# Brain-derived neurotrophic factor in traumatic brain injury, post-traumatic stress disorder, and their comorbid conditions: role in pathogenesis and treatment

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**As US military service members return from the wars in Iraq and Afghanistan with elevated rates of traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD), attention has been increasingly focused on TBI/PTSD comorbidity, its neurobiological mechanisms, and novel and effective treatment approaches. TBI and PTSD, and their comorbid conditions, present with a spectrum of common clinical features such as sleep disturbance, depression, anxiety, irritability, difficulty in concentrating, fatigue, suicidality, chronic pain, and alterations in arousal. These TBI and PTSD disorders are also thought to be characterized by overlapping neural mechanisms. Both conditions are associated with changes in hippocampal, prefrontal cortical, and limbic region function because of alterations in synaptogenesis, dendritic remodeling, and neurogenesis. Neural changes in TBI and PTSD result from pathophysiological disturbances in metabolic, cytotoxic, inflammatory, and apoptic processes, amongst other mechanisms. Neurotrophins have well-established actions in regulating cell growth and survival, differentiation, apoptosis, and cytoskeleton restructuring. A body of research indicates that dysregulation of neural brain-derived neurotrophic factor (BDNF) is found in conditions of TBI and PTSD. Induction of BDNF and activation of its intracellular receptors can produce neural regeneration, reconnection, and dendritic sprouting, and can improve synaptic efficacy. In this review, we consider treatment approaches that enhance BDNF-related signaling and have the potential to restore neural connectivity. Such treatment approaches could facilitate neuroplastic changes that lead to adaptive neural repair and reverse cognitive and emotional deficits in both TBI and PTSD. *Behavioural Pharmacology* 21:427–437 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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As US military service members continue to return from the wars in Iraq (Operation Iraqi Freedom; OIF) and Afghanistan (Operation Enduring Freedom; OEF) with elevated rates of traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD), attention has been increasingly focused on TBI/PTSD comorbidity, neurobiological mechanisms, and novel treatment approaches. PTSD and mild TBI (mTBI) present with common clinical features, share more extensive combat as a risk factor (the same specific event sometimes serving as a precipitating exposure), and seem to be characterized by overlapping pathophysiological brain mechanisms. Not surprisingly, there is significant concern that the two conditions may exacerbate each other, leading to particularly complicated clinical presentations. In this study, we examine the dysregulation of brain-derived neurotrophic factor (BDNF) as a relevant neurobiological mechanism in both mTBI and PTSD. We also consider whether treatment-induced enhancements of BDNF can facilitate both neural integrity and recovery of function in mTBI and PTSD.

## Definitions of mild traumatic brain injury and post-traumatic stress disorder

TBI refers to the injury that may occur subsequent to the application of a mechanical (e.g. blunt trauma) or biomechanical (e.g. blast injury) force sufficient to result in neuronal injury. Battle-related TBI often develops when a high explosive detonation creates pressure changes that displace brain structure. The explosive detonation occurs when a solid or liquid is instantaneously converted into a gas under very high pressure, resulting in a blast wave that induces extreme pressure oscillation. The rapidly expanding gases first produce an intense positive pressure wave that flows away from the explosion, and then produce a drop in atmospheric pressure that results in a reversed pressure wave (Taber *et al.*, 2006). Such extreme explosion-induced pressure differences can result in sudden acceleration, deceleration, and rotation of the head, exerting both the shearing and tensile forces that cause the primary pathological changes associated with TBI (Povlishock, 1993; Ray *et al.*,



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2002). The initial 'blast wave' is followed by a negative pressure wave in which particles of debris, shrapnel, and fragments can cause secondary injury. Subsequently, tertiary injuries can result from being thrown to the ground or against a stationary object such as a wall or vehicle. Quaternary-level injuries can result from burns, broken bones, amputations, breathing toxic fumes, or crush injuries from falling structures after such explosions.

Although sometimes confused with resulting clinical symptoms, the term 'TBI' in itself does not address whether or not there is associated clinical dysfunction. Types of TBI vary greatly in their severity, ranging from mild injury associated with only brief alterations or loss of consciousness and limited sequelae (also referred to as a 'concussion'), to a very severe injury that is associated with prolonged coma, enduring brain damage, and clinical impairment, or even death. In addition to the application of an external force, the categorization of a head injury as a TBI also requires at least some alteration of consciousness at the time of injury. For the TBI to be classified as mild (as opposed to moderate or severe), most classification systems and definitions limit the duration of loss of consciousness to no longer than 30 min and the period of post-traumatic amnesia (i.e. the failure to reliably form new memories that can later be reconstructed) to no longer than 24 h (Kay *et al.*, 1993; Holm *et al.*, 2005; Department of Veterans Affairs and Department of Defense, 2009). 'Postconcussive syndrome' refers to clinical symptoms occurring after the injury, with 'persistent postconcussive syndrome' referring to enduring symptoms (Bigler, 2008).

PTSD is a mental disorder that may follow exposure to life-threatening, psychologically traumatic events, such as those commonly occurring in war-zone contexts. The diagnosis of PTSD requires exposure to a traumatic event and an associated response of fear, helplessness, or horror (American Psychiatric Association, 2000). PTSD symptoms include re-experience of the trauma (e.g. nightmares, intrusive distressing thoughts), avoidance of reminders of the trauma, emotional numbing (e.g. restricted range of affect, failure to enjoy earlier enjoyable activities), and hyperarousal (e.g. irritability, sleep disturbance, hypervigilance to potential threat). Distinguished from acute stress responses, PTSD symptoms must endure for at least 1 month and result in clinically significant functional impairment. As with TBI exposures and postconcussive syndrome, not all people exposed to a psychological trauma will develop PTSD.

## Clinical description, epidemiology, and course of mild traumatic brain injury and post-traumatic stress disorder in OEF/OIF veterans

With improved battlefield medical care and protective equipment, service members are currently surviving injuries that would have proven fatal in earlier wars. In part related to these increased survival rates, many service members now return with multiple physical and psychological injuries. The estimated prevalence rates of TBI and PTSD among returning OEF/OIF veterans have varied according to sampling methods and measures, but a pattern emerges in which significant subsets of veterans return with either one or both of these conditions. For example, in a crosssectional study of 2234 OEF/OIF veterans from the Mid-Atlantic US, approximately 12% of the veterans are screened positive for mTBI and 11% for PTSD (Schneiderman *et al.*, 2008), with significant overlap in the two groups. Hoge *et al.* (2008) similarly found that approximately 10% of 2525 army soldiers selected from two combat brigades were screened positive for mTBI, although the rates were considerably lower (5%) when the definition of mTBI was restricted to cases associated with outright loss of consciousness (as opposed to altered consciousness). Of those returning service members reporting head injury with loss of consciousness, approximately 44% also screened positive for PTSD. Using stratified random sampling to obtain a more representative sample of contemporary war zone veterans, Research and development (2008) documented a somewhat higher prevalence of TBI (19%), but reported a PTSD prevalence (13%) generally consistent with other studies (e.g. Hoge *et al.*, 2004; Vasterling *et al.*, 2010). Rates of both TBI and PTSD are higher in clinical samples, receiving care in both Department of Defense and Department of Veterans Affairs healthcare settings (e.g. Warden, 2006; Tanelian *et al.*, 2008; Sayer *et al.*, 2009).

Immediately after being injured, a person with mTBI may express a number of postconcussive syndrome symptoms, including irritability, anxiety, fatigue, sleep disturbance, trouble concentrating, memory disturbance, and headaches (Stein and McAllister, 2009). In addition, soon after the injury, mTBI may also be associated with measurable impairment on performance-based neuropsychological tests. The most frequently observed neuropsychological performance deficits include impaired speed of information processing (Barrow *et al.*, 2006), working memory (McAllister *et al.*, 2006), executive functioning, verbal fluency, new learning, and memory (Alexander, 1995; Belanger *et al.*, 2005).

Although recovery from these neuropsychological deficits of mTBI typically occurs within 1–3 months of injury (Schretlen and Shapiro, 2003; Belanger *et al.*, 2005), the course of recovery is far from uniform and less information is available from military populations. Mild neuropsychological deficits may persist in a subset of mTBI cases (Pertab *et al.*, 2009), with subjective postconcussive syndrome symptoms persisting in an even larger proportion of mTBI cases. For example, one recent study suggested that as many as 50% of patients with complicated mTBI (i.e. showing computerized tomographic abnormality and/or post-traumatic amnesia greater than 24 h) and 44% of patients with uncomplicated mTBI reported at least three postconcussive syndrome symptoms at 1-year postinjury (Dikmen *et al.*, 2010). With

the possible exception of the cumulative effects of multiple concussions (Guskiewicz *et al.*, 2003), mTBI injury attributes seem to be less important predictors of subsequent recovery than individual difference characteristics such as the clinical context of the assessment (Belanger *et al.*, 2005), premorbid alcohol use and psychiatric disorders (Dikmen *et al.*, 2010), and subsequent life stressors (Ponsford *et al.*, 2000).

The course of primary PTSD symptoms varies across individuals, with some trauma survivors showing consistently low levels, or reduction, of symptoms over time, but others showing a more chronic symptom course (e.g. Schnurr *et al.*, 2003; Orcutt *et al.*, 2004; Solomon and Mikulincer, 2006). In somewhat smaller subsets of people exposed to psychological trauma, onset of PTSD symptoms may even be delayed (Andrews *et al.*, 2007). Neuropsychological dysfunction, however, has been well documented in both acute and chronic presentations of PTSD (Vasterling *et al.*, 2009), a recent study indicating that neuropsychological dysfunction may increase as symptoms become more chronic (Marx *et al.*, 2009). Finally, PTSD is sometimes associated with physical symptoms and declines in health-related functioning (e.g. Jakupcak *et al.*, 2008; Vasterling *et al.*, 2008; Vanderploeg *et al.*, 2009), which may progress into cardiovascular disease and other clinically significant somatic disorders over time (Kubzansky *et al.*, 2007; Boscarino, 2008).

In clinical contexts, patients with mTBI and PTSD often present with other clinical settings that reflect physical injuries (e.g. orthopedic injury) extending beyond the TBI, and other concerns (e.g. substance use disorders, depression, suicidal behavior, pain disorders) (Sayer *et al.*, 2009; Stein and McAllister, 2009). Review of the medical records of over 300 veterans treated in Veterans Affairs polytrauma settings, for example, indicated high rates of chronic pain (82%), PTSD (68%), and persistent postconcussive syndrome (67%), with 42% of the sample diagnosed with all three conditions (Lew *et al.*, 2009). More than half of those hospitalized after TBI developed major depression in the first year, which predicts poorer quality of life (Bombardier *et al.*, 2010). With regard to psychiatric diagnoses, a recent longitudinal study of over 1000 traumatically injured patients indicated that patients with TBI, compared with other injury types, were more likely to have developed PTSD and several other anxiety disorders 1 year later (Bryant *et al.*, 2010). Not surprisingly, the association of TBI and PTSD with multiple comorbidities has proven to be particularly challenging in developing and implementing models of coordinated healthcare (Sayer *et al.*, 2009).

## Neuropathological and neuroanatomical features in traumatic brain injury

One way in which TBI can be classified is by either primary or secondary brain injury (vs. primary or quaternary brain injury to person described earlier). Neuropathological and microvascular changes associated with primary TBI include hemorrhages in the white matter, neuronal degeneration, subdural hemorrhage, venous engorgement, and perivascular space enlargement (Ray *et al.*, 2002). In reviews of the TBI literature, 59% of the cases showed hippocampal atrophy as the major lesion as identified by magnetic resonance imaging (MRI) (Orrison *et al.*, 2009). Although the shearing forces from blast injury primarily affect deep frontal white matter and subcortical structures (Cicerone *et al.*, 2006), the more common tensile effects produce axonal stretching (Buki and Povlishock, 2006) that can result in traumatic axonal injury (TAI), more commonly called diffuse axonal injury (DAI). In mTBI, such tensile effects on the axon can be significant and can produce a pathological cascade that makes the neuron dysfunctional. Autopsy findings from patients with TBI showed that DAI/TAI is most frequently reported in the cortical lobes, corpus collosum, and brainstem (Belanger *et al.*, 2007). In combat, veterans with chronic postconcussive syndrome symptoms show a consistent regional hypometabolism in medial temporal brain regions from positron emission tomography studies (Peskind *et al.*, 2010). US veterans from OEF with major depression after blast-related concussion showed greater regional activation (compared with blast-related concussed veterans without depression) in a limbic region (amygdala) during fear trials. During these fear trials of depressed veteran's postconcussion symptoms, activation is reduced in the dorsolateral prefrontal cortex, a fear inhibitory brain region (Matthews *et al.*, 2010). Thus, it seems that the prefrontal cortex, medial temporal regions, hippocampus, amygdala, and corpus callosum represent brain regions of interest in TBI.

Although DAI sometimes occurs when neurons are mechanically torn at the moment of impact, TAI is more common and is a progressive event that evolves from focal axonal alteration to delayed axonal disconnection (Buki and Povlishock, 2006). TAI/DAI produces both anterograde and retrograde degeneration and disconnection over several months postinjury. It is hypothesized that this axonal degeneration and disconnection contribute to the associated neurocognitive and behavioral deficits. TAI/DAI is often not visible with conventional computerized tomography and MRI, but may be seen with diffusion tensor imaging, a type of diffusion MRI that measures the functional integrity of white matter but has not yet shown clinical utility. The delays in disconnection of TAI/DAI highlight that the process is potentially amenable to therapeutic intervention (Buki and Povlishock, 2006).

In contrast to the immediate occurrence of primary TBI, secondary TBIs develop over a period of hours or days after the initial impact to the head. Resulting from cellular processes triggered by the trauma, secondary injury is associated with the synthesis and release of

various neurochemicals that affect brain metabolism, altered cerebral blood flow, ion homeostasis, and other sources of neuronal injury that overlap between TBI and PTSD (Ray *et al.*, 2002; Risling *et al.*, 2010). The mechanisms of neuronal and vascular damage include calcium-mediated cell toxicity through proteolytic pathways, glutamate-mediated excitotoxicity, swelling and rupture of mitochondria, production of oxygen-free radicals, release of apoptotic substances and inflammatory cytokines, and secondary damage from mass lesion formation and ischemia (Ray *et al.*, 2002; Buki and Povlishock, 2006). Exposure to the primary blast wave in experimental rat models also produces alterations in neural gene expression, including the downregulation of genes involved in neurogenesis and synaptic transmission (Risling *et al.*, 2010).

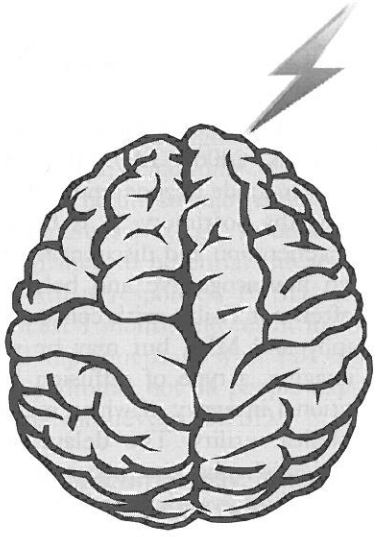
After primary and secondary brain damage in TBI, neurons seem capable of reorganizing and repairing connections. After axonal disconnection, there is the possibility of subsequent neuroplastic changes that can lead to either favorable changes or maladaptive repair (see Fig. 1). More severe TBI often induces maladaptive changes that result in inappropriate neuronal growth (Erb and Povlishock, 1991; Phillips *et al.*, 1994) and continued neural disconnection. Proteinases seem to assist in reconnection processes by enabling synaptogenesis in the neuropil, and can influence the neural growth patterns (Reeves *et al.*, 2003). Though a small proportion of damaged neurons may show severe damage early after TBI because of activation of proteases, most injured axons die more gradually. This progressive neural dysfunction could be reduced using rationally targeted therapies that target proteolysis, mitochondrial damage, and cytoskeletal alteration, or neurotrophic factors such as BDNF that can facilitate reconnection in TBI (Buki and Povlishock, 2006).

## Neuropathological and neuroanatomical features in post-traumatic stress disorder

PTSD is a condition in which much of the neural damage is similar to the secondary injuries found in TBI. PTSD has been associated with structural abnormalities such as reduced volume in medial prefrontal cortex structures (Rauch *et al.*, 2003; Yamasue *et al.*, 2003; Kasai *et al.*, 2003), and in the hippocampus (e.g. Gurvits *et al.*, 1996; Gilbertson *et al.*, 2002) and amygdala (Karl *et al.*, 2006). Within the hippocampus, PTSD is also associated with specific volume loss of the CA3 and dentate gyrus subfields, suggesting that severe or chronic stress suppresses neurogenesis and dendritic branching in these subregions (Wang *et al.*, 2010). These reductions in hippocampal volume are associated with functional deficits in hippocampal-based memory (Bremner *et al.*, 1995). This last study used MRI to measure hippocampal volume in Vietnam combat veterans with PTSD and controls. Deficits in verbal memory were associated with reductions in hippocampal volume only in the patients with PTSD.

In both TBI and PTSD, inadequate frontal inhibition of the limbic structures results in exaggerated amygdala responses and resultant heightened responsivity to

**Fig. 1**



1. Primary injury

Shearing and tensile effects → traumatic axonal injury and neuronal disconnection

2. Secondary injury

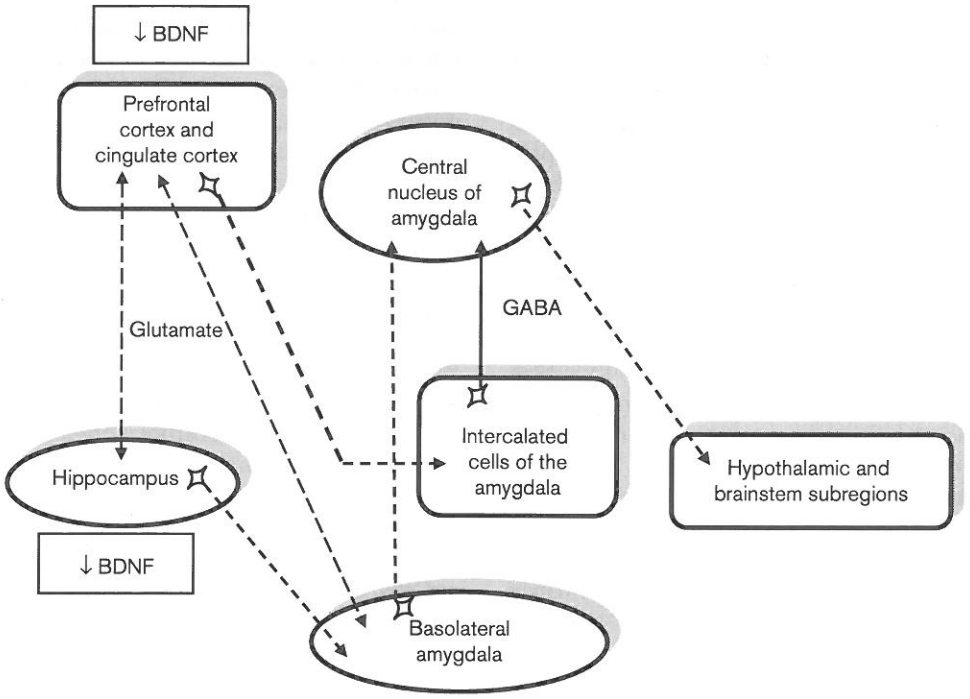
Neuronal and vascular damage → proteolytic pathways, excitotoxicity, oxygen-free radicals, apoptosis, inflammatory processes, and ischemia

3. Repair

Increases in BDNF and neurotrophic factors → reconnection through fiber sprouting and synaptogenesis

Pathogenesis in traumatic brain injury and role of brain-derived neurotrophic factor (BDNF). Acute traumatic brain injury is characterized by two injury phases, primary and secondary. Primary brain injury is the direct injury to the brain cells incurred at the time of the initial impact with traumatic and diffuse axonal injury, whereas secondary brain injury is caused by a combination of ischemic, inflammatory, cytotoxic, and apoptotic processes. Evidence suggests that reactive increases in BDNF play a prominent role in the cellular events that occur after brain trauma. This suggests that BDNF may provide a neuroprotective and repair function and restore connectivity in disrupted areas after brain injury.

**Fig. 2**




Neural circuitry of post-traumatic stress disorder (PTSD) and its associated changes in brain-derived neurotrophic factor (BDNF) neuroplasticity. The prefrontal cortex (PFC), hippocampus, and basolateral amygdala (BLA) are key sites of synaptic plasticity and mediate the acquisition of fear conditioning and its extinction. Fear-related sensory information enters the amygdala through its basolateral nuclei. The hippocampus is critical in contextual associative learning, memory consolidation, and the retrieval of episodic memories. The PFC and anterior cingulate cortex send glutamatergic excitatory projections (dashed lines) to the sites of fear memory storage in the BLA, and also project to GABAergic neurons and projections (straight line) of the intercalated cell masses positioned between the two amygdala subregions. It has been hypothesized that extinction learning in PTSD represents an increase in excitatory drive to the intercalated cell masses and decreased output from the BLA. Projections from the central nucleus of the amygdala provoke expression of fear responses through downstream projections to the midbrain and hypothalamic regions. Chronic stress can impair prefrontal cortical and hippocampal functioning by producing dendritic retraction, restructuring, and disconnection. BDNF protein levels are shown to be reduced in the PFC and hippocampus in PTSD, which may result in impairments in regeneration, reconnection, and dendritic sprouting in these regions. GABA, γ-aminobutyric acid.

potential threat. Both the hippocampus (Rauch *et al.*, 2006) and medial prefrontal cortex (Liberzon and Sripada, 2008) are critical for processing contextual integration related to fear responses. In PTSD, functional imaging studies have shown decreased activation in the hippocampus, anterior cingulate, and orbital frontal cortex in response to symptom provocation (e.g. Rauch *et al.*, 1996; Lanius *et al.*, 2001; Shin *et al.*, 2004), and a simultaneously exaggerated response of the amygdala (Rauch *et al.*, 2006). Impairments in medial prefrontal activation are hypothesized to result in repeated re-experiencing of traumatic memories in PTSD (Rauch *et al.*, 2006). In addition, reductions in anterior cingulate cortex function are hypothesized to produce impairments of emotional self-control and behavioral response to changing contexts in PTSD (Schuff *et al.*, 2010).

The hippocampus normally displays structural plasticity through synaptogenesis, dendritic remodeling, and neurogenesis. After chronic stress, elevations in excitatory amino acids and glucocorticoids suppress hippocampal neurogenesis and potentiate the damage produced by ischemia and seizures (McEwen, 2007). Many animal studies show that chronic or severe stress produces changes in hippocampal, prefrontal cortical, and anterior cingulate structure and function, through increases in circulating glucocorticoids, reductions in neurotrophic factors, and impairment in neurogenesis (Bremner, 2006; Schuff *et al.*, 2010). Genetic mechanisms for PTSD come from autopsy samples showing genetic abnormalities associated with mitochondrial dysfunction, oxidative phosphorylation, and apoptosis (Su *et al.*, 2008). In PTSD and TBI, the brain shows capacity for plasticity with cognitive treatments, antidepressant medication, and environmental enrichment, which all can reverse the effects of stress on hippocampal neurogenesis (Bremner *et al.*, 2008). As a mechanism for neuroplasticity and neurogenesis, neurotrophic factors have been a source of adaptation in both TBI and PTSD.

## Roles of neurotrophic factors in cortical and hippocampal plasticity

Neurotrophins (NTs) have well-established actions in regulating cell growth and survival, differentiation,

apoptosis, and cytoskeleton restructuring. Four NTs have been characterized in mammals – neural growth factor, BDNF, NT-3, and NT-4 – with similar sequence and structure (e.g. Hallbook, 1999). Though derived from a common gene, NTs interact with structurally and functionally different receptors: the tropomyosin-related tyrosine kinase (Trk) receptors and the p75 NT receptor (Lipsky and Marini, 2007). Each receptor has differing specificity for ligands and activates different intracellular cascades. Through these receptors, NTs are involved in the processes of synaptic transmission and neuronal plasticity (Lu, 2003). Plasticity refers to modification of brain substrates as a result of some changes in condition (i.e. experience), with the assumption that such modification is adaptive for the continued survival and optimal functioning of the organism. Though the vast majority of neurons in the mammalian brain are formed prenatally, they are subject to modification over time. NT synthesis is rapidly regulated by neuronal activity and NTs are released in an activity-dependent manner from neuronal dendrites. This knowledge, along with findings that NTs enhance transmitter release, suggests a role for NTs as selective retrograde messengers that regulate synaptic activity. Consequently, NTs and their receptors maintain brain plasticity in healthy individuals and those suffering from neuropsychiatric disorders (Lipsky and Marini, 2007).

Much of this focus has revolved around BDNF, an NT that has emerged as a major regulator of both synaptic transmission and plasticity at adult synapses in many regions of the central nervous system. BDNF has been variously shown to increase the survival of neurons, and to increase synaptic transmission (Lipsky and Marini, 2007), long-term potentiation, and long-term depression, along with certain forms of short-term synaptic plasticity (Desai *et al.*, 1999). These BDNF effects have implications for the formation of memories, in healthy individuals and those with impairments in memory and cognition, as found in TBI and PTSD. This unique role of BDNF within the NT family is attributable to its widespread distribution and the colocalization of BDNF and its receptor, TrkB, at glutamate synapses.

## Role of brain-derived neurotrophic factor in traumatic brain injury and post-traumatic stress disorder

Several lines of evidence suggest that NTs play a prominent role in the cellular events that occur after brain trauma. Of the two categories of TBI, direct primary injury and subsequent secondary injury, research indicates that NTs may play a large role in the latter. As discussed earlier, secondary brain injury is caused by a combination of subsequent ischemic, inflammatory, cytotoxic, and apoptotic processes. BDNF seems to play a major role in reducing the impact of secondary brain injury, through alterations in BDNF-induced gene expression in traumatized tissue. In addition BDNF can affect remote areas subjected to secondary mechanical stress, and brain areas connected by fiber pathways to the injured zone. Many studies also show increases in hippocampal BDNF mRNA after experimental brain trauma of moderate severity for several hours or within days of injury. Brain injury in animal models, such as penetrating brain injury (Nieto-Sampedro *et al.*, 1982), cortical ablation (Whittemore *et al.*, 1985), or deafferentation (Needels *et al.*, 1986), has been shown to acutely increase NT levels. BDNF expression is increased in the cortex (Oyesiku *et al.*, 1999; Griesbach *et al.*, 2002) and hippocampus (Hicks *et al.*, 1997; Grundy *et al.*, 2000) hours after experimental brain injury in rats. Increases in BDNF mRNA within the cortex are accompanied by an increase in BDNF protein for several days after injury (Oyesiku *et al.*, 1999; Truettner *et al.*, 1999; Griesbach *et al.*, 2002; Mahmood *et al.*, 2009). Levels of BDNF mRNA or protein expression after TBI were elevated in the cortex and hippocampus for several weeks in another study (Chen *et al.*, 2005). The limitations of these studies are that they use different animal models of TBI and different measures of BDNF. Genetic knockout studies suggest that BDNF may provide a neuroprotective and repair function and restore connectivity in disrupted areas after brain injury (Gao *et al.*, 2009).

A large body of research indicates that dysregulation of BDNF is found in conditions of TBI and PTSD. In TBI, BDNF and other NTs reduce secondary injury, provide neuroprotection, and restore connectivity. In contrast, chronic stress or prolonged exposure to glucocorticoids can reduce BDNF levels and impair hippocampal functioning, by producing dendritic retraction, restructuring, and disconnection. Dendritic retraction after stress may persist for weeks, months, or even years, and may increase the period of hippocampal vulnerability. These studies are from animal models of stress or fear conditioning and therefore their relationship to human populations is unclear. Repeated stress can lead to neuronal atrophy and loss in several brain regions, including the hippocampus (McEwen, 2000; Duman and Monteggia, 2006), and it reduces the expression of BDNF mRNA expression (Smith *et al.*, 1995; Duman and Monteggia, 2006). Similarly, subjects showing ongoing behavioral disturbances after stress showed BDNF downregulation and TrkB upregulation in the CA1 subregion of the hippocampus, compared with controls. (Kozlovsky *et al.*, 2007). Chronically elevated cortisol exposure in rats (similar to chronic stress) also produces reductions in BDNF in the ventromedial cortex (Gourley *et al.*, 2009) that was associated with stress-related behaviors. Rasmusson *et al.* (2002) showed that repeated footshocks, co-terminating with associated tones, decreased hippocampal BDNF mRNA expression. After a return to normal 2 days later, re-exposure to the fear context and fear cues decreased hippocampal BDNF mRNA. Similarly, early life stress produces enduring downregulation

of BDNF mRNA and protein levels in the hippocampus CA1 subregion, and this effect may underlie changes in neural plasticity and synaptic functioning (Bazak *et al.*, 2009). There are very limited studies in humans verifying these studies in animal models. For example, there is a significantly lower level of plasma BDNF in patients with PTSD, compared with healthy individuals, suggesting its possible involvement in the pathophysiology of PTSD in humans (Dell'osso *et al.*, 2009).

Through BDNF expression, the hippocampus can potentially recover from dendritic retraction without any discernable loss of neurons (Conrad *et al.*, 2008). For example, induction of BDNF and activation of its intracellular receptor TrkB can produce neural regeneration, reconnection, and dendritic sprouting, and can enhance synaptic efficacy (Lipsky and Marini, 2007). Although chronic defeat stress-induced hippocampal BDNF downregulation, antidepressant treatment reversed this effect, through chromatin modification at BDNF promoters. Thus, BDNF expression and histone remodeling may be critical in the pathophysiology and treatment of chronic stress (Tsankova *et al.*, 2006).

Genetic studies highlight the importance of BDNF in anxiety and stress. An inbred genetic knockin mouse strain expressing a human variant BDNF (associated with PTSD) showed the behavioral effects of the human polymorphism (Soliman *et al.*, 2010). In this study, both humans and knockin mice with the BDNF variant showed impairments in extinction learning to conditioned fear, thus indicating that the BDNF allele may be relevant to the efficacy of cognitive treatments using extinction learning (i.e. exposure therapy) in anxiety disorders. Mice with another BDNF genetic variant (Val66Met) showed slower extinction learning compared with wild-type mice, a learning impairment that can be reversed with a cognitive enhancer drug, D-cycloserine (Yu *et al.*, 2009). This genetic variant mouse also showed reduced volume and dendritic complexity in the ventromedial prefrontal cortex, a region critical to extinction learning. In summary, data from these studies in animal models suggest that conditioned cue-associated and context-associated fear and unconditioned stress decrease hippocampal and prefrontal cortical BDNF levels. In PTSD models, the loss of neuroprotective BDNF may result in atrophy of the hippocampus and ventromedial prefrontal cortex, and may produce deficits in hippocampal-based memory and extinction learning in fear conditioning (Bremner, 2006; Yu *et al.*, 2009).

## Brain-derived neurotrophic factor treatment approaches for traumatic brain injury and post-traumatic stress disorder

As we described earlier, adult brains have the ability to recruit and regenerate new neurons that are lost by injury or disease, with neurogenesis being shown in the hippocampus, striatum, thalamus, septum, and hypothalamus in healthy humans (Pencea *et al.*, 2001). This ability is thought to be affected by NTs that can enhance neuronal survival, stimulate neurite sprouting, and increase functional connectivity. As a mechanism for neuroplasticity, neurotrophic factors have been a source of adaptation in both TBI and PTSD. As both TBI and PTSD are associated with overlapping neuropathological changes, neurochemical dysregulation, and deficits in neural structure and function, increases in BDNF have been postulated to enhance connectivity and function. Consequently, this section focuses on different treatment approaches to increase BDNF so as to repair neural connections and reduce the behavioral sequelae of TBI and PTSD.

Therapeutic strategies that administer BDNF after TBI have been shown to be neuroprotective in animal models and may have therapeutic value in humans. As there are limited therapeutic studies using BDNF as a treatment, studies using spinal cord illustrate some of the potential utility of this agent, for example, NTs have been shown to protect injured nerve tissues by reducing axonal degeneration (Sayer *et al.*, 2002) and by inhibiting apoptosis (Cao *et al.*, 2002). These studies have limits in applicability in that they were performed in spinal cord preparations. In mild ischemic brain injury, continuous intracerebral infusion of BDNF protects against striatal neuronal loss (Galvin and Oorschot, 2003). BDNF infusions reversed stress-induced impairments in spatial learning and memory and enhanced hippocampal long-term potentiation in rats (Radecki *et al.*, 2005). Another study examined the delivery of bone marrow stromal cells cultured with BDNF protein (Mahmood *et al.*, 2002). Cells were transplanted into adult rat brains after controlled cortical impact and the subjects receiving stromal cells with BDNF had a higher number of engrafted cells and better motor function. Using human mesenchymal stem cells transfected with a mutant adenovirus vector with the BDNF gene, stem cell therapeutic effects have been measured after brain injury in rats (Nomura *et al.*, 2005). In this study, after middle cerebral artery occlusion, stem cells reduced lesion volume and enhanced function compared with control treatment. However, the effects were greater in the BDNF-human mesenchymal stem cell group versus the control stem cell group. Similarly, intravenous human mesenchymal stem cell treatment increased neurological functional outcome and BDNF levels in rat TBI models (Kim *et al.*, 2010). However, some results of studies attempting BDNF treatment have been negative in animal models. Rats undergoing TBI in the parietal cortex and treated with intracranial infusions of BDNF for 2 weeks did not show improvements in neurological function, learning, memory, or neuronal loss (Blaha *et al.*, 2000). In addition, in genetic studies of BDNF/TrkB overexpression in the hippocampus of mice, there was no protection for controlled cortical impact brain injury, as measured by motor

function or pyramidal neuronal survival (Conte *et al.*, 2008). The effects of BDNF treatment on brain injury and function seem to vary greatly in these heterogeneous models and treatment delivery systems. To understand BDNF treatment effects, some degree of standardization is needed in animal models, drug delivery systems, and measures of neural and cognitive function.

Antidepressants are partially effective treatments in PTSD and TBI, some effects of which seem to be mediated by activating the BDNF pathways (Chen *et al.*, 2006; Martinowich *et al.*, 2007). As mentioned, mice with a Val66Met BDNF genetic variant showed impairments in extinction learning that could be reversed with a cognitive enhancer drug, D-cycloserine (Yu *et al.*, 2009). Moreover, chronic treatment with the tricyclic antidepressant desipramine, the selective serotonin reuptake inhibitor fluoxetine, and the monoamine oxidase inhibitor phenelzine increased BDNF protein levels in the frontal cortex (Dias *et al.*, 2003). In contrast, mice lacking the TrkB receptor in hippocampal progenitor cells show impairments in neural proliferation and neurogenesis, and show insensitivity to antidepressant treatment in depression and anxiety models (Li *et al.*, 2008). Nonetheless, antidepressants are only partially effective in their treatment of PTSD and are known to cause significant and negative side-effects. Consequently, agents that selectively enhance BDNF levels and increase synaptic plasticity and reconnection may be more effective treatment options.

One indirect approach for enhancing BDNF is through exercise. In one study, in which rats received either sham injury or TBI and were housed with or without access to a running wheel, brain-injured rats showed increased levels of BDNF and enhancement of cognitive performance following exercise (Griesbach *et al.*, 2004). Thus, exercise might enhance cognitive performance in PTSD and TBI models through BDNF mechanisms. Another way to enhance BDNF is through chromatin remodeling, a process in which post-translational changes in histones produce alterations in gene expression. BDNF has four transcripts, which are each regulated by a specific promoter that is sensitive to epigenetic modification (Martinowich *et al.*, 2003). Bredy *et al.* (2007) show a relationship between histone modification, epigenetic regulation of BDNF gene expression, and extinction learning. In cellular and animal models, histone deacetylase inhibitor (HDACi) treatment increases BDNF expression in neuron–glia cultures (Wu *et al.*, 2008), glioma cells (Morita *et al.*, 2009), and when given *in vivo* in various brain regions (Kim *et al.*, 2009). The implication is that HDACis may be more specifically effective as treatments for PTSD and TBI through the enhancement of synaptic plasticity. Studies are needed in both TBI and PTSD animal models and in humans to examine the promise of these agents.

HDACis such as valproate and sodium butyrate (SB) have been shown to enhance long-term memory and learning (Bredy *et al.*, 2007; Lattal *et al.*, 2007). Valproate has been shown to strengthen reconsolidation of the original fear memory or enhance long-term memory for extinction, such that it becomes independent of context (Bredy and Barad, 2008). In addition, brain-injured rats treated with SB show enhanced neurogenesis in a variety of regions including the subventricular zone, hippocampus, striatum, and frontal cortex (Kim *et al.*, 2009). Other TBI studies in rats suggest a similar effect of another commericially available medication, simvastatin, on hippocampal BDNF levels and neurogenesis that is associated with cognitive enhancement (Wu *et al.*, 2008). The omnipresence of HDACis makes their pharmacological inhibitors potential therapeutic tools in neuropsychiatric disorders such as TBI and PTSD. In addition, the fact that both SB and the antidepressant fluoxetine have been shown to reduce 'behavioral despair' in animal models has potential implications for the novel use of HDACis as adjuncts to behavioral therapy in the extinction of conditioned fear responses and in PTSD (Schroeder *et al.*, 2007). However, much more basic and human research is needed in this area.

In TBI and PTSD, there are overlapping cellular and genetic abnormalities in the prefrontal cortical, hippocampal, and other regions, resulting in well-characterized neural and behavioral deficits. A large body of research indicates common pathophysiological brain mechanisms, resulting in dysregulation of BDNF, in both TBI and PTSD disorders. As a treatment, BDNF improves synaptic transmission and efficiency and increases the survival of neurons. This unique role of BDNF may be critical in reversing dendritic retraction, restructuring, and disconnection that is found in TBI and PTSD. Future studies are needed to examine better the role of BDNF, using better-standardized animal models of TBI and PTSD, and in humans. New preclinical and clinical studies are needed to test the effects of BDNF and its analogs, along with HDACis, which increase BDNF levels, on neural repair, reconnection, and their clinical correlates.

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