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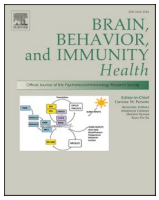

# Inflammation, brain connectivity, and neuromodulation in post-traumatic headache

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ABSTRACT

Post-traumatic headache (PTH) is a debilitating condition that affects individuals with different levels of traumatic brain injury (TBI) severity. The difficulties in developing an effective treatment are related to a lack of understanding the complicated mechanisms and neurobiological changes in brain function after a brain injury. Preclinical studies have indicated that peripheral and central sensitization of the trigeminal nociceptive pathways contributes to PTH. While recent brain imaging studies have uncovered widespread changes in brain functional connectivity following trauma, understanding exactly how these networks contribute to PTH after injury remains unknown. Stimulation of peripheral (trigeminal or vagus) nerves show promising efficacies in PTH experimental animals, likely mediated by influencing TBI-induced pathological plasticity by decreasing neuroinflammation and neuronal apoptosis. Non-invasive brain stimulations, such as transcranial magnetic or direct current stimulations, show analgesia for multiple chronic pain conditions, including PTH. Better mechanistic understanding of analgesia achieved by neuromodulations can define peripheral and central mechanisms involved in the development, the resolution, and the management of PTH.

## 1. Introduction

Traumatic brain injury (TBI) is a clinical condition caused by the action of an external mechanical force on the brain that alters the pattern of brain functioning and the involved structures. This type of injury is considered a global health problem, as it is the main cause of mortality in young adults and a major cause of death and disability at all ages (Maas et al., 2017). The severity of TBI is generally classified according to clinical indicators (Frey, 2003), and different changes in brain function depend on the severity of the trauma. The four levels of severity include:

(I) Concussion is a mild impact of the head causing less than 10% loss of consciousness (Laker, 2011), which is often under-reported and undermanaged (Baldwin et al., 2018; Reid et al., 2022). A definition of concussion by the International Conference on Concussion is "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces" (McCrory et al., 2009). Among the main causes are contact sports (Laker, 2011).

(II) Mild TBI is "a traumatically induced physiologic disruption of brain function" by the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (Silverberg et al., 2023). Mild TBI leads to a brief loss of consciousness (<30 min), a Glasgow Coma Scale (GCS) of 13–15, and post-traumatic amnesia (PTA) lasting <24 h ("Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study, 2016.," 2019; Laker, 2011; Taylor et al., 2017). The occurrence is often underestimated (Laker, 2011), and a population study has shown that mild TBI occurs in 95% of cases (Feigin et al., 2013).

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(III) Moderate TBI is characterized by a loss of consciousness and PTA >30 min, GCS 9–12, and includes patients with skull fractures (Frey, 2003; "Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study, 2016.," 2019; Taylor et al., 2017).

(IV) Severe TBI is characterized by a loss of consciousness and PTA >24 h, GCS ≤8, and includes patients with a brain contusion and intracerebral hematoma (ICH) (Frey, 2003; "Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study, 2016.," 2019; Taylor et al., 2017).

Epidemiological studies have indicated that approximately 2.8 million people experienced a TBI in the United States of America (USA) in 2013 (Taylor et al., 2017). One study found that over seven years in Washington state, there were 928 TBI cases, with a lifetime claim cost of $159 million (Wrona, 2006). These injuries often result from rotational or angular accelerations and shear forces acting on the brain. Several comorbidities resulting from a TBI can lead to the incapacity of injured individuals, which may persist for years after damage. One such incapacitating comorbidity is post-traumatic headache (PTH), considered a secondary headache with acute and chronic phases (Ashina et al., 2019; "Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition.," 2018). Headaches are pain in the head region with distinct types, subtypes, and subforms, with PTH being a type of headache attributed to TBI or neck trauma. Thus, patients can receive different diagnoses and treatments.

The pathophysiological mechanisms of PTH remain unclear, which has led to poor patient recovery and an indistinct disease classification (Capi et al., 2020; Leung, 2020). One recent challenge within the research community has been to understand how the brain communicates both naturally and after brain trauma. Several current reports on humans have pointed to the necessity of understanding functional brain connectivity after TBI, including all severities of trauma (Roine et al., 2022). Altered functional brain connectivity can also be one of the factors involved in PTH (Lu et al., 2020; Ofoghi et al., 2020). Interestingly, fear and pain circuits share similar brain networks and include regions such as the anterior cingulate cortex (ACC), prefrontal cortex (PFC), hippocampus, nucleus accumbens, and amygdala (Simons et al., 2015). Therefore, novel, high-efficacy treatments are necessary to reduce headaches after a TBI. This review aims to address the general information known about clinical PTH, discuss the inflammatory mechanisms involved in PTH animal models, and main connectivity pathways observed in human. In addition, the present review will point to new therapeutic approaches, such as electrical stimulation, as a novel strategy for the treatment of PTH.

## 2. Clinical characteristics of PTH

It is estimated that the occurrence of PTH after damage to the brain ranges from 30 to 90% of TBI patients (Hoffman et al., 2011; Lucas, 2011). According to the Classification by the Headache Classification Committee of the International Headache Society ("Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition.," 2018), acute PTH is characterized by the onset of pain reported seven days after the injury or after recovery of consciousness, with the pain ending up to the third month after the trauma. Another important criterion is the discontinuation of analgesic drugs to evaluate the acute period. However, chronic PTH is characterized when the pain persists for more than three months. In this sense, 18–33% of TBI patients continue to experience persistent headaches after TBI, even one year beyond post-injury (Stacey et al., 2017). Approximately 40% of moderate to severe TBI patients develop persistent, sometimes disabling, disorders—one of the most common being PTH (Anderson et al., 2015; Defrin, 2014; Stacey et al., 2017). Moreover, the majority of PTH cases occur with a mild type of trauma, and many go under-reported (Lucas et al., 2014; Nampiaparampil, 2008).

PTH is commonly associated with sleep disturbances and cognitive and psychiatric consequences (Lemme et al., 2021; Minen et al., 2016), which makes the condition more aggravating for patients. Although pain after TBI can occur in different parts of the body, such as the neck, back, and limbs, PTH is the most common chronic pain (Linder, 2007; Nampiaparampil, 2008). Regarding its etiology, PTH can be induced by repetitive concussions or a single TBI event ("Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition.," 2018; Seifert et al., 2017). However, some reports have shown that genetic mutations can facilitate the condition of preexisting headaches to trauma (Barros et al., 2013; Tottene et al., 2005).

PTH may result from direct injuries to the skull, the brain, the meninges, the cerebral vasculature, or the neck ("Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition.," 2018), leading to maladaptive plasticity of the trigeminal system. Furthermore, it can manifest a phenotype similar to primary headaches, such as migraines or tension-type headaches (Baandrup and Jensen, 2005; "Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition.," 2018; Zasler, 2011). It is well known that the symptoms of PTH resemble migraines and can produce between 15 and 30 headache days per month after a mild TBI (Kothari et al., 2022). However, despite its high prevalence and persistence, the mechanisms underlying PTH in TBI patients remain poorly understood.

## 3. Pathophysiology of PTH and associated mechanisms after TBI

### 3.1. Neuroanatomy related to PTH

PTH is a neurological disorder characterized by an enduring predisposition to generate pain symptoms in the head. Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). Nociception is, however, "the neural process of encoding noxious stimuli" and can be observed in several animal models and humans (Prescott et al., 2014; St John Smith, 2018). Pain is an important physiological system alerting the body to disturbances, including endogenous/exogenous irritations, which allow us to avoid harmful stimuli. However, acute pain from tissue damage or injury debilitates an individual and restricts their ability to perform daily activities. Chronic pain can induce suffering and reduce life quality. Moreover, personal experiences of pain depend not only on sensory discrimination but on emotional, psychological, and social factors.

A subpopulation of primary sensory neurons transduces noxious stimuli through multiple sensory receptors from organs throughout the body. C and Aδ fibers are primarily responsible for transmitting nociceptive signals to the brain via action potentials. Tissue damage or long-term noxious stimuli induce a prolonged barrage of nociceptive inputs from primary afferents to the brain, which can sensitize second-order neurons in the dorsal horn of the spinal cord or trigeminal sensory nucleus (i.e., central sensitization). Central sensitization of central nociceptive neurons of the brainstem, thalamus, and cortical and subcortical structures contributes to maintaining chronic pain, even in the absence of apparent peripheral lesions. While the somatosensory cortex is an important cortical structure involved in pain sensation, the activation of the insular cortex has been implicated in pain mediated by trigeminal stimulus. For example, following a nasal nociceptive stimulus, individuals exhibited more activation in two regions of the brain that contain the primary and secondary somatosensory areas and the insular cortices, which are similar to the operculo-insular cortex (Lötsch et al.,

2012). Patients with trigeminal neuralgia disorder also present with a reduced cortical convolution magnitude, predominantly in the left insular cortex, as shown by local gyrification index analysis (Wang et al., 2018).

Anatomically, the trigeminal nerve is the fifth pair of cranial nerves and is responsible for responses arising from innocuous and noxious stimuli to the face and part of the head. Activation of the trigeminal nerves leads to activation of the trigeminal nociceptive system, including the trigeminal ganglia (TG) and the trigeminal nucleus complex, which includes the trigeminal nucleus caudalis (Vc), thalamic nuclei, and the insular and somatosensory cortices. Therefore, lesions occurring on the face or skull as a result of a TBI can induce nociception and pain through the trigeminal nociceptive system, leading to PTH (Fig. 1).

### 3.2. Neuroinflammation and sensitization of trigeminal nociceptive pathways

While the pathophysiological mechanisms of PTH remain unclear, studies using TBI animal models have pointed to inflammation as the cellular and molecular basis. Headaches after trauma can occur alone or together with several other symptoms that occur in migraine attacks ("Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition.," 2018). Therefore, the pathogenesis of PTH might overlap with migraines, with inflammation and cerebral metabolism involvement. Although different TBI animal models present distinct characteristics of pathology, similar symptoms like PTH have been observed after injury in some of these models. In this review, we focus on the symptoms of PTH in animal models related to TBI and concussion, whose clinical condition is similar to humans. This is important because the pathology, complications, and therapeutic approaches in the trauma models can be better translated into civil and military injuries. We focus on peripheral and central sensitizations along trigeminal nociceptive pathways. We also review the plasticity of brain activity over regions associated with sensory and affective pain. The effects of neuromodulation on brain plasticity are reviewed to understand the brain mechanisms involved in the development and resolution of PTH.

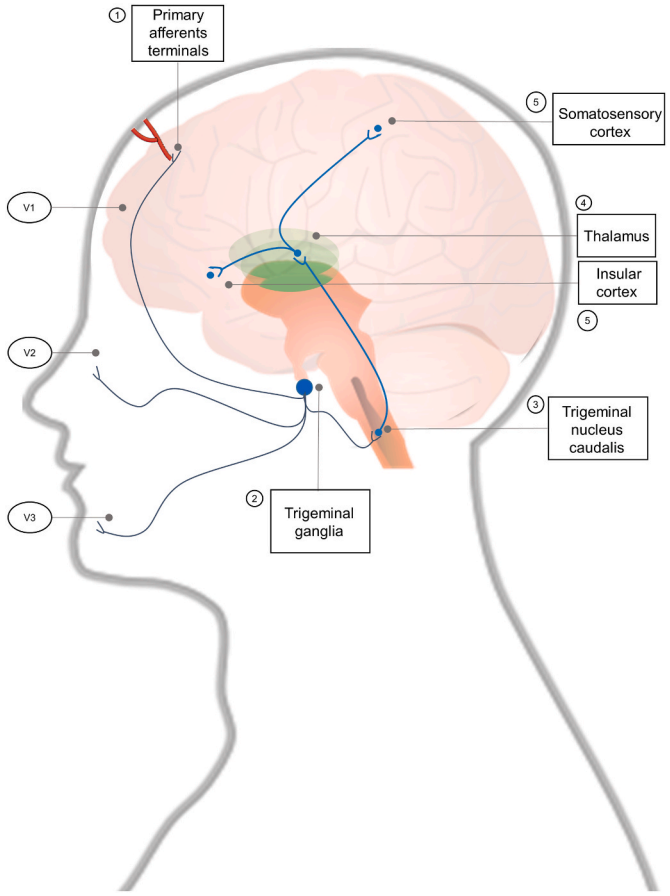


**Fig. 1. Anatomic pathway of the trigeminal system.** 1) Primary afferent terminals are located at the skull, meninges, and blood vessels; 2) Trigeminal ganglia contain the cell bodies of pseudounipolar neurons with peripheral branches going toward peripheral tissues in three branches (V1, V2, and V3) and central branches going toward the brainstem; 3) The trigeminal nucleus caudalis is the site of termination of the central branches of the trigeminal afferents, and the secondary neurons send axonal projections in the direction of the thalamus; 4) Tertiary neurons in the thalamus send axonal projections to the somatosensory cortex; 5) The somatosensory and insular cortices are the main locations of pain perception. V, fifth; V1, ophthalmic (periorbital) innervation of the fifth cranial nerve; V2, maxillary innervation of the fifth cranial nerve; V3, mandibular innervation of the fifth cranial nerve.

### 3.3. Peripheral sensitization

Primary afferents' peripheral terminals projected to the meningeal layers, blood vessels, and skull respond to diverse inflammatory mediators released after a traumatic injury, leading to initial inflammatory pain (Fig. 2). The skull bone contains a considerable number of blood vessels and efferent nerves (Kosaras et al., 2009) that are likely to be damaged after contact trauma. A skull fracture can potentially increase the TG response, causing peripheral sensitization. TBI induces the recruitment of leukocytes, particularly neutrophils and monocytes, to the injury site and increases the inflammatory process during the acute phase (Liu et al., 2018; Shi et al., 2019) via pro-inflammatory toll-like receptor 4 and nuclear factor κB (NFκB) signaling (Liu et al., 2021). TBI induces the early release of cytokines and chemokines in the brain (Dalgard et al., 2012; Di Battista et al., 2016), and both molecules perform important actions at the damage site, leading to cellular necrosis or apoptosis. Pro-inflammatory molecules also influence the survival of cells proximal and adjacent to the damaged site. Pro-inflammatory cytokines cause the activation and sensitization of nociceptive C and Aδ fibers in the meninges, skull, and blood vessels (Fontaine et al., 2018; Hanko et al., 1985; Kosaras et al., 2009; Melo-Carrillo et al., 2017), leading to the peripheral sensitization of trigeminal primary afferent neurons. Molecularly, neutrophils express the C-X-C motif chemokine receptor 2 and are directed to the damage site by chemical endogenous ligands, such as CXC-chemokine ligand 1 (Liang et al., 2017), leading to an increase in the early release of tumor necrosis factor (TNF) (Dalgard et al., 2012). TNF promotes immune cell infiltrations into the brain, further amplifying inflammatory activation, aggravating the compromised blood-brain barrier integrity, and inducing extravasation of blood products such as damage-associated molecular patterns (DAMPs) (Sayed et al., 2010). Moreover, increased pathogen-associated molecular patterns (PAMPs) enhance the activation of toll-like receptors (TLRs) and lead to the activation of resident cells, aggravating the pro-inflammatory process (Olson and Miller, 2004; Rosa et al., 2021). For example, macrophages can induce the expression of inducible nitric oxide synthase (iNOS), causing a release of nitric oxide (NO) and vasodilation of the blood vessels.

Several studies using different experimental models have demonstrated the effects of TBI and concussions on PTH (Bree and Levy, 2018; da Silva Fiorin et al., 2018; Daiutolo et al., 2016; Elliott et al., 2012; Macolino et al., 2014; Meidahl et al., 2018; Studlack et al., 2018; Tyburski et al., 2017). These investigations have demonstrated the involvement of neuropeptides, mainly calcitonin gene-related peptide (CGRP), associated with PTH in several regions of the trigeminal nociceptive system (Bree and Levy, 2018; Daiutolo et al., 2016; Elliott et al., 2012; Wang et al., 2017). CGRP is upregulated in meningeal afferent terminals after a controlled cortical impact (CCI) (Daiutolo et al., 2016). Consistent with this, the administration of a CGRP antagonist (MK8825)

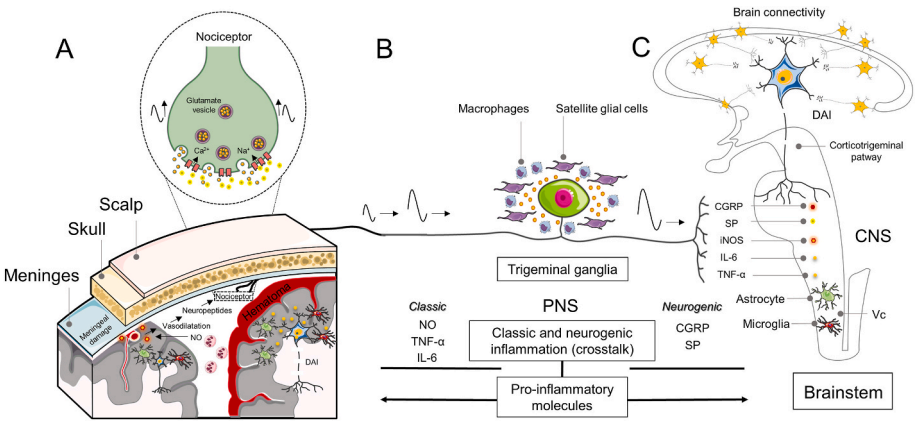


**Fig. 2. The proposed molecular pathways and mechanisms involved in headache and brain connectivity after traumatic brain injury (TBI).** A) TBI leads to meningeal damage, intracerebral hematoma, and diffuse axonal injury (DAI) in cortical neurons, and it targets neutrophils to the site of damage. Neutrophils release NO, leading to vasodilatation together with blood leakage and the release of inflammatory mediators due to physical damage. Nociceptors present in the skull, meninges, and blood vessels are activated and sensitized, increasing the influx of $Ca^{2+}$ and $Na^{+}$ to the cells. Glutamate can be released due to a $Ca^{2+}$ and $Na^{+}$ influx, causing more excitatory activation in the nociceptors. B) Excitatory activation sends action potentials through trigeminal ganglia (TG) neurons. Excitation of TG neurons increases the release of classic inflammatory and neurogenic mediators from the soma, which activates satellite glial cells and resident macrophages to release more inflammatory mediators to further enhance the sensitivity and action potentials. C) Peripheral sensitization in afferent terminals and the TG can lead to an increased release of classic inflammatory mediators, neurotransmitters, and neurogenic mediators in the brainstem. In response, increased astrocytes and microglia release more inflammatory mediators, leading to increased sensitivity of second-order neurons (central sensitization). Corticotrigeminal projections can suffer DAI due to cortical damage (intracerebral hematoma, as indicated in panel A) and/or the inflammatory process in the Vc. NO, nitric oxide; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; CGRP, calcitonin gene-related peptide; SP, substance P; iNOS, inducible nitric oxide synthase; Vc, subnucleus of the caudal spinal tract; PNS, peripheral nervous system; CNS, central nervous system.

attenuates periorbital allodynia after CCI in mice (Daiutolo et al., 2016). A variety of other molecules involved with pain sensations, such as NO and substance P (SP), are also upregulated in trigeminal signaling pathways immediately after an injury (Daiutolo et al., 2016; Elliott et al., 2012). Peripheral sensitization of nociceptors in the dura can further aggravate ongoing inflammation. The transient receptor potential vanilloid subtype 1 (TRPV1) channel is highly colocalized with CGRP and SP in the TG (Chung et al., 2020), and its activation induces the release of CGRP and SP (Markowitz et al., 1987; Tognetto et al., 2001), leading to vasodilation in the dura (Dux et al., 2003). TRPV1 and the transient receptor potential ankyrin subtype 1 channel can be involved in neurogenic inflammatory responses following TBI through Aδ and C-fibers (Corrigan et al., 2016; da Silva Fiorin et al., 2020; X.-J. Yang et al., 2022). A subset of Aδ nociceptors can also be directly activated or sensitized by irritant chemical stimuli such as protons, prostaglandins, or bradykinin (Lang et al., 1990; Martin et al., 1987; Steen et al., 1992). The mechanical impact of a TBI leads to the acute activation of resident cells and inflammatory mediator release (Rosa et al., 2021), which may activate Aδ nociceptors. However, the time course of the changes in the expression of cytokines and chemokines in the lesion is too transient to fully account for persistent hyperalgesia.

In the TG, sensory neurons are closely enveloped by satellite glial cells (SGCs), and the mechanisms involved in neuron-glia crosstalk in the TG have been widely studied in the context of craniofacial pain (Chung et al., 2020; Iwata et al., 2017). A recent study of experimental fluid percussion injury (FPI) in rats found that glial fibrillary acidic protein (GFAP), a peripheral marker of satellite glia, and ionized calcium-binding adapter molecule 1 (IBA-1), a marker of macrophages, were upregulated in the TG, ipsilateral to the injury (da Silva Fiorin et al., 2020). Moreover, the chemical depletion of most peptidergic primary afferents expressing TRPV1 channels reduced glial cell activation and painful responses in rats after TBI (da Silva Fiorin et al., 2020). These findings strongly suggest the involvement of neuron-glia interactions within the TG in PTH. SGCs express a diversity of receptors that respond to inflammatory molecules. The release of CGRP from peptidergic afferents followed by its binding to receptors in SGCs increases iNOS expression and NO release (Li et al., 2008). iNOS was increased in the TG two weeks after an experimental CCI injury in mice (Daiutolo et al., 2016). The iNOS increase was colocalized with GFAP and IBA-1 (Daiutolo et al., 2016). Interestingly, iNOS was localized both in neuronal and non-neuronal cells following a TBI, suggesting that the release of NO is involved in pro-inflammatory pathways after injury (Daiutolo et al., 2016). Therefore, interactions of SGCs and trigeminal nociceptors within the TG may contribute to the aggravation and maintenance of persistent PTH.

### 3.4. Central sensitization

The sensitization of central neurons in TBI patients is an important mechanism of chronic pain (Jang et al., 2016), and the pathways of the maladaptive modulation of neurons and glia in the central nervous system (CNS) can be important in headaches after a TBI. Several brain areas of TBI animals have shown increased neuroinflammation, markedly by tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (Clausen et al., 2011; Mota et al., 2012; Niesman et al., 2014; Singh et al., 2016). Reports using several rodent TBI models have demonstrated increased levels of SP, CGRP, TNF-α, interleukin-6 (IL-6), and iNOS together with elevated expressions of GFAP and IBA-1 (markers of astrocytes and microglia, respectively) in the CNS, including the Vc area (da Silva Fiorin et al., 2020; Daiutolo et al., 2016; Elliott et al., 2012; Tyburski et al., 2017; Wang et al., 2017). The inflammatory process can directly sensitize second-order nociceptive neurons in the Vc that send axonal projections to the thalamic nuclei, which could sensitize third-order neurons in the thalamus and cortex, as indicated in other headache conditions (Akerman et al., 2011; Hryciw et al., 2023). In fact, astrogliosis and microgliosis have been observed in the thalamus after experimental TBI (Onyszchuk et al., 2009).

The roles of astrocytes and microglia in TBI pathobiology are well-established (Mira et al., 2021). Although cytokines and chemokines in the brains of injured rats peak 4 h after TBI, with a gradual decrease in 12 h, 24 h, 3 days, and 7 days (Dalgard et al., 2012), inflammatory responses are dependent on other factors, such as the TBI severity and model used. Moreover, persistent inflammatory processes driven by glial cells after experimental TBI are common (Elliott et al., 2012). Reactive astrogliosis after TBI is both a gradual response and heterogeneous, which may reflect the severity of CNS tissue damage (Burda et al., 2016;

Burda and Sofroniew, 2014). This damage can be varied, e.g., local degeneration, the disruption of the blood-brain barrier with subsequent extravasation of inflammatory cells, the degeneration of synapses due to distal axonal injury, and exposure to PAMPs. These damages can influence the function of astrocytes and result in astrogliosis (Lee et al., 2022). Experimental periorbital allodynia is accompanied by transient increases in SP, CGRP, and GFAP in the brainstem after TBI, together with increased astrocytes in the somatosensory cortex (Elliott et al., 2012). Hypertrophic reactive astrogliosis occurs in the Vc after mild TBI in rats and is concomitant to the inflammatory process in the somatosensory cortex (da Silva Fiorin et al., 2020). These hypertrophic reactive astrocytes are interposed between neurons surviving the injury and being found viable in the area of injured neural tissue (Brandebura et al., 2023; Burda and Sofroniew, 2014). Thus, the reactivity of astrocytes in the periphery of the damaged area may influence neurons and glia in healthy tissue distal to the lesion, leading to aberrant excitatory synaptic activities. Astrocytes can respond by producing immunomodulatory molecules, including cytokines, in addition to DAMPs-type inflammatory mediators. This is due to the presence of TLR receptors and advanced glycation end products in the astrocytic membrane (Fu et al., 2016; Kumar, 2019). The activation of astrocytes can trigger NFκB activation and increase the production and release of pro-inflammatory cytokines such as TNF-α, IL-6, and the inflammatory mediator cyclooxygenase-2 (COX2) (Font-Nieves et al., 2012; Gorina et al., 2011; Ponath et al., 2007). COX2 participates in various types of migraines (Li et al., 2017), and the increased activity of COX2 could be involved in the molecular mechanisms of hyperalgesia induced by glial cells in PTH. Moreover, NFκB signaling activated by astrocytes results in swelling cellular and cytotoxic edema after TBI (Jayakumar et al., 2014).

In injury processes such as TBI, microglia become highly activated resulting in changes in cell morphology and activity. These changes are due, in part, to microglia expressing pathogen recognition receptors similar to those found in peripheral immune cells. Among these receptors are the TLRs that respond to PAMPs and 'NOD-like receptors' that respond to DAMPs secreted after mechanical impact (Hanisch and Kettenmann, 2007). These glial cells also exhibit other types of receptors for different factors released by damage, including ATP, glutamate, growth factors, and cytokines (Kumar and Loane, 2012). Thus, chronic activation of the microglia after a TBI can lead to a persistent inflammatory process and make cell survival or maintaining its normal physiological state difficult. In mice, increased microglia in the somatosensory cortex persist nearly one month after experimental TBI and do so concomitantly with periorbital allodynia (Elliott et al., 2012).

Pro-inflammatory processes occurring at a brain site adjacent to an injury could cause retrograde axonal degeneration of corticotrigeminal neurons, leading to failure of excitatory and inhibitory communication between the brainstem and the cortex, as corticotrigeminal axons densely innervate the Vc area (Castro et al., 2017). It was also demonstrated, in both mice and rats, that stimulating axons from the somatosensory cortex induced suppression of nociceptive responses in the Vc area and produced behavioral hypoalgesia (Castro et al., 2017). Thus, altered connectivity after TBI may be a consequence of primary damage directly to brain structures, as well as secondary diffuse axonal injury caused by inflammation (Fig. 2). Therefore, a connectivity evaluation after TBI in headache patients must be clarified to determine the altered neural activities of the brain areas involved in PTH.

### 3.5. Changes in functional brain connectivity

The brain is a complex structure comprising numerous and widespread connections between different regions. Subsets of neurons from different areas of the brain can fire in synchrony, generating activity patterns that can be evaluated to identify the network and its functional connectivity. Electrical cerebral signals of higher and lower frequencies can have relationships between brain areas over time, and these interactions can be defined through statistical analysis, leading to an understanding of functional connectivity (Gaudet et al., 2020). Structural connectivity has relationships with the physical connections among brain areas through fiber tracts, while functional connectivity shows correlated activity through similar frequency, phase, and/or amplitude. There are techniques to perform brain connectivity analysis, such as functional magnetic resonance imaging (fMRI), which relies on the coupling between underlying neuronal activation and cerebral blood flow and can show high spatial resolution in millimeters (Gaudet et al., 2020). Electroencephalography can collect neuronal electric activity with a resolution of less than 1 ms and promote direct temporal information through electrodes, with data analyzed via the frequency domain (Cacioppo et al., 2007; Del Rocio Hernandez-Castanon et al., 2021). Magnetoencephalography can measure magnetic fields and neuronal activity in milliseconds, including the cortical sulci with high temporal resolution (Kida et al., 2015). Thus, the brain communicates with itself through connectivity networks, and several MRI studies have allowed for the incipient comprehension of whole-brain networks and the characterization of functional and structural changes associated with TBI and PTH symptoms (Tables 1 and 2, respectively).

A recent study (Lemme et al., 2021) evaluated the extent to which PTH and resting-state functional connectivity (RS-Fc) were altered in a cohort of young patients with acutely resolved (PTH-R) and those with persistent (PTH-P) headaches. Although both cohorts exhibited alterations in functional connectivity in several brain areas, individuals with PTH-P displayed decreased connectivity between the amygdala and the ACC while simultaneously increasing connectivity between the PFC and the ACC. These results suggest the persistence of PTH modulates the affective component of pain. In addition, the decreased connectivity between the amygdala and the ACC was associated with reductions in the effect of sadness on pain (Yoshino et al., 2010). In contrast, the high PFC-ACC connectivity partially explains the painful sensation induced by PTH after mild TBI (Ofoghi et al., 2021). The activation of the ACC during PTH has been shown using neuroimaging (Leung et al., 2016b), indicating that headaches are mediated by affective responses.

In patients with acute symptoms of PTH, studies have shown decreased connectivity between the cerebellum and temporal lobe (for PTH-R) (Lemme et al., 2021) and among periaqueductal gray, the inferior parietal lobule, and the angular gyrus (for PTH evaluated within seven days post-TBI) (Niu et al., 2020). The cerebellum is a structure

**Table 1**
Functional changes in PTH after TBI.

| Stage of PTH | Comparison | Brain areas/networks | Reference |
|---|---|---|---|
| Acute | Control group | ↓Cerebellum/temporal lobe ↑Amygdala/ACC | Lemme et al. (2021) |
| Chronic | Control group | ↑PFC/ACC and cerebellum | |
| Chronic | sFNC analysis | ↑DNM/VN | Li et al. (2021) |
| | dFNC analysis | ↑DNM/SMN | |
| Unknown | Control group | ↑PFC/ACC | Ofoghi et al. (2021) |
| Chronic | No-PTH | ↓Hypothalamus/MFG and mSFG | Lu et al. (2020) |
| Acute | Control group | ↓PAG/IPF, AG and precuneus ↑PAG/MTG | Niu et al. (2019) |
| Chronic | sFNC analysis | ↑Left middle cingulate/right pulvinar ↑Right posterior insula/left hypothalamus | Dumkrieger et al. (2019) |

Legend: PAG: periaqueductal gray; IPF: inferior parietal lobule; AG: angular gyrus; MTG: middle temporal gyrus; ACC: anterior cingulate cortex; PFC: prefrontal cortex; sFNC: static functional network connectivity; dFNC: dynamic functional network connectivity; DMN: default mode network; VN: visual network; SMN: sensorimotor network; MFG: middle frontal gyrus; mSFG: medial superior frontal gyrus; Control group: non-disabled individuals; No-PTH: people with TBI; Acute: 7 days to 1 month; Chronic: after 1 month; ↑ = represents increases of connectivity; ↓ = represents decreases of connectivity.

**Table 2**
Structural changes in PTH after TBI.

| Stage PTH | Comparison | Volume | Gray matter[a] | White matter[a] | References |
|---|---|---|---|---|---|
| Acute | Control group | *CT*: ↓left caudal ACC, ↓left insula, *CSA*: ↓SFG | – | – | Xu et al. (2023) |
| Chronic | No-PTH | *GM*: ↓left and right MTG, STG, parietal operculum, right ITG, angular gyrus, supramarginal gyrus, S1 and M1 | – | – | Burrowes et al. (2020) |
| Acute and chronic | – | *GM*: ↓ACC, M1 and cerebellum | – | – | Niu et al. (2020) |
| Chronic | Control group | – | *(t)*: ↓ middle/superior frontal gyrus, precentral gyrus, right supramarginal, superior and inferior parietal and precuneus regions | – | Chong et al. (2018) |
| Acute | No-PTH | – | – | *(s)*: ↓ fornix-septohippo- campal circuit | Alhilali et al. (2017) |
| Chronic | No-PTH | – | – | *(s)*: ↓ splenium of the corpus callosum<br>*(s)*: ↑ genu of the corpus callosum | Ghodadra et al. (2016) |

[a] refers to thickness (t), surface (s) or folding (f) of gray and white matter. Legend: CSA: cortical surface area; CT: cortical thickness; GM: gray matter; MTG: middle temporal gyrus; SFG: superior frontal gyrus; STG: superior temporal gyrus; ITG: inferior temporal gyrus; S1: primary somatosensory cortex; M1: primary motor cortex; ACC: anterior cingulate cortex; Control group: non-disabled individuals; No-PTH: people with TBI; Acute: 7 days to 1 month; Chronic: after 1 month.

consisting of several interaction networks (Legrain et al., 2011), but its role in pain needs to be better clarified. The increased functional connectivity observed before a potentially painful stimulus indicates that the cerebellum is important for managing emotional expectations. However, in migraines (a probable symptom of PTH) the same anatomical sub-region exhibits limited connectivity with the default mode network (DMN) (Ke et al., 2020), an intrinsic brain network also altered in PTH patients post-TBI (Li et al., 2021).

The DMN, comprising the prefrontal regions, precuneus bilateral lateral parietal cortices, and the dorsal posterior cingulate cortex, is considered a common network path for encoding pain and cognitive processing (Baliki et al., 2014; Bonnelle et al., 2011). After TBI, the presence of a headache decreases activity in the dorsolateral prefrontal cortex (DLPFC) (Vaninetti et al., 2021) and modulates the DMN network under stationary and dynamic connectivity functional conditions. (Li et al., 2021) found an increase in the stationarity of the connections between the DMN and sensorimotor network, and a reduction between the DMN and visual network (Li et al., 2021)—a scenario that may prevent the desirable and healthy integration of cognitive and sensory information during pain processing (Zou et al., 2021). An aberrant flow of information transfer in regions within the DMN was found during the measurement of dynamic connectivity function (Li et al., 2021). This alteration in connectivity has been identified as a predictor of limited resilience (i.e., limited adaptive responses) to pain in chronic pain conditions (Hemington et al., 2018).

A recent study has found that the hypothalamus, another region involved in pain processing, could mediate PTH symptoms following a TBI. (Lu et al., 2020) showed decreased functional connectivity between the hypothalamus and the middle and medial superior frontal gyrus after mild TBI. This decreased connectivity was statistically correlated with increased headache frequency and intensity (Lu et al., 2020). Although the involvement of the hypothalamus may be incipient after traumatic PTH, some studies have provided evidence of its role in other headache disorders. Recently, (Messina et al., 2022) showed that during the interictal phase of episodic migraine, the RS-Fc connectivity among the hypothalamus and parahippocampal gyrus, orbitofrontal gyrus, cerebellar lobule VI, lingual gyrus, and inferior temporal gyrus were decreased when compared to a control group. The same authors also showed that the reduced network (reduced connectivity) between the hypothalamus and frontal region (orbitofrontal gyrus) was positively correlated with the effect of headaches on the social life of people with migraines over the long term (Messina et al., 2022). Together, these findings suggest that changes in hypothalamus connectivity interfere with the frequency and intensity of headaches and the welfare of individuals with PTH or TBI (Fig. 3).

### 3.6. Structure of brain areas involved in PTH

In addition to functional connectivity findings, previous literature has also shown structural changes in brain regions and associations with PTH, summarized as a reduction of cortical thickness (gray matter [GM]) and parenchymal volume in individuals with PTH (Ofoghi et al., 2020). It is impossible to assume an order (i.e., cause–consequence), but concomitant changes in function (connectivity) and structure likely occur in PTH. For example, in adults with PTH-P, the cortical surface is reduced in the inferior parietal and precuneus (Chong et al., 2018), and there is reduced parenchymal volume in the DLPFC, angular gyrus, and somatosensory cortex (Burrowes et al., 2020; Niu et al., 2020), regions that match with impaired connectivity. However, an increase in GM volume was found after PTH-P and acute PTH in the ACC, primary motor cortex, and cerebellum (Niu et al., 2020), indicating that the structural changes induced by PTH are dependent on the brain area and the onset of headache.

PTH may also induce changes in white matter (WM) microstructure, observed in the corpus callosum and fornix-septohippocampal circuit (Ofoghi et al., 2021). The deterioration of WM in the splenium and the simultaneous high proportion of myelin in the genu of the corpus callosum are linked to PTH risk factors after TBI (Ghodadra et al., 2016). The loss of myelin has also been observed in the fornix-septohippocampal circuit after injury (Alhilali et al., 2017), an important pathway for learning, memory, and locomotion (Khakpai et al., 2013; Müller and Remy, 2018). Therefore, it is plausible that altered brain connectivity is associated with maladaptive cellular changes leading to decreased or increased activity of pain-related brain regions, and novel approaches capable of modulating brain function might contribute to the treatment of PTH.

### 3.7. Mechanistic insights into PTH from drugs and neuromodulation

#### 3.7.1. Pharmacological approaches

Pharmacological therapies are used for tension- and migraine-like headaches in PTH patients, including analgesics and non-steroidal anti-inflammatory agents (Heyer and Idris, 2014; Mavroudis et al., 2023). Interestingly, although analgesics and non-steroidal anti-inflammatories can be prescribed for the acute phase of PTH, one study showed that acute administration of ibuprofen, acetaminophen, or both did not decrease the incidence of headaches seven days after injury in children and youth (aged 5–18 years) (Ledoux et al., 2022). Moreover,

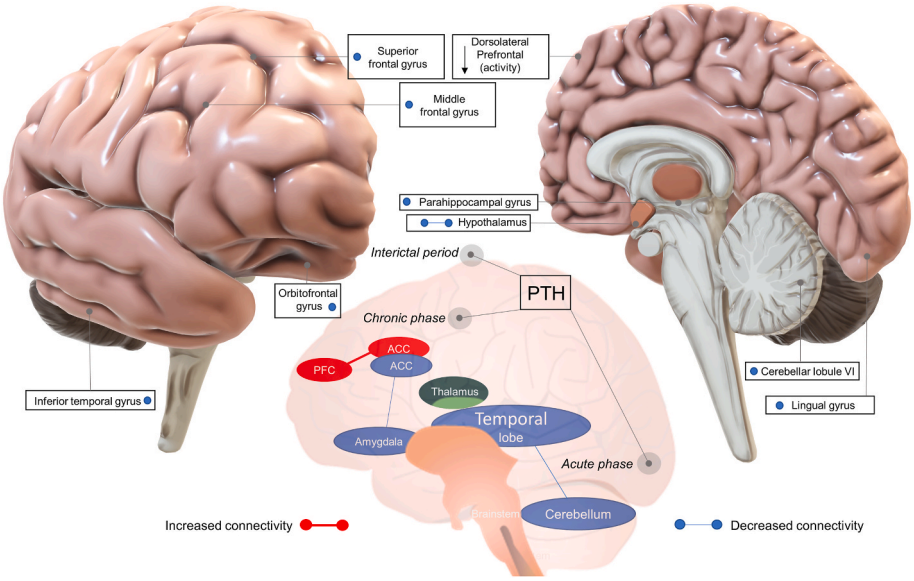


**Fig. 3. Functional changes in brain connectivity after traumatic brain injury (TBI) in patients with post-traumatic headache (PTH).** Decreased connectivity between the cerebellum and temporal lobe mediates acute symptoms, while decreased connectivity between the amygdala and the anterior cingulate cortex (ACC) and concomitant increased connectivity between the prefrontal cortex (PFC) and the ACC is presented in persistent PTH. Decreased functional connectivity between the hypothalamus and middle and medial superior frontal gyrus after mild TBI mediate PTH symptoms. Decreased connectivity between the hypothalamus and parahippocampal gyrus, orbitofrontal gyrus, cerebellar lobule VI, lingual gyrus, and inferior temporal gyrus occurs during the interictal phase of episodic migraines.

the excessive use of analgesics can lead to chronic headaches in some adolescents with PTH (Heyer and Idris, 2014).

Pharmacological treatments for migraines, such as triptans, decrease painful sensations of chronic PTH. Although CGRP in plasma is lower in individuals with chronic PTH (Ashina et al., 2020a), its administration causes the exacerbation of headaches in people with migraines and PTH (Ashina et al., 2020b; Hansen et al., 2010). In contrast, anti-CGRP monoclonal antibodies prevent migraine attacks (Goadsby et al., 2017; Silberstein et al., 2017) and reduce the frequency of moderate to severe headaches in chronic PTH patients (Ashina et al., 2020c). Botulinum toxin type A, another medication for the treatment of chronic migraines, decreased the frequency and pain severity of headaches in military veterans with PTH (Zirovich et al., 2021). However, to date, the pharmacological treatment for PTH is based on medical opinion, given the various headache features and a scarcity of data from controlled trials (Ashina et al., 2021; Larsen et al., 2019). Other classes of drugs tested on PTH, such as anti-epileptics and anti-depressants, have provided improvements in the short term but without long-term significance compared to non-treated individuals (Cushman et al., 2019). Currently, opioids are not recommended for chronic use (Ashina et al., 2021; Pinchefsky et al., 2015).

### *3.7.2. Neuromodulation approaches*

Electrical stimulation is a useful and promising neuromodulation technique applied directly to the skull and peripheral nerves, including the TG and vagus nerve, or to the CNS, such as the spinal cord and brain. In recent years, neuromodulation through electrical stimulation has been tested in individuals with chronic headaches. However, these techniques need to be improved, as invasive methods such as deep brain stimulation entail higher risks, while semi-invasive and non-invasive methods only partially reduce headaches and chronic migraines (Coppola et al., 2022).

Recent evidence points to functional improvement in patients after TBI using neuromodulation (Tiefenbach et al., 2022). Improvements in motor function after TBI using functional electrical stimulation have been demonstrated through the reorganization of cortical areas (Milosevic et al., 2021). Although the functional recoveries demonstrated in recent reports do not include PTH evaluations, a case series reported that repetitive transcranial magnetic stimulation (rTMS) reduced the intensity of pain and frequency of headache episodes in individuals with mild TBI who had developed recurrent headaches (Leung et al., 2016a). In that report, rTMS was shown to have beneficial effects on men of different ages and with different prior histories of headache and medication use (Leung et al., 2016a). Currently, few studies using rTMS have demonstrated the amelioration of headaches in TBI individuals.

Studies using animal models of TBI and electrical stimulation can help in understanding cellular mechanisms and lead to new approaches to decrease PTH. For example, bilateral trigeminal nerve stimulation (TNS) (the infraorbital branch of the maxillary nerve (V2); a current intensity of 0.1 mA; pulse width of 200 μs; frequency of 10 Hz for 30 s/min) for 60 min one day after TBI in mice markedly reduced neuroinflammation by TNF-α and IL-6 (Q. Yang et al., 2022). Pro-inflammatory mediators were concomitantly downregulated in the caspase-3 signaling pathway, while brain edema was reduced, and the blood-brain barrier was protected (Q. Yang et al., 2022). TNS has been associated with a protective effect against brain injuries such as epilepsy and is associated with reduced inflammation and apoptosis (da Silva Fiorin et al., 2021; Wang et al., 2016). It is plausible that the anti-apoptotic effects of TNS occur via inhibition of NF-κB (Inohara and Nuñez, 2003). fMRI has shown that increased and decreased activation depends on the brain areas after electrical trigeminal stimulation. For example, 30 min after TNS induction, BOLD activation is increased in the olfactory bulb, most areas of the motor cortex, the prelimbic area, and the hippocampus of mice (Q. Yang et al., 2022). Another study showed the efficacy of 60 min of cortical electrical stimulation (frequency of 20 Hz; 2 ms biphasic bipolar pulse; a current intensity of 100 μA) during the first seven days after TBI in rats (Wang et al., 2022). Electrical stimulation reduces apoptosis and astrogliosis in the perilesional cortex and increases hippocampal neurogenesis via upregulation of phosphatidylinositol 3-kinases/protein kinase B (PI3k/Akt), mitogen-activated protein kinases/extracellular signal-regulated kinases, and Wnt/βcatenin signaling pathways (Wang et al., 2022). Another study that used different parameters of spinal cord electrical stimulation (seven consecutive days of 30 min of stimulation once a day at 50 Hz, pulse width of 100 μs, current of 0.4–0.6 mA) found that brain-derived neurotrophic factor and vascular endothelial growth

factor increased in the injured brains of rats in a TBI model (Zhao et al., 2022). Electrical stimulation-induced upregulation in the PI3k/Akt pathway and anti-apoptotic B-cell lymphoma (Bcl-2) protein while reducing the expression of pro-apoptotic Bcl-2-like protein and caspase-3 in the brain tissue of the injured area (Zhao et al., 2022). These studies, using peripheral and central electrical stimulations, uncovered decreased neuronal apoptosis (Wang et al., 2022; Q. Yang et al., 2022; Zhao et al., 2022), suggesting electrical stimulation of pain pathways affects the modulation of TBI by influencing the maintenance and survival of neurons. Previous studies have demonstrated the protection of neurons through vagus nerve stimulation (VNS) after experimental TBI. For instance, VNS applied 24 h post-injury every 30 min for 14 days at 20 Hz, a biphasic pulse of 0.5 ms, and a current of 0.5 mA, in trains of 30 s showed a protective effect on GABAergic neurons in the cortex of rats with injuries using an FPI model (Neese et al., 2007). Moreover, the acute, beneficial effects of VNS (every 30 min to the left vagus nerve 48 h post-injury) were evidenced in the reduction of edema in the cortex after FPI in rats (with frequency of 20 Hz, a biphasic pulse of 0.5 ms, and current of 0.5 mA, with trains of 30 s) (Clough et al., 2007). Continuous stimulation for 20 min (frequency 5 Hz; pulse width of 5 V; current of 10 mA) 1 h after an explosive injury model in rabbits decreased brain edema (Zhou et al., 2014), while VNS in continuous stimulation (frequency 30 Hz; pulse width of 0.5 mA; current of 1.0 mA) attenuated cortical edema and the necrosis area (Tang et al., 2020). A recent review has also shown the potential effects of VNS after TBI from in vivo and clinical studies (Srihagulang et al., 2022).

Although studies using electrical stimulation in animal models and patients with TBI have increased, it is necessary to advance our understanding of the clinical evidence and its mechanisms of action to treat PTH.

#### *3.7.3. Brain stimulation to modulate pain and TBI-related symptoms*

When the brain is injured by trauma or other insults, the resulting deficits appear to be compensated by newly forming cortical and subcortical connections and by reorganizing neural networks (Zaninotto et al., 2019). However, these compensatory mechanisms are often suboptimal, unable to fully restore function, and may lead to maladaptive effects, lower functionality, and a poor quality of life.

Non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS), may provide an excellent alternative in both restoring supraspinal functional deficits and providing headache relief, thereby improving clinical outcomes and quality of life (Zaninotto et al., 2019). tDCS is a safe and non-invasive form of neuromodulation, where a constant, low-amperage (usually 1–2 mA) electric current is applied to the skull through anodal and cathodal stimulation, reaching the cortical areas and modulating the resting membrane potential of individual neurons (Nitsche et al., 2003, 2008; Zaninotto et al., 2019). Since the introduction of this technology in its current form, positive results have been reported in psychiatry (Blumberger et al., 2012; Demirtas-Tatlidede et al., 2013; Martin et al., 2011) and neurorehabilitation (Hernandez-Pavon and Harvey, 2019; Lindenberg et al., 2012). tDCS has also been suggested as a promising therapy for patients with several chronic pain conditions, including fibromyalgia (Villamar et al., 2013), pain due to traumatic spinal cord injury (Fregni et al., 2006; Soler et al., 2010), chronic pelvic pain (Divandari et al., 2019; Fenton et al., 2009), refractory orofacial pain (Antal and Paulus, 2011), postherpetic neuralgia (DosSantos et al., 2012), painful diabetic polyneuropathy (Kim et al., 2013), chronic neuropathic pain following a burn injury (Portilla et al., 2013), trigeminal neuralgia (Hagenacker et al., 2014), lower back pain (Schabrun et al., 2014), and migraines (Antal et al., 2011; de Brito Aranha et al., 2022; Viganò et al., 2013). The modulatory effects of tDCS are reversible and painless, and its portability represents the possibility of home-based pain treatment (Nitsche et al., 2008; Pacheco-Barrios et al., 2020). Anodal tDCS is typically used to increase excitability and, depending on the parameters, can target different cerebral networks, including those involved in cognition and pain processing (Pacheco-Barrios et al., 2020; Seminowicz and Moayedi, 2017; Zaninotto et al., 2019). According to a meta-analysis, there is scientific evidence that anodal tDCS decreases pain levels in patients and increases sensory/pain thresholds in healthy individuals (Vaseghi et al., 2014). For example, a study investigating patients with chronic pelvic pain showed that a single session of anodal tDCS applied to two brain regions, the DLPFC and primary motor cortex, reduced pain and improved quality of life and disability measures (Divandari et al., 2019). tDCS has also been shown to improve TBI-related symptoms (Kang et al., 2012; O'Neil-Pirozzi et al., 2017; Shirvani et al., 2021). Anodal tDCS applied to the PFC is effective in reducing mental fatigue, increasing the quality of life of mild TBI patients, and improving the working memory of severe TBI patients (Kang et al., 2012; O'Neil-Pirozzi et al., 2017; Shirvani et al., 2021). Furthermore, a single session of anodal tDCS applied to the DLPFC improved attention compared to sham stimulation, suggesting its potential role in improving attention in TBI patients (Kang et al., 2012).

## 4. Conclusion

PTH is a condition induced by injury of the head or neck and can become intractable. Although several reports have put forth possible treatments, PTH often remains resistant to current therapies. PTH is mediated by complicated peripheral and central mechanisms along trigeminal pain pathways with comprehensive anatomical and functional alterations in the brain. Although these mechanisms are not clearly defined, neuromodulation through electrical stimulation can potentially provide substantial alleviation of PTH. Importantly, understanding the brain plasticity involved in PTH and its neuromodulatory effects is important to better define the critical brain activities involved in the development and resolution of chronic pain. Not all patients develop chronic PTH following trauma, nor do all patients respond to pharmacological treatments and neuromodulation. Therefore, determining the detailed phenotypes of large patient cohorts with a variety of PTH subtypes before and after treatment should help improve our understanding of the intricate neurobiology of PTH. Brain plasticity after neuromodulation can also be tested in animal models to decipher critical biological processes. Such a reverse translational approach for the mechanistic study of the underlying progress, resolution, and treatment of PTH should lead to the development of novel strategies for the management of patients with PTH.

## CRediT authorship contribution statement

**Fernando da Silva Fiorin:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing, Investigation, Project administration, Supervision. **Caroline Cunha do Espírito Santo:** Conceptualization, Investigation, Methodology, Visualization, Writing – original draft. **Joyce T. Da Silva:** Conceptualization, Investigation, Methodology, Visualization, Writing – original draft. **Man-Kyo Chung:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

There are no conflicts of interest to report for any of the authors.

## Data availability

No data was used for the research described in the article.

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## References


Akerman, S., Holland, P.R., Goadsby, P.J., 2011. Diencephalic and brainstem mechanisms in migraine. Nat. Rev. Neurosci. 12, 570–584. https://doi.org/10.1038/nrn3057.

Alhilali, L.M., Delic, J., Fakhran, S., 2017. Differences in callosal and forniceal diffusion between patients with and without postconcussive migraine. AJNR. Am. J. Neuroradiol. 38, 691–695. https://doi.org/10.3174/ajnr.A5073.

Anderson, K., Tinawi, S., Lamoureux, J., Feyz, M., de Guise, E., 2015. Detecting migraine in patients with mild traumatic brain injury using three different headache measures. Behav. Neurol. 2015, 693925 https://doi.org/10.1155/2015/693925.

Antal, A., Kriener, N., Lang, N., Boros, K., Paulus, W., 2011. Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine. Cephalalgia 31, 820–828. https://doi.org/10.1177/0333102411399349.

Antal, A., Paulus, W., 2011. A case of refractory orofacial pain treated by transcranial direct current stimulation applied over hand motor area in combination with NMDA agonist drug intake. Brain Stimul. 4, 117–121. https://doi.org/10.1016/j.brs.2010.09.003.

Ashina, H., Al-Khazali, H.M., Iljazi, A., Ashina, S., Jørgensen, N.R., Amin, F.M., Ashina, M., Schytz, H.W., 2020a. Low plasma levels of calcitonin gene-related peptide in persistent post-traumatic headache attributed to mild traumatic brain injury. Cephalalgia 40, 1276–1282. https://doi.org/10.1177/0333102420941115.

Ashina, H., Eigenbrodt, A.K., Seifert, T., Sinclair, A.J., Scher, A.I., Schytz, H.W., Lee, M. J., De Icco, R., Finkel, A.G., Ashina, M., 2021. Post-traumatic headache attributed to traumatic brain injury: classification, clinical characteristics, and treatment. Lancet Neurol. 20, 460–469. https://doi.org/10.1016/S1474-4422(21)00094-6.

Ashina, H., Iljazi, A., Al-Khazali, H.M., Christensen, C.E., Amin, F.M., Ashina, M., Schytz, H.W., 2020b. Hypersensitivity to calcitonin gene-related peptide in post-traumatic headache. Ann. Neurol. 88, 1220–1228. https://doi.org/10.1002/ana.25915.

Ashina, H., Iljazi, A., Al-Khazali, H.M., Eigenbrodt, A.K., Larsen, E.L., Andersen, A.M., Hansen, K.J., Bräuner, K.B., Mørch-Jessen, T., Chaudhry, B., Antic, S., Christensen, C. E., Ashina, M., Amin, F.M., Schytz, H.W., 2020c. Efficacy, tolerability, and safety of erenumab for the preventive treatment of persistent post-traumatic headache attributed to mild traumatic brain injury: an open-label study. J. Headache Pain 21, 62. https://doi.org/10.1186/s10194-020-01136-z.

Ashina, H., Porreca, F., Anderson, T., Amin, F.M., Ashina, M., Schytz, H.W., Dodick, D. W., 2019. Post-traumatic headache: epidemiology and pathophysiological insights. Nat. Rev. Neurol. 15, 607–617. https://doi.org/10.1038/s41582-019-0243-8.

Baandrup, L., Jensen, R., 2005. Chronic post-traumatic headache–a clinical analysis in relation to the International Headache Classification. Cephalalgia 25, 132–138. https://doi.org/10.1111/j.1468-2982.2004.00818.x, 2nd Edition.

Baldwin, G.T., Breiding, M.J., Dawn Comstock, R., 2018. Epidemiology of sports concussion in the United States. Handb. Clin. Neurol. 158, 63–74. https://doi.org/10.1016/B978-0-444-63954-7.00007-0.

Baliki, M.N., Mansour, A.R., Baria, A.T., Apkarian, A.V., 2014. Functional reorganization of the default mode network across chronic pain conditions. PLoS One 9, e106133. https://doi.org/10.1371/journal.pone.0106133.

Barros, J., Damásio, J., Tuna, A., Alves, I., Silveira, I., Pereira-Monteiro, J., Sequeiros, J., Alonso, I., Sousa, A., Coutinho, P., 2013. Cerebellar ataxia, hemiplegic migraine, and related phenotypes due to a CACNA1A missense mutation: 12-year follow-up of a large Portuguese family. JAMA Neurol. 70, 235–240. https://doi.org/10.1001/jamaneurol.2013.591.

Blumberger, D.M., Tran, L.C., Fitzgerald, P.B., Hoy, K.E., Daskalakis, Z.J., 2012. A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. Front. psychiatry 3, 74. https://doi.org/10.3389/fpsyt.2012.00074.

Bonnelle, V., Leech, R., Kinnunen, K.M., Ham, T.E., Beckmann, C.F., De Boissezon, X., Greenwood, R.J., Sharp, D.J., 2011. Default mode network connectivity predicts sustained attention deficits after traumatic brain injury. J. Neurosci. Off. J. Soc. Neurosci. 31, 13442–13451. https://doi.org/10.1523/JNEUROSCI.1163-11.2011.

Brandebura, A.N., Paumier, A., Onur, T.S., Allen, N.J., 2023. Astrocyte contribution to dysfunction, risk and progression in neurodegenerative disorders. Nat. Rev. Neurosci. 24, 23–39. https://doi.org/10.1038/s41583-022-00641-1.

Bree, D., Levy, D., 2018. Development of CGRP-dependent pain and headache related behaviours in a rat model of concussion: implications for mechanisms of post-traumatic headache. Cephalalgia 38, 246–258. https://doi.org/10.1177/0333102416681571.

Burda, J.E., Bernstein, A.M., Sofroniew, M.V., 2016. Astrocyte roles in traumatic brain injury. Exp. Neurol. 275 (Pt 3), 305–315. https://doi.org/10.1016/j.expneurol.2015.03.020.

Burda, J.E., Sofroniew, M.V., 2014. Reactive gliosis and the multicellular response to CNS damage and disease. Neuron 81, 229–248. https://doi.org/10.1016/j.neuron.2013.12.034.

Burrowes, S.A.B., Rhodes, C.S., Meeker, T.J., Greenspan, J.D., Gullapalli, R.P., Seminowicz, D.A., 2020. Decreased grey matter volume in mTBI patients with post-traumatic headache compared to headache-free mTBI patients and healthy controls: a longitudinal MRI study. Brain Imaging Behav 14, 1651–1659. https://doi.org/10.1007/s11682-019-00095-7.

Cacioppo, J.T., Tassinary, L.G., Berntson, G., 2007. Handbook of Psychophysiology. Cambridge university press.

Capi, M., Pomes, L.M., Andolina, G., Curto, M., Martelletti, P., Lionetto, L., 2020. Persistent post-traumatic headache and migraine: pre-clinical comparisons. Int. J. Environ. Res. Public Health 17. https://doi.org/10.3390/ijerph17072585.

Castro, A., Raver, C., Li, Y., Uddin, O., Rubin, D., Ji, Y., Masri, R., Keller, A., 2017. Cortical regulation of nociception of the trigeminal nucleus caudalis. J. Neurosci. Off. J. Soc. Neurosci. 37, 11431–11440. https://doi.org/10.1523/JNEUROSCI.3897-16.2017.

Chong, C.D., Berisha, V., Chiang, C.-C., Ross, K., Schwedt, T.J., 2018. Less cortical thickness in patients with persistent post-traumatic headache compared with healthy controls: an MRI study. Headache 58, 53–61. https://doi.org/10.1111/head.13223.

Chung, M.K., Wang, S., Yang, J., Alshanqiti, I., Wei, F., Ro, J.Y., 2020. Neural pathways of craniofacial muscle pain: implications for novel treatments. J. Dent. Res. 99, 1004–1012. https://doi.org/10.1177/0022034520919384.

Clausen, F., Hånell, A., Israelsson, C., Hedin, J., Ebendal, T., Mir, A.K., Gram, H., Marklund, N., 2011. Neutralization of interleukin-1β reduces cerebral edema and tissue loss and improves late cognitive outcome following traumatic brain injury in mice. Eur. J. Neurosci. 34, 110–123. https://doi.org/10.1111/j.1460-9568.2011.07723.x.

Clough, R.W., Neese, S.L., Sherill, L.K., Tan, A.A., Duke, A., Roosevelt, R.W., Browning, R.A., Smith, D.C., 2007. Cortical edema in moderate fluid percussion brain injury is attenuated by vagus nerve stimulation. Neuroscience 147, 286–293. https://doi.org/10.1016/j.neuroscience.2007.04.043.

Coppola, G., Magis, D., Casillo, F., Sebastianelli, G., Abagnale, C., Cioffi, E., Di Lenola, D., Di Lorenzo, C., Serrao, M., 2022. Neuromodulation for chronic daily headache. Curr. Pain Headache Rep. 26, 267–278. https://doi.org/10.1007/s11916-022-01025-x.

Corrigan, F., Mander, K.A., Leonard, A.V., Vink, R., 2016. Neurogenic inflammation after traumatic brain injury and its potentiation of classical inflammation. J. Neuroinflammation 13, 264. https://doi.org/10.1186/s12974-016-0738-9.

Cushman, D.M., Borowski, L., Hansen, C., Hendrick, J., Bushman, T., Teramoto, M., 2019. Gabapentin and tricyclics in the treatment of post-concussive headache, a retrospective cohort study. Headache 59, 371–382. https://doi.org/10.1111/head.13451.

da Silva Fiorin, F., de Araújo E Silva, M., Rodrigues, A.C., 2021. Electrical stimulation in animal models of epilepsy: a review on cellular and electrophysiological aspects. Life Sci. 285, 119972 https://doi.org/10.1016/j.lfs.2021.119972.

da Silva Fiorin, F., do Espírito Santo, C.C., do Nascimento, R.S., Cassol, G., Plácido, E., Santos, A.R.S., Marques, J.L.B., Brocardo, P.S., Fighera, M.R., Royes, L.F.F., 2020. Capsaicin-sensitive fibers mediate periorbital allodynia and activation of inflammatory cells after traumatic brain injury in rats: involvement of TRPV1 channels in post-traumatic headache. Neuropharmacology 176, 108215. https://doi.org/10.1016/j.neuropharm.2020.108215.

da Silva Fiorin, F., do Espírito Santo, C.C., Santos, A.R.S., Fighera, M.R., Royes, L.F.F., 2018. Implication of surgical procedure in the induction of headache and generalized painful sensation in a fluid percussion injury model in rats. J. Neurosci. Methods 307, 23–30. https://doi.org/10.1016/j.jneumeth.2018.06.004.

Daiutolo, B.V., Tyburski, A., Clark, S.W., Elliott, M.B., 2016. Trigeminal pain molecules, allodynia, and photosensitivity are pharmacologically and genetically modulated in a model of traumatic brain injury. J. Neurotrauma 33, 748–760. https://doi.org/10.1089/neu.2015.4087.

Dalgard, C.L., Cole, J.T., Kean, W.S., Lucky, J.J., Sukumar, G., McMullen, D.C., Pollard, H.B., Watson, W.D., 2012. The cytokine temporal profile in rat cortex after controlled cortical impact. Front. Mol. Neurosci. 5, 6. https://doi.org/10.3389/fnmol.2012.00006.

de Brito Aranha, R.E.L., Torro-Alves, N., Andrade, S.M., de Oliveira, E.A., da Silva, B.N. V., da Fonseca, É.K.G., Lima Dos Santos, G.E., Guedes, N.M., Dos Santos Falcão Silva, T., Fernández-Calvo, B., 2022. Effects on pain and cognition of transcranial direct current stimulation over the dorsolateral prefrontal cortex in women with chronic migraine. Neurophysiol. Clin. 52, 333–338. https://doi.org/10.1016/j.neucli.2022.07.005.

Defrin, R., 2014. Chronic post-traumatic headache: clinical findings and possible mechanisms. J. Man. Manip. Ther. 22, 36–44. https://doi.org/10.1179/2042618613Y.0000000053.

Del Rocio Hernandez-Castanon, V., Le Cam, S., Ranta, R., 2021. Sparse EEG source localization in frequency domain. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Int. Conf. 2021, 6428–6432. https://doi.org/10.1109/EMBC46164.2021.9630279.

Demirtas-Tatlidede, A., Vahabzadeh-Hagh, A.M., Pascual-Leone, A., 2013. Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology 64, 566–578. https://doi.org/10.1016/j.neuropharm.2012.06.020.

Di Battista, A.P., Rhind, S.G., Hutchison, M.G., Hassan, S., Shiu, M.Y., Inaba, K., Topolovec-Vranic, J., Neto, A.C., Rizoli, S.B., Baker, A.J., 2016. Inflammatory cytokine and chemokine profiles are associated with patient outcome and the hyperadrenergic state following acute brain injury. J. Neuroinflammation 13, 40. https://doi.org/10.1186/s12974-016-0500-3.

Divandari, N., Manshadi, F.D., Shokouhi, N., Vakili, M., Jaberzadeh, S., 2019. Effect of one session of tDCS on the severity of pain in women with chronic pelvic pain. J. Bodyw. Mov. Ther. 23, 678–682. https://doi.org/10.1016/j.jbmt.2017.12.014.

DosSantos, M.F., Love, T.M., Martikainen, I.K., Nascimento, T.D., Fregni, F., Cummiford, C., Deboer, M.D., Zubieta, J.-K., Dasilva, A.F.M., 2012. Immediate effects of tDCS on the μ-opioid system of a chronic pain patient. Front. psychiatry 3, 93. https://doi.org/10.3389/fpsyt.2012.00093.

Dumkrieger, G., Chong, C.D., Ross, K., Berisha, V., Schwedt, T.J., 2019. Static and dynamic functional connectivity differences between migraine and persistent post-traumatic headache: a resting-state magnetic resonance imaging study. Cephalalgia 39, 1366–1381. https://doi.org/10.1177/0333102419847728.

Dux, M., Sántha, P., Jancsó, G., 2003. Capsaicin-sensitive neurogenic sensory vasodilatation in the dura mater of the rat. J. Physiol. 552, 859–867. https://doi.org/10.1113/jphysiol.2003.050633.

Elliott, M.B., Oshinsky, M.L., Amenta, P.S., Awe, O.O., Jallo, J.I., 2012. Nociceptive neuropeptide increases and periorbital allodynia in a model of traumatic brain injury. Headache 52, 966–984. https://doi.org/10.1111/j.1526-4610.2012.02160.x.
Feigin, V.L., Theadom, A., Barker-Collo, S., Starkey, N.J., McPherson, K., Kahan, M., Dowell, A., Brown, P., Parag, V., Kydd, R., Jones, K., Jones, A., Ameratunga, S., 2013. Incidence of traumatic brain injury in New Zealand: a population-based study. Lancet Neurol. 12, 53–64. https://doi.org/10.1016/S1474-4422(12)70262-4.
Fenton, B.W., Palmieri, P.A., Boggio, P., Fanning, J., Fregni, F., 2009. A preliminary study of transcranial direct current stimulation for the treatment of refractory chronic pelvic pain. Brain Stimul. 2, 103–107. https://doi.org/10.1016/j.brs.2008.09.009.
Font-Nieves, M., Sans-Fons, M.G., Gorina, R., Bonfill-Teixidor, E., Salas-Pérdomo, A., Márquez-Kisinousky, L., Santalucia, T., Planas, A.M., 2012. Induction of COX-2 enzyme and down-regulation of COX-1 expression by lipopolysaccharide (LPS) control prostaglandin E2 production in astrocytes. J. Biol. Chem. 287, 6454–6468. https://doi.org/10.1074/jbc.M111.327874.
Fontaine, D., Almairac, F., Santucci, S., Fernandez, C., Dallel, R., Pallud, J., Lanteri-Minet, M., 2018. Dural and pial pain-sensitive structures in humans: new inputs from awake craniotomies. Brain 141, 1040–1048. https://doi.org/10.1093/brain/awy005.
Fregni, F., Boggio, P.S., Lima, M.C., Ferreira, M.J.L., Wagner, T., Rigonatti, S.P., Castro, A.W., Souza, D.R., Riberto, M., Freedman, S.D., Nitsche, M.A., Pascual-Leone, A., 2006. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain 122, 197–209. https://doi.org/10.1016/j.pain.2006.02.023.
Frey, L.C., 2003. Epidemiology of posttraumatic epilepsy: a critical review. Epilepsia 44, 11–17. https://doi.org/10.1046/j.1528-1157.44.s10.4.x.
Fu, J., Shi, Q., Song, X., Liu, Z., Wang, Yawen, Wang, Yuxin, Song, E., Song, Y., 2016. From the cover: tetrachlorobenzoquinone exerts neurological proinflammatory activity by promoting HMGB1 release, which induces TLR4 clustering within the lipid raft. Toxicol. Sci. 153, 303–315. https://doi.org/10.1093/toxsci/kfw124.
Gaudet, I., Hüsser, A., Vannasing, P., Gallagher, A., 2020. Functional brain connectivity of language functions in children revealed by EEG and MEG: a systematic review. Front. Hum. Neurosci. https://doi.org/10.3389/fnhum.2020.00062.
Ghodadra, A., Alhilali, L., Fakhran, S., 2016. Principal component analysis of diffusion tensor Images to determine white matter injury patterns underlying postconcussive headache. AJNR. Am. J. Neuroradiol. 37, 274–278. https://doi.org/10.3174/ajnr.A4505.
Global, 2019. regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18, 56–87. https://doi.org/10.1016/S1474-4422(18)30415-0.
Goadsby, P.J., Reuter, U., Hallström, Y., Broessner, G., Bonner, J.H., Zhang, F., Sapra, S., Picard, H., Mikol, D.D., Lenz, R.A., 2017. A controlled trial of erenumab for episodic migraine. N. Engl. J. Med. 377, 2123–2132. https://doi.org/10.1056/NEJMoa1705848.
Gorina, R., Font-Nieves, M., Márquez-Kisinousky, L., Santalucia, T., Planas, A.M., 2011. Astrocyte TLR4 activation induces a proinflammatory environment through the interplay between MyD88-dependent NFκB signaling, MAPK, and Jak1/Stat1 pathways. Glia 59, 242–255. https://doi.org/10.1002/glia.21094.
Hagenacker, T., Bude, V., Naegel, S., Holle, D., Katsarava, Z., Diener, H.-C., Obermann, M., 2014. Patient-conducted anodal transcranial direct current stimulation of the motor cortex alleviates pain in trigeminal neuralgia. J. Headache Pain 15, 78. https://doi.org/10.1186/1129-2377-15-78.
Hanisch, U.-K., Kettenmann, H., 2007. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat. Neurosci. 10, 1387–1394. https://doi.org/10.1038/nn1997.
Hanko, J., Hardebo, J.E., Kåhrström, J., Owman, C., Sundler, F., 1985. Calcitonin gene-related peptide is present in mammalian cerebrovascular nerve fibres and dilates pial and peripheral arteries. Neurosci. Lett. 57, 91–95. https://doi.org/10.1016/0304-3940(85)90045-x.
Hansen, J.M., Hauge, A.W., Olesen, J., Ashina, M., 2010. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia 30, 1179–1186. https://doi.org/10.1177/0333102410368444.
Headache Classification Committee of the International Headache Society (IHS), 2018. The International Classification of Headache Disorders, third ed., pp. 1–211. https://doi.org/10.1177/0333102417738202 Cephalalgia 38.
Hemington, K.S., Rogachov, A., Cheng, J.C., Bosma, R.L., Kim, J.A., Osborne, N.R., Inman, R.D., Davis, K.D., 2018. Patients with chronic pain exhibit a complex relationship triad between pain, resilience, and within- and cross-network functional connectivity of the default mode network. Pain 159, 1621–1630. https://doi.org/10.1097/j.pain.0000000000001252.
Hernandez-Pavon, J.C., Harvey, R.L., 2019. Noninvasive transcranial magnetic brain stimulation in stroke. Phys. Med. Rehabil. Clin. N. Am. 30, 319–335. https://doi.org/10.1016/j.pmr.2018.12.010.
Heyer, G.L., Idris, S.A., 2014. Does analgesic overuse contribute to chronic post-traumatic headaches in adolescent concussion patients? Pediatr. Neurol. 50, 464–468. https://doi.org/10.1016/j.pediatrneurol.2014.01.040.
Hoffman, J.M., Lucas, S., Dikmen, S., Braden, C.A., Brown, A.W., Brunner, R., Diaz-Arrastia, R., Walker, W.C., Watanabe, T.K., Bell, K.R., 2011. Natural history of headache after traumatic brain injury. J. Neurotrauma 28, 1719–1725. https://doi.org/10.1089/neu.2011.1914.
Hryciw, G., Wong, J., Heinricher, M.M., 2023. Brainstem pain-modulating neurons are sensitized to visual light in persistent inflammation. Neurobiol. pain (Cambridge, Mass 13, 100111. https://doi.org/10.1016/j.ynpai.2022.100111.
Inohara, N., Nuñez, G., 2003. NODs: intracellular proteins involved in inflammation and apoptosis. Nat. Rev. Immunol. 3, 371–382. https://doi.org/10.1038/nri1086.
Iwata, K., Katagiri, A., Shinoda, M., 2017. Neuron-glia interaction is a key mechanism underlying persistent orofacial pain. J. Oral Sci. 59, 173–175. https://doi.org/10.2334/josnusd.16-0858.
Jang, S.H., Park, S.M., Kwon, H.G., 2016. Relation between injury of the periaqueductal gray and central pain in patients with mild traumatic brain injury: observational study. Medicine (Baltim.) 95, e4017. https://doi.org/10.1097/MD.0000000000004017.
Jayakumar, A.R., Tong, X.Y., Ruiz-Cordero, R., Bregy, A., Bethea, J.R., Bramlett, H.M., Norenberg, M.D., 2014. Activation of NF-κB mediates astrocyte swelling and brain edema in traumatic brain injury. J. Neurotrauma 31, 1249–1257. https://doi.org/10.1089/neu.2013.3169.
Kang, E.-K., Kim, D.-Y., Paik, N.-J., 2012. Transcranial direct current stimulation of the left prefrontal cortex improves attention in patients with traumatic brain injury: a pilot study. J. Rehabil. Med. 44, 346–350. https://doi.org/10.2340/16501977-0947.
Ke, J., Yu, Y., Zhang, X., Su, Y., Wang, X., Hu, S., Dai, H., Hu, C., Zhao, H., Dai, L., 2020. Functional alterations in the posterior insula and cerebellum in migraine without aura: a resting-state MRI study. Front. Behav. Neurosci. 14, 567588 https://doi.org/10.3389/fnbeh.2020.567588.
Khakpai, F., Nasehi, M., Haeri-Rohani, A., Eidi, A., Zarrindast, M.R., 2013. Septo-hippocampo-septal loop and memory formation. Basic Clin. Neurosci. 4, 5–23.
Kida, T., Tanaka, E., Kakigi, R., 2015. Multi-dimensional dynamics of human electromagnetic brain activity. Front. Hum. Neurosci. 9, 713. https://doi.org/10.3389/fnhum.2015.00713.
Kim, Y.J., Ku, J., Kim, H.J., Im, D.J., Lee, H.S., Han, K.A., Kang, Y.J., 2013. Randomized, sham controlled trial of transcranial direct current stimulation for painful diabetic polyneuropathy. Ann. Rehabil. Med. 37, 766–776. https://doi.org/10.5535/arm.2013.37.6.766.
Kosaras, B., Jakubowski, M., Kainz, V., Burstein, R., 2009. Sensory innervation of the calvarial bones of the mouse. J. Comp. Neurol. 515, 331–348. https://doi.org/10.1002/cne.22049.
Kothari, S.F., Eggertsen, P.P., Frederiksen, O.V., Thastum, M.M., Svendsen, S.W., Tuborgh, A., Næss-Schmidt, E.T., Rask, C.U., Schröder, A., Kasch, H., Nielsen, J.F., 2022. Characterization of persistent post-traumatic headache and management strategies in adolescents and young adults following mild traumatic brain injury. Sci. Rep. 12, 2209. https://doi.org/10.1038/s41598-022-05187-x.
Kumar, A., Loane, D.J., 2012. Neuroinflammation after traumatic brain injury: opportunities for therapeutic intervention. Brain Behav. Immun. 26, 1191–1201. https://doi.org/10.1016/j.bbi.2012.06.008.
Kumar, V., 2019. Toll-like receptors in the pathogenesis of neuroinflammation. J. Neuroimmunol. 332, 16–30. https://doi.org/10.1016/j.jneuroim.2019.03.012.
Laker, S.R., 2011. Epidemiology of concussion and mild traumatic brain injury. Pharm. Manag. PM R 3, S354–S358. https://doi.org/10.1016/j.pmrj.2011.07.017.
Lang, E., Novak, A., Reeh, P.W., Handwerker, H.O., 1990. Chemosensitivity of fine afferents from rat skin in vitro. J. Neurophysiol. 63, 887–901. https://doi.org/10.1152/jn.1990.63.4.887.
Larsen, E.L., Ashina, H., Iljazi, A., Al-Khazali, H.M., Seem, K., Ashina, M., Ashina, S., Schytz, H.W., 2019. Acute and preventive pharmacological treatment of post-traumatic headache: a systematic review. J. Headache Pain 20, 98. https://doi.org/10.1186/s10194-019-1051-7.
Ledoux, A.-A., Tang, K., Freedman, S.B., Gravel, J., Boutis, K., Yeates, K.O., Mannix, R.C., Richer, L.R., Bell, M.J., Zemek, R.L., 2022. Early analgesic administration and headache presence 7 days post-concussion in children. CJEM 24, 876–884. https://doi.org/10.1007/s43678-022-00367-0.
Lee, H.-G., Wheeler, M.A., Quintana, F.J., 2022. Function and therapeutic value of astrocytes in neurological diseases. Nat. Rev. Drug Discov. 21, 339–358. https://doi.org/10.1038/s41573-022-00390-x.
Legrain, V., Iannetti, G.D., Plaghki, L., Mouraux, A., 2011. The pain matrix reloaded: a salience detection system for the body. Prog. Neurobiol. 93, 111–124. https://doi.org/10.1016/j.pneurobio.2010.10.005.
Lemme, J., Holmes, S., Sibai, D., Mari, J., Simons, L.E., Burstein, R., Zurakowski, D., Lebel, A., O'Brien, M., Upadhyay, J., Borsook, D., 2021. Altered brain network connectivity underlies persistent post-traumatic headache following mild traumatic brain injury in youth. J. Neurotrauma 38, 1632–1641. https://doi.org/10.1089/neu.2020.7189.
Leung, A., 2020. Addressing chronic persistent headaches after MTBI as a neuropathic pain state. J. Headache Pain 21, 77. https://doi.org/10.1186/s10194-020-01133-2.
Leung, A., Fallah, A., Shukla, S., Lin, L., Tsia, A., Song, D., Polston, G., Lee, R., 2016a. rTMS in alleviating mild TBI related headaches–A case series. Pain Physician 19, E347–E354.
Leung, A., Shukla, S., Yang, E., Canlas, B., Kadokana, M., Heald, J., Davani, A., Song, D., Lin, L., Polston, G., Tsai, A., Lee, R., 2016b. Diminished supraspinal pain modulation in patients with mild traumatic brain injury. Mol. Pain 12. https://doi.org/10.1177/1744806916662661.
Li, C., Zhu, Q., He, Q., Wang, J., Wang, F., Zhang, H., 2017. Plasma levels of cyclooxygenase-2 (COX-2) and visfatin during different stages and different subtypes of migraine headaches. Med. Sci. Monit. Int. Med. J. Exp. Clin. Res. 23, 24–28. https://doi.org/10.12659/msm.899269.
Li, F., Lu, L., Shang, S., Chen, H., Wang, P., Muthaiah, V.P., Yin, X., Chen, Y.-C., 2021. Altered static and dynamic functional network connectivity in post-traumatic headache. J. Headache Pain 22, 137. https://doi.org/10.1186/s10194-021-01348-x.
Li, J., Vause, C.V., Durham, P.L., 2008. Calcitonin gene-related peptide stimulation of nitric oxide synthesis and release from trigeminal ganglion glial cells. Brain Res. 1196, 22–32. https://doi.org/10.1016/j.brainres.2007.12.028.
Liang, D.-Y., Shi, X., Liu, P., Sun, Y., Sahbaie, P., Li, W.-W., Yeomans, D.C., Clark, J.D., 2017. The chemokine receptor CXCR2 supports nociceptive sensitization after

traumatic brain injury. Mol. Pain 13, 1744806917730212. https://doi.org/10.1177/1744806917730212.
Lindenberg, R., Zhu, L.L., Schlaug, G., 2012. Combined central and peripheral stimulation to facilitate motor recovery after stroke: the effect of number of sessions on outcome. Neurorehabilitation Neural Repair 26, 479–483. https://doi.org/10.1177/1545968311427568.
Linder, S.L., 2007. Post-traumatic headache. Curr. Pain Headache Rep. 11, 396–400. https://doi.org/10.1007/s11916-007-0223-3.
Liu, N., Han, J., Li, Y., Jiang, Y., Shi, S.X., Lok, J., Whalen, M., Dumont, A.S., Wang, X., 2021. Recombinant annexin A2 inhibits peripheral leukocyte activation and brain infiltration after traumatic brain injury. J. Neuroinflammation 18, 173. https://doi.org/10.1186/s12974-021-02219-7.
Liu, Y.-W., Li, S., Dai, S.-S., 2018. Neutrophils in traumatic brain injury (TBI): friend or foe? J. Neuroinflammation 15, 146. https://doi.org/10.1186/s12974-018-1173-x.
Lötsch, J., Walter, C., Felden, L., Nöth, U., Deichmann, R., Oertel, B.G., 2012. The human operculo-insular cortex is pain-preferentially but not pain-exclusively activated by trigeminal and olfactory stimuli. PLoS One 7, e34798. https://doi.org/10.1371/journal.pone.0034798.
Lu, L., Li, F., Wang, P., Chen, H., Chen, Y.-C., Yin, X., 2020. Altered hypothalamic functional connectivity in post-traumatic headache after mild traumatic brain injury. J. Headache Pain 21, 93. https://doi.org/10.1186/s10194-020-01164-9.
Lucas, S., 2011. Headache management in concussion and mild traumatic brain injury. Pharm. Manag. PM R 3, S406–S412. https://doi.org/10.1016/j.pmrj.2011.07.016.
Lucas, S., Hoffman, J.M., Bell, K.R., Dikmen, S., 2014. A prospective study of prevalence and characterization of headache following mild traumatic brain injury. Cephalalgia 34, 93–102. https://doi.org/10.1177/0333102413499645.
Maas, A.I.R., Menon, D.K., Adelson, P.D., Andelic, N., Bell, M.J., Belli, A., Bragge, P., Brazinova, A., Büki, A., Chesnut, R.M., Citerio, G., Coburn, M., Cooper, D.J., Crowder, A.T., Czeiter, E., Czosnyka, M., Diaz-Arrastia, R., Dreier, J.P., Duhaime, A.-C., Ercole, A., van Essen, T.A., Feigin, V.L., Gao, G., Giacino, J., Gonzalez-Lara, L.E., Gruen, R.L., Gupta, D., Hartings, J.A., Hill, S., Jiang, J.-Y., Ketharanathan, N., Kompanje, E.J.O., Lanyon, L., Laureys, S., Lecky, F., Levin, H., Lingsma, H.F., Maegele, M., Majdan, M., Manley, G., Marsteller, J., Mascia, L., McFadyen, C., Mondello, S., Newcombe, V., Palotie, A., Parizel, P.M., Peul, W., Piercy, J., Polinder, S., Puybasset, L., Rasmussen, T.E., Rossaint, R., Smielewski, P., Söderberg, J., Stanworth, S.J., Stein, M.B., von Steinbüchel, N., Stewart, W., Steyerberg, E.W., Stocchetti, N., Synnot, A., Te Ao, B., Tenovuo, O., Theadom, A., Tibboel, D., Videtta, W., Wang, K.K.W., Williams, W.H., Wilson, L., Yaffe, K., 2017. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol. 16, 987–1048. https://doi.org/10.1016/S1474-4422(17)30371-X.
Macolino, C.M., Daiutolo, B.V., Albertson, B.K., Elliott, M.B., 2014. Mechanical allodynia induced by traumatic brain injury is independent of restraint stress. J. Neurosci. Methods 226, 139–146. https://doi.org/10.1016/j.jneumeth.2014.01.008.
Markowitz, S., Saito, K., Moskowitz, M.A., 1987. Neurogenically mediated leakage of plasma protein occurs from blood vessels in dura mater but not brain. J. Neurosci. Off. J. Soc. Neurosci. 7, 4129–4136. https://doi.org/10.1523/JNEUROSCI.07-12-04129.1987.
Martin, D.M., Alonzo, A., Mitchell, P.B., Sachdev, P., Gálvez, V., Loo, C.K., 2011. Fronto-extracephalic transcranial direct current stimulation as a treatment for major depression: an open-label pilot study. J. Affect. Disord. 134, 459–463. https://doi.org/10.1016/j.jad.2011.05.018.
Martin, H.A., Basbaum, A.I., Kwiat, G.C., Goetzl, E.J., Levine, J.D., 1987. Leukotriene and prostaglandin sensitization of cutaneous high-threshold C- and A-delta mechanonociceptors in the hairy skin of rat hindlimbs. Neuroscience 22, 651–659. https://doi.org/10.1016/0306-4522(87)90360-5.
Mavroudis, I., Ciobica, A., Luca, A.C., Balmus, I.-M., 2023. Post-traumatic headache: a review of prevalence, clinical features, risk factors, and treatment strategies. J. Clin. Med. 12 https://doi.org/10.3390/jcm12134233.
McCrory, P., Meeuwisse, W., Johnston, K., Dvorak, J., Aubry, M., Molloy, M., Cantu, R., 2009. Consensus statement on concussion in sport 3rd international conference on concussion in sport held in Zurich, november 2008. Clin. J. Sport Med. Off. J. Can. Acad. Sport Med. 19, 185–200. https://doi.org/10.1097/JSM.0b013e3181a501db.
Meidahl, A.C., Eisenried, A., Klukinov, M., Cao, L., Tzabazis, A.Z., Yeomans, D.C., 2018. Intranasal oxytocin attenuates reactive and ongoing, chronic pain in a model of mild traumatic brain injury. Headache 58, 545–558. https://doi.org/10.1111/head.13248.
Melo-Carrillo, A., Strassman, A.M., Nir, R.-R., Schain, A.J., Noseda, R., Stratton, J., Burstein, R., 2017. Fremanezumab-A humanized monoclonal anti-CGRP antibody-inhibits thinly myelinated (Aδ) but not unmyelinated (C) meningeal nociceptors. J. Neurosci. Off. J. Soc. Neurosci. 37, 10587–10596. https://doi.org/10.1523/JNEUROSCI.2211-17.2017.
Messina, R., Rocca, M.A., Valsasina, P., Misci, P., Filippi, M., 2022. Clinical correlates of hypothalamic functional changes in migraine patients. Cephalalgia 42, 279–290. https://doi.org/10.1177/03331024211046618.
Milosevic, M., Nakanishi, T., Sasaki, A., Yamaguchi, A., Nomura, T., Popovic, M.R., Nakazawa, K., 2021. Cortical Re-organization after traumatic brain injury elicited using functional electrical stimulation therapy: a case report. Front. Neurosci. 15, 693861 https://doi.org/10.3389/fnins.2021.693861.
Minen, M.T., Boubour, A., Walia, H., Barr, W., 2016. Post-concussive syndrome: a focus on post-traumatic headache and related cognitive, psychiatric, and sleep issues. Curr. Neurol. Neurosci. Rep. 16, 100. https://doi.org/10.1007/s11910-016-0697-7.
Mira, R.G., Lira, M., Cerpa, W., 2021. Traumatic brain injury: mechanisms of glial response. Front. Physiol. 12, 740939 https://doi.org/10.3389/fphys.2021.740939.
Mota, B.C., Pereira, L., Souza, M.A., Silva, L.F.A., Magni, D.V., Ferreira, A.P.O., Oliveira, M.S., Furian, A.F., Mazzardo-Martins, L., Silva, M.D., da Santos, A.R.S., Ferreira, J., Fighera, M.R., Royes, L.F.F., 2012. Exercise pre-conditioning reduces brain inflammation and protects against toxicity induced by traumatic brain injury: behavioral and neurochemical approach. Neurotox. Res. 21, 175–184. https://doi.org/10.1007/s12640-011-9257-8.
Müller, C., Remy, S., 2018. Septo-hippocampal interaction. Cell Tissue Res. 373, 565–575. https://doi.org/10.1007/s00441-017-2745-2.
Nampiaparampil, D.E., 2008. Prevalence of chronic pain after traumatic brain injury: a systematic review. JAMA 300, 711–719. https://doi.org/10.1001/jama.300.6.711.
Neese, S.L., Sherill, L.K., Tan, A.A., Roosevelt, R.W., Browning, R.A., Smith, D.C., Duke, A., Clough, R.W., 2007. Vagus nerve stimulation may protect GABAergic neurons following traumatic brain injury in rats: an immunocytochemical study. Brain Res. 1128, 157–163. https://doi.org/10.1016/j.brainres.2006.09.073.
Niesman, I.R., Schilling, J.M., Shapiro, L.A., Kellerhals, S.E., Bonds, J.A., Kleschevnikov, A.M., Cui, W., Voong, A., Krajewski, S., Ali, S.S., Roth, D.M., Patel, H. H., Patel, P.M., Head, B.P., 2014. Traumatic brain injury enhances neuroinflammation and lesion volume in caveolin deficient mice. J. Neuroinflammation 11, 39. https://doi.org/10.1186/1742-2094-11-39.
Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F., Pascual-Leone, A., 2008. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 1, 206–223. https://doi.org/10.1016/j.brs.2008.06.004.
Nitsche, M.A., Liebetanz, D., Lang, N., Antal, A., Tergau, F., Paulus, W., 2003. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. https://doi.org/10.1016/s1388-2457(03)00235-9.
Niu, X., Bai, L., Sun, Y., Wang, S., Cao, J., Sun, C., Wang, Z., Xu, H., Gan, S., Fan, G., Huang, W., Gu, C., Yin, B., Bai, G., Xu, X., Zhang, M., 2019. Disruption of periaqueductal grey-default mode network functional connectivity predicts persistent post-traumatic headache in mild traumatic brain injury. J. Neurol. Neurosurg. Psychiatry 90, 326–332. https://doi.org/10.1136/jnnp-2018-318886.
Niu, X., Bai, L., Sun, Y., Wang, Y., Bai, G., Yin, B., Wang, S., Gan, S., Jia, X., Liu, H., 2020. Mild traumatic brain injury is associated with effect of inflammation on structural changes of default mode network in those developing chronic pain. J. Headache Pain 21, 135. https://doi.org/10.1186/s10194-020-01201-7.
O'Neil-Pirozzi, T.M., Doruk, D., Thomson, J.M., Fregni, F., 2017. Immediate memory and electrophysiologic effects of prefrontal cortex transcranial direct current stimulation on neurotypical individuals and individuals with chronic traumatic brain injury: a pilot study. Int. J. Neurosci. 127, 592–600. https://doi.org/10.1080/00207454.2016.1216415.
Ofoghi, Z., Dewey, D., Barlow, K.M., 2020. A systematic review of structural and functional imaging correlates of headache or pain after mild traumatic brain injury. J. Neurotrauma 37, 907–923. https://doi.org/10.1089/neu.2019.6750.
Ofoghi, Z., Rohr, C.S., Dewey, D., Bray, S., Yeates, K.O., Noel, M., Barlow, K.M., 2021. Functional connectivity of the anterior cingulate cortex with pain-related regions in children with post-traumatic headache. Cephalalgia Reports 4, 25158163211009476.
Olson, J.K., Miller, S.D., 2004. Microglia initiate central nervous system innate and adaptive immune responses through multiple TLRs. J. Immunol. 173, 3916–3924. https://doi.org/10.4049/jimmunol.173.6.3916.
Onyszchuk, G., LeVine, S.M., Brooks, W.M., Berman, N.E.J., 2009. Post-acute pathological changes in the thalamus and internal capsule in aged mice following controlled cortical impact injury: a magnetic resonance imaging, iron histochemical, and glial immunohistochemical study. Neurosci. Lett. 452, 204–208. https://doi.org/10.1016/j.neulet.2009.01.049.
Pacheco-Barrios, K., Cardenas-Rojas, A., Thibaut, A., Costa, B., Ferreira, I., Caumo, W., Fregni, F., 2020. Methods and strategies of tDCS for the treatment of pain: current status and future directions. Expet Rev. Med. Dev. 17, 879–898. https://doi.org/10.1080/17434440.2020.1816168.
Pinchefsky, E., Dubrovsky, A.S., Friedman, D., Shevell, M., 2015. Part II–Management of pediatric post-traumatic headaches. Pediatr. Neurol. 52, 270–280. https://doi.org/10.1016/j.pediatrneurol.2014.10.015.
Ponath, G., Schettler, C., Kaestner, F., Voigt, B., Wentker, D., Arolt, V., Rothermundt, M., 2007. Autocrine S100B effects on astrocytes are mediated via RAGE. J. Neuroimmunol. 184, 214–222. https://doi.org/10.1016/j.jneuroim.2006.12.011.
Portilla, A.S., Bravo, G.L., Miraval, F.K., Villamar, M.F., Schneider, J.C., Ryan, C.M., Fregni, F., 2013. A feasibility study assessing cortical plasticity in chronic neuropathic pain following burn injury. J. Burn care Res. Off. Publ. Am. Burn Assoc. 34, e48–e52. https://doi.org/10.1097/BCR.0b013e3182700675.
Prescott, S.A., Ma, Q., De Koninck, Y., 2014. Normal and abnormal coding of somatosensory stimuli causing pain. Nat. Neurosci. 17, 183–191. https://doi.org/10.1038/nn.3629.
Raja, S.N., Carr, D.B., Cohen, M., Finnerup, N.B., Flor, H., Gibson, S., Keefe, F.J., Mogil, J. S., Ringkamp, M., Sluka, K.A., Song, X.-J., Stevens, B., Sullivan, M.D., Tutelman, P. R., Ushida, T., Vader, K., 2020. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain 161, 1976–1982. https://doi.org/10.1097/j.pain.0000000000001939.
Reid, S.A., Farbenblum, J., McLeod, S., 2022. Do physical interventions improve outcomes following concussion: a systematic review and meta-analysis? Br. J. Sports Med. 56, 292–298. https://doi.org/10.1136/bjsports-2020-103470.
Roine, T., Mohammadian, M., Hirvonen, J., Kurki, T., Posti, J.P., Takala, R.S.K., Newcombe, V.F., Tallus, J., Katila, A.J., Maanpää, H.-R., Frantzen, J., Menon, D., Tenovuo, O., 2022. Structural brain connectivity correlates with outcome in mild traumatic brain injury. J. Neurotrauma 39, 336–347. https://doi.org/10.1089/neu.2021.0093.
Rosa, J.M., Farré-Alins, V., Ortega, M.C., Navarrete, M., Lopez-Rodriguez, A.B., Palomino-Antolín, A., Fernández-López, E., Vila-Del Sol, V., Decouty, C., Narros-

Fernández, P., Clemente, D., Egea, J., 2021. TLR4 pathway impairs synaptic number and cerebrovascular functions through astrocyte activation following traumatic brain injury. Br. J. Pharmacol. 178, 3395–3413. https://doi.org/10.1111/bph.15488.

Sayed, B.A., Christy, A.L., Walker, M.E., Brown, M.A., 2010. Meningeal mast cells affect early T cell central nervous system infiltration and blood-brain barrier integrity through TNF: a role for neutrophil recruitment? J. Immunol. 184, 6891–6900. https://doi.org/10.4049/jimmunol.1000126.

Schabrun, S.M., Jones, E., Elgueta Cancino, E.L., Hodges, P.W., 2014. Targeting chronic recurrent low back pain from the top-down and the bottom-up: a combined transcranial direct current stimulation and peripheral electrical stimulation intervention. Brain Stimul. 7, 451–459. https://doi.org/10.1016/j.brs.2014.01.058.

Seifert, T., Sufrinko, A., Cowan, R., Scott Black, W., Watson, D., Edwards, B., Livingston, S., Webster, K., Akers, D., Lively, M., Kontos, A.P., 2017. Comprehensive headache experience in collegiate student-athletes: an initial report from the NCAA headache task force. Headache 57, 877–886. https://doi.org/10.1111/head.13104.

Seminowicz, D.A., Moayedi, M., 2017. The dorsolateral prefrontal cortex in acute and chronic pain. J. Pain 18, 1027–1035. https://doi.org/10.1016/j.jpain.2017.03.008.

Shi, K., Zhang, J., Dong, J.-F., Shi, F.-D., 2019. Dissemination of brain inflammation in traumatic brain injury. Cell. Mol. Immunol. 16, 523–530. https://doi.org/10.1038/s41423-019-0213-5.

Shirvani, S., Davoudi, M., Shirvani, M., Koleini, P., Hojat Panah, S., Shoshtari, F., Omidi, A., 2021. Comparison of the effects of transcranial direct current stimulation and mindfulness-based stress reduction on mental fatigue, quality of life and aggression in mild traumatic brain injury patients: a randomized clinical trial. Ann. Gen. Psychiatr. 20, 33. https://doi.org/10.1186/s12991-021-00355-1.

Silberstein, S.D., Dodick, D.W., Bigal, M.E., Yeung, P.P., Goadsby, P.J., Blankenbiller, T., Grozinski-Wolff, M., Yang, R., Ma, Y., Aycardi, E., 2017. Fremanezumab for the preventive treatment of chronic migraine. N. Engl. J. Med. 377, 2113–2122. https://doi.org/10.1056/NEJMoa1709038.

Silverberg, N.D., Iverson, G.L., Cogan, A., Dams-O-Connor, K., Delmonico, R., Graf, M.J. P., Iaccarino, M.A., Kajankova, M., Kamins, J., McCulloch, K.L., McKinney, G., Nagele, D., Panenka, W.J., Rabinowitz, A.R., Reed, N., Wethe, J.V., Whitehair, V., Anderson, V., Arciniegas, D.B., Bayley, M.T., Bazarian, J.J., Bell, K.R., Broglio, S.P., Cifu, D., Davis, G.A., Dvorak, J., Echemendia, R.J., Gioia, G.A., Giza, C.C., Hinds, S. R. 2nd, Katz, D.I., Kurowski, B.G., Leddy, J.J., Sage, N. Le, Lumba-Brown, A., Maas, A.I., Manley, G.T., McCrea, M., Menon, D.K., Ponsford, J., Putukian, M., Suskauer, S.J., van der Naalt, J., Walker, W.C., Yeates, K.O., Zafonte, R., Zasler, N.D., Zemek, R., 2023. The American congress of rehabilitation medicine diagnostic criteria for mild traumatic brain injury. Arch. Phys. Med. Rehabil. 104, 1343–1355. https://doi.org/10.1016/j.apmr.2023.03.036.

Simons, L.E., Erpelding, N., Hernandez, J.M., Serrano, P., Zhang, K., Lebel, A.A., Sethna, N.F., Berde, C.B., Prabhu, S.P., Becerra, L., Borsook, D., 2015. Fear and reward circuit alterations in pediatric CRPS. Front. Hum. Neurosci. 9, 703. https://doi.org/10.3389/fnhum.2015.00703.

Singh, K., Trivedi, R., Devi, M.M., Tripathi, R.P., Khushu, S., 2016. Longitudinal changes in the DTI measures, anti-GFAP expression and levels of serum inflammatory cytokines following mild traumatic brain injury. Exp. Neurol. 275 (Pt 3), 427–435. https://doi.org/10.1016/j.expneurol.2015.07.016.

Soler, M.D., Kumru, H., Pelayo, R., Vidal, J., Tormos, J.M., Fregni, F., Navarro, X., Pascual-Leone, A., 2010. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. Brain 133, 2565–2577. https://doi.org/10.1093/brain/awq184.

Srihagulang, C., Vongsfak, J., Vaniyapong, T., Chattipakorn, N., Chattipakorn, S.C., 2022. Potential roles of vagus nerve stimulation on traumatic brain injury: evidence from in vivo and clinical studies. Exp. Neurol. 347, 113887 https://doi.org/10.1016/j.expneurol.2021.113887.

St John Smith, E., 2018. Advances in understanding nociception and neuropathic pain. J. Neurol. 265, 231–238. https://doi.org/10.1007/s00415-017-8641-6.

Stacey, A., Lucas, S., Dikmen, S., Temkin, N., Bell, K.R., Brown, A., Brunner, R., Diaz-Arrastia, R., Watanabe, T.K., Weintraub, A., Hoffman, J.M., 2017. Natural history of headache five years after traumatic brain injury. J. Neurotrauma 34, 1558–1564. https://doi.org/10.1089/neu.2016.4721.

Steen, K.H., Reeh, P.W., Anton, F., Handwerker, H.O., 1992. Protons selectively induce lasting excitation and sensitization to mechanical stimulation of nociceptors in rat skin, in vitro. J. Neurosci. Off. J. Soc. Neurosci. 12, 86–95. https://doi.org/10.1523/JNEUROSCI.12-01-00086.1992.

Studlack, P.E., Keledjian, K., Farooq, T., Akintola, T., Gerzanich, V., Simard, J.M., Keller, A., 2018. Blast-induced brain injury in rats leads to transient vestibulomotor deficits and persistent orofacial pain. Brain Inj. 32, 1866–1878. https://doi.org/10.1080/02699052.2018.1536282.

Tang, Yunliang, Dong, X., Chen, G., Ye, W., Kang, J., Tang, Yang, Feng, Z., 2020. Vagus nerve stimulation attenuates early traumatic brain injury by regulating the NF-κB/NLRP3 signaling pathway. Neurorehabilitation Neural Repair 34, 831–843. https://doi.org/10.1177/1545968320948065.

Taylor, C.A., Bell, J.M., Breiding, M.J., Xu, L., 2017. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths - United States, 2007 and 2013. Morb. Mortal. Wkly. Rep. - Surveillance Summ. 66, 1–16. https://doi.org/10.15585/mmwr.ss6609a1.

Tiefenbach, J., Chan, H.H., Machado, A.G., Baker, K.B., 2022. Neurostimulation for functional recovery after traumatic brain injury: current evidence and future directions for invasive surgical approaches. Neurosurgery 91, 823–830. https://doi.org/10.1227/neu.0000000000002134.

Tognetto, M., Amadesi, S., Harrison, S., Creminon, C., Trevisani, M., Carreras, M., Matera, M., Geppetti, P., Bianchi, A., 2001. Anandamide excites central terminals of dorsal root ganglion neurons via vanilloid receptor-1 activation. J. Neurosci. Off. J. Soc. Neurosci. 21, 1104–1109. https://doi.org/10.1523/JNEUROSCI.21-04-01104.2001.

Tottene, A., Pivotto, F., Fellin, T., Cesetti, T., van den Maagdenberg, A.M.J.M., Pietrobon, D., 2005. Specific kinetic alterations of human CaV2.1 calcium channels produced by mutation S218L causing familial hemiplegic migraine and delayed cerebral edema and coma after minor head trauma. J. Biol. Chem. 280, 17678–17686. https://doi.org/10.1074/jbc.M501110200.

Tyburski, A.L., Cheng, L., Assari, S., Darvish, K., Elliott, M.B., 2017. Frequent mild head injury promotes trigeminal sensitivity concomitant with microglial proliferation, astrocytosis, and increased neuropeptide levels in the trigeminal pain system. J. Headache Pain 18, 16. https://doi.org/10.1186/s10194-017-0726-1.

Vaninetti, M., Lim, M., Khalaf, A., Metzger-Smith, V., Flowers, M., Kunnel, A., Yang, E., Song, D., Lin, L., Tsai, A., Lee, R., Golshan, S., Leung, A., 2021. fMRI findings in MTBI patients with headaches following rTMS. Sci. Rep. 11, 9573. https://doi.org/10.1038/s41598-021-89118-2.

Vaseghi, B., Zoghi, M., Jaberzadeh, S., 2014. Does anodal transcranial direct current stimulation modulate sensory perception and pain? A meta-analysis study. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 125, 1847–1858. https://doi.org/10.1016/j.clinph.2014.01.020.

Viganò, A., D'Elia, T.S., Sava, S.L., Auvé, M., De Pasqua, V., Colosimo, A., Di Piero, V., Schoenen, J., Magis, D., 2013. Transcranial Direct Current Stimulation (tDCS) of the visual cortex: a proof-of-concept study based on interictal electrophysiological abnormalities in migraine. J. Headache Pain 14, 23. https://doi.org/10.1186/1129-2377-14-23.

Villamar, M.F., Wivatvongvana, P., Patumanond, J., Bikson, M., Truong, D.Q., Datta, A., Fregni, F., 2013. Focal modulation of the primary motor cortex in fibromyalgia using 4×1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation. J. Pain 14, 371–383. https://doi.org/10.1016/j.jpain.2012.12.007.

Wang, L.-C., Wei, W.-Y., Ho, P.-C., 2022. Short-term cortical electrical stimulation during the acute stage of traumatic brain injury improves functional recovery. Biomedicines 10. https://doi.org/10.3390/biomedicines10081965.

Wang, Q.-Q., Zhu, L.-J., Wang, X.-H., Zuo, J., He, H.-Y., Tian, M.-M., Wang, L., Liang, G.-L., Wang, Y., 2016. Chronic trigeminal nerve stimulation protects against seizures, cognitive impairments, hippocampal apoptosis, and inflammatory responses in epileptic rats. J. Mol. Neurosci. 59, 78–89. https://doi.org/10.1007/s12031-016-0736-5.

Wang, Y., Zhang, Y., Zhang, Jinlei, Wang, J., Xu, J., Li, J., Cui, G., Zhang, Jiuquan, 2018. Structural and functional abnormalities of the insular cortex in trigeminal neuralgia: a multimodal magnetic resonance imaging analysis. Pain 159, 507–514. https://doi.org/10.1097/j.pain.0000000000001120.

Wang, Z., Wang, Q., Wang, C., Xu, X., Yu, H., 2017. Tetramethylpyrazine attenuates periorbital allodynia and neuroinflammation in a model of traumatic brain injury. J. Inflamm. 14, 13. https://doi.org/10.1186/s12950-017-0161-8.

Wrona, R.M., 2006. The use of state workers' compensation administrative data to identify injury scenarios and quantify costs of work-related traumatic brain injuries. J. Saf. Res. 37, 75–81. https://doi.org/10.1016/j.jsr.2005.08.008.

Xu, H., Xu, C., Gu, P., Hu, Y., Guo, Y., Bai, G., 2023. Neuroanatomical restoration of salience network links reduced headache impact to cognitive function improvement in mild traumatic brain injury with posttraumatic headache. J. Headache Pain 24, 43. https://doi.org/10.1186/s10194-023-01579-0.

Yang, Q., Zhang, S., Xu, Z., Liu, L., Fan, S., Wu, S., Ma, C., 2022. The effectiveness of trigeminal nerve stimulation on traumatic brain injury. Neuromodulation 25, 1330–1337. https://doi.org/10.1016/j.neurom.2021.10.014.

Yang, X.-J., Ling, S., Zhou, M.-L., Deng, H.-J., Qi, M., Liu, X.-L., Zhen, C., Chen, Y.-X., Fan, X.-R., Wu, Z.-Y., Ma, F.-C., Rong, J., Di, G.-F., Jiang, X.-C., 2022. Inhibition of TRPA1 attenuates oxidative stress-induced damage after traumatic brain injury via the ERK/AKT signaling pathway. Neuroscience 494, 51–68. https://doi.org/10.1016/j.neuroscience.2022.02.003.

Yoshino, A., Okamoto, Y., Onoda, K., Yoshimura, S., Kunisato, Y., Demoto, Y., Okada, G., Yamawaki, S., 2010. Sadness enhances the experience of pain via neural activation in the anterior cingulate cortex and amygdala: an fMRI study. Neuroimage 50, 1194–1201. https://doi.org/10.1016/j.neuroimage.2009.11.079.

Zaninotto, A.L., El-Hagrassy, M.M., Green, J.R., Babo, M., Paglioni, V.M., Benute, G.G., Paiva, W.S., 2019. Transcranial direct current stimulation (tDCS) effects on traumatic brain injury (TBI) recovery: a systematic review. Dement. Neuropsychol. 13, 172–179. https://doi.org/10.1590/1980-57642018dn13-020005.

Zasler, N.D., 2011. Pharmacotherapy and posttraumatic cephalalgia. J. Head Trauma Rehabil. 26, 397–399. https://doi.org/10.1097/HTR.0b013e31822721f8.

Zhao, P.-C., Huang, Z.-S., Xu, S.-N., Deng, P.-C., Qian, F., Shi, J., Zhang, Y.-M., 2022. Investigation of the effects of high cervical spinal cord electrical stimulation on improving neurological dysfunction and its potential mechanism in rats with traumatic brain injury. Neuroreport 33, 509–517. https://doi.org/10.1097/WNR.0000000000001811.

Zhou, L., Lin, Jinhuang, Lin, Junming, Kui, G., Zhang, J., Yu, Y., 2014. Neuroprotective effects of vagus nerve stimulation on traumatic brain injury. Neural Regen. Res. 9, 1585–1591. https://doi.org/10.4103/1673-5374.141783.

Zirovich, M.D., Pangarkar, S.S., Manh, C., Chen, L., Vangala, S., Elashoff, D.A., Izuchukwu, I.S., 2021. Botulinum toxin type A for the treatment of post-traumatic headache: a randomized, placebo-controlled, cross-over study. Mil. Med. 186, 493–499. https://doi.org/10.1093/milmed/usaa391.

Zou, Y., Tang, W., Qiao, X., Li, J., 2021. Aberrant modulations of static functional connectivity and dynamic functional network connectivity in chronic migraine. Quant. Imag. Med. Surg. 11, 2253–2264. https://doi.org/10.21037/qims-20-588.