Title

Linking the Gap Between Traumatic Brain Injuries and Cognitive Impairments Through the Creation of Machine Learning-Based Diagnostic and Prognostic Clinical Tools

ISBN

9798247951681

Author

Ashikyan, Sonya

Publication Date

2026-06-01

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Linking the Gap Between Traumatic Brain Injuries and Cognitive Impairments Through the Creation of Machine Learning-Based Diagnostic and Prognostic Clinical Tools

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Psychology

by

Sonya Arayi Ashikyan

2026

ABSTRACT OF THE DISSERTATION

Linking the Gap Between
Traumatic Brain Injuries and Cognitive Impairments
Through the Creation of
Machine Learning-Based Diagnostic and
Prognostic Clinical Tools

by

Sonya Arayi Ashikyan
Doctor of Philosophy in Psychology
University of California, Los Angeles, 2026
Professor Martin M. Monti, Co-Chair
Professor Barbara J. Knowlton, Co-Chair

A traumatic brain injury (TBI) is a condition in which normal brain function is disrupted because of an external force which impacts the head. There are three main types of TBI: mild, moderate, and severe, with sports-related concussions (SRC) being a subcategory of mild cases. Mild TBI and sports-related concussions often involve slowed processing speed, attention deficits, difficulty recalling memories, trouble sleeping, and mood swings. On the other hand, moderate-to-severe cases involve more pronounced brain damage leading to challenges with language, executive function, memory loss, and in many cases, death. In the United States alone, TBI is the

cause of over 5.3 million individuals living with a disability and each year an additional 1.7 million Americans also suffer across their lifespan, especially vulnerable groups, such as youth and older adults. Moderate-to-severe TBI leads to about 52,000 deaths each year in the United States alone, making it the main result of injury-induced death and disability with about 86% of these deaths being caused by the withdrawal of life-sustaining therapy. The great majority of those who do survive such an injury typically do not have a full recovery and are forced to live with life-long impairments.

This dissertation offers and tests various solutions for the clinical and research settings discussed in the first chapter, which presents a brief literature review of traumatic brain injuries. In the second chapter, the relationship between clinical assessments and structural neural consequences are investigated at the single mild TBI level. In the third chapter, the interaction between sleep quality and structural and functional neural correlates are investigated in sports-related concussions (SRC). The fourth chapter investigates the relationship between outcome measures and the structural neural consequences of patients with moderate-to-severe TBI experiencing disorders of consciousness (DOC). Lastly, the fifth chapter presents a tool that automates this process by creating a machine learning based clinical tool which serves diagnostic and prognostic purposes using the mild TBI dataset. Overall, this dissertation presents a series of studies suggested to better understand the relationship between cognitive impairments and neural states after a single mild TBI, sports-related concussions, and moderate-to-severe TBI, and offers a solution to incorporate neuropsychological assessments in the real world setting through the creation of a deep learning model.

The dissertation of Sonya Arayi Ashikyan is approved.

Christopher C. Giza

Marco Iacoboni

Jeffrey N. Chiang

Martin M. Monti, Committee Co-Chair

Barbara J. Knowlton, Committee Co-Chair

University of California, Los Angeles

2026

DEDICATION

To my husband, Arman Ghazaryan, who has given me the strength and courage to make this work possible. You have believed in me since the day we met. Your motivation, support, and patience have given me the stability to overcome any difficulty, no matter what the circumstances. You give me confidence in achieving my goals even when I feel doubtful. I am fortunate to have you by my side; words cannot express the appreciation I have for you. You are the inspiration behind all the years of work that went into the creation of this dissertation. I had you in mind every step of the way. I would not have been able to make this work happen without you.

I love you.

To my parents, Ara Ashikyan and Hasmik Yepremyan, whose sacrifices made it possible for me to access the opportunities that led to this work, and who never stopped encouraging me to dream bigger. To my brother, Sargis Ashikyan, who has always stood by my side and brought constant positivity, even in times of uncertainty. Throughout every struggle and setback along this path, I reminded myself of the sacrifices that were made so that I could have these opportunities. No words can fully capture the pride and respect I have for you all. You have raised me with the work ethic, resilience, and character necessary to accomplish what is presented in this dissertation. I am privileged to call you, my family.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGMENTS

The completion of the work that went into this dissertation would not have been possible without the people mentioned below, those who I cannot thank enough and have immeasurable gratitude for. It has truly been an honor of mine to have received such genuine support along the years.

First and foremost, I would like to give special thanks to my advisor, Dr. Martin Monti, who has given me mentorship as an undergraduate researcher and graduate student for the past five years. During the early stages of my doctoral training, he taught me how to think clearly and effectively like a scientist; encouraging originality while grounding ideas in strong theoretical and methodological foundations. This experience fostered a sense of belonging within the scientific community and laid the foundation for my professional confidence and independence as a researcher. I cannot thank him enough for always believing in my ideas and in my potential, his encouragement has shaped me into who I am as a scientist. I would also like to thank a fellow lab member, Amber Hopkins, who has become a great friend of mine. For the past four years, she has always been the person I can rely on for support and understanding as well as advice in this program, as we both went through each milestone together. She helped shape a big part of my graduate experience, immensely, and for that I am forever grateful. I would also like to thank Dr. Micah Johnson for his guidance and endless hours investing in the development of my technical skills.

I would also like to thank my secondary advisor and undergraduate mentor, Dr. Barbara Knowlton, whose laboratory was the first I joined at UCLA and opened many doors for me. When I first began working with Dr. Knowlton six years ago, I was 18 years old on the pre-med track with very little experience, somehow, she saw the potential in me as a scientist. She never doubted my capabilities and offered strong endorsement for my acceptance into this program. I

am beyond grateful for her years of encouragement and I am undoubtedly extremely fortunate to have had the opportunity to work with her for so long.

I would like to express my appreciation for Dr. Aaron Blaisdell, who was the first person to ever suggest that I consider a science career. Five and a half years ago, Dr. Blaisdell expressed that he believed that I would make a great scientist. From that day on, I had finally reached the realization of what I wanted to do. He helped me find my passion, which had certainly changed my life for the better and for that I am forever appreciative. He taught me how to feel comfortable expressing my thoughts and theories during meetings. When I felt out-of-place, he helped me build confidence in those ideas and to not fear taking them forward. Dr. Valeria Gonzalez Diaz, who I had the pleasure of working under at the Blaisdell Lab, took the time to introduce me to science. She did so because she truly believed that I would find fulfillment in conducting my own independent research, she was most definitely right. I am deeply touched by her kindness, consideration, and devotion in making me realize my dream of becoming a scientist and guiding me to that goal through direct mentorship. She is the predominant reason why I was fortunate enough to receive acceptance into this program and for that I am obliged.

I would also like to express my gratitude to Dr. William Grisham and Dr. Avishek Adhikari as they have both shaped me as an academic instructor. They have both continuously reassured me and helped me build confidence as an instructor who worked with thousands of students over the course of two years. I am truly fortunate to have been able to work with you both under your guidance.

Last but certainly not least, I wish to convey my most sincere appreciation to my parents-in-law, Artak Ghazaryan and Lilit Khachatryan, for their unwavering support and faith in my abilities. I am truly fortunate to have such uplifting and accommodating new extended family.

It is inevitable that I cannot thank everyone who has shaped this journey. Nevertheless, I would like to acknowledge all the friends and family who have given me positivity and motivation over the years, who were completely understanding when I had to miss countless gatherings due to work.

BIOGRAPHICAL SKETCH

SONYA A. ASHIKYAN

Education

Sept 2022 – Dec 2023	**University of California, Los Angeles (UCLA)** *Master of Arts (M.A.) in Psychology* Cumulative GPA: 3.7/4.0
Sept 2019 – Jun 2022	**University of California, Los Angeles (UCLA)** *Bachelor of Science (B.S.) in Cognitive Science* Cumulative GPA: 3.7/4.0

Patents

Mar 2026	**Ashikyan, S.A.,** Monti, M.M., Chiang, J.N. (2026). Machine Learning System for Predicting Cognitive Deficits from Multimodal Brain Imaging Data Following Brain Injury (U.S. Provisional Patent Application No. 64/000,751). United States Patent and Trademark Office (USPTO)

Publications

Apr 2026	**Ashikyan, S.A.,** Chiang, J.N., Giza, C.C., Bickart, C.K., Monti, M.M. (2026). Correlating Sleep Quality with Multimodal Neuroimaging Data in Sports-Related Concussions (In-Progress)
Oct 2025	**Ashikyan, S.A.,** Chiang, J.N., Monti, M.M. (2026). Creating a Diagnostic and Prognostic Machine Learning Tool for Mild Traumatic Brain Injuries (In-Progress)
Oct 2025	**Ashikyan, S.A.,** Lutkenhoff E., Monti, M.M. (2025). Pairing Multimodal Neuroimaging Data with Outcome Measures in Moderate-to-Severe Traumatic Brain Injury (In-Progress)
Sept 2025	**Ashikyan, S.A.,** Robertson, C.S., Monti, M.M. (2025). High T2-Weighted Multi-Echo and FLAIR Signals Associate with High Stress and Low Resilience After Mild Traumatic Brain Injury (In-Progress)
Jun 2025	**Ashikyan, S.A.*,** De Guzman, H.*, Castel, A.D., Rissman, J., Knowlton, B.J. (2025). Effects of Transcranial Direct Current Stimulation on the Left Ventrolateral Prefrontal Cortex in Value Directed Remembering (Preregistered & In-Progress)
Apr 2024	González, V. V., Zhang, Y., **Ashikyan, S. A.**, Rickard, A., Yassine, I., Romero-Sosa, J. L., Blaisdell, A. P., & Izquierdo, A. (2024). A special role for Anterior Cingulate Cortex, but not Orbitofrontal Cortex or Basolateral Amygdala, in choices involving information. *Cerebral Cortex,* Volume 34, Issue 4, April 2024, bhae135 https://doi.org/10.1093/cercor/bhae135

Conferences

Mar 2026	**Ashikyan, S.A.,** Robertson, C.S., Monti, M.M., Chiang, J.N. Predicting Recovery Group following Mild Traumatic Brain Injury using Multimodal MRI and Machine Learning. *Annual Conference*

	for the North American Brain Injury Society (NABIS). Washington, D.C. (Talk)
Jun 2025	**Ashikyan, S.A.,** Monti, M.M. The neural consequences of traumatic brain injury and cognitive impairment. *Annual International Conference for the Organization of Human Brain Mapping (OHBM).* Brisbane, Australia.
Oct 2024	**Ashikyan, S.A.,** Holder, A., Monti, M.M. Mild Traumatic Brain Injury and Cognitive Impairment: Multimodal Magnetic Resonance Imaging Analysis. *Annual International Conference for the Society for Neuroscience (SfN).* Chicago, Illinois.
Mar 2023	**Ashikyan, S**.**A**., De Guzman, H., Retika, C., Castel, A., Rissman, J., Knowlton, B. Modulating the Control of Value-Directed Remembering with Transcranial Direct-Current Stimulation of Prefrontal Cortex. *30th Annual Conference for Cognitive Neuroscience Society (CNS)*. San Francisco, California.
Dec 2021	**Ashikyan, S**.**A**., Gonzalez, V.V., Sadeghi, S. and Blaisdell, A. Conjunction Bias in Rats. *20th Biennial Meeting of the International Society for Comparative Psychology*. Virtual Conference (Santiago, Chile).

Funding

May 2023	**Psychology Summer Graduate Student Mentorship (PGSRM)** *Amount: $1,000*
Jun 2023	**Mangasar M. Mangasarian Privately Endowed Fellowship** *Amount: $15,000*
Apr 2022	**Eugene V. Cota-Robles Fellowship Recipient** *Amount: $115,600*
Apr 2022	**Summer Mentored Research Fellowship Recipient (SMRF)** *Amount: $6,000*

Teaching Experience

Mar 2024 – Sept 2025	**Associate Instructor** *Cognitive Psychology* - One quarter *Behavioral Neuroscience Laboratory* - Four Quarters *Principles of Behavioral Neuroscience* - One Quarter
Sept 2022 – Mar 2024	**Teaching Assistant** *Principles of Behavioral Neuroscience* - Two Quarters *Introduction to Psychology* - One Quarter

Programs

Oct 2025	**UCLA - Institute for Quantitative and Computational Biosciences** *Machine Learning with Python*
May 2024 – Jun 2026	**Society for Neuroscience (SfN)** *Neuroscience Scholars Program (NSP)*
Apr 2023 – Jun 2023	**UCLA – Graduate Programs in Bioscience - Center for the Improvement of Mentored Experience in Research (CIMER)** *Entering Mentoring Training Program (EMT)*

Chapter 1: Introduction to Traumatic Brain Injuries in Adults

1.1 Background

A traumatic brain injury (TBI) is defined as a condition which is characterized by the disruption of normal brain function resulting from an external force impacting the head that may or may not cause penetration (Capizzi et al., 2020). TBI can be caused by different types of impacts; direct impact, acceleration-deceleration, and shock wave injury (Figure 1.1; Suer & Abd-Elsayed, 2020). Direct impact injuries occur when the head and an object meet at extreme force, leading the brain to hit the skull. Acceleration-deceleration injury occurs when the head does not meet an object; however, the force of accelerating then decelerating quickly leads the brain to hit the skull. Lastly, like acceleration-deceleration injuries, shock wave injuries also do not occur from the head and an object meeting impact and instead are obtained from a strong shock force such as a blast explosion. TBIs are alarmingly prevalent, with over 5.3 million individuals in the United States living with a disability caused by TBI, and an additional 1.7 million Americans sustaining a TBI each year (Dixon, 2017). There are three main types of TBIs: mild, moderate, and severe. Mild TBI, often referred to as a concussion, may involve the temporary loss of consciousness or confusion and is typically associated with cognitive impairments such as difficulties with attention and concentration, and slowed processing speed. Moderate and severe TBIs, on the other hand, involve more pronounced brain damage including fractures of the skull, traumatic hemorrhage, hydrocephalus, and can require emergency surgical removal of brain matter, which can necessitate an extended period of pharmacologically induced coma (Taylor et al., 2017). This leads to more profound cognitive impairments, including loss of consciousness from several minutes to hours, significant memory deficits, difficulties with executive functions

such as planning and problem-solving, and challenges with language and communication (Pavlovic et al., 2019).

1.1.1 General Population

Understanding TBI is of paramount importance for the general population due to its significant global impact. In the United Kingdom, TBI is the primary cause of death and disability among

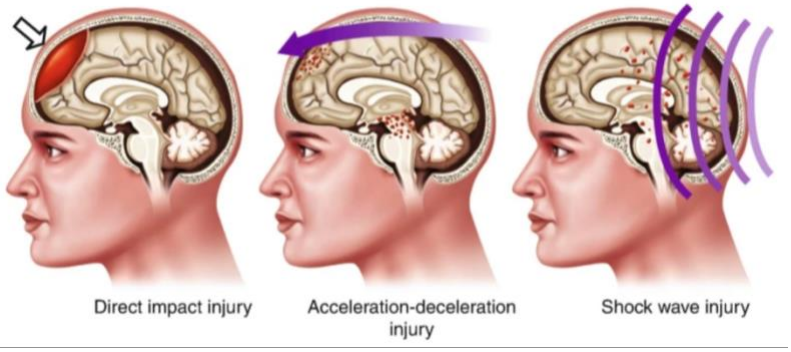


Figure 1.1. Types of impacts which cause Traumatic Brain Injuries (Suer & Abd-Elsayed, 2020)

individuals under 40 years old, highlighting its profound impact on the younger population. Furthermore, in low-income and middle-income countries, higher rates of morbidity and mortality are observed (Khellaf et al., 2019). In the United States, TBI is the leading cause of death and disability among trauma patients, who are typically between the ages of 1 to 45 years old, with over 50,000 deaths per year (Vella et al., 2017). Falls caused 35% of TBIs while motor vehicle collisions caused 17%. These two causes of injury are the most common causes of TBI and while motor vehicle collisions contribute to less of the percentage of cases, they are still responsible for most of the fatalities caused by TBI (Vella et al., 2017). These statistics underscore the urgent need to understand and address all three types of TBI, as it affects individuals across all socioeconomic backgrounds and carries significant implications for public health and the economy.

1.1.2 Sports-Related Concussions

Sports-Related Concussions (SRC) are typically due to both linear accelerations, causing intracranial pressure, and rotational acceleration, causing the brain tissue to trigger a microstructural strain response (Figure 1.2; Jordan, 2013). Although many sports require helmets

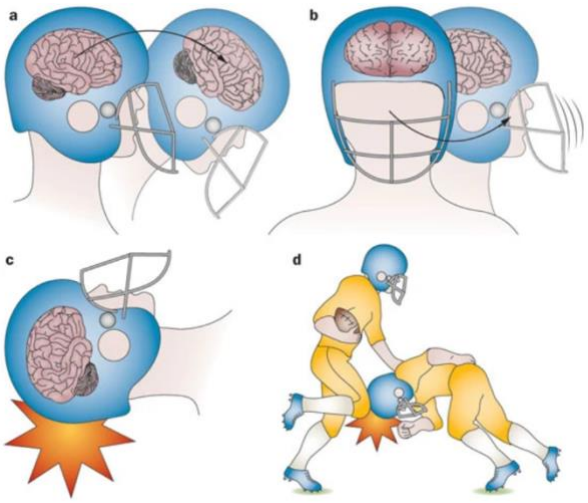


Figure 1.2. Types of sports-related concussions (SRC; Jordan, 2013)

Note. (a) Linear acceleration (b) Rotational acceleration (c) Impact deceleration (d) Secondary impact deceleration

as part of their uniform, helmets only mitigate linear acceleration forces, not rotational acceleration. Unfortunately, it is suggested that this rotational acceleration is the main cause of the SRC (McKeithan et al. 2019). In the United States, it is estimated that approximately 10% of TBIs are attributed to sports and recreational activities (Sahler & Greenwald, 2012). The long-term consequences of SRCs can have a significant impact on the well-being of athletes. Some individuals may experience cognitive impairments years after their TBI occurred, with a clear association between these deficits and multiple prior concussions. Studies show that former non-professional American football athletes do not have an increased risk of being diagnosed with neurodegenerative diseases in their lifetime. However, there is evidence suggesting that former professional American football athletes are more likely to have an increased risk of experiencing

cognitive impairments and being diagnosed with neurodegenerative diseases (Manley et al., 2017). For this reason, all athletes who are suspected to have obtained an SRC should be diagnosed and examined for further spinal cord injuries. To prevent SRCs from worsening, administrators should create a stricter removal-from-play protocol which will take SRC patient injuries more seriously (Marklund et al., 2019).

1.1.3 Military Personnel

Research indicates that mTBI occurs in a considerable percentage in the veteran population, ranging from 8-22% for United States soldiers who served in Afghanistan and Iraq only (Krainin et al., 2011). The consequences of mTBI in veterans are far-reaching, as recent studies show a 56% increase in likelihood of developing Parkinson's disease (Gardner et al., 2018). Moreover, between 5-35% of military personnel sustained a mTBI during their service, highlighting its prevalence within this population (Lindberg et al., 2022). During the Global War on Terror, the use of explosive devices led to a dramatic increase in blast injuries sustained by military

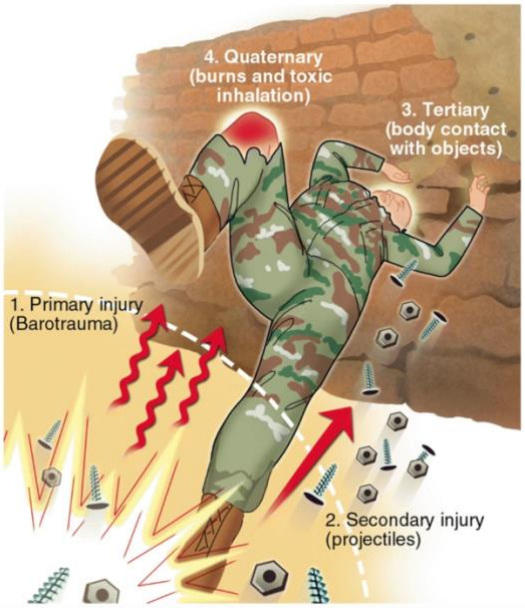


Figure 1.3. Types of impacts of blast injuries (Weppner et al., 2019)

personnel with many of them obtaining a severe TBI because of shrapnel penetration to the head,

with about 70% of all injuries being blast injuries and about 30% being a result of gunshot wounds (Figure 1.3; Weppner et al., 2019). To avoid further blast injuries, the overwhelming use of explosive devices led to two thirds of the wartime evacuations (Lindberg et al., 2022). In all TBI cases, the visual system is particularly vulnerable, as damage to the primary visual cortex can lead to visual field impairments. 74% of individuals who obtained a TBI had experienced visual impairments with 38% of them experiencing mild to complete blindness (Hussain et al., 2021). With TBI research rapidly evolving, U.S. military guidelines must also be updated with changes to discharge regulations that consider the severity of all types of TBI.

1.2 Levels of Severity

1.2.1 Glasgow Coma Scale Assessment

In assessing the severity of TBI, the Glasgow Coma Scale (GCS) is frequently used. The GCS evaluates three main components to determine the level of consciousness and neurological function following a TBI (Figure 1.4; Mehta et al., 2019). These three components use the following scoring system: eye opening (maximum 4 points), verbal response (maximum 5 points), and motor response (maximum 6 points). These components combine into a total score

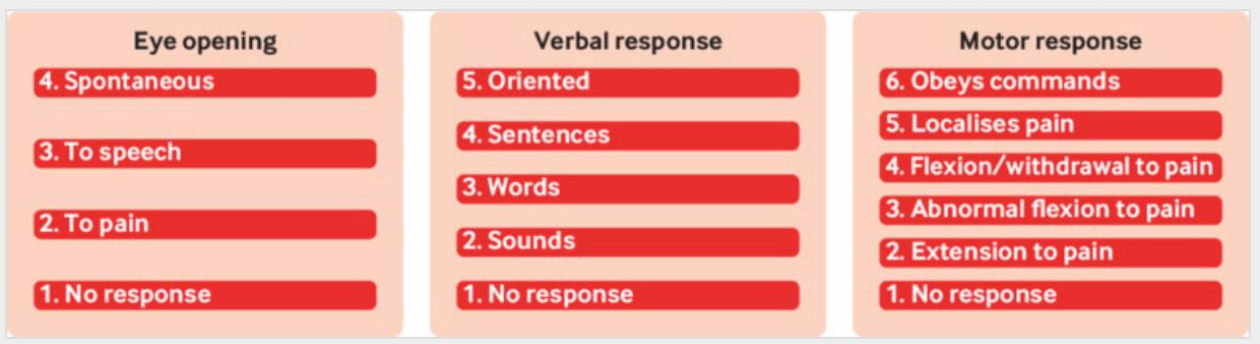


Figure 1.4. Glasgow Coma Scale (GCS) Characteristics (Mehta et al., 2019)

which can thus range from 3 (indicating deep unconsciousness) to 15 (indicating normal

consciousness). This scale plays a crucial role in guiding treatment decisions and prognosticating outcomes for individuals with TBI, aiding healthcare professionals in developing appropriate intervention strategies tailored to the individual's needs. The GCS assessment is used to distinguish the severity of TBI patients by classifying their symptoms within the categories of TBI. A total score between 3-8 indicates a severe TBI, while a total score between 9-12 indicates a moderate TBI, and a total score between 13-15 indicates a mild TBI (Table 1.1; Hassett, 2023). Other ways of determining TBI severity include the analysis of post-traumatic amnesia and loss of consciousness duration. Patients who experience post-traumatic amnesia for 0-24 hours are characterized as mild, 24 hours-7 days are characterized as moderate, and more than 7 days are considered severe. Additionally, patients who lose consciousness for 0-30 minutes are considered mild, 30 minutes-24 hours are characterized as moderate, and any duration that is longer than 24 hours is considered severe.

Injury severity	Post-traumatic amnesia	Glasgow Coma Scale	Loss of consciousness
Mild	0 to 24 h	13 to 15	0 to 30 min
Moderate	> 24 h to 7 d	9 to 12	> 30 min to 24 h
Severe:	> 7 d	3 to 8	> 24 h

Table 1.1. Three ways of determining the level of traumatic brain injury severity (Hassett, 2023)

1.2.2 Traumatic Brain Injury: Repetitive Mild

Physiopathology. Prior studies have also shown major impacts of demyelination after repeated mTBI (rmTBI), specifically leading to double concentric myelin sheaths in key areas of damage (Fehily & Fitzgerald, 2017). Due to the negative impacts of rmTBI, the brain copes by releasing

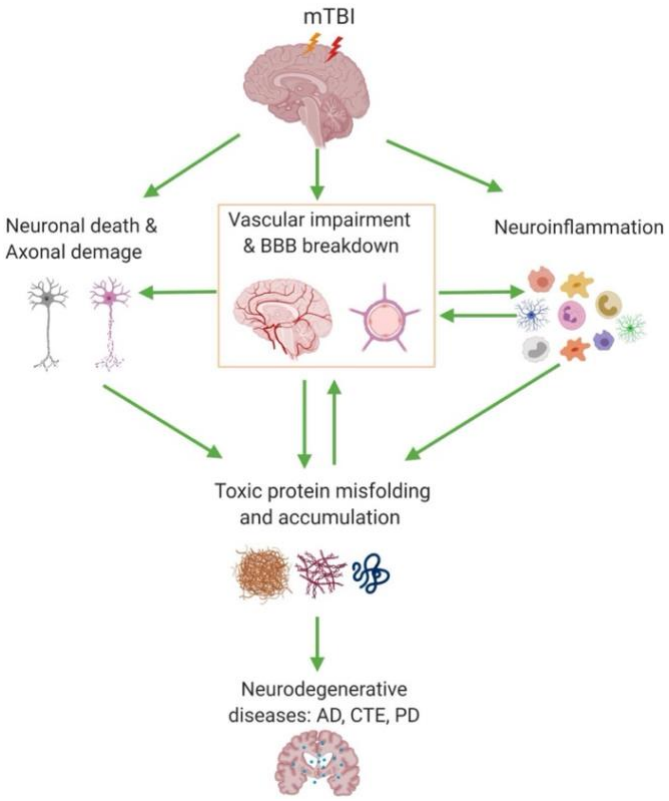


Figure 1.5. Effects of damaged Blood Brain Barrier (BBB) post-mild traumatic brain injury (mTBI; Wu et al., 2020)

an immune response which essentially increases the level of astrocytes as an effort to restore neuronal shape (Hoogenboom et al., 2019). Another immune response to such injury includes neuroinflammation which is a strong indicator of the true severity of the brain injury, causing notable damage to the blood-brain barrier (BBB) and brain edema (build-up of fluid in brain tissue; Figure 1.5; Wu et al., 2020). Severity includes the strength of impact, the number of mTBIs obtained, and the duration of time passed between each injury. Ultimately, understanding

the neural consequences and cognitive impairments associated with rmTBI is essential for recognizing the potential risks and developing strategies to mitigate long-term effects.

Chronic Traumatic Encephalopathy. Repetitive TBI can have significant consequences, including the delayed manifestation of Chronic Traumatic Encephalopathy (CTE). CTE is associated with psychiatric disturbances and often leads to major changes in personality and suicidal behavior, especially among athletes. In addition to psychiatric symptoms, CTE is characterized by dysarthric speech, tremors, attention difficulties, memory and executive function deficits, incoordination, and pyramidal signs (hyperreflexia, Babinski sign, spasticity, etc.) (Lohia & McKenzie, 2023). This condition is believed to result from progressive neuronal loss, which develops over time (Galgano et al., 2017). These deficits are so significant that epilepsy, depression, and Alzheimer Disease are strong predictors of whether an individual has obtained repeated TBIs at some point in their life (Chauhan et al., 2022). Repetitive mild head injuries, especially during the 6-month recovery period following a previous injury, can induce long-term white matter pathology. These changes are correlated with behavioral deficits, suggesting that the long-term consequences of repeated mild TBI may resemble the alterations observed in moderate and severe injuries, reflecting the cumulative effect of subsequent mild TBIs (Galgano et al., 2017).

1.2.3 Traumatic Brain Injury: Moderate-to-Severe

Non-Surgical Intervention: Ventilation. Since TBI patients are prone to experiencing high levels of intracranial pressure (ICP), mechanical ventilators are often used to reduce these ICP levels (Figure 1.6; Galgano et al., 2017). The most up-to-date recommendation for ventilation uses in the first 24-hours after experiencing a TBI suggests maintaining normoxia (PaO_2 60–100 mm Hg) and normocapnia (intraarterial carbon dioxide partial pressure (PaCO2) 35–45 mm Hg; El-

Swaify et al., 2022). Some specialists still suggest the use of hyperventilation to further lower ICP levels because of its ability to cause vasoconstriction. However, the majority agree against hyperventilation because it also leads to a decline in cerebral blood volume levels (Galgano et al., 2017). Nevertheless, there is a consensus on the importance of ventilation balance, as poor ventilation in severe TBI patients has been proven to spike mortality rates (Knapp et al. 2023). On the other hand, mechanical ventilation also poses the risk of causing acute lung injury from ventilator-induced lung injury and therefore must be used cautiously on this already vulnerable population (El-Swaify et al., 2022).

Lastly, patients who need respiratory support for a long period of time after a TBI, such as those in a comatose state in the ICU, are good candidates for a tracheostomy (Wiles, 2022). A tracheostomy is the surgical procedure of opening a new airway in the trachea and placing a tube through the newly created path (Robba et al., 2020). Early tracheostomy intervention (≤ 7 days) has been proven to reduce rates of ventilator-associated pneumonia (VAP; Chorath et al., 2021).

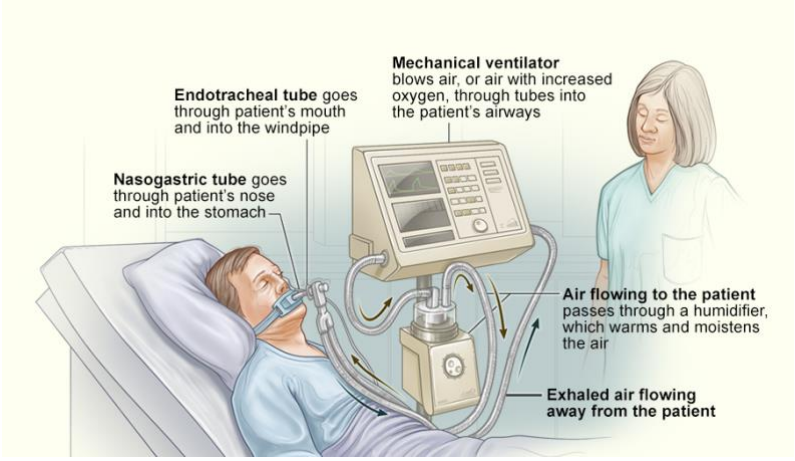


Figure 1.6. Mechanical ventilation system (National Heart, Lung, and Blood Institute)

Non-Surgical Intervention: Medically Induced Comatose State. Medically induced comatose states are administered to severe TBI patients who experience dangerously high refractory intracranial hypertension even after surgical ICP-lowering therapy (Galgano et al., 2017).

Clinicians achieve this state typically through the infusion of a benzodiazepine (ex. midazolam) or a barbiturate (ex. pentobarbital), which aids in lowering the metabolic demands on the brain. High metabolic demands on the brain put the patient at risk for pulmonary oedema, stress myocardium, and hyperadrenergic response, which could potentially cause a secondary brain injury (Kurni et al., 2023).

Surgical Intervention: Craniectomy & Craniotomy. In more severe cases, mechanical ventilators cannot reduce ICP levels leading to intracranial hypertension and a decompressive craniectomy (DC) or craniotomy is considered by physicians (Hutchinson et al., 2016). A craniectomy and a craniotomy are surgical procedures which include the removal of the skull to relieve pressure on the brain and therefore significantly reduce ICP levels. However, a craniotomy includes the replacement of the removed portion of the skull, but a craniectomy does not immediately replace the bone. In a decompressive craniectomy, after the skull is removed, later a cranioplasty (skull reconstruction) is performed (Guo et al., 2022).

Refractory intracranial hypertension (RICH) occurs when a patient experiences high levels of ICP for a prolonged period (10-15 minutes; (Menat et al., 2023). Patients who experience RICH are good candidates for a decompressive craniectomy as it has been found to decrease mortality rates and increase the likelihood of independent functioning at home (Stocchetti et al., 2017). Prior results have proven that during a DC removing a larger portion of the skull, rather than smaller, significantly improves outcomes (Dheansa et al., 2023). On the other hand, specialists recommend against the use of bifrontal DC, even though the procedure does greatly reduce ICP levels, it still leads to worsened outcomes when compared to continued medical management (Marehbian et al., 2017).

Early Posttraumatic Seizures. Moderate-to-severe TBI patients are at risk of experiencing early posttraumatic seizures (EPS) which is associated with posttraumatic epilepsy (PTE). EPS has also been proven to be a strong predictor of long-term impacts. In a follow-up study with patients who experienced moderate-to-severe TBI two years prior, a significantly higher proportion of patients who initially endured EPS were severely disabled or deceased. More specifically, about 25% of patients who endured EPS were deceased within the two-year period, while this was true for only 14% of patients who did not experience EPS (Laing et al., 2022). Such a result might indicate the need for greater attention toward EPS as it might be a key predictor of the individual's future health complications.

Patient Transfer. Patients who are diagnosed with a moderate-to-severe TBI at a general hospital are sometimes transferred to regional trauma centers that specialize in posttraumatic treatments. However, the opportunity to transfer to these centers is often not available for patients who are older adults. In Central Norway, only 16% of patients who were 80 years old or older were transferred to regional trauma centers and the remaining proportion was forced to seek care at a general hospital. However, the specialized posttraumatic care that was provided at these centers proved to be effective even in the older populations. The fatality rate of the older adults who remained at the general hospital was 67%, while the fatality rate at the trauma centers was only 36% (Rahim et al., 2022). These findings suggest that specialized posttraumatic recovery centers are effective for even the most vulnerable populations and therefore patient transfers from general hospitals should not only be encouraged but should also be improved.

1.3 Outcome

Introduction. Depending on the severity of the TBI, it can take anywhere from months to years for patients to return to work (RTW) or school, and in some cases, individuals do not return to

either of these activities. Here, we will discuss the duration of time needed for patients to RTW across different levels of severity (Schneider et al., 2022).

Mild. Within the first 6-9 months of injury about 50% of patients had returned to work. Additionally, patients who stated a greater feeling of fear avoidance were also less likely to return within the 6–9-month period (Snell et al., 2023). Individuals who scored highly on the Fear Avoidance Behavior after Traumatic Brain Injury (FAB-TBI) questionnaire worried that returning to work and regular daily activities would trigger or worsen post-injury symptoms. A focus on alleviating this fear would benefit the remaining 50% of individuals who were not able to return to these activities in the stated period and would also aid in managing stress after injury.

Mild-to-Moderate. 60% of patients who followed the standard treatment plan, per the Oslo University Hospital of Norway guidelines, returned to work within a 3-month period and 84% of patients RTW within a 6-month period (Fure et al., 2021). However, in these cases, 6-months of compensatory cognitive training and supported employment (CCT-SE) was shown to significantly improve patients' abilities to RTW compared to the patients who received standard treatment care at the 3-month period in which 84% of these patients RTW. These findings suggest that the patient's ability to feel prepared to resume their prior daily life activities can be reached quicker with the use of CCT-SE treatment.

Moderate-to-Severe. Lastly, the great majority of patients in this severity level typically either do not RTW at all or return but with a dramatic decline of hours employed. Only about 16% of patients returned to work within the first 6-months of injury, after the first 3-years of injury about 50% of patients reportedly returned (Spitz et al., 2019). These results are largely determined by the type of disability obtained paired with a major loss of motivation.

1.4 Neuropathology

1.4.1 Blood Biomarkers

Introduction. Scientific literature has continuously proven the importance of connecting blood biomarkers with TBI recovery and outcomes. Blood biomarkers offer insight into the current standing of the brain's diverse responses to injury. Post-TBI injuries include neuroinflammation, axonal injury, glial cell injury, neuronal cell injury, and extracellular vesicle injuries (Figure 1.7, Ghaith et al., 2022). Moreover, specific blood biomarker levels can be assessed to diagnose or predict the type of injury which occurred because of a TBI.

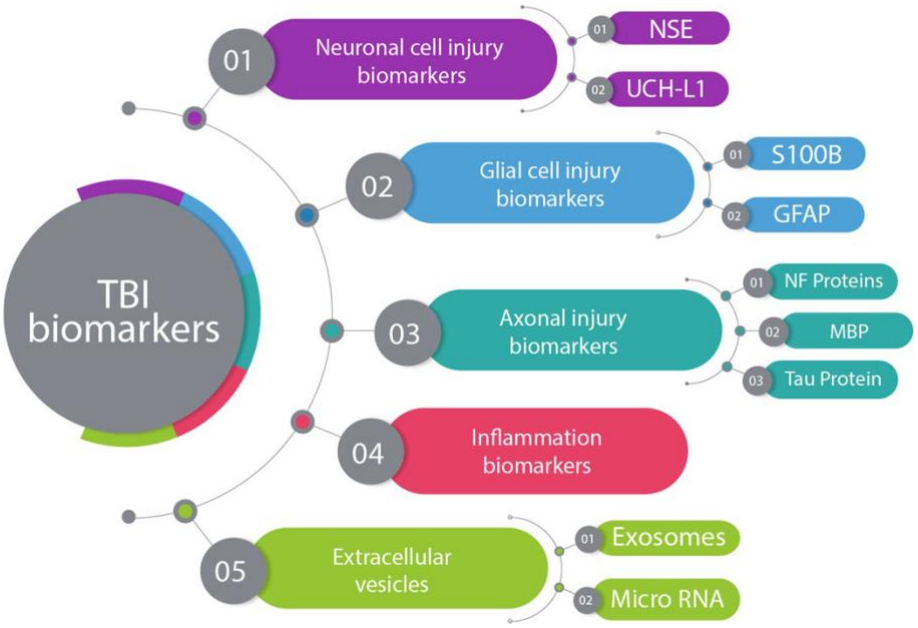


Figure 1.7. Flow diagram of notable blood biomarkers for traumatic brain injuries (TBI; Ghaith et al., 2022)

Neuronal Cell Injury. Neuron-specific enolase (NSE) is an enzyme located inside neuron cell bodies which is primarily responsible for neural maturation (Figure 1.8; Isgrò et al., 2015). Levels of NSE increase when a TBI is obtained leading to rapid cell proliferation. Extremely high levels of NSE in the cerebrospinal fluid (CSF) indicate a high mortality rate, hence NSE is a strong indicator of how likely a patient is to survive after a severe TBI is obtained (Zetterberg et

al., 2013). Ubiquitin carboxyl-terminal hydrolase isoenzyme L1 (UCH-L1) is also an enzyme located inside neuronal cell bodies, except it is responsible for breaking down unwanted proteins to maintain axonal integrity (Bishop et al., 2016). High levels of UCH-L1 indicate neurodegeneration taking place and is a sign of a brain injury.

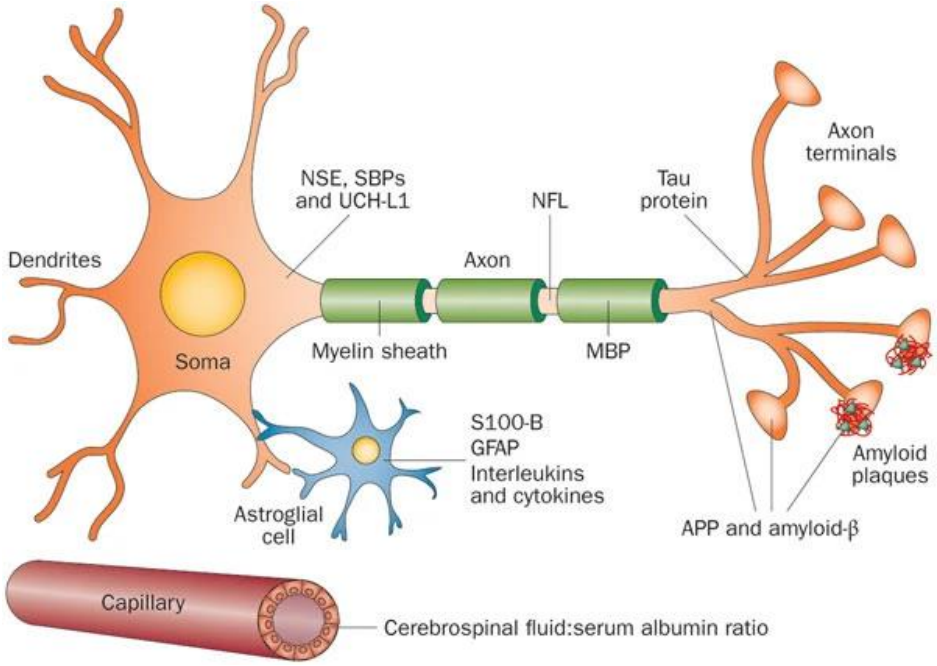


Figure 1.8. Diagram presenting where blood biomarkers are in the neuron (Zetterberg et al., 2013)

Glial Cell Injury. Glial fibrillary acidic protein (GFAP) is typically used to identify when a glial cell injury has occurred with increased GFAP levels in a blood test indicating gliosis and astroglia injury (Schnakers et al., 2021). GFAP levels of TBI patients have been found to significantly correlate with structural changes found in computed tomography (CT) scan when compared to healthy participants, suggesting that GFAP is a strong predictor of major structural changes occurring post-TBI (Yue et al., 2020). On the other hand, S100 calcium-binding protein B (S100B) is found in both Schwann cells and glia with increased levels in the blood post-TBI due to its neurite extension promoting properties which are released immediately. These proteins are quickly released to encourage the creation of new neuronal connections in dendrites and axon

terminals. However, S100B rapidly decreases after the injury lasting in the body from minutes to four hours, making it difficult to assess in patients (Hier et al., 2021).

Axonal Injury. Myelin basic protein (MBP) functions alongside the lipid bilayer to maintain healthy myelin in neurons, making it highly concentrated in white matter tracts. Low levels of MBP cause demyelination leading to the degradation of axons causing conditions such as multiple sclerosis (MS). However, in TBI patients, MBP levels are eight times higher of those who are healthy, and levels continue to remain abnormally high throughout the entire lifetime of the TBI patient (Bohnert et al., 2021). An elevation of MBP levels is a strong indicator that the TBI is either moderate or severe, determining diagnosis with 94% accuracy. In mild cases, TBI causes mechanical deformation which forces calcium out of the neurons leading to a spike in tau protein concentration (Flavin et al., 2023). Lastly, increased levels of tau proteins are often viewed as strong predictors of slow recovery by a TBI patient, especially in severe cases, and are quick and easy to detect by clinicians (Gan et al., 2019).

1.4.2 Genetics

Midkine. Midkine (MK) is a small protein which is upregulated in the adult brain to promote cell proliferation, renewal, migration, and differentiation after TBI which results in neuroinflammation and degeneration, especially after multiple injuries. Its main function is to provide neuroprotection and neuro-generation to restore healthy neuronal functions as an immune response (Ross-Munro et al., 2020). However, this neuroinflammation response has been found to worsen other aspects of the brain (White et al., 2016). In an experimental TBI study examining rodents, the disruption of the MK gene increased brain tissue filtration of microglia and macrophages, which in turn reduced neuroinflammation and neuronal apoptosis, especially at the targeted site of injury. This led to an improvement in behavioral outcomes with

an increase in the speed of recovery as well (Takada et al., 2020). The disruption of the gene also led to less brain tissue loss and decrease in apoptotic neurons, elimination of damaged/unwanted cells, compared to rodents with the healthy MK gene.

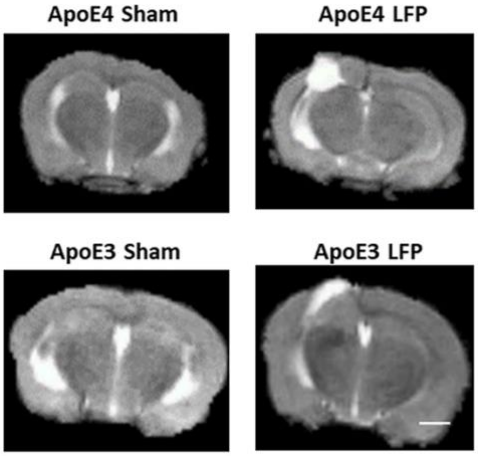


Figure 1.9. Mice brain post-repeated mild traumatic brain injury (TBI) comparing apolipoprotein (APO) E3 gene and APOE4 gene (Giarratana et al., 2020)

APOE4. Apolipoprotein E (APOE4) is a gene which is most known for severely increasing the risk of Alzheimer's disease dementia in humans without a history of TBI. It is most prominent in individuals from European descent and increases the likelihood of Alzheimer's disease diagnosis by the age of 85 by 60% compared to all other APOE gene variations (Sienski et al., 2021). Individuals who carry this gene and experience repeated mild TBI have significantly worsened outcomes of TBI compared to other gene carriers due to severe levels of neuroinflammation, apoptosis, p-tau, neurodegeneration, activated microglia, greater edema volumes, especially in the hippocampus and cortex from baseline to 3 weeks post-TBI (Figure 1.9, Giarratana et al., 2020). This leads to greater hippocampal damage which in turn causes more centralized impact to functions of memory. The APOE gene has overall been found to be the most influential of the other genes involved in post-TBI recovery response by impacting cognition, behavior/emotion, survival/global functioning, and medical sequelae (Figure 1.10, Kurowski et al., 2017).

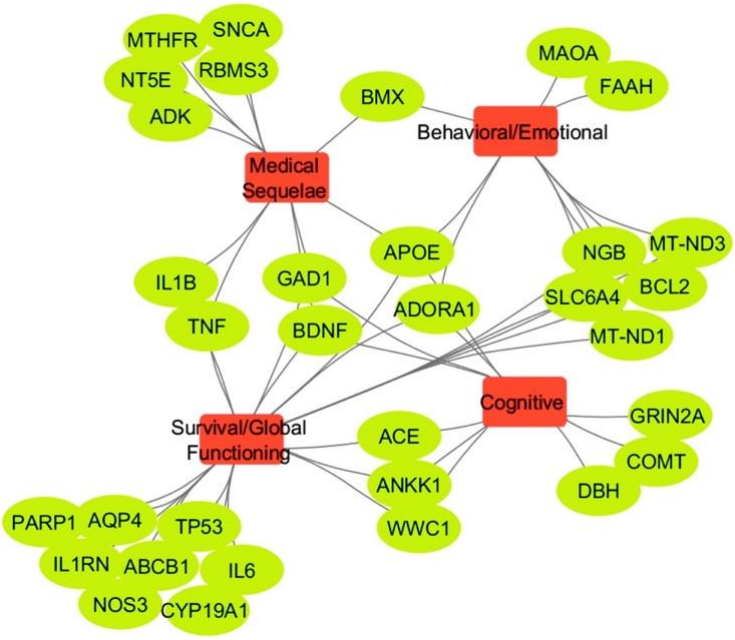


Figure 1.10. Flow diagram depicting genes involved in traumatic brain injury (TBI) recovery (Kurowski et al., 2017)

1.5 Patterns of Sleep

The sleep-wake cycle is driven by the circadian rhythm, which functions 24-hours at a time. In healthy individuals, the number of hours spent awake positively correlate with the number of hours then needed to sleep. The balance between both sleep and wakefulness is crucial; however, this balance can be disrupted by all forms of TBI. In mild cases of TBI, 36% of patients experienced circadian rhythm sleep disorder, 30% experienced insomnia, and 25% experienced obstructive sleep apnea (Figure 1.11; Morse & Kothare, 2018). Other disorders of sleep were also reported but were not as common among patients. This includes sleep apnea, periodic limb movement disorder, and narcolepsy. After a brain injury is sustained, some of the most frequently damaged regions include the hypothalamus, midbrain, and the suprachiasmatic nuclei; all of which are a part of sleep regulating pathways (Singh et al., 2016). *Circadian Rhythm Sleep Disorder.* Circadian rhythm sleep disorder is caused by damage to the hypothalamus, specifically in the suprachiasmatic nuclei (Figure 1.12). These changes also lead to the reduction of

melatonin production and decline of neurogenesis (generation and integration of new neurons) and cell proliferation (cell growth and division). Irregular sleep-wake patterns reduced rapid eye movement (REM) sleep, and delayed sleep phase syndrome are all results of these sudden changes in the brain.

Insomnia. Patients diagnosed with insomnia struggled with both falling asleep and remaining asleep. These patients experienced a heightened rate of anxiety and depression as well as a prolonged phase of recovery, meaning that returning to work/school was more difficult (Wolfe et al., 2018). 61% of patients who were diagnosed with insomnia had consistent symptoms even after one-year post-injury (Bell et al., 2023). This further points towards the problem of TBI patients going untreated for a long period of time. Sleep disturbances such as insomnia in

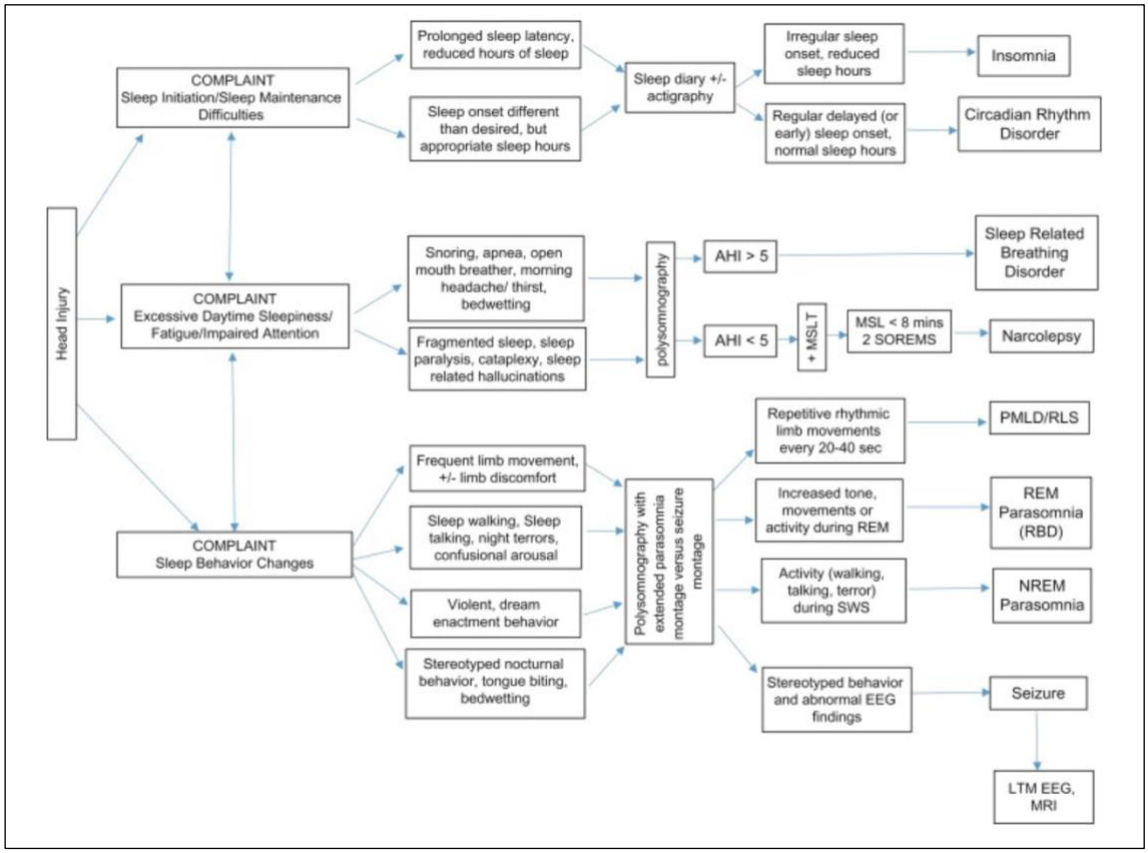


Figure 1.11. Diagnosing Posttraumatic Sleep Disorders (Morse & Kothare, 2018)

moderate-to-severe cases also led to delusions, apathy, and hallucinations up to one-year post-injury (Poulsen et al., 2021).

Hypersomnia. While some TBI patients struggle with getting enough sleep, others struggle with sleeping too much. Hypersomnia is also a common aftermath of obtaining a TBI and it is characterized by excessive daytime sleepiness and difficulty remaining awake throughout the day. This feeling of excessive sleepiness is not related to the amount of activity the patient completed throughout the day but has instead been associated heavily by the patient's stress and anxiety levels (Portillo et al., 2023). Patients who have obtained a repetitive mTBI who also experienced high levels of stress and anxiety are more likely to also experience hypersomnia instead of insomnia. Furthermore, patients who were male were more likely to experience this consequence than their female counterparts.

Sleep Apnea. There are three main types of sleep apnea: obstructive, central, and complex. In all cases, breathing stops and starts again while the individual is asleep. This sleep disorder is common among TBI patients with obstructive sleep apnea being the most prominent among the

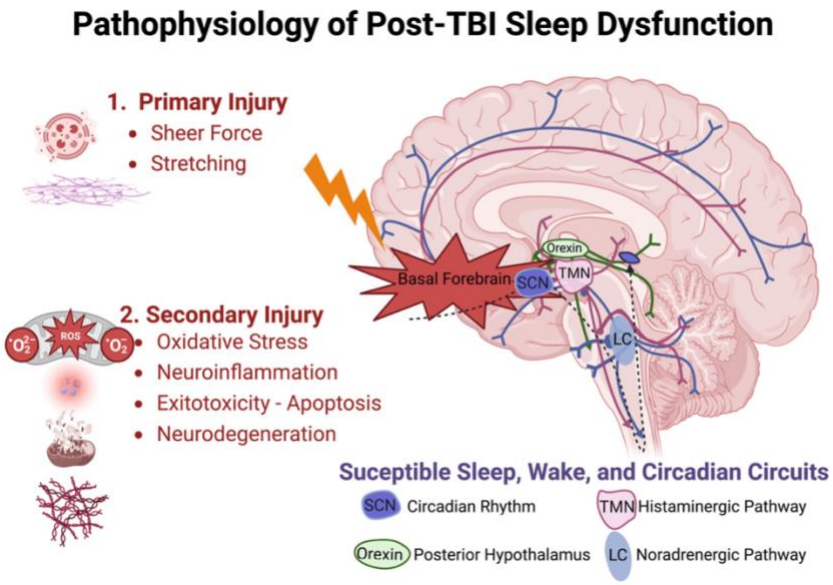


Figure 1.12. Disorders of sleep impacting the brain (Bell et al., 2023)

three and is specifically characterized by daytime sleepiness, early awakenings, nightmares, and overall poor sleep quality. Patients diagnosed with obstructive sleep apnea suffered from worse cognitive impairments, especially in functions of memory and attention when compared to TBI patients without any sleep disordered breathing condition (Singh et al., 2016). Noncognitive, but physical health concerns are also reported including an increase in blood pressure, pulse rate, and blood sugar levels, all of which combine to create an increased risk of cardiovascular disease (Weymann & Rourke, 2021). Notably, evidence of histaminergic tuberomammillary neuron impairment after severe TBI has found a loss of approximately 41% of these wake-promoting neurons, coupled with the 29% loss of melanin-concentrating hormones and 21% loss of orexin A neurons (Valko et al., 2015). Damage to the neural integrity of these regions lead to the increased need of sleep which is what causes daytime sleepiness among patients diagnosed with obstructive sleep apnea or hypersomnia.

1.6 Other Considerations

1.6.1 Behavioral & Psychological State

Mild. Even the least severe type of TBI, mild cases, is strongly associated with increased symptoms of depression, anger, and risk of committing suicide. However, the driving cause of the high risk of suicide is more so due to high levels of anger rather than levels of depression (Stanley et al., 2017). Symptoms of depression in mild TBI patients are so severe that they mirror the symptoms experienced by patients diagnosed with Major Depression Disorder (MDD) who have no history of any type of TBI (Silverberg & Panenka, 2019). Other mental health issues also arise after a mTBI is sustained with about 88% of patients being clinically diagnosed with PTSD, 65.9% reporting alcohol abuse, 65.9% reporting symptoms of anxiety and 68.3% reporting anger dysregulation (Figure 1.13; Wojtowicz et al., 2017). These large percentages of

diagnoses are partly due to increased comorbidity post-TBI with 22% of patients being diagnosed with two or more mental illnesses and 23% being diagnosed with three or more conditions.

Moderate-to-Severe. Personality changes are especially life changing for msTBI patients when it comes to one's ability to maintain prior and new social relationships. These changes include severe irritability, impulsivity, aggressive behavior, suspiciousness, apathy, and affective instability all of which are characterized as Personality Change Due to Another Medical Condition in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; Howlett et al., 2022). Mood swings/emotional instability worsen these extreme emotional changes and patients often lack awareness of these changes ever taking place. Patients also have

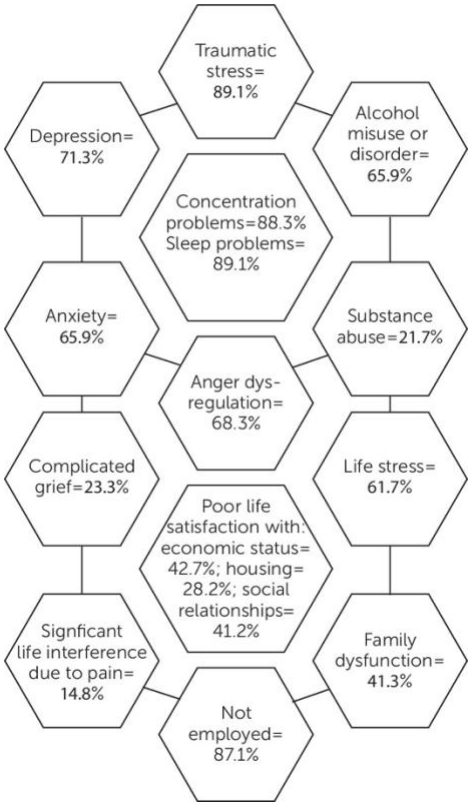


Figure 1.13. Clinical diagnoses post-traumatic brain injury (Wojtowicz et al., 2017)

a difficult time recognizing others' emotion, experience altered self-awareness, worsened theory of mind capabilities, and hindered decision-making abilities (Calvillo & Irimia, 2020).

1.6.2 Attention & Processing Speed

Mild. Difficulties in maintaining attention and slowed processing speed is often reported in TBI patients. Patients with mild cases of injury showed hindered performance on the ability to maintain visual attention compared to healthy subjects after completing the multiple object tracking (MOT) task (Alnawmasi & Khuu, 2022). More specifically, as the number of visual targets to be tracked or number of distractors present on the screen increase, accuracy in visual detection decreased more significantly when compared to healthy controls. Additionally, as the tracking duration increased, detection abilities also decreased. In conclusion, a single mild TBI is enough to significantly impair visual attention capabilities.

Moderate-to-Severe. After injury, about 60% of moderate-to-severe TBI patients experienced continuous hindered attention, which lasted for 10 or more years (Ponsford et al., 2023). On the other hand, 40-60% of mild cases experienced attention deficits, which only lasted a few months then resolved entirely (Polich et al., 2019). In moderate-to-severe subjects, information processing speed declines so significantly that social interactions are negatively affected therefore causing mental fatigue (Schiff et al., 2023). Abilities related to organization and switching tasks are also worsened after injury.

1.6.3 Learning & Memory

Mild. Up until recently, the memory deficits of mTBI remained unknown. However, current findings provide evidence of significant decline in episodic memories, with intact semantic memories. More specifically, poor performance of verbal and associative episodic memories in

mTBI patients was associated with low fractional anisotropy (FA) in the fornix and hippocampal formation (Wammes et al., 2017). Low FA indicates abnormal directional diffusion of fluids in the brain, which offers more information in understanding the state of white matter tracts, such as providing evidence of abnormal directional diffusion. Patients with mild injuries also show deficits in their working memory, specifically when completing dual task conditions, by exhibiting slower processing rates, lower accuracy levels, and were more sensitive to distractors. Executive functions were impaired as well; mTBI patients recalled approximately 15% to 18% fewer words than healthy participants when completing the Hopkins Verbal Learning Test-Revised (HVLT-R) (Broadway et al., 2019).

Severe. It is not uncommon for patients who experience a severe TBI to fall into a comatose state. Generally, the patients who awaken from this state also experience post-traumatic amnesia (PTA), which is accompanied by the inability to determine the current time and place, as well as receive and store information that is new to them (Azouvi et al., 2017). Additionally, these individuals have retrograde amnesia; however, memories slowly return to the patient as they become comfortable with their post-comatose state. Unfortunately, in 67.5% of these patients, difficulties with recalling old memories remain a problem even four-years post-injury.

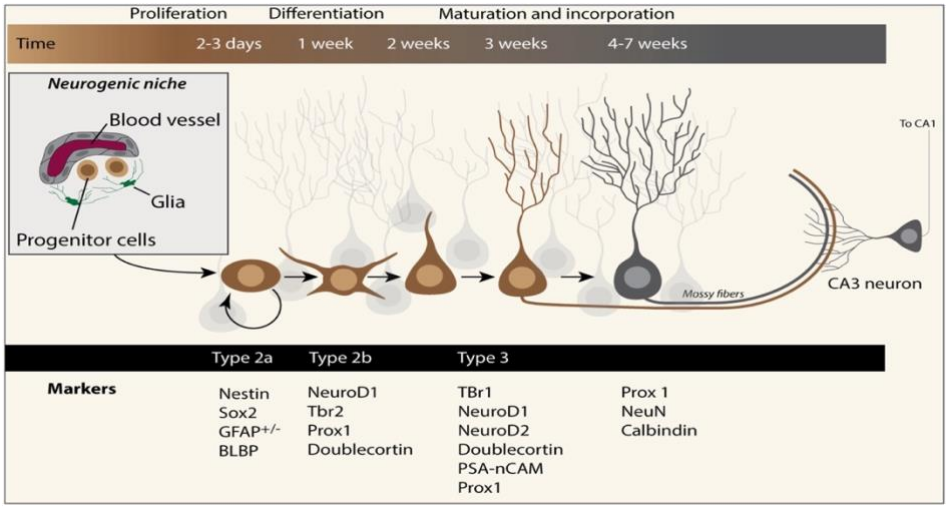


Figure 1.14. Healthy cell proliferation and maturation (Redell et al., 2020)

Experimental. Experimental TBIs in rodents offer deeper insight into individual neuronal damage after a brain injury is sustained. The hippocampus is one of the most prominent brain regions for studying learning and memory. Progenitor cells within the hippocampus are proliferating cells which have the capability to create newborn neurons from the sub-granular zone to the dentate gyrus where they eventually become adult neurons (Figure 1.14). These newborn neurons are involved in learning and memory, especially goal-directed functions using pattern separation methods. TBIs target these newborn neurons and lead to a decline in their population, hence changing hippocampal neurogenesis while causing the hyper-proliferation of progenitor cells (Figure 1.15; Redell et al., 2020). This leads to deficits in goal-directed learning and memory functions, especially when involving pattern separations after a TBI is sustained.

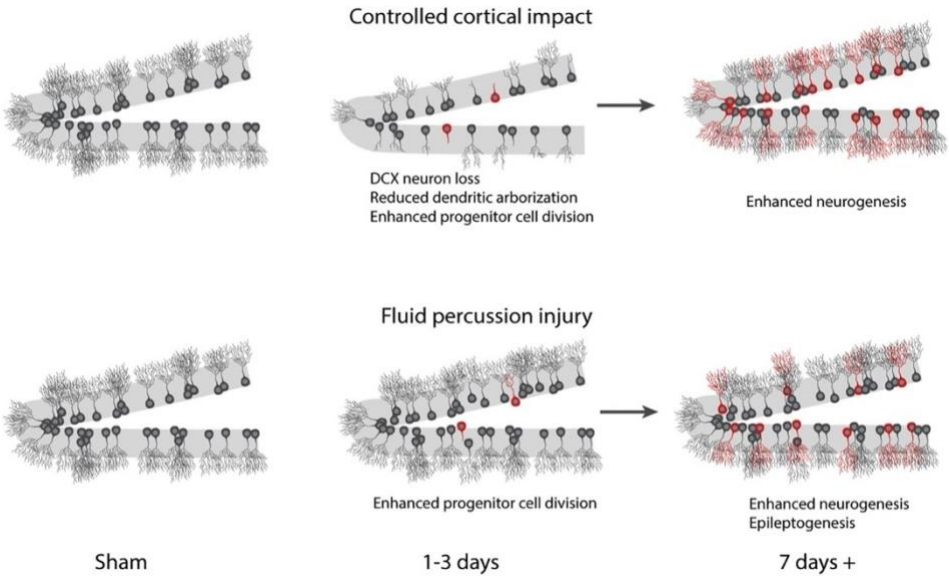


Figure 1.15. Post-injury cell proliferation and maturation (Redell et al., 2020)

Chapter 2: Clinical Assessments and Mild Traumatic Brain Injury

2.1 Abstract

Introduction. Mild traumatic brain injury (mTBI) triggers, through biomechanical strain, a neurometabolic cascade and network dysfunction that is difficult to characterize, *in vivo*, in the clinic and thus to relate to the cognitive, emotional, and behavioral sequelae of such injuries. Here we leverage a recent multimodal fusion technique to integrate data from multiple Magnetic Resonance Imaging (MRI) modalities, each sensitive to different aspects of the mTBI pathophysiology, and associate its change to different profiles on self-report measures of post-traumatic stress, depression, and resilience.

Methods. Prospective longitudinal neuroimaging and neuropsychological data following mild TBI were acquired from the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System. In the final analyzed sample of 67 individual patients, data included multiple neuroimaging modalities (T1-weighted, T1w; multi-echo T2-weighted, T2w; susceptibility-weighted imaging, SWI; and Fluid-Attenuated Inversion Recovery, FLAIR), collected within 24h post injury and at 3 months, and multiple self-reported measures of mental health (e.g., Posttraumatic Stress Disorder Checklist for Acute Stress Disorder, ASD; Center for Epidemiologic Studies-Depression Scale, CESD; and Connor-Davidson Resilience Scale, CDRISC) collected within 24h post-injury, as well as at 1 week, 1 month, and 3 months post injury. The scores in mental health measurements were entered in a functional data analysis (FDA) with clustering to assess the presence of groups of individuals with different mental health profiles over time. Neuroimaging data were preprocessed (e.g., brain extracted, transformed in standard template space) and entered in a non-parametric combination (NPC) analysis, as implemented in FSL-PALM (Permutation Analysis of Linear Models), to correlate

baseline, follow-up measurements, as well as their change between the two timepoints, to mental health profiles (as detected with FDA), while controlling for additional variables (e.g., age, sex).

Results. The FDA clustering on the neuropsychological data revealed two distinct clusters of individuals: patients self-reporting high resiliency levels and low PTSD-ASD and depression ratings (Resilient group; n=59) and patients self-reporting the opposite pattern (Stress group; n=31). A repeated measures ANOVA shows, for all three scores, a significant cluster by time interaction. As assessed with the NPC approach, the two mental health clusters exhibited significantly different patterns of change over time in multimodal imaging in deep parts of the brain mostly localized to deep white matter ($p<0.05$). Analysis of the contribution of individual modalities shows brain-wide significant differences between the two groups driven mainly by T1, T2w, and FLAIR, particularly high signals in major white matter tracts in the stress group suggesting possible neuroinflammation and demyelination.

Conclusion. Our finding in the neural change analysis shows significant and notably high T1, FLAIR, and T2w ME signals in the stress group but not the resilient group. This indicates possible demyelination and inflammation in major white matter tracts for the stress group only, particularly for regions responsible for emotion regulation. Moreover, after a single mild TBI, some subjects experience significant demyelination of major white matter tracts related to emotional regulation which correlates to clinically high scores of PTSD-ASD and depression. For future direction, we plan to create a machine-learning model which categorizes new patients in either the stress group or resilient group and predicts neuropsychological and neural changes 3-months post-injury. Our research aims to highlight the individualized experience of patients diagnosed with the same condition.

2.2 Introduction

Traumatic Brain Injury (TBI) is a devastating condition that affects millions of individuals worldwide and has gained significant attention in recent years due to its associated cognitive impairments and long-term consequences. As a result, individuals with TBI often face challenges in various aspects of their daily lives, including school/work, relationships, and overall quality of life. In the United States alone, TBI is the cause of over 5.3 million individuals living with a disability and each year an additional 1.7 million Americans also suffer across the lifespan, and vulnerable groups, such as youth and older adults, in particular (Dixon, 2017). At the lower end of the severity spectrum, approximately 42 million individuals globally suffer from mild TBI (mTBI) each year (Gardner & Yaffe, 2015), defined as a blow to or jolting of the head causing an acute disruption of brain function, manifested by a brief loss of consciousness, confusion, or transient posttraumatic amnesia not accounted for by factors such as psychological trauma or alcohol/drug intoxication (Holm et al., 2005). Additionally, between the years 2000 and 2022, almost half a million U.S. military personnel sustained a TBI, 80% of which were cases of mild TBI specifically, as stated by the Defense and Veterans Brain Injury Center (DVBIC).

Although 90–95% of individuals with mTBI show no notable intracranial injury as observed with CT, other biomarkers can reveal evidence of brain damage (Maas et al., 2022). Some blood-based biomarkers sensitive to astrocytic and neural damage, for example, have shown to be elevated following mTBI and to distinguish individuals with mTBI from contact sport controls (Shahim et al., 2014; Meier et al., 2020; Giza et al., 2021; McCrea et al., 2020). Nonetheless, possibly since these biomarkers are very sensitive to non-mTBI features (e.g., age, assessment time), their performance is currently less high than desirable (i.e., up to 80%; Posti & Tenovuo, 2022). Advanced Magnetic Resonance Imaging (MRI) techniques are also able to detect

signatures of brain injury that go undetected in CT or visual examination of clinical MRI assessments (Maas et al., 2022). For example, prior work using Fluid-Attenuated Inversion Recovery (FLAIR) MRI data in TBI found white matter hyperintensities in over half the patients (Riedy et al., 2016). Similarly, susceptibility weighted imaging (SWI) has also found evidence of microhemorrhages in individuals with mild TBI (Trifan et al., 2017).

The case for multimodal imaging. While this research has shown promising results, there remains significant variability in findings across studies (Sassani et al., 2025; Joyce et al., 2022; Lindsey et al., 2023; Wang et al., 2020). One still underexplored avenue in this context is the use of multimodal MRI as a means of increasing sensitivity to brain-behavior associations (Narayana et al., 2015; Sibilia et al., 2023; Lunkova et al., 2025). Different MRI sequences are differently sensitive to the signatures of brain tissues and might thus be uniquely sensitive to different aspects of the pathophysiology of mTBI (Sassani et al., 2025; Giza et al., 2018; Levin et al., 2013; Chen et al., 2025). Indeed, susceptibility-weighted imaging (SWI), is ideal to detect micro-hemorrhages (Halefoglu & Yousem, 2022; Hageman et al., 2022; Huang et al., 2015), diffusion weighted imaging (DWI) can detect white matter lesions and characterize edema (Drake-Perez et al., 2018; Mascalchi et al., 2005; Romano et al., 2003), fluid-attenuated inversion-recovery (FLAIR) sequences are sensitive to axonal injury and burden of white matter hyperintensities (Riedy et al., 2016), while T1-/T2-weighted imaging (T1w,T2w) are ideal to detect structural and volumetric changes (Lutkenhoff et al., 2020). In what follows, we leverage a previously acquired longitudinal dataset (Robertson et al., 2017) to assess the ability of multimodal MRI fusion to uncover associations between brain tissue following mTBI and self-reported measures of depressive symptom burden, post-traumatic stress symptomatology, and resilience, which are

linked to quality of life, risk of suicide, substance-use disorders, and mood and sleep disorders (Kim et al., 2023; Haagsma et al., 2015; Stein et al., 2019; Bryan et al., 2013).

2.3 Methods

Data description. Data employed in the present work were acquired from a prior study aimed at assessing the safety and efficacy of atorvastatin in a continuous sample of post-concussion individuals (clinical trial NCT01013870; Robertson et al., 2017) and downloaded from the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system. In the original study, a total of 177 individuals, including 104 with mTBI, were enrolled in a prospective clinical trial collecting, at multiple timepoints (up to 6 months), outcome information (e.g., return to work or school), imaging data, and a battery of questionnaires assessing symptoms, mental health, substance-use risk, cognition, functioning, among others (cf., Robertson et al., 2017 Fig 1 and Table 1 for details of the full clinical trial). Participants enrolled in the TBI group were characterized as mild on the basis of international criteria (i.e., GCS between 13-15, loss of consciousness for less than 30 minutes, less than 24-hours of post-traumatic amnesia; Malec et al., 2007), presented normal computed tomography scans (i.e., no complicated mTBI), and did not report prior neurological and/or psychological conditions.

Analyzed sample. The original data set included 177 subjects in both groups, case and control; however, the control group was excluded leaving 104 subjects. From this sample size, 14 more subjects were excluded due to missing mental health questionnaire data. Therefore, the analysis of mental health questionnaires included the sample size of 90 subjects, but due to missing imaging data, the imaging analysis included only 67 participants (see Figure 2.2– the data flowchart). The age range for the mental health analysis was between 18 to 49 with the average

age being 29.5, 26 of the subjects were female (n=90). The age range for the imaging analysis was between 18 to 49 with the average age being 29.5, 16 of the subjects were female (n=67).

Cognitive Data. Three questionnaires were considered in the present work. Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item self-reported questionnaire aimed at assessing recent depression symptomatology frequency (with higher scores implying greater symptoms; Radloff, 1977). Posttraumatic Stress Disorder Checklist Civilian Version - Appendix for Acute Stress Disorder (PTSD-ASD; Weathers et al., 1993) is a 17-item self-report questionnaire for assessing key symptoms of PTSD through a 5-point scale (1-5) rating system with higher values indicating worse symptoms of PTSD. Connor-Davidson Resilience Scale (CDRISC; Connor & Davidson, 2003) is a 25-item self-report assessment with each question rated on a 5-point scale (0-4) with a higher score rating more resilience through measuring stress coping mechanisms.

Each questionnaire was administered longitudinally at five time points: less than 24-hours post-injury (baseline), 1-week post-injury, 1-month post-injury, 3-months post-injury, and 6-months post-injury (Figure 2.1).

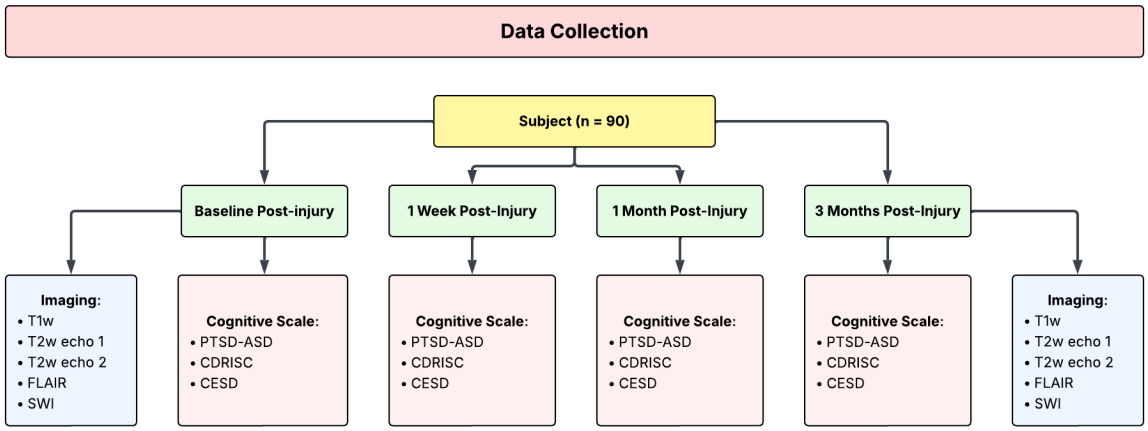


Figure 2.1. Diagram of data collection structure

Imaging Data. Five MRI modalities were collected: Fluid-Attenuated Inversion Recovery (FLAIR), Susceptibility-weighted imaging (SWI), multi-echo T2-weighted (T2w), and T1-weighted (T1w). All images were obtained using a 3T Philips scanner. For the T1 modality, the repetition time (TR) is 8.07ms and echo time (TE) is 3.68ms. For the T2w echo 1 and echo 2 scans, the TR is 509.99ms and the TE is 16.00ms, while for the FLAIR modality, the TR is 8,000.00ms and the TE is 337.16ms with an inversion time of 2,400ms. Lastly, for the SWI modality, the TR is 50.00ms and the TE is 40.00ms.

All MRI modalities were collected at two timepoints; baseline and 3-months post-injury (Figure 2.1). Ultimately, the imaging data included 67 subjects across four modalities (T1, T2w ME, SWI, and FLAIR) in three timepoints (baseline, 3-months post-injury, and difference), totaling 804 scans being processed for the final analysis.

Questionnaire Data Analysis. Given the longitudinal nature of the data, the total score of each questionnaire (i.e., ASD, CES-D, CD-RISC) at each of the four timepoints (baseline, 1 week, 1 month, 3 months) was entered into a functional data analysis (FDA; Wang et al., 2016) with clustering aimed at grouping participants into different clusters capturing, on the basis of the scores' evolution over time, different post-injury mental health phenotypes. The FDA was performed in Matrix Laboratory (MATLAB; The MathWorks Inc., 2022). First, a cubic polynomial regression model was fit to each subject's data to create smooth functional representations to capture the underlying trend while minimizing noise (Ramsay & Silverman, 2005). Second, a functional Principal Component Analysis (fPCA; Greven et al., 2011; Silverman, 1996) was performed on the transformed data to reduce dimensionality while preserving the most informative variance in psychological recovery trajectories, retaining components explaining at least 95% of the variance. Finally, to discover distinct post-injury

trajectory phenotypes, a *k*-means clustering (with 10 random replicates to ensure stability) was run over candidate solutions (over the interval $k = 2\text{-}8$) in the reduced PC space (Steinley, 2006). The solution (*k*) yielding the highest mean silhouette coefficient (Roisseeuw, 1987; Shahapure & Nicholas, 2020) was selected as the optimal number of clusters. The selected *k*-means solution (i.e., number of clusters) was thus used to group participants into a post-injury mental health trajectory phenotype. Finally, a Repeated Measures Analysis of Variance (ANOVA) accounting for sex and age was performed, on each of the three questionnaire's timeseries, using Jeffreys' Amazing Statistics Program (JASP; JASP Team, 2025), to describe the characteristics of the obtained post-injury mental health trajectory phenotypes.

Imaging Data Analysis. For each participant, each image modality at each timepoint was first processed with FMRIB Software Library (FSL)'s *fsl_anat* to produce bias corrected images (Jenkinson et al., 2012). All images were then skull-stripped using FreeSurfer's *SynthStrip* function and registered to standard T1 Montreal Neurological Institute (MNI) space at 2-millimeter (mm) resolution using FreeSurfer's *SynthMorph* (Hoopes et al., 2022; Hoffman et al., 2022). For the T2w scans, the first echo time was 16 milliseconds (ms), and the second echo time was 32ms. Using both provided echo times, a new combined T2w modality was created called T2-weighted multi-echo (T2w ME; Schall et al., 2018; Halder et al., 2023). Moreover, the analysis was done in four modalities T1, T2w ME, SWI, and FLAIR. To assess any association between multimodal brain data and mental-health phenotype (i.e., the clusters obtained over the questionnaires described above), images were entered into FSL's Permutation Analysis of Linear Models (PALM) tool to perform a Non-Parametric Combination (NPC) test for joint inferences (Winkler et al., 2014; Winkler et al., 2016). As described previously (Winkler et al), NPC provides a robust, distribution-free, voxel wise inference approach to integrate information

across multiple imaging modalities into one coherent test. To this end, NPC first conducts "partial tests" with a permutation-based approach on each modality separately, generating *u*-values for each voxel – a quantity derived from the principles that underlie direct combination of statistics, that behaves similarly to *p*-values while allowing for combination that would otherwise not be feasible given the size of MRI data. Importantly, the permutations in each partial test are synchronized across modalities, meaning that for each permutation subject labels are shuffled in the same way in all modalities. These modality specific *u*-values are then combined, at each voxel, thus producing a single joint statistic that reflects evidence across partial tests while accommodating cross-modality dependencies.

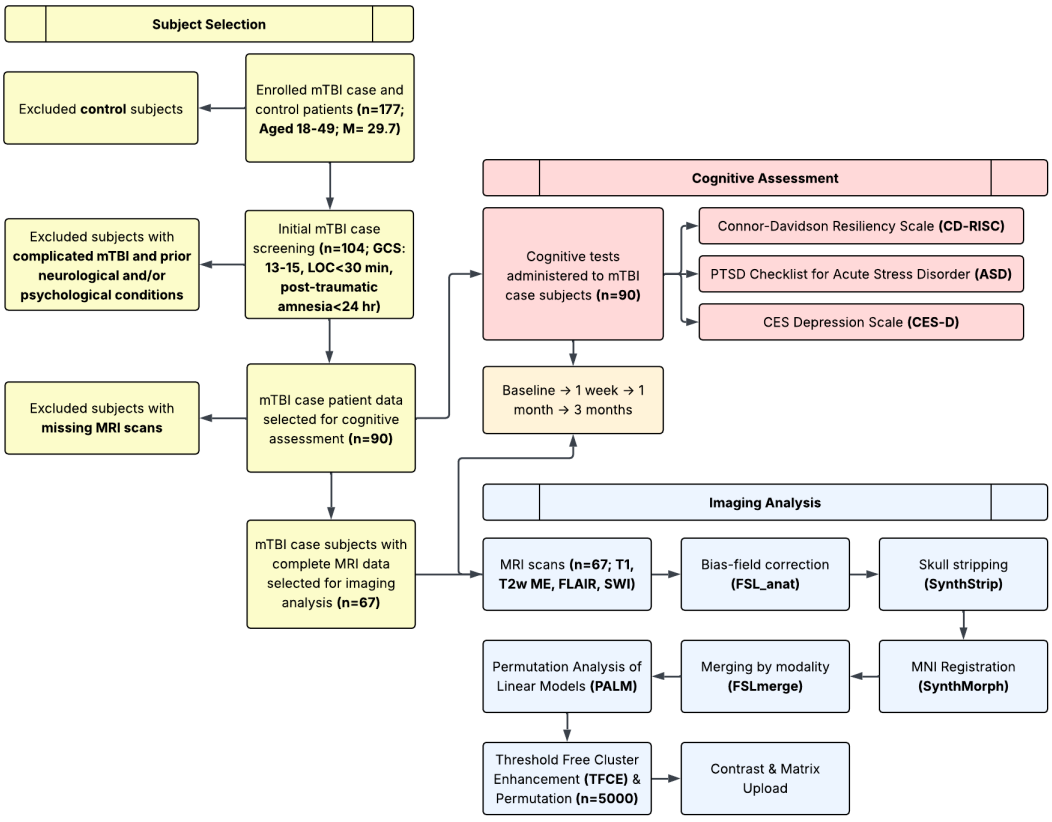


Figure 2.2. Diagram of data exclusion and data analysis

Here, we apply the NPC approach to perform three separate analyses aimed at assessing associations between mental-health trajectory phenotype (i.e., cluster membership) and multimodal data at baseline, multimodal data at 3 months, and change in multimodal data between the two timepoints, respectively. In addition to cluster membership, the independent variable of interest, all analyses also included age, sex, and drug condition (i.e., atorvastatin versus placebo) as covariates to parcel out their effect on any association between brain data and mental-health phenotypes. Analyses were performed in PALM, and inferences were based on a non-parametric approach (with 5,000 permutations) with familywise correction for multiplicity (Threshold-Free Cluster Enhancement, TFCE; Smith & Nichols, 2009). Whether or not the signal of each modality was high was determined using the t-statistic voxel values, where positive values indicate positive Contrast of Parameter Estimates (COPE; Lindquist et al., 2012). Significant results were visualized using MRI Conversion, Viewing, and Analysis Graphics Library (MRIcroGL Rorden, 2025). The atlas parameters include a threshold intensity of 0.95, neighbors with 6 faces, and bimodal results with a minimum cluster size of 0 mm^3. Lastly, networks were defined using European Brain Research Infrastructure's (EBRAINS) Software Interfaces for Interacting with Brain Atlases' (Siibra Explorer) Multilevel Human Atlas with the MNI 152 ICBM 2009c Nonlinear Asymmetric template (Amunts et al., 2020).

2.4 Results

Post-injury mental health phenotypes. The FDA with *k*-means clustering analysis returned two post-injury mental-health trajectory phenotypes when using four timepoints: baseline, 1-week, 1-month, 3-months post-injury. The 6-month timepoint was excluded because the imaging data only went up to the 3-month point. One cluster (henceforth, *resilient cluster*; n = 59, 28.8% female) showed lower symptom burden and higher resilience (ASD: M = 30.07, SD = 7.96; CES-D: M = 6.50, SD = 5.82; CD-RISC: M = 85.86, SD = 12.03), whereas the other (henceforth, *stress cluster*; n = 31, 29% female) showed higher symptom burden and lower resilience (ASD: M = 50.81, SD = 15.13; CES-D: M = 19.01, SD = 10.34; CD-RISC: M = 75.33, SD = 17.76; Figure 2.3). The two clusters did not differ significantly on age (Mann-Whitney U=851, p=0.592) or sex distribution (χ^2 (1) = 0.000, p = 0.983). As described through individual repeated measures ANOVAs, all three questionnaires exhibited a significant time by cluster interaction (using a Greenhouse-Geisser correction due to a significant deviation from sphericity, as assessed with the Mauchly test; ASD: F(2.233, 189.823) = 12.862, p<0.001, ω^2_p = 0.053;

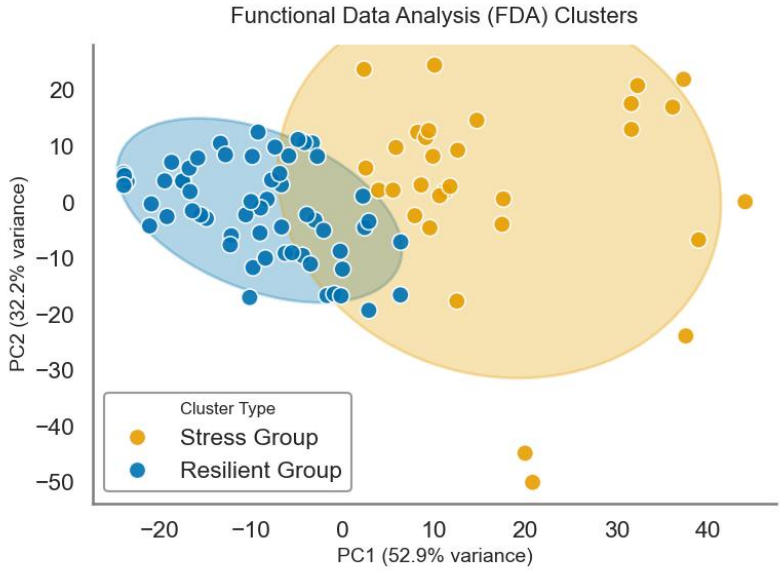


Figure 2.3. Functional data analysis (FDA) cluster spread

CES-D: F(2.645, 224.784) = 5.990, p = 0.001, ω^2_p = 0.025; CD-RISC: F(2.296, 195.167) = 6.197, p=0.002, ω^2_p = 0.016). A main effect of cluster was observed for both the ASD and CES-D scores (ASD: F (1, 85) = 105.27, p < 0.001, ω^2_p = 0.545; CES-D: F (1, 85) = 70.98, p < 0.001, ω^2_p = 0.446). Finally, apart from the main effect of time (F (2.233, 189.823) = 10.035, p<0.001, ω^2_p = 0.041) and sex (F (1, 85) = 4.406, p = 0.039, ω^2_p = 0.038) for the ASD questionnaire, no other significant effect or interaction (e.g., with age or sex) were detected (Figure 2.4).

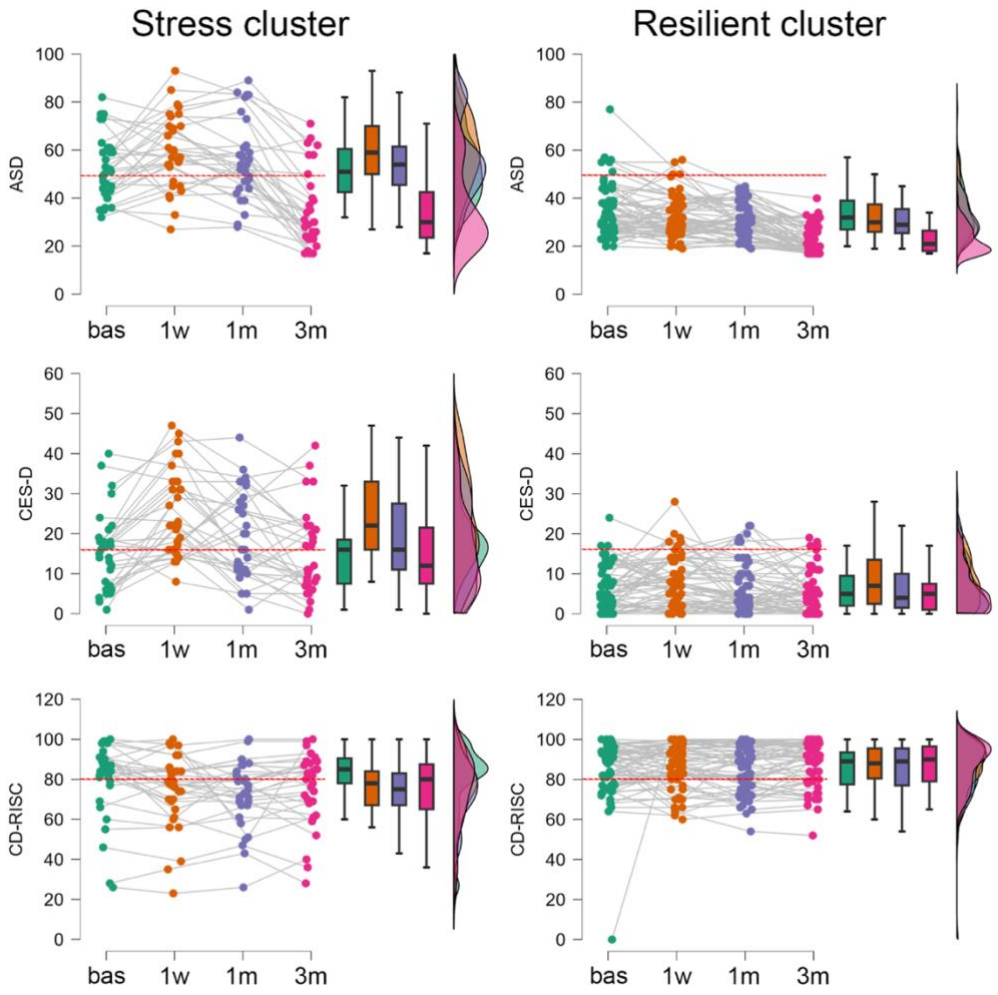
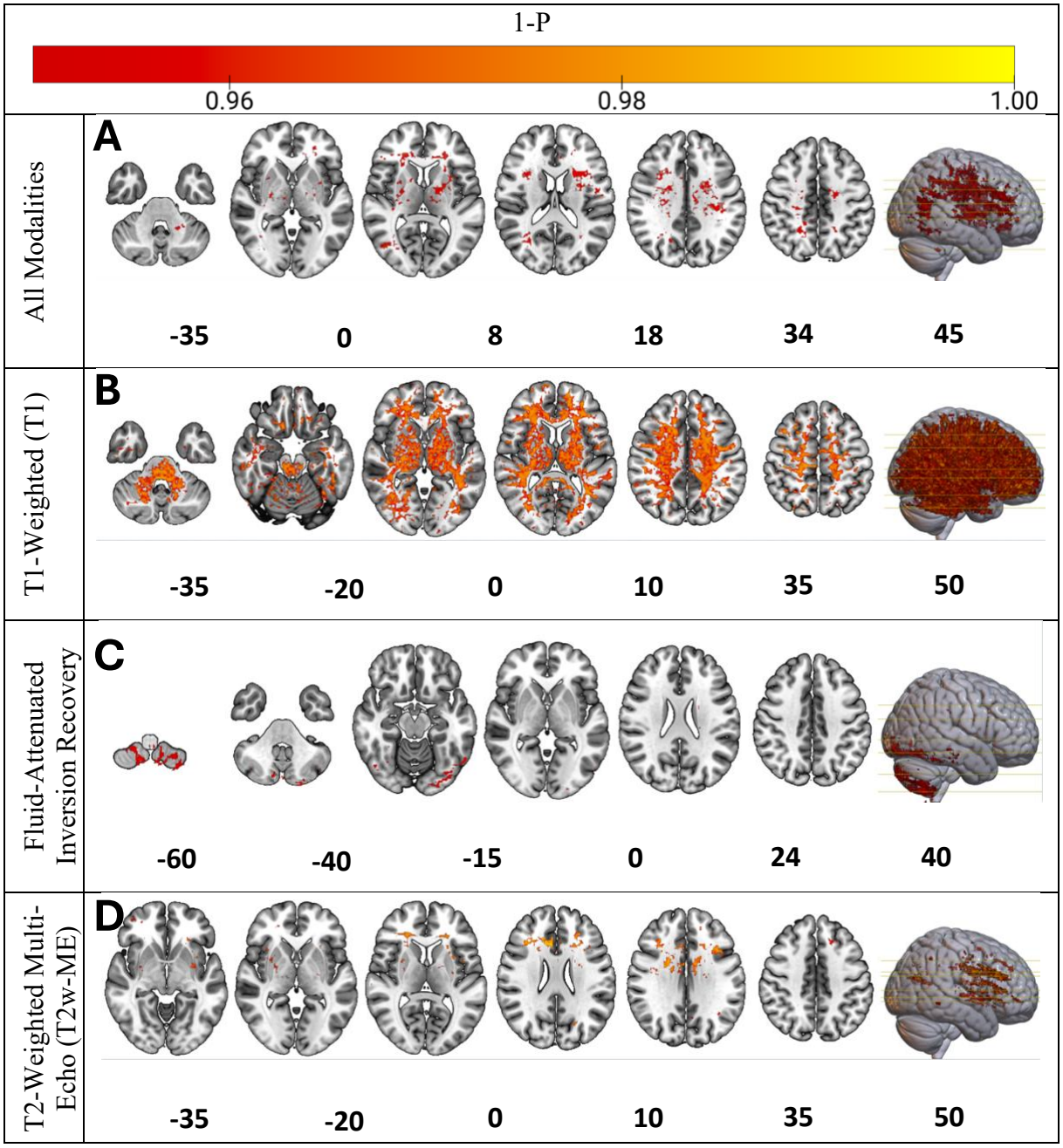


Figure 2.4. Stress and resilient clusters represented by individual neuropsychological test scores

Note. Horizontal dashed lines indicate the cutoff for clinical acute stress disorder and clinical depression score, and the average general population resilience score, for ASD, CES-D, and CD-RISC, respectively. See supplementary online materials for further details. (Abbreviations: bas., baseline; 1w, 1-week post-injury; 1m, 1-month post-injury; 3m, 3 months post-injury.)

Neuroimaging analysis. Multimodal analysis of the association between post-injury mental-health trajectory phenotypes and multimodal imaging returned no results for either baseline or 3 months data. However, extensive associations were detected when relating the mental-health trajectory phenotypes to change over time of multimodal MR data.

Figure 2.5. Permutation analysis of linear models (PALM) results



Note. PALM paired with the non-parametric combination (NPC) approach to compare the difference within mild traumatic brain injury (mTBI) patients 3-months post-injury and immediate post-injury (baseline) scans while also comparing across two groups within the patient population; patients with high stress (stress group) and patients with high resilience (resilient group). All analyses covaried for age, sex, and drug condition. The underlying image is the standard MNI template. The red-yellow color bar indicates statistical significance with more yellow voxels being of higher significance (1-P-value; p<=0.05). (A) Statistically significant difference between the stress group and the resilient group combined across all four modalities. (B) T1-Weighted modality (C) Fluid-Attenuated Inversion Recovery (FLAIR) modality (D) T2-Weighted Multi-Echo (T2w ME) modality.

All Modalities. The multimodal NPC analysis combining the four modalities revealed significant brain differences across the Stress and Resilient groups. The findings indicate the overlapped high signals across all modalities for the Stress group in the difference between the patient's 3-month scan compared to their baseline scan, particularly in the Pars triangularis and superior frontal gyrus bundles (Figure **2.5**A). Using the cluster peaks for each modality, the network associated with the regions within the cluster allows for a deeper dive into the function impacted as a whole, particularly using the fiber architecture parcellations. In the across all modality results, the cluster peak was 7,562 mm^3 (-9.4×-14.2×37.4) which largely includes the left short cingulate fibers (Guevara et al., 2019; Movahedian Attar et al., 2020).

T1. When looking at the partial analyses for the same comparison (i.e., change over time for Stress group compared to Resilient group), several significant differences were observed in the T1 modality. In the T1 modality results, the cluster peak was 1,145 mm^3 (-53.6×-64.3×-17.9) which is largely dominated by cortical and subcortical white matter intensities (Figure **2.5**B).

FLAIR. The individual analysis of the T1 modality in the difference analysis compared the Stress group and Resilient group. The findings indicate high T1 signals for the Stress group in the difference between the patient's 3-month scan compared to their baseline scan, particularly across major white matter tracts. In this modality, a high signal typically indicates structural neural changes (Figure **2.5**C). In the FLAIR modality results, the cluster peak was 297,662 mm^3 (37.8×30.1×36.6) which largely includes the right rostral middle frontal gyrus (Labra-Avila et al., 2023; Japee et al., 2015).

T2w ME. The individual analysis of the T2w ME modality in the difference analysis compared the Stress group and Resilient group. The findings indicate high T2w ME for the Stress group in

the difference between the patient's 3-month scan compared to their baseline scan, particularly in the frontal lobe. In the T2w ME modality results, the cluster peak was 1,449 mm^3 (12.0×22.0×26.3) which largely includes the right short cingulate fibers (Figure **2.5**D; Guevara et al., 2018). In this modality, a high signal typically indicates demyelination. Within the difference PALM analysis, follow-up analyses were completed, which found no significant difference between ages, sexes, and drug condition. There was also no interaction between group and sex and no interaction between group and age.

SWI. There is no significant finding in this modality.

2.5 Discussion

This evidence suggests that a single mild TBI causes a major increase in T1, FLAIR, and T2w ME signals which indicate possible demyelination, neuroinflammation, and structural neuronal change in the difference between the 3-months MRI scan and baseline post-injury scan for patients with clinically high levels of PTSD and Depression when compared to subjects with above average resilience.

Our findings confirm prior work which was done by Lindemer and colleagues (2013), which found a strong relationship between both PTSD and mTBI and reduced cortical thickness. These findings were more prominent compared to patients who only had PTSD, suggesting that mTBI heightens the effects that PTSD causes on cortical thinning. Other work also found whole brain level white matter reduction for patients diagnosed with PTSD and mTBI (de Souza et al., 2023). In addition to cortical thinning and white matter specific damages, certain regions in the brain have been found to be more vulnerable to PTSD. Variance in the superior frontal cortex has been found to be a clear predictor of PTSD with emotional processing networks having the strongest

impacts (Stein et al., 2021; Jagger-Rickels et al., 2022). Prior work has been done supporting the microscopic demyelination effects in white matter tissue in patients with TBI and PTSD (Spadoni et al., 2018). This supports our results which also investigate the comorbidity effects of PTSD and mTBI, in addition to depression, finding high T2w ME signals indicating possible demyelination, especially in the frontal lobe, as well as high T1 signals across white matter tracts at the whole brain level. While other studies also consider the comorbidity effects of PTSD and mTBI, they miss the key effects of depression, which our study aims to provide.

Although literature exists discussing the neural consequences of depression, measured by the CES-D, the joint comorbidity effects paired with mTBI and PTSD are largely missing. However, literature focusing on depression alone has found effects of smaller total brain volume and larger white matter hyperintensities (Geerling et al., 2012; Qiu et al., 2017; Godin et al., 2008). Our results stated large whole brain white matter hyperintensities through our T2w ME modality, suggesting that a single mTBI induces a strong enough impact to cause similar neural consequences which mimics the neural changes caused by major depressive disorder (MDD).

A gap in the literature exists linking the relationship between resilience scores and mTBI. Work has been done on CDRISC's resilience scale finding lower resilience correlates to excessive instability in brain network flexibility across the entire brain (Long et al., 2019; Miyagi et al., 2020). Other research studies have found that a lower local gyrification index (LGI) score, particularly in the interior frontal gyrus, also indicate lower resilience scores (Jung et al., 2024). Our results also depict a similar story, in which the strongest impacts were found in the frontal lobe in our T2w ME modality and across the whole brain networks in our T1 modality, with both findings being highlighted in our combined modality analysis. Resilience is notably the defining

factor of the resilience group with scores being above the average healthy individual, while the stress group exhibited below average scores.

Overall, our results replicate and confirm prior research findings, while simultaneously adding the key components together for patients diagnosed with a single non-complicated mild traumatic brain injury. We also highlight the differing neuropsychological impacts with patients diagnosed not only with the same condition, but also with similar medical history records. This approach led to the creation of two distinct patient groups: stress group and resilient group. Here, we also emphasize the importance of incorporating the comorbidity effects of depression, PTSD, and resilience after a mTBI occurs and the correlation of these differing psychological experiences with vastly different neural consequences. These neural differences were also prominent in white matter and the frontal lobe with slight impacts of the posterior regions. This paper also aims to underline the complex nature of even single mTBI with showcasing the widespread neural changes through the multimodal analytic approach. This approach led to our major structural MRI findings in volumetric (T1), fluidic (T2w ME), white matter (FLAIR), microbleeds (SWI), and the combination of all modalities together.

Limitations. The main limitation of our study is the small sample size. We hope that for future studies we can use a larger sample size to increase power. Additionally, working with an existing data set also comes with its set of limitations. For example, we did not choose the neuropsychological tests that were collected from the patients, which forced us to use the existing neuropsychological measures. Additionally, subjects were excluded due to missing data points in neuropsychological measures and imaging scans because of the multiple follow-up timepoints across the 3-month period.

Future Direction. The second part of this study will focus on creating a machine-learning artificial intelligence (AI) tool, which will automate this process and characterize a new subject's image/neuropsychological data to one of the two clusters: Stress or Resilient group. By identifying the new subject's cluster group, clinicians will be able to have a new look into the patient's neurological and psychological state after injury. This information will guide clinicians to possibly schedule post-injury follow-ups, prescribe medications to combat neural damage, and refer the patient to therapy treatments. Additionally, we are also interested in conducting studies which evaluate the longitudinal effects of these findings, perhaps 1- to 3-years post-injury, and the functional effects of these results through Diffusion Tensor Imaging (DTI) or functional magnetic resonance imaging (fMRI) analysis.

Acknowledgments. We would like to thank the FITBIR team from which our data was sourced. We would also like to acknowledge our Research Assistants; Kieran Hsiao and Matthew Vardanyan, for their data visualization contributions, and Abigail Holder, for her data cleaning efforts.

Funding. This study was supported by the National Institute of Health (NIH) grant #1R21EB034428-01 A1 (Monti).

Chapter 3: Sleep Quality and Sports-Related Concussions

3.1 Abstract

Introduction. In the United States alone, approximately 4 million individuals are diagnosed with a sports-related concussion (SRC) annually, about 85% of those considered to have resolved symptoms continue to experience cognitive deficits. Notably, sleep disturbances have been found to be one of the most common consequences of SRC that in turn had led to those cognitive impairments therefore prolonging recovery time. Nevertheless, sleep disorders are not part of the standardized assessments for SRC even with the abundance of existing evidence. We hypothesize that patients who have low sleep quality also have neural differences compared to those who have high sleep quality. We also expected that the patients with the worst sleep quality would be predominantly SRC patients, with in-sport control (ISC) athletes being second worst in sleep quality, given their history of SRCs, and out-of-sport control (OSC) subjects having the best sleep scores.

Methods. Subjects were recruited from Los Angeles area high schools, combat sports, and colleges through the University of California, Los Angeles (UCLA) Steve Tisch BrainSPORT Program and Clinic. After exclusion, the total sample size was 95 across three cohorts (female n=41, mean age=20.60, SD=2.09; age range=18-35); SRC (n=28, female n=13), ISC (n=34, female n=16), and OSC (n=33, female n=12). The analyses focus on the Graded Symptom Checklist (GSC)'s three sleep components; Drowsiness, Trouble Falling Asleep, and Fatigue, which creates the calculated sleep sum score ranging from 0-18 (0=not present, 18=severe). The data was collected within one-week post-injury for the SRC group. The structural imaging includes T1-weighted Magnetization-Prepared Rapid Gradient-Echo (MPRAGE), Fluid-Attenuated Inversion Recovery (FLAIR), and Diffusion Tensor Imaging (DTI), while functional

imaging includes resting-state functional MRI (rsMRI). After preprocessing all scans accordingly (skull stripping, standard space transformation, etc.), the rsMRI scans were used to select 10 networks of focus (default mode network, sensorimotor network, etc.) using the dual regression method. The ten rsMRI networks selected, MPRAGE, FLAIR, and four components of DTI were inputted into FMRIB Software Library (FSL)'s Permutation Analysis of Linear Models (PALM). Significant results were visualized and the largest cluster of significant finding was found using the MRI Conversion, Viewing, and Analysis Graphics Library (MRIcroGL).

Results. To assess whether a difference exists in sleep quality between the cohorts, the sleep sum scores were normalized using Yeo Johnson (YJ) transformation and plugged into an Analysis of Covariance (ANCOVA) test. This revealed a significant relationship with the Cohort groups ($F_{(2,88)}$=4.930, p=0.009, ω^2p=0.076) with post-hoc test finding a significant relationship between the Sports-Related Concussion (SRC) group and the Out-of-Sport Control (OSC) group (t=3.079, P_{Holm}=0.008), but not the SRC group compared to the In-Sport Control (ISC) group (t=2.171, P_{Holm}=0.065), although trending towards significance, and the two control groups compared to each other (t=1.007, P_{Holm}=0.317). No effect of age and sex or an interaction of the two between the cohort groups was found. The PALM analysis was covaried for demeaned age and sex and assess cohort neural differences as well as sleep sum score differences using 16 modalities of neuroimaging. PALM revealed that the Ventral Attention Network (VAN) signals were significantly higher in the ISC cohort compared to the OSC cohort ($p<0.05$) in the left fusiform gyrus (88%). The Dorsal Attention Network (DAN) signals were significantly higher in the ISC cohort compared to the SRC cohort ($p<0.05$) in the left lingual gyrus (66%) and left cerebellum (34%). The FLAIR signals were significantly higher in the SRC cohort compared to the OSC cohort ($p<0.05$), showing the largest effect in major white matter tracts (44%), right lingual gyrus

(19%), and right calcarine cortex (15%). Lastly, paradoxical findings were revealed across all four DTI modalities (FA, MD, RD, and AD) with each modality showing significantly higher whole-brain wide signals within subjects diagnosed with SRC who had lower sleep sum scores.

Discussion. Our analyses found that the Sports-Related Concussion group had significantly worse sleep quality in terms of Drowsiness levels and Trouble Falling Asleep as well as overall in their Sleep Sum scoring when compared to the Out-of-Sport Controls (OSC). We also found significantly higher severity in Drowsiness and Trouble Falling Asleep between the Sports-Related Concussion patients and the In-Sport-Controls (ISC), while the Sleep Sum YJ variable was trending towards significance. This analysis offers a different lens, that the impacts of sleep are not the same among all athletes including those who had a prior history of SRC, but are more representative of current concussion impacts. Interestingly, no differences were found in the Fatigue levels among the three cohort groups. The PALM results found that sport participation increased connectivity in the ventral attention network (VAN), especially in the left fusiform gyrus, strengthening voluntary attention processing specifically for motor control. However, an in-sport concussive causes a loss of connectivity in the dorsal attention network (DAN), primarily in the left lingual gyrus and left cerebellum, hindering involuntary attention. Lastly, sports-related concussions, compared to non-sport controls, had widespread white matter hyperintensities emphasizing neuroinflammation and demyelination in the right lingual gyrus and calcarine cortex mainly impacting visual processes.

3.2 Introduction

Relevance. In the United States alone, approximately 4 million individuals are diagnosed with a sports-related concussion (SRC) annually (Harmon et al., 2013). Additionally, about 85% of athletes with SRC who are considered to have resolved symptoms continue to experience

cognitive deficits (Hallock et al., 2023). Recent research has found significant slowed speech in athletes with prior SRC diagnoses compared with control athletes (Banks et al., 2021). The current on-field assessment includes checking for red flags (ex. neck pain, headache), observable signs (ex. blank look), memory assessment Maddocks questions, examination Glasgow Coma Scale (GCS), and cervical spine assessment (ex. limb strength check). Presenting one or more of these symptoms account for the diagnoses of an SRC, lead to an off-the-field assessment which states that the athlete cannot return to play until the symptoms are resolved (McKeithan et al., 2019). Prior work has proposed return-to-play protocols to differ depending on the sport to increase efficiency due to differences in symptoms and damage depending on the form of impact (Prock et al., 2024).

Potential Advancements. Given the sensitive nature of an SRC, it is difficult to track neural damage after an injury takes place. Magnetic resonance imaging (MRI) offers the level of detail to catch even minor damages (ex. shear-strain injuries) that otherwise a less detailed imaging method such as computerized tomography (CT) typically does not display (Dabas et al., 2024, Kim & Gean, 2011). Evidence suggests that the current most accurate display of chronic traumatic encephalopathy (CTE), a condition caused by multiple SRC occurrences, is through an MRI, allowing for early intervention (Zamzam et al., 2024). For instance, a SRC may cause a high level of strain to the brainstem, specifically the dorsal raphe, locus coeruleus, and parabrachial complex, leading to a temporary loss of consciousness (Zimmerman et al., 2023).

Proposed Solution. In this study, we propose and test the idea that structural and functional multimodal MRI data paired with post-injury athletes' assessment scales can be used to link corresponding neural damage for professional athletes diagnosed with SRC. This research will both aid in current human brain mapping efforts as well as increase our understanding of the

neural consequences of SRC. We aim to answer the following research questions; Can multimodal neuroimaging data determine whether a subject had a SRC or not? Are there differences at the first timepoint in behavior which correlate to neural damage? Lastly, is there an interaction between these two components?

3.3 Methods

Participant Consent and Compensation. The study received approval from the UCLA Institutional Review Board (IRB). Informed consent was obtained from adults and from parents/guardians of minors. Participants received compensation in the form of a gift card after each visit, where subjects in the SRC group received a maximum amount of $350 per visit and subjects in the control groups received up to $100 for their one visit.

Participants. Subjects were recruited from Los Angeles area high schools, combat sports, and colleges through the University of California, Los Angeles (UCLA) Steve Tisch BrainSPORT Program and Clinic. A total of 240 subjects were recruited for 6 cohorts with about 40 subjects in each group. The age range of these subjects was 17-35 years old with the average age being about 21 years old. The 6 cohort groups are defined in Table **3.1** below. Given our focus on the MRI data, we will only be analyzing cohort 1, 3, and 5. Participants in the SRC group/cohort 1 participated across three timepoints, the first session was 0-4 days post-injury, the second session was 10-14 days post-injury, and the third session was 60-90 days post-injury. The two control groups (cohort 3 and 5) only participated for one session visit. The inclusion criteria for subjects in all cohorts included being between the age 14 and 40 years old. The inclusion criteria for the mTBI group/cohort 1 included a SRC diagnosis, for the contact-sport control group/cohort 3 included participating in collision or contact sports, but not suffering a concussive event, and for the non-contact-sport controls/cohort 5 included not participating in collision or contact sports

and not suffering a concussive event. The exclusion criteria for all cohorts include moderate-to-severe TBI (Glasgow Coma Scale, GCS ≤ 12), neurological/pulmonary disease, skull fracture/open-head injury, vulnerable groups, soft tissue trauma to the temporal region, and current pregnancy. Subjects with a concussion in the last 6-months were excluded from the control groups.

Cohort	Subject Group	Imaging Collected
1	Sports-Related Concussion (SRC)	Transcranial Doppler Ultrasonography (TCD) Magnetic Resonance Imaging (MRI)
2	Sports-Related Concussion (SRC)	Transcranial Doppler Ultrasonography (TCD)
3	In-Sport Control	Transcranial Doppler Ultrasonography (TCD) Magnetic Resonance Imaging (MRI)
4	In-Sport Control	Transcranial Doppler Ultrasonography (TCD)
5	Out-of-Sport Control	Transcranial Doppler Ultrasonography (TCD) Magnetic Resonance Imaging (MRI)
6	Out-of-Sport Control	Transcranial Doppler Ultrasonography (TCD)

Table 3.1. Type of imaging collected by cohort

Subjects who had missing questionnaire data and imaging data were excluded, leaving us with the final total sample size of 95 subjects across the three cohorts (age range = 18-35 years; Table **3.3**). Of the total sample size, 54 subjects were male, while 41 were female with the average age across everyone being 20.60 years old (SD=2.09). In Cohort 1 (SRC group), there are 28 subjects between the ages of 19 to 24 (mean age = 20.54, SD = 1.20, female = 13). In Cohort 3 (In-Sport Control), there are 34 subjects between the ages of 18 to 26 (mean age = 20.53, SD = 1.80, female = 16). Lastly, in Cohort 5 (Out-of-Sport Control), there are 33 subjects between the ages of 18-35 (mean age = 20.73, SD = 2.88, female = 12).

Subject Demographics by Group

Group	n	Age M	Age SD	Age Range	Male / Female
All Subjects	95	20.6	2.1	18–35	54 / 41
Cohort 1	28	20.5	1.2	19–24	15 / 13
Cohort 3	34	20.5	1.8	18–26	18 / 16
Cohort 5	33	20.7	2.9	18–35	21 / 12

Table 3.2. Subject demographics by group and sample size

Neuropsychological Data. Clinical evaluations were performed by Dr. Meeryo Choe, Dr. Christopher Giza, and study staff at the BrainSPORT Clinic located in the Wasserman Building. The neuropsychological data collected from all subjects include Immediate Post-Concussion Assessment and Cognitive Test (ImPACT), Graded Symptom Checklist (GSC), Clinical Reaction Time Drop-stick, Balance Error Scoring System (BESS), King-Devick evaluation, Sport Concussion Assessment Tool 3 (SCAT 3), and NeuroCom VSR Sport Stability Evaluation Test (SET).

Imaging Data. MRI was performed by study staff at the Staglin International Mental Health Research Organization (IMHRO) Center for Cognitive Neuroscience (CCN). Imaging was conducted using a 3.0 T whole-body scanner with a 32-channel phase-array head coil. The MRI sequencing consists of structural and functional imaging. The imaging protocol was adopted from the National Collegiate Athletic Association–Department of Defense (NCAA-DoD) Concussion Assessment, Research and Education (CARE) consortium advanced imaging protocol. The structural imaging includes T1-weighted Magnetization-Prepared Rapid Gradient-Echo (MPRAGE), Fluid-Attenuated Inversion Recovery (FLAIR), and Diffusion Tensor Imaging (DTI), while functional imaging includes resting-state functional MRI (fMRI) and Arterial Spin Labeling (ASL). The ASL modality was excluded due to the high quantity of missing data. The MRI CVR component was performed through resting state functional imaging with CO_2

inhalation. The subject alternated between breathing room air and a “challenge air” composed of a 5% CO2/air mixture through an MRI safe air delivery system. In this analysis, we only focus on the MRI and CVR component only and will not be including the TCD and CVR-only components.

Neuropsychological Data Analysis. We will be focusing on one major component impacted by sports-related concussions, sleep. The Graded Symptom Checklist (GSC) contains subcategories, one of which is sleep, and is derived of three parts: Trouble Falling Asleep, Drowsiness, and Fatigue (Janusz et al., 2012). Each of these scales are self-reported by subjects ranging from a score between 0 to 6 points, where the higher score indicates a more severe/worse outcome and were collected one-week post-injury. In the GSC scale, 0 indicates “not present”, 1 indicates “mild”, 2 indicates “mild-to-moderate” and so on. A combination of these scores was calculated by finding the sum of sleep scores called “Sleep Sum”, which ranges from 0 to 18, where again, a higher score indicates a worse outcome (DuPrey et al., 2022). To maintain the initial questionnaire’s scoring system, the same format was translated to conform with the 0-18 scale. A score of 0 still indicates “not present”, but now a score between 1-6 is considered “mild”, 7-12 is considered “moderate”, and a score between 13-18 is considered “severe”. The naming convention was then transformed into numeric format where “not present” is a 0, “mild” is a 1, “moderate” is a 2, and “severe” is a 3 (Sleep Severity). Lastly, the sleep sum scores are used as input along with demeaned age, binary format sex, and cohort group for our FMRIB Software Library (FSL)’s Permutation Analysis of Linear Models (PALM; Winkler et al., 2014).

Imaging Data Analysis. All data was de-identified prior to analysis and clinical data was scored according to standardized test guidelines. For each participant, the structural modalities at each timepoint were first processed with FMRIB Software Library (FSL)’s fsl_anat to produce bias

corrected images (Jenkinson et al., 2012). Bias corrected images were then skull-stripped using FreeSurfer's SynthStrip (synthetic skull stripping) function and registered to standard T1 Montreal Neurological Institute (MNI) space at 2-millimeter (mm) resolution using FreeSurfer's SynthMorph (synthetic morphing; Hoopes et al., 2022; Hoffman et al., 2022). The final processed and MNI space images are then merged (fslmerge) into a single 4D NIFTI image per modality.

For the functional modality, resting-state fMRI (rsMRI), resting BOLD data were processed using FSL (v6.0.7.14) and Freesurfer (v8.0.0). First, to avoid biases linked to different total samples acquired, the data for two individuals with fewer than 50 scans were removed from the analysis (both from Cohort 5) and data including more timepoints than 236 (i.e., 21, 22, and 25 for cohorts 1, 3, and 5, respectively) were truncated so that for all participants the same number of volumes were input in the analysis (i.e., 236 ms). In addition, the first 4 volumes of each acquisition were discarded to allow the MR signal to reach a steady-state equilibrium. Functional data underwent motion correction, slice timing correction, and were realigned to an MNI space template. In addition, to mitigate the effect of motion on resting-state correlations (Power et al., 2014; Marina Weiler et al., 2024), we performed a nuisance regression including, for each participant, the average signals from the full brain (i.e., global signal), white matter, and CSF, one regressor per each volume featuring excessive motion (as determined by fsl_motion_outliers), and 24 motion parameters (i.e., translation and rotation in 3 dimensions, their temporal derivatives, and their squares). The residuals from this spike regression were then band-pass filtered between the frequencies of 0.01 and 0.1 Hz. The preprocessed images were then inputted into FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) for single-session Independent Components Analysis

(ICA) (Wang et al., 2015). The components created by MELODIC are then set into FSL's cross-correction (*fslcc*) tool with Neuroimaging Tools and Resources Collaboratory (NITRC)'s Resting State Network 20 (RSN20) which overlaps 20 network spatial maps onto the MELODIC component output (Smith et al., 2009). We extracted only the anterior and posterior Default Mode Network (DMN), Sensorimotor Network (SMN-M; Motor-based), Ventral Attention Network (VAN), left and right Frontoparietal Networks (FPN), Sensorimotor Network (SMN-S; Sensory-based), Subcortical Network (SUBCORTEX), Dorsal Attention Network (DAN), and Motor Network. The ten final components were selected through visual quality check using FSLeyes to select final components, which were then inputted into FSL's *dual_regression* (Beckmann et al., 2009). Dual regression creates an individualized network spatial map for each subject using the inputted group-specific template using 5,000 permutations. This output is then inputted as a single 4D rsMRI modality into the Permutation Analysis of Linear Models (PALM) analysis paired with the structural MRI modalities.

To assess any association between multimodal brain data and the clinical assessments, images were entered into FSL's PALM tool to perform multivariate analyses test (Winkler et al., 2014; Winkler et al., 2016). Importantly, the permutations in each partial test are synchronized across modalities, meaning that for each permutation subject labels are shuffled in the same way in all modalities. These modality specific *u*-values are then combined, at each voxel, thus producing a single joint statistic that reflects evidence across partial tests while accommodating cross-modality dependencies. In addition to clinical assessment dataset, the independent variable of interest, all analyses also included age and sex as covariates to parcel out their effect on any association between brain data and clinical phenotypes. Analyses were performed in PALM, and inferences were based on the multivariate approach (with 5,000 permutations) with familywise

correction for multiplicity (Threshold-Free Cluster Enhancement, TFCE; Smith & Nichols, 2009). Significant results were visualized using MRI Conversion, Viewing, and Analysis Graphics Library (MRIcroGL Rorden, 2025). The atlas parameters include a threshold intensity of 0.95, neighbors with 6 faces, and bimodal results with a minimum cluster size of 0 mm^3.

3.4 Results

Neuropsychological Data. The data was well balanced across all three groups in terms of age differences and sample size (Table **3.3**). A descriptive statistical analysis of all three raw subcategories; Drowsiness (M=0.76; SD=1.30), Fatigue (M=1.25; SD=1.37), and Trouble Falling Asleep (M=0.41; SD=0.98), and the Sleep Sum score (M=2.42; SD=3.09; Table **3.4**) paired with the Shapiro-Wilk method revealed that all four variables were not normally distributed and therefore the normality assumption is violated ($p<0.001$). The Levene's Test for Equality of Variance confirmed these findings for the raw Sleep Sum score with a significant outcome ($F_{(5,89)}=6.841$, $p<0.001$). To combat this issue, the Yeo Johnson (YJ) transformation was applied to the Sleep Sum scores, and the normality issue was resolved (lambda = 0; $F_{(5,89)}=1.367$, $p=0.245$). The same Levene's Test for Equality of Variance violation of normality was found in the raw Drowsiness ($F_{(5,89)}=6.734$, $p<0.001$) and Trouble Falling Asleep ($F_{(5,89)}=24.075$, $p<0.001$) variables, but not the Fatigue ($F_{(5,89)}=0.902$, $p=0.484$) variable. However, the same Yeo Johnson transformation did not resolve the normality issue for the Drowsiness YJ ($F_{(5,89)}=3.159$, $p=0.011$), Trouble Falling Asleep YJ ($F_{(5,89)}=24.075$, $p<0.001$) variables, while the Fatigue YJ ($F_{(5,89)}=1.154$, $p=0.338$) variable remained normally distributed.

Sleep Sum YJ. An Analysis of Covariance (ANCOVA) test using the Yeo Johnson transformation values for the Sleep Sum scores revealed a significant relationship with the Cohort groups

($F_{(2,88)}$=4.930, p=0.009, ω^2p=0.076) but not affected by the subject's age and sex or interaction between cohort and sex. These results led us to conduct a post-hoc test, which found a significant relationship between the Sports-Related Concussion (SRC) group and the Out-of-Sport Control (OSC) group (t=3.079, P_{Holm}=0.008), but not the SRC group compared to the In-Sport Control (ISC) group (t=2.171, P_{Holm}=0.065), although trending towards significance, and the two control groups compared to each other (t=1.007, P_{Holm}=0.317).

Drowsiness. The ANCOVA for the Drowsiness scores also found a significant relationship with the Cohort groups ($F_{(2,88)}$=4.616, p=0.012, ω^2p=0.071) but not affected by the subject's age and sex or interaction between cohort and sex. Unlike the Sleep Sum YJ findings, the post-hoc test results found a significant relationship between both the SRC group compared to the OSC (t=2.691, P_{Holm}=0.026) cohort and the ISC (t=2.633, P_{Holm}=0.026) cohort. Similarly, the two cohorts did not have a significant relationship (t=0.126 P_{Holm}=0.900).

Trouble Falling Asleep. The ANCOVA for the Trouble Falling Asleep scores also found a significant relationship with the Cohort groups ($F_{(2,88)}$=10.994, p<0.001, ω^2p=0.174) but not affected by the subject's age and sex or interaction between cohort and sex. Like the Drowsiness findings, the post-hoc test results found a significant relationship between both the SRC group compared to the OSC (t=4.405, P_{Holm}<0.001) cohort and the ISC (t=3.717, P_{Holm}<0.001) cohort. Similarly, the two cohorts did not have a significant relationship (t=0.816 P_{Holm}=0.417).

Fatigue. Lastly, unlike the Drowsiness and Trouble Falling Asleep findings, the ANCOVA for the Fatigue scores did not reveal any significant relationship with the Cohort groups ($F_{(2,88)}$=1.990, p=0.143, ω^2p=0.020) or an effect of the subject's age and sex or interaction between cohort and sex. Therefore, a post-hoc test was not necessary for this variable.

GSC Sleep Variables by Group: Drowsiness, Trouble Falling Asleep, Fatigue, and Sleep Sum

	Drowsiness	Trouble Falling Asleep	Fatigue	Sleep Sum
Group	M (SD)	M (SD)	M (SD)	M (SD)
All Subjects	0.76 (1.30)	0.41 (0.98)	1.25 (1.37)	2.42 (3.09)
Cohort 1	1.39 (1.79)	1.07 (1.46)	1.68 (1.44)	4.14 (4.31)
Cohort 3	0.53 (0.99)	0.21 (0.64)	1.24 (1.35)	1.97 (2.17)
Cohort 5	0.45 (0.87)	0.06 (0.24)	0.91 (1.26)	1.42 (1.92)

Table 3.3. Graded Symptom Checklist (GSC) sleep variables by cohort

Since the Sleep Sum score encompasses the effects of all three subcategories, the Sleep Sum score served as our dependent variable and the cohort group served as our independent variables in the PALM analysis. To check the extent of which these two variables overlap for each subject, we compare the percent of subjects which are in each Cohort and each of the four severity scales (Sleep Severity; Table **3.4**). Across all Cohorts, 35.8% (n=34) are in the "Not Present" severity level, 52.6% (n=50) are in the Mild severity level, 9.5% (n=9) are in the Moderate stage, and 2.1% (n=2) are in the Severe level. Focusing only on the SRC Cohort, 21.4% (n=6) had no symptoms present, while 50.0% (n=14) experience Mild symptoms and 21.4% (n=6) have Moderate symptoms with the remaining subjects having Severe symptoms (7.1%; n=2). On the other hand, the In-Sport Control group had more subjects without symptoms (32.4%; n=11) with more subjects in the Mild symptoms group (61.8%; n= 21), but much less subjects in the Moderate (5.9%; n=2) and no subjects in the Severe levels. Lastly, the Out-of-Sport Control group had even more subjects without symptoms present (51.5%; n=17) and therefore less subjects in both the Mild (45.5%; n=15) and Moderate (3.0%; n=1) levels, with again no individuals experiencing Severe symptoms. Given these results, the Sleep Severity levels and the Cohort groups do not perfectly overlap and that external variables might very well be influencing

the two control groups' sleep scales as well. Hence, why in the final PALM analysis, Cohort variable will be set for a pairwise comparison and the Sleep Severity variable will be set for a linear trend analysis while covarying for demeaned age and sex. The sleep sum revealed

GSC Sleep Severity Classification by Group: Frequency and Percentage

	Not Present	Mild	Moderate	Severe
Group	n (%)	n (%)	n (%)	n (%)
All Subjects	34 (35.8%)	50 (52.6%)	9 (9.5%)	2 (2.1%)
Cohort 1	6 (21.4%)	14 (50.0%)	6 (21.4%)	2 (7.1%)
Cohort 3	11 (32.4%)	21 (61.8%)	2 (5.9%)	0 (0.0%)
Cohort 5	17 (51.5%)	15 (45.5%)	1 (3.0%)	0 (0.0%)

Table 3.4. Graded Symptom Checklist (GSC) sleep quality classification by cohort

Neuroimaging + Neuropsychological Data. Across the 8 tested contrasts, 6 cohort-based and 2 sleep-based, each contrast had a single significant PALM finding with no cross-modality significant finding overall. The SRC>OSC and OSC>SRC contrasts mirror one another with the same confirmatory findings, FLAIR signals were significantly higher in the SRC cohort compared to the OSC cohort ($p<0.05$; Figure 3.1A). This contrast group had the strongest effect across the whole brain with over ~32,000 voxels total across ~319 clusters. The largest cluster contains 21,725 of those voxels, mainly spanning across major white matter tracts (44%), right lingual gyrus (19%), and right calcarine cortex (15%). Other large clusters include the bilateral thalamus, right putamen, left caudate, left pallidum, bilateral hippocampus, and bilateral amygdala.

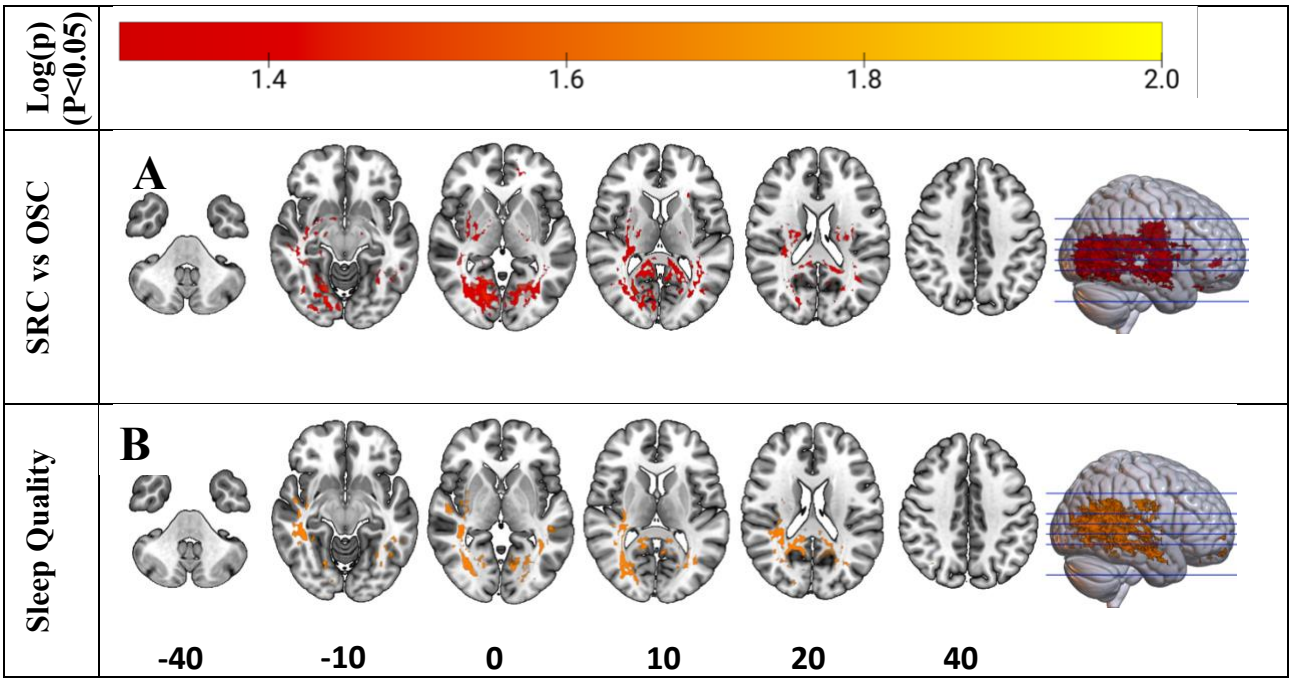


Figure 3.1. Permutation analysis of linear models (PALM) results for sleep quality and cohort effects in FLAIR

Note. SRC=Sport-related concussion, OSC=Out-of-sport control, FLAIR=Fluid-attenuated inversion recovery

The SRC>ISC and ISC>SRC contrasts mirror one another with the same confirmatory findings, Dorsal Attention Network (DAN) signals were significantly higher in the ISC cohort compared to the SRC cohort ($p<0.05$; Figure 3.2A). The higher signal here indicates more connectivity. This contrast group had a small effect with one cluster with the size of 38 voxels mm^3 covering the left lingual gyrus (66%) and left cerebellum (34%).

The ISC>OSC and OSC>ISC contrasts mirror one another with the same confirmatory findings, Ventral Attention Network (VAN) signals were significantly higher in the ISC cohort compared to the OSC cohort ($p<0.05$; Figure 3.2B). The higher signal here indicates more connectivity. Here, we see a small effect with 239 voxels total across four clusters, with the largest cluster having 191 voxels which encompasses most of the left fusiform gyrus (88%), while the remaining voxels were unassigned (12%). Other clusters include regions such as the left hippocampus, left para-hippocampal gyrus, and left inferior temporal gyrus.

The sleep positive and sleep negative linear trend contrasts mirror one another as well and confirm one another's results. The FLAIR modality was significantly higher for subjects with lower sleep sum scores ($p<0.05$; Figure 3.1B). This contrast group had a large effect with 189 clusters spanning across 20,417 voxels total with the largest cluster being 14,556 voxels in size covering major white matter tracts (42%), right precuneus (30%), right calcarine gyrus (17%), and left posterior cingulum gyrus (8%) along with other minor regions. Other large clusters include the left lingual gyrus, left inferior temporal gyrus, left middle occipital gyrus along with others.

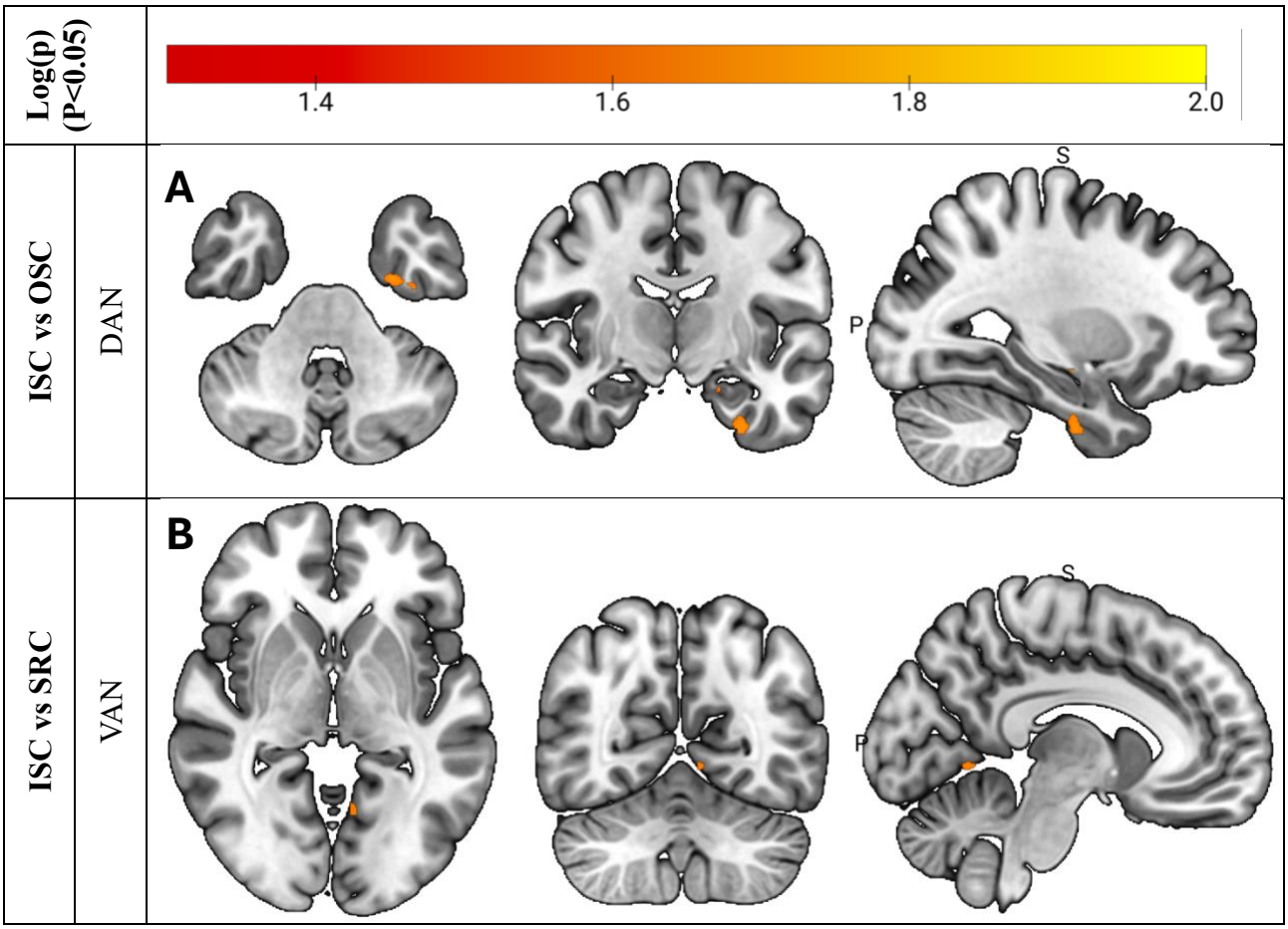


Figure 3.2. Permutation analysis of linear models (PALM) results for cohort effects in attention networks
Note. SRC=Sport-related concussion, ISC=In-sport control, OSC=Out-of-sport control, VAN=Ventral attention network, DAN=Dorsal attention network

Given the counterintuitive sleep quality results, an additional sleep quality follow-up test was conducted in the sport-related concussion (SRC; n=28) group alone with the same PALM parameters (permutation n=5,000). The DTI Fractional Anisotropy (FA) modality was significantly higher for subjects with lower sleep sum scores ($p<0.05$; Figure **3.3**A). This contrast group had a whole-brain wide effect with 172 clusters spanning across 646,783 voxels total with the largest cluster being 645,486 voxels in size covering unassigned cortical areas (39%), cerebellum (~11%), right superior temporal gyrus (1%), thalamus (2%), right precuneus (1%), right insula (1%) among other regions. The second largest cluster's volume is 174 voxels 90% of which encompasses the left Inferior frontal triangular gyrus with the remaining 10% covering the left middle frontal gyrus. The DTI Mean Diffusivity (MD) modality was significantly higher for subjects with lower sleep sum scores as well ($p<0.05$; Figure **3.3**B). This contrast group had a whole-brain wide effect with 16 clusters spanning across 1,618,392 voxels total with the largest cluster being 1,618,382 voxels in size covering unassigned cortical areas (27%), bilateral middle temporal gyrus (4%), bilateral middle temporal gyrus (4%), right inferior gyrus (2%) along with other regions. The second largest cluster's volume is 174 voxels 90% of

which encompasses the left Inferior frontal triangular gyrus with the remaining 10% covering the left middle frontal gyrus.

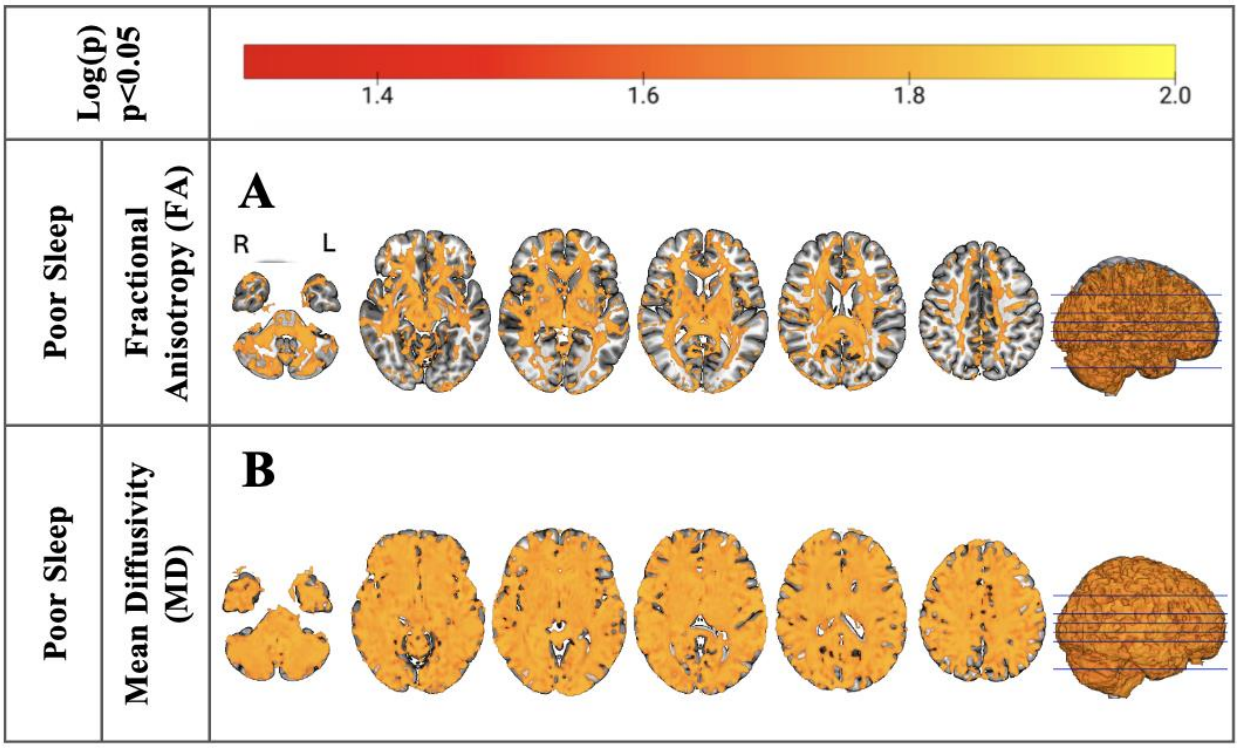


Figure 3.3. Permutation analysis of linear models (PALM) results within the SRC cohort in DTI modalities FA and MD
Note. SRC=Sport-related concussion, DTI=Diffusion Tensor Imaging

The DTI Radial Diffusivity (RD) modality was significantly higher for subjects with lower sleep sum scores as well ($p<0.05$; Figure **3.4**A). This contrast group had a whole-brain wide effect with 6 clusters spanning across 1,490,501 voxels total with the largest cluster being 1,490,500 voxels in size covering unassigned cortical areas (26%), bilateral middle temporal gyrus (4%), bilateral middle temporal gyrus (4%), right inferior gyrus (2%) along with other regions, like the MD findings. The DTI Axial Diffusivity (AD) modality was significantly higher for subjects with lower sleep sum scores as well ($p<0.05$; Figure **3.4**B). This contrast group had a whole-brain wide effect with 12 clusters spanning across 1,615,751 voxels total with the largest cluster being 1,615,739 voxels in size covering unassigned cortical areas (26%), bilateral middle

temporal gyrus (4%), bilateral middle temporal gyrus (4%), right inferior gyrus (2%) along with other regions, similar to the MD and RD results.

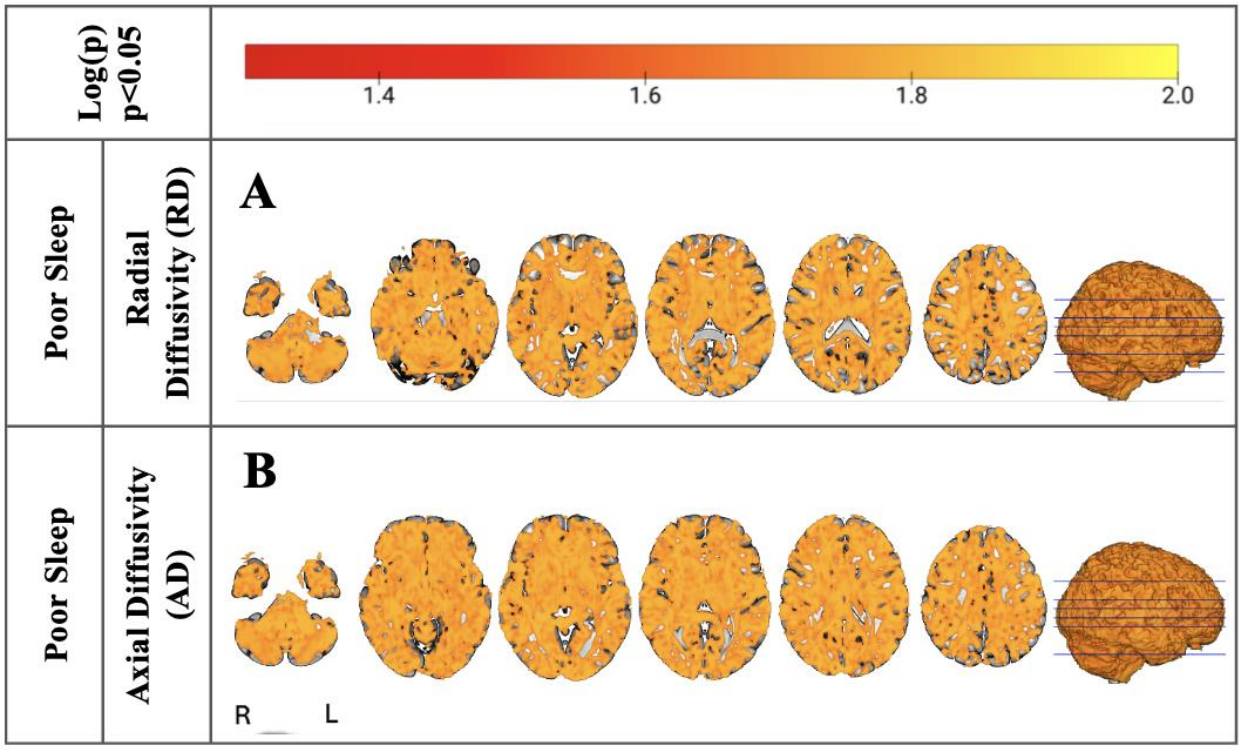


Figure 3.4. Permutation analysis of linear models (PALM) results within the SRC cohort in DTI modalities RD and AD
Note. SRC=Sport-related concussion, DTI=Diffusion Tensor Imaging

The same follow-up analysis found effects within the resting-state fMRI (rsMRI) modality with the Dorsal Attention Network (DAN) being higher the worse the sleep quality score was ($p<0.05$; Figure **3.5**A). There was a small effect with 6 clusters spanning across 576 voxels total with the largest cluster being 538 voxels in size covering the left precuneus (99%) and the remaining portion touching upon the left middle cingulum. All remaining clusters solely covered the left precuneus. On the other hand, the Ventral Attention Network (VAN) which was also significantly higher in the lower sleep sum scores but had a substantially larger effect ($p<0.05$; Figure **3.5**B). There were 48 clusters spanning across 147,663 voxels total with the largest cluster being 145,264 voxels covering the bilateral middle temporal gyrus (18%), bilateral superior temporal gyrus (10%), unassigned regions (9%), bilateral lingual gyrus (7%) among other areas. Notably,

the second largest cluster's volume is 468 voxels 74% of which encompasses the left precuneus with the remaining covering the right precuneus (9%) and other minor regions.

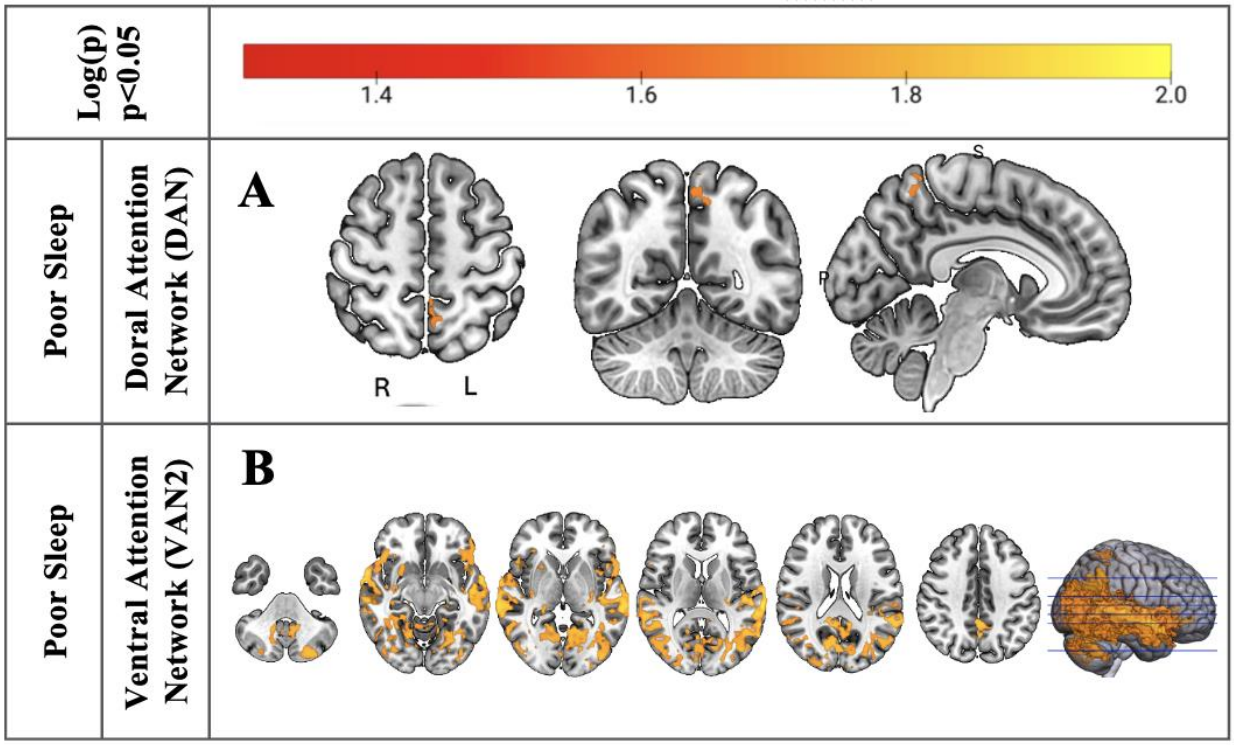


Figure 3.5. Permutation analysis of linear models (PALM) results within the SRC cohort in rsMRI attention network
Note. SRC=Sport-related concussion and rsMRI=resting-state functional magnetic resonance imaging

The follow-up analysis found effects within the resting-state fMRI (rsMRI) modality with the Sensorimotor Network (SMN) being higher the worse the sleep quality score was ($p<0.05$; Figure **3.6**A). There was a notable effect with 9 clusters spanning across 5,340 voxels total with the largest cluster being 5,174 voxels in size covering the right postcentral gyrus (41%), right Rolandic operculum (29%), right superior temporal gyrus (11%), right supramarginal gyrus (8%), right Heschl's gyrus (2%), and the right precentral gyrus (1%). However, the Default Mode Network (DMN) which was also significantly higher in the higher sleep sum scores but had an almost negligible effect ($p<0.05$; Figure **3.6**B). There was a notable effect with 2 clusters spanning across 57 voxels total with the largest cluster being 44 voxels in size covering the left

superior frontal gyrus (75%) and left superior medial frontal gyrus (25%). The only other cluster's volume is 13 voxels 100% of which encompasses the left superior medial frontal gyrus.

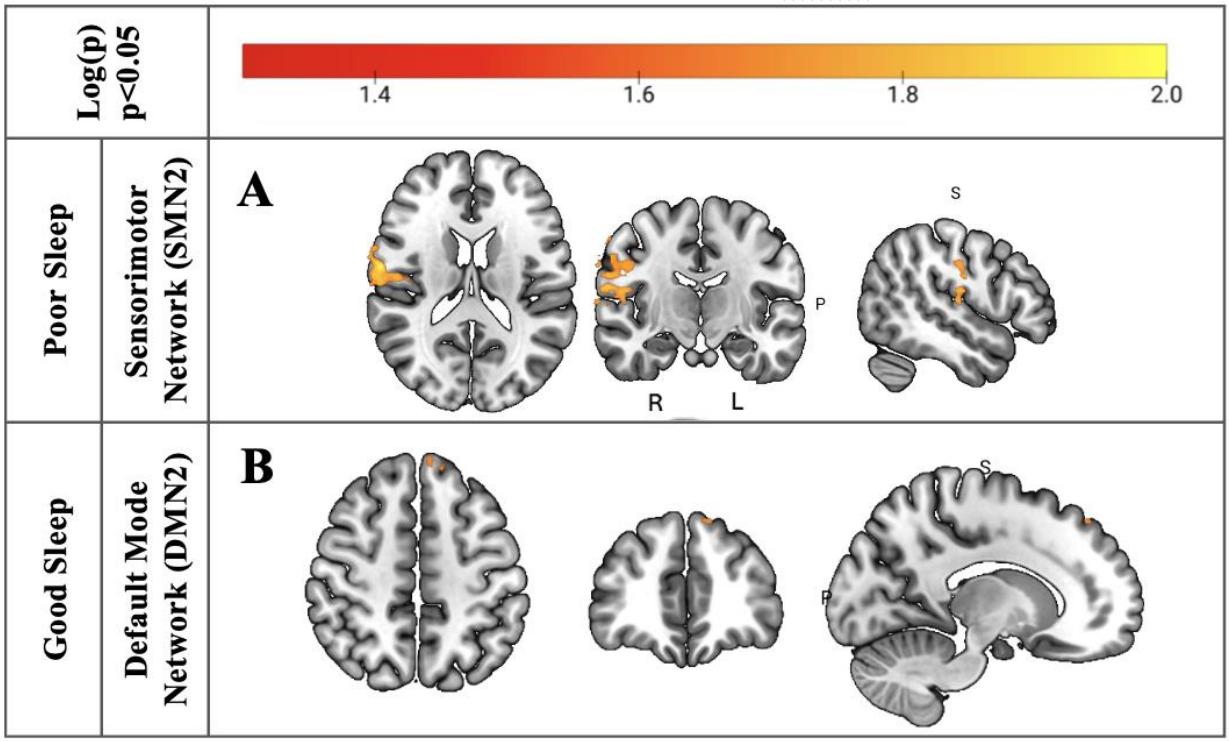


Figure 3.6. Permutation analysis of linear models (PALM) results within the SRC cohort in rsMRI network
Note. SRC=Sport-related concussion and rsMRI=resting-state functional magnetic resonance imaging

3.5 Discussion

Sleep disturbances have been found to be one of the most common consequences of Sports-Related Concussions (SRC), which in turn leads to emotional and cognitive impairments therefore prolonging recovery time (Grigg-Damberger, 2023). Unfortunately, sleep disorders are not part of the standardized assessments for sports-related concussions even with the abundance of existing evidence and its links with pain endurance, headaches, and heightened cognitive impairment (Stevens et al., 2022; Gosselin et al., 2010). Although like mild traumatic brain injuries (mTBI) experienced among the general population, sports concussions are unique in their pathophysiology with repeated injuries being frequently reoccurring and beginning at a young age for athletes (Giza & Kutcher, 2014). Notably, cognitive deficits in this patient

population have been linked to neural damages, particularly a major decrease in the Diffusion Tensor Imaging (DTI)'s Fractional Anisotropy (FA) indicating negative impacts to white matter tracts (Symons et al., 2021; Keightley et al., 2011; Jindal et al., 2021). Functional MRI has been found to have potential in uncovering the recovery time after a sports-related concussion and offers network-specific damage tracking which is more insightful than identifying independent brain structures differences (Walter et al., 2018; Meier et al., 2020; Dogra et al., 2024). On the other hand, sleep-specific linkage related to the neural consequences following sports concussions have not been well documented. Nevertheless, work highlighting white matter differences among healthy controls and concussed athletes which are detectable through Magnetic Resonance Imaging (MRI) offers promising results (Hellewell et al., 2021). Additional work also found that the multimodal approach has the potential in offering a more holistic view in understanding the neural consequences (Hasan et al., 2018). This paper aims to fill in the gap between neural impacts of concussion-related sleep disturbances, as they are currently largely unknown.

Sleep Results. In this paper we selected three sleep measures collected one-week post-injury; Drowsiness, Trouble Falling Asleep, and Fatigue, and created a combined and normalized new variable called Sleep Sum YJ (Yeo Johnson-corrected). Our analyses found that the Sports-Related Concussion group had significantly worse sleep quality in terms of Drowsiness levels and Trouble Falling Asleep as well as overall in their Sleep Sum scoring when compared to the Out-of-Sport Controls (OSC). These findings highlight the substantial differences in sleep health among the patients both currently participating in a sport and suffering from a concussion and those who are meant to represent a completely healthy population. We also found significantly higher severity in Drowsiness and Trouble Falling Asleep between the Sports-Related

Concussion patients and the In-Sport-Controls (ISC), while the Sleep Sum YJ variable was trending towards significance. Here, we place the emphasis on the difference of sleep quality for patients who are currently suffering with a concussion, but sport participation is standardized between the two groups. This analysis offers a different lens, that the impacts of sleep are not the same among all athletes including those who had a prior history of SRC, but are more representative of current concussion impacts. When comparing the two control groups with one another, no notable differences are detected in sleep levels, further indicating that the sleep disturbances are substantially impacted by the recent concussion. Interestingly, no differences were found in the Fatigue levels among the three cohort groups, which might signal that not all aspects of sleep are impacted, but specific types of sleep experiences are changed. Lastly, no effect of age or sex were found, including interactions related to cohort groups; therefore, we expect similar findings in the imaging results as well. Given the sleep quality severity differences among the concussion group and the Out-of-Sport control group, we expect to observe significant differences between the neural states of these groups as well.

Cohort + Imaging Results. Our analyses revealed that subjects diagnosed with sports-related concussion within one-week post-injury and participate in a sport (cohort 1; SRC) had significantly higher Fluid-Attenuated Inversion Recovery (FLAIR) signals than the out-of-sport control group of healthy non-sport subjects. These signals were primarily in major white matter tracts, indicating white matter hyperintensities (WMH), right lingual gyrus, and calcarine cortex (Maillard et al., 2013; Major et al., 2021). High FLAIR signals indicate neuroinflammation, edema, and/or demyelination. In this case, our results indicate WMH in major tracts ranging across the whole brain and neuroinflammation/demyelination effects in the right lingual gyrus and right calcarine cortex (V1). The right lingual gyrus is responsible for visual memory, while

the right calcarine gyrus processes visual information from left visual field using input from both eyes (Palejwala et al., 2021). Hence, these results indicate damage to the right lingual and calcarine gyri, which in turn is likely to cause hindered visual processing in the concussed athletes (Meier et al., 2025). These finding align with prior research which linked SRC with neuroinflammation in athletes with notable disruptions of white matter tissue (Marklund et al., 2021; Huang et al., 2025).

The results between the in-sport control group and out-of-sport control group revealed different results, healthy subjects who participated in a sport had more connectivity in the ventral attention network (VAN), especially in the left fusiform gyrus (Weiner & Zilles, 2016). The ventral attention network is primarily responsible for involuntary attention processing. Our findings are confirmed with prior work which also found increased connectivity in the VAN specifically, indicating better visual attention and motor control developed from sport participation (Yan et al., 2025).

When comparing the sport-related concussion group with the in-sport control group the key difference lies within the concussive event, as both groups participate in a sport. Here, we found that the in-sport control group again had more connectivity, but this time in the dorsal attention network (DAN) focused on the left lingual gyrus and left cerebellum, the voluntary attention processing network. Our findings align with research revealing increased functional connectivity in the dorsal attention network in healthy individuals compared to concussed individuals (Suss et al., 2022; Wu et al., 2023). This indicates that a concussive event hinders the attention network connectivity developed from sport participation, which could be linked to the increased FLAIR finding with whole brain wide white matter hyperintensities.

Sleep + Imaging Results. The sleep quality assessment result revealed increased FLAIR signal in subjects with better sleep quality (lower sleep sum score). The impacts were vast with white matter hyperintensities and localized effects on the right precuneus, right calcarine cortex, and left posterior cingulum gyrus along with other minor regions. However, these results are counterintuitive, as literature emphasizes the opposite effects; demyelination associated with poor sleep quality (Morse & Kothare, 2018). The notion that sleep quality heavily impacts sports-related concussions are important as sleep disturbances also lead to additional brain injuries (Raikes et al., 2019). These findings might be due to the imbalanced groups within the sleep scoring scale, as the great majority of subjects had lower sleep scores because most of the sample size was made up by the two control groups.

SRC-Specific Sleep + Imaging Results. Due to this counterintuitive finding which does not align with literature, we are currently analyzing additional follow-up tests within the sleep quality scale to better understand the results. The diffusion tensor imaging (DTI) modalities; FA, MD, RD, and AD, were all high in signal across the whole-brain for subjects with lower sleep sum scores compared to those with higher scores. These results indicate that poor sleep quality in concussed athletes is linked with whole-brain level demyelination, axonal degeneration, edema, and necrosis across (Patil et al., 2025). Notably, the existence of both high signals in fractional anisotropy (FA) and mean diffusivity (MD) in this setting highlights acute brain injury which overlaps with the timepoint the data was collected, 0-4 days post-injury (Lin et al., 2016; Asken et al., 2018). The resting-state fMRI (rsMRI) modality displayed minor effects in the Default Mode Network (DMN) and Dorsal Attention Network (DAN), while strong effects were observed in the Ventral Attention Network (VAN) and the Sensorimotor Network (SMN). The largest rsMRI effect was presented in the VAN with higher signals for subjects with lower sleep

sum scores in mostly the middle and superior temporal gyri, lingual gyri, and precuneus. Ultimately, these results suggest that poor overall sleep quality in concussed athletes is linked with hyperconnectivity in regions responsible for involuntary attention processing (Muller & Virji-Babul, 2018). Lastly, higher signals in the SMN were observed in patients with lower sleep sum scores in mainly the right postcentral gyrus and right Rolandic operculum. These findings suggest that poor overall sleep quality in concussed athletes is linked with hyperconnectivity in regions responsible for voluntary motor control (Hides et al., 2017; Hillary et al., 2015; Churchill et al., 2018).

In summary, sports-related concussions cause whole brain wide white matter hyperintensities indicating neuroinflammation and demyelination, especially in the right lingual gyrus and calcarine cortex, affecting visual memory and visual processing. In-sport concussive events are also linked with a decline in functional connectivity in the dorsal attention network (DAN), primarily in the left lingual gyrus and left cerebellum, impacting involuntary attention processing. On the other hand, sport participation increased functional connectivity in the ventral attention network (VAN), especially in the left fusiform gyrus. In other words, sport participation strengthens voluntary attention processing by reinforcing motor control and visual attention development. Overall, athletes without a current concussion have strong voluntary attention processing, while athletes with a current concussion have weakened involuntary attention processing, but maintained voluntary attention control.

Future Direction. We plan to leverage this dataset to create a sports-related concussion-specific diagnostic and prognostic machine learning model. This model will attempt to process both functional and structural MRI data and predict the extent of brain damage caused by repeated sport concussions.

Conflict of Interest. The authors have no competing interests to disclose.

Funding. This research was supported by the following funding: National Institute of Health (NIH) Small Business Innovation Research (SBIR) R44NS092209 in partnership with NeuraSignal Inc.; the UCLA Steve Tisch BrainSPORT Program; UCLA Easton Clinic for Brain Health; UCLA Brain Injury Research Center; The Harry O. Parker Neuroscience Research Fund; and Stanley and Patti Silver.

Chapter 4: Outcome Measures and Moderate-to-Severe Traumatic Brain Injury

4.1 Abstract

Introduction. Globally, traumatic brain injuries (TBI) impact millions of individuals every year, with a 2021 study reporting over 20 million new injury occurrences with about 56% being characterized as moderate-to-severe TBI (msTBI) cases. The Glasgow Outcome Scale–Extended (GOSE) scoring system scales from 1 to 8 points, where a score of 1 indicates death as an outcome, 2 indicates a vegetative state, and 3-8 indicates some form of wakefulness and responsiveness from these patients. Given the prominence of moderate-to-severe TBI, we have devised a study which incorporates GOSE scoring 6-months post-injury to measure patient outcome rates and link them to potential neural consequences using magnetic resonance imaging (MRI). We aim to answer the following research question; is it possible to correlate acute multimodal neuroimaging data to 6-month patient outcome?

Methods. Data from 91 patients diagnosed with moderate-to-severe TBI (female n=18; average age ~= 37.74) were collected at UCLA Health's Brain Injury Research Center (BIRC). The Glasgow Coma Scale (GCS) was used to diagnose TBI severity, while the GOSE was used to determine outcome severity 6-months after injury. The GOSE scores were used to create two outcome groups. The modalities include: T1-weighted magnetization prepared rapid gradient echo (T1-MPRAGE), T2-weighted fluid-attenuated inversion recovery (FLAIR) turbo inversion recovery (TIR), susceptibility weighted imaging (SWI), and apparent diffusion coefficient (ADC). FMRIB Software Library (FSL)'s Permutation Analysis of Linear Models (PALM) was used to correlate the multimodal MRI data to the outcome groups. The analyses were done at the whole-brain level, with a high T1-MPRAGE signal indicating vast volumetric changes and the

combined modality analysis indicating a variety of structural changes concatenated across all four modalities.

Results. The GOSE scores were used to create two patient groups; good outcome (GOSE >= 5; n = 52) and bad outcome (GOSE < 5; n = 39). FSL-PALM's NPC test revealed significant neural differences among the bad outcome group compared to the good outcome group in the T1-MPRAGE modality individually and the combined modality analysis ($p<0.05$). In the T1-MPRAGE analysis, the largest cluster size was 533,859 mm^3 with the center being the medial thalamus (0.0mm×-24.0mm×16.00mm). In the combined modality analysis, the largest cluster size was 70,639 mm^3 with the center being the internal capsule (20.0mm×-9.0mm×32.0mm). At the whole-brain level, strong volumetric differences are seen between the two groups, particularly in the frontal lobe and in deeper regions such as the medial thalamus and internal capsule.

Conclusion. The neural consequences include hyperintensities revealed by the T1-MPRAGE modality, which were prominent for the bad outcome group compared to the good outcome group. These results highlight the ability to measure neural impact severity using structural MRI alone for patients who exhibit a good outcome compared to a bad outcome 6-months post-injury.

4.2 Introduction

Globally, traumatic brain injuries (TBI) impact millions of individuals every year, with a 2021 study reporting over 20 million new injury occurrences with about 56% being characterized as moderate-to-severe TBI (msTBI) cases (Yan et al., 2025). Additionally, within the general population, traffic accidents and falls are some of the leading causes of TBI (Rahim et al., 2022). To determine the severity of a TBI, the Glasgow Coma Scale (GCS) is the current standard tool administered with a score between 1 to 8 indicating a severe injury, 9 to 12 indicating a moderate injury, and 13 to 15 indicating a mild injury (Kowalski et al., 2021; Jain et al., 2025). On the other hand, the Glasgow Outcome Scale–Extended (GOSE) is used to measure the outcome of the injury, especially for moderate-to-severe TBI patients who experience disorders of consciousness (DOC; Wilson et al., 2021). The GOSE scoring system scales from 1 to 8 points, where a score of 1 indicates death as an outcome, 2 indicates a vegetative state, and 3-8 indicates some form of wakefulness and responsiveness from patients (Ranson et al., 2019). GOSE includes the Disability Rating Scale (DRS) which assesses the level of handicap and disability (Neese et al., 2000). Research has found that within one-year post-TBI, the mortality rate was roughly 30% for severe cases, while in moderate cases the rate fell to approximately 13%. Of those deaths, about 70% of patients died within 2-weeks (McCrea et al., 2021). Most studies that focus on this topic utilize a single neuroimaging modality; however, each modality available offers different information about the neural state of the brain (Hao et al., 2013). Prior research has found that the multimodal neuroimaging approach has the power to increase diagnostic accuracy (Zhang et al., 2025).

Given the prominence of moderate-to-severe TBI, we have devised a study which incorporates GOSE scoring 6-months post-injury to measure patient outcome rates and link them to potential

neural consequences using magnetic resonance imaging (MRI). We aim to answer the following research question; is it possible to correlate acute multimodal neuroimaging data to 6-month patient outcome?

4.3 Methods

Participants. UCLA Health's Brain Injury Research Center (BIRC) provided data from 113 patients from the general population, 18 of which were excluded for missing at least one MRI modality. Out of the remaining 95 patients, 4 were missing the follow-up GOSE score, leaving us with a final sample size of 91 patients, refer to Figure 4.1. Of the 91 subjects, 18 were female and 67 were male with the average age being about 37.74, with ages ranging from 16 to 84. Data collection was done at the University of California, Los Angeles (UCLA) Brain Injury Research Center (BIRC).

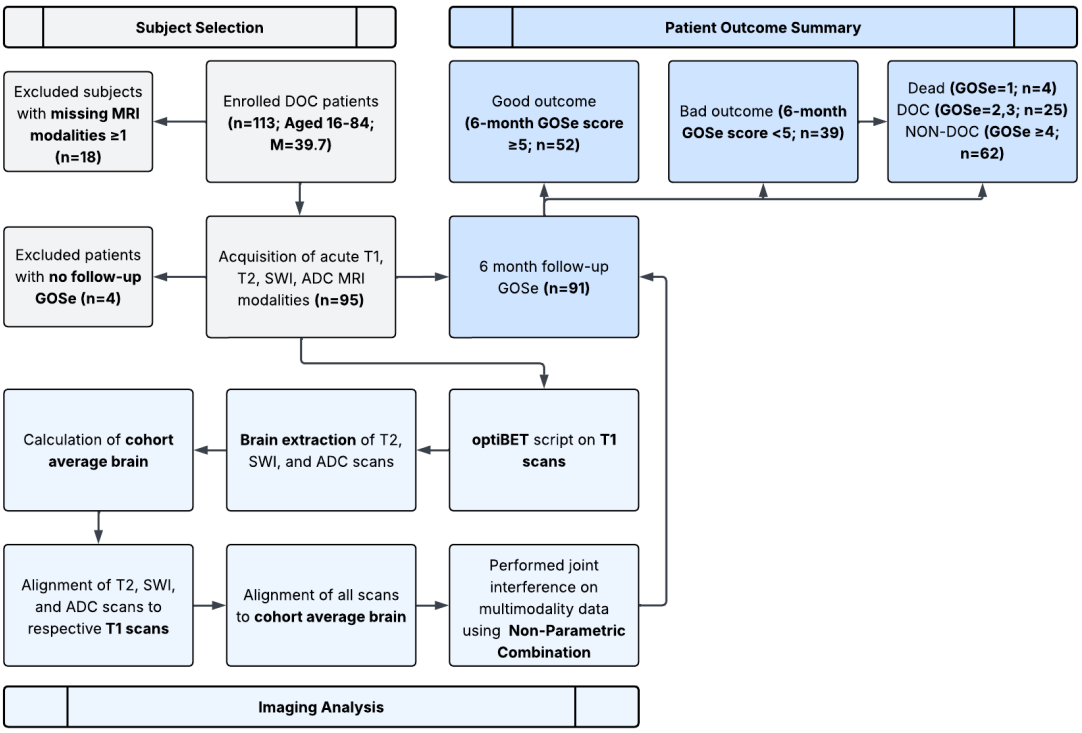


Figure 4.1. Data exclusion and data analysis structure

Outcome Data. Three outcome measures were derived out of the 6-month follow-up Glasgow Outcome Scale-Extended (GOSE) scores (binary; Figure 4.2). The binary measure includes whether the patient had a good outcome (GOSE >= 5; n = 52) or bad outcome (GOSE < 5; n = 39).

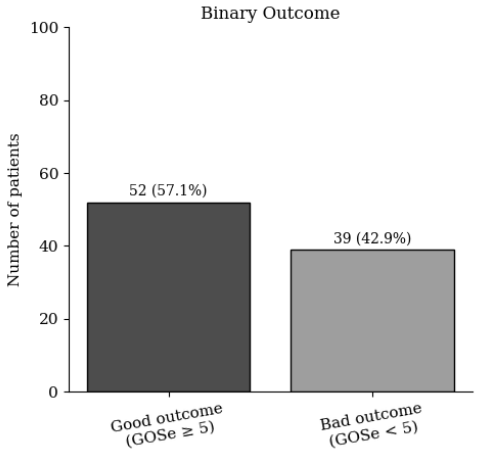


Figure 4.2. Sample size representation for binary analysis

Imaging Data. All subjects had MRI scans across four modalities: T1-weighted magnetization prepared rapid gradient echo (T1-MPRAGE), T2-weighted fluid-attenuated inversion recovery (FLAIR) turbo inversion recovery (TIR), susceptibility weighted imaging (SWI), and apparent diffusion coefficient (ADC) mean. The images were obtained using a 3T Philips scanner. The T1-MPRAGE sequence was acquired with a repetition time (TR) of 13.07 ms and echo time (TE) of 3.07 ms. The FLAIR sequence was acquired with a TR of 12,000 ms, TE of 139.4 ms, and inversion time (TI) of 2,709.3 ms. The SWI sequence was acquired with a TR of 37.1 ms and TE of 23.16 ms. Lastly, the diffusion-weighted imaging (DWI) sequence, from which ADC maps were derived, was acquired with a TR of 8,000 ms and TE of 59.0 ms.

Imaging Processing. Firstly, FMRIB Software Library (FSL)'s function, *optiBET* was used to perform brain extraction. Then, the cohort average brain was created and the FLAIR, SWI, and ADC modalities were aligned with the corresponding T1-MPRAGE scans then to the newly

created cohort average brain, which is then transferred into MNI space. The images were then merged using FSL's *fslmerge* function to create single 4-dimensional space images per modality.

Imaging Data Analysis. FSL's Permutation Analysis of Linear Models (PALM), a Non-Parametric Combination (NPC; (Winkler et al., 2014; Winkler et al., 2016)) test was used for performing three separate joint inference analyses regressing the four multimodal images on the binary "good vs. bad" outcome (henceforth, binary outcome analysis). The NPC test is a voxel-wise approach that is distribution free, allowing the cohesive use of multiple modalities in a single analysis. NPC works by first running partial analyses using permutations for each modality alone which created *u*-values for per voxel, like a *p*-value. Notably, each permutation is synchronized across every modality. Lastly, each modality's *u*-values are combined by each voxel, creating a single joint cross-modality test. In this paper, we refer to the cross-modality test as combined modalities or all modalities.

In each analysis, age, sex, time since injury, and MRI scanner, were also included as covariates. Analyses were conducted with a classical multivariate approach, using the tail approximation acceleration method, and results were corrected for multiple comparisons using threshold free cluster enhancement (TFCE; Smith & Nichols, 2009) and Family-Wise Error (FWE) cluster correction with 500 permutations and two-tailed test were used. A two-tailed test is recommended for NPC analyses. To interpret the output, the signal level (high or low) for each modality was defined by the voxel value's t-statistic. The t-statistic voxel value is positively correlated with the Contrast of Parameter Estimates (COPE; Lindquist et al., 2012).

Data visualization was created using MRI Conversion, Viewing, and Analysis Graphics Library (MRIcroGL Rorden, 2025). MRIcroGL was also used to identify the largest cluster's brain region identification for each analysis with the following parameters: neighbors with 6 faces

(default), threshold intensity of log(p10) 1.30 ($p<0.05$), bimodal, and minimum cluster size of 0 mm^3 (cluster size is due to the TFCE correction already applied). Finally, the European Brain Research Infrastructure's (EBRAINS) Software Interfaces for Interacting with Brain Atlases' (Siibra Explorer) Multilevel Human Atlas with the MNI 152 ICBM 2009c Nonlinear Asymmetric template was used to identify the main networks running through the brain region with the largest significant cluster of voxels (Amunts et al., 2020).

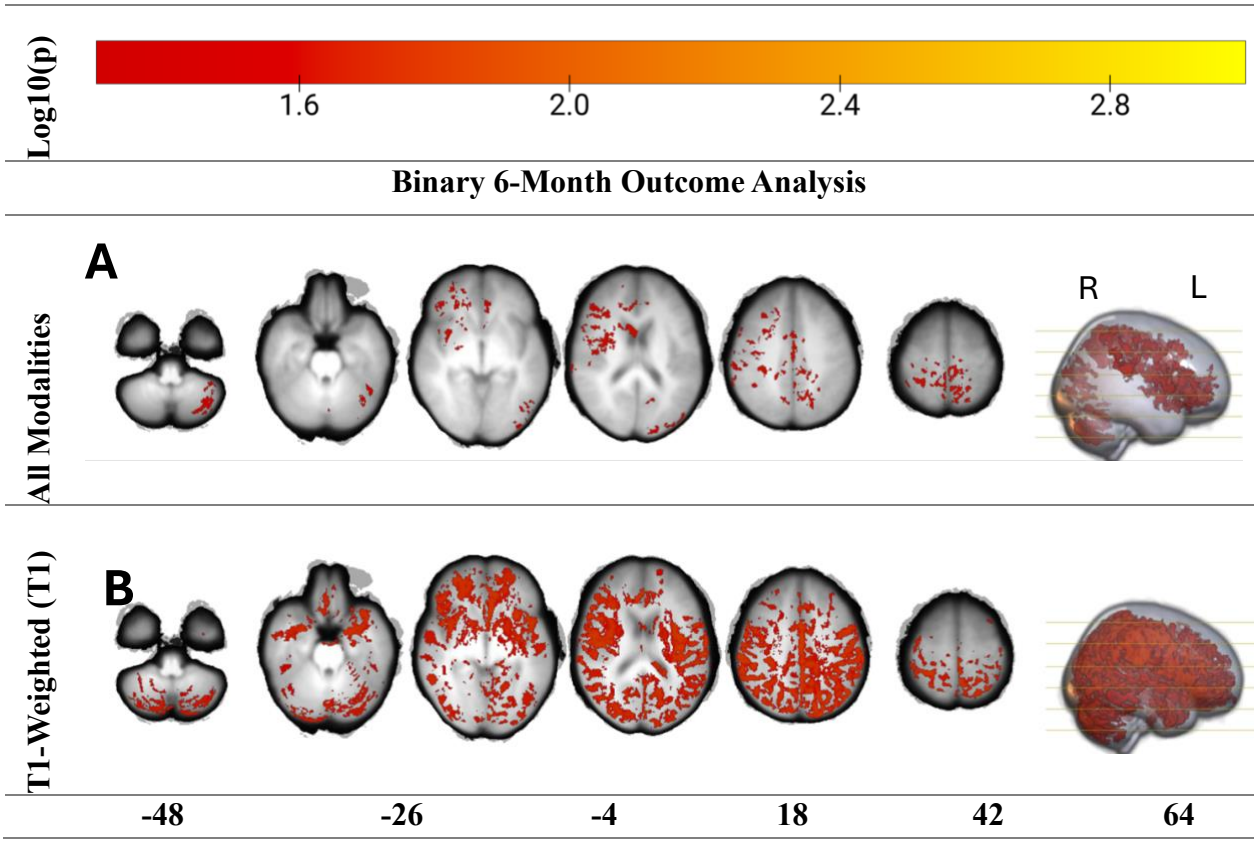
4.4 Results

Summary. The 6-month post-injury outcome results present a significant structural difference in the binary analysis (good outcome vs. bad outcome) across all modalities combined (Figure **4.3**A), but the results placed an emphasis particularly in the T1-MPRAGE modality (Figure **4.3**B). The remaining modalities (SWI, FLAIR, and ADC) individually did not show a statistically significant effect.

All Modalities. The multimodal non-parametric combination (NPC) analysis revealed significant structural neural differences across all four modalities between patients who experienced a good outcome compared to the patients who experienced a bad outcome after a msTBI (Figure **4.3**A).

T1-MPRAGE. The multimodal non-parametric combination (NPC) analysis revealed significant structural neural differences in the T1-MPRAGE modality between patients who experienced a good outcome compared to the patients who experienced a bad outcome after a msTBI (Figure **4.3**B). The remaining three modalities did not present significant differences across groups individually.

Figure 4.3. Permutation analysis of linear models (PALM) results



Note. Non-parametric combination (NPC) was paired with permutation analysis of linear models (PALM) to investigate the neural differences between patients' outcome 6-months post-injury of moderate-to-severe traumatic brain injury (msTBI). The underlying image is the cohort average brain in standard MNI space. The overlaying voxels in red and yellow represent regions which are statistically significantly different between the corresponding groups ($p<=0.05$). The color bar shows the gradient of the voxels in log10(p-value). (A) Binary analysis results combined across all modalities (B) Binary analysis results in the T1-MPRAGE modality only.

Region Identification. The cluster peak of the largest cluster for each modality's results is used to find the network/tract associated with the region with the strongest effect using the parcellation of functional modes. In the combined modality result, the largest cluster size being 70,639 mm^3 with the center being at 20.0mm×-9.0mm×32.0mm. This region includes mostly the internal capsule. In the T1-MPRAGE modality only, the largest cluster size is 533,859 mm^3 with the center being 0.0mm×-24.0mm×16.00mm. This center is located at the medial thalamus.

4.5 Discussion

This paper assesses the neural differences between patients who exhibit a good outcome compared to those who exhibit a bad outcome 6-months after a moderate-to-severe TBI occurs. Multiple structural MRI modalities were utilized to incorporate the diverse neural consequences after msTBI including T1-MPRAGE for volumetric impacts, SWI for possible microbleeds, FLAIR for white matter changes, and ADC for fluid diffusion. FSL-PALM's NPC tests revealed vast whole-brain level differences in the T1-MPRAGE modality analysis and the combined modality test, while the remaining modalities were not statistically different across the two groups. These results highlight the notable volumetric differences among patients with bad outcomes 6-months after the injury takes place, compared to those who have good outcomes. Moreover, this work allows for a quantitative measure of neural damage severity which seemingly determines whether a patient will recover and if the recovery is high enough to produce a good outcome score. These results also allow us to find the brain regions which are correlated to worse quality of life outcomes and disability levels, such as the internal capsule which is responsible for voluntary movement and the medial thalamus which is responsible for cognitive functions such as executive control (Emos et al., 2023; Mitchell & Chakraborty, 2013).

Our results are supported by prior work which also found substantial neural differences between severe TBI patients who presented good outcome 6-months post-injury (GOSE ≥ 5) and those who had a poor outcome (GOSE ≤ 4). This was most affected by the amplification of fractional amplitude of low-frequency fluctuation (fALFF) and decrease of functional connectivity (FC; Li et al., 2023). Additional work also found evidence of diffuse axonal injury (DAI) and different lesion volumes between patients with good outcome (GOSE = 6–8) versus those with poor

outcome (GOSE = 1–5) using FLAIR signals, while SWI signals revealed those with poor outcomes had increased volume of hemorrhaging particularly in the deeper regions (Yuan et al., 2015). While our results did not have any differences among the FLAIR and SWI modality, the T1-MPRAGE modality and combined modality tests revealed higher signals in the deeper regions as well, such as the medial thalamus, in the bad outcome group as well. In moderate-to-severe TBI patients (6-months post-injury GOSE = 1-4), those with DAI also had higher neuron-specific enolase (NSE) to GCS score ratio (NGR) compared to those without DAI, these individuals also had the higher probability of having poor outcomes later in their recovery (Chen et al., 2022). These neural consequences have been associated with cortical thinning and brain atrophy in both gray and white matter, especially in the frontal areas, as seen in the T1-MPRAGE results of Chapter 4 (Irimia et al., 2017). Similarly, outcome levels were also negatively correlated with lesion and hemorrhage volume size, impacting attention and memory processes in the long term (Martin et al., 2017). Studies looking at 5-years post-injury found that patients with an unfavorable outcome (GOSE 3-5) also had lasting neural damage with a decline in whole brain white matter volume and deep grey nuclear regions (Simeone et al., 2022; Galanaud et al., 2012). This directly supports our whole brain level analysis impacts of major white matter tracts and highlights the deeper regions impacts in terms of volumetric damage, but notes this damage remains prominent years post-injury.

This further supports the vast neural dissimilarities found between patients diagnosed with a moderate-to-severe TBI but experience worse outcomes 6-months post-injury. This work may allow us to predict whether a patient will recover well or worsen over time, leading to death or prolonged vegetative state, by analyzing deeper brain region's atrophy using structural MRI.

Limitations. Our sample size was rather small, especially in representing the female population. Whether the cause of death within the 6-months was caused by injury severity or withdrawal of life-sustaining treatment was not considered for the bad outcome group patients.

Future Direction. We plan to incorporate this same data set to create a machine learning (ML) model which uses the multimodal structural imaging data as input to predict patient outcome severity (good outcome vs bad outcome) 6-months post-injury.

Funding. This work was funded in part by NIH NIBIB (R21EB034428; MMM, JC), DOD CDMRP (HT9425-24-1-1081; MMM), UCLA Brain Injury Research Center. Sonya Ashikyan was funded through the University of California's (UC) Eugene Cota-Robles Award.

Chapter 5: Diagnostic and Prognostic Machine Learning Tool

5.1 Abstract

Introduction. Globally, traumatic brain injuries (TBI) are so prominent that they account for one of the most neuro-disabilities with about 85% of all TBIs being characterized as mild. The current standard protocol at the emergency room for mTBIs includes triage, then a cranial computed tomography (CT) scan, lastly a physician reassessment. In this protocol, no medication or treatment is prescribed, and no follow-up is scheduled with the patient. This model aims to increase diagnostic confidence and offers individualized patient care, since all brains are structurally different, and therefore all injuries naturally influence patient's neural and neuropsychological states differently.

Methods. The mild TBI groups were created using three self-report questionnaires: Center for Epidemiologic Studies-Depression Scale (CES-D), Posttraumatic Stress Disorder Checklist Civilian Version - Appendix for Acute Stress Disorder (PTSD-ASD), and Connor-Davidson Resilience Scale (CDRISC). The questionnaire's progression was five different timepoints: less than 24-hours post-injury (baseline) to 6-months post-injury (n=90; female n=31; average age = 29.7; age range 18-49). The stress group had clinically high levels of depression and PTSD-ASD with below healthy average resilient scores, while the resilient group had above healthy average resiliency scores. The imaging data (n=67) includes Fluid-Attenuated Inversion Recovery (FLAIR), Susceptibility-weighted imaging (SWI), T2-weighted multi-echo (T2w ME), and T1-weighted (T1w). Six total models were created with each one predicting the patient's group: stress group or resilient group. The input of each model included one or both neuroimaging modalities and the scores of each of the three questionnaires scores at baseline only.

Results. The logistic regression (LR) model (Model 1) with baseline behavioral input was the most accurate one with the mean AUROC of 0.906 (SD=0.078, Mean AUPRC = 0.860, SD = 0.117; "excellent"). The LR classification model (Model 2) uses the regions of interest (ROI) on the baseline images as input, which had a relatively low accuracy level with a mean AUROC of 0.565 (SD=0.124, Mean AUPRC = 0.549, SD = 0.123; "fail"). Model 3a implements voxel-based whole-brain level imaging using Principal Component Analysis (PCA) method, the accuracy increased to a mean AUROC of 0.613 (SD=0.179, Mean AUPRC = 0.548, SD = 0.139; "poor"). The deep learning (DL) three-dimensional convolutional neural network (3D-CNN) model (Model 3b) was paired with the pre-computed MedSAM2 foundation model embeddings. This led to yet another increase in model accuracy with a mean AUROC of 0.810 (SD=0.196, Mean AUPRC = 0.788, SD = 0.199; "good"). The DL 3D-CNN model (Model 4) uses the baseline images as the predictor variable had a mean AUROC of 0.539 (SD=0.164, Mean AUPRC = 0.484, SD = 0.095; "fail"). Lastly, Model 5, which was Model 3b with the use of MedSAM2 with the additional input data of baseline questionnaire scores had an increased accuracy of mean AUROC of 0.828 (SD=0.126, Mean AUPRC = 0.801, SD = 0.136, "good").

Discussion. Model 3b (MedSAM2) is both the most accurate imaging-only model and the first machine learning (ML) model to successfully predict neuropsychological group using multimodal imaging data alone. Model 5 is the most accurate imaging-incorporated model; however, this is not surprising given the remaining circulatory problem within the neuropsychological input component. Notably, the neuropsychological input data increases the model accuracy but not substantially, indicating that neuropsychological input makes the model more precise but is not necessarily required for the creation of a successful model. Therefore, this

allows clinicians the ability to more accurately treat patients by scheduling appropriate follow-ups and offering referrals to mental health resources, such as therapy.

5.2 Introduction

Globally, traumatic brain injuries (TBI) are so prominent that they account for one of the most neuro-disabilities with about 85% of all TBIs being characterized as mild (mTBI; Visser et al., 2022). Mild cases are defined as a disruption of brain function which typically results in loss of consciousness for less than 30 minutes, loss of memory, and other difficulties such as attention deficits (Sussman et al., 2018). The current standard protocol at the emergency room for mTBIs includes triage, then a cranial computed tomography (CT) scan, lastly a physician reassessment (Michelson et al., 2018; Figure **5.1**). In this protocol, no medication or treatment is prescribed, and no follow-up is scheduled with the patient. This standard treatment route also led for most mTBI neuroimaging research to focus on the effects of CT scans (Molaei-Langroudi et al., 2019). The CT scan is the method of choice due to its low cost and quick results; however, CT scans have low resolution, leading to some injuries to go undetected that a magnetic resonance imaging (MRI) scan could detect (Kim et al., 2013). This issue leads patients with brain injuries, such as microbleeds and diffuse axonal injury to go untreated (Dabas et al., 2024). Recent research has begun to investigate the role that artificial intelligence (AI) can play in combating this issue (Montalt-Tordera et al., 2021).

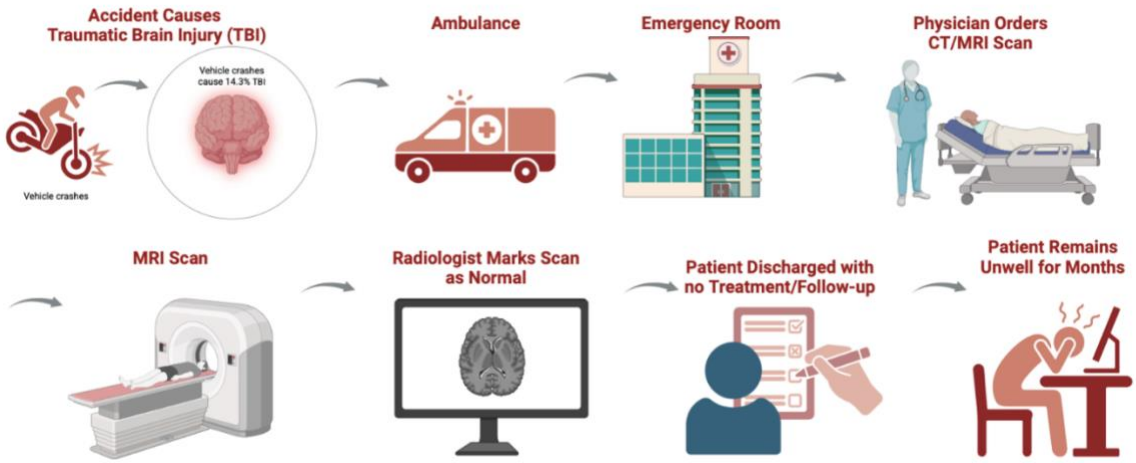


Figure 5.1. Standard Emergency Protocol in the United States for traumatic brain injuries

We suggest leveraging the power of detail sensitivity that the MRI can provide, since mild cases often have subtle lesions. Additionally, we also suggest utilizing machine learning's (ML) convolutional neural network (CNN) techniques paired with transfer learning through Meta's Medical Segment Anything Model 2 (MedSAM2) to create and test an automated diagnostic and prognostic tool by integrating both multimodal neuroimaging data and neuropsychological data (Ma et al., 2024). The data from mild TBI patients across multiple timepoints will be used as the training data for this model. This model aims to increase diagnostic confidence and offers individualized patient care, since all brains are structurally and functionally different, and therefore all injuries naturally influence patient's neural and cognitive states differently. Hence, we must also treat patients in such a personalized manner.

5.3 Methods

Participants. All data points were acquired from the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system from an existing data set (Robertson et al., 2017). For our analyses, only the individuals from the case group were considered (n=90). Each TBI was characterized as mild by scoring between 13-15 on the GCS administered by a clinician, had lost

consciousness for less than 30 minutes, experienced less than 24-hours of post-traumatic amnesia. All mTBI subjects had normal computed tomography (CT) scans, meaning no complicated mTBI subjects were included. Subjects did not have prior neurological and/or psychological conditions including a prior TBI. From this sample, 59 were male and 31 were female with the average age between both groups being 29.70 years old with the age range being 18-49. This sample size was used for behavioral clustering analysis; however, 23 subjects were excluded due to missing imaging data. Therefore, a sample size of 67 was used for the entirety of this study.

Cognitive Data. Three questionnaires were considered: Center for Epidemiologic Studies-Depression Scale (CES-D), Posttraumatic Stress Disorder Checklist Civilian Version - Appendix for Acute Stress Disorder (PTSD-ASD), and Connor-Davidson Resilience Scale (CDRISC; Connor & Davidson, 2003; Weathers et al., 2013; Radloff, 1977). Each questionnaire was readministered at five different time points: less than 24-hours post-injury (baseline), 1-week post-injury, 1-month post-injury, 3-months post-injury, and 6-months post-injury (Figure **5.1**). The total score of each neuropsychological questionnaire's were used in Functional Data Analysis (FDA) with Clustering using Matrix Laboratory (MATLAB) across all five timepoints. We utilized two timepoints for this study; less than 24-hours post-injury (baseline) and 3-months post-injury.

Imaging Data. Five MRI modalities were collected: Fluid-Attenuated Inversion Recovery (FLAIR), Susceptibility-weighted imaging (SWI), T2-weighted echo 1 (T2w), and T2-weighted echo 2, and T1-weighted (T1w). For the T2w scans, the first echo time was 16 milliseconds (ms), and the second echo time was 32ms. Using both provided echo times, a new combined T2w modality was created called T2-weighted multi-echo (T2w ME). Moreover, the analysis was

done in four modalities T1, T2w ME, SWI, and FLAIR. All images were obtained using a 3T Philips scanner using the following parameters: TR=16ms, TE=32ms. All MRI modalities were collected at two timepoints; baseline and 3-months post-injury. Ultimately, the imaging data included 67 subjects across five modalities in two timepoints, totaling 670 scans being processed for the final analysis.

Model 1 (Behavioral - LR): The binary logistic regression classification model uses the three cognitive measures (CESD, PTSD-ASD, and CDRISC) at the baseline timepoint as the predictor variable (X) and the cluster group (stress group or resilient group) as the response variable (y). The maximum iterations were set to 100 with no dimensionality reduction and stratified 5-fold cross-validation. In this method, the model predicts whether patient is in the stress group or resilient group based on their three cognitive scores.

Model 2 (Imaging - ROI): The binary logistic regression classification model uses the regions of interest (ROI) on the baseline timepoint multimodal images as the predictor variable (X) and the cluster group (stress group or resilient group) as the response variable (y). Each imaging modality was parcellated into 400 total ROIs using the Schaefer 2018 atlas, which then calculated the mean signal of each ROI concatenated across the four modalities. Then, the z-scores were normalized and stratified 5-fold cross-validation was used. The output also includes images of the group mean ROI differences through Nilearn's glass brain plotting method. In this method, the model predicts whether patient is in the stress group or resilient group based on the ROIs inputted.

Model 3a (Imaging - PCA): This model implements voxel-based whole-brain level baseline multimodal MRI feature extraction by flattening and concatenating images per subject into a single high dimensional vector. Two hidden-layer Multilayer Perceptron (MLPs) were

implemented, then variance scaling and principal component analysis (PCA) remained up to 20 components. Lastly, stratified 5-fold cross-validation was used and the cluster group was outputted as the response variable.

Model 3b (Imaging – MedSAM2): The deep learning (DL) three-dimensional convolutional neural network (3D-CNN) model uses the baseline timepoint multimodal images as the predictor variable (X) and the cluster group (stress group or resilient group) as the response variable (y). The pre-computed MedSAM2 foundation model embeddings was used for the input imaging data, which calculated the global mean for all dimensions (modalities × slices × channels; Zhong et al., 2025). The final global mean gave each subject a single scalar feature. The random forest method of 50 trees was used then the z-score was normalized. Then, the stratified 5-fold cross-validation method was implemented.

Model 4 (Imaging - CNN): The deep learning (DL) three-dimensional convolutional neural network (3D-CNN) model uses the baseline timepoint multimodal images as the predictor variable (X) and the cluster group (stress group or resilient group) as the response variable (y). 70% of the data was used for training, 10% was used for validation and 20% was used for testing. This model was created from scratch, and imaging data was classified using whole brain level data rather than focusing on specific regions of interest. To prevent overfitting and increase generalizability, data augmentation was done at random by flipping spatial axes and utilizing affine transformations. In this method, the model predicts whether patient is in the stress group or resilient group based on actual imaging data across all four modalities (Figure 5.2).

Model 5 (Imaging & Behavioral – MedSAM2): The deep learning neural network model uses the baseline timepoint multimodal images and the three cognitive variables as the predictor variables (X) and the cluster group (stress group or resilient group) as the response variable (y).

MedSAM2 embedding was used for the imaging data, which was then paired with the behavioral data as matrices where 5-fold cross-validation was done. The classification portion was processed using PyTorch's late-fusion Multilayer Perceptron (MLP). In this method, the model predicts whether patient is in the stress group or resilient group based on actual imaging data across all four modalities paired with the corresponding cognitive measures. The train test split method was also used. This test is used to understand which predictor variable is more necessary to receiving accurate results, the multimodal imaging data alone, the cognitive data alone, or the pairing of both cognitive and imaging data.

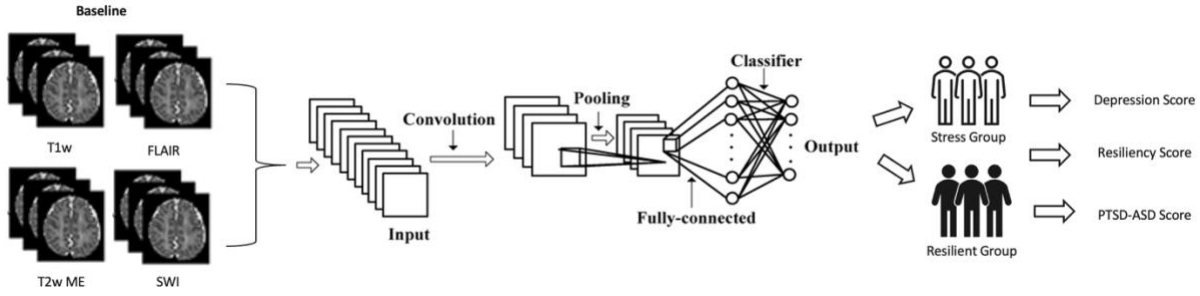


Figure 5.2. Convolutional neural network (CNN) model (Liu et al., 2018)

5.4 Results

Model 1 (Behavioral - LR): Out of the 6 models presented, the behavioral input logistic regression model (Model 1) was the most accurate one with the mean AUROC of 0.906 and a standard deviation of 0.078 (Mean AUPRC = 0.860, SD = 0.117). The accuracy level is categorized as "excellent" (Nahm, 2022). However, this is not necessarily surprising given the baseline behavioral data of the three neuropsychological measures (depression, PTSD-ASD, and resilience) were the exact same measures used to create the two cluster groups (stress and resilient) with four additional timepoints (1-week, 1-month, three-months, and 6-months). Moreover, although accurate, a clear circulatory problem exists within model 1, that does not exist within the imaging-only input models such as Model 2, 3a, and 4 (Table **5.1** A).

Model 2 (Imaging - ROI): The region of interest model had a relatively low accuracy level with a mean AUROC of 0.565 and a standard deviation of 0.124 (Mean AUPRC = 0.549, SD = 0.123; Table **5.1** B), categorized as a "failure". Notably, this model was the only one which created clear images of the brain, giving insight on which region of the 400 parcellations, were most telling of which group the patient is predicted to be from (Figure **5.3**; Figure 5.4). Although this is a major strength of the model, it also came with the price, as the generation of the images significantly slowed down the model's analysis time.

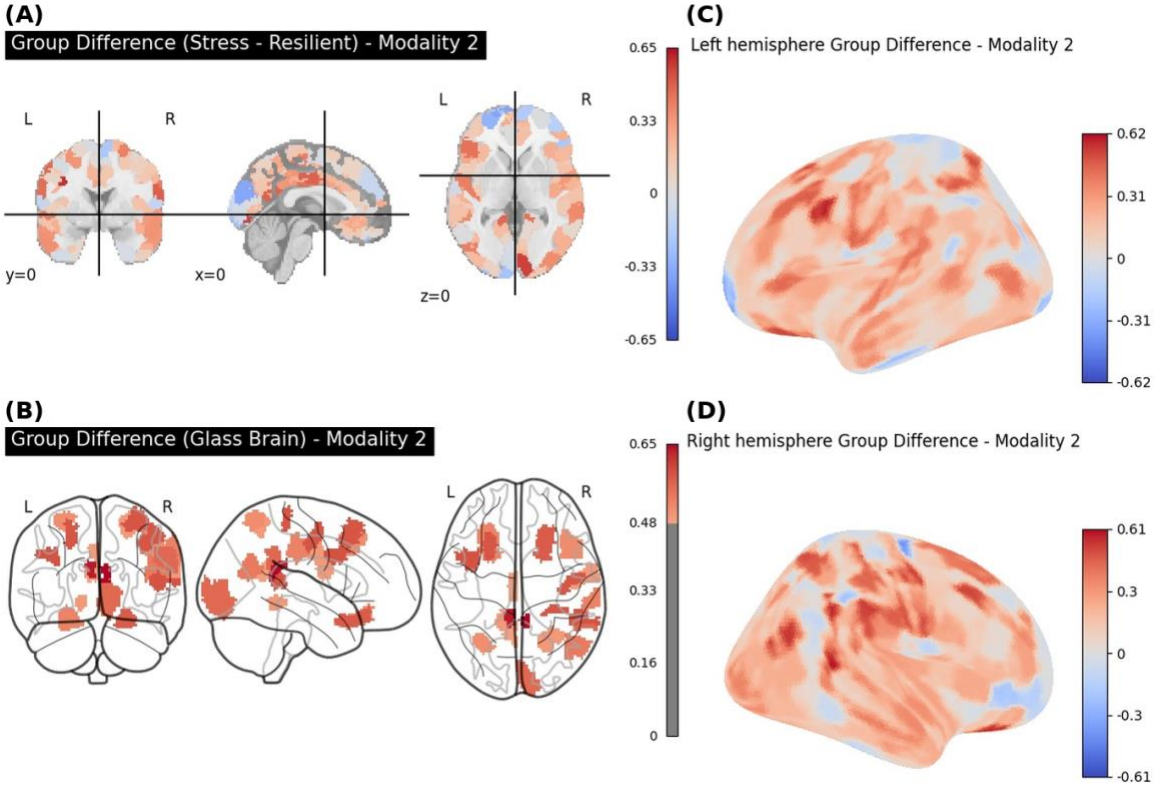


Figure 5.3. Group differences in brain activity between Stress and Resilient groups (Modality 2)

Note. **(A)** Whole-brain group difference map (Stress − Resilient) displayed in coronal, sagittal, and axial views (y=0, x=0, z=0), with warm colors (red) indicating greater activation in the Stress group and cool colors (blue) indicating greater activation in the Resilient group (color scale: −0.65 to 0.65). **(B)** Glass brain projection of the group difference map highlighting significant clusters of differential activation across frontal, parietal, and subcortical regions (color scale: 0 to 0.65). **(C)** Cortical surface rendering of group differences projected onto the left hemisphere, showing widespread positive differences (Stress > Resilient) across lateral and medial surfaces. **(D)** Cortical surface rendering of group differences projected onto the right hemisphere, revealing a predominantly positive difference pattern with focal negative regions in anterior and temporal areas. All color scales reflect the magnitude of group differences in standardized units.

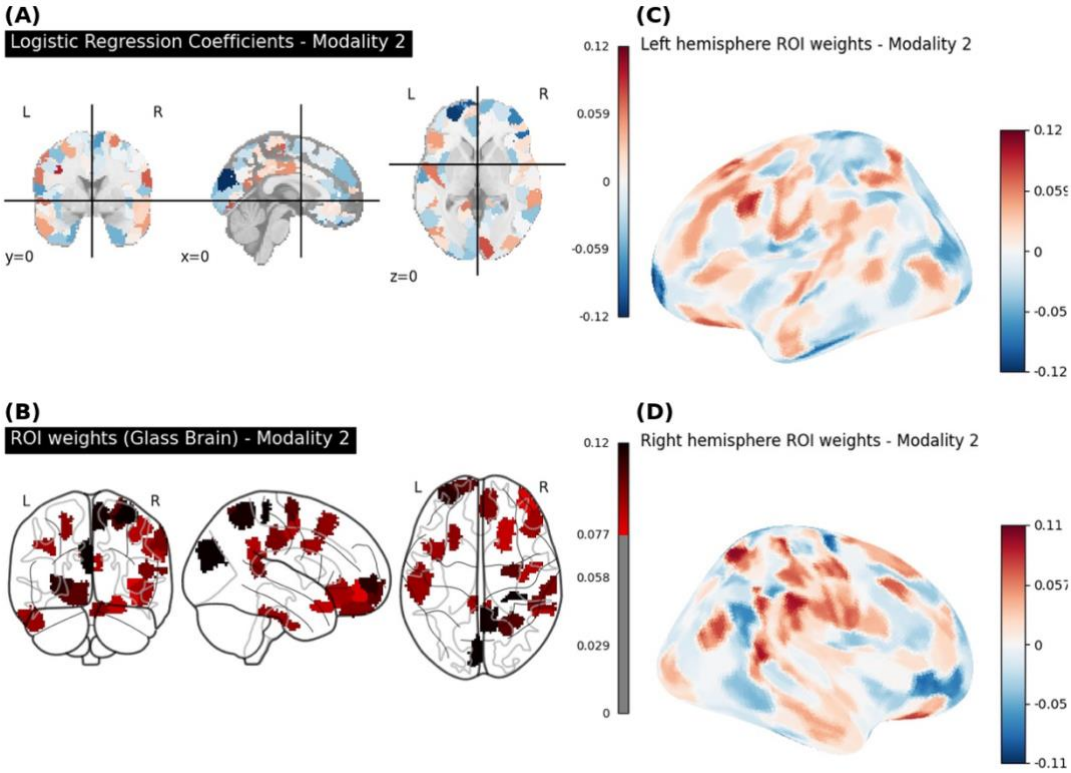


Figure 5.4. Regions of Interest (ROI) weights from logistic regression classifier distinguishing Stress and Resilient groups (Modality 2)

Note. **(A)** Whole-brain logistic regression coefficient map displayed in coronal, sagittal, and axial views (y=0, x=0, z=0), with warm colors (red) indicating positive coefficients and cool colors (blue) indicating negative coefficients (color scale: −0.12 to 0.12). **(B)** Glass brain projection of ROI weights highlighting clusters of greatest discriminative power across frontal, parietal, and subcortical regions (color scale: 0 to 0.12). **(C)** Cortical surface rendering of ROI weights projected onto the left hemisphere, showing a mixed pattern of positive and negative discriminative regions. **(D)** Cortical surface rendering of ROI weights projected onto the right hemisphere, revealing predominantly positive weights across lateral prefrontal and parietal cortices with focal negative regions. Color scales reflect the magnitude of logistic regression coefficients in standardized units.

Model 3a (Imaging - PCA): Since the ROI approach did not yield high enough accuracy and slowed the model down, the next step was the whole-brain analysis approach using a PCA. Again, with only multimodal MRI imaging (FLAIR, T1w, T2w ME, and SWI) as the input, the accuracy increased to a mean AUROC of 0.613 with a standard deviation of 0.179 (Mean AUPRC = 0.548, SD = 0.139). Although higher in accuracy, the model is still categorized as "poor" and is still slow in runtime (Table **5.1** C).

Model 3b (Imaging – MedSAM2): It is clear the whole-brain approach is better performing than the ROI-based approach for imaging-only input. The MedSAM2 embedding approach was implemented and led to yet another increase in model accuracy with a mean AUROC of 0.810 and a standard deviation of 0.196 (Mean AUPRC = 0.788, SD = 0.199). The model is now categorized as "good", meaning that the MedSAM2 embedding was established as a clear aid in increasing accuracy by serving as a strong foundation model and substantially increased the runtime by producing output within a few seconds (Table **5.1** D).

Model 4 (Imaging - CNN): To establish a model created from scratch that specializes in mild TBI neuroimaging data, the CNN model was created. The results from Model 3a and Model 3b clearly indicated that the whole-brain approach was the right path, with the same multimodal input data, the new model saw a major decrease in accuracy and increased runtime significantly. The mean AUROC became 0.539 and a standard deviation of 0.164 (Mean AUPRC = 0.484, SD = 0.095), which is categorized as a "fail". These results establish the need to utilize a strong foundation model, while maintaining the whole-brain analysis approach (Table **5.1** E).

Model 5 (Imaging & Behavioral – MedSAM2): Given the high accuracy and short runtime of Model 3b with the use of MedSAM2, the same model was created with the additional input data of baseline behavioral measures. Not surprisingly, the model accuracy increased and the speed remained roughly the same with the mean AUROC of 0.828 and a standard deviation of 0.126 (Mean AUPRC = 0.801, SD = 0.136), categorized as a "good" performance (Table **5.1** F).

Classification Performance Across Models (5-Fold Stratified Cross-Validation)					
Figure	*Model*	*Input type*	*Mean AUROC (±SD)*	*Mean AUPRC (±SD)*	*Discrimination category*[a]
(A)	**Model 1:** Logistic regression	Behavioral	0.906 (0.078)	0.860 (0.117)	Excellent
(B)	**Model 2:** Logistic regression (ROI)	Imaging	0.565 (0.124)	0.549 (0.123)	Fail
(C)	**Model 3a:** MLP (PCA + voxel)	Imaging	0.613 (0.179)	0.548 (0.139)	Poor
(D)	**Model 3b:** Random forest (MedSAM2)	Imaging	0.810 (0.196)	0.788 (0.199)	Good
(E)	**Model 4:** 3D CNN	Imaging	0.539 (0.164)	0.484 (0.095)	Fail
(F)	**Model 5:** Late-fusion MLP (MedSAM2)	Imaging + behavioral	0.828 (0.126)	0.801 (0.136)	Good

Table 5.1. Classification performance across machine learning models

Note. a Discrimination category based on Nahm (2022): 0.9 ≤AUC = Excellent; 0.8 ≤AUC < 0.9 = Good; 0.7 ≤AUC < 0.8 = Fair; 0.6 ≤AUC < 0.7 = Poor; 0.5 ≤AUC < 0.6 = Fail. Nahm F. S. (2022). Receiver operating characteristic curve: overview and practical use for clinicians. Korean Journal of Anesthesiology, 75(1), 25–36. https://doi.org/10.4097/kja.21209 (A) Behavioral-only logistic regression. (B) ROl-based multimodal logistic regression. (C) Voxel-based multimodal MLP with PCA dimensionality reduction. (D) MedSAM2 embedding-based random forest. (E) Voxel-based 3D convolutional neural network (F) Late-fusion multimodal MLP combining MedSAM2 embeddings and behavioral features. Values are mean (±SD) across 5-fold stratified cross-validation folds. AUROC = area under the receiver operating characteristic curve; AUPRC= area under the precision-recall curve; ROI = region of interest; MLP = multilayer perceptron; PCA = principal component analysis; CNN = convolutional neural network; MedSAM2 = Medical Segment Anything Model 2; SD = standard deviation.

5.5 Discussion

The growing advancement and integration of machine learning modeling in the healthcare field has opened endless opportunities (Liu et al., 2024). This paper discusses the creation of one of the first artificial intelligence (AI) models that specialize in mild TBI neuroimaging data. The key component is the connection between neural damage and neuropsychological changes, which research in moderate-to-severe TBI has shown to be important (Lutkenhoff et al., 2015).

More specifically, this model's novelty exists within its ability to take in baseline (<24 hrs post-injury) multimodal MRI data of mild TBI patients and predict neuropsychological groups (stress vs resilient) within the next six-month trajectory. Prior research has also confirmed the strength that multimodal imaging has within AI predictive models in the healthcare field by giving the model more types of brain data to leverage (Ferger et al., 2025). By predicting a neuropsychological group, the model also predicts the patient's trajectory of resilience, depression, and PTSD-ASD. Prior research has proven that assessing patient's neuropsychological profiles immediately post-injury is a poor representation of the true impacts of the TBI, as psychological damages worsen significantly one-week post-injury (Mavroudis et al., 2024). This tool would allow clinicians to predict whether a specific patient will experience such stress or will remain resilient mentally. Therefore, this allows clinicians the ability to more accurately treat patients by scheduling appropriate follow-ups and offering referrals to mental health resources, such as therapy.

To create the final model (Model 5), additional models were also created to find the most optimal path. Before incorporating the imaging data, a neuropsychological input model was created (Model 1), which offered the highest accuracy of all models, categorized as "excellent", but had an inherent circulatory problem. This is a key limitation of Model 1, as the input data is the baseline neuropsychological scores of all three behavioral measures, one of the five timepoint measures used to compute the two patient groups. Notably, this problem only exists within models 1 and 5, as they are the only ones which input the baseline behavioral data. Models 2 through 4, contain imaging data as their only input, meaning they are free of the circulatory problem. In Model 2, multimodal regions of interest (ROI) were submitted as input, creating images of brain regions by modality as output which were most representative of the group

assignment. However, the generation of the images requires a significant increase of runtime and a major reduction in accuracy (Fail). On the other hand, Models 3a (Principal Component Analysis (PCA) method) and Model 4 (Convolutional Neural Network (CNN) method) also had a similar problem of slowed runtime and low accuracy but did not output brain data visualizations (Fail/Poor).

Model 3b (MedSAM2) is the first machine learning (ML) model to successfully predict neuropsychological group using multimodal imaging data alone and is also the most accurate imaging-only model. This model's key difference lies within its integration of the novel CNN model that is specific to reading mild TBI multimodal data and the foundation model that can read any type of image from the internet. Transfer learning gives this model the power to combine the strengths of high imaging reading knowledge with mild TBI specific MRI imaging knowledge to create a single more reliable tool. Although the performance is categorized as merely "good", the model has the potential to increase in accuracy by adding more training data, since the sample size of 67 is considerably small for patient-use thus far. Model 5 uses the same transfer learning method but with the added neuropsychological input data at baseline. This creates the most accurate imaging-incorporated model; however, this is not surprising given the remaining circulatory problem within the neuropsychological input component. Notably, the neuropsychological input data increases the model accuracy but not substantially, indicating that neuropsychological input makes the model more precise but is not strictly necessary for the creation of a successful model. Nevertheless, this work highlights the future opportunities AI has in the healthcare field which better allocates resources to patients who need them most.

The tool allows clinicians to bridge the major gap between the neurological and psychological/psychiatric medical fields, offering a more holistic view of both the patients' mental and physical health by considering individual neural differences. Due to this gap in specialties, the mental health impacts of neurological diseases are often ignored, and patients go untreated and existing resources go unused, this tool offers a modern solution in which resources could be better allocated to those with predicted worse conditions (Figure 5.5).

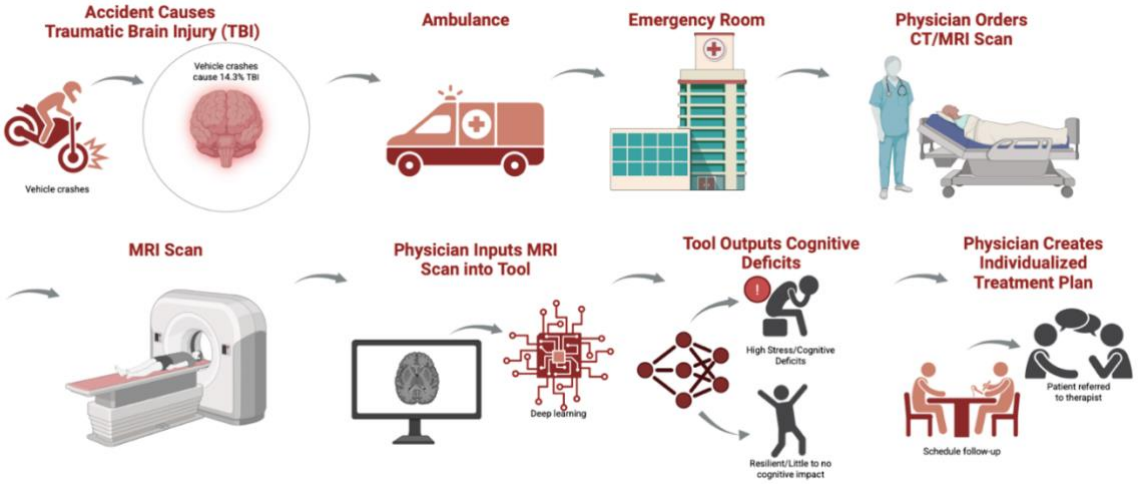


Figure 5.5. Embedding-based convolutional neural network model (Model 3b) applied in standard emergency protocol in the United States

Limitations. As mentioned before, a circularity problem exists within the models which input baseline neuropsychological data (Model 1 and Model 5), as the same datapoints were one of five timepoints used to create the clusters the models are all predicting. All models, except for the ROI-based method (Model 2), are unable to indicate which whole-brain voxels are contributing to the model's final prediction for the patient. However, it is important to note that there is currently no standardized method to do this in ML thus far. To incorporate a model which indicates the regions used, we cannot use the whole-brain analysis path, instead we used the regions of interest (ROI) option. This model was however unsuccessful, further proving the need to create a more powerful standardized region/voxel contribution model.

Future Direction. This work has proven the potential AI has within advancing the current medical field by considering individual differences among patients, interconnecting neurological and psychological/psychiatric specialists, and allocating currently existing medical resources more effectively. To further develop this tool, we plan to create a single more advanced MedSAM2 embedding-based model with increased training data. Lastly, we plan to broaden the tool's structure to work for other non-TBI conditions, such as neurodegenerative diseases which can predict years post-diagnosis rather than months post-injury.

Acknowledgements. We would like to thank the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System team from which our data was sourced.

Funding. This study was supported by the National Institute of Health (NIH) grant #1R21EB034428-01 A1 (Monti).

Chapter 6: Conclusion

Traumatic brain injuries are complex and greatly vary across patients. They range across three levels of severity (mild, moderate, and severe) and target vulnerable individuals, such as the elderly and young in the general population and span across athletes and military personnel. Large proportions of specific groups' injuries raise questions regarding possible ways to improve return-to-play protocols for athletes, discharge regulations in military personnel, and airbag/seatbelt safety in the general population. Furthermore, different levels of severity call for different approaches and concerns in patient outcomes such as chronic traumatic encephalopathy in repetitive mild TBI patients as well as neurodegeneration over one's lifetime. In moderate-to-severe cases, early posttraumatic seizures cause serious difficulties in the rehabilitation of patients and interventions must be weighed including the administration of mechanical ventilation, a medically induced comatose state, and craniectomy/craniotomy. The importance of monitoring outcome variables such as returning-to-work are used to establish which procedure is most effective for patients across all levels of severity. Neuropathology, notably blood biomarkers and genetics, are used as a window into the neurological changes caused by a traumatic brain injury. Lastly, recent research has claimed sleep to be an important factor of TBI, as a multitude of sleep disorders arise after a brain injury is incurred (ex. sleep apnea, insomnia, hypersomnia, etc.).

6.1 Research Approach

Three key main points stand as pillars for our research approach. Firstly, the scientific community has clearly established the strong and specific relationship neural structures have with cognitive processes (Menon, 2013). It has also been well-established that damage to a brain structure results in corresponding impairments to the neuropsychological processes it governs,

including in the context of traumatic brain injury (Wojtowicz et al., 2017). Thirdly, each neuroimaging modality highlights a specific aspect of the brain, with, for example, T1-weighted (T1w) data reflecting gray matter volume and Fluid Attenuated Inversion Recovery (FLAIR) data reflecting white matter integrity (Figure 6.1; Sassani et al., 2025). With these three components in mind, the scientific question of whether brain damage can be linked to corresponding neuropsychological outcomes becomes more tractable.

Magnetic Resonance Imaging (MRI) specifically has recently been used to characterize traumatic brain injury across all levels (mild to severe); however, the vast majority of this work has been unimodal (Bedggood et al., 2024). To fill the research gap, two multimodal fusion approaches, voxel-wise non-parametric combination (NPC) and 3D Convolutional Neural Networks (3D CNN) machine learning, are integrated across mild TBI (Winkler et al., 2016; Anwar et al., 2018; Dutta et al., 2020). The non-parametric approach takes unimodal data and performs fusion through the joint inference technique. The tool is powerful as it makes minimal assumptions and results in both an independent modality analysis and a joint multimodal analysis output. This approach is used in Chapter 2 to 4, where results are depicted by both individual modalities and a combined single result across all modalities together. On the other hand, the deep learning neural network learns spatial patterns by focusing on learning simple features in the early layers (voxels), then combining modalities to learn more complex features (regions/networks). The deep learning method allows for the detection of connectivity patterns

which can identify even marginal neural damage which might have otherwise been missed (Ma et al., 2024).

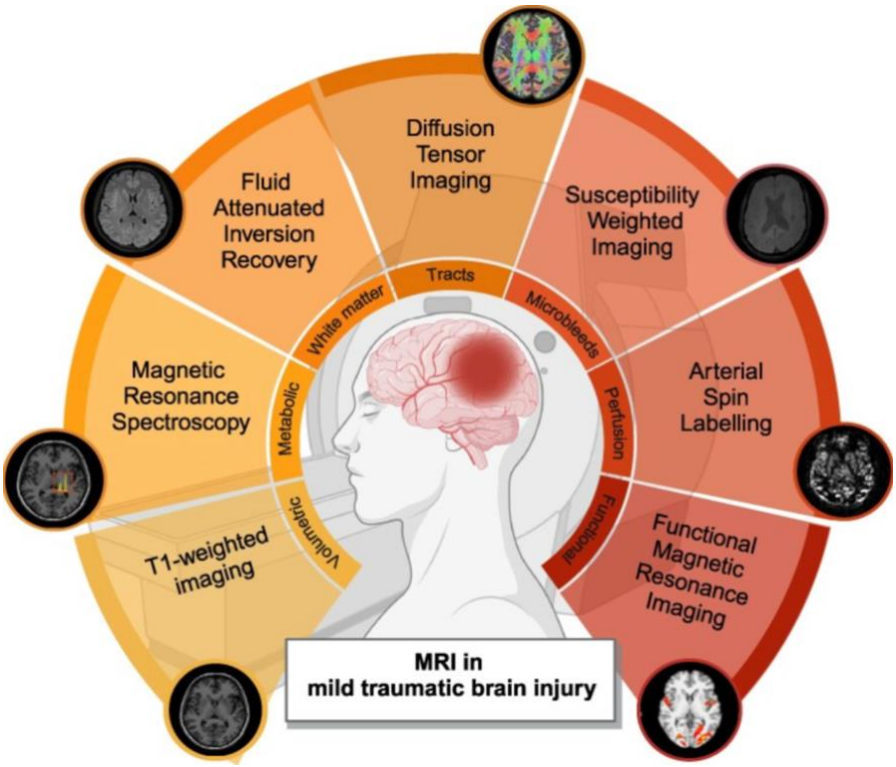


Figure 6.1. Magnetic resonance imaging (MRI) structural and functional modalities and uses (Sassani et al., 2025)

6.2 Main Findings & Scientific Contributions

The series of studies presented in this dissertation successfully linked various severities of traumatic brain injuries to corresponding neuropsychological data points through the creation of a novel scientific analysis approach (Chapters 2-4). The overarching hypothesis across all bodies of work posited that significant psychological differences present following a brain injury would be mirrored in their corresponding brain structures. Moreover, psychological changes over time would also correlate to significant changes in brain tissue. Lastly, given the complex nature of traumatic brain injuries and vast individual structural and functional neural differences, the hypothesis also predicted significant differences across imaging modalities.

In Chapter 2, the neuropsychological markers; PTSD-ASD, depression, and resilience, were significantly correlated to structural neurological changes across the whole-brain 3-months after a single concussive event (mild TBI) in the general population. Specific structural integrity differences were identified with profound impacts of white matter hyperintensities (FLAIR), volumetric changes (T1w), fluid shifts (T2w ME), and overall cross-modality effects (SWI). These differences in images between 3-months and less than 24 hours post-injury were primarily seen in emotion regulation-based regions, such as the middle and superior frontal gyri, which overlapped with the corresponding neuropsychological questionnaire findings. Finally, the neuropsychological analyses alone revealed distinct patient-experience clusters (stress cluster vs resilient cluster) and presented compelling evidence that patients diagnosed with the same neurological condition with similar medical history, experienced vastly different psychological outcomes.

In Chapter 3, the neuropsychological markers focused on sleep quality; drowsiness, fatigue, and trouble falling asleep, in both the healthy general population (out-of-sport control; OSC) and athletes who were either healthy (in-sport control; ISC) or had a concussion within one week (sports-related concussion; SRC). Due to the promising structural findings presented in Chapter 2, structural neural investigation was maintained with the addition of functional data (resting state MRI). Between cohort analyses revealed that individuals who participated in a sport had increased functional connectivity in the ventral attention network using the resting-state fMRI modality indicating strengthened involuntary attention processing. However, this development was impaired after a sport-related concussive event, leading to a loss in connectivity in the dorsal attention network which ultimately hinders voluntary attention control between athletes. Lastly, between concussed athletes and healthy individuals, concussive events occurring due to sport

participation led to whole brain level white matter hyperintensities revealed through the FLAIR modality, again in attention-based regions. Although a counterintuitive finding, overall sleep quality was successfully correlated to brain regions related to consciousness (precuneus, thalamus, etc.) through the FLAIR modality.

In Chapter 4, the neuropsychological measure was the patient 6-month post-injury binary outcome, where a good outcome includes upper good recovery and a bad outcome includes death, in moderate-to-severe traumatic brain injuries in the general population. Substantial volumetric differences were uncovered between the good outcome and bad outcome groups through the T1-MPRAGE modality and overall neural differences across the combination of all modalities (FLAIR, SWI, ADC, T1-MPRAGE). These outcome predictor markers were widespread with major impacts of the internal capsule and medial thalamus, both regions whose function is embedded in consciousness. This work confirms the notion that each condition's appropriate neuropsychological measure overlaps with corresponding functional regions and that multimodal neuroimaging data is a better representation of the neural consequences of traumatic brain injuries.

With the replicable evidence presented from Chapter 2 to 4, Chapter 5 aimed to offer a potential solution to the problem of linking neuropsychological impairments to their neural correlates. Using the dataset presented in Chapter 2, the baseline (<24 hours) multimodal neuroimaging data (T1w, T2w ME, SWI, and FLAIR) of the mild traumatic brain injury patients were used as input for the machine learning (ML) model (Model 3b). The tool specifically utilized Meta's Medical Segment Anything Model 2 (MedSAM2) embedding to transfer its abilities to read any image across the internet to our concussion-specific existing 3-dimensional convolutional neural network (3D-CNN) model. This allowed the model to predict which neuropsychological cluster

the patient was in; stress cluster or resilient cluster, which therefore also predicts the patient's 6-month post-injury mental state. By analyzing the whole-brain through the voxel-wise approach, the model resulted in a roughly 81% probability in predicting the cluster (i.e., resilient vs stress group) correctly. Lastly, the second successful model (Model 5) had both baseline multimodal neuroimaging data and baseline neuropsychological data (PTSD-ASD, depression, and resilience scores) as input and resulted in a roughly 82.8% probability in accurately predicting the patient's cluster. Model 5's main purpose was to determine whether neuropsychological data was strictly necessary for the successful performance of the predictive tool or if multimodal neuroimaging data alone provided enough information for the model to function. The findings suggest that multimodal structural neuroimaging data alone is enough to perform successfully. This work not only further confirmed the neural linkage with its neuropsychological differences between brain injured patients but also resulted in the first machine learning tool specializing in mild traumatic brain injuries.

6.3 Limitations

The most inevitable limitation in clinical research is the limited sample size. It is extremely difficult, time consuming, and costly to collect traumatic brain injury patient data, especially in the most severe cases. We worked with data collected at multiple sites, including existing datasets to hasten the process, which varied in sample size and imaging modality variety to aid in alleviating this issue (Rakocz et al., 2021). However, to increase the generalizability of our scientific findings as well as the application of our machine learning tool, a larger sample size would provide more reliable results. Therefore, we plan to replicate these results and train our model with new traumatic brain injury data sets. Additionally, there is a great level of heterogeneity in each brain injury which is more profound in severe cases due to lesions and

deformities (Van Essen et al., 2013). This makes it difficult to process imaging data by applying currently available MRI software and as a result leads to data exclusion, possibly resulting in increased exclusion of patients with more severe injuries.

References

[1] Alnawmasi, M. M., & Khuu, S. K. (2022). Deficits in multiple object-tracking and visual attention following mild traumatic brain injury. *Scientific reports*, *12*(1), 13727. https://doi.org/10.1038/s41598-022-18163-2

[2] Anwar SM, Majid M, Qayyum A, Awais M, Alnowami M, Khan MK. Medical Image Analysis using Convolutional Neural Networks: A Review. J Med Syst. 2018;42(11):226. Epub 2018/10/10. doi: 10.1007/s10916-018-1088-1. PubMed PMID: 30298337.

[3] Asken, B. M., DeKosky, S. T., Clugston, J. R., Jaffee, M. S., & Bauer, R. M. (2018). Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): a systematic critical review. *Brain imaging and behavior*, *12*(2), 585–612. https://doi.org/10.1007/s11682-017-9708-9

[4] Azouvi, P., Arnould, A., Dromer, E., & Vallat-Azouvi, C. (2017). Neuropsychology of traumatic brain injury: An expert overview. *Revue neurologique*, *173*(7-8), 461–472. https://doi.org/10.1016/j.neurol.2017.07.006

[5] Beckmann, C., Mackay, C., Filippini, N., & Smith, S. (2009). Group comparison of resting-state FMRI data using multi-subject ICA and dual regression. *NeuroImage, 47*.

[6] Bedggood, M. J., Essex, C. A., Theadom, A., Holdsworth, S. J., Faull, R. L. M., & Pedersen, M. (2024). Individual-level analysis of MRI T2 relaxometry in mild traumatic brain injury: Possible indications of brain inflammation. NeuroImage. Clinical, 43, 103647. https://doi.org/10.1016/j.nicl.2024.103647

[7] Bell A, Hewins B, Bishop C, Fortin A, Wang J, Creamer JL, Collen J, Werner JK Jr. Traumatic Brain Injury, Sleep, and Melatonin—Intrinsic Changes with Therapeutic Potential. *Clocks & Sleep*. 2023; 5(2):177-203. https://doi.org/10.3390/clockssleep5020016

[8] Bell, D. R., Guskiewicz, K. M., Clark, M. A., & Padua, D. A. (2011). Systematic review of the balance error scoring system. *Sports health*, *3*(3), 287–295. https://doi.org/10.1177/1941738111403122

[9] Biegon A. (2021). Considering Biological Sex in Traumatic Brain Injury. *Frontiers in neurology*, *12*, 576366. https://doi.org/10.3389/fneur.2021.576366

[10] Bishop, P., Rocca, D., & Henley, J. M. (2016). Ubiquitin C-terminal hydrolase L1 (UCH-L1): structure, distribution and roles in brain function and dysfunction. *The Biochemical journal*, *473*(16), 2453–2462. https://doi.org/10.1042/BCJ20160082

[11] Bohnert, S., Wirth, C., Schmitz, W., Trella, S., Monoranu, C. M., Ondruschka, B., & Bohnert, M. (2021). Myelin basic protein and neurofilament H in postmortem cerebrospinal fluid as surrogate markers of fatal traumatic brain injury. *International journal of legal medicine*, *135*(4), 1525–1535. https://doi.org/10.1007/s00414-021-02606-y

[12] Broadway, J. M., Rieger, R. E., Campbell, R. A., Quinn, D. K., Mayer, A. R., Yeo, R. A., Wilson, J. K., Gill, D., Fratzke, V., & Cavanagh, J. F. (2019). Executive function predictors of delayed memory deficits after mild traumatic brain injury. *Cortex; a journal devoted to the study of the nervous system and behavior*, *120*, 240–248. https://doi.org/10.1016/j.cortex.2019.06.011

[13] Bryan, C. J., Clemans, T. A., Hernandez, A. M., & Rudd, M. D. (2013). Loss of consciousness, depression, posttraumatic stress disorder, and suicide risk among deployed

military personnel with mild traumatic brain injury. *The Journal of head trauma rehabilitation*, *28*(1), 13-20.

[14] Calvillo, M., & Irimia, A. (2020). Neuroimaging and Psychometric Assessment of Mild Cognitive Impairment After Traumatic Brain Injury. *Frontiers in psychology*, *11*, 1423. https://doi.org/10.3389/fpsyg.2020.01423

[15] Carney, N., Totten, A. M., O'Reilly, C., Ullman, J. S., Hawryluk, G. W., Bell, M. J., Bratton, S. L., Chesnut, R., Harris, O. A., Kissoon, N., Rubiano, A. M., Shutter, L., Tasker, R. C., Vavilala, M. S., Wilberger, J., Wright, D. W., & Ghajar, J. (2017). Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery*, *80*(1), 6–15. https://doi.org/10.1227/NEU.0000000000001432

[16] Capizzi, A., Woo, J., & Verduzco-Gutierrez, M. (2020). Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management. *The Medical clinics of North America*, *104*(2), 213–238. https://doi.org/10.1016/j.mcna.2019.11.001

[17] Chen, W., Wang, G., Yao, C., Zhu, Z., Chen, R., Su, W., & Jiang, R. (2022). The ratio of serum neuron-specific enolase level to admission Glasgow coma scale score is associated with diffuse axonal injury in patients with moderate to severe traumatic brain injury. *Frontiers in neurology*, *13*, 887818. https://doi.org/10.3389/fneur.2022.887818

[18] Chen, X., Wright, D., Chung, S., & Lui, Y. (2025). The Role of MRI in Debunking the Fallacy of "Mild" Traumatic Brain Injury. *Journal of Magnetic Resonance Imaging*.

[19] Chorath, K., Hoang, A., Rajasekaran, K., & Moreira, A. (2021). Association of Early vs Late Tracheostomy Placement with Pneumonia and Ventilator Days in Critically Ill Patients: A Meta-analysis. *JAMA otolaryngology-- head & neck surgery*, *147*(5), 450–459. https://doi.org/10.1001/jamaoto.2021.0025

[20] Chauhan, A. V., Guralnik, J., dosReis, S., Sorkin, J. D., Badjatia, N., & Albrecht, J. S. (2022). Repetitive Traumatic Brain Injury Among Older Adults. *The Journal of head trauma rehabilitation*, *37*(4), E242–E248. https://doi.org/10.1097/HTR.0000000000000719

[21] Cherup, N. P., Robayo, L. E., Vastano, R., Fleming, L., Levin, B. E., & Widerström-Noga, E. (2023). Neuropsychological Function in Traumatic Brain Injury and the Influence of Chronic Pain. *Perceptual and motor skills*, *130*(4), 1495–1523. https://doi.org/10.1177/00315125231174082

[22] Chin, E. Y., Nelson, L. D., Barr, W. B., McCrory, P., & McCrea, M. A. (2016). Reliability and Validity of the Sport Concussion Assessment Tool-3 (SCAT3) in High School and Collegiate Athletes. *The American journal of sports medicine*, *44*(9), 2276–2285. https://doi.org/10.1177/0363546516648141

[23] Churchill, N. W., Hutchison, M. G., Graham, S. J., & Schweizer, T. A. (2018). Connectomic markers of symptom severity in sport-related concussion: Whole-brain analysis of resting-state fMRI. *NeuroImage. Clinical*, *18*, 518–526. https://doi.org/10.1016/j.nicl.2018.02.011

[24] Connor, K. M., & Davidson, J. R. (2003). Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depression and anxiety*, *18*(2), 76–82. https://doi.org/10.1002/da.10113

[25] Cox R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and biomedical research, an international journal*, *29*(3), 162–173. https://doi.org/10.1006/cbmr.1996.0014

[26] Covassin, T., Elbin, R. J., 3rd, Stiller-Ostrowski, J. L., & Kontos, A. P. (2009). Immediate post-concussion assessment and cognitive testing (ImPACT) practices of sports medicine professionals. *Journal of athletic training*, *44*(6), 639–644. https://doi.org/10.4085/1062-6050-44.6.639

[27] Dabas, M. M., Alameri, A. D., Mohamed, N. M., Mahmood, R., Kim, D. H., Samreen, M., Kim, J. W., Shehryar, A., Gyambrah, S., Bedros, A. W., Rehman, A., & Khan, S. (2024). Comparative Efficacy of MRI and CT in Traumatic Brain Injury: A Systematic Review. *Cureus*, *16*(10), e72086. https://doi.org/10.7759/cureus.72086

[28] de Souza, N. L., Esopenko, C., Jia, Y., Parrott, J. S., Merkley, T. L., Dennis, E. L., Hillary, F. G., Velez, C., Cooper, D. B., Kennedy, J. E., Lewis, J. D., York, G. E., Menefee, D. S., McCauley, S. R., Bowles, A. O., Wilde, E. A., & Tate, D. F. (2023). Discriminating Mild Traumatic Brain Injury and Posttraumatic Stress Disorder Using Latent Neuroimaging and Neuropsychological Profiles in Active-Duty Military Service Members. *The Journal of head trauma rehabilitation*, *38*(4), E254–E266. https://doi.org/10.1097/HTR.0000000000000848

[29] Dheansa, S., Rajwani, K. M., Pang, G., Bench, S., Kailaya-Vasan, A., Maratos, E., Lavrador, J. P., Bhangoo, R., & Tolias, C. M. (2023). Relationship between guideline adherence and outcomes in severe traumatic brain injury. *Annals of the Royal College of Surgeons of England*, *105*(5), 400–406. https://doi.org/10.1308/rcsann.2022.0031

[30] *Dickscheid, T., Gui, X., Simsek, A. N., Koehnen, L., Marcenko, V., Schiffer, C., Bludau, S., & Amunts, K. (2025). siibra-python (v1.0.1-alpha.8). Zenodo. https://doi.org/10.5281/zenodo.15591482*

[31] Dixon K. J. (2017). Pathophysiology of Traumatic Brain Injury. *Physical medicine and rehabilitation clinics of North America*, *28*(2), 215–225. https://doi.org/10.1016/j.pmr.2016.12.001

[32] Dogra, S., Arabshahi, S., Wei, J., Saidenberg, L., Kang, S. K., Chung, S., Laine, A., & Lui, Y. W. (2024). Functional Connectivity Changes on Resting-State fMRI after Mild Traumatic Brain Injury: A Systematic Review. *AJNR. American journal of neuroradiology*, *45*(6), 795–801. https://doi.org/10.3174/ajnr.A8204

[33] Drake-Perez M., Boto J., Fitsiori A., Lovblad K., Vargas M.I. Clinical applications of diffusion weighted imaging in neuroradiology. Insights Imaging. 2018;9(4):535-47. Epub 2018/05/31. doi: 10.1007/s13244-018-0624-3. PubMed PMID: 29846907; PMCID: PMC6108979.

[34] DuPrey, K. M., Char, A. S., Loose, S. R., Suffredini, M. V., Walpole, K., & Cronholm, P. F. (2022). Effect of Sleep-Related Symptoms on Recovery from a Sport-Related Concussion. *Orthopedic journal of sports medicine*, *10*(7), 23259671221105256. https://doi.org/10.1177/23259671221105256

[35] Dutta P, Upadhyay P, De M, Khalkar RG. Medical Image Analysis using Deep Convolutional Neural Networks: CNN Architectures and Transfer Learning. Proceedings of the 5th International Conference on Inventive Computation Technologies (Icict-2020). 2020:175-80. PubMed PMID: WOS:000566949800039.

[36] El-Swaify, S. T., Refaat, M. A., Ali, S. H., Abdelrazek, A. E. M., Beshay, P. W., Kamel, M., Bahaa, B., Amir, A., & Basha, A. K. (2022). Controversies and evidence gaps in the early management of severe traumatic brain injury: back to the ABCs. *Trauma surgery & acute care open*, *7*(1), e000859. https://doi.org/10.1136/tsaco-2021-000859

[37] Emos, M. C., Khan Suheb, M. Z., & Agarwal, S. (2023). Neuroanatomy, Internal Capsule. In *StatPearls*. StatPearls Publishing.

[38] Fehily, B., & Fitzgerald, M. (2017). Repeated Mild Traumatic Brain Injury: Potential Mechanisms of Damage. *Cell transplantation*, *26*(7), 1131–1155. https://doi.org/10.1177/0963689717714092

[39] Ferber, D., El Nahhas, O. S. M., Wölflein, G., Wiest, I. C., Clusmann, J., Leßmann, M. E., Foersch, S., Lammert, J., Tschochohei, M., Jäger, D., Salto-Tellez, M., Schultz, N., Truhn, D., & Kather, J. N. (2025). Development and validation of an autonomous artificial intelligence agent for clinical decision-making in oncology. *Nature cancer*, *6*(8), 1337–1349. https://doi.org/10.1038/s43018-025-00991-6

[40] Flavin, W. P., Hosseini, H., Ruberti, J. W., Kavehpour, H. P., Giza, C. C., & Prins, M. L. (2023). Traumatic brain injury and the pathways to cerebral tau accumulation. *Frontiers in neurology*, *14*, 1239653. https://doi.org/10.3389/fneur.2023.1239653

[41] Fure, S. C. R., Howe, E. I., Andelic, N., Brunborg, C., Sveen, U., Røe, C., Rike, P. O., Olsen, A., Spjelkavik, Ø., Ugelstad, H., Lu, J., Ponsford, J., Twamley, E. W., Hellstrøm, T., & Løvstad, M. (2021). Cognitive and vocational rehabilitation after mild-to-moderate traumatic brain injury: A randomised controlled trial. *Annals of physical and rehabilitation medicine*, *64*(5), 101538. https://doi.org/10.1016/j.rehab.2021.101538

[42] Galgano, M., Toshkezi, G., Qiu, X., Russell, T., Chin, L., & Zhao, L. R. (2017). Traumatic Brain Injury: Current Treatment Strategies and Future Endeavors. *Cell transplantation*, *26*(7), 1118–1130. https://doi.org/10.1177/0963689717714102

[43] Gan, Z. S., Stein, S. C., Swanson, R., Guan, S., Garcia, L., Mehta, D., & Smith, D. H. (2019). Blood Biomarkers for Traumatic Brain Injury: A Quantitative Assessment of Diagnostic and Prognostic Accuracy. *Frontiers in neurology*, *10*, 446. https://doi.org/10.3389/fneur.2019.00446

[44] Gao J, Li P, Chen Z, Zhang J. A Survey on Deep Learning for Multimodal Data Fusion. Neural Comput. 2020;32(5):829-64. Epub 2020/03/19. doi: 10.1162/neco_a_01273. PubMed PMID: 32186998.

[45] Galanaud, D., Perlbarg, V., Gupta, R., Stevens, R. D., Sanchez, P., Tollard, E., de Champfleur, N. M., Dinkel, J., Faivre, S., Soto-Ares, G., Veber, B., Cottenceau, V., Masson, F., Tourdias, T., André, E., Audibert, G., Schmitt, E., Ibarrola, D., Dailler, F., Vanhaudenhuyse, A., … Neuro Imaging for Coma Emergence and Recovery Consortium (2012). Assessment of white matter injury and outcome in severe brain trauma: a prospective multicenter cohort. *Anesthesiology*, *117*(6), 1300–1310. https://doi.org/10.1097/ALN.0b013e3182755558

[46] Galgano M, Toshkezi G, Qiu X, Russell T, Chin L, Zhao L-R. Traumatic Brain Injury: Current Treatment Strategies and Future Endeavors. Cell Transplantation. 2017;26(7):1118-1130. doi:10.1177/0963689717714102

[47] Gardner, R. C., Byers, A. L., Barnes, D. E., Li, Y., Boscardin, J., & Yaffe, K. (2018). Mild TBI and risk of Parkinson disease: A Chronic Effects of Neurotrauma Consortium Study. *Neurology*, *90*(20), e1771–e1779. https://doi.org/10.1212/WNL.0000000000005522

[48] Geerlings, M. I., Brickman, A. M., Schupf, N., Devanand, D. P., Luchsinger, J. A., Mayeux, R., & Small, S. A. (2012). Depressive symptoms, antidepressant use, and brain volumes

on MRI in a population-based cohort of old persons without dementia. *Journal of Alzheimer's disease: JAD*, *30*(1), 75–82. https://doi.org/10.3233/JAD-2012-112009

[49] Georges A, M Das J. Traumatic Brain Injury. [Updated 2023 Jan 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459300/#

[50] Ghaith, H. S., Nawar, A. A., Gabra, M. D., Abdelrahman, M. E., Nafady, M. H., Bahbah, E. I., Ebada, M. A., Ashraf, G. M., Negida, A., & Barreto, G. E. (2022). A Literature Review of Traumatic Brain Injury Biomarkers. *Molecular neurobiology*, *59*(7), 4141–4158. https://doi.org/10.1007/s12035-022-02822-6

[51] Giarratana, A. O., Zheng, C., Reddi, S., Teng, S. L., Berger, D., Adler, D., Sullivan, P., Thakker-Varia, S., & Alder, J. (2020). APOE4 genetic polymorphism results in impaired recovery in a repeated mild traumatic brain injury model and treatment with Bryostatin-1 improves outcomes. *Scientific reports*, *10*(1), 19919. https://doi.org/10.1038/s41598-020-76849-x

[52] Giza, C., Greco, T., & Prins, M. L. (2018). Concussion: pathophysiology and clinical translation. *Handbook of clinical neurology*, *158*, 51-61.

[53] Giza, C. C., & Kutcher, J. S. (2014). An introduction to sports concussions. *Continuum (Minneapolis, Minn.)*, *20*(6 Sports Neurology), 1545–1551. https://doi.org/10.1212/01.CON.0000458975.78766.11

[54] Giza CC, McCrea M, Huber D, et al. Assessment of blood biomarker profile after acute concussion during combative training among US military cadets: a prospective study from the

NCAA and US department of defense CARE consortium. *JAMA Netw Open*. 2021; **4**(2): e2037731.

[55] Godin, O., Dufouil, C., Maillard, P., Delcroix, N., Mazoyer, B., Crivello, F., Alpérovitch, A., & Tzourio, C. (2008). White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study. *Biological psychiatry*, *63*(7), 663–669. https://doi.org/10.1016/j.biopsych.2007.09.006

[56] Gosselin, N., Saluja, R. S., Chen, J. K., Bottari, C., Johnston, K., & Ptito, A. (2010). Brain functions after sports-related concussion: insights from event-related potentials and functional MRI. *The Physician and sportsmedicine*, *38*(3), 27–37. https://doi.org/10.3810/psm.2010.10.1805

[57] Greven, S., Crainiceanu, C., Caffo, B., & Reich, D. (2011). Longitudinal functional principal component analysis. In *Recent advances in functional data analysis and related topics* (pp. 149-154). Heidelberg: Physica-Verlag HD.

[58] Grigg-Damberger M. M. (2023). Sleep/Wake Disorders After Sports Concussion: Risks, Revelations, and Interventions. *Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society*, *40*(5), 417–425. https://doi.org/10.1097/WNP.0000000000000931

[59] Guo, Z., Ding, W., Cao, D., Chen, Y., & Chen, J. (2022). Decompressive Craniectomy vs. Craniotomy Only for Traumatic Brain Injury: A Propensity-Matched Study of Long-Term Outcomes in Neuropsychology. *Frontiers in neurology*, *13*, 813140. https://doi.org/10.3389/fneur.2022.813140

[60] Haagsma, J. A., Scholten, A. C., Andriessen, T. M., Vos, P. E., Van Beeck, E. F., & Polinder, S. (2015). Impact of depression and post-traumatic stress disorder on functional outcome and health-related quality of life of patients with mild traumatic brain injury. *Journal of neurotrauma*, *32*(11), 853-862.

[61] Hageman, G., Hof, J., & Nihom, J. (2022). Susceptibility-weighted MRI and microbleeds in mild traumatic brain injury: prediction of posttraumatic complaints? *European Neurology*, *85*(3), 177-185.

[62] Halefoglu AM, Yousem DM. Susceptibility weighted imaging: Clinical applications and future directions. World J Radiol. 2018;10(4):30-45. Epub 2018/06/01. doi: 10.4329/wjr. v10.i4.30. PubMed PMID: 29849962; PMCID: PMC5971274H

[63] Hao, X., Xu, D., Bansal, R., Dong, Z., Liu, J., Wang, Z., Kangarlu, A., Liu, F., Duan, Y., Shova, S., Gerber, A. J., & Peterson, B. S. (2013). Multimodal magnetic resonance imaging: The coordinated use of multiple, mutually informative probes to understand brain structure and function. *Human brain mapping*, *34*(2), 253–271. https://doi.org/10.1002/hbm.21440

[64] Harper B., Shiraishi M., & Soangra R. (2023). A portable and reliable tool for on-site physical reaction time (RT) measurement. *Invention Disclosure*, Volume 3 https://doi.org/10.1016/j.inv.2023.100013

[65] Hasan, K. M., Keser, Z., Schulz, P. E., & Wilde, E. A. (2018). Multimodal Advanced Imaging for Concussion. *Neuroimaging clinics of North America*, *28*(1), 31–42. https://doi.org/10.1016/j.nic.2017.09.001

[66] Hassett L. (2023). Physiotherapy management of moderate-to-severe traumatic brain injury. *Journal of physiotherapy*, *69*(3), 141–147. https://doi.org/10.1016/j.jphys.2023.05.015

[67] Hellewell, S. C., Welton, T., Pearce, A. J., Maller, J. J., & Grieve, S. M. (2021). Diffusion MRI as a complementary assessment to cognition, emotion, and motor dysfunction after sports-related concussion: a systematic review and critical appraisal of the literature. *Brain imaging and behavior*, *15*(3), 1685–1704. https://doi.org/10.1007/s11682-020-00336-0

[68] Hides, J. A., Franettovich Smith, M. M., Mendis, M. D., Smith, N. A., Cooper, A. J., Treleaven, J., Leung, F., Gardner, A. J., McCrory, P., & Low Choy, N. L. (2017). A prospective investigation of changes in the sensorimotor system following sports concussion. An exploratory study. *Musculoskeletal science & practice*, *29*, 7–19. https://doi.org/10.1016/j.msksp.2017.02.003

[69] Hier, D. B., Obafemi-Ajayi, T., Thimgan, M. S., Olbricht, G. R., Azizi, S., Allen, B., Hadi, B. A., & Wunsch, D. C., 2nd (2021). Blood biomarkers for mild traumatic brain injury: a selective review of unresolved issues. *Biomarker research*, *9*(1), 70. https://doi.org/10.1186/s40364-021-00325-5

[70] Hillary, F. G., Roman, C. A., Venkatesan, U., Rajtmajer, S. M., Bajo, R., & Castellanos, N. D. (2015). Hyperconnectivity is a fundamental response to neurological disruption. *Neuropsychology*, *29*(1), 59–75. https://doi.org/10.1037/neu0000110

[71] Holm L., Cassidy J.D., Carroll L.J., et al. Summary of the WHO collaborating centre for neurotrauma task force on mild traumatic brain injury. *J Rehabil Med*. 2005;37(3):137-141

[72] Hoogenboom, W. S., Branch, C. A., & Lipton, M. L. (2019). Animal models of closed-skull, repetitive mild traumatic brain injury. *Pharmacology & therapeutics*, *198*, 109–122. https://doi.org/10.1016/j.pharmthera.2019.02.016

[73] Howitt, S., Brommer, R., Fowler, J., Gerwing, L., Payne, J., & DeGraauw, C. (2016). The utility of the King-Devick test as a sideline assessment tool for sport-related concussions: a narrative review. *The Journal of the Canadian Chiropractic Association*, *60*(4), 322–329.

[74] Howlett, J. R., Nelson, L. D., & Stein, M. B. (2022). Mental Health Consequences of Traumatic Brain Injury. *Biological psychiatry*, *91*(5), 413–420. https://doi.org/10.1016/j.biopsych.2021.09.024

[75] Huang, Y. L., Kuo, Y. S., Tseng, Y. C., Chen, D. Y. T., Chiu, W. T., & Chen, C. J. (2015). Susceptibility-weighted MRI in mild traumatic brain injury. *Neurology*, *84*(6), 580-585.

[76] Huang, W., Yan, J., Zheng, Y., Wang, J., Hu, W., & Zhang, J. (2025). Microstructural Alterations of Gray and White Matter in Active Young Boxers with Sports-Related Concussions. *Journal of neurotrauma*, *42*(1-2), 33–45. https://doi.org/10.1089/neu.2024.0015

[77] Hussain, S. F., Raza, Z., Cash, A. T. G., Zampieri, T., Mazzoli, R. A., Kardon, R. H., & Gomes, R. S. M. (2021). Traumatic brain injury and sight loss in military and veteran populations- a review. *Military Medical Research*, *8*(1), 42. https://doi.org/10.1186/s40779-021-00334-3

[78] Hutchinson, P. J., Kolias, A. G., Timofeev, I. S., Corteen, E. A., Czosnyka, M., Timothy, J., Anderson, I., Bulters, D. O., Belli, A., Eynon, C. A., Wadley, J., Mendelow, A. D., Mitchell, P. M., Wilson, M. H., Critchley, G., Sahuquillo, J., Unterberg, A., Servadei, F., Teasdale, G. M., Pickard, J. D., … RESCUEicp Trial Collaborators (2016). Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. *The New England journal of medicine*, *375*(12), 1119–1130. https://doi.org/10.1056/NEJMoa1605215

[79] Irimia, A., Goh, S. M., Wade, A. C., Patel, K., Vespa, P. M., & Van Horn, J. D. (2017). Traumatic Brain Injury Severity, Neuropathophysiology, and Clinical Outcome: Insights from Multimodal Neuroimaging. *Frontiers in neurology*, *8*, 530. https://doi.org/10.3389/fneur.2017.00530

[80] Isgrò, M. A., Bottoni, P., & Scatena, R. (2015). Neuron-Specific Enolase as a Biomarker: Biochemical and Clinical Aspects. *Advances in experimental medicine and biology*, *867*, 125–143. https://doi.org/10.1007/978-94-017-7215-0_9

[81] Jain, S., Margetis, K., & Iverson, L. M. (2025). Glasgow Coma Scale. In *StatPearls*. StatPearls Publishing.

[82] Jagger-Rickels, A., Rothlein, D., Stumps, A., Evans, T. C., Bernstein, J., Milberg, W., McGlinchey, R., DeGutis, J., & Esterman, M. (2022). An executive function subtype of PTSD with unique neural markers and clinical trajectories. *Translational psychiatry*, *12*(1), 262. https://doi.org/10.1038/s41398-022-02011-y

[83] Janusz JA, Sady MD, Gioia GA. Postconcussion symptom assessment. In: Kirkwood MW, Yeates KO, editors. In Mild Traumatic Brain Injury in Children and Adolescents: From Basic Science to Clinical Management.New York: Guilford Press; 2012. pp. 241–263.

[84] JASP Team (2025). JASP (Version 0.95.3) [Computer software]

[85] Jenkinson, M., Bannister, P., Brady, J. M. and Smith, S. M. Improved Optimisation for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. NeuroImage, 17(2), 825-841, 2002.

[86] Jindal, G., Gadhia, R. R., & Dubey, P. (2021). Neuroimaging in Sports-Related Concussion. *Clinics in sports medicine*, *40*(1), 111–121. https://doi.org/10.1016/j.csm.2020.08.004

[87] Jung, H. Y., Bak, H., Bang, M., Lee, S. H., & Lee, K. S. (2024). Neural Correlates of Trait Impulsivity among Adult Healthy Individuals. *Clinical psychopharmacology and neuroscience: the official scientific journal of the Korean College of Neuropsychopharmacology*, *22*(2), 345–353. https://doi.org/10.9758/cpn.23.1128

[88] Jordan, B. The clinical spectrum of sport-related traumatic brain injury. *Nat Rev Neurol* 9, 222–230 (2013). https://doi.org/10.1038/nrneurol.2013.33

[89] Joyce J.M., La P.L., Walker R., Harris A.D. Magnetic resonance spectroscopy of traumatic brain injury and subconcussive hits: A systematic review and meta-analysis. J Neurotrauma. 2022;39(21–22):1455–1476.

[90] Keightley, M., Green, S., Reed, N., Agnihotri, S., Wilkinson, A., & Lobaugh, N. (2011). An investigation of the effects of sports-related concussion in youth using functional magnetic resonance imaging and the head impact telemetry system. *Journal of visualized experiments: JoVE*, (47), 2226. https://doi.org/10.3791/2226

[91] Khellaf, A., Khan, D. Z., & Helmy, A. (2019). Recent advances in traumatic brain injury. *Journal of neurology*, *266*(11), 2878–2889. https://doi.org/10.1007/s00415-019- 09541-4

[92] Kim, duS., Kong, M. H., Jang, S. Y., Kim, J. H., Kang, D. S., & Song, K. Y. (2013). The usefulness of brain magnetic resonance imaging with mild head injury and the negative findings of brain computed tomography. *Journal of Korean Neurosurgical Society*, *54*(2), 100–106. https://doi.org/10.3340/jkns.2013.54.2.100

[93] Knapp, J., Doppmann, P., Huber, M., Meuli, L., Albrecht, R., Sollid, S., & Pietsch, U. (2023). Pre-hospital endotracheal intubation in severe traumatic brain injury: ventilation targets and mortality-a retrospective analysis of 308 patients. *Scandinavian journal of trauma, resuscitation and emergency medicine*, *31*(1), 46. https://doi.org/10.1186/s13049-023-01115-8

[94] Kowalski, R. G., Hammond, F. M., Weintraub, A. H., Nakase-Richardson, R., Zafonte, R. D., Whyte, J., & Giacino, J. T. (2021). Recovery of Consciousness and Functional Outcome in Moderate and Severe Traumatic Brain Injury. *JAMA neurology*, *78*(5), 548–557. https://doi.org/10.1001/jamaneurol.2021.0084

[95] Krainin, B. M., Forsten, R. D., Kotwal, R. S., Lutz, R. H., & Guskiewicz, K. M. (2011). Mild traumatic brain injury literature review and proposed changes to classification. *Journal of special operations medicine: a peer reviewed journal for SOF medical professionals*, *11*(3), 38–47. https://doi.org/10.55460/D7HH-ZGPK

[96] Kurni, M., Kaloria, N., Hazarika, A., Jain, K., Gupta, S. K., & Walia, R. (2023). Comparison of Midazolam and Propofol Infusion to Suppress Stress Response in Patients with Severe Traumatic Brain Injury: A Prospective, Randomized Controlled Trial. *Korean journal of neurotrauma*, *19*(1), 70–81. https://doi.org/10.13004/kjnt.2023.19.e4

[97] Kurowski, B. G., Treble-Barna, A., Pitzer, A. J., Wade, S. L., Martin, L. J., Chima, R. S., & Jegga, A. (2017). Applying Systems Biology Methodology to Identify Genetic Factors Possibly Associated with Recovery after Traumatic Brain Injury. *Journal of neurotrauma*, *34*(14), 2280–2290. https://doi.org/10.1089/neu.2016.4856

[98] Laing, J., Gabbe, B., Chen, Z., Perucca, P., Kwan, P., & O'Brien, T. J. (2022). Risk Factors and Prognosis of Early Posttraumatic Seizures in Moderate to Severe Traumatic Brain Injury. *JAMA neurology*, *79*(4), 334–341. https://doi.org/10.1001/jamaneurol.2021.5420

[99] Levin, H. S., & Robertson, C. S. (2013). Mild traumatic brain injury in translation. *Journal of neurotrauma*, *30*(8), 610-617.

[100] Li, B., Li, W. G., Guo, Y., Wang, Y., Xu, L. Y., Yang, Y., Xu, S. G., Tan, Z. L., Mei, Y. R., & Wang, K. Y. (2023). Integrating fractional amplitude of low-frequency fluctuation and functional connectivity to investigate the mechanism and prognosis of severe traumatic brain injury. *Frontiers in neurology*, *14*, 1266167. https://doi.org/10.3389/fneur.2023.1266167

[101] Lindberg, M. A., Moy Martin, E. M., & Marion, D. W. (2022). Military Traumatic Brain Injury: The History, Impact, and Future. *Journal of neurotrauma*, *39*(17-18), 1133–1145. https://doi.org/10.1089/neu.2022.0103

[102] Lin, M., He, H., Schifitto, G., & Zhong, J. (2016). Simulation of changes in diffusion related to different pathologies at cellular level after traumatic brain injury. Magnetic resonance in medicine, 76(1), 290–300. https://doi.org/10.1002/mrm.25816

[103] Lindemer, E. R., Salat, D. H., Leritz, E. C., McGlinchey, R. E., & Milberg, W. P. (2013). Reduced cortical thickness with increased lifetime burden of PTSD in OEF/OIF Veterans and the impact of comorbid TBI. *NeuroImage. Clinical*, *2*, 601–611. https://doi.org/10.1016/j.nicl.2013.04.009

[104] Lindquist, M. A., Spicer, J., Asllani, I., & Wager, T. D. (2012). Estimating and testing variance components in a multi-level GLM. *NeuroImage*, *59*(1), 490–501. https://doi.org/10.1016/j.neuroimage.2011.07.077

[105] Lindsey H.M., Hodges C.B., Greer K.M., Wilde E.A., Merkley T.L. Diffusion-weighted imaging in mild traumatic brain injury: A systematic review of the literature. Neuropsychology Rev. 2023;33(1):42–121.

[106] Lininger, M. R., Leahy, T. E., Haug, E. C., & Bowman, T. G. (2018). TEST-RETEST RELIABILITY OF THE LIMITS OF STABILITY TEST PERFORMED BY YOUNG ADULTS USING NEUROCOM® VSR SPORT. *International journal of sports physical therapy*, *13*(5), 800–807.

[107] Liu, X., Sun, Q., Meng, Y., Fu, M., & Bourennane, S. (2018). Hyperspectral Image Classification Based on Parameter-Optimized 3D-CNNs Combined with Transfer Learning and Virtual Samples. Remote Sensing, 10(9), 1425. https://doi.org/10.3390/rs10091425

[108] Liu, X., Woo, J., Ma, C., Ouyang, J., & El Fakhri, G. (2024). Point-supervised Brain Tumor Segmentation with Box-prompted Medical Segment Anything Model. *IEEE Nuclear Science Symposium conference record. Nuclear Science Symposium*, *2024*, 10.1109/nss/mic/rtsd57108.2024.10656071. https://doi.org/10.1109/nss/mic/rtsd57108.2024.10656071

[109] Lohia, A., & McKenzie, J. (2023). Neuroanatomy, Pyramidal Tract Lesions. In *StatPearls*. StatPearls Publishing.

[110] Long, Y., Chen, C., Deng, M., Huang, X., Tan, W., Zhang, L., Fan, Z., & Liu, Z. (2019). Psychological resilience negatively correlates with resting-state brain network flexibility in young healthy adults: a dynamic functional magnetic resonance imaging study. *Annals of translational medicine*, *7*(24), 809. https://doi.org/10.21037/atm.2019.12.45

[111] Lunkova, E., Amir, J., Chen, J. K., McCabe, S., Saluja, R. S., & Ptito, A. (2025). Multimodal Approach in the Identification of Biomarkers of Mild Traumatic Brain Injury: Resting State fMRI, ASL, and SWI. *Clinical Neuroimaging*, *2*(1), e70026.

[112] Lutkenhoff, E. S., Chiang, J., Tshibanda, L., Kamau, E., Kirsch, M., Pickard, J. D., Laureys, S., Owen, A. M., & Monti, M. M. (2015). Thalamic and extrathalamic mechanisms of consciousness after severe brain injury. *Annals of neurology*, *78*(1), 68–76. https://doi.org/10.1002/ana.24423

[113] Lutkenhoff ES, Wright MJ, Shrestha V, Real C, McArthur DL, Buitrago-Blanco M, Vespa PM, Monti MM. The subcortical basis of outcome and cognitive impairment in TBI: A longitudinal cohort study. Neurology. 2020;95(17): e2398-e408. Epub 2020/09/11. doi: 10.1212/WNL.0000000000010825. PubMed PMID: 32907958; PMCID: PMC7682912.

[114] Lutkenhoff ES, McArthur DL, Hua X, Thompson PM, Vespa PM, Monti MM. Thalamic atrophy in antero-medial and dorsal nuclei correlates with six-month outcome after severe brain injury. Neuroimage Clin. 2013; 3:396-404. Epub 2013/11/26. doi: 10.1016/j.nicl.2013.09.010. PubMed PMID: 24273723; PMCID: PMC3815017.

[115] Ma, J., He, Y., Li, F., Han, L., You, C., & Wang, B. (2024). Segment anything in medical images. *Nature communications*, *15*(1), 654. https://doi.org/10.1038/s41467-024-44824-z

[116] Maas, A. I., Menon, D. K., Manley, G. T., Abrams, M., Åkerlund, C., Andelic, N., ... & Zemek, R. (2022). Traumatic brain injury: progress and challenges in prevention, clinical care, and research. *The Lancet Neurology*, *21*(11), 1004-1060.

[117] Major, B., Symons, G. F., Sinclair, B., O'Brien, W. T., Costello, D., Wright, D. K., Clough, M., Mutimer, S., Sun, M., Yamakawa, G. R., Brady, R. D., O'Sullivan, M. J., Mychasiuk, R., McDonald, S. J., O'Brien, T. J., Law, M., Kolbe, S., & Shultz, S. R. (2021).

White and Gray Matter Abnormalities in Australian Footballers with a History of Sports-Related Concussion: An MRI Study. *Cerebral cortex (New York, N.Y.: 1991)*, *31*(12), 5331–5338. https://doi.org/10.1093/cercor/bhab161

[118] Maillard, P., Carmichael, O., Harvey, D., Fletcher, E., Reed, B., Mungas, D., & DeCarli, C. (2013). FLAIR and diffusion MRI signals are independent predictors of white matter hyperintensities. *AJNR. American journal of neuroradiology*, *34*(1), 54–61. https://doi.org/10.3174/ajnr.A3146

[119] Manley, G., Gardner, A. J., Schneider, K. J., Guskiewicz, K. M., Bailes, J., Cantu, R. C., Castellani, R. J., Turner, M., Jordan, B. D., Randolph, C., Dvořák, J., Hayden, K. A., Tator, C. H., McCrory, P., & Iverson, G. L. (2017). A systematic review of potential long- term effects of sport-related concussion. *British journal of sports medicine*, *51*(12), 969– 977. https://doi.org/10.1136/bjsports-2017-097791

[120] Marehbian, J., Muehlschlegel, S., Edlow, B.L. *et al.* Medical Management of the Severe Traumatic Brain Injury Patient. *Neurocrit Care* **27**, 430–446 (2017). https://doi.org/10.1007/s12028-017-0408-5

[121] Marklund, N., Bellander, B. M., Godbolt, A. K., Levin, H., McCrory, P., & Thelin, E. P. (2019). Treatments and rehabilitation in the acute and chronic state of traumatic brain injury. *Journal of internal medicine*, *285*(6), 608–623. https://doi.org/10.1111/joim.12900

[122] Marklund, N., Vedung, F., Lubberink, M., Tegner, Y., Johansson, J., Blennow, K., Zetterberg, H., Fahlström, M., Haller, S., Stenson, S., Larsson, E. M., Wall, A., & Antoni, G. (2021). Tau aggregation and increased neuroinflammation in athletes after sports-related concussions and in traumatic brain injury patients - A PET/MR study. *NeuroImage. Clinical*, *30*, 102665. https://doi.org/10.1016/j.nicl.2021.102665

[123] Martin, R. M., Wright, M. J., Lutkenhoff, E. S., Ellingson, B. M., Van Horn, J. D., Tubi, M., Alger, J. R., McArthur, D. L., & Vespa, P. M. (2017). Traumatic hemorrhagic brain injury: impact of location and resorption on cognitive outcome. *Journal of neurosurgery*, *126*(3), 796–804. https://doi.org/10.3171/2016.3.JNS151781

[124] Mascalchi M., Filippi M., Floris R., Fonda C., Gasparotti R., Villari N. Diffusion-weighted MR of the brain: methodology and clinical application. Radiol Med. 2005;109(3):155-97. Epub 2005/03/19. PubMed PMID: 15775887.

[125] Malec, J. F., Brown, A. W., Leibson, C. L., Flaada, J. T., Mandrekar, J. N., Diehl, N. N., & Perkins, P. K. (2007). The mayo classification system for traumatic brain injury severity. *Journal of neurotrauma*, *24*(9), 1417-1424.

[126] Mavroudis, I., Ciobica, A., Bejenariu, A. C., Dobrin, R. P., Apostu, M., Dobrin, I., & Balmus, I. M. (2024). Cognitive Impairment following Mild Traumatic Brain Injury (mTBI): A Review. *Medicina (Kaunas, Lithuania)*, *60*(3), 380. https://doi.org/10.3390/medicina60030380

[127] McCrea M, Broglio SP, McAllister TW, et al. Association of blood biomarkers with acute sport-related concussion in collegiate athletes: findings from the NCAA and department of defense CARE consortium. *JAMA Netw Open*. 2020; **3**(1): e1919771

[128] McCrea, M. A., Giacino, J. T., Barber, J., Temkin, N. R., Nelson, L. D., Levin, H. S., Dikmen, S., Stein, M., Bodien, Y. G., Boase, K., Taylor, S. R., Vassar, M., Mukherjee, P., Robertson, C., Diaz-Arrastia, R., Okonkwo, D. O., Markowitz, A. J., Manley, G. T., TRACK-TBI Investigators, Adeoye, O., … Zafonte, R. (2021). Functional Outcomes Over the First Year After Moderate to Severe Traumatic Brain Injury in the Prospective, Longitudinal TRACK-TBI Study. *JAMA neurology*, *78*(8), 982–992. https://doi.org/10.1001/jamaneurol.2021.2043

[129] McInnes K, Friesen CL, MacKenzie DE, Westwood DA, Boe SG (2017) Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. PLOS ONE 12(4): e0174847. https://doi.org/10.1371/journal.pone.0174847

[130] McKeithan, L., Hibshman, N., Yengo-Kahn, A. M., Solomon, G. S., & Zuckerman, S. L. (2019). Sport-Related Concussion: Evaluation, Treatment, and Future Directions. *Medical sciences (Basel, Switzerland)*, *7*(3), 44. https://doi.org/10.3390/medsci7030044

[131] McLoughlin, R. J., & Swanson, R. L., 2nd (2023). Hypopituitarism After Mild Traumatic Brain Injury: A Case Report. *Cureus*, *15*(7), e41282. https://doi.org/10.7759/cureus.41282

[132] Mehta, R., GP trainee, Chinthapalli, K., & consultant neurologist (2019). Glasgow coma scale explained. *BMJ (Clinical research ed.)*, *365*, l1296. https://doi.org/10.1136/bmj.l1296

[133] Meier, T. B., Giraldo-Chica, M., España, L. Y., Mayer, A. R., Harezlak, J., Nencka, A. S., Wang, Y., Koch, K. M., Wu, Y. C., Saykin, A. J., Giza, C. C., Goldman, J., DiFiori, J. P., Guskiewicz, K. M., Mihalik, J. P., Brooks, A., Broglio, S. P., McAllister, T., & McCrea, M. A. (2020). Resting-State fMRI Metrics in Acute Sport-Related Concussion and Their Association with Clinical Recovery: A Study from the NCAA-DOD CARE Consortium. *Journal of neurotrauma*, *37*(1), 152–162. https://doi.org/10.1089/neu.2019.6471

[134] Meier TB, Huber DL, Bohorquez-Montoya L, et al. A prospective study of acute blood-based biomarkers for sport-related concussion. *Ann Neurol*. 2020

[135] Menat, S., Jacquens, A., Mathon, B. *et al.* Corticosteroid treatment for refractory intracranial hypertension: a rescue therapy in patients with severe traumatic brain injury with

contusional lesions—a feedback. *Acta Neurochir* **165**, 717–725 (2023). https://doi.org/10.1007/s00701-023-05507-8

[136] Menon V. (2013). Developmental pathways to functional brain networks: emerging principles. *Trends in cognitive sciences*, *17*(12), 627–640. https://doi.org/10.1016/j.tics.2013.09.015

[137] Mercier, L. J., Kruger, N., Le, Q. B., Fung, T. S., Kline, G. A., & Debert, C. T. (2021). Growth hormone deficiency testing and treatment following mild traumatic brain injury. *Scientific reports*, *11*(1), 8534. https://doi.org/10.1038/s41598-021-87385-7

[138] Mitchell, A. S., & Chakraborty, S. (2013). What does the mediodorsal thalamus do? *Frontiers in systems neuroscience*, *7*, 37. https://doi.org/10.3389/fnsys.2013.00037

[139] Michelson, E. A., Huff, J. S., Loparo, M., Naunheim, R. S., Perron, A., Rahm, M., Smith, D. W., Stone, J. A., & Berger, A. (2018). Emergency Department Time Course for Mild Traumatic Brain Injury Workup. *The western journal of emergency medicine*, *19*(4), 635–640. https://doi.org/10.5811/westjem.2018.5.37293

[140] Miyagi, T., Oishi, N., Kobayashi, K., Ueno, T., Yoshimura, S., Murai, T., & Fujiwara, H. (2020). Psychological resilience is correlated with dynamic changes in functional connectivity within the default mode network during a cognitive task. *Scientific reports*, *10*(1), 17760. https://doi.org/10.1038/s41598-020-74283-7

[141] Molaei-Langroudi, R., Alizadeh, A., Kazemnejad-Leili, E., Monsef-Kasmaie, V., & Moshirian, S. Y. (2019). Evaluation of Clinical Criteria for Performing Brain CT-Scan in Patients with Mild Traumatic Brain Injury; A New Diagnostic Probe. *Bulletin of emergency and trauma*, *7*(3), 269–277. https://doi.org/10.29252/beat-0703010

[142] Montalt-Tordera, J., Muthurangu, V., Hauptmann, A., & Steeden, J. A. (2021). Machine learning in Magnetic Resonance Imaging: Image reconstruction. *Physica medica: PM: an international journal devoted to the applications of physics to medicine and biology: official journal of the Italian Association of Biomedical Physics (AIFB)*, *83*, 79–87. https://doi.org/10.1016/j.ejmp.2021.02.020

[143] Morse, A. M., & Kothare, S. V. (2018). Sleep disorders and concussion. *Handbook of clinical neurology*, *158*, 127–134. https://doi.org/10.1016/B978-0-444-63954-7.00013-6

[144] Muller, A. M., & Virji-Babul, N. (2018). Stuck in a State of Inattention? Functional Hyperconnectivity as an Indicator of Disturbed Intrinsic Brain Dynamics in Adolescents with Concussion: A Pilot Study. ASN neuro, 10, 1759091417753802. https://doi.org/10.1177/1759091417753802

[145] Nahm F. S. (2022). Receiver operating characteristic curve: overview and practical use for clinicians. *Korean journal of anesthesiology*, *75*(1), 25–36. https://doi.org/10.4097/kja.21209

[146] Narayana, P. A., Yu, X., Hasan, K. M., Wilde, E. A., Levin, H. S., Hunter, J. V., ... & McCarthy, J. J. (2015). Multi-modal MRI of mild traumatic brain injury. *NeuroImage: Clinical*, *7*, 87-97.

[147] Palejwala, A. H., Dadario, N. B., Young, I. M., O'Connor, K., Briggs, R. G., Conner, A. K., O'Donoghue, D. L., & Sughrue, M. E. (2021). Anatomy and White Matter Connections of the Lingual Gyrus and Cuneus. *World neurosurgery*, *151*, e426–e437. https://doi.org/10.1016/j.wneu.2021.04.050

[148] Patil, S., Kata, R., Aydin, S., Karabacak, M., Margetis, K., & Bisdas, S. (2025). Clinical utility of diffusion tensor imaging in sport-related concussion: a systematic review. BJR open, 7(1), tzaf024. https://doi.org/10.1093/bjro/tzaf024

[149] Pavlovic, D., Pekic, S., Stojanovic, M., & Popovic, V. (2019). Traumatic brain injury: neuropathological, neurocognitive and neurobehavioral sequelae. *Pituitary*, *22*(3), 270– 282. https://doi.org/10.1007/s11102-019-00957-9

[150] Polich, G., Iaccarino, M. A., & Zafonte, R. (2019). Psychopharmacology of traumatic brain injury. *Handbook of clinical neurology*, *165*, 253–267. https://doi.org/10.1016/B978-0-444-64012-3.00015-0

[151] Ponsford, J., Velikonja, D., Janzen, S., Harnett, A., McIntyre, A., Wiseman-Hakes, C., Togher, L., Teasell, R., Kua, A., Patsakos, E., Welch-West, P., & Bayley, M. T. (2023). INCOG 2.0 Guidelines for Cognitive Rehabilitation Following Traumatic Brain Injury, Part II: Attention and Information Processing Speed. *The Journal of head trauma rehabilitation*, *38*(1), 38–51. https://doi.org/10.1097/HTR.0000000000000839

[152] Portillo, E., Zi, X., Kim, Y., Tucker, L. B., Fu, A., Miller, L. A., Valenzuela, K. S., Sullivan, G. M., Gauff, A. K., Yu, F., Radomski, K. L., McCabe, J. T., & Armstrong, R. C. (2023). Persistent hypersomnia following repetitive mild experimental traumatic brain injury: Roles of chronic stress and sex differences. *Journal of neuroscience research*, *101*(6), 843–865. https://doi.org/10.1002/jnr.25165

[153] Posti, J. P., & Tenovuo, O. (2022). Blood-based biomarkers and traumatic brain injury—A clinical perspective. *Acta Neurologica Scandinavica*, *146*(4), 389-399.

[154] Poulsen, I., Langhorn, L., Egerod, I., & Aadal, L. (2021). Sleep and agitation during subacute traumatic brain injury rehabilitation: A scoping review. *Australian critical care: official journal of the Confederation of Australian Critical Care Nurses*, *34*(1), 76–82. https://doi.org/10.1016/j.aucc.2020.05.006

[155] Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048

[156] Qiu, W. Q., Himali, J. J., Wolf, P. A., DeCarli, D. C., Beiser, A., & Au, R. (2017). Effects of white matter integrity and brain volumes on late life depression in the Framingham Heart Study. *International journal of geriatric psychiatry*, *32*(2), 214–221. https://doi.org/10.1002/gps.4469

[157] Race, N. S., Andrews, K. D., Lungwitz, E. A., Vega Alvarez, S. M., Warner, T. R., Acosta, G., Cao, J., Lu, K. H., Liu, Z., Dietrich, A. D., Majumdar, S., Shekhar, A., Truitt, W. A., & Shi, R. (2021). Psychosocial impairment following mild blast-induced traumatic brain injury in rats. *Behavioural brain research*, *412*, 113405. https://doi.org/10.1016/j.bbr.2021.113405

[158] Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement. 1977;1(3):385-401

[159] Rahim, S., Laugsand, E. A., Fyllingen, E. H., Rao, V., Pantelatos, R. I., Müller, T. B., Vik, A., & Skandsen, T. (2022). Moderate and severe traumatic brain injury in general hospitals: a ten-year population-based retrospective cohort study in central Norway. *Scandinavian journal of trauma, resuscitation and emergency medicine*, *30*(1), 68. https://doi.org/10.1186/s13049-022-01050-0

[160] Raikes, A. C., Athey, A., Alfonso-Miller, P., Killgore, W. D. S., & Grandner, M. A. (2019). Insomnia and daytime sleepiness: risk factors for sports-related concussion. *Sleep medicine*, *58*, 66–74. https://doi.org/10.1016/j.sleep.2019.03.008

[161] Ramsay, J. O., & Silverman, B. W. (2005). *Functional Data Analysis*. Springer.

[162] Rakocz N, Chiang JN, Nittala MG, Corradetti G, Tiosano L, Velaga S, Thompson M, Hill BL, Sankararaman S, Haines JL, Pericak-Vance MA, Stambolian D, Sadda SR, Halperin E. Automated identification of clinical features from sparsely annotated 3-dimensional medical imaging. NPJ Digit Med. 2021;4(1):44. Epub 2021/03/10. doi: 10.1038/s41746-021-00411-w. PubMed PMID: 33686212; PMCID: PMC7940637.

[163] Ranson, J., Magnus, B. E., Temkin, N., Dikmen, S., Giacino, J. T., Okonkwo, D. O., Valadka, A. B., Manley, G. T., Nelson, L. D., & TRACK-TBI Investigators (2019). Diagnosing the GOSE: Structural and Psychometric Properties Using Item Response Theory, a TRACK-TBI Pilot Study. *Journal of neurotrauma*, *36*(17), 2493–2505. https://doi.org/10.1089/neu.2018.5998

[164] Redell, J. B., Maynard, M. E., Underwood, E. L., Vita, S. M., Dash, P. K., & Kobori, N. (2020). Traumatic brain injury and hippocampal neurogenesis: Functional implications. *Experimental neurology*, *331*, 113372. https://doi.org/10.1016/j.expneurol.2020.113372

[165] Riedy, G., Senseney, J. S., Liu, W., Ollinger, J., Sham, E., Krapiva, P., ... & Oakes, T. R. (2016). Findings from structural MR imaging in military traumatic brain injury. *Radiology*, *279*(1), 207-215.

[166] Robba, C., Poole, D., McNett, M., Asehnoune, K., Bösel, J., Bruder, N., Chieregato, A., Cinotti, R., Duranteau, J., Einav, S., Ercole, A., Ferguson, N., Guerin, C., Siempos, I. I., Kurtz,

P., Juffermans, N. P., Mancebo, J., Mascia, L., McCredie, V., Nin, N., … Stevens, R. D. (2020). Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus. *Intensive care medicine*, *46*(12), 2397–2410. https://doi.org/10.1007/s00134-020-06283-0

[167] Romano A., Bozzao A., Bonamini M., Fasoli F., Ferrante M., Floris R., Colonnese C., Fantozzi L.M. Diffusion-weighted MR Imaging: clinical applications in neuroradiology. Radiol Med. 2003;106(5-6):521-48. Epub 2004/01/22. PubMed PMID: 14735019.

[168] Ross-Munro, E., Kwa, F., Kreiner, J., Khore, M., Miller, S. L., Tolcos, M., Fleiss, B., & Walker, D. W. (2020). Midkine: The Who, What, Where, and When of a Promising Neurotrophic Therapy for Perinatal Brain Injury. *Frontiers in neurology*, *11*, 568814. https://doi.org/10.3389/fneur.2020.568814

[169] Rousseeuw, P. J. (1987). Silhouettes: a graphical aid to the interpretation and validation of cluster analysis. *Journal of computational and applied mathematics*, *20*, 53-65.

[170] Sahler, C. S., & Greenwald, B. D. (2012). Traumatic brain injury in sports: a review. *Rehabilitation research and practice*, *2012*, 659652. https://doi.org/10.1155/2012/659652

[171] Sassani, M., Ghafari, T., Arachchige, P. R., Idrees, I., Gao, Y., Waitt, A., ... & Fernández-Espejo, D. (2025). Current and prospective roles of magnetic resonance imaging in mild traumatic brain injury. *Brain Communications*, *7*(2), fcaf120.

[172] Schiff, N. D., Giacino, J. T., Butson, C. R., Choi, E. Y., Baker, J. L., O'Sullivan, K. P., Janson, A. P., Bergin, M., Bronte-Stewart, H. M., Chua, J., DeGeorge, L., Dikmen, S., Fogarty, A., Gerber, L. M., Krel, M., Maldonado, J., Radovan, M., Shah, S. A., Su, J., Temkin, N., … Henderson, J. M. (2023). Thalamic deep brain stimulation in traumatic brain injury: a phase 1,

randomized feasibility study. *Nature medicine*, *29*(12), 3162–3174. https://doi.org/10.1038/s41591-023-02638-4

[173] Schnakers, C., Divine, J., Johnson, M. A., Lutkenhoff, E., Monti, M. M., Keil, K. M., Guthrie, J., Pouratian, N., Patterson, D., Jensen, G., Morales, V. C., Weaver, K. F., & Rosario, E. R. (2021). Longitudinal changes in blood-based biomarkers in chronic moderate to severe traumatic brain injury: preliminary findings. *Brain injury*, *35*(3), 285–291. https://doi.org/10.1080/02699052.2020.1858345

[174] Schneider, A. L. C., Huie, J. R., Boscardin, W. J., Nelson, L., Barber, J. K., Yaffe, K., Diaz-Arrastia, R., Ferguson, A. R., Kramer, J., Jain, S., Temkin, N., Yuh, E., Manley, G. T., Gardner, R. C., & TRACK-TBI Investigators (2022). Cognitive Outcome 1 Year After Mild Traumatic Brain Injury: Results From the TRACK-TBI Study. *Neurology*, *98*(12), e1248–e1261. https://doi.org/10.1212/WNL.0000000000200041

[175] Shahapure, K. R., & Nicholas, C. (2020, October). Cluster quality analysis using silhouette score. In *2020 IEEE 7th international conference on data science and advanced analytics (DSAA)* (pp. 747-748). IEEE.

[176] Shahim P, Tegner Y, Wilson DH, et al. Blood biomarkers for brain injury in concussed professional ice hockey players. *JAMA Neurol*. 2014; **71**(6): 684.

[177] Shinoda, J., & Asano, Y. (2017). Disorder of Executive Function of the Brain after Head Injury and Mild Traumatic Brain Injury - Neuroimaging and Diagnostic Criteria for Implementation of Administrative Support in Japan. *Neurologia medico-chirurgica*, *57*(5), 199–209. https://doi.org/10.2176/nmc.ra.2016-0293

[178] Sibilia, F., Custer, R. M., Irimia, A., Sepehrband, F., Toga, A. W., Cabeen, R. P., ... & Zafonte, R. (2023). Life after mild traumatic brain injury: Widespread structural brain changes

associated with psychological distress revealed with multimodal magnetic resonance imaging. *Biological psychiatry global open science*, *3*(3), 374-385.

[179] Sienski, G., Narayan, P., Bonner, J. M., Kory, N., Boland, S., Arczewska, A. A., Ralvenius, W. T., Akay, L., Lockshin, E., He, L., Milo, B., Graziosi, A., Baru, V., Lewis, C. A., Kellis, M., Sabatini, D. M., Tsai, L. H., & Lindquist, S. (2021). *APOE4* disrupts intracellular lipid homeostasis in human iPSC-derived glia. *Science translational medicine*, *13*(583), eaaz4564. https://doi.org/10.1126/scitranslmed.aaz4564

[180] Simeone, P., Auzias, G., Lefevre, J., Takerkart, S., Coulon, O., Lesimple, B., Torkomian, G., Battisti, V., Jacquens, A., Couret, D., Naccache, L., Bayen, E., Bruder, N., Perlbarg, V., Puybasset, L., & Velly, L. (2022). Long-term follow-up of neurodegenerative phenomenon in severe traumatic brain injury using MRI. *Annals of physical and rehabilitation medicine*, *65*(6), 101599. https://doi.org/10.1016/j.rehab.2021.101599

[181] Silverberg, N. D., & Panenka, W. J. (2019). Antidepressants for depression after concussion and traumatic brain injury are still best practice. *BMC psychiatry*, *19*(1), 100. https://doi.org/10.1186/s12888-019-2076-9

[182] Silverman, B. W. (1996). *Smoothed Functional Principal Component Analysis*. Journal of the Royal Statistical Society.

[183] Singh, K., Morse, A. M., Tkachenko, N., & Kothare, S. V. (2016). Sleep Disorders Associated with Traumatic Brain Injury-A Review. *Pediatric neurology*, *60*, 30–36. https://doi.org/10.1016/j.pediatrneurol.2016.02.013

[184] Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., Watkins, K. E., Toro, R., Laird, A. R., & Beckmann, C. F. (2009). Correspondence of the

brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(31), 13040–13045. https://doi.org/10.1073/pnas.0905267106

[185] Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, *44*(1), 83–98. https://doi.org/10.1016/j.neuroimage.2008.03.061

[186] Snell, D. L., Faulkner, J. W., Williman, J. A., Silverberg, N. D., Theadom, A., Surgenor, L. J., Hackney, J., & Siegert, R. J. (2023). Fear avoidance and return to work after mild traumatic brain injury. *Brain injury*, *37*(6), 541–550. https://doi.org/10.1080/02699052.2023.2180663

[187] Spadoni, A. D., Huang, M., & Simmons, A. N. (2018). Emerging Approaches to Neurocircuits in PTSD and TBI: Imaging the Interplay of Neural and Emotional Trauma. *Current topics in behavioral neurosciences*, *38*, 163–192. https://doi.org/10.1007/7854_2017_35

[188] Spitz, G., Mahmooei, B. H., Ross, P., McKenzie, D., & Ponsford, J. L. (2019). Characterizing Early and Late Return to Work after Traumatic Brain Injury. *Journal of neurotrauma*, *36*(17), 2533–2540. https://doi.org/10.1089/neu.2018.5850

[189] Stanley, I. H., Joiner, T. E., & Bryan, C. J. (2017). Mild traumatic brain injury and suicide risk among a clinical sample of deployed military personnel: Evidence for a serial mediation model of anger and depression. *Journal of psychiatric research*, *84*, 161–168. https://doi.org/10.1016/j.jpsychires.2016.10.004

[190] Stein, M. B., Jain, S., Giacino, J. T., Levin, H., Dikmen, S., Nelson, L. D., ... & TRACK-TBI Investigators. (2019). Risk of posttraumatic stress disorder and major depression in civilian

patients after mild traumatic brain injury: a TRACK-TBI study. *JAMA psychiatry*, *76*(3), 249-258.

[191] Stein, M. B., Yuh, E., Jain, S., Okonkwo, D. O., Mac Donald, C. L., Levin, H., Giacino, J. T., Dikmen, S., Vassar, M. J., Diaz-Arrastia, R., Robertson, C. S., Nelson, L. D., McCrea, M., Sun, X., Temkin, N., Taylor, S. R., Markowitz, A. J., Manley, G. T., Mukherjee, P., & TRACK-TBI Investigators (2021). Smaller Regional Brain Volumes Predict Posttraumatic Stress Disorder at 3 Months After Mild Traumatic Brain Injury. *Biological psychiatry. Cognitive neuroscience and neuroimaging*, *6*(3), 352–359. https://doi.org/10.1016/j.bpsc.2020.10.008

[192] Steinley, D. (2006). K-means clustering: a half-century synthesis. *British Journal of Mathematical and Statistical Psychology*, *59*(1), 1-34.

[193] Stevens, D. J., Alghwiri, A., Appleton, S. L., Rogers, J. M., Plummer, S. L., Grant, C., Bickley, K., Alvaro, P. K., Kennett, S., Adams, R., & Holtzhausen, L. (2022). Should We Lose Sleep Over Sleep Disturbances After Sports-Related Concussion? A Scoping Review of the Literature. *The Journal of head trauma rehabilitation*, *37*(3), E206–E219. https://doi.org/10.1097/HTR.0000000000000701

[194] Stocchetti, N., Carbonara, M., Citerio, G., Ercole, A., Skrifvars, M. B., Smielewski, P., Zoerle, T., & Menon, D. K. (2017). Severe traumatic brain injury: targeted management in the intensive care unit. *The Lancet. Neurology*, *16*(6), 452–464. https://doi.org/10.1016/S1474-4422(17)30118-7

[195] Suer, M., Abd-Elsayed, A. (2020). Patient with Traumatic Brain Injury. In: Abd-Elsayed, A. (eds) Guide to the Inpatient Pain Consult. Springer, Cham. https://doi.org/10.1007/978-3-030-40449-9_29

[196] Suss, S. J., Manelis, A., Lima Santos, J. P., Holland, C. L., Stiffler, R. S., Bitzer, H. B., Mailliard, S., Shaffer, M., Caviston, K., Collins, M. W., Phillips, M. L., Kontos, A. P., & Versace, A. (2022). Resting State Functional Connectivity between Dorsal Attentional Network and Right Inferior Frontal Gyrus in Concussed and Control Adolescents. *Journal of clinical medicine*, *11*(9), 2293. https://doi.org/10.3390/jcm11092293

[197] Sussman, E. S., Pendharkar, A. V., Ho, A. L., & Ghajar, J. (2018). Mild traumatic brain injury and concussion: terminology and classification. *Handbook of clinical neurology*, *158*, 21–24. https://doi.org/10.1016/B978-0-444-63954-7.00003-3

[198] Symons, G. F., Clough, M., Mutimer, S., Major, B. P., O'Brien, W. T., Costello, D., McDonald, S. J., Chen, Z., White, O., Mychasiuk, R., Law, M., Wright, D. K., O'Brien, T. J., Fielding, J., Kolbe, S. C., & Shultz, S. R. (2021). Cognitive ocular motor deficits and white matter damage chronically after sports-related concussion. *Brain communications*, *3*(3), fcab213. https://doi.org/10.1093/braincomms/fcab213

[199] Takada, S., Sakakima, H., Matsuyama, T., Otsuka, S., Nakanishi, K., Norimatsu, K., Itashiki, Y., Tani, A., & Kikuchi, K. (2020). Disruption of Midkine gene reduces traumatic brain injury through the modulation of neuroinflammation. *Journal of neuroinflammation*, *17*(1), 40. https://doi.org/10.1186/s12974-020-1709-8

[200] Taylor, C. A., Bell, J. M., Breiding, M. J., & Xu, L. (2017). Traumatic Brain Injury Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. *Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C.: 2002)*, *66*(9), 1–16. https://doi.org/10.15585/mmwr.ss6609a1

[201] The MathWorks Inc. (2022). MATLAB version: 9.13.0 (R2022b), Natick, Massachusetts: The MathWorks Inc. https://www.mathworks.com

[202] Trifan, G., Gattu, R., Haacke, E. M., Kou, Z., & Benson, R. R. (2017). MR imaging findings in mild traumatic brain injury with persistent neurological impairment. *Magnetic resonance imaging*, *37*, 243–251. https://doi.org/10.1016/j.mri.2016.12.009

[203] Valko, P. O., Gavrilov, Y. V., Yamamoto, M., Finn, K., Reddy, H., Haybaeck, J., Weis, S., Scammell, T. E., & Baumann, C. R. (2015). Damage to histaminergic tuberomammillary neurons and other hypothalamic neurons with traumatic brain injury. *Annals of Neurology.*, *77*(1), 177–182. https://doi.org/10.1002/ana.24298

[204] Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K, Consortium WU-MH. The WU-Minn Human Connectome Project: an overview. Neuroimage. 2013; 80:62-79. Epub 2013/05/21. doi: 10.1016/j.neuroimage.2013.05.041. PubMed PMID: 23684880; PMCID: PMC3724347.

[205] Vella, M. A., Crandall, M. L., & Patel, M. B. (2017). Acute Management of Traumatic Brain Injury. *The Surgical clinics of North America*, *97*(5), 1015–1030. https://doi.org/10.1016/j.suc.2017.06.003

[206] Visser, K., Koggel, M., Blaauw, J., van der Horn, H. J., Jacobs, B., & van der Naalt, J. (2022). Blood-based biomarkers of inflammation in mild traumatic brain injury: A systematic review. *Neuroscience and biobehavioral reviews*, *132*, 154–168. https://doi.org/10.1016/j.neubiorev.2021.11.036

[207] Walter, A., Finelli, K., Bai, X., Johnson, B., Neuberger, T., Seidenberg, P., Bream, T., Hallett, M., & Slobounov, S. (2018). Neurobiological effect of selective brain cooling after concussive injury. *Brain imaging and behavior*, *12*(3), 891–900. https://doi.org/10.1007/s11682-017-9755-2

[208] Wammes, J. D., Good, T. J., & Fernandes, M. A. (2017). Autobiographical and episodic memory deficits in mild traumatic brain injury. *Brain and cognition*, *111*, 112–126. https://doi.org/10.1016/j.bandc.2016.11.004

[209] Wang Y., Bartels H.M., Nelson L.D. A systematic review of ASL perfusion MRI in mild TBI. Neuropsychol Rev. 2020; 33:160–191.

[210] Wang, J. L., Chiou, J. M., & Müller, H. G. (2016). Functional data analysis. *Annual Review of Statistics and its application*, *3*(1), 257-295.

[211] Wang, Y., & Li, T. Q. (2015). Dimensionality of ICA in resting-state fMRI investigated by feature optimized classification of independent components with SVM. *Frontiers in human neuroscience*, *9*, 259. https://doi.org/10.3389/fnhum.2015.00259

[212] Weathers, F. W., Litz, B., Herman, D., Juska, J., & Keane, T. (1993). *PTSD Checklist—Civilian Version (PCL-C)* [Database record]. APA PsycTests. https://doi.org/10.1037/t02622-000

[213] Weiler, M., Lutkenhoff, E. S., de Campos, B. M., Casseb, R. F., Vespa, P. M., Monti, M. M., & EpiBioS4Rx Study Group (2024). Early alterations of thalami- and hippocampi-cortical functional connectivity as biomarkers of seizures after traumatic brain injury. *Neuroimage. Reports*, *4*(3), 100217. https://doi.org/10.1016/j.ynirp.2024.100217

[214] Weiner, K. S., & Zilles, K. (2016). The anatomical and functional specialization of the fusiform gyrus. *Neuropsychologia*, *83*, 48–62. https://doi.org/10.1016/j.neuropsychologia.2015.06.033

[215] Weppner, J., Linsenmeyer, M. & Ide, W. Military Blast-Related Traumatic Brain Injury. *Curr Phys Med Rehabil Rep* **7**, 323–332 (2019). https://doi.org/10.1007/s40141-019-00241-8

[216] Weymann, K. B., & Rourke, J. M. (2021). Sleep after Traumatic Brain Injury. *The Nursing clinics of North America*, *56*(2), 275–286. https://doi.org/10.1016/j.cnur.2021.02.006

[217] White, T. E., Surles-Zeigler, M. C., Ford, G. D., Gates, A. S., Davids, B., Distel, T., LaPlaca, M. C., & Ford, B. D. (2016). Bilateral gene interaction hierarchy analysis of the cell death gene response emphasizes the significance of cell cycle genes following unilateral traumatic brain injury. *BMC genomics*, *17*, 130. https://doi.org/10.1186/s12864-016-2412-0

[218] Wiles M. D. (2022). Management of traumatic brain injury: a narrative review of current evidence. *Anaesthesia*, *77 Suppl 1*, 102–112. https://doi.org/10.1111/anae.15608

[219] Williamson T, Ryser MD, Ubel PA, Abdelgadir J, Spears CA, Liu B, Komisarow J, Lemmon ME, Elsamadicy A, Lad SP. Withdrawal of Life-supporting Treatment in Severe Traumatic Brain Injury. JAMA Surg. 2020;155(8):723-31. Epub 2020/06/26. doi: 10.1001/jamasurg.2020.1790. PubMed PMID: 32584926; PMCID: PMC7301301.

[220] Wilson, L., Boase, K., Nelson, L. D., Temkin, N. R., Giacino, J. T., Markowitz, A. J., Maas, A., Menon, D. K., Teasdale, G., & Manley, G. T. (2021). A Manual for the Glasgow Outcome Scale-Extended Interview. *Journal of neurotrauma*, *38*(17), 2435–2446. https://doi.org/10.1089/neu.2020.7527

[221] *Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. NeuroImage, 2014;92:381-397 (Open Access)*

[222] Wojtowicz, M., Silverberg, N. D., Bui, E., Zafonte, R., Simon, N., & Iverson, G. L. (2017). Psychiatric Comorbidity and Psychosocial Problems Among Treatment-Seeking Veterans with a History of Mild Traumatic Brain Injury. *Focus (American Psychiatric Publishing)*, *15*(4), 384–389. https://doi.org/10.1176/appi.focus.20170028

[223] Wolfe, L. F., Sahni, A. S., & Attarian, H. (2018). Sleep disorders in traumatic brain injury. *NeuroRehabilitation*, *43*(3), 257–266. https://doi.org/10.3233/NRE-182583

[224] Wu, H., Song, Y., Yang, X., Chen, S., Ge, H., Yan, Z., Qi, W., Yuan, Q., Liang, X., Lin, X., & Chen, J. (2023). Functional and structural alterations of dorsal attention network in preclinical and early-stage Alzheimer's disease. *CNS neuroscience & therapeutics*, *29*(6), 1512–1524. https://doi.org/10.1111/cns.14092

[225] Wu, Y., Wu, H., Guo, X., Pluimer, B., & Zhao, Z. (2020). Blood–Brain Barrier Dysfunction in Mild Traumatic Brain Injury: Evidence from Preclinical Murine Models. *Frontiers in Physiology*, *11*, 1030–1030. https://doi.org/10.3389/fphys.2020.01030

[226] Yan, Z., Zhao, M., Qi, Y., Chen, A., Mou, H., Jia, X., & Wang, Y. (2025). A systematic review and coordinate-based meta-analysis of resting-state fMRI in athletes from open and closed skills sports. *Scientific reports*, *15*(1), 21870. https://doi.org/10.1038/s41598-025-07192-2

[227] Yan, J., Wang, C., & Sun, B. (2025). Global, regional, and national burdens of traumatic brain injury from 1990 to 2021. *Frontiers in public health*, *13*, 1556147. https://doi.org/10.3389/fpubh.2025.1556147

[228] Yuan, L., Wei, X., Xu, C., Jin, Y., Wang, G., Li, Y., Tian, H., & Chen, S. (2015). Use of multisequence 3.0-T MRI to detect severe traumatic brain injury and predict the outcome. *The British journal of radiology*, *88*(1052), 20150129. https://doi.org/10.1259/bjr.20150129

[229] Yue, J. K., Upadhyayula, P. S., Avalos, L. N., Deng, H., & Wang, K. K. W. (2020). The Role of Blood Biomarkers for Magnetic Resonance Imaging Diagnosis of Traumatic Brain Injury. *Medicina (Kaunas, Lithuania)*, *56*(2), 87. https://doi.org/10.3390/medicina56020087

[230] Zetterberg, H., Smith, D. H., & Blennow, K. (2013). Biomarkers of mild traumatic brain injury in cerebrospinal fluid and blood. *Nature reviews. Neurology*, *9*(4), 201–210. https://doi.org/10.1038/nrneurol.2013.9

[231] Zhang, H., Hu, Y., Yu, Y., Zhou, Z., Sun, Y., Qi, C., Yang, L., Xie, H., Zhang, J., & Zhu, H. (2025). The value of multimodal neuroimaging in the diagnosis and treatment of post-traumatic stress disorder: a narrative review. *Translational psychiatry*, *15*(1), 208. https://doi.org/10.1038/s41398-025-03416-1

[232] Zhong, H., Zhang, J., & Zhao, L. (2025). MedSAM/MedSAM2 Feature Fusion: Enhancing nnUNet for 2D TOF-MRA Brain Vessel Segmentation. *Journal of imaging*, *11*(6), 202. https://doi.org/10.3390/jimaging11060202