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Neuropsychological and Neuropsychiatric Deficits Following Traumatic Brain Injury: Common Patterns and Neuropathological Mechanisms

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Abstract

Traumatic brain injury (TBI) in all degrees of injury severity mainly induces deviant cognitive, emotional and behavioral alterations that lead to their respective disorders. This brief overview strives to define the variables that determine the risk of occurrence of these disorders and to describe the common patterns of these disorders and their relevant neuropathogenetic mechanism(s). In addition, post-traumatic deficits can interact and exacerbate the probability, , persistence and severity of each variable relative to one another. Since, neural substrates and pathways further complicate these TBI sequels, identifying the neuropathogenetic basis of these deficits using human brain mapping techniques has been a milestone in the investigations of the TBI field. It has been found that TBI-induced functional disturbance of one or more specific neural networks may cause a distinct disorder. However, this matter is a topic of discussion in TBI research. Evidently, prevalent, unpleasant TBI consequences such as motivational deficits, antisocial behaviors, aggression, disability of inhibitory control and executive function are mostly associated with the disruption of neural circuits originated from separate parts of the prefrontal cortex connected to thalamic nuclei and basal ganglia. Evidence strictly emphasizes the abnormality of the default mode network (DMN) either within the network or between it and other neural networks for a majority of cognitive, emotional and sleep disorders after TBI. Therefore, imbalanced neural circuits due to TBI may serve as diagnostic and prognostic biomarkers for post-traumatic neuropsychological and neuropsychiatric disorders as well as a guide for circuit-based neurotherapy.

Key words: Traumatic brain injury, Intrinsic neural networks, Neurotransmitter systems, Behavior, Cognition, Emotion

Introduction

Traumatic brain injury (TBI) is a major cause of morbidity and disability in developing countries (1-6), which disrupts the health status of patients and jeopardizes their functional independence and quality of life (7-11). Today, health policy-makers tend to mainly focus on preventive programs to reduce the occurrence of TBI as well as optimal management and the early rehabilitation of individuals suffering TBI. Therefore, a growing number of neuroscience studies have been assessing the behavioral, cognitive and emotional consequences of TBI to discover the underlying neuropathological mechanisms and the various risk factors of the related complications (12-19). Evidently, varying complications that are attributable to the mentioned aspects may occur following TBI in different types and severities of the neural lesion (20-29). Disabilities caused by focal lesions have symptoms similar to those of stroke, specific to the impaired anatomic brain region. In such disabilities, considering the injured part of the brain structure and the severity and extent of the lesion, the underlying neural function that controls the behavior is disturbed which in turn leads to local disability (30). However, the disabilities that originate from diffuse lesions can extensively disrupt the networks and neural circuits (30, 31), contributing to deficiencies in information processing speed and information integrity which are fundamental for performing high-level cognitive and emotional functions (32-35). Focal lesions are mainly caused by the impact of the brain with the intracranial bones. Hence, the frontal and temporal bridges are very vulnerable to these lesions, due to their proximity to the sharp edges of the sphenoid bone. Though the anterior regions of the brain, the junction of white and gray matter, and the rostral areas of the brain stem are the most vulnerable areas to diffuse lesions due to the shearing and compression of the brain tissue and axons after linear and angular acceleration and deceleration of the brain (17, 36). In minor TBI, post-traumatic disorders often happen despite the lack of a visible brain abnormality on CT scans or conventional MRIs. However, the existence of these disorders in mild TBI patients may be associated with the subtle impairments of brain structures and functions represented by the advanced neuroimaging techniques. Therefore, an early diagnosis and accurate prognosis of the post-traumatic neuropsychological and neuropsychiatric deficits might, at least partly, assign a proper detection of neural substrates correlated to each disorder. Fundamentally, neuroscientists attribute cognitive, emotional and behavioral disabilities to the presence of maladaptive neuroplasticities which are known to increase and decrease the power of the synapse in adjacent and distant regions of the lesion, disturbing the normal networking inside the brain (37). This compensatory neuroplasticity is probably induced by secondary insults promoted through neuropathological processes that may initiate from the first few minutes post TBI and remain for a long time (38, 39). Thus, it is suggested that early

rehabilitative interventions accompanied by non-invasive brain stimulations may modulate these compensatory neuroplasticities, leading to potent clinical improvement (40). In this regard, identifying TBI-induced abnormal neural networks involved in post-TBI deficits in order to target them using neuromodulatory approaches is necessary . The purpose of this narrative review is to provide a brief overview of the common patterns of neuropsychological and neuropsychiatric disorders after TBI and to present the disrupted neural circuits and imbalanced neurochemical or neurotransmitter systems that are the underlying mechanisms of these disorders, according to human brain mapping and preclinical data in TBI subjects.

Common cognitive disorders after TBI

Cognitive disorders following TBI include reduced processing speed of visual and verbal information, attention and working memory deficits, retrograde and anterograde amnesia, communicative deficits and poor executive function (41). Depending on the TBI severity, the deficits can have varying severities (18). In severe injuries, the disorders occur in the first phase and may persist days or months after the event of the TBI (29). Acute mild TBIs may produce early cognitive impairments (42). However, the prevalence of constant cognitive problems in patients with mild TBI is under 20% (23). Factors such as the level of cognition before the injury (43-45) and the presence of psychiatric or somatic symptoms accompanied by cognitive deficits after TBI (46) are involved in the sustainability of cognitive impairment. According to results from previous studies, major changes in the concentrations of brain metabolites such as N-acetyl aspartate (NAA), glutamine, lactate, myoinositol and choline (Cho) as well as neural function, especially in the ventromedial prefrontal cortex (vmPFC) and the dorsolateral prefrontal cortex (DLPFC), is presumed to be related to post-traumatic cognitive deficits and recovery (47-54). Likewise, the tractography data in these patients indicated that the reduced integrity of neural fibers such as fronto-striato-thalamic circuits, the corpus callosum, and fornix are associated with cognitive impairments after TBI (55-59). In recent decades, neuroscientists have found the related evidence on the existence of these metabolic and functional alterations in the brain in the early phase of minor TBI, despite the manifestation of normal findings in CT and conventional MRI (53), insisting the necessary utilization of advanced imaging techniques in order to identify patients at risk for post-concussion syndrome which may occur long after a mild TBI.

Attention and working memory deficits

Evidently, attention and working memory deficits usually occur together. The involved neural substrates are the cortical areas in the middle temporal gyrus, parietal cortex, cingulate gyrus, and DLPC. According to the evidence, neurotransmitter systems that are mainly involved in attention deficit and working memory include catecholaminergic and cholinergic systems. Reduced concentration of acetylcholine, dopamine, and norepinephrine in neural synapses of these areas have found to be correlated with post-TBI cognitive deficits (16). Therefore, drugs which increase acetylcholine in central synapses such as anticholinesterases (e.g. donepezil), and catecholamines (e.g. methylphenidate) have been recommended to improve cognitive potential in TBI patients (60). Post-traumatic attention deficit depends on the severity of the lesion(s). In patients with severe lesions whose ascending reticular activating system (ARAS) is also damaged, the attentional bottom-up processing and arousal state are disrupted (61). In mild traumatic injuries, generally the top-down attentional processing is disrupted (62) which weakens various forms of attention including selective, sustained, alternative, and comprehensive attention (63). Studies have shown that the reduction of fractional anisotropy of cingulum fiber in diffusion tensor imaging (DTI) during the acute phase of mild TBI is associated with enduring attention deficits in the acute and chronic phases (64). Besides, studies on PET scans have revealed that the glucose reduction in the frontal cortex, posterior cingulate cortex, and cerebellum are associated with working memory impairment after TBI (65). Based on findings from MR spectroscopy studies, the decreased concentration of NAA metabolite and increased choline, myoinositol and lactate in the splenium of the corpus callosum are related to impaired attention and working memory (66).

Executive function deficit

Another cognitive domain that is disturbed by TBI is the executive function (67), mediated by a neural network called ECN (Executive Control Network) (68). The network consists of several nodes connected by axons, the most important of which are DLPFC and posterior parietal cortex (PPC). Furthermore, intact executive function appears to be controlled by default mode network (DMN) constituted by some neural regions including vmPFC, precuneus, posterior cingulate cortex (PCC) and white matter fibers connecting those together. Particularly, ECN has an inverse relationship with the DMN (69). Hence, the majority of the neuroscientists believe that after TBI, the activity of DMN is excessive, which inhibits the ECN network and causes subsequent poor performance of the patients in relevant cognitive tasks (70). TBI patients with poor ECN have problems in high-level cognitive activities that tie with everyday activities like problem-solving skills, abstract thinking, judgment, decision-making, self-monitoring,

flexibility, and planning (6). These cognitive dysfunctions not only impair the patient's personal life but also heavily affect their social life and participation in the community (71). It seems that executive dysfunction and verbal communication disabilities in the initial phase of lesion formation are the most important predictors of long-term neuropsychiatric disorders after TBI (19).

Communicative disorders

It is important to note that post-TBI communicative disorders are observed in most TBI cases and are fundamentally cognitive where a patient's interactions are disturbed both verbally and non-verbally. Following TBI, a large spectrum of communication deficits can be manifested. Patients with TBI with verbal impairment show flight of ideas due to sustained attention. They lose the coherence of thought and the message and intention of the conversation (72). Indeed, linguistic deficits after TBI are mostly characterized by deficits in lexical, syntax, semantic and pragmatic dimensions of language. Hence, the typical pattern of linguistic dysfunction after TBI is similar to the lingual profile represented in the fluent aphasia. Highly prevalent in this group of patients, anomia inhibits patients to express their verbal message (14). Moreover, exploring the non-verbal dimensions has proved that pragmatic skills are restrained in TBI patient. . Thus, the patient is unable to understand the feelings and emotions of the other person (partner) through the prosody of the speech and the gesture of the face and body language and does not observe turn-taking in conversation (71, 73, 74). These verbal and non-verbal communication disabilities are rooted in weak high-level cognitive functions, which require the integrated function of neural networks in temporal, parietal, and frontal lobes (14). These disabilities occur with higher probability in patients with damages to the fronto-temporal lobe and multiple damages including contusions co-occurring with subdural or intracortical hemorrhage (14). According to tractography data, the arcuate fasciculus, uncinate fasciculus and corpus callosum are particularly vulnerable to TBI and their disruption appears to be related to the linguistic deficit after TBI (75). It seems that a decrease in the concentration of NAA/Cho in the left frontal lobe is correlated to post-traumatic linguistic dysfunction regardless of the lesion side (76). Given that the linguist problems after TBI is mainly generated from deficient sustained attention and executive function (77), it is suggested that increased activity of DMN may be associated with a perturbation of cognitive elements involved in language processing after TBI (70, 78).

Amnesia

Post-traumatic amnesia (PTA) is mostly observed following TBI in which patients cannot remember the events which have occurred after the incident. They may even forget their personal information (79). PTA may last from less than an hour to more than a week and even a month. A high proportion of TBI patients have PTA for longer than one week or even one month (80). Given the evidence, PTA duration is able to predict the length of the hospital, risk of early and late epilepsy, and post-traumatic cognitive function status (79). Likewise, research has shown a positive correlation between the duration of PTA and retrograde amnesia (81, 82). Based on neuroscience knowledge, individuals with lesions in the anterior temporal and frontal lobes are at risk of retrograde amnesia, in which long-term declarative memory including semantic and episodic memories, as well as dimensions of procedural memory may be impaired (83). Sometimes post-TBI amnesia is anterograde, which in most cases accompanies retrograde amnesia. Usually, in the anterograde amnesia, neural lesions which have been caused by trauma are observed in the middle regions of the temporal cortex and the papez circuit with a gray matter composed of the anterior thalamus nucleus and mammillary body of the hypothalamus, and the cingulate gyrus, the entorhinal complex, the parahippocampus and hippocampus (83, 84). Based on the data obtained from DTIs, disruption of the white matter fibers of the brain, including fornix, mammillothalamic tract and thalamocortical tracts is usually observed in people with anterograde amnesia after TBI (83, 85, 86).

Common emotional and neuropsychiatric disorders after TBI

The most common abnormal emotional behaviors after TBI include impulsivity, irritability, aggression, physical/verbal outbursts (87-89), affective instability, intolerance, apathy (90, 91), rigidity and inflexibility, risky behaviors (92), lack of empathy (93), and lack of motivation/initiative (94). Data supports the predisposing role of executive function impairment during the acute phase of TBI on the subsequent appearance of impulsive and anti-social behaviors [27, 28]. Based on previous studies, the most common chronic psychiatric disorders after brain trauma include aggression, apathy, depression, and PTSD which can strongly be predicted by factors such as TBI severity, subcortical lesions and early post-traumatic linguistic dysfunction [6]. However, the development of post-traumatic neuropsychiatric disorders depends on multiple factors including baseline patients' characteristics and preexisting medical conditions such as past psychiatric diagnosis, premorbid behavioral problems, and the history of neurological disorder and substance abuse (95). Essentially, the most important neural substrates involved in the emotional and motivational behaviors are the ventromedial prefrontal-striatum-ventral thalamus (96, 97) which require a strong

interaction between glutamatergic, GABAergic and dopaminergic neurotransmitter systems for normal functioning (98). The dopaminergic projections of the ventral tegmental area (VTA) of the midbrain to the thalamus nuclei and ventral striatum are vital for modulating the activity of this circuit (99, 100). Damage to the structure and function of this circuit leads to a defect in motivation-related behaviors such as akinetic mutism, abulia, and apathy (101). Empirical studies have demonstrated that damage to dopaminergic, serotonergic and adrenergic, mesolimbic and mesocortical projections is generally the neuropathological cause of emotional disorders after TBI (102). These disorders are developed from all TBI severity. Human brain mapping investigations have indicated that the probability of occurrence of post-traumatic neuropsychiatric disorders is correlated with a reduction of functional connectivity in the anterior DMN following minor TBI.

Aggression

Aggression is typically characterized by signs such as physical and verbal outbursts, akathisia, maladaptive behavior, explosive anger, and irritabilit. The prevalence of aggression after TBI has been reported to be from 37% to 71% (103). Based on the evidence, it seems that variables such as age, gender, and TBI severity have not influenced the risk of aggression after TBI. However, psychosocial impairment and dependence in daily life activities after TBI appear to be the main risk factors of post-traumatic aggression appearance (88). Furthermore, a wide range of factors including environment, patient's medical history (104), genetics (105), and neuroendocrine and neurochemistry functions (106) may be associated with aggression in TBI patients. Aggressive behaviors negatively affect recovery rate during inpatient and outpatient rehabilitation interventions (107, 108). Thus, medical management for the recovery of post-traumatic aggression, especially in a high-risk population, is a serious priority. . Literature supports the effectiveness of beta-blockers and anticonvulsants for the treatment of agitation and aggressive behaviors after TBI (109). However, due to their troublesome side effects, they are not widely accepted to be prescribed to this population by clinicians (110). So far, the neuropathogenesis of aggression is not well elucidated. The few studies that have been done to understand the neural correlates of aggression use human brain mapping techniques. Furthermore, the findings of a resting-state functional MRI study has revealed that an elevation of functional connectivity between the right hippocampus and mid-cingulate cortex may be associated with aggression after mild TBI (111). Recent preclinical data have suggested that the reduction of the serotonin release by the serotonergic projections of Raphe nuclei to DLPFC may be related to anti-social behavior and aggression. Based on this dysregulation, the activity of

DLPFC and consequently the loss of the inhibiting control of the prefrontal cortex on the emotional processing of the limbic network result causes uncontrolled, illogical, automatic, and emotional outputs (112). Hence, it seems that aggressive patients with this pattern of neural dysfunction may benefit from SSRIs (89). However, in the last decade, the association between SSRI use and aggression has been considered (113, 114). Undoubtedly, it is a controversial matter that requires further accurate investigations, especially for this population.

Depression

Depression commonly develops in the first post-TBI year (115). Depressive disorders after TBI may be usually associated with anxiety disorders and aggression (89, 116). Various factors including genetic, demographic, developmental, and psychosocial variables appear to influence the risk factors of depression development following TBI (116). It seems that the female gender, pre-injury depression, post-injury unemployment, and lower brain volume increase the risk of major depression following TBI (117). However, evidence on the demographic risk factors of post-TBI depression has not provided a definitive conclusion (118-120). From a neuropathological point of view, the serotonergic and adrenergic projections, which originate from the locus coeruleus and Raphe nuclei, reach the subcortical limbic and prefrontal ventromedial cortex, which play an important role in regulating the mood (121), are disturbed in patients with depression after TBI (122). Investigations of the neural function imaging of patients with persistent post-TBI neuropsychiatric disorders such as depression support the increased function of DMN (123). The study on resting network integrity following TBI has indicated that integrity within the anterior cingulate cortex (ACC), insula, and thalamus may determine post-traumatic depression severity. Furthermore, an increase in the connectivity between the insula and superior temporal lobe and a connectivity decline between thalamus and DLPFC may be associated with depressive symptomatology of TBI patients (124). So far, antidepressants and selective serotonin reuptake inhibitors (SSRIs) have been used for the remediation of mood disorders after TBI (125, 126). Recently, it is suggested that after TBI the dysregulation of pro-inflammatory cytokines, like tumor necrosis factor (TNF) which may lead to an increase in activity of serotonin transporter and consequently a decrease in serotonin at the synapse, are the neuropathogenic basis of depression after TBI (127). Accordingly, pharmacological targeting of pro-inflammatory cytokines may be recommended as a new option for the treatment of post-traumatic depression.

Post-traumatic stress disorder (PTSD)

Post-traumatic stress disorder (PTSD) is categorized in the anxiety disorders after trauma which, as a result of traumatic events, can cause horror and intense fear and helplessness in persons. ICD-10 criteria for detecting PTSD include the re-experience of the traumatic event to form the hallucination, visualization, illusion, or nightmares,, to forego a reminder of the traumatic event plus hypervigilance, hyperarousal states, and a decrease in concentration and increased irritability lasting for more than a month (128, 129). According to available data, the prevalence of PTSD after road traffic accidents varies from 20% to 58% (130-132). Several studies have investigated the risk factors and predictors of PTSD in pediatric and adult patients with TBI. It has been disclosed that personal variables such as age, gender, education level, and work status may predict the appearance of PTSD following TBI (130). Apparently, shorter PTA, early post-traumatic symptoms (117) and TBI severity (95) appear to be risk factors of PTSD in TBI patients. Recently, it has been revealed that the sustained attention deficit after pediatric TBI may be a key predictor of PTSD appearance, especially in children with mild TBI (133). Human brain mapping studies have indicated that there is a decrease in functional connectivity between PCC and hippocampus in PTSD patients and the degree of connectivity between these two neural regions is negatively correlated to avoidance symptoms (134). Likewise, it is found that the reduction of functional connectivity strength within DMN may increase PTSD severity (135, 136). PTSD seems to be related with hyperactivity of the amygdala-based fear processing pathways and its projections to the cortex. Amygdala is a key mediator of emotional memory stabilization (137, 138). Increasing the strength and durability of memories fixed in the presence of a severe fear may predispose people to other anxiety disorders, including agoraphobia (139). Although antidepressants are suggested and used to resolve PTSD (140, 141), in most patients, the need for cognitive-behavioral therapy is emphasized as an auxiliary or alternative therapy (142, 143).

Sleep-wake disturbances after TBI

According to literature, the prevalence of sleep disorders is between 30% and 80% after trauma (26, 144-146). Insomnia and excessive daytime sleepiness (EDS) are the most common types of sleep disorders after TBI. They are usually associated with chronic fatigue and neuropsychiatric disorders (26). Clinical manifestations of sleep disturbances after trauma occur in different degrees and phases after TBI (147) and interfere with the restoration of the nervous system and the process of primary neural recovery. As the sleep disturbances sustain, patients become unable to take part in rehabilitation programs (148, 149). According to previous reports, sleep disturbance after trauma is associated with mood disorders and fatigue throughout the day and nighttime pain after TBI (150, 151). The severity

of brain damage seems to be associated with the likelihood of hypersomnia long after the onset of TBI (144). In addition, low levels of orexin in the cerebrospinal fluid (CSF) in the early hours and 6 months after TBI is strongly correlated with EDS after the trauma (152). However, findings concerning the prognostic role of the severity and location of the lesion in the occurrence of sleeping-awakening cycle problems after TBI are inconsistent (26, 144, 148, 150-152). It is worth noting that sleep disturbances after brain trauma negatively affect cognitive and emotional functions [18, 29] and, as a risk factor for chronic traumatic encephalopathy, play a role in the onset and exacerbation of its symptoms, including poor cognition, aggression, and impulsivity [30, 31]. Several observations have also proposed that sleep disorders may be the cause of cognitive impairment and Alzheimer's disease [32, 33]. However, others suggest that patients with neuropsychological deficits in the early phase of TBI are more likely to be at risk of post-TBI persistent sleep disorders (26). From the neuro-pathophysiological point of view, the imbalance between the neural function of the centers which regulate the sleep/wake cycle in the brain stem and hypothalamus induced by TBI underpin the sleep disorders. Neuroscience findings have supported the dysfunction of neural pathways involved in the sleep/wake cycle after TBI. It seems that the disruption of the inhibitory projections of the ventricular hypothalamus nucleus on locus coeruleus nucleus belonging to ARAS (153) and the lack or reduction of the basal forebrain cholinergic outputs for the modulation of the function of the sleep/wake cycle centers in the hypothalamus underlie pathobiological insomnia. Furthermore, brain stem lesions are particularly associated with symptoms of hypersomnia and EDS (154). Insomnia is thought to be associated with overactivation of DMN (155) which appears to be unbalanced after TBI (156). Indeed, it is thought that the lack of DMN deactivation during rest may cause insomnia (155). Based on a classical hypothesis, hyperarousal is a possible explanation for the etiology of insomnia (157). It is suggested that primary insomnia may be related to a decrease in functional connectivity between DMN and medial temporal gyrus, insula, and thalamus which are core regions of the salience network (SN) (158). Hence, it seems that aberrant functional connectivity among neural networks occurred after TBI, especially between DMN and SN (31), may be the underlying neuropathological mechanism of post-traumatic insomnia. In order to increase the understanding of the neural signatures of post-traumatic sleep disorders, the investigation of the correlation between abnormal neural networks and types of sleep disturbances after TBI deserves further attention in the future.

Conclusion

Neuropsychological and neuropsychiatric impairments after TBI are detrimental to the health of patients. These deficits interact or exacerbate each other and bring about major problems in personal and social settings. A wide range of personal, educational, occupational, social and medical variables may be associated with the risk of appearance of these disorders. From a neuroscience perspective, the emergence and persistence of any undesirable cognitive and emotional outcomes following TBI can be detected and predicted by early employment of advanced imaging techniques that evaluate the brain metabolites and structural and functional integrity. Evidently, the dysfunction of cortico-striato-thalamo-cortical circuits from the prefrontal cortex appears to be responsible for the common post-traumatic cognitive and emotional deficits. Furthermore, abnormal activity of DMN and/or other neural networks correlated to that may be characterized as a possible neuropathogenesis mechanism(s) of the majority of these disorders. TBI-induced aberrant neural networks may serve as the diagnostic and prognostic biomarkers of post-TBI neuropsychological and neuropsychiatric disorders and their severity even in cases with minor TBI could be potentially helpful in developing neural circuit-based therapeutic approaches. Neuromodulatory techniques attempt to modify abnormal inter or/and intra-networks connectivities due to compensatory neuroplasticity following injury. Therefore, understanding the neuropathophysiology and patterns of neural dysfunction after TBI, from which post-TBI neuropsychological and neuropsychiatric defects may originate, is a major priority for achieving optimal efficacy by neuromodulation-based therapies.

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