Review Article
How can transcranial magnetic stimulation change the way we treat traumatic brain injury?

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Abstract: Background: Traumatic brain injury (TBI) is a major health and socioeconomic problem worldwide. Despite improvements in the acute management of TBI over the past decades, which has led to better outcomes, there remains a need for novel treatment protocols that facilitate or enhance neuroplasticity and brain repair. There have been an increasing number of scientific publications describing the use of transcranial magnetic stimulation (TMS) for assessment and treatment in many research settings and clinical conditions, including TBI. Method: This study aimed to identify the role of TMS, a noninvasive brain stimulation technique, in the assessment and treatment of TBI by reviewing articles published to date from the PubMed database. Results: Most published articles on TMS in TBI are case reports. The use of TMS was reported as both a diagnostic tool and therapeutic instrument. There are few controlled trials of TMS in patients with TBI. Conclusion: TMS has the potential to modify the care of patients with TBI. TMS is an important instrument for evaluating brain injury from a functional perspective and also providing insights into neuromodulation approaches that may enhance recovery.

Keywords: Brain Injury, noninvasive brain stimulation, rehabilitation, repetitive transcranial magnetic stimulation

Introduction

Traumatic brain injury (TBI) is a major health and socioeconomic problem worldwide [1-3]. TBI is currently the leading cause of mortality and disability among young adults, and TBI incidence has been rising mainly due to increases in motor vehicle use. The World Health Organization (WHO) has estimated that death from road traffic injuries was the ninth leading cause of death in 2012, and the WHO projects that death from road traffic injuries will surpass diseases such as diarrheal diseases, HIV/AIDS, and diabetes mellitus to become the fifth leading cause of death worldwide by 2030 [4].

The prognosis following TBI varies from complete recovery to death. Many patients experience long-term disabilities. The consequences of TBI include motor, behavioral, and cognitive disabilities, which greatly affect quality of life and work capacity [5, 6]. Cognitive dysfunction remains the leading cause of disability following TBI [7].

The neuropathophysiology of TBI is complex, involving many pathways that lead to a broad spectrum of lesions. This complexity limits the success of conventional strategies, which are focused on functional recovery. Indeed, most neurosurgical interventions focus on reducing sequelae of the primary brain insult. In addition, all clinical trials that have evaluated pharmacological neuroprotection have failed to prove any benefit [8, 9]. Thus, there is an urgent need for novel approaches to enhance functional recovery following TBI.

Materials and methods

This study aimed to assess whether TMS, a noninvasive brain stimulation (NBS) technique,

is valuable to TBI assessment and treatment. In order to analyze the published data, the most used scientific databases for medical and health sciences (MEDLINE, PubMed) we searched for original, case reports, Systematic reviews and meta-analysis papers using the following MESH terms: "traumatic brain injury"; "TBI"; "transcranial magnetic stimulation"; "non-invasive brain stimulation"; "posttraumatic disorder"; in the title/abstract/keywords. Abstracts were carefully read according to the following criteria: (a) psychiatric, rehabilitation or psychological assessment as the main aim/outcome of the study; (b) TBI symptom as independent variable; (c) published in a peer-reviewed journal; (d) full text written in English; (e) participants over 18 years old. Studies up to December 2015 were selected. Therefore, in order to avoid confounding variables and several overlapping data, all duplicate articles were excluded.

Results

Since its first clinical use in 1985 by Barker and collaborators [10], TMS has proven to be a valuable instrument. TMS induces electrical currents in the brain via Faraday's principle [11] of electromagnetic induction. Most TMS application is restricted to superficial layers of the brain, although new devices allow stimulation of deep brain regions. TMS is a technique that is constantly evolving. The number and type of neuropsychiatric conditions that are being treated by TMS continues to increase [10, 12]. At the time of this review, over 10,000 papers related to TMS were published on PubMed, which demonstrates the significant interest in this technique.

TMS has been found to be safe when used according to the recommended guidelines established by the consensus of two international conferences [13, 14]. The major side effect of TMS is seizure induction. Although exceedingly rare, TMS can induce seizures in 1 of 1,000 applications. Other side effects that have been reported are mostly temporary and include headache, syncope, and acute hearing loss. There are several TMS protocols, each of which assesses different aspects of brain circuitry or leads to changes in cortical excitability when used as a diagnostic or therapeutic tool, respectively, as described below.

TMS as a diagnostic tool

The integrity of the corticospinal tract, spinal cord, and peripheral nerve as well as modifications to cortical dynamics can be assessed by single-pulse (sp-TMS) and paired-pulse TMS (pp-TMS).

Single-Pulse TMS: sp-TMS was introduced in the 1980s to study the motor system at stimulation intensities that produce a motor-evoked potential (MEP) as measured by surface electromyography (EMG). MEP latency is mainly reflective of the number of synapses and fiber characteristics, such as the diameter, myelin sheath thickness, and integrity. MEP magnitude, which is usually referred to as the peak-to-peak amplitude, is the most frequently measured outcome variable in sp-TMS protocols. sp-TMS protocols can assess a variety of elements present in the human cortex and white matter tracts. Three outcome variables from the sp-TMS protocols have been widely used: motor threshold (MT), input/output (I/O) curve, and silent period (SP).

MT is the most widely used sp-TMS protocol, and has been reported in the majority of the published articles in this field. Several studies suggest that MT may reflect membrane excitability as well as excitatory synapses of cortico-cortical axons with corticospinal neurons [15]. An increase in the MT measure is typically observed in diseases associated with significant damage to the corticospinal tract, such as in stroke, TBI, and spinal cord injury. As mentioned by Chistyakov and collaborators [16-18], MT has been demonstrated to be significantly elevated in patients with TBI, suggesting a reduction in corticospinal excitability or damage to this tract.

The I/O curve is useful in assessing cortical elements. It has been suggested that the I/O curve protocol can evaluate the activity of neurons that are less excitable and distant from the TMS center of maximum activation [19].

In the SP protocol, the inhibitory effect of sp-TMS is represented by a suppression of the background EMG activity that follows the MEP. This period of EMG inactivity (isoelectric line), which may last up to hundreds of milliseconds, is referred to as the SP. Longer SP durations have been observed in athletes who have sus-

Table 1. TMS studies performed in patients with TBI according to a PubMed database search

Author/year	Patient selection, TBI type	TMS protocol	Results
Louise-Bender Pape, 2009 [26]	26-year-old patient 287 days after severe TBI, post-traumatic vegetative state	Thirty sessions of excitatory rTMS over the right DLPFC, 110% of MT.	No adverse effects. Incremental neurobehavioral improvements between days 15 and 25 and decline between days 25 and 30.
Bonni, 2013 [27]	20-year old patient 2 years after severe TBI, mild left hemiparesis with signs of dysmetria, spasticity, ophthalmoparesis, and neglect.	Two-week course of cTBS over the left posterior parietal cortex (position P3 of the 10-20 system). Two sessions per day, 15-min intervals. 80% of active MT, total of 600 pulses.	Marked cognitive improvement as assessed by the BIT scale.
Nielson, 2014 [28]	48-year-old male patient 5 years after severe TBI with focal lesions (fractures and contusions). The patient developed severe medication-resistant anxiety and depression following TBI.	Thirty minutes of 1-Hz rTMS, 110% of MT, 5 times per week for 6 weeks over the right DLPFC.	No adverse effects. Improvements in depression, anhedonia, and global function.
Kosky, 2014 [29]	Fifteen patients who sustained mild TBI and PCS, all of whom were at least 6 months post-injury.	Five consecutive weekdays for 4 weeks (total of 20 sessions), 10-Hz stimulation, 110% of MT with an intertrain interval of 25 s, over the left DLPFC.	12/15 completed all sessions. No seizures were reported. Headache (3/12), vertigo (1/12), sleep disturbances (3/12) were reported as adverse effects. A reduction in PCS symptom severity was observed. No significant changes in the majority of neuropsychological test scores were observed.
Consentino, 2010 [30]	TBI associated with continuous music hallucinations (complex auditory hallucinosis)	Low-frequency rTMS applied to the right temporal area.	The auditory hallucinations were significantly reduced by rTMS treatment.
Kreuzer, 2013 [31]	53-year-old male patient suffering from severe tinnitus after TBI.	10 sessions of 2000 stimuli each, 1-Hz stimulation over the left primary auditory cortex, 110% of MT.	No adverse effects. Tinnitus complaints improved.

TBI: Traumatic brain injury; TMS: Transcranial magnetic stimulation; rTMS: Repetitive transcranial magnetic stimulation; DLPFC: Dorsolateral prefrontal cortex; MT: motor threshold; cTBS: Continuous theta burst stimulation; BIT: Behavioral inattention test; PCS: Post-concussion syndrome.

tained multiple concussions [20]. The contra-lateral SP is associated with $GABA_B$ receptor-mediated inhibitory neurotransmission, whereas the ipsilateral SP is mediated by transcallosal pathways [21, 22].

Paired-Pulse TMS: pp-TMS provides a noninvasive assessment of excitatory and inhibitory corticocortical connections. For pp-TMS, two pulses are applied on the same cortical location in sequence (paired) separated by a variable inter-stimulus interval (ISI). Although pp-TMS protocols have been used for almost two decades, the mechanisms of the circuits involved remain unknown. Whereas sp-TMS evaluates corticospinal integrity, pp-TMS can provide insight into specific intracortical processes.

Commonly used protocols for pp-TMS include intracortical inhibition (ICI) and intracorti-cal facilitation (ICF). In these protocols, two sequence stimuli (conditioning stimulus-CS and test stimulus-TS) are applied over the same cortical location separated by an ISI. The overall inhibitory or excitatory cortical process is a function of the CS intensity and ISI [23, 24].

TMS as a therapeutic instrument

As a therapeutic method, the Food and Drug Administration (FDA) of the United States has approved TMS for medication-resistant depression and pain relief caused by migraine headaches with aura [25]. A substantial and growing interest for repetitive TMS (rTMS) application in patients with TBI has shown encouraging results for the treatment of specific symptoms. A summary of TMS studies that have been conducted in patients with TBI is presented in **Table 1**.

TMS has been used in a variety of conditions associated with TBI, such as: depression, tinnitus, auditory hallucinosis, post-concussion syndrome, consciousness disorders, and cognitive dysfunction.

Discussion

Although the benefits of TMS in patients with TBI remain uncertain, published evidence suggests that rTMS is worthy of investigation as an intervention for TBI (see **Table 1**). To the best of our knowledge, no randomized clinical trials of TMS in patients with TBI have been conducted, and there is only one non-controlled trial published so far. Although no major adverse effects have been reported, most published articles are case reports.

The delayed attempts to use TMS on patients with TBI may be related to the fact that TBI has been considered a relative contraindication for TMS, especially due to the risk of seizures. In fact, structural lesions secondary to the primary brain insult may theoretically carry a higher risk of TMS-related seizures. However, none of the studies in patients with TBI reported seizures as a side effect. This may be due to compliance with safety standards for TMS regardless of experimental environment. TBI is an extremely heterogeneous disease, and clinical trials may be on hold until there is robust evidence for the safety of TMS in other acquired brain injuries, such as stroke.

There is substantial diagnostic and therapeutic potential for TMS in TBI [32, 33]. Both sp-TMS and pp-TMS may provide valuable information about cortical element function and corticospinal tract integrity. Spasticity, gait disorders, pain syndromes, and mood disorders may also be therapeutic targets of rTMS in patients with TBI, despite the current lack of evidence for its efficacy in this patient population. The possible applications of TMS in patients with TBI are summarized in **Table 2**.

TBI is a major risk factor for age-related cognitive decline. Neurophysiological measurements on TBI using TMS may identify individuals at higher risk of developing neurological disability later in life. Pathological values measured by pp-TMS have been reported in numerous neuropsychiatric conditions [34-40].

The development of a TMS protocol for TBI may provide insight into neuronal plasticity, which would have prognostic utility. Bernabeu and collaborators [41] as well as other studies [20, 42-46] have reported cortical disinhibition in patients with TBI and post-traumatic stress disorder. It has also been observed that changes in cortical excitability were more pronounced according to the diffuse axonal injury severity and motor dysfunction. For example, Bashir and collaborators [46] found significantly higher ICF and absent ICI two weeks after TBI but normal values 6 weeks after TBI. The remaining

Table 2. Possible applications of TMS in patients with TBI according to different protocols

Diagnostic	Therapeutic
Single-pulse protocols (sp-TMS)	Repetitive TMS protocols (rTMS)
Assessment of membrane excitability	Enhancement of:
Appraisal of corticospinal integrity	Motor recovery
	Cognitive rehabilitation (language, visuospatial function, decision-making, working memory, and executive function).
Paired-pulse protocols (pp-TMS)	Mood disorders (depression, post-traumatic stress disorder)
Further study of cortical excitability	Auditory hallucinosis
Assessment of cortical circuits integrity	Tinnitus
Indirect evaluation of GABAergic and possibly glutamatergic pathways	Post-concussion syndrome
	Pain syndromes
	Spasticity
	Gait disturbances

three TMS studies in patients with mild TBI found no significant differences in pp-TMS measures [20, 41-44].

Most treatment for TBI focuses on the pri-mary lesion and the prevention of secondary lesions, especially during the acute phase. Indeed, a large number of patients surpass this challenging phase but end up with severe disability. To overcome this obstacle, restorative strategies represent a shift in therapeutic goals. Several basic clinical principles have been identified. For example, spontaneous recovery is expected to happen within 3 to 6 months, and cognitive dysfunctions are more prone to show recovery beyond this period when compared to motor deficits [47]. However, there remains a need for novel treatment protocols that could lead to facilitation or enhancement of neuroplasticity and brain repair in TBI [48].

Conclusion

There is good evidence supporting the use of TMS in depressive and cognitive disorders. It is believed that TMS is ready to be tested in homogeneous groups of patients with TBI. According to the ClinicalTrials.gov website [49] (https://clinicaltrials.gov/ct2/home), there are currently at least five active clinical trials evaluating the implementation of TMS in patients with TBI.

We believe that TMS can significantly modify the treatment of patients with TBI as both an important instrument to assess brain injury from a functional perspective and as a technique that provides insights into neuromodulation approaches that may enhance recovery.

The authors of this paper are also implementing a randomized, double-blind, controlled clinical trial of TMS as a cognitive rehabilitation instrument following severe TBI [50].

Disclosure of conflict of interest

None.

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