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TRAUMATIC BRAIN INJURY, THE GUT MICROBIOME, AND SOCIOECONOMIC STATUS: A REVIEW

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Abstract

This article reviews existing literature on three bidirectional relationships. These are traumatic brain injury (TBI) and gut microbiome relationship, the TBI and socioeconomic status (SES) relationship, and the gut microbiome and SES relationship. Literature on the relationship between TBIs and the gut microbiome underscores the loop created through the gut-brain axis, leading TBI to disrupt gut microbiota composition and diversity, which in turn aggravate existing neuroinflammation in the brain. Literature on the relationship between TBIs and SES links lower SES to higher occurrence rates of TBI and poorer recovery outcomes. Literature on the relationship between the gut microbiome and SES, links lower SES to gut dysbiosis, presenting as imbalanced gut microbiota composition and lower diversity. The TBI-gut microbiome, TBI-SES, and gut microbiome-SES bidirectional relationships reinforce health inequity and call for social justice advocacy for the protection of brain health of people of lower socioeconomic backgrounds.

Keywords

Traumatic Brain Injury, Gut Microbiome, Socioeconomic Status, Social Justice

1. Introduction

While the relationships between Traumatic Brain Injuries (TBI), a person's gut microbiome, and their Socioeconomic Status (SES) have been explored in research, there hasn't been an integrative review of all three concepts and their respective interactions. This study reviews the literature on three sets of relationships. These are the TBI and gut microbiome relationship, the TBI and SES relationship, and the gut microbiome and SES relationship.

A TBI refers to the disturbance of the brain's normal operations due to a piercing laceration, or a wound through collision, push, or a hard stroke (Rusnak, 2013). TBIs can be minor, without visible alterations in mental functioning (Ojo et al., 2016), mild, otherwise known as concussions, with brief alterations in cognitive functioning and levels of consciousness, or severe, with an extended period of unconsciousness and with memory loss after the brain traumatization (Norins et al., 2019). TBIs can also be repetitive when occurring more than once in a short period (Fehily et al., 2017).

TBI is a leading global cause of disease, death, and disability of people under 45 years of age (Humphreys et al., 2013). It is also linked to premature morbidity through accidents and to suicide through self-harm (Marklund et al., 2011). Perceptions of TBI have shifted given scientific discoveries over the past decade. Researchers now claim that even a minor TBI that is not depicted in magnetic reasoning imaging (MRI) scans can cause structural and functional damage to the brain. This suggests that even light cases of head trauma should not be dismissed but should be followed up by health care professionals (Dashnaw et al., 2012). Another important shift in the conceptualization of TBI claims that injuries of the head should no longer be viewed or treated as a singular event whose effects are immediately evident on a patient's scans. It claims that head injuries should be treated as the catapult of a process in the brain and the body. This implies that the management of a TBI should not terminate soon after the initial treatment but should continue for a while to maximize recovery (Masel et al., 2010).

Falls, being hit with an object, motor vehicle accidents, and self-harm have been deemed the leading causes of TBI in the United States over the past decade. Exposure to explosions has also been deemed an important cause of TBI in the country (Norins et al., 2019). In 2014, falls were responsible for 48% of all-age, Emergency Room (ER) TBI- related visits, and for 81% of older adults, TBI-related ER visits. Falling off a motor vehicle accounted for 52% of TBI-related ER visits. Being hit by or against a physical object accounted for 17% of TBI-related ER visits. Motor vehicle collisions

accounted for 20% of ER visits and premeditated self-harm leading to TBI, accounted for 33% of ER visits in 2014 (Huang, 2013).

TBI risk factors were assumed through data emerging from death and hospitalization reports on TBI cases in the first half of the 2010- 20 decade. Regarding TBI- related deaths, people who were 75 years or older were at higher risk. Falls were found to be linked to TBI- related deaths in people 65 or older. Premeditated self-harm was linked to TBI- related deaths in people between the ages of 45 and 64. Motor vehicle collisions and accidents were linked to TBI-related deaths in people between the ages of 15 to 34 and in people who were 75 years or older. Murder was linked to TBI- related deaths in children from zero to four years old (Centers of Disease, 2019).

TBI- related hospitalizations were also higher for people over 75 years. TBI-related ER visits were high for people over 75 years and for children between the ages of zero to four. Falls were linked to TBI- related ER visits and hospitalizations of children and older individuals, while being hit by a physical object was linked to ER visits of children between five and 14 years of age. Motor vehicle collisions were linked to TBI- related hospitalizations of people from 15 to 44 years of age (Centers of Disease, 2019).

Effects of TBI on the body vary, and they can appear early on after the injury or later. Effects can be both physiological and psychological (Maas et al., 2008). Early physiological effects of a TBI may include direct injury of the intracranial neural tissue that can be followed by a hematoma, edema, changes in blood flow in the brain, increased intracranial pressure, damage of nerve cells, intracranial hemorrhage, axonal damage or contusion, and neuroinflammation (Jassam et al., 2017). Neurological effects of TBI include short or long- term cognitive and motor impairments and seizures (Barman et al., 2016). Neurodegenerative diseases may also begin from a TBI. Later psychological effects of TBI include and are not limited to personality changes and psychiatric disorders, including anxiety and depression (Iverson et al., 2015).

Regarding the gut microbiome, about 300 to 500 species live in the human GI tract, comprising about 2 million genes, otherwise known as the microbiome (Quigley, 2013). The concentration of bacteria in the colon, the last part of the GI tract, reaches 1011 cells per gram (Kelly et al., 2015). The gastrointestinal wall is a four-layered tissue around the GI tract that serves as a human's largest interconnection with the environment, as it covers a much larger surface than a person's epidermis (Turner, 2009). The gastrointestinal wall regulates the absorption of different

nutrients, water, and electrolytes and is selectively permeable, acting as a filter and acts as a barrier that prevents the entrance of pathogens into the rest of the body (Farhadi et al., 2003).

In cases in which the GI tract is jeopardized, its ability to act as a barrier to pathogens deteriorates, the gastrointestinal wall becomes more permeable to pathogens that, in turn, hinder normal physiological operations of the body (Gallo et al., 2012). The gastrointestinal wall also becomes more permeable to toxins and antigens that leave the GI tract and enter the bloodstream, causing inflammation in the body (Bischoff et al., 2014). Increased permeability of the gastrointestinal wall has also been linked to chronic inflammation in the body, which can contribute to various maladies (Ohland et al., 2010). The microorganisms that live in the GI tract have been found to play a pivotal role in supporting this barrier function in cases in which the gastrointestinal wall is compromised (Kharrazian, 2015). The microbiome in the GI tract has also been found to have a direct effect on overall human physiology and health, even though many of its functions remain unexplored by research and vice versa (Bengmark, 2013).

The third concept that this research explores, namely Socioeconomic Status (SES), refers to one's social standing, measured through their level of income, education, and through their profession. SES comparisons often underscore inequity in access to resources, along with the privilege and power of certain groups. The language used in research suggests that there are five main social groups in the United States depending on their SES. These are upper, upper-middle, middle, working, and lower class (Peverill et al., 2020).

Table 1: *Definitions of Terms Explored in This Review*

Terms Explored	Definition
Traumatic brain injury	the disturbance of the brain's normal operations due to a piercing laceration or a wound through collision, push, or a hard stroke
Gut microbiome	300 to 500 species live in the human GI tract, comprising about 2 million genes
Socioeconomic status	one's social standing, measured through their level of income, education, and profession

Source: Self

This study aims to explore the relationships between TBI and the gut microbiome, TBI and SES, as well as the gut microbiome and SES. The reason why this exploration is important is that

findings bear implications on health equity, social justice, and the challenges faced by people of lower socioeconomic backgrounds, in particular when faced with a TBI. Through this integrative review, the researcher can pinpoint some of the sources of these inequities and suggest implications for policymakers.

2. Traumatic Brain Injury and The Gut Microbiome

After the brain experiences an injury, potentially resulting in hematoma and neuroinflammation, among other things, there is a second wave of reactions that are activated throughout different physiological systems, including the immune system. The body's gastrointestinal tract (GI tract) may also be one of the peripheral organs that are affected by a TBI (Treangen et al., 2018). While experimental conditions aiming at studying TBI focus on the brain, accidents that cause TBIs in real life have an impact on the entire body, and trauma is not isolated to the head (Yang et al., 2013).

The GI tract is a 30 ft tract that extends from a person's mouth to their anus and includes every part and organ of their digestive system, specifically their mouth, esophagus, stomach, and intestines (Maranki et al., 2019). The gut flora otherwise referred to as the gut microbiota, refers to the microorganisms that live in humans' GI tracts. These microorganisms are bacteria, archaea, and fungi (Moszak et al., 2020). The gut-brain axis is the sequence of afferent and efferent signals that occur between the GI tract and a person’s Central Nervous System (CNS) that includes their brain and spinal cord (Wang et al., 2014). Signals between the GI tract and the CNS can be triggered by neurological, hormonal, or immune processes in the body, while dysfunctions that may occur in the gut-brain axis can have pathological effects on the entire body (Cryan et al., 2012). While the literature on the effects of the CNS on the GI tract is ample, research on the effects of the GI tract on the CNS is a developing field (Mayer et al., 2015). There is no debate, however, on the notion that the gut-brain axis is bidirectional and that each part can affect the other (Romjin et al., 2008). Crucial in gut-brain communication are the microorganisms that live in and beyond the human GI tract. An estimate of 3x1013 bacterial cells live in the entirety of the human body (Sender et al., 2016), creating an ecosystem, otherwise known as the human biome (Dinan et al., 2017).

Gut dysbiosis, or else an imbalance of the gut microbiota, has been linked to psychological disorders and has also been linked to more neurologically- based disorders, such as TBI, schizophrenia, and stroke (Bailey et al., 2017). Particularly following a TBI, there is evidence of

radical changes in the versatility and number of microorganisms in the GI tract occurring within 72 hours after a TBI (Zhu et al., 2018). These changes are different from the changes that occur in the microbiota after an ischemic brain injury, signifying that different forms of a brain injury affect the brain in a unique way (Rice et al., 2019).

Experiments conducted with mice confirm that TBI injuries cause significant changes in the composition and versatility of gut bacteria, showing that they occur within the first two hours after the injury and that they are still detectable seven days later (Treangen et al., 2018). TBIs have also been shown to cause acute dysbiosis (Bansal et al., 2009) and substantial drainage of good types of bacteria that exist in the GI tract of mice (Matharu 35 al., 2019).

The impact of a TBI on the gut microbiota can be described in the following steps. First, neurological trauma in the brain may result in local inflammation that primes microglial cells, responsible for removing damaged neurons and fighting off infections, and for protecting the CNS from dysfunction (Kumar et al., 2012). These microglial cells then trigger intense immune responses to internal or external attacks of the body, such as infections or secondary TBIs, respectively (Witcher et al., 2015). Hyperactive microglial cells may then become neurotoxic and trigger pathological responses in the brain, including depression (Najjar et al., 2013) or even neurodegeneration, such as through Alzheimer's' disease (Norden et al., 2015). As mentioned earlier, TBI causes damage to the GI tract (Hu et al., 2013) leading to increased gastrointestinal permeability (Palin et al., 2008), inflammation, and a systemic immune response (Arrieta et al., 2006). The inflammation that occurs due to the gastrointestinal wall permeability then affects the microglial cells, thus aggravating the existing neuroinflammation in the brain (Cunningham, 2013).

Research focusing on the gut-brain axis emphasizes the chronic and bidirectional interactions between the brain and the gut after a TBI, which may affect recovery. The loop described above of the TBI affecting the microbiota and vice versa has helped in diagnosing and identifying TBI severity through monitoring the extent of dysbiosis in the GI tract (Cunningham, 2013).

Besides diagnosis, the bidirectional interactions of the gut-brain axis have also been utilized in the service of finding a treatment for TBI. More specifically, eubiotic treatments, including transplants of a healthy microbiota and the use of pre or probiotics, have been explored in research as potential treatment routes for TBI. Gut microbiota has been found to affect the progress of TBI and to reverse the possibilities of developing Post Traumatic Stress Disorder (PTSD) after such an

injury (Cunningham, 2013). While these findings are significant, the field of TBI treatment through focusing on the GI tract is nascent.

Table 2: *Themes found in TBI – gut microbiome relationship*

Themes	Details
The relationship is bidirectional	The gut affects the brain and the brain affects the gut
The gut affects the brain	Gut dysbiosis may lead to psychological and neurological disorders
The brain affects the gut	TBI may lead to radical changes in the versatility of composition of the gut microbiome and may lead to dysbiosis Probiotics may be useful in the treatment of TBIs

Source: Self

3. Traumatic Brain Injury Recovery and Socioeconomic Status

Research describes the different stages of recovery after a moderate or severe brain injury. The early stages of recovery may include a comma in which the patient is unconscious and unable to communicate due to swelling in the brain, among other reasons. In a vegetative state, the patient can breathe on their own. They can sleep and wake- up, and their reflexes are functioning (Steel et al., 2017). In a minimally conscious state, the patient is partially conscious but cognitive and motor functions remain impaired (Qubty et al., 2020). A state of the confusion comes after these initial stages, in which the patient is disoriented and tends to forget things. Cognitive functions are still somewhat impaired, and behaviors tend to be inconsistent (Dischinger et al., 2009). In later stages of recovery, cognitive and motor functions are often restored with time (Wagner et al., 2013).

Improvements after a TBI tend to happen in six months after the injury, with the rate and presence of improvement (Silverberg et al., 2015) varying depending on the patients' characteristics (Missios et al., 2016). These characteristics have been described as static or dynamic. Static factors affecting recovery are age, sex, IQ, and level of education before the injury, as well as mental illness and neuropsychological history before the injury as well (Holland et al., 2015). Dynamic factors include social support (Yeates et al., 2004), quality of nutrition and exercise, as well as the patients' socioeconomic status (Bruns et al., 2003).

SES has been described as a pivotal predictor of TBI recovery (Kane et al., 2014), while a low SES has been shown to increase the likelihood of a TBI (Haines et al., 2019; Anderson et al., 2001). A low SES has been shown to increase in-hospital mortality, shorten a patient's length of stay in a hospital setting, and deny patients of rehabilitation opportunities (Hefferman et al., 2011). A lack of insurance that is linked to lower SES is inextricably bound to access to both intervention and rehabilitation services after a TBI and is a decisive factor influencing recovery (Schmidt et al., 2010). Being uninsured often leads to fewer necessary operations and procedures to address the effects of the TBI, thus leading to higher rates of in-hospital mortality. It also decreases the chance of having access to care after being discharged from the hospital (Rabinowitz et al., 2015).

SES has been found to affect recovery in multiple areas of function, including cognitive, emotional, social skills, and adaptive ability. Particularly regarding cognition, a low SES is a significant predictor of poor cognitive performance and persistent symptoms of cognitive deterioration following a TBI. The effect of SES on cognitive function following a TBI has also been grasped structurally in the brain. More specifically, patients of lower SES backgrounds who have lesions in the left hemisphere of their brain, where logic processes occur, have been found to have poor recovery outcomes following a TBI (Braveman et al., 2010).

What is important to mention here is that the link between SES and TBI is bidirectional. This means that regardless of patients' SES, TBI often leads to chronic conditions post-injury that have a direct and grave impact on one's ability to care for themselves, to be independent, and to be productive at work. Given the negative effects that a TBI has on a person's cognitive, emotional, and social skills, such an injury may indirectly aggravate a person's SES. TBIs may thus reproduce existing health inequities or create new ones, given the adverse effects that it has on people of lower SES (Brown et al., 2011).

Table 3: *Themes found in TBI – SES relationship*

Themes	Details
The relationship is bidirectional	SES affects TBI incidence and recovery and TBI incidence affects SES
SES affects TBI	People of lower SES are more prone to suffer a TBI and have poor recovery outcomes

TBI affects SES	The long recovery process of TBI aggravates SES and inequities

Source: Self

4. Gut Microbiota and Socioeconomic Status

Three sets of bidirectional relationships are important in this research. The first is the bidirectional relationship between the brain and the gut (Bennike et al., 2014). The second is the bidirectional relationship of SES and TBI occurrence and recovery. The third that is discussed in this section of the paper is the bidirectional relationship between the gut microbiota and a person's SES (Nathan et al., 2010). SES has been found to affect microbiome diversity and, conversely, microbiome diversity has been found to attenuate negative health predictions due to lower SES (Garrett, 2015).

This section addresses the biological mechanisms that may explain long-noted health discrepancies across different SES levels among people with varying demographic characteristics (Sekirov et al., 2010). As low SES has been linked to increased rates of chronic illnesses, including asthma, diabetes, heart disease, stroke, and overall mortality levels, research has been conducted to pinpoint the pathogens that may be causing these diseases, that have been described as inflammatory (Jackson et al., 2016).

A link between these inflammatory, chronic diseases and gut dysbiosis has been established in research (Rothschild et al., 2018). More specifically, patients with obesity, diabetes, bowel disease, asthma, heart disease, and certain forms of cancer have been found to have a less diverse composition of microbiota in their GI tract than healthy controls (Moeller et al., 2016). Chronically ill patients' gut flora diversity, however, increased significantly as their SES increased as well and was significantly less in people living in poverty (Lax et al., 2014). SES, thus, does not only affect gut microbiota diversity but the respective health outcomes as well (Claesson et al., 2012).

Gut flora diversity in the GI tract varies across different people, and even monozygotic twins have different microbiomes. Genetic factors are only partially accountable for the composition of gut microbiota in a person, thus leading researchers to environmental factors that may play a role. While research on the social and environmental factors that affect the microbiome structurally and functionally is incipient, findings suggest that the social environment has an influence at different points in a person’s lifespan (Dowd et al., 2018).

The social environment may affect a person's microbiome in childhood, depending on whether they were born vaginally or through a cesarean, whether they were breastfed or not, and whether they used antibiotics. It may also affect the microbiome based on whether they were exposed to indoor and/or outdoor environments and on their early childhood diets (Mueller et al, 2015).

Social relationships may affect the diversity of one's gut microbiota in childhood and later in life, as people who interact socially tend to share some microbiota (Moeller et al., 2016), and so do people who live in the same home (Lax et al., 2014). Elderly people who transition from living with their families to living in a home with fewer social interactions have also been found to experience a shift in gut microbiome composition, with a fewer diversity of microbiota when they live in isolation (Claesson et al., 2012). Psychological stressors have also been found to alter peoples' microbiomes by limiting their diversity and causing dysbiosis (Bailey, 2016).

Social and psychological stressors, as well as one's social environment, may affect the microbiome, not only through diet but also in ways that have not yet been comprehended in research (Sekirov et al., 2010). All of these factors are inextricably bound to peoples' SES, which may affect them from the time they were born, depending on whether their parents could afford a cesarean over vaginal delivery, to later in life through ongoing stressors associated with lower incomes, social marginalization and options of care in later life (Walter et al., 2011).

Research focusing on SES in particular, and its effects on microbiome diversity, has linked lower SES levels to a lower alpha diversity. Alpha diversity is the average species diversity in the gut and is responsible for rich microbiota composition. Lower alpha diversity is linked to poorer health outcomes. Lower SES has also been linked to more Bacteroides in the GI tract. Bacteroides are significant clinical pathogens leading to gut dysbiosis and other health conditions (Sekirov et al., 2010). In summary, the gut microbiota's diversity and composition are adversely affected by lower SES.

Table 4: *Themes found in SES- gut microbiome relationship*

Themes	Details
The relationship exists	SES negatively affects the gut composition
SES and inflammation	Low SES leads to life conditions that aggravate the gut, leading to chronic inflammation

Inflammation and chronic illness	Chronic inflammation linked to lower SES leads to chronic illnesses, more prevalent in poor parts of the population
SES and susceptibility to disease	People of lower SES are more susceptible to disease, through inflamed gut among other reasons

Source: Self

5. Conclusion, Limitations, Future Directions

Brought together, the findings of this paper bear important implications on the occurrence and recovery of TBIs among people of lower SES. More specifically, people of lower socioeconomic backgrounds are not only more prone to suffering a TBI, but they are also more likely to suffer adverse consequences and to not be able to recover as well as more affluent TBI patients due to the compromised structure and diversity of their gut microbiomes.

Limitations of this study include an omission of confounding variables that may affect peoples' TBI recovery, such as access to rehabilitation, and stress that also affect recovery. Gut-brain research is a nascent field with most findings generated in labs with non-human participants, yet the implications are important. Caution should thus be raised when reading this review. Future research on this matter could include human participants through a focus on nutrition, probiotics, and other factors that affect the composition of the gut microbiome. Future research could also address confounding variables, particularly through twin studies or based on cross-cultural hospital databases.

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