all patients with mild head injuries, especially those outside of the sports setting who fit the CISG concussion criteria but do not fulfill the diagnostic criteria for mTBI. Research to date has also tended to focus on concussion specifically in the sport context, which has led to those who play sports having a better understanding of these injuries than the general public (McKinlay et al., 2011). As our study identified that concussions do occur in the general population, distinct from mTBI, future research should aim to ensure that the concussion definition is fully understood by the general

population. This will also contribute to gaining more reliable incidence data for both mTBI and concussion.

The findings of this study may also have significant medicolegal ramifications. With differences in fMRI activation patterns seen between the concussion and mTBI group, insurance companies may need to be aware of and acknowledge both injuries separately, particularly in situations involving workman's compensation. While mTBI seems to be more severe than concussion, there may be a need for adjustments to disability leave and/or return to work recommendations, as individuals with different injuries may require different arrangements.

Finally, our findings have important implications in the research context. It may be necessary to now enrol individuals with mTBI and concussion as separate patient populations due to the differences we presented in fMRI activation patterns and neuropsychological testing results between groups. While this will drastically impact the recruitment process of patients in future studies on these head injuries, it may also decrease the number of failed studies testing concussion therapies and contribute to more solidified results after years of confusion with heterogenous patient populations.

It is important to consider the limitations of our findings. First, we address that this study included participants up to five weeks post injury and it may be important to determine if varied time since injury influenced fMRI activation patterns. Further, heterogeneity in mechanism of injury may create conflicting findings and limit the reproducibility of such a study; investigators should continue to define the various clinical profiles that commonly occur following these head injuries. Other factors, including education, hormone levels, medication use (outside of those mentioned in the exclusion criteria), aging, and stress may also inevitability play a role in variability between patients and is thus important to consider when interpreting the results.

Further, while task-based fMRI has shown the most consistent and reproducible results in the diagnosis of concussion and mTBI of the current advanced neuroimaging tools available, there are some disadvantages. First, the ability to only study a specific subset of cognitive processes, in this case working memory, creates drawbacks, as a vast number of other cognitive processes have not been considered but may be equally worth studying after injury. Factors such as patient performance, poor effort, fatigue, and different learning styles may also act as confounding issues and account for variability between participants (Wu et al., 2016).

It is also important to note that there were sex differences within and between groups. However, average t-maps of both males and females were compared and analyzed to determine if there were differences in fMRI activation patterns. With no significant differences found, we deemed it acceptable to group both males and females together for the purpose of this study.

Finally, focusing on our study's sample size, it is worth mentioning that our study focused on a relatively small sample size, which may limit the generalizability of our findings. Alternatively, however, the group differences we have found thus far may represent a large and genuine effect. Future directions include increasing sample size to improve reliability of such a study.

Conclusion

Over the years, there have been increasing recommendations to investigate and differentiate mTBI and concussion. Prior to the work presented here, no studies have attempted to unravel the complex pathophysiological processes that underlie mTBI and concussion. As a

result, the main purpose of this study was to determine if alterations in fMRI activations were found between those who fit the concussion definition and those who fit the mTBI definition.

The overall findings of our study indicated that concussion and mTBI may need to be treated as distinct diagnostic entities, as differences in altered BOLD signal changes were found between the two groups. We suggested that the TBI spectrum should be modified to depict the optimal classification system, with concussion being less severe than mTBI.

Next steps on this topic will focus on relating BOLD signal changes found in this study to neuropsychological test results measured outside of the scanner to determine if they are explanatory of the differences between groups. This is a subject of study that has already been initiated by our group.

Taken together, this study aimed to clarify and advance the empirical and clinical understanding of mTBI and concussion, addressing the public health concern that is TBI. Future directions largely include knowledge translation efforts. As the CISG definition of concussion was originally designed for the sports context, it seems appropriate for use in the general population. These findings should thus be disseminated to clinical and research settings.

This study used fMRI as a initial measure to determine differences between mTBI and concussion, however utilization of neuroimaging techniques for the diagnostic process is currently in its initial phases (Cook & Hawley, 2014). Follow-up research could focus on determining if differences between mTBI and concussion groups found in this study are also present using other advanced neuroimaging techniques (i.e., resting-state fMRI, diffusion tensor imaging). Another future avenue that should be explored is developing more accessible and simple diagnostic methods for these injuries, as fMRI is often impractical in clinical settings due to its complex procedures. Areas of active research currently moving in conjunction with fMRI

include genetic sequencing, blood biomarkers, computerized tests, and other advanced neuroimaging techniques (Cade & Turnbull, 2022; Hiskens et al., 2020; McKeithan et al., 2019). Combined, these techniques are leading to improved diagnosis of mTBI and concussion, with the potential to yield a more accurate understanding of the severity of each head injury.

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