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Depression following traumatic brain injury: a comprehensive overview

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Abstract: Traumatic brain injury (TBI) represents a major health concern affecting the neuropsychological health; TBI is accompanied by drastic long-term adverse complications that can influence many aspects of the life of affected individuals. A substantial number of studies have shown that mood disorders, particularly depression, are the most frequent complications encountered in individuals with TBI. Post-traumatic depression (P-TD) is present in approximately 30% of individuals with TBI, with the majority of individuals experiencing symptoms of depression during the first year following head injury. To date, the mechanisms of P-TD are far from being fully understood, and effective treatments that completely halt this condition are still lacking. The aim of this review is to outline the current state of knowledge on the prevalence and risk factors of P-TD, to discuss the accompanying brain changes at the anatomical, molecular and functional levels, and to discuss current approaches used for the treatment of P-TD.

Keywords: animal models; antidepressant; depression; inflammation; post-traumatic depression; traumatic brain injury.

Introduction

Traumatic Brain Injury (TBI) remains a leading cause of death and a major public health problem among adults and children globally where ~1 million persons sustain TBI each year (Lecky et al. 2017). Across all ages, TBI signifies 30–40% of all injury-related deaths, and neurological injury is expected to remain the primary cause of disability from neurological diseases until 2030 (WHO 2006). According to the latest surveillance report published by the Centers for Disease Control and Prevention (CDC) in 2014 alone, the number of TBI-related emergency department visits, hospitalizations, and deaths in the USA reached 2.87 million, which is 53% higher than the number estimated in 2006. Of all TBI-related emergency department visits recorded, the leading cause of TBI was unintentional falls accounting for almost half (47.9%) followed by being unintentionally struck by or against an object (17.1%) and motor vehicle crashes (13.2%) (Centers for Disease Control and Prevention 2014). Post-traumatic complications experienced by TBI survivors can last for a few days, months and even years post-TBI depending on the head injury mode and severity. According to published data, approximately only 25% of TBI patients achieve long-term functional independence (Ahmed et al. 2017). Besides the significant effects of short-term and long-term complications on individuals, their families and the healthcare systems, the financial cost of such impairments is huge. Annually, TBI alone costs the international economy around US $400 billion (Maas et al. 2017). The financial burden is further enhanced when patients become vulnerable to neurological diseases such as epilepsy, seizures and dementia (Shlosberg et al. 2010). Furthermore, approximately 75% of TBI patients suffer from mild TBI injuries known as concussions and many of them never seek medical help due to false-negative diagnosis (Gean and Fischbein 2010; Saatman et al. 2008). Hence, the real impact and cost of TBI may be much more than what is currently estimated.

TBI is caused by a blow, bump or jolt to the head that disrupts the normal function of the brain. Depending on the physical mechanism of insult, TBI can be classified into three categories: (a) closed head, (b) open or penetrating and (c) explosive blast TBI (Ng and Lee 2019). The severity of such injuries may range from mild (concussive injury), which are considered as a brief change in consciousness or mental status, to moderate and severe injuries that are characterized with an extended period of unconsciousness or memory loss that can be classified by different classification systems of

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which is the Glasgow Coma Scale (GCS) score (ALS-FRS-R 2015). Nevertheless; post-traumatic impairments are not restricted only to severe cases, they are as well frequent postmoderate or mild TBIs.

Even among young patients suffering from mild injuries and having a good preinjury status, one-third failed to achieve functional recovery and are left with impairments (WHO 2006). Disabilities documented among TBI survivors include complications related to movement, memory or thinking, emotional functioning or sensation (Park et al. 2020). However, of the wide array of consequences occurring post-TBI, emotional deficits are considered among the most prevalent, persistent and challenging to treat (Neumann 2017). The frequently observed deficits include anger and aggression, anxiety, depression, reduced emotional and behavioral self-control, poor emotional self-awareness and impaired recognition of emotional cues from other persons (Blennow et al. 2016; Neumann 2017). According to the World Health Organization (WHO), depressive disorders are characterized by persistent sadness, loss of interest or pleasure, disturbed sleep or appetite, feelings of guilt or low self-worth, tiredness, and poor concentration (Depression and Other Common Mental Disorders 2017). Depression is a common mood disorder worldwide affecting more than 264 million people ("Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017," 2018). It can be recurrent or long-lasting, substantially impairing an individual's ability to function or cope with daily life. At its most, severe, depression can lead to suicide ("Depression and Other Common Mental Disorders," 2017).

The overarching goal of this review is to provide a comprehensive overview of the prevalence and risk factors of depression following TBI and to discuss the anatomical, molecular, behavioral and functional changes that are associated with post-traumatic depression (P-TD). This paper also describes the most commonly employed animal models of TBI and the experimental paradigms that are used to study depression. This paper finally outlines the available treatment modalities for P-TD and discusses future research directions.

Prevalence and risk factors of depression after TBI

In one study, at 5 years post-TBI, psychiatric diagnoses were reported in 75.2% of individuals, with the majority (77.7%) emerging in the first year (Alway et al. 2016). Similarly, another study indicated clinical significant psychiatric symptoms in 42% of adults with TBI at 6 months postinjury (Hart et al. 2014). Depression is one of the common psychological sequelae of TBI, in which up to 56% of individuals develop its symptoms at 10-week postinjury (Singh et al. 2018). Overall, P-TD has an estimated point prevalence of 30%, in which around 50% of patients with moderate to severe TBI experience episodes of P-TD in the first year after injury alone (Juengst et al. 2017a). In fact, developing depression appears to be the highest during the first year after injury. Nonetheless, in TBI patients, the risk of developing depression is higher compared to the general population, even several years after the injury (Koponen et al. 2002).

While the prevalence of depression after TBI is known to be elevated, the frequency with which depressive disorders manifest varies significantly in patients with TBI depending on the source. The literature proposes frequencies ranging between 6 and 77% (Seel et al. 2010). The large disparity in frequencies can be probably explained by the differences between studies in terms of the population studied and time elapsed since injury, in addition to differences in the measures and cutoff points used to diagnose depression (Guillamondegui et al. 2011a; Jorge, 2017). In a cohort study enrolling hospitalized TBI patients, no major differences in the rate of depression was observed among individuals with complicated mild, moderate and severe TBI, though cautious needs to be taken when extrapolating these results to individuals with uncomplicated mild TBI (Bombardier et al. 2010). Also, a longitudinal study examining the severity of depressive symptoms in men and women with mild-to-severe TBI found to gender-specific differences, underscoring the need for equal identification and treatment of P-TD for both genders (Lavoie et al. 2017). Clarification of depression severity can be attained through several validated scales including Beck Depression Inventory (BDI), Hamilton Depression Scale (HAM-D), Neurobehavioral Functioning Inventory Depression Scale and the Center for Epidemiologic Scales for Depression. For TBI patients in particular, clinically administered scales are considered beneficial and more advantageous than relying solely on patients' self-report of their experiences (Jorge 2017).

P-TD has severe consequences as it affects interpersonal, occupational and social functioning, impairs overall quality of life, and increases the risk of suicide (Durga Roy 2018). The etiology of P-TD; however, is difficult to determine. Although the data regarding risk factors for depression after TBI have been inconsistent, especially concerning gender and age variables (Jorge and Arciniegas 2014), it is accepted that a wide range of factors is involved. A scoping review conducted by Laliberté Durish et al. found that injury-related factors such as brain lesions as well as noninjury factors such as aging and poor socioeconomic status, may be predictive of P-TD (Laliberté Durish et al. 2018). In addition, a recent cohort study, conducted in a large national sample, found that the history of psychiatric disturbances pre-TBI is highly associated with the manifestation of depression following the injury (Albrecht et al. 2019). The strongest predictor was diagnosis of depression pre-TBI (OR 10.26; 95% CI: 9.95, 10.58), followed by bipolar disorder (OR 2.17; 95% CI: 2.02, 2.33), anxiety (OR 2.15; 95% CI: 2.08, 2.22), alcohol dependence (OR 1.50; 95% CI: 1.43, 1.56) and substance abuse (OR 1.50; 95% CI: 1.45, 1.54). Other risk factors significantly contributing to the development of P-TD include Alzheimer's disease and related dementias (OR 1.60; 95% CI: 1.53, 1.67) and female sex (OR 1.59; 1.55, 1.72). Such findings are consistent with other studies performed in the past few years. Cnossen et al., in a recent meta-analysis, reported that a history of depression was associated with higher odds of developing major depressive disorder post-TBI (OR 3.86; 95% CI 2.26, 6.59) (Cnossen et al. 2017). Moreover, in SHEFBIT (Sheffield Brain Injury after Trauma) cohort study involving mixed TBI population of all severities and etiologies, the 3-month prevalence of depression post-TBI was found to be very high and related to several injuries and demographic factors (Singh et al. 2018). P-TD was significantly associated with increasing severity of CT scan findings, nonwhite ethnicity, female gender, psychiatric history, alcohol intoxication at the injury onset, increasing TBI severity and in those who were unable to return to work in any capacity (Singh et al. 2018). Taking into consideration the location and severity of the brain injury, studies using resting-state neuroimaging have implicated disruption of frontal brain networks as a potential contributor to the development of major depression (Kaiser et al. 2015). Jorge et al. determined the structural neuroimaging correlates of major depression occurring during the first year after TBI in patients with closed head injury (Jorge et al. 2004a). It was reported that, in both patients with a history of depressive or anxiety disorders and in patients without a history of psychiatric illness, major P-TD was significantly associated with reduced left prefrontal gray matter volumes, particularly in the ventrolateral and dorsolateral regions.

However, it is unclear if the reduced prefrontal volumes observed are the result of the pathophysiological mechanisms initiated by TBI or they constitute a preexistent trait associated with an increased risk to develop mood disorders. In a recent review and meta-analysis, Kumar et al. illustrated the interrelationship of P-TD and other common secondary complications of a moderate-to-severe TBI including pain, fatigue, poor cognition, poor functional recovery and lower self-satisfaction (Kumar et al. 2018). The study proposed that developing depression post-TBI rarely occurs in isolation therefore patients likely have other chronic co-occurring conditions that may have a cumulative deleterious effect on quality of life. The evaluated studies yielded mixed results; however, evidence suggests that P-TD precedes the development of executive dysfunction, and there is a strong association between fatigue and P-TD, with fatigue preceding P-TD. The importance of this study relies on the fact that these conditions are common in TBI populations but rarely manifest alone.

It is important to understand the inter-relationship between such impairments for better treatment and rehabilitation planning. Interestingly, genetic polymorphism has been researched as well as a predictor of P-TD. In the study conducted by Chan et al., investigating serotonin transporter (5HTT) polymorphism and the incidence or severity of depression after TBI did not support a significant association between the two (Chan et al. 2008). Nonetheless, it is possible that genetic variants of the 5HTT possibly modify a patient's response to antidepressant treatment. In another study, Lanctôt and colleagues (2010) investigated, in a TBI population, the effects of patients' genotype with their response to citalopram (Lanctôt et al. 2010). It has been shown that C-(677) T polymorphism of the methylene tetrahydrofolate reductase (MTHFR) gene and the val66met polymorphism of the brain-derived neurotrophic factor (BDNF) gene were associated with favorable treatment response (Lanctôt et al. 2010). Depression does not arise from a single known pathogenic mechanism (Belmaker and Agam 2008). A prior history of mood disorders and other comorbidities, demographic, behavioral, psychosocial, biological and genetic factors may contribute to the development of depression post-TBI. It is important to understand the heterogeneity in P-TD risk factors and its underlying causes after TBI in order to develop targeted disease-modifying therapies (Bodnar et al. 2018).

Anatomical and molecular changes associated with TBI and post-traumatic depression

An extensive body of research indicates that TBI is associated with changes at the neuroanatomical and molecular levels that can progress over weeks or even months after the initial insult, and that could eventually lead to long-term behavioral changes. Neuropathologically, TBI is known to be accompanied by alterations in cortical and subcortical areas, and by changes in the density and morphology of white matter connecting these structures (Jorge and Starkstein 2005). It is also frequently associated with diffuse neuronal damage and cell loss in brain regions like the prefrontal cortex, the neocortex, the hippocampus, the thalamus, the basal ganglia, the striatum and the amygdala (Golarai et al. 2001; Jorge and Starkstein 2005; Raghupathi et al. 2000; Smith et al. 1997). This is only true, however, in the case of closed head nonpenetrating injury; in cases of open head injury, focal rather than diffused injury where a marked primary and secondary injury phases are clearly marked.

In animal models of depression or in individuals diagnosed with depression following TBI, P-TD was also shown to be associated with several abnormalities at the anatomical and molecular levels (Table 1). For instance, investigators reported the presence of left dorsolateral frontal and/or left basal ganglia lesions in individuals with P-TD (Fedoroff et al. 1992). P-TD was also associated with reduced gray matter volume in the left prefrontal cortex as suggested by magnetic resonance imaging (MRI)-based experiments (Jorge et al. 2004b). Furthermore, TBI individuals with depression were shown to have significantly smaller left inferior frontal, left middle, and left superior gyrus volumes compared to nondepressed TBI individuals (Jorge et al. 2004b). Also noteworthy to mention are two independent studies showing that depressive symptoms are commonly observed among TBI patients with right hemisphere (Jorge et al. 1993) and right orbitofrontal (Grafman et al. 1996) lesions, indicating that damage of these two regions is highly associated with increased risk of developing depression.

Accumulating evidence has also indicated that inflammatory biomarkers may contribute to the development of P-TD following TBI (Bodnar et al. 2018; Miller and Raison 2016). In the past few years, a number of studies have yielded intriguing findings, demonstrating a link between TBI-induced inflammatory biomarkers such as cytokine and chemokines, and the risk of developing depression (Bodnar et al. 2018; Juengst et al. 2015; Sharma et al. 2017). Cytokines are signaling proteins that act on specific receptors, yielding either a pro-inflammatory or an anti-inflammatory response. They can also act as primarily lymphocyte growth factors and can polarize the immune response to foreign antigens (Dinarello 2007). On the other hand, chemokines are a subclass of cytokines and are essentially involved in endocrine functions and in the migration of white blood cells, namely leukocytes (Hughes and Nibbs 2018). In TBI patients from a military population, studies found that elevated levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), two pro-inflammatory cytokines were associated with the occurrence of depression (Devoto et al. 2017). Elevated TNF-α and IL-6 levels were also found to be associated with moderate-to-severe TBI independent of the presence of depressive symptoms, with effects typically lasting 1 week postinjury (Juengst et al. 2014; Kumar et al. 2016b; Nwachuku et al. 2016b; Roberts et al. 2013; Yan et al. 2014). However, no significant changes in TNF-α following TBI were found in other studies (Aisiku et al. 2016; Kumar et al. 2016a; Nwachuku et al. 2016a). Such discrepancies among findings are also observed in studies investigating the changes in IL-1β, another pro-inflammatory cytokine, with some studies showing elevated IL-1β level (Mellergard et al. 2011; Nwachuku et al. 2016a; Roberts et al. 2013) while other studies showing no change at all (Aisiku et al. 2016; Frugier et al. 2010; Kumar et al. 2016a) following a TBI. The discrepancy in biomarker levels among the reported studies could be attributed to differences in injury severity.

Furthermore, there is extensive evidence in the literature studies indicating changes in neurotransmitter level resulting from TBI. For instance, results from clinical reports indicate that the concentration of the excitatory neurotransmitter, glutamate, is markedly elevated in the cerebrospinal spinal fluid (CSF) of individuals with TBI (Yamamoto et al. 1999). The elevation in extracellular level of glutamate associated with excitotoxicity may lead to neurological and cognitive abnormalities (Biegon et al. 2004). Interestingly, an increase in glutamate level was also demonstrated in animal models of depression. Recent findings from preclinical and clinical studies have strongly implicated glutamate and its receptors in the pathophysiology of depression (Niciu et al. 2014). Thus, alterations in glutamatergic neurotransmission appear to be an important link between TBI and depression. More importantly, disruption of excitatory transmission is also balanced by a disturbance in inhibitory pathways. GABA, the principal inhibitory neurotransmitter that modulates excitatory transmission in the brain is decreased following TBI (Cantu et al. 2015). The loss of GABAergic neurons and their receptors in affected brain areas disrupt the balance of

Table 1: Human and animal studies reporting anatomical, molecular and/or functional changes in P-TD.

Author and year	Study sample	Methodology	Anatomical, molecular and/or functional changes associated with P-TD
Human studies			
Fedoroff et al. 1992	66 patients with closed head injury (19 with P-TD)	Computer tomography scans	– Presence of left dorsolateral frontal lesions and/or left basal ganglia lesions associated with increased risk of P-TD – Parietal-occipital and right hemisphere lesions associated with increased risk of P-TD – Reduced global outcome in individuals with P-TD
Jorge et al. 1993	66 patients with TBI (7 with anxiety and depression, 10 with depression alone)	Neuroimaging techniques	– Right hemisphere lesions in TBI individuals with both anxiety and depression – Left anterior lesions in TBI individuals with depression alone
Fann et al. 1995	50 patients with TBI (13 with depression, 12 with anxiety disorder, and 4 with substance use disorder)	Questionnaires and functioning examination tests	– Reduced emotional role functioning, mental health, and general health perceptions in TBI individuals with depression and anxiety compared to non-depressed and non-anxious TBI individuals
Grafman et al. 1996	57 control and 279 veterans with penetrating head injury	Family observations and self-questionnaires	– TBI individuals with right orbitofrontal lesions have increased risk of developing depression
Jorge et al. 2004	91 patients with TBI (30 with P-TD)	MRI during the year that followed the injury; overt aggression scale; social functioning examination scores; memory and executive functioning tests	– Reduced left prefrontal gray matter volumes in the ventrolateral and dorsolateral regions in P-TD – Reduced left inferior frontal, left middle, and left superior gyrus volumes in P-TD – Reduced social, memory and executive functioning in P-TD – Significant aggression behavior in TBI patients with P-TD
Dawson et al. 2007	46 TBI individuals and 15 control	Structured interview. Return to productivity was assessed by the ability to return to work and/or school	– Correlation between P-TD among TBI individuals and poor return to productivity
Bombardier et al. 2010	559 patients with mild to severe TBI (53% diagnosed with depression)	Patient health questionnaire depression and anxiety modules	– Higher risk of developing co-morbid anxiety disorder in depressed TBI patients compared to non-depressed TBI patients
Devoto et al. 2017	20 control and 63 TBI individuals with reported symptoms of P-TD	Measurement of cytokine level in the plasma	– Increased TNF-α and IL-6 plasma level in the TBI individuals with P-TD
Animal studies			
Milman et al. 2005	Weight-drop impact acceleration injury TBI mouse model and control mice	Swim T-maze, passive avoidance test, and forced swimming test	– Symptoms of depression in TBI mice were accompanied by deficits in cognitive learning ability
Cope et al. 2012	Controlled cortical impact to the medial frontal cortex in Sprague-Dawley rats	2-Bottle saccharin preference test of anhedonia	– Decrease preference for saccharin in TBI rats – Improved depression-like behavior in TBI rats given zinc injection and fed with the zinc supplement diet
Fenn et al. 2015	Midline fluid percussion injury in adult male BALB/c mice	Tail suspension test	– Increased immobility time in the tail suspension test – Brain edema and enhanced expression of inflammatory genes

Table 1: (continued)

Author and year	Study sample	Methodology	Anatomical, molecular and/or functional changes associated with P-TD
Taylor et al. 2006	Cortical contusion injury in adult male Sprague-Dawley rats	Forced swim test	– Increased immobility during the forced swimming test – Reduced febrile response to immune challenge – Reduced plasma levels of corticosterone in response to restraint stress
Piao et al. 2019	Adult male CD1 mice subjected to closed-skull midline TBI	Quantitative real-time PCR, Western Blot, tail suspension test, forced swim test, sucrose preference test	– Decreased mRNA and protein expression of glutamate transporters – Increased immobility in the tail suspension and forced swim tests – Reduced sucrose preference

excitation and inhibition leading to cell damage and impaired behavior. Given the crucial roles of GABAergic neurons, it is not surprising that GABAergic system dysfunction has been implicated in anxiety and major depression disorders (Luscher et al. 2011; Nuss 2015).

Changes in the cholinergic system were also reported among TBI individuals, with findings indicating increased cholinergic neuronal activity during the initial stages of TBI, and a decreased cholinergic neuronal activity occurring during later phases (Dixon et al. 1996; McIntosh et al. 1998; Shao et al. 1999). Damage to the cholinergic system following TBI is believed to contribute to abnormalities in memory and cognition (Murdoch et al. 2002; Salmond et al. 2005). There is finally evidence in TBI of altered dopamine neurotransmission, including reduced dopamine transporter protein level (Yan et al. 2002) and disruption of nigrostriatal dopamine pathway (Donnemiller et al. 2000), as well as altered serotonin neurotransmission, including increased serotonin receptor 1A (5-HT1A) level (Wilson and Hamm 2002). More recently, P-TD was shown to be associated with increased hippocampal stress-induced glutamate level and a downregulation of astrocyte glutamate transporters in mice (Piao et al. 2019). Dysfunction of these neurotransmitter systems may ultimately contribute to the development of depression after TBI, though more work is needed to better understand the causal relationship between neurotransmitter level and P-TD.

Altogether, the above-mentioned findings indicate that TBI and P-TD are accompanied by various anatomical and molecular changes that include reduced prefrontal gray matter, lesions in the basal ganglia and frontal cortex, increased pro-inflammatory cytokine level, and dysfunction in neurotransmitter systems, including the cholinergic, glutamatergic, dopaminergic and serotonergic systems. However, the majority of studies, to date, have focused on individuals with TBI without particularly looking at the link with P-TD. More research is therefore needed to better understand the anatomical and molecular biomarkers that are associated with the occurrence of P-TD following TBI.

Behavioral and functional changes associated with post-traumatic depression

There is an extensive literature regarding the behavioral and functional changes associated with P-TD (Table 1) and TBI. The vast majority of neuropsychological findings point to impaired performance in attention paradigms and working memory tasks in individuals with TBI (McAllister et al. 2004; McDowell et al. 1998; Zhang et al. 2004). There is also evidence showing deficits in autobiographical memory following TBI (Dritschel et al. 1998; Levine et al. 1998; Tulving et al. 1988; Wheeler and Stuss 2003) and dysexecutive syndrome, which encompasses impaired planning and reasoning, as well as deficits in stimuli saliency attribution and selection of appropriate behavior (Alexander and Stuss 2000; Levin et al. 2002; Levin and Kraus 1994). In addition, disability from TBI frequently includes difficulty in finding employment and in maintaining social relationships (Hibbard et al. 1998 ; Kreutzer et al. 2003; Sander et al. 1996). Symptoms of depression are, however, the leading adverse effects that follow a TBI, and can influence many aspects of the life of affected individuals (Bodnar et al. 2018).

Depression, also referred to as major depression or major depressive disorder, is a neuropsychiatric disorder characterized by a persistent feeling of sadness and a loss of interest (Fakhoury 2015). Symptoms such as reduced appetite, impaired sleep, and thoughts of suicide are also commonly observed in depressed individuals (American

Psychiatric Association 2013). In addition to the detrimental effects on the individual, this disease can be a heavy burden to the society in terms of health care costs but also to caregivers of affected individuals. In patients with TBI, symptoms of depression such as impaired sleep and appetite may occur as a consequence of brain injury independent of the associated mood disturbance (Figure 1A) (Jorge and Starkstein 2005). P-TD is also associated with reduced global outcomes (Fedoroff et al. 1992), reduced quality of life (Christensen et al. 1994; Rutherford 1977) and deficits in cognitive learning ability (Milman et al. 2005). Post-concussive symptoms such as headache, blurred vision, dizziness and poor mental health are also highly reported in P-TD (Figure 1A) (Fann et al. 1995; Rutherford 1977).

In a study investigating depression-related symptoms across the first 10 years post-TBI, Seel and colleagues (2003) showed that the most commonly reported symptoms in affected individuals were fatigue, poor attention, rumination, self-criticism and feelings of guilt (Seel et al. 2003). In another study, Jorge and colleagues (2004) compared the behavioral symptoms between TBI patients with and without depression. Results of their study found no differences in activities of daily living and global measures of cognition between depressed and nondepressed TBI patients, as measured by Functional Independence Measure scores and Mini-Mental State Examination scores, respectively (Jorge et al. 2004b). However, the authors of the study found that TBI patients who developed depression had poorer psychosocial outcomes in the social functioning examination test at the 6-month and 12-month follow-up examination compared to TBI patients who did not develop depression (Jorge et al. 2004b). Lower scores on memory and executive functioning were also observed in depressed TBI individuals as compared to nondepressed TBI individuals (Jorge et al. 2004b). Interestingly, in a prospective cohort study conducted by Dawson and colleagues in 2007, the severity of depression among TBI individuals related to poor ability to return to work (Dawson et al. 2007). A strong negative correlation between other mood disorders (like anxiety disorders) and the ability to return to work was also found in patients with acquired brain injury (for review see Garrelfs et al. (2015)). P-TD was also shown to be associated with disrupted behavior (Jorge et al. 2004b; Juengst et al. 2017c), with evidence indicating that depression preceded the occurrence of behavioral disruption (Juengst et al. 2017b; Myrga et al. 2016).

Taken together, a substantial number of studies showed that P-TD is associated with a numeral debilitating psychiatric conditions such as aggression, anxiety, panic disorder and post-traumatic stress disorder (PTSD) (Figure 1A) (Fann et al. 1995; Guillamondegui et al. 2011b; Jorge et al. 2004b). Anxiety disorders and aggressive behavior are the most prevalent, affecting up to 60% of depressed TBI patients (Bombardier et al. 2010; Fann et al. 1995; Jorge et al. 2004b; Jorge et al. 1993). On the other hand, PTSD and panic disorders are observed in approximately 40 and 15% of depressed individuals, respectively, while being nearly absent in the nondepressed TBI population (Bombardier et al. 2006; Fann et al. 1995).

Animal models of TBI and experimental paradigms to study depression

Owing to the heterogeneous clinical nature of TBI, a wide array of animal models have been developed and employed to mimic the pathophysiology of this disorder and its associated neuropsychiatric symptoms (Albert-Weissenberger and Sirén 2010; Malkesman et al. 2013; Xiong et al. 2013). These models are essential to understand the neuropathological and functional characteristics

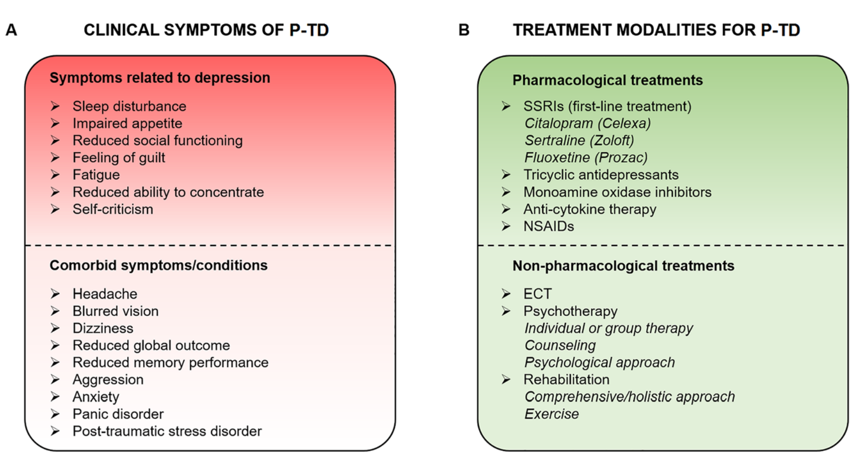

Figure 1: Schematic illustrating the symptoms and treatment modalities for P-TD
(A) Clinical symptoms and comorbid conditions associated with P-TD
(B) Pharmacological and nonpharmacological treatments for P-TD.

associated with TBI and P-TD, and could be used to investigate potential therapeutic modalities. Rodent models are the most frequently used owing to their modest cost and small size, and they are relatively easy to manipulate (Xiong et al. 2013). Among the rodent models of TBI, the most employed models include the weight-drop impact acceleration injury model (Foda and Marmarou 1994; Marmarou et al. 1994), the fluid percussion injury model (Carbonell et al. 1988; Dixon et al. 1987), the controlled cortical impact injury model (Dixon et al. 1991; Smith et al. 1995), the closed head injury model (Bodnar et al. 2019) and the blast injury model (Yarnell et al. 2013).

Although several animal models were successfully developed to mimic the symptoms of TBI, only few studies using TBI models were able to observe depression-like symptoms. For instance, Milman and colleagues (2005) used the forced swimming test, a behavioral paradigm to assess depression-like symptoms (Yankelevitch-Yahav et al. 2015), to show that mice with experimental TBI caused by a weight-drop impact acceleration injury exhibit severe depressive-like symptoms compared to control animals (Milman et al. 2005). Similarly, Taylor and colleagues (2006) found that TBI rats induced by cortical contusion injury showed increased immobility during the forced swimming test, which is indicative of depressive-like symptoms, and showed reduced febrile response to an immune challenge and reduced corticosterone level to restraint stress (Taylor et al. 2006). In another study, Fenn and colleagues (2015) used the tail suspension test; a behavioral paradigm for assessing depression-like symptoms based on the immobility time as a measure of behavioral despair (Cryan et al. 2005). Results of their study demonstrated that mice with TBI based on a fluid percussion injury had increased immobility time compared to the control sham-operated mice, suggesting that TBI is associated with the presence of depressive-like symptoms (Fenn et al. 2015). Interestingly, TBI was also associated with an inflammatory response that manifested itself by the presence of brain edema and an increase in inflammatory gene expression and microglia activation (Fenn et al. 2015). Also, noteworthy to mention is the study by Cope and colleagues (2012) using the 2-bottle saccharin preference test in rats with controlled cortical impact TBI (Cope et al. 2012). The saccharin (or sucrose) preference test is a well-established behavioral test for depressive-like symptoms, and is based on the fact that normal rodents with normally exhibit a higher preference toward the sweeter solution, and that this preference will diminish in rodents exhibiting anhedonia, a depression-like symptom (Pucilowski et al. 1993; Willner et al. 1987). Using this behavioral test, Cope and colleagues (2012) showed that TBI rats showed a significantly lower preference for saccharin compared to the control sham rat 8 days following injury, indicating the development of anhedonia (Cope et al. 2012). Interestingly, dietary zinc supplements combined with an early intraperitoneal zinc injection significantly reduced anhedonia in TBI rats, suggesting that zinc supplementation may be an effective treatment option for P-TD (Cope et al. 2012). Last but not least, a study employing adult mice subjected to closed-skull midline TBI reported a significant increase in immobility during the tail suspension and forced swim tests and a marked reduction in sucrose preference, which are all indicative of depression-like symptoms (Piao et al. 2019).

However, several other studies using animal models of TBI failed to observed depressive-like symptoms; such discrepancies are likely attributed to differences in experimental settings and animal models used (Jones et al. 2008; Schwarzbold et al. 2010; Vucković et al. 2008). Interestingly, one study showed that activation of the immune and inflammatory systems (through peripheral injection of lipopolysaccharide) is needed to establish a depressive-like phenotype subsequent to the induction of TBI (Fenn et al. 2014), a process referred to as inflammatory “priming” (Witcher et al. 2015).

Altogether, animal models of TBI represent a unique tool to investigate the molecular and behavioral changes associated with brain injury and P-TD. Due to the heterogeneous and complex nature of TBI, several models were developed over the past few years so as to mimic different aspects of brain injury. These models have been crucial in better understanding the neurobiology underlying P-TD, and have helped researchers develop novel and effective therapeutic strategies for this condition. These strategies are discussed in the following section.

Therapeutic interventions for treating post-traumatic depression

From all the hypothesis on depression, the serotonin (5-HT) hypothesis, which states that a reduction in brain 5-HT level plays a role in the pathophysiology of depression, is the most studied and influential to date (Fakhoury 2016). Since its formulation, several studies have investigated the possibility of using the 5-HT system as a potential target for treating depression. The Food and Drug Administration (FDA) now approves the used of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression, anxiety and other mood disorders (FDA 2014) (Figure 1B). Correspondingly, and given their favorable side effect profile, SSRIs are also recommended for treatment of depressive symptoms in individuals with TBI (INESS-ONF 2015) and have been the subject of several human trials over the past few years. In an open-label, single-arm design trial that included individuals with mild-to-moderate TBI, citalopram, an SSRI sold under the name of Celexa, was shown to be effective in ameliorating depression-related symptoms as assessed by the HAM-D scale in more than 40% of participants (Rapoport et al. 2008).

Similarly, the SRRI sertraline (Zoloft), yielded positive responses as assessed by the HAM-D scale in individuals with a TBI that lasted for more than 6 months (Ashman et al. 2009) or more than 1 year (Fann et al. 2017). In another randomized clinical trial that included depressed individuals with mild-to-moderate TBI, the combination of sertraline with methylphenidate—a central nervous system (CNS) stimulation used to treat attention deficit hyperactivity disorder (ADHD)—yielded greater improvements in HAM-D scores compared to the placebo group, and provided added benefits compared to results of monotherapy, though the small sample size (30 patients) and short duration of the study (4 weeks) limit the ability to draw reliable conclusions (Lee et al. 2005). Moreover, treatment with the SSRI, fluoxetine (Prozac), for a period of 35 weeks led to improvements of depression-related symptoms in TBI patients as measured by the HAM-D score (Horsfield et al. 2002). Other antidepressants, including the tricyclic antidepressants (Dinan and Mobayed 1992; Saran 1985; Wroblewski et al. 1996) and the monoamine oxidase inhibitors (Newburn et al. 1999) have also been investigated for the treatment of post-TBI depression, though results have not always been favorable, and SSRIs remain the firstline of treatment by clinicians (for review, see Fann et al. (2009); Kreitzer et al. (2018); Silverberg and Panenka (2019); Yue et al. (2017)).

The secondline of pharmacological treatment for post-TBI depression includes the use of anti-inflammatory drugs (Figure 1B). Based on evidence that inflammation may contribute to the development of P-TD, several investigators have explored the possibility of using anti-inflammatory drugs, including molecules that inhibit cytokine production, as a therapeutic strategy for post-TBI depression (Simon et al. 2017). To date, there are no published data on completed clinical trials investigating the use of anti-cytokine treatment for depression following TBI, however, there is ample evidence from preclinical research exploring this therapeutic strategy. For instance, in a study using a closed head injury model of diffuse TBI, suppression of pro-inflammatory cytokines production, including TNF-α and IL-1β, with MW151, a CNS-penetrant and water soluble molecule, was shown to improve recovery in learning and memory (Bachstetter et al. 2015). Similar findings were found with MW151 treatment in a closed head injury mouse model of Alzheimer's disease (Webster et al. 2015). There is also extensive evidence showing that nonsteroidal anti-inflammatory drugs (NSAIDs) exert anti-inflammatory activity in experimental models of TBI through inhibition of inflammatory cytokines and prostaglandins, though this anti-inflammatory effect was not shown to be sufficient and effective in reversing the functional impairments produced by TBI (Bergold 2016). Also noteworthy to mention are studies showing that minocycline, an antibiotic with immunomodulatory and anti-inflammatory properties (Adembri et al. 2014; Garrido-Mesa et al. 2013), reduces chronic inflammatory (Scott et al. 2018) and improves neurological outcomes post-TBI (Koulaeinejad et al. 2019). Minocycline was also shown to exert robust antidepressant activity (Rosenblat and McIntyre 2018) and to ameliorate motor, anxiety and memory-related symptoms of mild blast-induced TBI (Kovesdi et al. 2012), though its antidepressant activity was not directly tested in animal models or patients with TBI.

Finally, there is evidence supportive of the efficacy of electroconvulsive therapy (ECT), psychotherapy and rehabilitation in treating P-TD (Fann et al. 2009) (Figure 1B). In a study by Kant and colleagues (1999), ECT was used in patients with closed-head injury to evaluate its effect on depression symptoms using the Montgomery-Åsberg Depression Rating Scale (MADRS) (Kant et al. 1999). Among the 9 patients with mood disorder following TBI, 2 patients show improved response to initial treatment with ECT and became responders during continuation ECT (Kant et al. 1999). More recently, Martino et al. (2008) presented the case of a 28-year-old man with symptoms of depression following a history of TBI. The patient initially failed to respond to antidepressant medication, but after 8 sessions of ECT, the patient reported feeling much better and his depression score, as assessed by the Hamilton Rating Scale for Depression ($HRSD_{24}$), significantly decreased (Martino et al. 2008). The patient subsequently received 4 continuation treatments after being discharged from his psychiatrist. These findings indicate that ECT constitutes a safe and effective alternative approach to antidepressant medication in patients with post-TBI depression. Other nonpharmacological approaches that have been investigated for treating depression in TBI patients include psychotherapy (i.e., individual or group therapy, counseling, psychological approach) and rehabilitation (i.e., comprehensive/holistic approach, exercise) (Fann et al. 2009). For instance, the case report by Ownsworth in 2015 using 13 weekly psychotherapy sessions with education on brain injury (Ownsworth 2005) and the randomized controlled trial by Tiersky and colleagues using neuropsychological rehabilitation combined with individualized cognitive behavioral therapy for 11 weeks (Tiersky et al. 2005) reported positive effects of treatment on depression-related symptoms as assessed by the Depression Anxiety Stress Scale (DASS) and the Symptom Checklist-core depression (SCL-90-R) scale, respectively. Other studies, however, reported no effect of psychotherapy or rehabilitation on post-TBI depression, though the lack of treatment effect may be due to several factors, including the heterogeneity of the study samples (Anson and Ponsford 2006; McMillan et al. 2002; Powell et al. 2002). More research is definitively needed prior to recommending psychotherapeutic or rehabilitation interventions for the treatment of P-TD.

Conclusion

As a complex and heterogeneous disorder, TBI has been associated with several neuropsychiatric conditions, the most frequent one being depression. Accumulating evidence has shown that P-TD is characterized with a wide array of anatomical and molecular changes that include reduced brain gray matter volume and increased production of pro-inflammatory cytokines. Results from animal and human studies also suggest that P-TD is associated with comorbid conditions and symptoms like anxiety, aggression, PTSD, panic disorder and reduced memory performance. Although animal models of TBI had relatively mixed success in mimicking the symptoms associated with depression, some studies were able to observe depressive-like behaviors after TBI using behavioral tasks such as the forced-swim test, tail suspension test and sucrose preference test. Also, findings from previous studies have shown that pharmacological interventions that help restore the aberrant immune and inflammatory response due to brain injury could hold great promise in treating P-TD. Antidepressant medications, including SSRIs, remain nonetheless the first-line of treatment for P-TD. For some patients, when antidepressant therapy is not effective or poorly tolerated, other therapeutic strategies should be considered, including ECT, psychotherapy and rehabilitation. However, in the majority of cases, the most adequate treatment should consist of a comprehensive combinatorial approach that includes pharmacotherapy as well as psychotherapy and rehabilitation.

Although there has been substantial progress in research to delineate the neural mechanisms underlying P-TD, there are still several missing gaps in the literature that need to be addressed. For instance, it is not well understood if P-TD constitutes a primary or secondary outcome to TBI. In particular, more work needs to be done to determine whether P-TD is a direct consequence of TBI's associated lesions of neural pathways, or if it occurs following changes in the individual's experience and mental state. Another issue in the existing literature is that the vast majority of studies investigating P-TD significantly vary in terms of their design, sample size and diagnosis of depression, which often leads to large variability in the reported results, hampering conclusions about prevalence and associated mechanisms. Meta-analyses that quantitatively analyzes the currently available literature studies and data are highly warranted. Effort is also needed to standardize the description of P-TD and the specification of treatment modalities, in particular rehabilitation and psychotherapy programs. Finally, future research should focus on clarifying the anatomical, molecular and functional changes associated with P-TD, since results of these investigations could eventually pave the way toward the development of novel and more efficient therapeutic approaches.

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