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PERSONALITY CHANGES IN TRAUMATIC BRAIN INJURY PATIENTS

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Abstract

Traumatic brain injury (TBI) is a major contemporary healthcare problem, and many TBI survivors suffer lifelong disability due to somatic, cognitive, or neurobehavioral sequelae. In this narrative review, we aimed to present a synopsis of the current understanding of TBI and its accompanying personality changes. This topic has been a scientific challenge ever since Phineas Gage fascinated the world with his bizarre frontal lobe injury. Evidence of correlation with neurobehavioral sequelae was found in the damage of prefrontal anatomical circuitry. Functional relationships have been defined: the dorsolateral prefrontal circuit mediates executive functions, the anterior cingulate circuit is involved with motivational mechanisms, and the orbitofrontal circuit is dedicated to emotional and behavioral regulation. The frontopolar area has been isolated as responsible for integrative/meta-cognitive functions. Damage to distinct parts of the prefrontal cortex and said circuitry elicits personality changes encompassed by three syndromes: abulic, dysexecutive, and behavioral. There is still no consensus on the treatment of personality changes following TBI. The approach of grouping some behavioral symptoms into metaphorical syndromes and treating them as such (e.g., depression-like syndrome, irritable mania-like syndrome) has proven useful. Another method is targeted pharmacological treatment of defined prefrontal areas with malfunction after TBI. Deep brain stimulation proved to be a promising new method that allows precise stimulation of deep brain nuclei and the reactivation of prefrontal circuitry. The environmental impact on the rehabilitation process in TBI patients should never be underestimated. The case of Phineas Gage also intrigued the medical world due to the potential recovery of his profound personality changes. The brain's frontal lobe is one of its most naturally plastic and integrated regions. Further focus on understanding its malleability could show great hope for the rehabilitation of TBI survivors and allow them to find their way back to who they used to be.

KEYWORDS: frontal lobe, neuronal plasticity, personality disorders, traumatic brain injuries

INTRODUCTION – THE STORY OF PHINEAS GAGE

Personality changes in traumatic brain injury (TBI) have fascinated the scientific community for more than 150 years – ever since neuroscience's most famous patient, Phineas Gage. His bizarre case study has widely influenced both the scientific and the general population's perception of the human brain. The tragic accident that occurred not only changed his life but also the whole neuroscientific view on the importance and functions of the prefrontal cortex.[1,2]

The incident occurred on September 13th, 1848, during the construction works of the train railway in which controlled blasting was used. Phineas Gage was a foreman of the group and was tamping the powder inside the hole. His attention wandered for a moment, in which a fuse was somehow lit, and the blast propelled a 109 cm long and 3 cm thick iron rod through his skull.[1,2] He was momentarily stunned but later claimed he did not lose consciousness. His friends carried him to a carriage, where he managed to sit upright the entire journey to the town. Later, he even climbed the stairs with little help. The doctor who took charge of his case that day was John Harlow, who later reported the case.[2] He cleared the wound the best he could, removed the impacted bony fragments, and bandaged the wound. In the following weeks, Gage was alternating between being relatively stable or comatose and on the verge of death. Six days after the incident, a severe fungal infection had started developing. During this time, he completely lost vision in his left eye. The inflammation of the brain tissue and the following infections undoubtedly caused even greater damage. Months later, he miraculously fully recovered with very few physical impairments, considering the scope of the injury. His speech, movement, memory, and intelligence all appeared to be the same as before the accident. What lay underneath was a profound change in his behavior, which Dr. Harlow described as a destroyed balance between his intellectual faculties and animal propensities.[2] Previously, he was socially well-adjusted, respectful, intelligent, responsible, and a favorite among his peers, but now his respect for social conventions vanished – he became disrespectful, irresponsible, unsteady, indulged in profanities, couldn't follow any devised plan through, did not listen to advice or abide by any restraint that conflicted with his desires. His friends and family described him as "no longer Gage".[2] He was laid off from his previous workplace and started living a reckless life while exhibiting his injury and the tamping iron that caused it

among many shows in the USA. After some time, he moved to Chile, where he worked for seven years as a carriage driver on challenging routes, which raised questions (stirred rumors) about his partial recovery.[2,3] Modern research indicates that he could not have lived independently and held such a highly skilled job without at least partially recovering the frontal lobe functions.[3] After Chile, Phineas Gage returned to live with his family in the USA, where he worked as a farm worker, and on May 21, 1860, he died after an epileptic seizure. He was buried alongside his tamping iron, but no autopsy was performed. Later, Dr. Harlow traced him and got permission from his family to exhume his remains and keep his skull as a medical specimen. Nowadays, the skull and the tamping iron that caused the injury are exhibited in the Warren Anatomical Medical Museum at Harvard University[1,2] (Figure 1).

Harlow wrote follow-up reports and implied that a part of the human brain is responsible for decision-making, rational thinking, and the planning and execution of socially appropriate behaviors. It should have made an impact comparable to the observations Broca (the neural basis for language) and Wernicke (the neural basis for movement) made on their patients, but he was largely ignored.[1,4,5] The academic atmosphere at that time considered Broca's and Wernicke's findings more acceptable because their patients underwent autopsy, which Harlow did not have to help validate his case. Some critics even concluded that the injured part of the frontal lobe had no special function because Gage could pass any neurological test of that time – his speech, intelligence, movement, and memory were all preserved. A rare outlier was psychologist David Ferrier, who, in 1878, described the consequences of Gage's injury to the left prefrontal cortex as mental degradation.[1] Phineas Gage's case study suggested a terrifying notion that people who suffered damage to the frontal lobes lose something fundamentally human inside them.

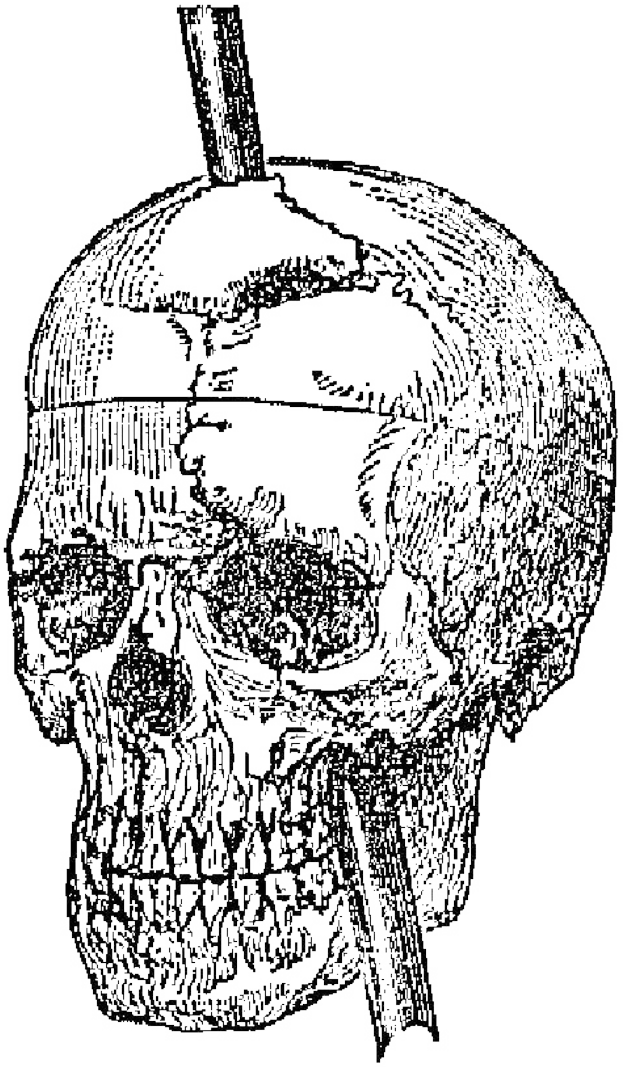


Figure 1. Dr. John Harlow's reconstruction of Phineas Gage's skull injury.
Source: image "Recovery from the passage of an iron bar through the head" by John Martyn Harlow (original) - from Wikimedia Commons, public domain. Published 1868 (original) and July 2015 (derivative). Accessed 14th February 2024.

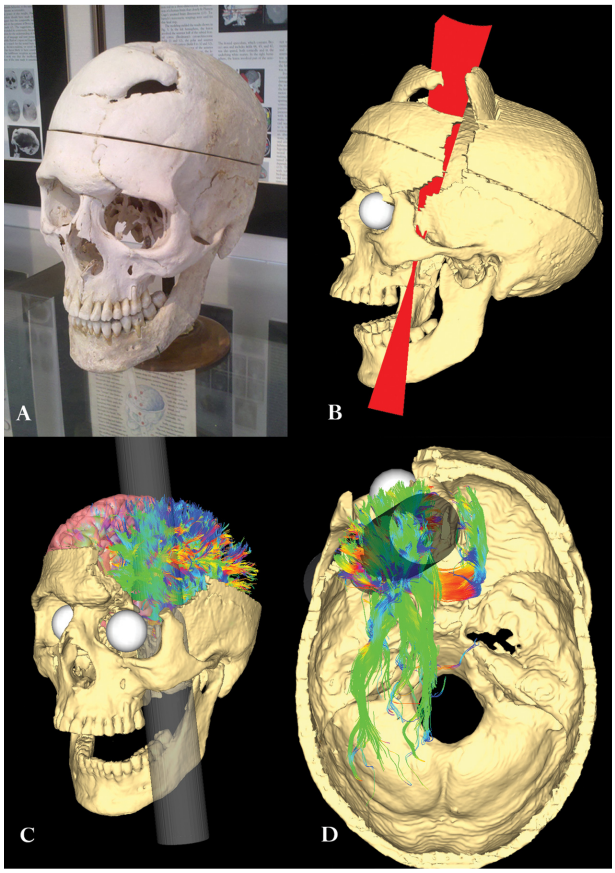


Figure 2. Modeling the path of the tamping iron through the Gage skull and its effects on white matter structure.

Source: image "Simulated Connectivity Damage of Phineas Gage" by Van Horn JD et al. (original) – from Wikimedia Commons, CC 2.5 license. Published May 16th, 2012. Accessed 14th March 2024.

In 1993, a team of scientists led by Hanna and Antonio Damasio tried to, with the help of computer technology, reconstruct the exact injury suffered by Phineas Gage and which part of his brain was damaged. They confirmed that the injured area was primarily restricted to the ventromedial parts of the prefrontal cortex, while the dorsolateral part was spared (Figure 2). A similar neuroanatomical injury pattern to Phineas Gage was found in 12 patients.[1] These modern Gage-like patients had a compromised ability to make rational decisions and abide by social conventions. The same patients retained their memory and the ability to understand the logic of abstract problems or perform mathematical calculations. The hypothesis was made that emotional processing was involved through the ventromedial frontal region in socially accepted decision-making. The ventromedial area of the prefrontal cortex has a reciprocal pathway to the subcortical nuclei (amygdala and hypothalamus) involved in elemental biological regulation of social conduct, cognition, emotional processing, etc. The ventromedial area also showed an elevated number of serotonin 2 receptors in socially well-adjusted monkeys, while on the contrary, it appeared low in hostile and socially unadjusted ones. Structures in the dorsolateral region were involved in cognition concerning extra-personal space, objects, language, and arithmetic. The intactness of this region in Gage-like patients allowed them to perform normally in traditional neuropsychological exams.[1]

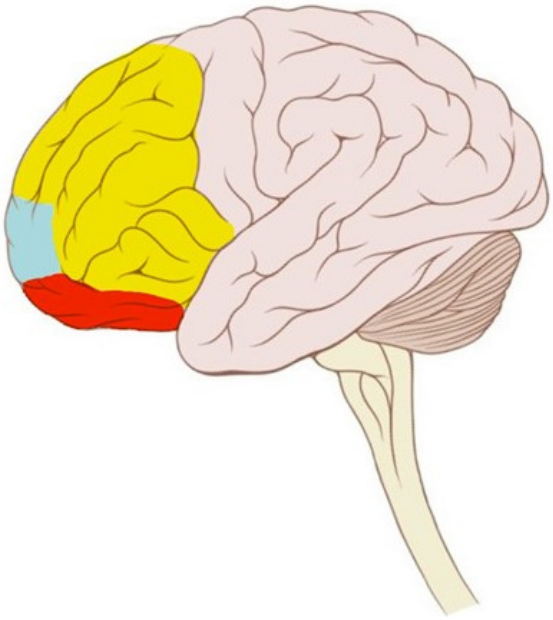


Figure 3. Lateral view of anatomical-functional prefrontal regions. Yellow – dorsolateral region; blue – frontopolar region; red – orbitofrontal region.

Source: original image "Brain human lateral view" by Patrick J. Lynch from Wikimedia Commons, Creative Commons 2.5, adapted according to Yasin S, Brain Sci. 2022;12(8):1103., 2022. Published 23rd December 2006. Accessed 14th March 2024.

THE ROLE OF THE FRONTAL LOBE IN PERSONALITY CHANGES

Human personality is greatly defined by what happens in the frontal lobe, which is particularly prone to TBI.[6,7] During recent decades, there has been a focus on determining neuroanatomical connections to different frontal lobe functions. What resulted from those studies was the framework of frontal lobe functional regions fractionated according to their respective functions. The results helped understand the pathophysiology of TBI's neurobehavioral sequelae in patients. Four anatomical-functional relationships have been identified: dorsomedial for energization, lateral frontal for executive functions (left dorsolateral for planning/task setting and right dorsolateral for monitoring), ventromedial/orbitofrontal for emotional and behavioral regulation, and frontopolar/BA10 for integrative/meta-cognitive functions[8] (Figures 3-4)[12]. Dorsomedial, lateral frontal, and ventromedial act per reported frontal-subcortical anatomical circuitry, which will be discussed. This division implies that several domain-general processes are independently laid out over different frontal regions that participate in the functioning of the neuronal circuits that connect the brain's frontal, subcortical, and even posterior parts.[8]

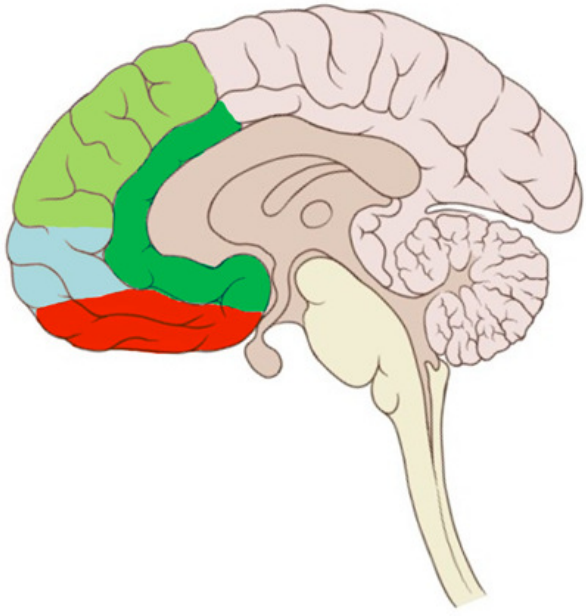


Figure 4. Medial view of anatomical-functional prefrontal regions. Green – ventromedial region (darker green furtherly specifies anterior cingulate cortex); blue – frontopolar region; red – orbitofrontal region.

Source: original image "Brain human sagittal section" by Patrick J. Lynch from Wikimedia Commons, Creative Commons 2.5, adapted according to Yasin S, Brain Sci. 2022;12(8):1103., 2022. Published 23rd December 2006. Accessed 14th March 2024.

Five significant frontal-subcortical circuits have been singled out. Three regulate different parts of non-motor behavior, while the other two originate in the supplementary motor area (SMA) and the oculomotor regulating frontal eye fields (BA8).[7,9] All five circuits start in the prefrontal cortex, project to the striatum, then link to the globus pallidus and substantia nigra, and from there connect to the thalamus with the last connection "closing the loop" back to the prefrontal cortex.

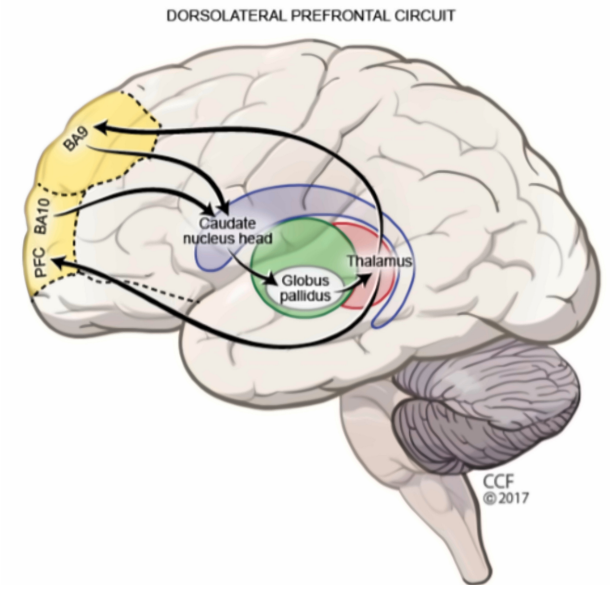


Figure 5. Dorsolateral circuit.

Source: adopted from L. Ghazi Saidi, 2020, Acta scientific neurology, 3, no. 4, p. 13, DOI:10.31080/ASNE.2020.03.0172, © 2020 Ghazi Saidi

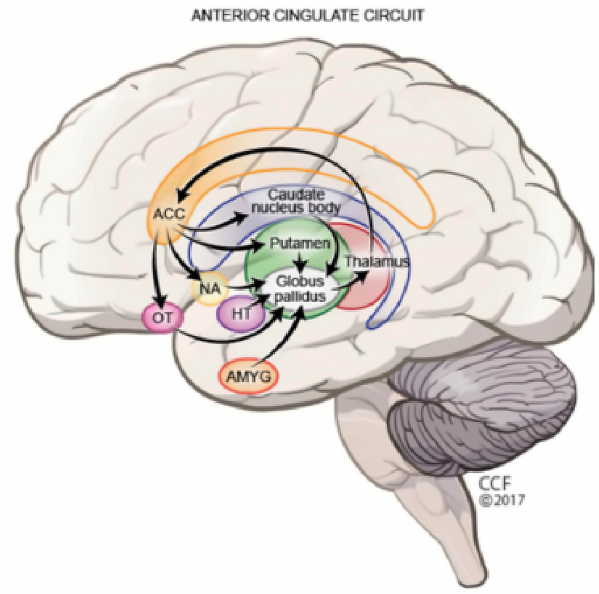


Figure 6. Anterior cingulate circuit.

Source: adopted from L. Ghazi Saidi, 2020, Acta scientific neurology, 3, no. 4, p. 13, DOI:10.31080/ASNE.2020.03.0172, © 2020 Ghazi Saidi

They also possess "open loop" efferent and afferent links to other cortical and subcortical formations. Furthermore, their names are based on their originating area in the cortex. The primary focus will be on the three circuits dedicated to non-motor behavior: executive control, social conduct, and the state of motivation. Those are the dorsolateral circuit that regulates executive control (Figure 5), the anterior cingulate circuit (originating in BA24) that regulates motivation (Figure 6), and the orbitofrontal circuit divided into lateral and medial parts (Figure 7). The medial part integrates visceral-amygdalar functions with the organism's internal state, while the lateral part integrates limbic and emotional information into contextually appropriate behavior.[10] The limbic system has links with both the anterior cingulate and the medial parts of the orbitofrontal circuit. The anterior cingulate circuit facilitates the deliberate choice of external stimuli according to their internal importance, while the medial orbitofrontal circuit regulates the data regarding only the internal environment and exhibits the highest relation with the amygdala.[9] Damage to distinct parts of the frontal cortex framework and their corresponding circuits elicits different sequelae.[11]

SYNDROMES OF DAMAGED NEUROANATOMICAL CIRCUITRY

TBI injuries to the frontal lobe have been divided into three syndromes: abulic, dysexecutive, and behavioral.[11]

Abulic syndrome (pseudo-depression) happens when there is damage to the dorsomedial cortex (including anterior cingulate and superior medial frontal regions) and its "circuitry of reward". The affected circuitry's key nodal points include the amygdala, hippocampi, VTA, MFB, entorhinal cortex, and the cingulate cortex. Catecholaminergic neurotransmitters, especially the mesolimbic dopaminergic system, play a crucial role in modulating the circuits.[7] Damaging them will disable motivated and reward-related behaviors, resulting in slow processing speed, lack of activation and enthusiasm, seeming disinterested, and lethargy. In addition to observable chronic apathy, an objective measure, such as reaction speed time, is also used to prove their slowness of initiation and delayed response.[11]

Dysexecutive syndrome (pseudo-dementia) happens when both ventrolateral and dorsolateral frontal regions and their related circuitry are damaged. The patients are left with impaired working memory, problem-solving, decision-making, mental flexibility, organization, planning, monitoring, task-setting, set-shifting, and reasoning. A standard frontal lobe neuropsychological test, like the Wisconsin card sorting task, can be used to evaluate the damage and assess the diagnosis.[11]

Behavioral syndrome (pseudo-psychopathia) is attributed to damage in the orbitofrontal region. It is the most interesting one when focusing strictly on personality changes. The abnormal behaviors exhibited after damage to this region include disinhibition, childishness, aggressiveness, abusive behavior, selfishness, impulsivity, etc. It impairs patients' intuitive social behavior and ability to self-monitor and self-correct in social situations. Patients are usually examined by the inquiry of their real-world behavior and the comparison to their previous personality traits. Some experts also suggest objective measuring of patients' impulse control and their ability to observe and use given feedback, such as in the Iowa gambling task[11] (Table 1).

Donald T. Stuss, in reference to the research by Zappala et al.,

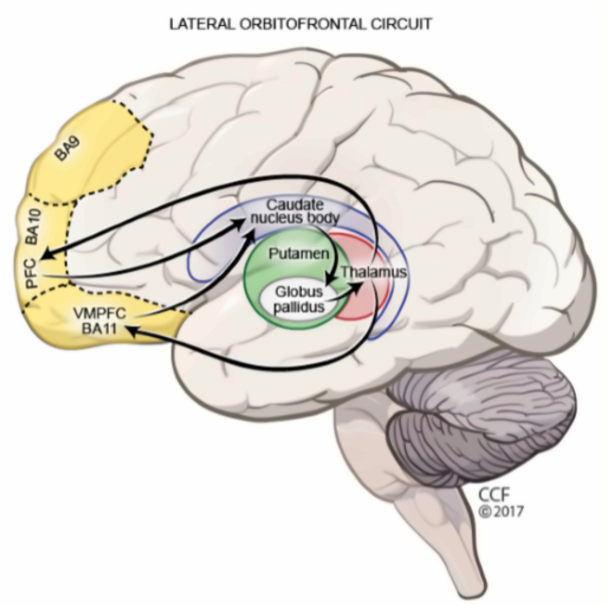


Figure 7. Lateral part of the orbitofrontal circuit.

Source: adopted from L. Ghazi Saidi, 2020, Acta scientific neurology, 3, no. 4, p. 11, DOI:10.31080/ASNE.2020.03.0172, © 2020 Ghazi Saidi

points out that there is no mention of the fourth region that, according to newer research, should be isolated alongside these.[8] That region is frontopolar/BA10, responsible for integrative/metacognitive functions, and one of the brain regions most often affected by traumatic accidents. That is probably due to that connection being only recently established and the difficulty of finding isolated cases of these TBI syndromes in patients.[8] What should also be mentioned in the context of TBIs is that damage to the medial temporal regions affects other memory features and the smooth merging of emotional memory with present awareness and instant evaluation of stimulus importance.[7]

In addition to the profile of regional brain injury described above, alternations of neurotransmitter secretions that have essential roles in preserving cognitive and behavioral homeostasis have also been confirmed in TBI patients. A significant dysfunction of catecholaminergic systems has been observed after TBI. The altered central cholinergic tone has also been found to be substantial because of its principal task in regulating many cognitive domains (especially attention and memory). Furthermore, it could also be important in the development of mood disorders like depression. A higher quantity of serotonin was also apparent, especially in areas of significant tissue damage and in connotation with decreased local cerebral glucose usage.[7]

UNDERSTANDING THE CLINICAL CONTEXT OF TBI

TBI has been described as a change in brain function or another indication of brain pathology caused by an outside force.[13,14] It is the predominant cause of death and disability throughout the world. The crude incident rates of TBI across a wide range of countries are 47.3-849 per 100,000 people per year.[15] TBIs are usually consequences of road traffic accidents, falls, assaults, or sport-related injuries. The primary cause is road traffic accidents, which are associated with young adult males, while the other risk groups are infants and elderly people who often endure falls. Lower social and economic class, previous mental disorders, and drug and alcohol abuse have also been related to a higher risk of enduring TBI.[13,16]

Clinical signs considered adequate to confirm the possible diagnosis usually include neurological deficits, acute intracranial injury on neuroimaging, unconsciousness, great confusion, amnesia for peritraumatic events, or comparable indications of altered mental state.[17] Physical symptoms typically present as headache, nausea, blurred vision, fatigue, dizziness, and hearing problems. Cognitive impairments usually consist of deficits in executive control and memory, while behavioral changes involve irritability, anxiety, emotional lability, and depression.

TBI has historically been classified according to the severity (mild, moderate, severe). The Glasgow Coma Scale (GCS) is used for quantifying the patient's state of consciousness alongside possible posttraumatic amnesia and the duration of unconsciousness if they are present. Those three factors are then used to measure the severity of the injury. These data can sometimes be helpful in the prognosis of the in-

Table 1. Prefrontal cortex damage and the associated brain disorders. Adapted from sources 6, 8, 10.

Brain area	***Brain function***	**Syndrome**
Lateral prefrontal	mediates executive functions	dysexecutive
Dorsomedial prefrontal	mediates motivational mechanism	abulic
Ventromedial/Orbitofrontal	emotional and behavioral regulation	behavioral
Frontopolar	integrative/meta-cognitive functions	

jury, but TBI's severity still does not sufficiently reflect the TBI sequelae because of too many dissimilarities between the patients.[18] Brain trauma injuries can be penetrating or non-penetrating (Figure 8). The non-penetrating injuries can be divided into contact/impact and inertial (acceleration or deceleration) categories.[7]

Impact injuries are the consequences of the brain's contact with an object (including external items and the skull) (Figure 9). The usual outcome is an injured scalp, skull, and brain surface (e.g., hematomas, contusions, lacerations). Commonly injured areas include the frontal poles, anterior temporal poles, orbitofrontal cortices, and inferior and lateral temporal cortices.[7,13] Inertial injuries caused by acceleration and deceleration usually have maximum effect on axons (white matter damage) and brain blood vessels because of the involvement of tensile, shear, and compression forces (Figure 10). The aftermath includes Wallerian degeneration, intracerebral hematomas, and tissue tears that usually result in widespread damage to the white matter called diffuse axonal injury (DAI).[7,13] The subfrontal white matter, rostral brainstem, and corpus callosum are frequently affected. Most often, the injuries are the result of both forces.[7] They can also be divided into primary, which occur immediately (e.g., penetrations, contusions), and secondary, which evolve over time due to systemic complications (e.g., inflammation, brain swelling, ischemia, or raised intracranial pressure).[7,13] Secondary injuries also include mechanical deformation of neurons that can activate excitotoxic injury cascades with an immense release of neurotransmitters. Hippocampi are frequently more excessively damaged than the rest of the brain, even in mild types of this injury.[7]

Explosive devices became a primary mode of conflict in modern war and introduced blast injury into the TBI spectrum. Explosion blasts produce a fast-moving wave of over-pressurized and over-heated air followed by a low-pressure trough. The most vulnerable areas are air and fluid-filled organs and cavities. The consequences are linked with both the mechanical effect of the pressurized wave that causes vascular and neural tissue deformation and the inertial effects of being pounded by alternating high- and low-pressure waves.[7] Other mechanisms of injury include inertia, impact, and penetration from shrapnel or debris. Consequently, typical blast injury is often a combination of all those mechanisms. The most frequently injured areas include the prefrontal cortex, sub-frontal white matter, rostral brainstem, basal ganglia, temporal lobes, and hippocampi.[7]

Another type of injury that can cause TBI is repetitive head impacts. They can trigger chronic traumatic encephalopathy (CTE), which causes a myriad of behavioral, psychiatric, and cognitive issues called traumatic encephalopathy syndrome (TES)[17] (Figure 11). It is often found in professional boxers or American footballers who endure such injuries (like concussions) at their work. TES symptoms include mood changes (e.g., depression), aggression, disinhibition, paranoia, substance abuse, etc. More research is needed to conclude further about TES.[17]

Magnetic resonance imaging (MRI) and computed tomography (CT) are often beneficial in acute diagnosis of intracranial injury but are not sensitive enough for DAI and cannot tell about the cognitive impairment and functional aftermath.[13] Positron emission tomography (PET) revealed the association of lower resting glucose utilization in the cingulate and prefrontal area with cognitive impairments of severe TBI patients in the absence of evident macroscopic lesions.[19] Diffusion tensor imaging (DTI) allows detailed analysis of alternations in white-matter pathway microstructure.[13] DTI was successfully used to differentiate even mild TBI patients from controls regardless of time since the injury occurred, and the relationship between its measures and cognitive outcomes was proved.[11,20] Functional MRI can evaluate altered brain activation of different regions during the execution of cognitive tasks. Reduced connectivity was often found to be correlated with TBI's executive and attentional dysfunctions.[13]

Mild TBI (mTBI) patients' psychological symptoms have long been discarded as "accident neurosis" connected to a wish for financial compensation, which was proven not to be true.[17] The vast majority of mTBI and nearly all of the more severe TBI survivors are affected with serious neurobehavioral consequences. Moreover, the recent reduction of TBI mortality rates connected with better safety regulations led to an increased number of patients who suffer from long-term personality changes.[7] It is essential to analyze and consider these emotional and behavioral manifestations alongside somatic and cognitive impairments.[17]

THE SPECTRUM OF PERSONALITY CHANGES IN TBI

Alternations in regulating emotions and behavior are often described as personality changes. They can appear in two ways: fundamental changes in response patterns or exaggerations of pre-injury characteristics.[7] Patients suffer a wide range of symptoms that include posttraumatic stress disorder (PTSD), affective instability, apathy, impulsivity/disinhibition, severe irritability, and anosognosia (lack of awareness of these changes).[7,13,17]

Family and caregivers, but even the survivors themselves, frequently describe both their exaggerated emotional expression and the pre-injury range of response to similar precipitating stimuli. Those changes are called affective instability. Previous momentary sadness is replaced by weeping and crying to the same stimuli. Earlier frowns and slight irritations are now angry verbal outbursts. They are often of short duration, accompanied by subsequent remorse, and have paroxysmal onset.[7]

Even though previous psychiatric disorders are a strong risk factor for TBI, numerous mood and anxiety disorders alongside psychotic and substance abuse problems are experienced de novo.[7,17] Almost half of TBI patients suffered a new Axis 1 disorder following their injury.[21] They tend to decrease over time, with prevalence rates returning to the base population for anxiety at year 2 and for depression at year 5.[22] All severities of TBI patients have a higher risk of affective disorders, but they are the most extreme in mTBI. More severe TBI survivors experience less emotional distress because of their impaired insight and apathy, as well as having a lower likelihood of PTSD due to worse amnesia. Athletes showed more affective durability after TBI, probably due to their better emotional functioning pre-injury than the general population.[17]

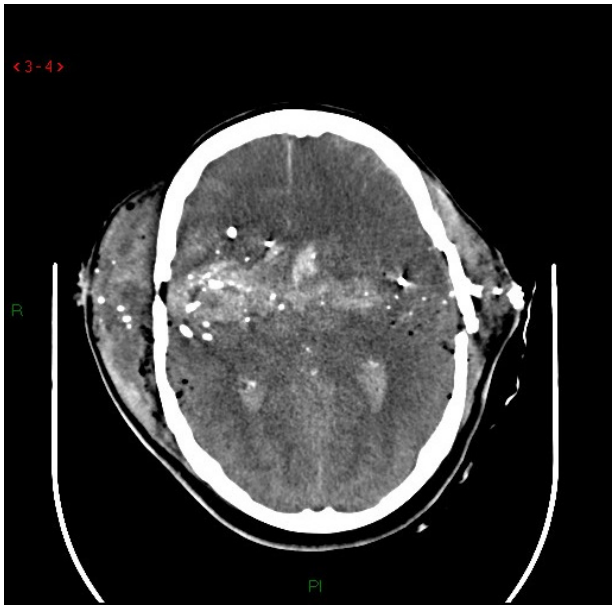


Figure 8. Penetrating severe TBI – fatal cranial gunshot wound with a transit of projectile in a 30-year-old male. CT scan.

Source: Sorrentino S, Fatal gunshot wound to the head. Case study, Radiopaedia.org (Accessed on 16th March 2024) https://doi.org/10.53347/rID-14487



Figure 9. Non-penetrating severe impact TBI – multiple traumatic intracranial hemorrhage in a 75-year-old female after a road traffic accident. CT scan.

Source: Knipe H, Traumatic intracranial hemorrhage with intracranial pressure monitor. Case study, Radiopaedia.org (Accessed on 16th March 2024) https://doi.org/10.53347/rID-38707

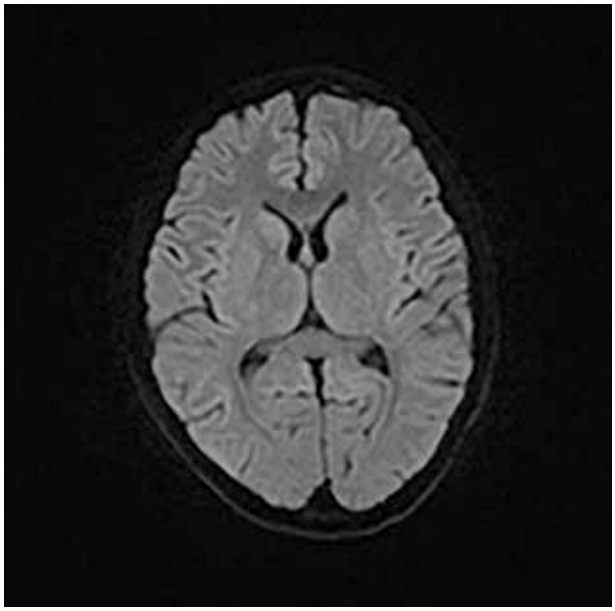


Figure 10. Diffuse axonal injury – multiple foci of altered signal in grey-white matter junction in a 20-year-old male presenting with posttraumatic confusion. MRI DTI scan.

Source: Elfeky M, Diffuse axonal injury. Case study, Radiopaedia.org (Accessed on 17th March 2024) https://doi.org/10.53347/rID-172613

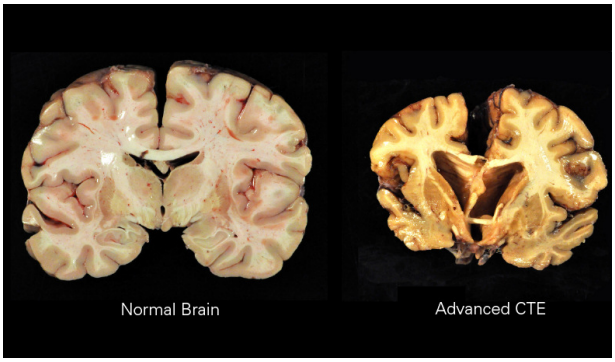


Figure 11. Comparison between a normal brain and a brain with advanced chronic traumatic encephalopathy (CTE).

Source: image „Chronic Traumatic Encephalopathy" by Boston University Center for the Study of Traumatic Encephalopathy – from Wikimedia Commons CC 4.0 license. Published 17th October 2014. Accessed on 16th March 2024.

https://commons.wikimedia.org/wiki/File:Chronic_Traumatic_Encephalopathy.png

PTSD is characterized by avoidance, re-experiencing symptoms, and alterations in mood, cognition, and arousal following exposure to a severe traumatic incident. mTBI patients carry the highest risk of PTSD because they experience minimal posttraumatic amnesia and unconsciousness, ergo the least defense mechanisms. Its connection to TBI is mainly documented in research works focused on military patients who carry psychological trauma from combat exposures, which is often difficult to disentangle from the physical damage of the TBI alone. The mechanism of genesis remains uncertain, but it could occur from the injured neural circuits that regulate fear responses and the reduced capacity of coping mechanisms.[17]

Apathy is often mistaken for depression or laziness, from which it is clinically distinct but sometimes difficult to distinguish, particularly in self-reported mood studies.[17] It is a major cause of why many patients fail their rehabilitation programs.[7] Apathy appears in more than half of the patients after TBI. As previously described, it is an important side-effect of the abulic syndrome and damage to the circuitry of "reward". Some scientists further divide TBI patients according to their scores in the different aspects of apathy: emotional numbness, lack of initiative, and lack of interest.[23]

TBI patients exhibit impulsive behavior through their physical actions, spontaneous decisions, verbal expressions, and poor judgment resulting from inadequate consideration of the consequences of their actions.[7] The concept of stimulus boundness in TBI survivors is closely related to such behavior. Patients tend to respond to the most prominent stimulus in their environment, disregarding any previously determined focus of attention or priority.[7] Four dimensions of impulsivity have also been defined. The first is urgency, which is experiencing strong reactions often under the state of negative affect. The second is the lack of premeditation, the struggle to think and reflect on the repercussions of the act before engaging in it. The third is the lack of perseverance, which is a struggle to remain focused on a difficult or tedious task. The last impulsivity dimension is sensation-seeking, the propensity to enjoy and pursue exciting and new experiences. The research found that the urgency, the lack of perseverance, and the lack of premeditation were all notably increased after TBI, while the sensation-seeking was notably decreased.[24]

Severe irritability is also frequently described in TBI patients. A legitimate stimulus could precipitate an irritated response, but it is often way out of proportion. It can range from verbal blowups to menacing aggression and assaults.[7] It is a very prevalent (over 67% incidence rate) symptom of TBI behavioral changes.[13,25]

Anosognosia of behavioral and cognitive disorders has often been reported in severe TBI survivors. It is, unfortunately, significantly related to poor engagement in rehabilitation programs and, thus, poorer injury outcomes.[13] Patients' families and caregivers, unlike the TBI patients themselves, are very aware of behavioral changes. TBI survivors could sometimes have a vague feeling of not being "who they used to be" but they have difficulty defining or grasping the scope of it.[7] Important correlations have been found between anosognosia and a patient's lack of ability to consider another person's mental state, ability to recognize facial expressions or emotions, difficulties in error monitoring, and difficulties in grasping another person's perspective. Unfortunately, no agreement still exists on how to measure anosognosia objectively.[13]

APPROACHES TO THERAPY

Therapy of the neuropsychological TBI sequelae should become the center of scientific research because of its direct effect on patients' well-being and recovery. Clinicians are often inclined to prescribe selective serotonin reuptake inhibitors or antipsychotics without even a hypothesis, let alone a precise diagnosis.[7] A symptomatic approach to treatment should always be the last resort. It can be justified only after ruling out Axis 1 disorders (e.g., mania, depression, psychosis), neurological conditions that could explain the behavior (e.g., pain, medication side effects, iatrogenic complications, complex partial seizures), or environmental factors that caused the behavior change.[7] However, sometimes the data are challenging to acquire, and the behavioral symptoms are so severe that clinicians are at a loss for their etiology and unsure of the treatment plan. The strategy should then be to conceptualize a bundle of symptoms as a particular syndrome. Depressive syndrome patients would then be put on an antidepressant regimen, or irritable manic-like syndrome patients on mood stabilizers. This treatment should be tested as a hypothesis with a time-limited trial. According to the results, the treatment should be adjusted or discontinued if the desired objective is not achieved. It is important to prioritize the rehabilitation environment as well. TBI survivors have a high degree of stimulus boundness and fondness for routine. Stimulus boundness is a sensitivity to immediate environmental events: patients struggle with complex, sustained, and selective attention, prioritizing incoming stimuli, and gating out those usually deemed of secondary significance.[7] Essentially, it presents as a difficulty in assigning appropriate attention to the continuous influx of stimuli from the environment. On the other hand, fondness for routine is a sensitivity to routine or schedule changes that may be related to deficits in executive function. Patients are often filled with anxiety and irritability and can even throw big outbursts over such changes.[7] When treating TBI, it is crucial to consider prescribed medication, environmental manipulation, and behavioral analysis. Not paying proper attention to all of the factors causing the symptoms will reduce the efficiency of medication and vice versa – even tremendous efforts in environmental manipulation and behavioral analysis would be useless without adequately prescribed medication.[7]

The frontal lobe fractionation framework previously discussed in this paper has great value in providing a better ability to characterize the potential underlying causes of cognitive dysfunctions after TBI, which can simplify the direction of rehabilitation efforts. The positive result of any rehabilitation therapy is directly affected by the location of the damage in the frontal lobe and its subsequent disorder.

The prefrontal cortex greatly depends on its neurochemical surroundings and, in turn, controls the arousal systems, which supply necessary modulation to the frontal regions. It was discovered that subregions and suboperations of the

prefrontal cortex might have distinct neurochemical needs.[8] The dorsolateral regions of the prefrontal cortex are sensitive to catecholamines, whereas the orbital-ventromedial part is sensitive to serotonin. Catecholamines are responsible for the regulation of the strength of dorsolateral frontal network connectivity through intracellular signaling pathways that change the state of the ion channels around synapses. They are complementary: dopamine D1 weakens inappropriate connections (noise), whereas norepinephrine alpha-2A increases appropriate connections (signals). This gives a new understanding of the state-dependent frontoexecutive functions with implications for a better comprehension of the cognitive disorders and their treatment.[8]

In the last decade, a novel treatment option for improving neuronal connectivity and plasticity has taken the form of neuromodulation by magnetic and electrical stimuli.[26] Hyper- and hypo-excitability of neurons, which occurs after TBI, has proven to be an excellent target for neuromodulation. Electrical stimulation can be performed in two ways: cathodic stimulation, which depolarizes the targeted neurons, and anodic stimulation, which hyperpolarizes the targeted neurons but subsequently, because of the ion flux, depolarizes a more distant neuron. Neuromodulation aims to strengthen or weaken the synapses. Synaptic plasticity is essential in the regeneration of high cognitive functions, like the formation of long-term memory or the process of learning.[26] Long-term potentiation and long-term depression are vital processes managing synaptic plasticity. Still, they are often hindered and dysregulated during TBI, which leads to its many accompanying cognitive dysfunctions. Several different methods are used to achieve neuromodulation; some are non-invasive, like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), while vagus nerve stimulation (VGS) and deep brain stimulation (DBS) are the most common invasive methods.[26] DBS consists of two implanted electrodes that precisely target deep brain nuclei. It has great potential because of its accuracy and the ability to target small areas without affecting their surroundings. It proved effective in treating cognitive impairments in all phases of TBI (acute, subacute, and chronic).[26] Data suggest that stimulating the prefrontal cortex, Papez circuit, and thalamic nuclei could bring the most benefit in recovering high-order brain function in TBI survivors.[27] Rezai et al. conducted a study with four participants who had chronic TBI sequelae, 6-20 years after the injury, that made them unable to live independently and function normally in society. DBS was used to target the Nucleus Accumbens (Nacc) and the anterior limb of the internal capsule. The goal was to help restore executive functioning, treat abulia, and improve self-control. The results two years later showed that three out of four participants improved on an adjusted scale based on a priori criteria for clinical significance, while one made a drastic improvement on all scales.[28] A newer study from 2022, in the form of a preclinical trial with a TBI model in mice, confirmed findings about Nacc but added the potential of DBS stimulating neuronal regeneration and its long-lasting benefits.[29] Another study from 2020, performed in non-human primates, showed that DBS of the medial dorsal thalamic tegmental tract (DTTm) boosted behavioral performance. Meanwhile, stimulation of the centromedian-parafascicularis pathway showed no results.[30] The newest study from 2023 was performed by Schiff et al. They targeted the central lateral thalamic nucleus and the related DTTm because of their vital role in frontostriatal pathways. Five patients with moderate to severe TBI, 3-18 years after the injury, completed the study. Based on a very precise trail-making exam, their processing speed improved 15-52% in all cases, surpassing the 10% benchmark for improvement.[31] Unfortunately, it has been noted that neuromodulation in patients with extensive DAI got little results, probably due to immense white matter damage and loss of structural pathway integrity.[32]

CONCLUSION

Understanding personality changes in TBI survivors has been a scientific pursuit ever since Phineas Gage's compelling case. Concrete evidence links neurobehavioral sequelae to damage in prefrontal anatomical circuitry. Functional relationships have also been defined: the dorsolateral prefrontal circuit mediates executive functions, the anterior cingulate circuit is involved with motivational mechanisms, and the orbitofrontal circuit is dedicated to emotional and behavioral regulation.[8,9,33] The frontopolar area has also been isolated as responsible for integrative/meta-cognitive functions.[8] TBI is a significant and relevant healthcare problem, impacting many people. Efforts to classify and define its clinical symptoms have been undertaken primarily to improve treatment. The approach of grouping some behavioral symptoms into metaphorical syndromes and treating them as such (e.g., depression-like syndrome, irritable mania-like syndrome) has proven useful.[7] Another method involves targeted pharmacological treatment of specific prefrontal areas affected by post-TBI dysfunction.[8] Clinicians must also acknowledge the environmental impact on the rehabilitation success.[7] DBS proved to be an exciting and promising new method that allows precise stimulation of deep brain nuclei and the reactivation of prefrontal circuitry.[26–31] Phineas Gage intrigued the world with his survival and personality change, but also by his later recovery – independent life and a demanding job.[2] His story is not a tale of tragedy but optimism and hope. The frontal lobe is one of the brain's most naturally plastic and integrated regions.[34] Although slow and still enigmatic, brain plasticity holds great promise for TBI patients' recovery. Further research into the brain's malleability might allow them to find their way back to who they used to be.

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PROMJENE OSOBNOSTI U TRAUMATSKIM OZLJEDAMA MOZGA

Sažetak

Traumatska ozljeda mozga (TOM) značajan je suvremeni zdravstveni problem, a mnogi preživjeli postaju doživotni invalidi zbog somatskih, kognitivnih ili neurobihevioralnih posljedica. Cilj ovog preglednog rada prikazati je trenutno razumijevanje TOM-a te promjena osobnosti kao njezinih kliničkih posljedica. Ova tema zaintrigirala je znanstvenike još otkako je Phineas Gage fascinirao svijet pretrpjevši bizarnu ozljedu frontalnog režnja. Dokazi o povezanosti TOM-a s neurobihevioralnim posljedicama preživjelih pacijenata pronađeni su u oštećenjima prefrontalnih anatomskih sklopova. Definirani su i njihovi funkcionalni odnosi: dorzolateralni prefrontalni krug posreduje u izvršnim funkcijama, anteriorni cingularni krug uključen je u motivacijske mehanizme, a orbitofrontalni krug posvećen je regulaciji ponašanja i emocija. Frontopolarno područje izolirano je kao odgovorno za integrativne/metakognitivne funkcije. Oštećenje različitih dijelova prefrontalnog korteksa i navedenih sklopova izaziva promjene osobnosti koje se mogu obuhvatiti u tri sindroma: abuličkom, disegzekutivnom i bihevioralnom. Još uvijek nema konsenzusa o specifičnom liječenju promjena osobnosti nakon TOM-a. Grupiranje simptoma u metaforičke sindrome (npr. sindrom sličan depresiji, sindrom sličan razdražljivoj maniji) pokazalo se korisnim. Obećavajuće je i ciljano farmakološko liječenje pojedinih oštećenih prefrontalnih područja sa specifičnim poremećajima funkcije. Duboka moždana stimulacija novija je metoda koja pokazuje puno potencijala zbog sposobnosti precizne stimulacije dubokih jezgri mozga i reaktivacije funkcija prefrontalnih krugova. Ne smije se podcijeniti niti utjecaj okoliša na proces rehabilitacije. Slučaj Phineasa Gagea dodatno je zaintrigirao njegovim mogućim oporavkom nakon prvotne duboke promjene osobnosti. Frontalni režanj jedno je od prirodno najplastičnijih i najintegriranijih područja mozga. Daljnje istraživanje plastičnosti mozga pruža nadu za rehabilitaciju preživjelih nakon TOM-a te da usprkos ozljedi pronađu prijašnjeg sebe.

KLJUČNE RIJEČI: plastičnost neurona, prednji režanj, promjene osobnosti, traumatska ozljeda mozga