biomedicines

MDPI

Review

A Scoping Review on the Use of Non-invasive Brain Stimulation Techniques for persistent Post-concussive Symptoms

Mohammad Hossein Khosravi [1,2] & Mélanie Louras [1,2], Géraldine Martens [1,3], Jean-François Kaux [4] , Aurore Thibaut [1,2,*,+] and Nicolas Lejeune [1,5,6*]

[1] Coma Science Group, GIGA Consciousness, University of Liège, Liège, Belgium
[2] Centre du Cerveau², University Hospital of Liège, Liège, Belgium
[3] Sport & Trauma Applied Research Lab, University of Montréal, Montréal QC, Canada
[4] Physical and Rehabilitation Medicine and Sport Traumatology Department, University Hospital of Liège, University of Liège, Liège, Belgium
[5] CHN William Lennox, Ottignies, Belgium
[6] Institute of NeuroScience, UCLouvain, Brussels, Belgium

*These authors share the senior position
+Correspondence: athibaut@uliege.be

Abstract: Background: in the context of managing persistent post-concussive symptoms (PPCS), existing treatments like pharmacotherapy, cognitive behavioral therapy, and physical rehabilitation show only moderate effectiveness. The emergence of neuromodulation techniques in PPCS management has led to debates regarding optimal stimulation parameters and their overall efficacy. Methods: this scoping review involved a comprehensive search of PubMed and ScienceDirect databases, focusing on controlled studies examining the therapeutic potential of non-invasive brain stimulation (NIBS) techniques in adults with PPCS. Results: among 940 abstracts screened, only 5 studies, encompassing 103 patients (12 to 29 per study) met the inclusion criteria. These studies assessed the efficacy of transcranial direct current stimulation (tDCS), or repetitive transcranial magnetic stimulation (rTMS) applied to specific brain regions (i.e., left dorsolateral pre-frontal cortex (DLPFC) or left motor cortex (M1)) for addressing cognitive, psychological symptoms, headaches, and general PPCS. Results indicated improvements in cognitive functions with tDCS. In contrast, reductions in headache intensity and depression scores were observed with rTMS, while no significant findings were noted for general symptoms with rTMS. Conclusion: although these pilot studies suggest promise for rTMS and tDCS in PPCS management, further research with larger-scale investigations and standardized protocols is imperative to enhance treatment outcomes for PPCS patients.

Keywords: Non-Invasive Brain Stimulation; Transcranial Direct Current Stimulation; tDCS; Transcranial magnetic stimulation; rTMS; Post-Concussive Symptoms

1. Introduction

Concussion, also referred to as mild traumatic brain injury (mTBI), represents a significant public health concern with an estimated incidence of 69 million people affected worldwide annually [1]. It is considered as a silent epidemic as up to 50% of patients with concussion will develop long-term impairments (>1 month), a clinical entity known as persistent post-concussive symptoms (PPCS) [2].

Although the pathophysiological mechanisms underlying PPCS are complex and not fully understood yet, they can be characterized by a cascade of events that includes a bioenergetic crisis, cytoskeletal and axonal alterations, and impairment in neurotransmission, which could lead to chronic neuronal dysfunctions [3]. Some patients with PPCS may experience symptoms for months or years after the accident, which have a significant impact on their quality of life, ability to return to work or school, representing consequently a significant socioeconomic burden on society [4,5]. PPCS symptoms are generally divided into four categories: somatic (e.g., headaches, dizziness, balance problem), cognitive (e.g., amnesia, poor attention capacities), emotional (e.g., anxiety, depression) and sleep-arousal complaints (e.g., fatigue, insomnia) [6,7]. Surprisingly, these persistent symptoms are still not addressed by any specific treatments. Current guidelines advise an initial period of 24-48h of rest - with limited screen time and cognitive activity - following concussion, with a gradual introduction of light-to-moderate aerobic exercise [8], gradual return to activities (learning and sport) and active rehabilitative interventions are also recommended to favour an optimal recovery [9–11]. However, these recommendations are not yet systematically applied [8].

Current medical care consists primarily of symptom relief through pharmacologic interventions (e.g., analgesics for headaches or sedatives for sleep disorders), rehabilitation services (e.g., physiotherapy for motor function disabilities or musculoskeletal pains), cognitive behavioral therapy (for sleep or mood disorders – especially in women [12]) and neuropsychology (for cognitive impairments) [13]. However, it is increasingly evident that these existing treatment modalities do not provide sufficient relief for individuals with PPCS [8].

Considering this, non-invasive brain stimulation (NIBS) approaches have emerged as a potential solution for addressing the unmet needs in concussion management and care. NIBS involves the modulation of neural activity using, for instance, electrical or magnetic stimulation, with the aim of modifying the excitability of the underlying brain cortex [14]. By targeting specific regions of interest, NIBS can directly influence brain plasticity, and potentially induce long-lasting neuroplastic positive changes in functional networks thought to be affected in PPCS such as the default mode network and the task positive network [15]. The default mode network, primarily associated with processes related to self-awareness is active during periods of rest [16], and the task-positive network comprises regions activated during externally directed behavior and the execution of effortful tasks [17]. In healthy individuals, there is a strong anticorrelation in resting state connectivity between these two networks, where activation of one results in deactivation of the other [18]. It is thought that changes in this anticorrelation may be linked to the symptoms observed in patients with PPCS [15], and that NIBS could potentially target these networks.

The main techniques currently used for this purpose are transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). tDCS can modulate cortical activity and activate targeted regions of the brain [19]. This technique is cost-effective, easy to use, and safe, causing only minor side effects (i.e., burning sensation, itching, and headache) [20]. Specific tDCS settings have shown potential in treating conditions like fibromyalgia, depression, and addictions/cravings [21]. Similarly, TMS utilizes magnetic fields for noninvasive electromagnetic brain stimulation. Two main types of TMS exist: single-pulse whose purpose is mainly to explore brain function, and repetitive TMS (rTMS) aiming to induce lasting brain activity changes [22,23]. rTMS has shown effectiveness in treating disorders like neuropathic pain, depression, and stroke recovery [21].

Given the potential therapeutic benefits of neuromodulation and the diverse range of symptoms experienced by patients with PPCS, our goal is to comprehensively examine the existing literature on the application of neuromodulation techniques for PPCS management. This scoping review will adopt a dual approach, focusing on both symptom-based and targeted area strategies.

2. Search Methodology

We searched on PubMed and ScienceDirect using related search terms including "Acquired brain injury", "Traumatic brain injury", "PPCS", "Persistent post concussive symptoms", "Persistent post-concussion syndrome", "Sports-related concussion", "Non-invasive brain stimulation", "Neuromodulation", "Transcranial magnetic stimulation", "Theta-burst stimulation", "Transcranial electrical stimulation" and "Transcranial direct-current stimulation". We applied no specific limitation for publication time range. The full search equation can be found in the appendix. A total of 1004 articles were retrieved.

The selected articles had to investigate the therapeutic effects of neuromodulation, in comparison to sham or other interventions, on post-concussion symptoms (i.e., cognitive symptoms, headache, fatigue, sleep disorders and psychological symptoms) in human subjects. One of the authors of the study (MHK) did the screening and extracted the data from the included studies. National Institute of Health Quality Assessment Tool for Controlled Intervention Studies was used to assess study quality and risk of bias [24] **(**see supplementary data). Concussion was considered as either no or less than 30 minutes of loss of consciousness, post-traumatic amnesia of less than 24 hours, a post-traumatic Glasgow Coma Scale of more than 13, and no neuroimaging abnormalities according to the Centers for Disease Control and Prevention and American Congress of Rehabilitation Medicine guidelines [25]. We included original studies and excluded review articles, case reports, conference proceedings, hypothesis articles and papers which were not in English as well as those not assessing neuromodulation on patients with concussion or evaluating it on patients with both concussion and other TBI severities. We eventually considered these additional articles for the discussion section.

Data on study design, demographic information, targeted location of stimulation, stimulation and sham protocol (e.g., number of sessions, pulses and frequency) and outcome measures were extracted from included articles. Results are presented in a symptom-based manner explaining findings of studies about the effects of their intervention on each symptom. We followed the PRISMA guidelines to evaluate the articles and report the results.

3. Results

Figure 1 shows a flow diagram of the study. We screened 940 records after removing 64 duplicates from the total of 1004 records retrieved from search on PubMed and ScienceDirect databases. In addition, we performed a citation search and retrieved 15 records from reference list of similar reviews. Finally, following exclusion of non-desirable records, we included 5 studies which had assessed the effect of tDCS or rTMS on headache, cognitive and psychological symptoms following concussion (De Launay et al., 2022; Leung et al., 2016; Leung et al., 2018; Stilling et al., 2020; Moussavi et al., 2019)[23,26–29].Table 1 summarizes the extracted data of the included studies.

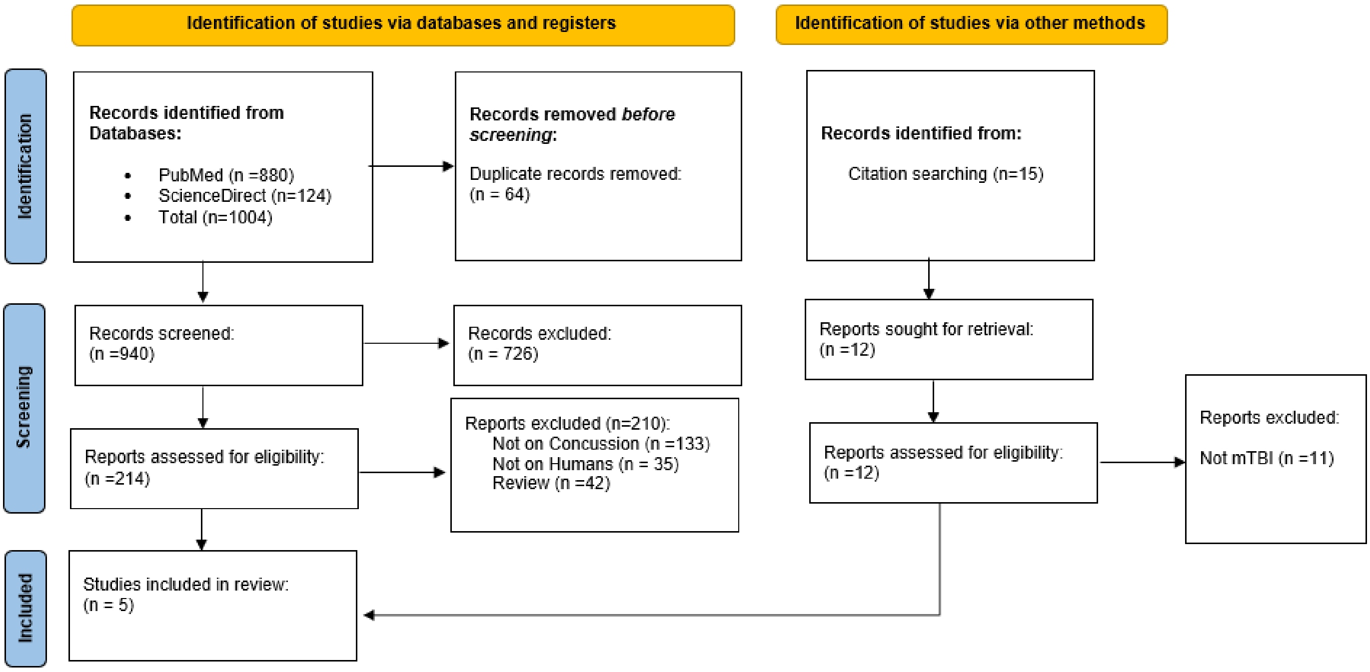

Figure 1. PRISMA diagram.

Table 1. Summary of characteristics and results of the included studies. DLPFC = Dorsolateral Prefrontal Cortex; Dual N-Back WMT = Dual N-Back Working Memory Test; HRSD = Hamilton Rating Scale for Depression; HIT-6 = Headache Impact Test-6; MADRS = Montgomery–Åsberg Depression Rating Scale; PHQ-9 = Participant Health Questionnaire-9; PPCS = Persistent Post Concussion Symptoms; RPQ = Rivermead Post-Concussion Questionnaire; rTMS = repeated Transcranial Magnetic Stimulation; tDCS = transcranial Direct Current Stimulation; VAS = Visual Analogue Scale.

Author [reference]	Design	Patients	Target	Outcome measure	Stimulation protocol	Sham protocol	Outcomes
De Launay et al. [26]	Double-blind sham-controlled clinical trial	N=12 with cognitive PPCS	Left DLPFC	Cognitive symptoms (working memory): Dual N-Back WMT	Three sessions of anodal tDCS for 20 minutes at 1.5 mA	Three sessions of sham tDCS for 20 minutes at 1.5 mA	-No changes in faster reaction time in both sham and active -Improved N2 and N3 level accuracy in active tDCS
Leung et al. [27]	Single-blind sham-controlled clinical trial	N=24 with post-concussion chronic headache	Left Motor Cortex	Headaches: Daily headache diary	Three sessions of rTMS 2000 pulses (20 trains of 100 pulses at 10Hz) in one week	Three sessions of sham rTMS 2000 pulses (20 trains of 100 pulses at 10Hz) in one week	Reduced intensity of persistent headache and debilitating headache exacerbation score in active rTMS
Leung et al. [28]	Single-blind sham-controlled clinical trial	N=29 with persistent concussion-related headaches (mTBI-HA)	Left DLPFC	Depression: HRSD Headaches: VAS	Four sessions of active rTMS (20 trains of 100 pulses at 10Hz)	Four sessions of sham rTMS (over treatment area)	-Improved HRSD level in active rTMS - Reduced intensity of persistent headache and debilitating

							headache exacerbation score in active rTMS at both one- and four-week assessments
Moussavi et al. [29]	Randomized double-blind sham-controlled trial	N=18 with PPCS and depression in two groups: short and long durations of symptoms	Left DLPFC	General PPCS: RPQ Depression: MADRS	13 treatment sessions of low- frequency rTMS within three weeks (25 trains of 30 pulses at 20 Hz)	13 treatment sessions of low frequency rTMS within three weeks	-Decreased RPQ3 and MADRS in both active and sham in group with short duration of symptoms - Decreased RPQ13 in active group with short duration of symptoms - Non-significant decrease of RPQ3 and 13 for patients with long duration of symptoms - No MADRS improvement for patients with with long duration of symptoms
Stilling et al. [23]	Randomized double-blind sham-controlled trial	N=20 patients with PTH and PPCS	Left DLPFC	Headaches: Daily headache diary + HIT-6 Depression: PHQ-9	10 sessions of rTMS 10 trains of 60 pulses and at 10Hz in two weeks	10 sessions of sham rTMS in two weeks	-Non-significant decreased headache severity in both active and sham groups -Significant decrease of depression in active group

In the following sections, using a symptom-based approach, we detail the literature upon therapeutic effects of tDCS and rTMS on patients with PPCS.

3.1. Cognitive Symptoms

Alterations in learning, attention, processing speed and executive functions are the most commonly reported cognitive symptoms in patients with PPCS [30]. Some studies report that up to 50% of patients who had a concussion still suffer from cognitive impairments at one-year follow up [31]. However, these alterations may not be always detectable on standard neuropsychological tests or simple cognitive tasks [32].

Our literature search retrieved only one double-blind sham-controlled crossover clinical trial investigating cognitive symptoms. This study evaluated the effectiveness and tolerability of multi-session anodal tDCS in a group of young patients (10 females and 2 males, mean age: 15.9 years) who sustained a concussion at least one month prior to inclusion and experience PPCS [26]. They applied three sessions of anodal tDCS to the left DLPFC (20 minutes at 1.5mA) and assessed its effect on the performance of working memory using a dual-task paradigm. All the patients were asked to perform an auditory-visuospatial dual N-Back working memory task with four levels of difficulty which was launched after the first minute of tDCS and terminated before the end of stimulation. Although both the active (n=6) and the sham (n=6) groups were performing at the ceiling level for the first two levels, the authors reported a continuous improvement for the two more difficult levels for the active tDCS group over the three sessions. Between group comparisons revealed that active tDCS group performed significantly better than sham tDCS group on day 2 in N-Back level 2 (p=0.019). No serious adverse events were reported for both the active and sham tDCS groups; however, itching, pain and burning were among the most prevalent minor side effects. In this quasi-randomized controlled trial, the authors concluded that tDCS was well tolerated and could improve working memory performance of young patients with PPCS, supplement to behavioural interventions. The authors delegated the determination of efficacy to subsequent clinical trials.

No research investigating the effects of rTMS on cognitive functions was found.

3.2. Headache

As defined by the 3rd edition of The International Classification of Headache Disorders, headaches beginning within the first 7 days of head injury are called "headaches attributed to traumatic injury to the head" (mTBI-HA) [33]. Acute mTBI-HA are those which are resolved within 3 months and headaches lasting more than 3 months are referred as to persistent post-traumatic headaches. To date, there is no pharmacological treatments able to fully alleviate these mTBI-HA and all the most commonly prescribed medications, such as narcotics, anticonvulsants, and tricyclics, are associated with abusive or undesired psychosomatic adverse effects [34].

In the context of NIBS, three studies were found investigating mTBI-HA.

A previous single-blind sham-controlled parallel clinical trial evaluated the therapeutic effects of three sessions of neuro-navigated rTMS on 24 patients (21 males and 3 females, mean age: 14.3±12.6, 12 patients per group) with chronic headaches following a concussion [27]. Mean duration of mTBI-HA was 178±176 months for active, and 163±142 months for sham group patients at baseline. Researchers delivered a total of 2000 pulses (20 trains of 100 pulses at 10Hz) on the left primary motor cortex in the 12 patients allocated to the active rTMS group (age: 41.2±14 years). For the patients in the sham group (age: 41.4±11.6 years), the location was the same but the treatment side of the coil was positioned 180° away from the scalp. After intervention, authors stratified patients in two subgroups according to headache type; "persistent" headaches referring to non-disappearing daily headaches, and "debilitating" headaches exacerbation which seriously alter the normal daily activity. One week after intervention, the active group showed a significantly higher reduction in the intensity of persistent headaches as assessed by visual analog scale compared to the sham group. In addition, the debilitating headaches were significantly reduced at four-week in the active group, while remaining similar in the sham group. However, authors did not directly compare the changes of headache measures between active and sham groups. Eventually, authors concluded that three sessions of rTMS delivered on the left M1 may diminish mTBI-HA symptoms without persistent side effects.

In another similar single-blind sham-controlled clinical trial conducted by the same team, the authors evaluated the headache-alleviating effects of four sessions of rTMS (20 trains of 100 pulses at 10Hz) on the left DLPFC in 29 (6 females and 23 males, mean age: 34.1±7.9 years) veterans with mTBI-HA [28]. They followed the same abovementioned procedure to determine the intensity of stimulation. However, the time since injury is not clearly reported, patients in the active group had a mean mTBI-HA duration of 95±83 months and 99±58 months in the sham group. The active group showed a significantly higher reduction in daily persistent headache intensity at one and four-week post-intervention visits compared to patients in the sham group (p<0.001). Regarding debilitating headaches, the active group showed a significant improvement at both one (p=0.0001) and four-week (p=0.001) post-intervention assessments, while no change was observed in the sham group. There were no adverse events. The authors concluded that this intervention could reduce the mTBI-HA symptoms; however, further investigation of a clinical protocol is needed to balance both patient compliance and treatment efficacy.

Finally, a double-blind randomized parallel controlled trial examined the efficacy of 10 sessions of left DLPFC rTMS on 20 patients (18 females and 2 males, mean age: 36±11.4 years) with persistent post-traumatic headache and PPCS [23]. rTMS was applied at 10Hz, in 10 trains of 60 pulses and within two weeks. The authors included 18 to 65 years old patients who had persistent post-traumatic headache according to the 3rd edition of International Classification of Headache Disorders criteria or PPCS based on the 10th edition of international classification of diseases, for a duration of at least 3 months and maximum 5 years. There was only one male patient in each group and the mean age was significantly higher in the active group compared to the sham group (40.3±11.2 vs. 31.6±10.4). Patients had an average number of previous concussions of 2.06±1.16 and the mean time from previous concussion was 2.5 years (32.5±13.9 months). In the active group, mean headache frequency showed a significant decrease at one-month post-intervention in comparison with baseline (p=0.030). In addition, descriptive models showed a higher decrease in headache frequency per 14 days for the active versus the sham. Finally, authors reported that 60% of patients in the rTMS group returned to work after completing the study; however, this rate was 10% for patients in the sham group (p=0.027) [23]. Therefore, these studies show that rTMS sessions seem to relieve persistent headaches experienced by patients. Although the results were not statistically significant, authors concluded that rTMS sessions seem to relieve persistent headaches experienced by patients.

No research investigating the effects of tDCS on headaches was found.

3.3. Psychological Symptoms

To date, the bio-psycho-socio-ecological model [35] integrates the effect of psychological factors on the recovery from concussion; thus, treatment of psychological symptoms might also impact the recovery of non-psychological complications [36]. Conventional medical therapies (e.g., antidepressants or anxiolytics), psychological approaches and rehabilitation interventions are commonly used for these symptoms [36]; however, they are mostly based on trials assessing primary mental health disorders, while brain depressants for treating TBI-related major depressive disorder have been challenged by a meta-analysis [37] and cognitive behavioural therapy has also shown limited benefits for immediate and short-term psychological PPCS [38].

Three clinical trials on NIBS aiming to treat psychological symptoms following concussion were identified.

A single-blind sham-controlled clinical trial assessed the effect of four sessions of high-frequency rTMS (10 Hz) on the left DLPFC on depression (as well as on headache, see previous section) [28]. Baseline evaluations showed that patients in both active and sham groups were suffering from a very severe degree of depression based on the Hamilton Rating Scale for Depression. One week after the intervention, patients in the active group had significantly lower depression scores in comparison with the sham group (p=0.033), reclassifying them from severe to moderate depression. Although not significantly different from the sham group, this improvement lasted until the last follow-up point, 4 weeks after the end of the stimulation sessions. Authors concluded that this short course rTMS intervention may have transient mood-enhancing effects.

Another randomized double-blind sham-controlled trial assessed the therapeutic effects of low-frequency rTMS (25 trains of 30 pulses at 20 Hz) on the left DLPFC in 18 (9 males and 9 females, mean age: 49.5±12.4 years) patients with PPCS and depression [29]. Each patient received a total of 13 treatment sessions over three weeks and the outcomes were measured using the Rivermead Post Concussion Questionnaire (RPQ) and the Montgomery-Åsberg Depression Rating Scale, immediately after, at one month and two months after the intervention. A total of 750 pulses per day (25 trains of 30 pulses at 20 Hz) were delivered to patients in active group. The general baseline Montgomery-Åsberg Depression Rating Scale score of 18 participants showed mild depression. Depression severity was significantly decreased in patients with shorter duration of symptoms in both active and sham groups and this improvement was significantly higher in patients in the active group. In contrast, patients with longer duration of symptoms showed no improvement in neither sham nor active group. Authors attributed this difference to the baseline Montgomery-Åsberg Depression Rating Scale score which was higher in patients with longer duration of symptoms. Authors compared the difference of Montgomery-Åsberg Depression Rating Scale score from baseline, between sham and active rTMS groups, which revealed no significant difference at any follow-up points in both subgroups of patients with longer and shorter duration of symptoms. Finally, authors concluded that rTMS is a potentially effective treatment for patients with PPCS with a recent concussion less than one year post injury.

In a study described above (see section on headaches), researchers used the Participant Health Questionnaire-9 for evaluating depression in post-traumatic headache patients [23]. They observed a significant decrease of depression score at one month after intervention in comparison with baseline in active group patients. Comparisons between sham and active rTMS groups did not reveal any significant differences.

No research investigating the effects of tDCS on psychological symptoms was found.

3.4. PPCS General Symptoms

Concussions and their related comorbidities are often viewed as a spectrum of disorders, and as a result, healthcare providers may encounter challenges when attempting to categorize all the associated signs and symptoms within a singular specific category. This complexity arises from variations in the mechanisms of injury and the high incidence of comorbid conditions [39]. To evaluate the extent of post-concussion symptomatology and compare it to the individual's pre-injury state, the RPQ questionnaire offers a comprehensive assessment [40].

Our search retrieved only one clinical trial reporting the effects of NIBS on general symptoms of PPCS.

In an abovementioned study (see section on psychological symptoms), researchers evaluated the effect of DLPFC rTMS on the general PPCS symptoms using RPQ, immediately after, 30 days and 60 days after intervention [29]. Considering two subgroups of patients with short- and long-term symptoms, RPQ3 (first three RPQ items) score was decreased in patients with short-term symptoms in both sham and active groups; however, there was no significant between-group differences. On the other hand, RPQ13 (next 13 RPQ items) score had a significantly higher decrease in patients with short-term symptoms who received active in comparison to sham patients. In contrast, no significant decrease of RPQ3 and RPQ13 scores was reported for the patients with longer duration of symptoms in both sham and active rTMS groups at any assessment points.

No research investigating the effects of tDCS on general symptoms was found.

4. Discussion

In the present review, we aimed to explore the potential of NIBS as a therapeutic approach to help managing PPCS. After conducting a comprehensive literature review, we included a total of five controlled studies: one using tDCS and four rTMS. The tDCS study focused on cognitive symptoms [26] while the rTMS studies considered a diversity of symptoms, including depression, headaches, and general manifestations of PPCS development [23,27–29]. The tDCS study and three of the rTMS studies stimulated the left DLPFC, while one rTMS study targeted the left primary motor cortex. Overall, the findings from these studies indicate a positive impact of neuromodulation techniques on the common symptoms experienced by patients with PPCS. Notably, improvements were observed in cognitive deficits, headaches, and psychological symptoms such as depression.

4.1. Which Post-Concussion Symptoms Were Investigated, and Which Ones Remain Unexplored?

PPCS is known to include a spectrum of symptoms, with the most common described as somatic, emotional, cognitive and sleep-related [6]. Regarding headaches, rTMS demonstrated a significant decrease in their intensity [23,27,28]. For cognitive functions, the only included tDCS study showed improvement on working memory [26]. Depression also exhibited significant improvement following rTMS sessions in one study [23], although its effectiveness appeared diminished four weeks post-treatment [28] or among patients with prolonged depression [29]. Lastly, the assessment of general symptoms using the RPQ did not yield any significant results after rTMS treatment [29]. Interestingly, none of the articles included in this review addressed sleep-related complaints, despite their common occurrence after concussion [39]. A recent study involving healthy student athletes found that bifrontal anodal tDCS appears to augment sleep duration and quality, as demonstrated by significant improvement on the Pittsburgh Sleep Quality Index, Insomnia Severity Index, and Athlete Sleep Screening Questionnaire following only two nights of tDCS treatment [41]. Additionally, a systematic review revealed that techniques such as rTMS and tDCS, targeting different brain areas (i.e., DLPFC, (pre)motor, sensorimotor, auditory, posterior parietal, parieto-occipital, temporal or cerebellar cortex), show promise in enhancing both subjective and objective sleep quality and reduce sleep disturbances in conditions like insomnia, as well as in other conditions in which sleep is deteriorated (e.g., Parkinson's disease, restless leg syndrome, depression, anxiety) [42]. However, these results have to be interpreted with caution as uncontrolled and quasi experimental studies with high risks of bias were included in this review [42]. Nonetheless, investigating such neuromodulation approaches on sleep disturbances deserves further investigation in the context of PPCS.

4.2. What Are the Main Targeted Brain Areas?

Four out of five studies focused on stimulating the left DLPFC. The DLPFC plays a pivotal role in the integration of motor and behavioral functions, as well as executive functions such as planning, working memory, and cognitive flexibilities [43]. This cortical region exhibits extensive connectivity with both cortical and subcortical brain regions such as the orbitofrontal cortex, basal ganglia, thalamus, and associative cortical areas [43,44]. The DLPFC seems further involved in depression as rTMS on DLPFC for treating clinical depression seems to be effective and has been FDA-approved for over 20 years. However, the underlying neural mechanisms of this antidepressant effect is not well understood yet [45]. One recently published neuroimaging study has shown that the orbitofrontal-hippocampal pathway may have a role in rTMS-mediated depression relief [45]. Furthermore, it is also assumed that the DLPFC has a role in inhibiting nociceptive transmission and thereby, high-frequency rTMS on this site can induce analgesic effects for patients suffering from migraines through restoring the motor cortical excitability [46]. The DLPFC therefore appears as a prime candidate to reduce psychological PPCS.

Another region that has been targeted in one study is the left motor cortex (M1). The M1 is primarily recognized for its crucial role in initiating voluntary movements by transmitting signals to lower motor neurons in the spinal cord [47]. Furthermore, NIBS techniques have provided indications that M1 may also contribute to higher cognitive processes, including attention, learning, and motor consolidation [48]. In another study, researchers opted to apply rTMS to M1, given its established effectiveness in alleviating pain associated with central nervous system origins [27]. Consequently, this approach held promise for reducing the intensity and duration of headaches [27]. The results demonstrated a significant reduction in mTBI-HA, suggesting that M1 could indeed be preferably targeted to alleviate mTBI-HA.

4.3. What is the Optimal NIBS Technique for Managing PPCS?

Despite the small number of studies, it is worth highlighting the noticeable disparity in the number of rTMS studies as opposed to tDCS. In recent years, rTMS has gained considerable attention due to its successful applications in a variety of conditions, including depression [49], obsessive compulsive disorder [50] or post-traumatic stress disorder [51]. This could be the reason why most studies utilized this technique. However, tDCS emerges as a valuable option compared to rTMS, as it offers several benefits, including the option for home-based interventions, easy administration, and cost-effectiveness [20]. These factors position tDCS as a more accessible and convenient alternative for the long-term treatment and management of symptoms related to PPCS. We therefore advocate for greater research attention for this approach.

However, neuromodulation, especially tDCS, should not be considered in isolation but rather combined with other therapeutic approaches, such as cognitive/physical rehabilitation, psychological interventions (e.g., cognitive behavioral therapy), or virtual reality [52,53] to enhance its effects overall patient outcomes. In particular, physical rehabilitation is increasingly recognized as a proactive way to prevent the development of PPCS. Indeed, although it is advised to rest in the initial 48 hours after a concussion [11], prolonged physical inactivity beyond this timeframe could hinder the patient's recovery process [54]. Recently, three studies explored the impact of aerobic exercise on athletes with early concussion symptoms (<10 days following sports-related concussion) [55–57]. The findings from these studies demonstrate that aerobic exercise, even after a single session, accelerates concussion recovery safely and reduces the risk of developing PPCS. A recent systematic review also highlighted the evidence supporting the idea that early aerobic treatment shortens recovery time [11]. Aerobic exercise is believed to yield positive psychological effects, potentially reducing the perception of symptoms in patients [58]. Furthermore, concussion pathophysiology involves metabolic and physiological changes, such as disruptions in the autonomic nervous system function and cerebral blood flow control [59]. Interestingly, it is suggested that sub-threshold aerobic exercise may alleviate persistent post-concussive symptoms by influencing the regulation of cerebral blood flow [60]. In addition, participants showed good adherence, tolerance, and no adverse effects. However, it is important to emphasize that the intensity of aerobic exercise may only be heightened in the absence of recurring symptoms [11]. This could be easily integrated with neuromodulation, potentially leading to further reduction in symptoms intensity and better recovery.

4.4. What Is the Existing Evidence in Other TBI Populations?

During the screening process, three tDCS and two rTMS studies were excluded because they did not met our concussion diagnosis inclusion criteria [61], or grouped patients with different levels of TBI [62–65]. Their results are nevertheless noteworthy to mention.

The effects of 10 daily 30-minute sessions of concurrent executive function training and active or sham anodal tDCS (2mA, left DLPFC) were evaluated on patients with mild and moderate TBI [66]. Post-traumatic symptoms and executive functions were significantly improved in both groups compared to baseline; however, the active tDCS group showed a significantly higher improvement in working memory reaction time and a lower connectivity between the executive and salience networks, as assessed by functional magnetic resonance imaging. In another study, the same team evaluated the effect of 10 sessions of 30-minute active or sham anodal tDCS (2mA, DLPFC) combined by computerized executive function training on PPCS in a group of patients with mild and moderate TBI [62]. Depression, anxiety, executive function and complex attention were significantly improved in both groups with no significant between-group differences. Moreover, active stimulation resulted in an increased cerebral blood flow in the right inferior frontal gyrus while sham was associated with reduced cerebral blood flow compared to baseline, as assessed by magnetic resonance imaging. In addition, a previous research reported that multiple sessions of 20-minute anodal tDCS (1.5 mA, anodal at left DLPFC and cathodal at right DLPFC) showed greater attenuation of aggression and an improved quality of life compared to the control group in concussed patients with objectifiable brain injury [61].

In the same study, another group received mindfulness-based stress reduction therapy and showed better improvement in aggression and quality of life compared to the tDCS group. This study was not included in the review because its inclusion criteria (i.e., post-traumatic amnesia >1 hour, skull fracture) were different from the ones used for this scoping review.

The effectiveness of low-frequency rTMS over the right DLPFC for 20 days was assessed in TBI-related depressive symptoms [64]. Neuropsychiatric symptoms were evaluated, and diffusion tensor imaging analysis was used to assess the effect of rTMS on white matter integrity after 20 sessions of rTMS compared to baseline. The authors reported a small (g=0.16) effect size of rTMS on depression scores using Hamilton Rating Scale for Depression, as well as a small (g=0.19) effect size on white matter changes and concluded limited benefits in this population of patients. Despite randomization, all patients in the active group had a mild TBI, while the sham group included both mild and moderate TBI. Treatment-resistant depression was also targeted using 20 sessions of high-frequency bilateral rTMS over the left and right dorsolateral prefrontal cluster based on individualized resting-state network mapping [65]. They included patients with mild and moderate TBI and reported a significantly higher improvement in Montgomery-Åsberg Depression Rating Scale score of the active group. Based on these findings, the current findings are similar to what was found for concussion. In this context, tDCS and rTMS appear beneficial in ameliorating a wide range of clinical manifestations following mild and moderate TBI. However, it remains evident that further research is necessary before their practical implementation in clinical settings can be fully realized.

4.5. Limitations

Several limitations must be considered when interpreting the findings of this review. One notable limitation is the scarcity of human studies specifically investigating the application of such neuromodulation techniques for patients with PPCS as only five studies were included. Furthermore, most studies included exhibited small sample sizes, ranging from 12 to 29 patients enrolled. The use of such limited cohorts may impact the statistical power and generalizability of the results. In addition, there is still subtle controversy and disparity in criteria for defining mTBI/concussion, which resulted in exclusion of some related studies from our review. It is strongly recommended that researchers adhere to united diagnostic criteria for concussion to favour between-studies comparability. The American Congress of Rehabilitation Medicine has recently developed diagnostic criteria for mTBI which has also been used by this review to filter studies on concussion [25].

Another important concern is the lack of standardized protocols for both tDCS and rTMS in the treatment of PPCS. In the studies reviewed, the number of treatment sessions varied from three to thirteen, and the number of pulses in rTMS varied significantly, ranging from 600 to 2000 pulses. This variability in stimulation parameters, such as intensity, duration, frequency, number of sessions, or electrode placement can lead to inconsistent results, making it difficult to reach definitive conclusions.

Moreover, the studies considered in the present review each employed protocols that showed significant variability in terms of time elapsed since the injury (ranging from 28 days up to five years). Consequently, there is a substantial range in both the prolonged nature of the injury and the persistence of symptoms, which likely impacts the potential effectiveness of the applied technique. Furthermore, the existing studies have primarily concentrated on employing neuromodulation as a treatment method after PPCS has already developed. Nonetheless, there is a significant rationale for utilizing neuromodulation as a preventive strategy in the acute stage of the injury. Indeed, this approach could potentially prevent the onset of PPCS, thus facilitating the recovery process. To the best of our knowledge, no studies have assessed the use of neuromodulation in patients with acute symptoms, and this aspect should also be subject to investigation.

Finally, there was a variety regarding outcome measures among the studies included in our review, primarily due to the use of different questionnaires. These discrepancies may interfere with the ability to directly compare the obtained findings. For example, two studies [27,28] utilized a simple numeric rating scale to assess headache intensity, while another study [23] used a more specific and validated questionnaire, the Headache Impact Test-6. Similarly, when measuring depression, two studies have used the Hamilton Rating Scale for Depression [27,28], one has used the Montgomery-Åsberg Depression Rating Scale [29], and another has used the Participant Health Questionnaire-9 [23]. These scales have different severity ranges for depression, potentially leading to different interpretations.

5. Conclusions

In conclusion, neuromodulation could improve some of the symptoms experienced by patients suffering from PPCS. Our review has highlighted several important findings that might guide future research and clinical practice in this field. Firstly, targeting the left DLPFC, due to its critical role in brain functions, appears to be the most promising approach for targeting the diversity of PPCS. Secondly, rTMS is the most frequently studied neuromodulation technique for improving outcome in patients with PPCS. Furthermore, it is increasingly apparent that advocating for the combination of techniques, such as neuromodulation and aerobic exercise, could offer greater benefits and be recommended for patients. While only tDCS and rTMS studies were conducted so far, other perspectives would be to explore alternative neuromodulation techniques, such as testing transcranial alternating current at specific frequencies (e.g., alpha) or employing bottom-up stimulations such as transcutaneous auricular vagus nerve stimulation, which could promote thalamocortical activation.

Finally, it is important to acknowledge that the existing literature in the field of neuromodulation for PPCS is still limited. The number of studies available is scarce, and the sample sizes in these studies remain relatively small. In addition, the lack of standardized protocols and questionnaires across studies prevents direct comparisons and definitive conclusions. In summary, while the application of neuromodulation techniques, specifically rTMS over the left DLPFC, shows promise in addressing PPCS symptoms, there is a need for more comprehensive research. Larger-scale studies and standardized protocols seem essential, specifically protocols targeting distinct symptoms or integrating neuromodulation with other strategies, in order to enhance treatment outcomes for individuals with PPCS.

Author Contributions: Conceptualization, A.T. and M.K.; methodology, M.K., A.T.; interpretation, M.H.K, M.L, A.T, N.L; writing—original draft preparation, M.K & M.L; writing—review and editing, M.L, G.M., J.F.K., A.T. & N.L.; supervision, A.T. & N.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Acknowledgments: The study was further supported by the University and University Hospital of Liège, the BIAL Foundation, the Belgian National Funds for Scientific Research (FRS-FNRS), the FNRS PDR project (T.0134.21), the ERA-Net FLAG-ERA JTC2021 project ModelDXConsciousness (Human Brain Project Partnering Project), the fund Generet, the King Baudouin Foundation, the Télévie Foundation, the European Space Agency (ESA) and the Belgian Federal Science Policy Office (BELSPO) in the framework of the PRODEX Programme, the Public Utility Foundation 'Université Européenne du Travail', "Fondazione Europea di Ricerca Biomedica", the BIAL Foundation, the Mind Science Foundation, the European Commission, the Fondation Leon Fredericq, the Mind-Care foundation, the National Natural Science Foundation of China (Joint Research Project 81471100) and the European Foundation of Biomedical Research FERB Onlus, the Horizon 2020 MSCA – Research and Innovation Staff Exchange DoC-Box project (HORIZON-MSCA-2022-SE-01-01; 101131344).

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Research question : ("Acquired brain injury" OR "Traumatic brain injury" OR "Brain injury" OR "Head injury" OR "Craniocerebral trauma" OR "PPCS" OR "persistent post concussive syndrome" OR "persistent post concussion syndrome" OR "concussion" OR "post concussion symptoms" OR "Brain Concussion" OR "Sports Related Concussion") AND ("NIBS" OR "non-invasive brain stimulation" OR "brain stimulation" OR "neuromodulation" OR "Transcranial magnetic stimulation" OR "Theta-burst stimulation" OR "Transcranial Electrical Stimulation" OR "Transcranial direct-current stimulation" OR "Transcranial Alternating current stimulation").

References

1. Dewan, M.C.; Rattani, A.; Gupta, S.; Baticulon, R.E.; Hung, Y.-C.; Punchak, M.; Agrawal, A.; Adeleye, A.O.; Shrime, M.G.; Rubiano, A.M.; et al. Estimating the Global Incidence of Traumatic Brain Injury. *J. Neurosurg.* **2018**, 1–18, doi:10.3171/2017.10.JNS17352.
2. Woodrow, R.E.; Winzeck, S.; Luppi, A.I.; Kelleher-Unger, I.R.; Spindler, L.R.B.; Wilson, J.T.L.; Newcombe, V.F.J.; Coles, J.P.; CENTER-TBI MRI Substudy Participants and Investigators; Amrein, K.; et al. Acute Thalamic Connectivity Precedes Chronic Post-Concussive Symptoms in Mild Traumatic Brain Injury. *Brain* **2023**, awad056, doi:10.1093/brain/awad056.
3. Giza, C.C.; Hovda, D.A. The New Neurometabolic Cascade of Concussion. *Neurosurgery* **2014**, *75*, S24–S33, doi:10.1227/NEU.0000000000000505.
4. Hiploylee, C.; Dufort, P.A.; Davis, H.S.; Wennberg, R.A.; Tartaglia, M.C.; Mikulis, D.; Hazrati, L.N.; Tator, C.H. Longitudinal Study of Postconcussion Syndrome: Not Everyone Recovers. *J. Neurotrauma* **2017**, *34*, 1511–1523, doi:10.1089/neu.2016.4677.
5. Tator, C., H.; Davis, H., S.; Dufort, P., A.; Tartaglia, M.C.; Davis, K., D.; Ebraheem, A.; Hiploylee, C. Postconcussion Syndrome: Demographics and Predictors in 221 Patients. *J. Neurosurg.* **2016**, *125*, 1204, doi:10.3171/2015.7.JNS151335.
6. Mayer, A.R.; Quinn, D.K.; Master, C.L. The Spectrum of Mild Traumatic Brain Injury: A Review. *Neurology* **2017**, *89*, 623–632, doi:10.1212/WNL.0000000000004214.
7. Audrit, H.; Beauchamp, M.H.; Tinawi, S.; Laguë-Beauvais, M.; de Guise, E. Development and Description of SAAM Intervention: A Brief, Multidimensional and Psycho-Educational Intervention for Adults with Mild Traumatic Brain Injury. *Ann. Phys. Rehabil. Med.* **2021**, *64*, doi:10.1016/j.rehab.2020.07.007.
8. Patricios, J.S.; Schneider, K.J.; Dvorak, J.; Ahmed, O.H.; Blauwet, C.; Cantu, R.C.; Davis, G.A.; Echemendia, R.J.; Makdissi, M.; McNamee, M.; et al. Consensus Statement on Concussion in Sport: The 6th International Conference on Concussion in Sport–Amsterdam, October 2022. *Br. J. Sports Med.* **2023**, *57*, 695–711, doi:10.1136/bjsports-2023-106898.
9. Putukian, M.; Purcell, L.; Schneider, K.J.; Black, A.M.; Burma, J.S.; Chandran, A.; Boltz, A.; Master, C.L.; Register-Mihalik, J.K.; Anderson, V.; et al. Clinical Recovery from Concussion–Return to School and Sport: A Systematic Review and Meta-Analysis. *Br. J. Sports Med.* **2023**, *57*, 798–809, doi:10.1136/bjsports-2022-106682.
10. Schneider, K.J.; Critchley, M.L.; Anderson, V.; Davis, G.A.; Debert, C.T.; Feddermann-Demont, N.; Gagnon, I.; Guskiewicz, K.M.; Hayden, K.A.; Herring, S.; et al. Targeted Interventions and Their Effect on Recovery in Children, Adolescents and Adults Who Have Sustained a Sport-Related Concussion: A Systematic Review. *Br. J. Sports Med.* **2023**, *57*, 771–779, doi:10.1136/bjsports-2022-106685.
11. Leddy, J.J.; Burma, J.S.; Toomey, C.M.; Hayden, A.; Davis, G.A.; Babl, F.E.; Gagnon, I.; Giza, C.C.; Kurowski, B.G.; Silverberg, N.D.; et al. Rest and Exercise Early after Sport-Related Concussion: A Systematic Review and Meta-Analysis. *Br. J. Sports Med.* **2023**, *57*, 762–770, doi:10.1136/bjsports-2022-106676.

12. Martens, G.; Khosravi, M.H.; Lejeune, N.; Kaux, J.-F.; Thibaut, A. Gender Specificities in Sleep Disturbances Following Mild Traumatic Brain Injury: A Preliminary Study. *Brain Sci.* **2023**, *13*, 323, doi:10.3390/brainsci13020323.
13. Quatman-Yates, C.C.; Hunter-Giordano, A.; Shimamura, K.K.; Landel, R.; Alsalaheen, B.A.; Hanke, T.A.; McCulloch, K.L.; Altman, R.D.; Beattie, P.; Berz, K.E.; et al. Physical Therapy Evaluation and Treatment After Concussion/Mild Traumatic Brain Injury: Clinical Practice Guidelines Linked to the International Classification of Functioning, Disability and Health From the Academy of Orthopaedic Physical Therapy of the American Physical Therapy Association. *J. Orthop. Sports Phys. Ther.* **2020**, *50*, CPG1–CPG73, doi:10.2519/jospt.2020.0301.
14. Kesikburun, S. Non-Invasive Brain Stimulation in Rehabilitation. *Turk. J. Phys. Med. Rehabil.* **2022**, *68*, 1–8, doi:10.5606/tftrd.2022.10608.
15. Mortaheb, S.; Filippini, M.M.; Kaux, J.F.; Annen, J.; Lejeune, N.; Martens, G.; Calderón, M.A.F.; Laureys, S.; Thibaut, A. Neurophysiological Biomarkers of Persistent Post-Concussive Symptoms: A Scoping Review. *Front. Neurol.* **2021**, *12*, doi:10.3389/fneur.2021.687197.
16. Zhou, Y.; Milham, M.P.; Lui, Y.W.; Miles, L.; Reaume, J.; Sodickson, D.K.; Grossman, R.I.; Ge, Y. Default-Mode Network Disruption in Mild Traumatic Brain Injury. *Radiology* **2012**, *265*, 882–892, doi:10.1148/radiol.12120748.
17. Sours, C.; Kinnison, J.; Padmala, S.; Gullapalli, R.P.; Pessoa, L. Altered Segregation between Task-Positive and Task-Negative Regions in Mild Traumatic Brain Injury. *Brain Imaging Behav.* **2018**, *12*, 697–709, doi:10.1007/s11682-017-9724-9.
18. Fox, M.D.; Snyder, A.Z.; Vincent, J.L.; Corbetta, M.; Van Essen, D.C.; Raichle, M.E. The Human Brain Is Intrinsically Organized into Dynamic, Anticorrelated Functional Networks. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 9673–9678, doi:10.1073/pnas.0504136102.
19. Nitsche, M.A.; Paulus, W. Excitability Changes Induced in the Human Motor Cortex by Weak Transcranial Direct Current Stimulation. *J. Physiol.* **2000**, *527*, 633–639, doi:10.1111/j.1469-7793.2000.t01-1-00633.x.
20. Santos Ferreira, I.; Teixeira Costa, B.; Lima Ramos, C.; Lucena, P.; Thibaut, A.; Fregni, F. Searching for the Optimal tDCS Target for Motor Rehabilitation. *J. NeuroEngineering Rehabil.* **2019**, *16*, 90, doi:10.1186/s12984-019-0561-5.
21. Lefaucheur, J.-P.; Antal, A.; Ayache, S.S.; Benninger, D.H.; Brunelin, J.; Cogiamanian, F.; Cotelli, M.; De Ridder, D.; Ferrucci, R.; Langguth, B.; et al. Evidence-Based Guidelines on the Therapeutic Use of Transcranial Direct Current Stimulation (tDCS). *Clin. Neurophysiol.* **2017**, *128*, 56–92, doi:10.1016/j.clinph.2016.10.087.
22. du Plessis, S.; Oni, I.K.; Lapointe, A.P.; Campbell, C.; Dunn, J.F.; Debert, C.T. Treatment of Persistent Postconcussion Syndrome With Repetitive Transcranial Magnetic Stimulation Using Functional Near-Infrared Spectroscopy as a Biomarker of Response: Protocol for a Randomized Controlled Clinical Trial. *JMIR Res. Protoc.* **2022**, *11*, e31308, doi:10.2196/31308.
23. Stilling, J.; Paxman, E.; Mercier, L.; Gan, L.S.; Wang, M.; Amoozegar, F.; Dukelow, S.P.; Monchi, O.; Debert, C. Treatment of Persistent Post-Traumatic Headache and Post-Concussion Symptoms Using Repetitive Transcranial Magnetic Stimulation: A Pilot, Double-Blind, Randomized Controlled Trial. *J. Neurotrauma* **2020**, *37*, 312–323, doi:10.1089/neu.2019.6692.
24. Study Quality Assessment Tools | NHLBI, NIH Available online: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (accessed on 2 February 2024).
25. 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.; et al. The American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury. *Arch. Phys. Med. Rehabil.* **2023**, *104*, 1343–1355, doi:10.1016/j.apmr.2023.03.036.

26. Quinn De Launay, K.; Cheung, S.T.; Riggs, L.; Reed, N.; Beal, D.S. The Effect of Transcranial Direct Current Stimulation on Cognitive Performance in Youth with Persistent Cognitive Symptoms Following Concussion: A Controlled Pilot Study. *Brain Inj.* **2022**, *36*, 39–51, doi:10.1080/02699052.2022.2034179.
27. Leung, A.; Shukla, S.; Fallah, A.; Song, D.; Lin, L.; Golshan, S.; Tsai, A.; Jak, A.; Polston, G.; Lee, R. Repetitive Transcranial Magnetic Stimulation in Managing Mild Traumatic Brain Injury-Related Headaches. *Neuromodulation J. Int. Neuromodulation Soc.* **2016**, *19*, 133–141, doi:10.1111/ner.12364.
28. Leung, A.; Metzger-Smith, V.; He, Y.; Cordero, J.; Ehlert, B.; Song, D.; Lin, L.; Shahrokh, G.; Tsai, A.; Vaninetti, M.; et al. Left Dorsolateral Prefrontal Cortex rTMS in Alleviating MTBI Related Headaches and Depressive Symptoms. *Neuromodulation J. Int. Neuromodulation Soc.* **2018**, *21*, 390–401, doi:10.1111/ner.12615.
29. Moussavi, Z.; Suleiman, A.; Rutherford, G.; Ranjbar Pouya, O.; Dastgheib, Z.; Zhang, W.; Salter, J.; Wang, X.; Mansouri, B.; Lithgow, B. A Pilot Randomised Double-Blind Study of the Tolerability and Efficacy of Repetitive Transcranial Magnetic Stimulation on Persistent Post-Concussion Syndrome. *Sci. Rep.* **2019**, *9*, 5498, doi:10.1038/s41598-019-41923-6.
30. Cunningham, J.; Broglio, S.P.; O'Grady, M.; Wilson, F. History of Sport-Related Concussion and Long-Term Clinical Cognitive Health Outcomes in Retired Athletes: A Systematic Review. *J. Athl. Train.* **2020**, *55*, 132–158, doi:10.4085/1062-6050-297-18.
31. McInnes, K.; Friesen, C.L.; MacKenzie, D.E.; Westwood, D.A.; Boe, S.G. Mild Traumatic Brain Injury (mTBI) and Chronic Cognitive Impairment: A Scoping Review. *PLoS ONE* **2017**, *12*, e0174847, doi:10.1371/journal.pone.0174847.
32. Bigler, E.D. Neuropsychology and Clinical Neuroscience of Persistent Post-Concussive Syndrome. *J. Int. Neuropsychol. Soc. JINS* **2008**, *14*, 1–22, doi:10.1017/S135561770808017X.
33. Arnold, M. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edition. *Cephalalgia Int. J. Headache* **2018**, *38*, 1–211, doi:10.1177/0333102417738202.
34. Capi, M.; Pomes, L.M.; Andolina, G.; Curto, M.; Martelletti, P.; Lionetto, L. Persistent Post-Traumatic Headache and Migraine: Pre-Clinical Comparisons. *Int. J. Environ. Res. Public. Health* **2020**, *17*, 2585, doi:10.3390/ijerph17072585.
35. *National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on Health Sciences Policy; Committee on Accelerating Progress in Traumatic Brain Injury Research and Care, Matney, C., Bowman, K., & Berwick, D. (Eds.). Traumatic Brain Injury: A Roadmap for Accelerating Progress. National Academies Press (US)* ***2022****. doi:10.17226/2539*436. Silverberg, N.D.; Mikolić, A. Management of Psychological Complications Following Mild Traumatic Brain Injury. *Curr. Neurol. Neurosci. Rep.* **2023**, *23*, 49–58, doi:10.1007/s11910-023-01251-9.
37. Kreitzer, N.; Ancona, R.; McCullumsmith, C.; Kurowski, B.G.; Foreman, B.; Ngwenya, L.B.; Adeoye, O. The Effect of Antidepressants on Depression After Traumatic Brain Injury: A Meta-Analysis. *J. Head Trauma Rehabil.* **2019**, *34*, E47, doi:10.1097/HTR.0000000000000439.
38. Chen, C.-L.; Lin, M.-Y.; Huda, M.H.; Tsai, P.-S. Effects of Cognitive Behavioral Therapy for Adults with Post-Concussion Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Psychosom. Res.* **2020**, *136*, 110190, doi:10.1016/j.jpsychores.2020.110190.
39. McCrory, P., Meeuwisse, W., Dvořák, J., Aubry, M., Bailes, J., Broglio, S., Cantu, R. C., Cassidy, D., Echemendia, R. J., Castellani, R. J., Davis, G. A., Ellenbogen, R., Emery, C., Engebretsen, L., Feddermann-Demont, N., Giza, C. C., Guskiewicz, K. M., Herring, S., Iverson, G. L., Johnston, K. M., … Vos, P. E. Consensus statement on concussion

in sport-the 5th international conference on concussion in sport held in Berlin, October 2016. *British journal of sports medicine*, **2017**, *51*(11), 838–847, doi: 10.1136/bjsports-2017-097699

40. King, N.S.; Crawford, S.; Wenden, F.J.; Moss, N.E.G.; Wade, D.T. The Rivermead Post Concussion Symptoms Questionnaire: A Measure of Symptoms Commonly Experienced after Head Injury and Its Reliability. *J. Neurol.* **1995**, *242*, 587–592, doi:10.1007/BF00868811.
41. Charest, J., Marois, A., & Bastien, C. H. Can a tDCS treatment enhance subjective and objective sleep among student-athletes?. *J of ACH*, **2021**, *69*(4), 378–389, doi: 10.1080/07448481.2019.1679152
42. Herrero Babiloni, A.; Bellemare, A.; Beetz, G.; Vinet, S.-A.; Martel, M.O.; Lavigne, G.J.; De Beaumont, L. The Effects of Non-Invasive Brain Stimulation on Sleep Disturbances among Different Neurological and Neuropsychiatric Conditions: A Systematic Review. *Sleep Med. Rev.* **2021**, *55*, 101381, doi:10.1016/j.smrv.2020.101381.
43. Thibaut, A.; Schiff, N.D. New Therapeutic Options for the Treatment of Patients with Disorders of Consciousness: The Field of Neuromodulation. In *Coma and Disorders of Consciousness*; Schnakers, C., Laureys, S., Eds.; Springer International Publishing: Cham, **2018**; pp. 207–223 ISBN 978-3-319-55964-3.
44. D'Esposito, M.; Detre, J.A.; Alsop, D.C.; Shin, R.K.; Atlas, S.; Grossman, M. The Neural Basis of the Central Executive System of Working Memory. *Nature* **1995**, *378*, 279–281, doi:10.1038/378279a0.
45. Han, S.; Li, X.-X.; Wei, S.; Zhao, D.; Ding, J.; Xu, Y.; Yu, C.; Chen, Z.; Zhou, D.-S.; Yuan, T.-F. Orbitofrontal Cortex-Hippocampus Potentiation Mediates Relief for Depression: A Randomized Double-Blind Trial and TMS-EEG Study. *Cell Rep. Med.* **2023**, *4*, 101060, doi:10.1016/j.xcrm.2023.101060.
46. Safiai, N.I.M.; Mohamad, N.A.; Basri, H.; Mat, L.N.I.; Hoo, F.K.; Rashid, A.M.A.; Khan, A.H.K.Y.; Loh, W.C.; Baharin, J.; Fernandez, A.; et al. High-Frequency Repetitive Transcranial Magnetic Stimulation at Dorsolateral Prefrontal Cortex for Migraine Prevention: A Protocol for a Systematic Review of Controlled Trials. *PLOS ONE* **2021**, *16*, e0251528, doi:10.1371/journal.pone.0251528.
47. Pearson, K. Motor Systems. *Curr. Opin. Neurobiol.* **2000**, *10*, 649–654, doi:10.1016/s0959-4388(00)00130-6.
48. Bhattacharjee, S.; Kashyap, R.; Abualait, T.; Annabel Chen, S.-H.; Yoo, W.-K.; Bashir, S. The Role of Primary Motor Cortex: More Than Movement Execution. *J. Mot. Behav.* **2021**, *53*, 258–274, doi:10.1080/00222895.2020.1738992.
49. Madore, M.R.; Kozel, F.A.; Williams, L.M.; Green, L.C.; George, M.S.; Holtzheimer, P.E.; Yesavage, J.A.; Philip, N.S. Prefrontal Transcranial Magnetic Stimulation for Depression in US Military Veterans - A Naturalistic Cohort Study in the Veterans Health Administration. *J. Affect. Disord.* **2022**, *297*, 671–678, doi:10.1016/j.jad.2021.10.025.
50. Carmi, L.; Tendler, A.; Bystritsky, A.; Hollander, E.; Blumberger, D.M.; Daskalakis, J.; Ward, H.; Lapidus, K.; Goodman, W.; Casuto, L.; et al. Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Prospective Multicenter Randomized Double-Blind Placebo-Controlled Trial. *Am. J. Psychiatry* **2019**, *176*, 931–938, doi:10.1176/appi.ajp.2019.18101180.
51. Philip, N.S.; Ridout, S.J.; Albright, S.E.; Sanchez, G.; Carpenter, L.L. 5-Hz Transcranial Magnetic Stimulation for Comorbid Posttraumatic Stress Disorder and Major Depression. *J. Trauma. Stress* **2016**, *29*, 93–96, doi:10.1002/jts.22065.
52. Martin, D.M.; Liu, R.; Alonzo, A.; Green, M.; Loo, C.K. Use of Transcranial Direct Current Stimulation (tDCS) to Enhance Cognitive Training: Effect of Timing of Stimulation. *Exp. Brain Res.* **2014**, *232*, 3345–3351, doi:10.1007/s00221-014-4022-x.
53. Yao, X.; Cui, L.; Wang, J.; Feng, W.; Bao, Y.; Xie, Q. Effects of Transcranial Direct Current Stimulation with Virtual Reality on Upper Limb Function in Patients with Ischemic Stroke: A Randomized Controlled Trial. *J. Neuroengineering Rehabil.* **2020**, *17*, 73, doi:10.1186/s12984-020-00699-x.

54. Silverberg, N.D.; Otamendi, T. Advice to Rest for More Than 2 Days After Mild Traumatic Brain Injury Is Associated With Delayed Return to Productivity: A Case-Control Study. *Front. Neurol.* **2019**, *10*, 362, doi:10.3389/fneur.2019.00362.
55. Leddy, J.J.; Master, C.L.; Mannix, R.; Wiebe, D.J.; Grady, M.F.; Meehan, W.P.; Storey, E.P.; Vernau, B.T.; Brown, N.J.; Hunt, D.; et al. Early Targeted Heart Rate Aerobic Exercise versus Placebo Stretching for Sport-Related Concussion in Adolescents: A Randomised Controlled Trial. *Lancet Child Adolesc. Health* **2021**, *5*, 792–799, doi:10.1016/S2352-4642(21)00267-4.
56. Worts, P.R.; Mason, J.R.; Burkhart, S.O.; Sanchez-Gonzalez, M.A.; Kim, J.-S. The Acute, Systemic Effects of Aerobic Exercise in Recently Concussed Adolescent Student-Athletes: Preliminary Findings. *Eur. J. Appl. Physiol.* **2022**, *122*, 1441–1457, doi:10.1007/s00421-022-04932-4.
57. Hutchison, M.G.; Di Battista, A.P.; Lawrence, D.W.; Pyndiura, K.; Corallo, D.; Richards, D. Randomized Controlled Trial of Early Aerobic Exercise Following Sport-Related Concussion: Progressive Percentage of Age-Predicted Maximal Heart Rate versus Usual Care. *PLOS ONE* **2022**, *17*, e0276336, doi:10.1371/journal.pone.0276336.
58. Gondoh, Y.; Sensui, H.; Kinomura, S.; Fukuda, H.; Fujimoto, T.; Masud, M.; Nagamatsu, T.; Tamaki, H.; Takekura, H. Effects of Aerobic Exercise Training on Brain Structure and Psychological Well-Being in Young Adults. *J. Sports Med. Phys. Fitness* **2009**, *49*, 129–135.
59. Leddy, J.J.; Kozlowski, K.; Fung, M.; Pendergast, D.R.; Willer, B. Regulatory and Autoregulatory Physiological Dysfunction as a Primary Characteristic of Post Concussion Syndrome: Implications for Treatment. *NeuroRehabilitation* **2007**, *22*, 199–205.
60. Clausen, M.; Pendergast, D.R.; Willer, B.; Leddy, J. Cerebral Blood Flow During Treadmill Exercise Is a Marker of Physiological Postconcussion Syndrome in Female Athletes. *J. Head Trauma Rehabil.* **2016**, *31*, 215–224, doi:10.1097/HTR.0000000000000145.
61. Shirvani, S.; Davoudi, M.; Shirvani, M.; Koleini, P.; Hojat Panah, S.; Shoshtari, F.; Omidi, A. 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. Psychiatry* **2021**, *20*, 33, doi:10.1186/s12991-021-00355-1.
62. Quinn, D.K.; Upston, J.; Jones, T.; Brandt, E.; Story-Remer, J.; Fratzke, V.; Wilson, J.K.; Rieger, R.; Hunter, M.A.; Gill, D.; et al. Cerebral Perfusion Effects of Cognitive Training and Transcranial Direct Current Stimulation in Mild-Moderate TBI. *Front. Neurol.* **2020**, *11*, 545174, doi:10.3389/fneur.2020.545174.
63. Quinn, D.K.; Story-Remer, J.; Brandt, E.; Fratzke, V.; Rieger, R.; Wilson, J.K.; Gill, D.; Mertens, N.; Hunter, M.; Upston, J.; et al. Transcranial Direct Current Stimulation Modulates Working Memory and Prefrontal-Insula Connectivity after Mild-Moderate Traumatic Brain Injury. *Front. Hum. Neurosci.* **2022**, *16*, 1026639, doi:10.3389/fnhum.2022.1026639.
64. Rao, V.; Bechtold, K.; McCann, U.; Roy, D.; Peters, M.; Vaishnavi, S.; Yousem, D.; Mori, S.; Yan, H.; Leoutsakos, J.; et al. Low-Frequency Right Repetitive Transcranial Magnetic Stimulation for the Treatment of Depression After Traumatic Brain Injury: A Randomized Sham-Controlled Pilot Study. *J. Neuropsychiatry Clin. Neurosci.* **2019**, *31*, 306–318, doi:10.1176/appi.neuropsych.17110338.
65. Siddiqi, S.H.; Trapp, N.T.; Hacker, C.D.; Laumann, T.O.; Kandala, S.; Hong, X.; Trillo, L.; Shahim, P.; Leuthardt, E.C.; Carter, A.R.; et al. Repetitive Transcranial Magnetic Stimulation with Resting-State Network Targeting for Treatment-Resistant Depression in Traumatic Brain Injury: A Randomized, Controlled, Double-Blinded Pilot Study. *J. Neurotrauma* **2019**, *36*, 1361–1374, doi:10.1089/neu.2018.5889.

66. Quinn, D.K.; Story-Remer, J.; Brandt, E.; Fratzke, V.; Rieger, R.; Wilson, J.K.; Gill, D.; Mertens, N.; Hunter, M.; Upston, J.; et al. Transcranial Direct Current Stimulation Modulates Working Memory and Prefrontal-Insula Connectivity after Mild-Moderate Traumatic Brain Injury. *Front. Hum. Neurosci.* **2022**, *16*, doi:10.3389/fnhum.2022.1026639.