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Minute Pulsed Electromagnetic Neurostimulation for Mixed Trauma Syndromes

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Abstract

Research regarding noninvasive brain stimulation technologies for the treatment of mild traumatic brain injury (mTBI), posttraumatic stress disorder (PTSD), and mixed (mTBI/PTSD) trauma syndromes has been increasing exponentially. Technologies with the greatest potential thus far include repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and cranial electrotherapy stimulation (CES). The nature and some of the controversies distinguishing mTBI, PTSD, and mTBI/PTSD are reviewed along with evidence for shared underlying mechanisms. An overview of treatment applications for rTMS, tDCS, and CES are also reviewed. A novel variant of a minute pulsed electromagnetic stimulation technology linked to ongoing electroencephalograph monitoring known as the Flexyx Neurotherapy System is introduced with an overview of the technology and technique, as well as a summary of supportive data to date that explores potential applications for amelioration of these syndromes.

Keywords

neurostimulation, brain stimulation, mild traumatic brain injury, posttraumatic stress disorder, neurotherapy, neurofeedback

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Distinguishing symptoms of mild traumatic brain injury (mTBI), posttraumatic stress disorder (PTSD), and mixed mTBI/PTSD syndromes is a challenging and controversial enterprise.[1] The therapeutic implications, however, are of potentially great significance. These conditions are often difficult to treat and sometimes refractory. Accordingly, this state of affairs has stimulated a search for novel conceptualizations and potentially novel treatments. External brain stimulation technologies have increasingly suggested utility for developing and adapting protocols for treatment.

In this regard, emerging technologies that involve noninvasive brain stimulation procedures have demonstrated some promise. The most studied of these include repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and cranial electrotherapy stimulation (CES). The scientific and clinical literature on these techniques has been growing at an exponential pace, but these procedures have not gained widespread acceptance and fall within the domain of complementary and alternative medicine; however, external brain stimulation techniques have great potential for inclusion into a more integrative framework. In addition, recently, a much lower energy alternative has received some attention. This involves a minutely pulsed electromagnetic variant of neurofeedback/neurotherapy (NT), and it may offer some advantages for treatment. The purpose of the present article is to provide an overview of this novel form of NT and suggest how it may also contribute to the integrative treatment of complex traumatic syndromes.

Herein, we briefly summarize the diagnostic indicators of mTBI, PTSD, and mTBI/PTSD, highlight their overlap in symptomatology and possible underlying mechanisms, and explore the potential application of NT for their amelioration.

Mild Traumatic Brain Injury

There is no universally accepted definition of mTBI. On the other hand, a number of features are common to existing definitions, and are generally noted—traumatically induced,

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external, biomechanical injury to the brain that results in some alteration of consciousness; loss of consciousness, if present, no longer than 30 minutes; Glasgow Coma Scale, if available, score of 13 to 15 after 30 minutes postinjury; and posttraumatic amnesia lasting less than 24 hours.[2-4] In addition, mTBI typically refers more to an event than any specific symptom presentation. The effect of the injury may include immediate micro damage to neural or cerebrovascular structures and set in motion a cascade of metabolic and neural alterations that yield different symptom presentations at different times postinjury.[5] Many of the typical symptoms experienced over time include various so-called postconcussive symptoms (PCS), which generally fall within 3 broad domains: somatic (eg, headaches being the most common; tendency to become easily fatigued; dizziness; light and noise sensitivity), psychological (eg, irritability, anxiety, depression, emotional lability, apathy), and cognitive (eg, concentration and memory impairments, deficits in information processing speed and reaction time)[6]. However, it is important to keep in mind that PCS are not unique to mTBI and are shared with an array of neuropsychiatric disorders as well, including PTSD.[1,7] This point has become particularly salient given the return of many veterans of the Afghanistan and Iraq wars (Operation Enduring Freedom or OEF; Operation Iraqi Freedom or OIF; Operation New Dawn or OND) who report traumatic impact and blast injuries that appear to meet criteria for both mTBI and PTSD (eg, Hoge, et al., 2008).[8]

Posttraumatic Stress Disorder

The diagnosis of PTSD requires the persistence of a set of clusters of symptoms that have their onset following the experience of a traumatic event (whether experiencing it directly, witnessing it occur to others, learning about it occurring to close family members or friends, or other extreme exposure to aspects of traumatic events). In addition, symptoms from each of these clusters must be present: intrusive reexperiencing (eg, distressing memories, nightmares, etc); persistent efforts to avoid re-experiencing of internal or external reminders, thoughts, or feelings about the trauma; any of a host of negative cognitions or mood associated with the trauma (eg, substantially increased frequency of a wide variety of negative emotional states, constriction of activity and social withdrawal); and hyperarousal or marked reactivity associated with the trauma (eg, irritability/anger, concentration problems, sleep disturbance). In addition, some individuals experience dissociative symptoms, including depersonalization or derealization.[9,10]

Mild Traumatic Brain Injury/Posttraumatic Stress Disorder

The comorbidity of mTBI and PTSD has long been recognized, but issues involved in mixed trauma syndromes have advanced more to the forefront of consideration due to the complex presentations of many OEF/OIF/OND veterans. Indeed, mTBI has become the "signature wound" of the Afghanistan and Iraq wars.[11] Of the approximately 2.5 million people who present to emergency rooms in the United States on an annual basis with TBI, the majority are classified as mTBI.[12,13] PTSD in the community is estimated to occur at about 7% and varies considerably by social background, with women being disproportionately represented, and with higher rates for those exposed to community violence.[10,14,15] Prevalence rates for individuals in the military or recent war veterans are even higher, with estimates up to 23% and 44%/for mTBI and PTSD, respectively.[11,16] For example, in one study, 33.8% of military personnel returning from service in OEF/OIF identified as having TBI also screened positive for PTSD.[11] Another report of US Army infantry soldiers found 15% of soldiers reported a deployment-related injury with loss of consciousness (LOC) or altered mental state; 43.9% with TBI reporting actual LOC screened positive for PTSD; and of those reporting altered mental status without actual LOC, 27.3% also screened positive for PTSD.[8] In logistic regression analyses, mTBI, particularly presentations associated with LOC, was predictive of PTSD as well as other somatic and PCS. On the other hand, except for headache, mTBI was no longer significantly associated with PCS after adjustment for PTSD and depression. These prevalence rates and similar analyses have invited controversy as to the role of mTBI in contributing to PTSD and vice versa. Increasing evidence suggests that experiencing mTBI can increase risk for PTSD, but also that some impairments seen with mTBI may be largely attributable to stress reactions after mTBI. Accordingly, it may be unwise to immediately attribute the presence of PCS to neurological insult.[1]

In addition, it is important to keep in mind that mTBI, PTSD, and mixed mTBI/PTSD presentations occur in civilians as well as military personnel.[17] The nature of the traumas sustained may be different (eg, single motor vehicle accident, one or more assaults, athletic injuries, single or multiple impact or blast injuries, etc), which may have different implications for neuropathological changes set in motion as sequelae, further complicating an understanding of the mTBI/PTSD overlap.[5] Also, as noted above, the nature of the comorbidity has become controversial due to the shared symptomatology of the 2 conditions, leading some to question the extent to which the triggering incidents actually incite one or the other or both.[1,8] As is readily apparent, there is substantial potential overlap of features associated with sequelae of mTBI and PTSD.[17] Also, dissociative states may seem to occur in both, as mTBI often results in an alteration of consciousness that has a dissociative quality, and a sizeable number of individuals with PTSD experience dissociation. Matters are complicated, as well, by the extensive co-morbidity with other complaints, including sleep disturbances, chronic pain, substance abuse, and preexisting psychiatric vulnerabilities.[10,16,18,19] Regardless, the co-occurrence of mTBI and PTSD (or other conditions) can exacerbate symptoms.[20,21]

Overlapping Mechanisms

Recently, models have been suggested to begin to identify overlapping mechanisms potentially shared by mTBI and PTSD. For example, the following neural regions and networks have been implicated from neuroimaging studies: the prefrontal cortex, frontal default mode network, posterior default mode network, striatum, hippocampus, amygdala, thalamus, corpus callosum, and salience network.[22] The interactions among these and extent and nature of their functional connectivity at rest or during activation are of interest.[23] Furthermore, it has been proposed that TBI-induced damage to networks that regulate the autonomic nervous system may increase vulnerability to PTSD,[24] and that hypothalamic-pituitary-adrenal axis dysfunction may characterize both.[25,26] Also, some common biochemical defect linkages in the brain (eg, due to oxidative stress, inflammation, excitotoxicity with glutamate release) may exist among them.[27] Hence, in addition to symptom overlap, there is potential neural overlap in systems that contribute to the mix of symptoms in individual cases.[22] This provides a rationale for examining the potential efficacy of treatments designed for mTBI and PTSD in addressing aspects of the mechanisms that may be shared by both. On the other hand, there is some potential neurobiological distinctiveness across mTBI, PTSD, and mTBI/PTSD, which may then lead to a need to better identify distinctive as well as similar interventions.[28]

External Brain Stimulation Technologies

The noninvasive brain stimulation technologies that have been suggested the most for the treatment of mTBI and PTSD include rTMS, tDCS, and CES.

Repetitive Transcranial Magnetic Stimulation

rTMS involves the placement of coils on the scalp that generate magnetic fields, which induce electrical current in the brain. Depending on the nature of the stimulation parameters (ie, coil shape, frequency, intensity, number of stimuli, number of sessions, etc) cortical (and subcortical) excitability or inhibition is induced.[29,30] Of the technologies discussed in this article, rTMS has received the greatest amount of attention thus far. An extensive array of neurological and psychiatric conditions has been explored, along with varying degrees of rigor in research (eg, case studies/series, clinical trials), with results suggesting potential efficacy to varying degrees of confidence.[29] rTMS has been approved by the US Food and Drug Administration for the treatment of refractory depression, and there is an emerging consensus that it is efficacious for some individuals with PTSD.[22,29,31-33] Treatment outcome studies of rTMS with individuals with TBI are less well represented in the literature, but also suggest potential efficacy for specifically targeted symptoms often seen in brain injuries, including motor, cognitive, and emotional/mood disturbances.[34-40]

Transcranial Direct Current Stimulation

tDCS involves the placement of 2 electrodes, typically one contralateral to the other on the scalp (although other placements for the secondary electrode are sometimes used). An electrical current is streamed from one electrode to the other. Polarity of the current appears to be significantly associated with the direction of effects.[41] Anodal or cathodal stimulation may be applied, yielding excitability or decreasing (over) activation in an area of the brain via processes of depolarization and hyperpolarization.[42] Local and distant plastic effects on the brain apparently occur, but the neurobiology is very incompletely understood at this stage.[43] Consecutive sessions may result in long-lasting changes in synaptic and nonsynaptic properties.[40]

The appeal of tDCS, in part, has to do with the lower cost and greater portability, relative to rTMS, of the technology. Clinical outcomes with tDCS have been examined in TBI in a small number of studies.[35,41,44] Some specific benefits have been observed in improving reaction time in chronic TBI and in augmenting motor function recovery in stroke patients.[41] However, efficacy in the treatment of mTBI remains unknown.[41,45] Some benefit has been reported for depression, but treatment for anxiety conditions remains relatively unexplored. However, the effects on fear memory consolidation is an active area of research, with one study reporting an effect of cathodal, but not anodal, tDCS to the dorsolateral prefrontal cortex to interfere with fear memory consolidation.[46,47]

Cranial Electrotherapy Stimulation

In contrast to the direct current approach of tDCS, CES involves administration of pulsed/alternating, low-intensity electrical current applied to the earlobes or scalp.[48] The effects of CES are believed to be due to changes induced through the limbic system, reticular activating system, and hypothalamus, as well as "cortical brain deactivation and . . . connectivity within the default mode network, specifically in the midline prefrontal and parietal regions"[49(p326)] and presumably through effects within the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal-medullary axis.[48] The US Food and Drug Administration has approved CES for treatment of anxiety, insomnia, and depression. A recent military service member and veteran survey suggested self-reported clinically significant improvements for individuals who used CES on a self-administered basis to treat anxiety, PTSD, insomnia, depression, pain, and headache, although the overall response rate was quite low (10%).[50] In addition, clinical trials with patients with mTBI, PTSD, or mTBI/PTSD have not yet been conducted. Advantages of CES devices include relatively low cost and portability.

Neurotherapy

The brain stimulation technologies discussed above all involve relatively large amounts of energy directed to neural structures,

although that associated with rTMS is clearly much greater than the others. The application of electrical current in tDCS and CES typically ranges over a period of a number of minutes. Induction of seizure is a small risk with rTMS. More commonly, headaches, painful scalp sensations, and facial twitching may occur, and hearing plugs are typically given to patients to limit complaints from sounds generated by the machinery. Headache, dizziness, nausea, and itching or skin irritation in the vicinity of the electrodes may occur with tDCS. With CES, headache, dizziness, decreased concentration, and malaise may occur, but these tend to be self-limiting. Potential skin irritation with CES is typically manageable and usually preventable. The minute pulsed electromagnetic energy used in the form of NT under discussion herein is much smaller and of much shorter duration than other technologies; and generally comes with very low risk of bothersome side effects, as subjects typically report no or only minimal, transient discomforts.

NT is a novel variant of EEG biofeedback (also known as neurofeedback) and falls within the bioenergy domain of complementary and elementary medicine. EEG biofeedback involves the placement of sensors on the scalp to detect, amplify, and record brainwave activity. In the traditional EEG biofeedback paradigm, this information is transformed into an external modality (eg, auditory tone, visual display) and subjects learn physiological control via computer software-generated feedback for rewarding and inhibiting the production of certain wavebands at one or more "active" recording sites. This occurs within an operant conditioning framework, which involves considerable time and effort.[51]

As an alternative to the traditional approach, pulsed low-energy systems have evolved over the years. Among the first was an EEG-Driven Stimulation system that involved subliminal flashing lights presented to individuals through goggles.[52,53] This involved a passive approach in which subjects did not actively seek to change brainwave activity; rather, they simply experienced change by the stimulation of the brain that was linked to their spontaneous production of brainwave activity, but offset from it. Over time it was discovered that the flashing light stimulation was not required. Indeed, lower and lower amounts of stimulation as electrode sites remained connected seemed to be sufficient to incite change. Although technology with additional reduction in stimulation has been developed, data for these newer systems have been sparse.[54] The technology most systematically studied and reported to date is the Flexyx Neurotherapy System (FNS), the focus of this article.

With FNS, subjects are not consciously learning to change brainwave activity; rather, the brainwave changes are the result of the brain, via EEG monitoring, continuously interacting with the resonant change in the feedback pulses. FNS provides minute pulses of feedback on an electromagnetic carrier wave to catalyze changes in brainwave patterns. FNS involves offsetting stimulation of brainwave activity by means of an external energy source as EEG sensors are connected and conduction of electromagnetic energy stimulation via the connecting EEG cables occurs at one or more connecting sites. The offsetting is done by linking the feedback frequency to the momentary peak frequency detected by the system. In the studies summarized below, FNS was further adapted by utilization of 2-channel, versus 1-channel only, neurofeedback.

FNS equipment consists of a laptop computer and J&J Enterprises (Poulsbo, WA) I-300 Compact 2 (C-2) Channel EEG module with on-board feedback generating power. Proprietary software is used to link the digital brainwave recording device (C-2 module) through the computer, which then sets the parameters for the C-2 module to emit pulsed electromagnetic stimulation.[55] The system returns a signal to the participant via conduction from the C-2 module, varying as a function of the detectable peak EEG frequency (but offset from it), thereby permitting strategic distortion of the EEG. For purposes of the research reported, the amount of electromagnetic stimulation was standardized with the feedback frequency being offset from the dominant EEG frequency at +20 Hz. Pulses of EM energy operated at a duty cycle of 1%, that is, of the maximum permissible on-time for each pulse, they were powered no more than 1% of the time (eg, the maximum on-time at 1% for 1-Hz pulse was 0.01 seconds). Testing revealed a power level in the picowatt range through the sensor cable (Lawrence Livermore National Laboratory, unpublished report).

In the studies reported below, participants typically attended approximately 2 to 3 sessions per week. They sat comfortably with eyes closed and engaged in no specific activity. Electrodes were placed in a predetermined order over all areas of the cortex over the course of the sessions (typical range 20-25 sessions, depending on the particular study under consideration). Each session included a total of 4 seconds of electromagnetic stimulation spaced over 4 minutes. The stimulation was not immediately discernible and adverse reactions (eg, transient increases in typical symptoms following the first few sessions), if they occurred, were minimal. Participants were not asked to discuss past traumas as part of the process.

Summary of NT Studies

A number of studies have been conducted with FNS, typically with individuals who have been refractory to numerous previous treatments and who often were severely dysfunctional. A summary of these is presented below and in Table 1. They include an initial provocative study with survivors of TBI, which set the stage for further exploration. Subsequently, studies of veterans of the Afghanistan and Iraq wars who experienced persistent TBI PCS as well as symptoms compatible with diagnosis of PTSD were conducted. Given the positive results, additional research was conducted with civilians. The amenability of treatment related to chronic duration of symptoms was also explored in Vietnam veterans with long-standing (ie, decades-long) mixed TBI/PTSD symptoms. Findings across all these studies have provided a framework to explore various aspects of efficacy of FNS. In addition, very preliminary work has been conducted to begin to explore potential biomarkers associated with symptom improvement.

Table 1. Overview of FNS Studies for TBI/PTSD Syndromes.

Study	Sample Composition	N	Study Design	Findings
Schoenberger et al (2001)[56]	Mild to moderately severe TBI	12	Randomized wait-list control	Significant improvements on measures of standardized instruments assessing emotional functioning (eg, depression), fatigue, and aspects of cognitive functioning; most experienced meaningful improvement in occupational and social functioning
Nelson and Esty (2012)[57]	OEF/OIF veterans with mixed TBI/PTSD symptoms	7	Clinical case series, pre-post comparisons	Significant reductions on multidimensional psychometric scales assessing neurobehavioral functioning and PTSD symptoms; significant linear trends on symptom ratings (cognitive clouding, fatigue, pain, sleep disturbance, anxiety, depression, anger) and overall activity level for improvement across individual treatment sessions
Nelson and Esty (2015)[60]	OEF/OIF veterans with chronic headache following TBI and with PTSD symptoms	9	Clinical case series, pre-post comparisons	All but one experienced significant reduction in headache along with reductions in posttraumatic stress and perceived cognitive dysfunction; subset had virtual elimination of headaches; one obtained modest headache reduction but no improvement on other symptoms
Keyser et al (2017)[64]	OEF/OIF veterans with TBI and PTSD symptoms	14	Clinical case series, pre-post comparisons	Significant reductions in postconcussive symptoms, PTSD, and other emotional symptom scales, and improvement in overall health status; P-300 ERP at Pz statistically significantly shortened, suggesting candidate neuromarker
Nelson and Esty (2010)[69]	Mix of civilian and military, including veterans, with TBI	35	Clinical case series, pre-post comparisons	Significant reductions as measured in linear trends for attention and other cognitive problems, difficulty following conversations, fatigue, headache, anger, anxiety, mood swings, motivation problems, and sleep disturbance
Nelson and Esty (2015)[70]	Vietnam veterans with persistent TBI and PTSD symptoms	2	Case studies	Both reported reductions on symptom rating measures of cognitive clouding, pain, sleep, fatigue, and mood/emotions, and increased overall activity level, as well as on posttraumatic stress scale scores

Abbreviations: FNS, Flexyx Neurotherapy System; TBI, traumatic brain injury; PTSD, posttraumatic stress disorder; ERP, event-related potential; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom.

An early study by Schoenberger et al (2001)[56] using an earlier version of FNS that involved subliminal flashing photic stimulation provided encouragement for pursuing evaluation of the current FNS that does not use photic stimulation and simply involves stimulation only through the connecting cables as described above. Also, a 1-channel only system and individually derived sequence of electrode placements was utilized. The investigators followed 12 participants (some assigned to a wait-list control group) with a range of TBI from mild to moderately severe who had significant cognitive complaints and who received 25 treatment sessions through to 3-month follow-up assessments. Wait-list control participants ultimately received the treatment. Positive outcomes were observed for depression, fatigue, and some other problematic symptoms, as well as on some measures of cognitive functioning.

Subsequent publications have involved 4 different sets of people with TBI referred for treatment. Nelson and Esty[57] studied 7 OEF/OIF veterans who had been experiencing mixed trauma syndromes refractory to previous treatments. Five of these individuals received 22 to 25 treatment sessions; one discontinued treatment after 13 sessions and another discontinued after 17 sessions due to experiencing sustained relief in a shorter period of time. Of the 5 who completed from 22 to 25 sessions, all had a history of at least mTBI, 3 with multiple episodes of loss of consciousness lasting up to 45 minutes; 4 involved in blast/explosive injuries (maximum of 9 episodes in 1 case), and motor vehicle accidents; a variety of assorted physical injuries; all with PTSD; and 3 with history of psychiatric hospitalization for suicidal ideation. Pre- to posttreatment comparisons revealed statistically significant improvements on 4 of the 6 subscales of the Neurobehavioral Functioning Inventory[58] (viz, Depression, Somatic, Memory/Attention, Communication) and strong trends for the other 2 subscales (viz, Aggression, Motor). In addition, significant decreases were observed in Posttraumatic Stress Scale[59] Total scores as well as the reexperiencing and avoidance symptoms clusters along with a strong trend for decrease in arousal symptoms. All pre- to posttreatment comparison effect sizes were large. Current 0 to 10 numerical symptom ratings made at the beginning of each of the individual treatment sessions exhibited highly significant linear trends for improvement, including cognitive clouding, pain, sleep quality, fatigue, anxiety,

depression, irritability/anger, and overall activity. Furthermore, substantial reductions in medication usage from levels at intake were reported.

As part of a study of a larger cohort of OEF/OIF veterans, 9 individuals with moderate to severe chronic headaches following service-connected TBI and complicated by posttraumatic stress symptoms were treated in 20 individual FNS sessions.[60] They periodically completed measures including the Brief Pain Inventory–Headache (BPI-HA) past week worst and average pain ratings,[61] the Posttraumatic Stress Disorder Checklist–Military version (PCL-M),[62,63] and an individual treatment session 0 to 10 numerical rating scale for degree of cognitive dysfunction. Beginning to end of treatment comparisons for the BPI-HA, PCL-M, and cognitive dysfunction indicated statistically significant decreases. All but one participant experienced reduction in headaches along with reductions in posttraumatic stress and perceived cognitive dysfunction, with a subset experiencing virtual elimination of headaches. One participant obtained modest headache relief but no improvement in posttraumatic stress or cognitive dysfunction.

Also, as part of that study of a larger cohort of OEF/OIF veterans with persistent PCS, 14 underwent laboratory assessment of event-related potentials (ERPs) in response to a visual oddball protocol, prior to undergoing FNS and again following 20 individual treatment sessions.[64] Five assessment instruments were administered at pre- and posttreatment, including the Short Form–36 (SF-36),[65] Symptom Checklist-90-R,[66] Posttraumatic Stress Disorder Checklist,[62,63] Rivermead Postconcussion Questionnaire,[67] and Patient Health Questionnaire–9.[68] Each of the 5 instruments exhibited highly statistically significant shifts in a positive direction, while the peak latency of the P-300 ERP component recorded at Pz also exhibited a statistically significant shortening. This study suggested, then, FNS may be an effective treatment for persistent PCS. It also suggested that the P-300 is a candidate neuromarker for improved brain function in individuals suffering from persistent PCS, although this is clearly only a preliminary finding.

Examination of the efficacy of FNS has also been extended to civilians as well as military personnel. A study of a mixed sample of 35 individuals with a history of TBI (range of number of head injuries 1-15; median 3; 18 with loss of consciousness) was conducted.[69] Prior to treatment, participants prioritized their most bothersome symptoms. At the beginning of each treatment session they rated each symptom on a 0 to 10 numerical rating scale with appropriate anchors. Symptoms were categorized as follows: those with prominent attention (concentration/focusing) problems, other cognitive (eg, fogginess, memory) problems, difficulty following conversations, fatigue, headache, anger (including irritability, rage, explosiveness), anxiety, mood swings (including depression), motivation problems (eg, difficulty finishing tasks, inertia, procrastination), and sleep disturbance. The number of treatment sessions ranged from 3 to 38 (median 20). Highly significant linear trends were in evidence in a positive direction for all bothersome symptom ratings over the course of the treatment sessions.

In addition, given potential issues that can accompany the highly persistent, long-term difficulties experienced by many individuals with TBI, the efficacy of FNS with two Vietnam veterans was explored.[70] These individuals had persistently bothersome PTSD symptoms and histories of TBI. They had been suffering for decades given both were in their 60 s at the time they were referred for FNS treatment. They completed pre- and posttreatment questionnaire assessments with the Posttraumatic Stress Scale.[59] Also, at the beginning of each treatment session, they recorded 0 to 10 numerical scale ratings, with appropriate anchors, of current levels of symptoms, including cognitive clouding, overall body pain, quality of sleep, fatigue, anxiety, depression, irritability/anger, and overall activity. One veteran also completed ratings for individual symptoms identified at the outset as his most personally bothersome, including tinnitus, "foggy" feeling, procrastination, night sweats, hypervigilance, and trouble "going to bed." Beginning to end of 25 treatment sessions comparisons revealed notable decreases for both veterans for all complaints, suggesting improvements across the broad domains of cognition, pain, sleep, fatigue, mood/emotion, and overall activity level. Although both reported significant decreases overall in post-traumatic symptoms on the Posttraumatic Stress Scale, one veteran did not rate his level of avoidance behavior at the end of treatment much lower than he did at the outset. However, this veteran also experienced very significant reductions across his most personally bothersome symptoms. Findings from these two veterans with mixed TBI/PTSD syndromes suggest FNS treatment may be of potential benefit for the partial amelioration of symptoms, even in veterans for whom symptoms have been present for decades, such as those who have served in Vietnam. On the other hand, the physical and emotional status of these individuals manifested much more complicated presentations, in part as a result of the greater passing of time, aging, and other chronic health problems. Furthermore, it is apparent that minor levels of symptoms persisted, although these were generally in the rather mild range (eg, 0.5-3.0 on the 0-10 numerical symptom rating scales).

Taken together, this series of studies suggests that at least in the short-term from beginning to end of treatment, both civilian and military personnel with symptoms associated with TBI and complicated by additional symptoms more specific to PTSD (as well as those symptoms that overlap) may benefit from this kind of very low energy stimulation treatment. They also suggest that long duration of symptoms and other complicating features do not necessarily impose an insurmountable barrier to obtaining a significant amount of relief. Furthermore, the viability of the P-300 ERP should be explored more as a potential biomarker for improvement.

Discussion

Given the high rates of mTBI, PTSD, and mTBI/PTSD seen in many individuals who have sustained a closed head injury, and especially given the very high rates of comorbidity observed in OEF/OIF/OND veterans, question has arisen as to the true

Table 2. Comparison of rTMS, tDCS, CES, and FNS on Selected Features.

Feature	rTMS	tDCS	CES	FNS
Amount of energy stimulation emitted	Very large	Small	Small	Extremely small
Energy stimulation linked to ongoing measured brain activity	No	No	No	Yes
Effectiveness demonstrated for treatment of PTSD	Yes, emerging consensus	Minimal data; some research regarding fear memory consolidation	Minimal data	Yes in multiple extended clinical case series for mixed TBI/PTSD syndromes
Effectiveness demonstrated for treatment of TBI	Minimal for selected symptoms	Minimal for selected symptoms	Minimal for selected symptoms	Yes in multiple extended clinical case series for mixed TBI/PTSD syndromes
FDA approvals for treatment of specific disorders	Refractory depression	None	Depression, anxiety, and insomnia	None
Relatively portable	No	Yes	Yes	Yes

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; CES, cranial electrotherapy stimulation; FNS, Flexyx Neurotherapy System; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury; FDA, US Food and Drug Administration.

distinctiveness of these syndromes. The nonspecificity of PCS further compounds uncertainty. Alteration of consciousness at the time of a traumatic event does not necessarily indicate mTBI; it may also reflect the intense stress reactions that are often a prelude to the development of PTSD; or it may reflect the neurocognitive effects and stress reactions common to mixed mTBI/PTSD presentations. While some neuroimaging research highlights some potentially distinctive neurobiological correlates of the three phenomena, there is also research that yields plausible models of at least some significantly overlapping cortical and subcortical regions of shared activation or inhibition as well as autonomic systems involvement.

In this regard, it is of interest that noninvasive brain stimulation technology applications appear to have potential efficacy for the treatment of mTBI, PTSD, and mTBI/PTSD to varying degrees. See Table 2 for a comparison of rTMS, tDCS, CES, and FNS on selected features. Of the technologies under consideration in this article, rTMS is approved by the US Food and Drug Administration only for treatment-resistant depression, but consensus has been forming that it has reasonably documented efficacy for PTSD and considerable suggestions of application to various specific symptoms associated with mTBI. Interest in tDCS has spawned a large and growing technical literature, but exploration is in a relatively infant state regarding potential therapeutic applications for mTBI and PTSD. CES has a significant literature and US Food and Drug Administration approval for treatment of depression, anxiety, and insomnia, which would appear to suggest some application to management of mTBI and PTSD; however, rigorous clinical trials for these are lacking.

The actual reasons these various techniques result in symptom improvement are presently unknown, and the possibilities are largely speculative. It is unlikely that their efficacy is due to focal stimulation per se, particularly as the understanding of brain networks has increasingly evolved and as the overlapping nature of the biochemical processes, as well as patterns of functional brain activity in TBI and PTSD has become better delineated.[23,27,71-76] It is possible that each of the techniques essentially taps into nodes of brain networks and influences changes in communication between these regions. The techniques vary widely in their range of stimulation parameters (eg, intensity; duration; EEG frequency ranges affected; intentionally focal impact versus targeting distantly linked coordination/communication; effects on EEG coherence, phase, and/or comodulation between sites; etc). The large or widespread areas of the brain stimulated are likely to overlap with nodes important in communication within or between one or more brain networks. Hence, the impact on functional connectivity in these syndromes may be key to future better understanding of much that underlies the efficacy of the various treatments.

FNS NT reviewed above has a growing body of data suggestive of efficacy in the treatment of mixed mTBI/PTSD syndromes. A major advantage of FNS is that it is involves extremely low energy administration over a very short period of time, compared to the much larger amounts of energy and/or time required for rTMS, tDCS, and CES. Anecdotally, often among the first symptoms to respond in the early stage of FNS treatment are headaches and sleep disturbances, as well as the calming of highly irritable, angry, or rageful reactions. These are symptoms that are common to both mTBI and PTSD. However, the growing body of information about FNS with mTBI and PTSD is based on open trials and case studies, without benefit of randomized clinical controlled conditions. There is an obvious need for more rigorous treatment investigations and more in-depth exploration of potentially associated biological mechanisms. It should also be pointed out that very low energy NT stimulation systems continue to evolve; our experience is primarily with the FNS described herein; it is possible that other emerging systems will share similar effects.

There is also a need across all the technologies for greater investigation of optimal conditions for application of stimulation. It is presently unknown whether administration or which

parameters of administration would result in better response under conditions of resting state or activation with specific tasks. Greater understanding is needed regarding the timing, sequencing, extent of overlap, and/or dosing of these treatments under resting state, activation, and/or implementation of other therapies.[30,38,41-43,45,47,48] It is quite possible that combined treatments with other interventions may yield better results.[40,76,77,78] In addition, comorbidity with trauma syndromes often also includes other neuropsychiatric and health concerns (eg, depression, substance abuse, other injuries, chronic pain, etc), further complicating the clinical presentation and which must be taken into account in treatment planning and implementation.[19,79] In general, then, though still largely in an infant state, noninvasive neurostimulation treatments for mixed trauma syndromes is a thriving, evolving field of research.

Author Contributions

Both authors, DVN and MLE contributed to the conceptualization, literature review, synthesis, writing up and approval of the draft manuscript.

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Ethical Approval

Ethical approval was not necessary since this is a topical review paper.

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