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Alterations to the Brain Following Traumatic Brain Injury

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Traumatic brain injuries (TBIs) have been labeled as a modern-day epidemic, increasing exponentially with the advancement of technology and society. Excluding war zones, TBIs are most likely to occur due to motor vehicle accidents, work-related injuries, assaults, and falls. In a population of 100,000 individuals, it is likely that 12 to 14 of them will endure a severe TBI every year (McDonald et al., 2018). It is estimated that over 50 million people endure a TBI each year, and half of the world's population is likely to experience at least one TBI in their lifetime. These injuries are a major cause of disability and mortality, even in developed countries with advanced medicine (Tang et al., 2020). Though the methods of treatment for brain injuries were questionable and flawed historically, the knowledge accumulated throughout time has brought modern medicine to where it is today. Gaining a better understanding of the cognitive paths, including the chemical and electrical signals of the brain, neural correlates, and possible interventions for TBI patients allows for the best possible outcome for every patient, and allows for the further advancement of care.

History of Traumatic Brain Injuries

Though the rates of TBIs have drastically increased, brain injuries themselves are not a new or unheard-of ailment. Physical evidence of TBIs has been dated back to 300,000 years ago, to the time of late hominids which walked erectly. This evidence includes skulls which have been trepanated. Skulls found in Peru, dated from 5,000 to 2,000 years ago, provide insight into these trepanations, which were made using instruments made of bronze or copper called *tumi*. it is unknown if any of the patients were anesthetized or comatose, but it is possible that anaesthetics or locally acting drugs of the time were used (Rose, 1997).

Written evidence has been found from almost 5,000 years ago, translated from Egyptian papyri (Rose, 1997). One of the most famous of these texts, named the Edwin Smith papyrus, outlines 48 different cases of medical examinations and diagnoses, of which a majority are traumatic injuries. Edwin Smith was in possession of the manuscript until his death in 1906, and the translation in English with commentary was not published until 1930. The papyrus that was obtained by Smith is thought to be a copy of a text dating around 3,000 B.C., believed to be authored by Imhotep, the High Priest of Heliopolis and the deity of medicine. Each of the 48 cases included ended with one of three prognoses, “an ailment which I will treat”, “an ailment with which I will contend” or “an ailment not to be treated”, with 13 of the cases ominously being labeled as “an ailment not to be treated” (Stiefel et al., 2006). These 13 cases reference skull fractures with neurological components, including motor skills, coordination, and reflexes, while the other injuries were simply soft tissue injuries or dislocations. These writings are the first time that the concepts of the brain, meninges and cerebrospinal fluid were included in any scientific or medical writings, and therefore these anatomical structures and fluids did not have common names. The brain was actually referred to as the “marrow of the head”, as the author compares what is being seen with what is known at the time. The treatment for these head wounds in Ancient Egypt would be the application of a piece of meat on the first day, followed by a linen cloth soaked in honey or fat. The patient would be kept in a sitting position, supported by bricks, and fed through a wooden brace only when pale and exhausted (Rose, 1997).

Head trauma has also been included in well-known historic pieces of literature. These include *The Bible* as well as the Homeric stories of the *Odyssey* and the *Iliad*, with the *Iliad* alone containing 31 fatal head injuries. Though these stories themselves contain accounts of head

injuries, early systematic and methodical descriptions of different head injuries were written by Hippocrates. All of the prognoses that were made in Hippocrates' writings were strictly based on clinical signs. He wrote about both trauma to the skull as well as trauma of the brain, and as a consequence of his writings, loss of speech was grounds for the diagnosis of a head injury for centuries. He also included descriptions of seizures contralateral to the injury, stating that convulsions seize the opposing side of the body, and therefore began the debate about contrecoup injuries (Rose, 1997). Contrecoup injuries refer to injuries which cause damage on the side of an organ opposite to the site of impact. Contrecoup injuries typically occur when a moving head strikes a stationary object, whereas a coup injury occurs when a moving object strikes a stationary head (Payne, 2021). For the management of all of the injuries Hippocrates described his recommendation for any depressed fracture was trepanation to allow for the drainage of any blood, but the trepanation was not necessary if there was a full fracture (Rose, 1997).

Some of the greatest medical minds of the Graeco-Roman period refuted Hippocrates' practices, especially the idea of contrecoup injuries. This period of time introduced the use of the words "autopsy" and "aneurysm", and it was the firm belief that the most severe brain injury was one which affected the brain-stem. Paulus Aegineta, author of the *Medical Companion in Seven Books*, was an influential physician of the Byzantine period in 7th century AD and diagnosed fractures of the skull by tapping the skull with a stick and listening for the sound of a broken pot. At this time, it was known that bleeding into the brain could occur without obvious injury to the skull, but it would not be until the Arabic period that it was known that injuries to the brain, newly coined as "concussions", could occur without obvious injuries to the skull. The physician

Albucasis wrote *Altacrif*, a collection of his medical treatments during the 10th century, and stated that symptoms of head injuries were vomiting, seizures, mental derangement, loss of speech, fainting, high fever, and protrusion and inflammation of the eyes, and that any patients with these symptoms should not be treated (Rose, 1997).

During the 12th century, Ruggiero Frugardi of Salerno recommended that rather than tapping the skull with a stick, fingers could be used to palpate the skull and detect fractures. His practices for treatment, known retrospectively as Salernitan medicine, were practiced into the early 13th century, and one of his associates, Brunus Longoburgi, discovered that penetrating injuries of the pia mater were dangerous, but those entering the ventricles were definitively fatal. Guglielmo di Saliceto, who lived during the 13th century and practiced Salernitan medicine, was able to recognize a skull fracture by stretching a thread between his pinky finger and the patient's teeth, and snapping the thread to make a sound. One of Guglielmo's colleagues, Walter of Agilon, emphasized the importance of dressing wounds with clean linens to prevent the wound from reaching the brain (Rose, 1997).

It was not until the end of the 13th century when Guido Lanfranchi described injuries which could occur to the brain without a fracture occurring to the skull. Lanfranchi’s conceptualization would not be elaborated on and included in medical literature until the 16th century by Ambroise Paré. As a French surgeon who had no formal university education, Paré published an anatomy book in 1561 describing a concussion, or *commotion du cerveau*. He also highlighted the importance of identifying contrecoup injuries, as originally described by Hippocrates. Though he recognized contrecoup injuries, he did not distinguish between skull fractures and brain injuries (Rose, 1997).

The 16th, 17th and 18th century progressions of medicine were heavily influenced by the prevalence of wars. Richard Wiseman served as a military surgeon in English, Spanish and Dutch armies during the 17th century, and published a book in 1676 based on more than 600 patients that he had treated. He not only discussed his removal of epidural hematomas, but also recommended that subdural hematomas be removed by incising the dura mater but cutting no deeper. Informed consent also began, as it was the idea that respectable surgeons would point out any dangers of operations or to the life of a patient. In 1773, Percival Pott was one of the first individuals to describe that symptoms of head injuries were not due to injury to the skull, but injury to the brain. He also noted that neurological status was what deemed the necessity of surgical intervention rather than a skull fracture, and advised against early trepanation. Pott stated that if there was not already a hole in the skull, one should not be made, as he disproved the idea that blood would become pus in extradural or subdural spaces. It was not until 1868 that the correlation between the dilation of pupils and concussions were made by Jonathon Hutchinson, when he described that the compression of the third nerve dilated the pupil (Rose, 1997). Prior to this discovery, the infamous case of Phineas Gage took place in 1848, proving that there was a connection between injuries to the brain and changes to cognitive abilities and personalities.

Though the instructions and treatments provided throughout history would be considered unconventional today, the treatments would have been the ideal practices based on the knowledge of the time. As medical advancements were made in the 1900s, the brain and brain injuries were gaining more awareness. The medical community gained a better understanding of TBIs because of the observation of injuries in soldiers, athletes and the general population. Due

to the accumulation of information that has been gathered and recorded since the times of Ancient Egypt, individuals today who sustain TBIs are met with high survival rates and advanced treatment methods.

Modern Classifications of Traumatic Brain Injuries

TBIs are classified using the Glasgow Coma Scale (GCS) to establish a prognosis. Developed in 1974 at the University of Glasgow, neurosurgery professors Graham Teasdale and Bryan Jennett revolutionized the way that a patient's acute state can be communicated to professionals in charge of their care, by creating an "effective method of describing the various states of impaired consciousness encountered in clinical practice" (Teasdale & Jennett, 1974, p.82). When first introduced in 1974, the GCS was divided into three tests, focusing on eye, verbal and motor responses. The motor responses aim to test the functioning of the central nervous system. The best possible response in this category is obeying commands. If there is no response, a painful stimulus is applied to determine if there is a localizing response, flexion response, abnormal extension or no response. In 1976, Teasdale and Jennett published an updated scale (Figure 1), distinguishing flexion responses into two separate categories, withdrawal from pain and abnormal flexion to pain (Teasdale & Jennett, 1976, p.46). The verbal response category measures verbal responses as oriented, confused conversation, inappropriate speech, incomprehensible speech, and no response. Finally, the eye response test categories are spontaneous eye opening, eyes opening to sound, eyes opening to pain, and no eye opening (Teasdale & Jennett, 1974, pp. 82-83).

These three categories in total produce a scale which ranges from the lowest score of 3 and the highest score of 14 (Teasdale & Jennett, 1974, pp. 82-83). However, differentiating between flexion responses in 1976 increased that total to 15. Classification is reported as the sum of scores, as well as individual elements, presented as GCS15=E4V5M6, with a mild TBI being GCS 13-15, moderate being GCS 9-12, and severe being GCS 3-8 (Shobhit & Iverson, 2021). From the time of its creation, there have been issues of concern regarding this form of assessment. Testing and including all of the components with accurate measurements is vital to the efficacy of the assessment, otherwise the score will be low and cause confusion. Pre-existing factors such as speech impediment, intellectual deficits and language barriers may unknowingly influence the outcome of the measurements. It is vital to understand the patient's baseline behaviors when using the GCS, as the pre-existing conditions may be the cause of a low GCS rather than an ailment due to the injury. Taking into consideration the original baseline of each patient allows for the scale to be used to its fullest capacity, as not taking into consideration these baselines could result in low scores and unnecessary treatments.

The test also has to take into consideration treatments which may be necessary for the patient in their current state, such as intubation or sedation, which would not allow for a proper examination to compute the GCS score (Shobit & Iverson, 2021). There have also been concerns regarding the effects of age, and previous research on the topic has found that when compared with younger patients with similar injury, elderly patients have significantly higher GCS scores. This information suggests that accommodations should be made by providing an alternative method for the diagnosis and prognosis of elderly patients, to ensure they are receiving the necessary treatments and the severity of their injuries are recognized (Rau et al., 2017).

At the time of its conception, the GCS was revolutionary in its classification method, allowing for comprehensible yet unambiguous information sharing for the caretakers of different patients. However, the classification being limited to mild, moderate, and severe does not truly encompass the heterogeneity of TBIs which can occur within those categories. Due to the complex nature of the brain, as well as the vast number of possible injury sites, the sub classification of TBIs even within the mild, moderate and severe categories has proven to be difficult for medical practitioners. Though the GCS is a successfully universal system to convey information to caretakers, very little advancements have been made since the time of its conception and refinement in 1974 and 1976. Determining a more refined sub-classification of TBIs would be extremely clinically useful and would also help to guide patient management and improve a patient's prognosis.

One of the most difficult aspects regarding the definition or clustering of the experience of individuals who sustain a TBI is that no two injuries are truly the same. The heterogeneous nature of neurological and behavioral outcomes makes characterizing outcomes exponentially more difficult. In an attempt to group individuals who sustained TBIs, Mark Sherer and colleagues used cluster analysis, variance ratio criterion and gap statistics to determine the optimal number of groups of individuals with TBIs differing in clinically meaningful ways that could be formed on the basis of 12 dimensions. These 12 dimensions were memory, cognitive processing speed, verbal fluency, self-reported cognitive symptoms, independence and self-esteem, resilience, emotional distress, post concussive symptoms, physical symptoms, physical functioning, economic and family support and performance validity. The optimal number of clusters determined by the statistical processes to have the smallest within-cluster variation and

largest between-cluster variation was 5. By comparing the normalized dimension scores, Sherer and colleagues were able to differentiate these clusters from one another and determine the levels of functioning and experience following a TBI for the individuals in each of the groups (Figure 2a, 2b). Groups 1 and 3 were found to have strong cognitive recovery, however group 3 held significant concern about their mental and physical wellbeing unlike group 1. Individuals in group 2 maintained substantial cognitive impairment with little concern about their functioning or symptoms, while individuals in group 4 showed high concern for their functioning and symptoms while making a moderate cognitive recovery. Group 5 individuals have the greatest cognitive impairment, and severe cognitive and emotional symptoms while reporting the lowest strengths, functioning and support levels (Sherer et al., 2017).

A 2018 study also aimed to subclassify mild TBIs (mTBIs) using a clustering approach, in an attempt to determine if their subgroups did correlate with different outcomes at 90 and 180 days post-TBI. Fifty-three clinical variables were evaluated and narrowed down into 12 variables. These variables included gender, employment status, marital status, TBI due to falling, brain CT scan result, systolic blood pressure, diastolic blood pressure, administration of IV fluids in the Emergency Department, alcohol use, tobacco use, history of neurologic disease, and history of psychiatric disease. Using these 12 different clinical variables, researchers were able to determine 5 mTBI subgroups differing at the 90 and 180 days post-TBI in varying domains including neuropsychological impairment and the persistence of TBI-related symptoms (Si et al., 2018).

Long Term Outcomes

One of the most understudied areas of TBIs is the long-term outcomes of patients past their initial treatment. It is typically anticipated that mTBI patients will recover from their injury within weeks, however a significant proportion report that they are still experiencing symptoms months and even years after their injuries occur. In 2020, Carroll and colleagues examined neurocognition, psychiatric symptoms, symptoms associated with post-concussion syndrome and quality of life using a longitudinal study. Participants were assessed at 2 weeks, 3 months, 6 months, 1 year and 2 years, being one of the first studies of its kind to report quality of life outcomes for patients outside of the typical post-acute period. Using face-to-face assessments, quality of life assessments and cognitive functioning tests, the researchers were able to use growth curve modeling to determine trends within the different testing areas. It was found that improvements were made rapidly in the first 3 months following injury for health and quality of life, as well as the first 6 months for cognitive functioning. However, improvements plateaued after their rapid improvement, and the scores of post-concussive symptoms and Glasgow Outcome Scores Extended tests fell below the trauma control norms at every recorded time point. Cognitive problems, like slowed thinking and poor concentration, were reported by no less than one-fifth of the participants at any given time. 2 years after patients sustained their injuries, approximately one third of the study population was still reporting post concussive symptoms, including headaches, fatigue, or sleep disturbances (Figure 3). Also 2 years post-injury, mental-health related symptoms were above the national averages, with 16% reporting depression, 9% post-traumatic stress disorder, and 35% harmful drinking habits (Figure 4) (Carroll et al., 2020). The implications of this study point toward the necessity for further research in the post-acute period for injuries, extending past the typical 2-week check-up.

Injuries and Imaging

The injuries associated with TBIs occur in two phases. Primary injuries, resulting directly from the damage at the site of injury include tissue damage, subarachnoid hemorrhage, epidural hematoma, subdural hematoma, and contusion. Secondary injuries interact with the primary injuries, with manifestations like inflammation, ischemia, excitotoxicity and energy failure (Shaito et al., 2020).

Following the primary injury, white matter injuries are of major concern, as the acceleration-deceleration forces that are experienced lead to white matter fibers being stretched, compressed and rotated, causing the axons to swell and resulting in damage in white matter tracts and shearing at the white-grey matter junction (McDonald et al., 2018). These injuries to white matter connections are better known as diffuse axonal injury (DAI), and these would be considered secondary brain injuries. It has previously been suggested that DAI may be one of the major components of cognitive impairments after a TBI (Raizman et al., 2020).

In order to identify DAI, diffusion tensor imaging (DTI) is used to detect microstructural changes to brain tissue as compared to more conventional neuroimaging techniques such as structural magnetic resonance imagining (MRI). DTI quantifies the diffusion of water molecules of the brain using a calculation of a diffusion model, also called a tensor. The diffusion in the brain is due to tissue heterogeneity in cellular membranes, with contribution from myelination and the packing of the axons to determine tissue orientation. Images of these tissues are created using MRI and sending pulses which cause phase shifts for molecules which have the ability to diffuse. The image will then have dark areas in which the white matter fiber tracts are parallel to

the gradient direction (Figure 5). The information gathered from these images is condensed into eigenvalues, or the values of diffusion for specified vectors. A measurement known as the mean diffusivity (MD) is calculated as the average of the diffusion tensor's eigenvalues. Fractional anisotropy (FA) is the normalized variance of the diffusion tensor's eigenvalues and measures white matter integrity in a range of values from 0 to 1. (O'Donnell & Westin, 2011).

Following mild TBI, it is likely to find lower FA and higher MD in regions including the corpus callosum, superior longitudinal fasciculus, corticospinal tract and sagittal stratum (Wallace et al., 2020). Reductions in FA are associated with decline in cognitive functions including memory, attention and executive functioning following a TBI. Low FA and high MD are associated with white matter damage, and the differences in FA and MD relative to the controls are smaller in mild TBI when compared to moderate to severe TBI (Kang et al., 2021).

Functional neuroimaging is also used to investigate neural correlates associated with cognitive dysfunction following TBI. For example, arterial spin-labeled (ASL) perfusion functional MRI (fMRI) can be used to quantify cerebral blood flow (CBF). Studies completed in the past have concluded that TBIs alter baseline cerebrovascular parameters, including CBF (Kim et al., 2012). Though the exact mechanisms responsible for the alterations are unknown, the cerebral glucose utilization increases, and the local CBF decreases. This decrease of CBF can restrict the flow of substrates like oxygen and glucose to the brain (Golding, 2002).

Dr. Junghoon Kim and colleagues (Kim et al., 2012) hypothesized that hypoperfused areas during resting state would display alterations in task evoked CBF changes. Their study including two tasks with the first being a visual sustained-attention task, used to examine the neural network that is involved with the maintenance of visual sustained attention. The second

task was a two-back task used to examine the neural network involved in continuous performance of a working-memory task. In both tasks, participants with TBI showed worse behavioral performance than the controls. The data supported the hypothesis that resting hypoperfusion may be associated with task-evoked CBF alterations in the same region, as the sensory areas with the changes during the two-back test were hypoperfused even during the resting state. However, not all of the areas that were hypoperfused showed task-induced activation, indicating that severe alterations may be in the visual and auditory sensory cortices. These findings indicate that attentional modulation deficits may contribute to higher cognitive dysfunction in TBI. They also found that there was not a significant relationship between TBI patients' accuracy and activation in the left parietal cortices, which indicates that there was more individual variation in the neural networks which support task performance. The control group did have a significant relationship between the accuracy and left parietal cortices, which is known to support task performance.

Hub Genes and Neural Correlates

Though it is known that the injuries associated with TBI are influenced by the primary and secondary injuries, there are no standardized treatment procedures, as each TBI and its outcomes are heterogeneous in nature. A study completed by the National Natural Science Foundation of China in 2020 (Tang et al., 2020) aimed to identify molecular mechanisms which are associated with the secondary brain injury following a TBI to gain a better understanding about the cellular processes involved with secondary neural damage. The research goal was to determine potential therapeutic strategies by investigating hub genes and pathways that are associated with the neurological deficits in early stages of TBI. Hub genes are genes which have

a large amount of connectivity with other genes, and the pathways are the ways in which information is communicated from one area of the neural system to another.

As the first study of its kind, the authors determined that there are 10 different hub genes, which they identified as TBI-associated. Fibronectin1 (Fn1), cellular myelocytomatosis oncogene (c-Myc) and protein tyrosine phosphatase receptor type C (Ptprc) are 3 of the 10 genes identified and may provide novel biomarkers or therapeutic targets for the treatment of TBI (Tang el at., 2020). Fn1 is a multi-functional glycoprotein which has been indicated to play a role in wound healing. The expression of this gene creates two types of Fn1 proteins, soluble and insoluble. Soluble Fn1 functions in the extracellular matrix binding to the surface of cells and is involved in blood clotting and wound healing. Insoluble Fn1contributes of the creation of fibers and the extracellular matrix, assisting with the migration and expansion of cells (“Fn1 gene”, 2020). Mitochondrial injuries following a TBI leads to oxidative stress and later apoptosis. The gene c-Myc is responsible for cell cycle progression and apoptosis (Hiebert, 2015). Ptprc is downregulated in Parkinson’s and palsy disorders and is an essential regulator of T-cells.

Treatments and Recovery

Though approximately ninety percent of TBIs that occur are ultimately labeled as mild, the effects that these injuries can have on the quality of life, as well as the trajectory of recovery for patient outcomes are of concern. Growth curve models are statistical figures which can be used to demonstrate the longitudinal changes of data. Latent growth curve models specifically use repeated measures to estimate trajectories, and allow for baseline, inter-individual differences within the baseline, rate of change and rate of change over time. The latent growth curve models produced by Carroll and colleagues paints a rather troubling recovery picture,

contradictory to the notion that recovery can be quick and relatively easy. Problems common after TBI, such as issues with emotional well-being, cognition, and symptoms like headaches and sleep disturbance, are often long-standing (Carroll et al., 2020). For example, a meta-analytical study found that individuals who sustain a TBI are three times more likely to experience depression than those who do not experience TBI (Hellewell et al., 2020). Early interventions and therapies for individuals are vital to the best possible outcome that one may have. These therapies can include physical, occupational, speech or cognitive therapies, being considered as either internal or external interventions. A 2021 meta-analytical study focusing on the effectiveness of memory remediation strategies (Lambez & Vakil, 2021) found that a combination of both internal and external interventions was the most effective for the reduction of memory impairments. The study hypothesized that external strategies are the most efficient in clinical approaches because they are more convenient and easier to implement than internal strategies. When all interventions were considered in the study, the effect size for positive change following intervention was the larger for moderate to severe TBI when compared to that of mild to moderate TBI, possibly due to a lower baseline functioning level (Lambez & Vakil, 2021).

TBIs are a physical health issue, and as with all other physical health, it is important to have healthy lifestyle factors to positively impact the healing process. A study completed in 2020 (Shaito et al., 2020) concluded that the modern western diet can actually negatively impact the recovery process of TBI patients, identifying key mechanisms which can reduce the responses to treatments, as well as preclude recovery. Toll-Like Receptor 4 (TLR-4) is a receptor expressed on brain microglia which binds to saturated fatty acid (Shaito et al., 2020). TLR-4 stimulates the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which is a

nuclear transcription factor which regulates pro-inflammatory genes which are involved in TBI reactions. TLR-4 contributes to the aggravation of neuroinflammation during the secondary injury phase of TBI, which mediates neurobehavioral deficits such as cognitive deficits, personality changes and psychiatric illnesses. The aggravation caused by TLR-4 due to the overaction of microglia causes irreversible neuronal damage and contributes to the development of secondary injuries. Therefore, when TLR-4 levels are reduced, TBI-induced neuroinflammation was reduced. Pharmacological interventions which inhibit TLR-4 signaling have been hypothesized to improve long term outcomes and reduce brain edema (Trotta et al., 2014).

Also of importance, the brain-derived neurotrophic factor (BDNF) supports the survival of neurons through synaptic plasticity. Expressed in the hippocampus, hypothalamus, and cerebral cortex, BDNF plays a role in the survival maintenance and growth of neurons. BDNF affects the formation and maintenance of presynaptic structures, facilitates neurotransmitter release and affects axonal growth through its phosphorylation of Synapsin 1. BDNF also phosphorylates cAMP response element binding protein (CREB) to play a role in gene expression and long-term memory (Beliharz et al., 2015). It was found that BDNF, Synapsin 1 and CREB response element-binding proteins were suppressed due to TBI-induced oxidative stress. This oxidative stress is aggravated by the western diet, as it produces an excessive accumulation of oxidized phospholipids. The implication of this accumulation is that these alterations contribute to impaired synaptic plasticity and cognitive functioning, due to the reduction of the expression of BDNF, and therefore the downstream suppression of Synapsin 1 and CREB. Though the implications of the western diet are still relatively unstudied, decreasing

the amounts of fat in the diets of TBI individuals may positively impact recovery times and the responses to treatments (Shaito et al., 2020).

Advancements have been made on the knowledge and treatments of TBIs for centuries, but just recently we have gained a better understanding of the brain and the lasting impacts which an injury can have on its functions. By revising and reassessing the ways in which TBIs are categorized and described the prognosis for recovery paints a more realistic view for each individual patient case. Ensuring that healthcare professionals are able to communicate with one another the level of severity of the injuries, the patient is more likely to receive all of the necessary care for a successful and timely recovery. The symptoms and impairments that may occur post-injury can be monitored and treated for individuals to lead their most successful and fulfilling life. From a healthcare perspective, gaining the knowledge of the neural correlates and neural network hubs which affect or are affected by injuries allows for the advancement of treatments and therapy methods which can promote better mental and physical recovery in the future. Though there are long-term implications for individuals who sustain a TBI, there is hope for recovery and healing, especially with interventions early post-injury.

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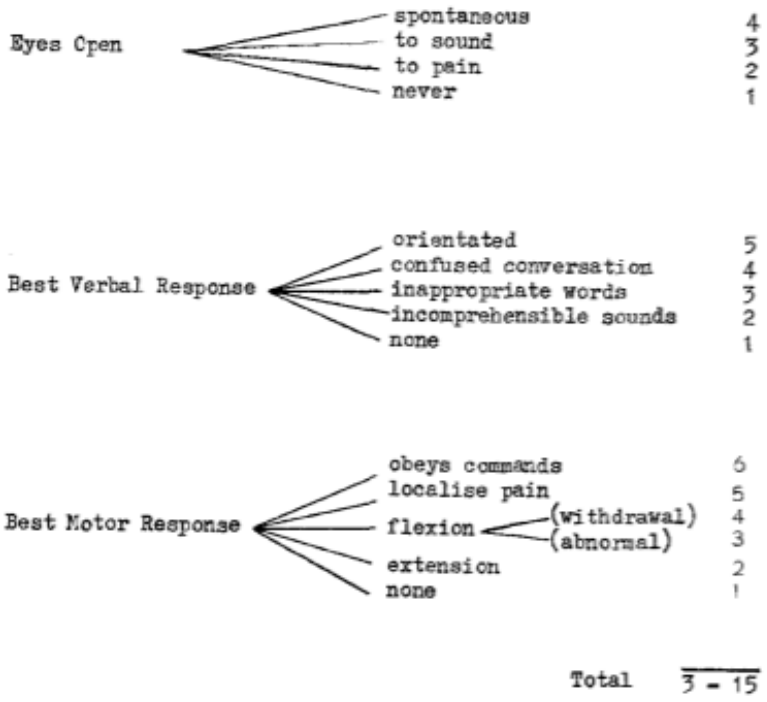
Appendix

Figure 1.

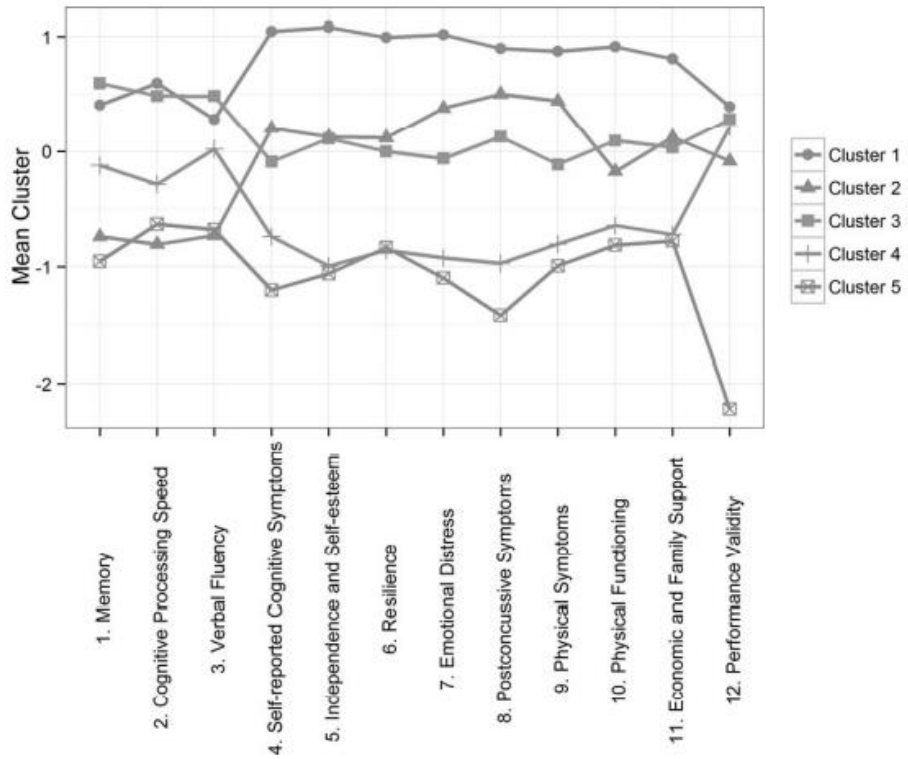
Glasgow Coma Scale Updated 1976



Note. Adapted from "Assessment and prognosis of coma after head injury," by G. Teasdale & B. Jennett, 1976, *Acta Neurochirurgica*, 34, p. 46. Copyright 1976 by Springer-Verlag.

Figure 2a.

Mean Profiles for 5 Groups of Persons with TBI Based on 12 Dimensions



Note. Adapted from "Groupings of persons with traumatic brain injury: a new approach to classifying traumatic brain injury in the post-acute period," by M. Sherer, T.G. Nick, A.M. Sander, M. Melguizo, R. Hanks, T.A. Novack, D. Tulsky, P. Kisala, C. Luo, & X. Tang, 2017, *Journal of Head Trauma Rehabilitation*, 32, p. 128. Copyright 2017 by Wolters Kluwer Health, Inc.

Figure 2b.

Comparison of the 5 Cluster Groups

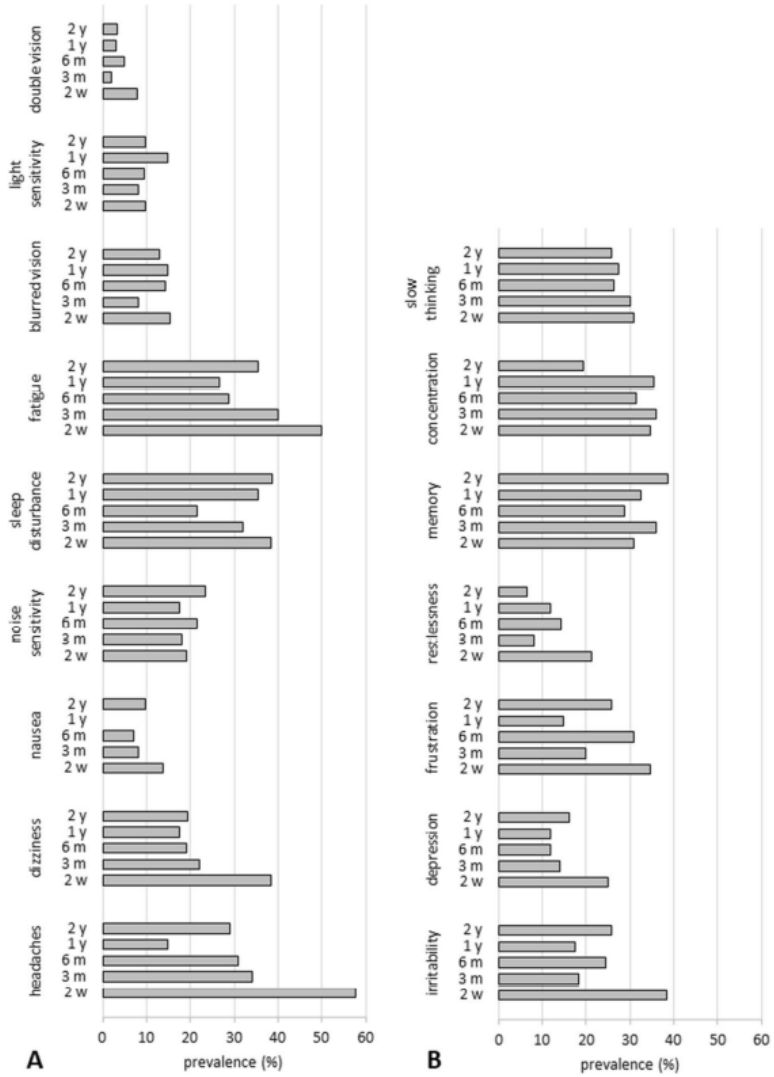
	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Memory[a]					
Mean (95% CI)	0.41 (0.26-0.56)	−0.74 (−0.91 to −0.57)	0.60 (0.47-0.73)	−0.12 (−0.28 to 0.04)	−0.95 (−1.25 to −0.66)
Pairwise Differences[b]	2, 4, 5	1, 3, 4	2, 4, 5	1, 2, 3, 5	1, 3, 4
Cognitive Processing Speed					
Mean (95% CI)	0.60 (0.45-0.75)	−0.81 (−0.97 to −0.64)	0.49 (0.36-0.62)	−0.29 (−0.44 to −0.13)	−0.63 (−0.91 to −0.36)
Pairwise Differences	2, 4, 5	1, 3, 4	2, 4, 5	1, 2, 3	1, 3
Verbal Fluency					
Mean (95% CI)	0.28 (0.13-0.44)	−0.73 (−0.90 to −0.56)	0.49 (0.35-0.63)	0.02 (−0.15 to 0.19)	−0.68 (−1.02 to −0.33)
Pairwise Differences	2, 5	1, 3, 4	2, 4, 5	2, 3, 4	1, 3, 4
Self-reported Cognitive Symptoms					
Mean (95% CI)	1.05 (0.91-1.18)	0.20 (0.04-0.37)	−0.09 (−0.19 to 0.01)	−0.74 (−0.85 to −0.62)	−1.20 (−1.39 to −1.02)
Pairwise Differences	2, 3, 4, 5	1, 3, 4, 5	1, 2, 4, 5	1, 2, 3, 5	1, 2, 3, 4
Independence and Self-esteem					
Mean (95% CI)	1.08 (0.99-1.17)	0.13 (−0.02 to 0.27)	0.11 (0.010.21)	−0.99 (−1.11 to −0.88)	−1.06 (−1.30 to −0.82)
Pairwise Differences	2, 3, 4, 5	1, 4, 5	1, 4, 5	1, 2, 3	1, 2, 3
Resilience					
Mean (95% CI)	0.99 (0.88-1.11)	0,12 (−0.06 to 0.30)	0.00 (−0.11 to 0.11)	−0.86 (−1.00 to −0.72)	−0.83 (−1.07 to −0.60)
Pairwise Differences	2, 3, 4, 5	1, 4, 5	1, 4, 5	1, 2, 3	1, 2, 3
Emotional Distress					
Mean (95% CI)	1.02 (0.91-1.13)	0.38 (0.25-0.52)	−0.06 (−0.15 to 0.03)	−0.92 (−1.05 to −0.79)	−1.10 (−1.34 to −0.86)
Pairwise Differences	2, 3, 4, 5	1, 3, 4, 5	1, 2, 4, 5	1, 2, 3	1, 2, 3
Postconcussive Symptoms					
Mean (95% CI)	0.90 (0.84-0.96)	0.50 (0.41-0.60)	0.13 (0.03-0.22)	−0.97 (−1.12 to −0.83)	−1.42 (−1.70 to −1.15)
Pairwise Differences	2, 3, 4, 5	1, 3, 4, 5	1, 2, 4, 5	1, 2, 3, 5	1, 2, 3, 4
Physical Symptoms					
Mean (95% CI)	0.88 (0.77, 0.98)	0.44 (0.28, 0.61)	−0.12 (−0.25, 0.02)	−0.80 (−0.94, −0.66)	−0.99 (−1.23, −.076)
Pairwise Differences	2, 3, 4, 5	1, 3, 4, 5	1, 2, 4, 5	1, 2, 3	1, 2, 3
Physical Functioning					
Mean (95% CI)	0.91 (0.79-1.04)	−0.18 (−0.37 to 0.02)	0.09 (−0.06 to 0.24)	−0.64 (−0.78 to −0.51)	−0.81 (−1.04 to −0.58)
Pairwise Differences	2, 3, 4, 5	1, 4, 5	1, 4, 5	1, 2, 3	1, 2, 3
Economic and Family Support					
Mean (95% CI)	0.81 (0.64, 0.98)	0.12 (−0.04, 0.28)	0.03 (−0.10, 0.16)	−0.72 (−0.86, −0.58)	−0.78 (−1.01, −0.54)
Pairwise Differences	2, 3, 4, 5	1, 4, 5	1, 4, 5	1, 2, 3	1, 2, 3
Performance Validity					
Mean (95% CI)	0.39 (0.30-0.49)	−0.09 (−0.26 to 0.09)	0.29 (0.17-0.40)	0.21 (0.11-0.32)	−2.21 (−2.53 to −1.90)
Pairwise Differences	2, 5	1, 3, 4, 5	2, 5	2, 5	1, 2, 3, 4
PART-O					
Mean (95% CI)	2.24 (2.14-2.34)	1.65 (1.53-1.78)	2.09 (1.99-2.19)	1.62 (1.50-1.73)	1.42 (1.27-1.56)
Pairwise Differences	2, 4, 5	1, 3	2, 4, 5	1, 3	1, 3

Abbreviations: CI, confidence interval; PART-O, Participation Assessment with Recombined Tools–Objective.
[a] Analysis of variance indicated that there were overall significance differences among the 5 clusters for all 12 dimension scores and for the PART-O scale. All *P*s < .001.
[b] Pairwise differences were examined using Tukey post hoc tests. Numbers for each cluster for each score indicate groups that were significantly different from group in this column. So, for example, the numbers 2, 4, and 5 in the Memory dimension row for the Cluster 1 column indicate that cluster 1 differed from clusters 2, 4, and 5 on the Memory dimension score. Dimensions scores are *z*-scores, whereas the PART-O scale score is the average raw score across items.

Note. Adapted from "Groupings of persons with traumatic brain injury: a new approach to classifying traumatic brain injury in the post-acute period," by M. Sherer, T.G. Nick, A.M. Sander, M. Melguizo, R. Hanks, T.A. Novack, D. Tulsky, P. Kisala, C. Luo, & X. Tang, 2017, *Journal of Head Trauma Rehabilitation*, 32, p. 131. Copyright 2017 by Wolters Kluwer Health, Inc.

Figure 3.

Incidence of Post-Concussion Symptoms for Patients With mTBI



Note. Adapted from "Mild traumatic brain injury recovery: A growth curve modelling analysis over 2 years," by E.L. Carroll, J.G. Outtrim, F. Forsyth, A.E. Manktelow, P. J. A. Hutchinson, O. Tenovuo, J. P. Posti, L.Wilson, B. J. Sahakian, D.K. Menon & V. F. J. Newcombe, 2020, *Journal of Neurology*, 267, p. 3228. Copyright 2020 by the authors of the article.

Figure 4.

Incidence of Health Conditions of Patients With mTBI

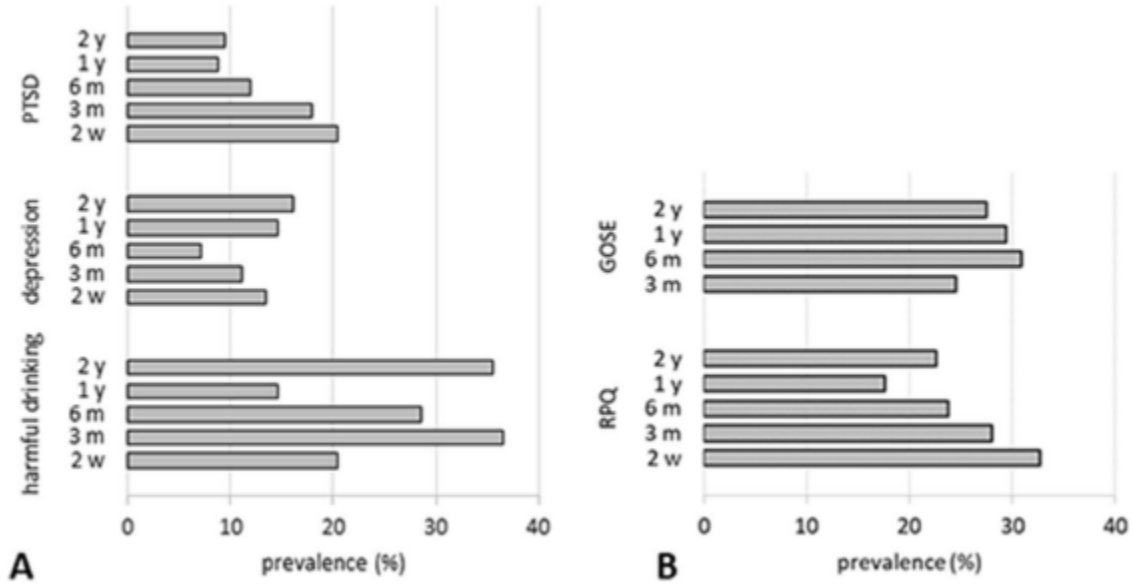


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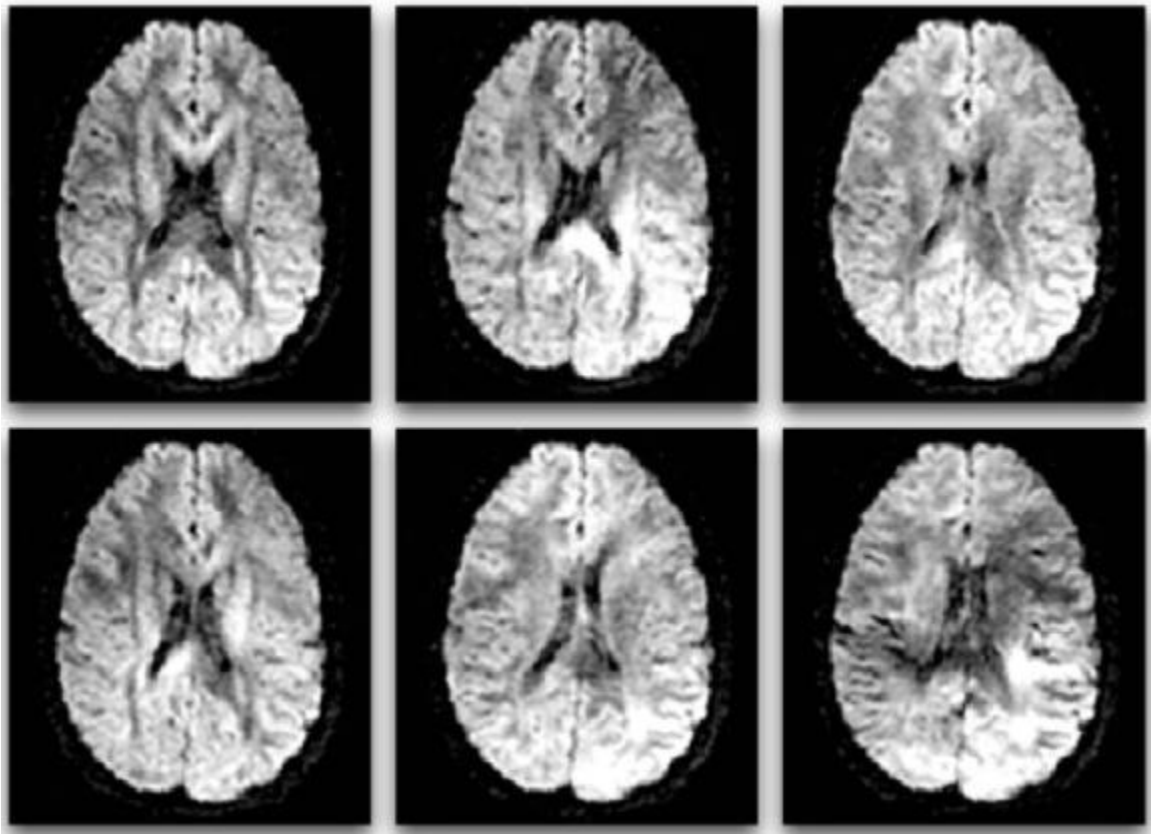
Figure 5

Six Diffusion-Weighted Images



Note. Adapted from "An introduction to diffusion tensor image analysis," by L.J. O'Donnell & C.F. Westin, 2011, *Neurosurgery Clinics of North America*, 22. Copyright 2011 by Elsevier Inc.