# Repetitive transcranial magnetic stimulation in traumatic brain injury: Evidence from animal and human studies

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ABSTRACT

We provide here the first systematic review on the studies dealing with repetitive transcranial magnetic stimulation (rTMS) for traumatic brain injury (TBI) in animals and humans. Several experimental studies in animal models have explored with promising results the use of rTMS to enhance neuroprotection and recovery after TBI. However, there are surprisingly few studies that have obtained substantial evidence regarding effects of rTMS in humans with TBI, many of them are case reports investigating the heterogeneous conditions linked to TBI.

The most studies have investigated the effects of rTMS in subjects with post-traumatic depression and variable effects have been observed. rTMS has been proposed as an experimental approach for the treatment of disorders of consciousness (DOC), but in subjects with TBI therapeutic effects on DOC have also been variously documented. Beneficial effects have been reported in subjects with cognitive/emotional disturbances and auditory dysfunction (tinnitus and hallucinations), although the results are somewhat conflicting. rTMS applied over the left prefrontal cortex may relieve, at least transiently, post-traumatic headache. Isolated rTMS studies have been performed in TBI patients with motor impairment, chronic dizziness or pain. Especially whether provided in combination, rTMS and neurorehabilitation may be synergistic in the potential to translate experimental findings in the clinical practice.

In order to reach definitive conclusions, well-designed randomized controlled studies with larger patient samples, improved design and optimized rTMS setup, are warranted to verify and corroborate the initial promising findings.

## 1. Introduction

Traumatic brain injury (TBI) represents a significant public health concern and has been associated with high rates of morbidity and mortality.

Neuromodulatory brain stimulation techniques, such as the repetitive transcranial magnetic stimulation (rTMS), can safely modulate neural activity within specific brain regions, thus inducing changes in cortical function and behavior (Hallett, 2000, 2007; Daskalakis et al., 2006).

rTMS is a promising technique that modulates neural networks. Indeed, rTMS is able to modulate cortical excitability, thus inducing lasting effects.

rTMS might thus decrease the cortical hyperexcitability which occurs acutely after TBI, modulate long-term synaptic plasticity as to avoid maladaptive consequences, and combined with physical and behavioral therapy, facilitate cortical reorganization and consolidation of learning in specific neural networks. It is conceivable that these

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interventions may help decrease the burden of disabling sequelae after TBI.

Therefore, the use of rTMS has been proposed also in patients with TBI, but only a few studies have obtained sufficient evidence regarding the matter and have evaluated the diagnostic and therapeutic potential of rTMS in humans after TBI. In fact, despite the potential wide-ranging significance of TMS and other non-invasive brain stimulation techniques in the treatment of many neurological diseases, including in stroke, pediatrics, traumatic brain injury, focal hand dystonia, neuropathic pain and spinal cord injury, rTMS is still not widely used and remain poorly understood in neurorehabilitation.

We aimed to perform a systematic review of the studies that have applied rTMS in animal and humans after TBI in order to provide a comprehensive perspective of past and current studies, and to develop valuable suggestions for future research.

## 2. Methods

A literature review was conducted using MEDLINE, accessed by PubMed (1966 – June 2019) and EMBASE (1980 – June 2019) electronic databases. The following medical subject headings (MeSH) and free terms were searched: “transcranial magnetic stimulation” OR “repetitive transcranial magnetic stimulation” AND “traumatic brain injury”.

Only articles written in English were considered eligible for inclusion. Review articles were excluded. For the selected titles full-text articles were retrieved, and reference lists of them were searched for additional publications. The principal investigators of included studied were contacted when necessary to require additional information. Two review authors independently screened the titles and abstracts of the initially identified studies, and then assessed the methodological quality of each study and risk of bias, including blinding. This search strategy yielded 31 studies (8 in animals and 23 in humans) which were included this review.

A flow-chart (Fig. 1) illustrates the selection/inclusion process.

## 3. Transcranial magnetic stimulation

RTMS is a non-invasive and relatively safe (Rossi et al., 2009) brain stimulation technique that uses brief, intense pulses of electric current delivered to a coil placed on the subject’s head in order to generate an electric field in the brain via electromagnetic induction. RTMS has been proven to influence cortical excitability and the metabolic activity of neurons (Fitzgerald et al., 2006; Hallett, 2007; Lefaucheur et al., 2020). Indeed, the induced electrical field modulates the neural transmembrane potentials and, thereby, neural activity. These effects depend on the intensity, frequency, and number of pulses applied, the duration of the course, the coil location and the type of coil used. RTMS can be applied as continuous trains of low-frequency (LF, 1 Hz) or bursts of higher frequency (HF, ≥ 5 Hz) rTMS. In general, LF rTMS is thought to reduce, and HF rTMS to enhance excitability in the targeted cortical region (Pascual-Leone et al., 1998; Fitzgerald et al., 2006; Lefaucheur, 2019). The physiological impact of rTMS and other neuromodulatory techniques involves synaptic plasticity, specifically long-term potentiation and long term depression.

A rTMS protocol named theta burst stimulation (TBS) employs low intensities and has robust, long-lasting effects in normal subjects (Huang et al., 2005). Different patterns of TBS delivery produce opposite effects on synaptic efficiency of the stimulated cortex. Continuous TBS (cTBS) decreases cortical excitability, while intermittent TBS (iTBS) was shown to increase motor cortical excitability.

There is sufficient body of evidence to accept with level A (definite efficacy) the analgesic effect of HF rTMS applied over the primary motor cortex contralateral to pain and the antidepressant effect of HF rTMS applied over the DLPFC (Lefaucheur et al., 2020). Overall, rTMS techniques have been shown to have potential therapeutic efficacy for various neurological and psychiatric conditions (Bersani et al., 2013; Lefaucheur et al., 2020).

## 4. Animal studies

Apoptotic and inflammatory cascades are important predictors of functional outcome after TBI (Viscomi and Molinari, 2014). The efficacy of rTMS in reducing remote degeneration and inflammation and in improving functional recovery has been examined in a rat model of focal brain damage. In rats who were undergoing hemicerebellectomy, rTMS was found to significantly reduce neuronal death and glial activation in remote regions, thus improving functional recovery (Sasso et al., 2016).

The effects of epidural electrical stimulation (EES) and rTMS on motor recovery and brain activity were explored in a model of diffuse TBI (Yoon et al., 2015a). The rats were pre-trained to perform a single-pellet reaching task (SPRT) and a rotarod test (RRT) for 14 days. SPRT improved significantly from day 8 to day 12 in the EES and from day 4 to day 14 in the TMS group while RRT improved significantly from day 6 to day 11 in EES and from day 4 to day 9 in TMS group compared to the sham group. The authors concluded that both techniques could be helpful to enhance motor recovery and brain activity.

By contrast, in a rat model of TBI a study suggests that rTMS did not have beneficial effects on motor recovery during early stages of TBI, even if an anti-apoptosis was observed in the peri-lesional area. In this study the effectiveness of rTMS on behavioral recovery and metabolic changes has been assessed using brain magnetic resonance spectroscopy (Yoon et al., 2015b).

TBI may lead to an abnormal neuronal hypoactivity in the non-injured primary somatosensory cortex (S1) in a controlled cortical impact (CCI) animal model of pediatric TBI (postnatal day 16–17). Therefore, it has been hypothesized that reshaping the abnormal post-injury neuronal activity may provide a suitable strategy to augment rehabilitation. HF rTMS delivered twice a week over a four-week period was able to reverse the adverse neuronal mechanisms activated post-TBI, thus improving the long-term functional neurophysiological and behavioral outcome in this pediatric animal model (Lu et al., 2015). TBI rats who received TMS showed significant increased evoked-fMRI cortical responses (189 %), evoked synaptic activity (46 %), evoked neuronal firing (200 %), expression of cellular markers of neuroplasticity in the non-injured S1, and less hyperactivity in behavioral tests, compared to TBI rats that did not receive TMS treatment.

In a more recent study, moderate TBI was induced in adult male Sprague Dawley rats using

Feeney's weight-dropping method (Lu et al., 2017). RTMS was administered to rats in the TMS group assigned to rTMS from post-TBI day 2. At post-TBI days 7, 14 and 28, three or four of the rats were sacrificed, and harvested brains were embedded in paraffin and sectioned. Sections were then treated with hematoxylin and eosin and immunohistochemical staining. The results of hematoxylin eosin staining revealed that relative cerebral parenchyma loss was lower at post-TBI day 28 in the TMS group compared with the control group, even if the differences were not statistically significant. According to an immunohistochemical staining, significantly higher level of proliferation (as indicated by bromodeoxyuridine) were detected in the subventricular zone in the TMS group compared with the control group. A significantly higher rate of neuron survival at day 2 (as indicated by NeuN indicating mature neurons) and a significantly reduced rate of apoptosis in the perilesional zone at days 7 and 14 ($P < 0.05$; indicated by caspase-3) were observed in the TMS group, as compared with the control group. These findings suggest that HF rTMS may promote neurogenesis and provide a basis for further studies in this area.

The effects of seventy consecutive sessions of perilesional HF (10 Hz) rTMS in the treatment of chronic neglect deficits have been assessed in a well-established feline model of visuospatial neglect (Afifi et al., 2013). The accrual of multiple sessions of rTMS applied to areas

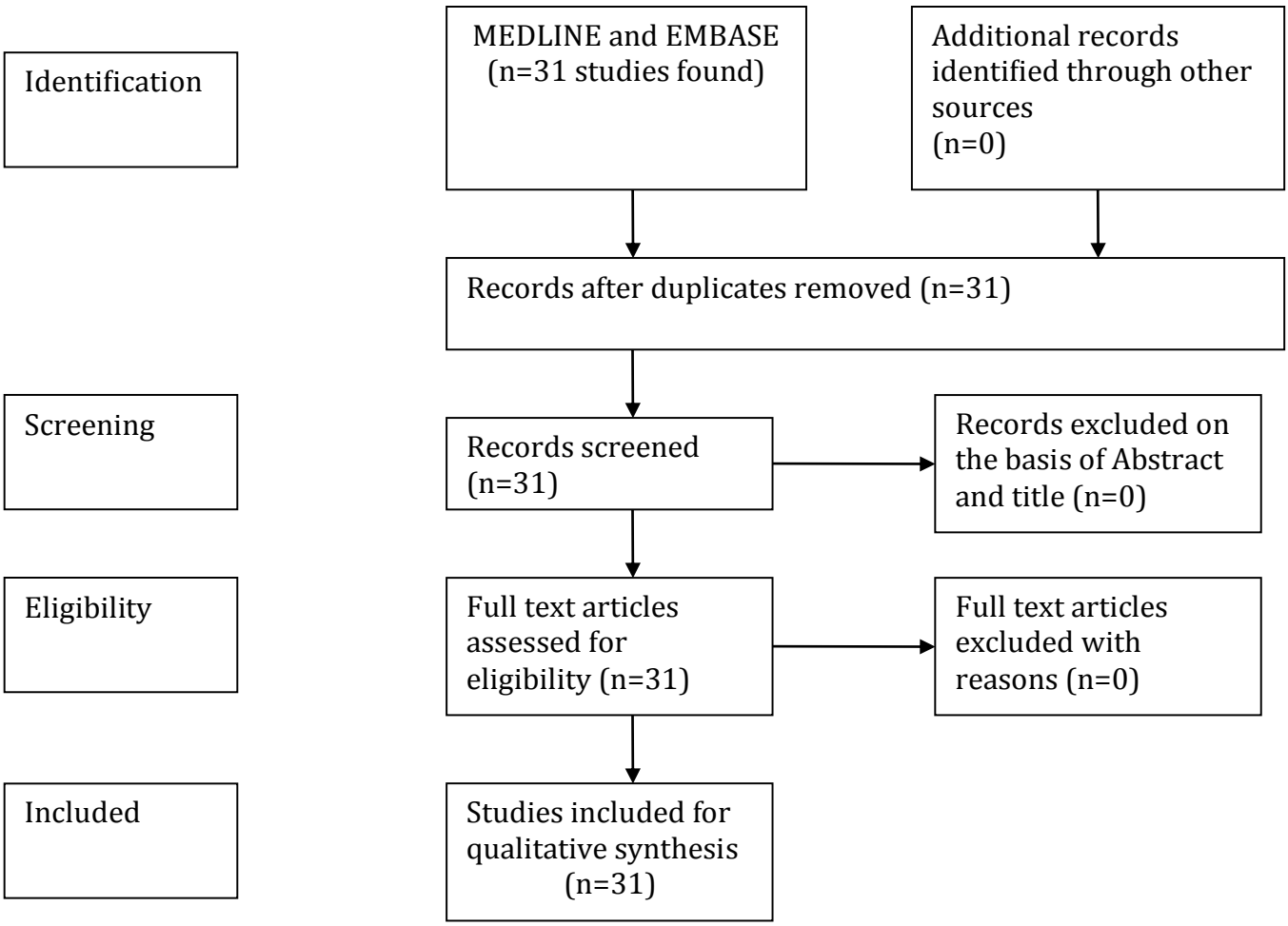


**Fig. 1.** Flow-chart showing the selection/inclusion process.

adjacent to lesion can provide high levels of lasting improvements for the symptoms of visuo-spatial neglect.

Verdugo and co-workers aimed to analyze the effect of intermediate-frequency rTMS (2 Hz) on behavioral and histological recovery following TBI in rats (Verdugo-Diaz et al., 2017). Male Wistar rats were divided into six groups: three groups without TBI (no manipulation, movement restriction plus sham rTMS, and movement restriction plus rTMS) and three groups subjected to TBI (TBI only, TBI plus movement restriction and sham rTMS, and TBI plus movement restriction and rTMS). Although the restriction of movement and sham rTMS per se promotes recovery, as measured using a neurobehavioral scale, but rTMS was associated with faster and superior recovery. Moreover, TBI causes alterations in the CA1 and CA3 subregions of the hippocampus which where are also partly restored by both movement restriction and rTMS. These findings indicated that also intermediate-frequency rTMS may promote behavioral and histologic recovery after TBI.

The effects of TMS with rehabilitative training in an environmental enrichment (EE) in rats were explored in another study (Shin et al., 2018). After CCI, the rats were assigned them to one of four groups: 1. No treatments (TBI), 2. EE after injury (TBI + EE), 3. TMS for one week (TBI + TMS), and 4 TMS for one week combined with EE (TBI + TMS/EE. At 7 days, TBI + TMS and TBI + TMS/EE groups had significantly increased primary somatosensory cortex local field potential (LFP) and TBI + TMS/EE group had significantly improved performance on beam walk test. At 6 weeks, TBI + TMS/EE showed significantly higher response for somatosensory cortex LFP, bicep motor evoked potentials (MEP), challenge ladder test performance, and fMRI responses to tactile forepaw stimulation.

## 5. Human studies

The demographic and clinical characteristics of the rTMS studies in humans are summarized in the Table 1.

### 5.1. Loss/disorders of consciousness

Effects and safety of rTMS have been explored in a 26-year-old male who remained in a vegetative state (VS) [Disorders of Consciousness Scale (DOCS) = 50.3] 287 days after a severe TBI with hemorrhage in the right temporal lobe and diffuse subarachnoid hemorrhage (Louise-Bender Pape et al., 2014). The patient was treated with neurostimulant drugs (amantadine and methylphenidate) and antispastic medications prior to rTMS intervention, but he did not receive any neurological medication during the course of the rTMS treatment. rTMS was applied over the right dorsolateral prefrontal cortex (DLPFC) at 110 % abductor pollicis brevis motor threshold RMT for 6 weeks. No adverse effects were reported, and electroencephalography (EEG) performed throughout and following the treatment has not revealed epileptiform discharges following rTMS. A change in classification of state of consciousness from VS to minimally conscious state (MCS) (DOCS: 15th session = 58.6; 30th = 53.7; 6 weeks post-treatment = 56.7) has been reported. Qualitative neurobehavioral improvements through the course of rTMS were observed, including markedly improved motor skills and visual ability, the appearance of vocalizations, and the development of basic communication. Continued qualitative improvements, without adverse events, were reported a year following rTMS treatment by the patient's family.

In another study HF- rTMS was administered to three patients with severe TBI, two classified as MCS and one in a VS (Manganotti et al., 2013). A single session was applied to the primary motor cortex (M1) at 100 % RMT. A clinical response was not observed in any of the three patients, with EEG demonstrating no reaction to brain stimulation. No adverse effects or seizures were reported.

Also the findings of a recent study did not provide evidence of therapeutic effect of 20 Hz rTMS of the M1 in in eleven patients classified as being in VS, two of them after TBI (Cincotta et al., 2015).

A more recent study explored the neuromodulatory effects of rTMS on clinical response and EEG reactivity and in 6 patients with DOC (He et al., 2018). In this randomized, sham-controlled, crossover study, real or sham 20 Hz rTMS was applied to the left M1 of patients with DOC for 5 consecutive days. Evaluations were blindly performed at the baseline (T0), immediately after the end of the 5 days of treatment (T1) and 1 week after the treatment (T2) using the JFK coma recovery scale-revised (CRS-R) and resting-state EEG. Only one patient, with a history of 2 months of TBI, showed long-lasting (at T1 and T2) behavioral and neurophysiological modifications after the real rTMS stimulation. The 5 remaining patients presented brain reactivity localized at several electrodes, and the EEG modification was not significant. The findings of this study indicate that this kind of rTMS stimulation may be only marginally effective in improving awareness and arousal of DOC after TBI.

### 5.2. Cognitive impairment

There is increasing evidence that non-invasive brain stimulation, by interacting with cortical activity, can positively affect the short-term cognitive performance and improve the rehabilitation potential of

**Table 1**
Demographic and clinical characteristics of the patients included in the reviewed studies.

| Studies | Patients | A (y) | G(F/M) | Time since TBI | Target | rTMS parameters | No sessions | Clinical assessment |
|---|---|---|---|---|---|---|---|---|
| **Depression** | | | | | | | | |
| Fitzgerald et al., 2011 | 1 | 41 | 1/0 | 14 y | Left and right DLPFC | 1 Hz right, 10 Hz left | 1 | MADRS, IDS-CR |
| George et al., 2014 | 41 | ? | ? | ? | Left PFC | 10 Hz, 120 % RMT 6000 pulses for 30 min | 9 | SSI, VAS |
| Iliceto et al., 2018 | 1 | 37 | 0/1 | 8m | Left DLPFC | 6 Hz, 120 % RMT 4-sec. trials, 3000 pulses | 30 | PHQ-9 |
| Lee and Kim, 2018 | 13 | 42.4 ± 11.3 (active group) | 4/9 | 3.8 ± 1.6 (active group) | Right DLPFC | 1 Hz, 100 % RMT 50 trains of 40 pulses | 10 | MADRS, TMT, SCWT |
| Hoy et al., 2019 | 21 | 46.3 ± 12.6 | 11/10 | ? | Left and right DLPFC | 1 Hz, 110 % RMT 5-sec trains, 1500 pulses | 20 | MADRS, IDS-CR, IDS-SR |
| Siddiqi et al., 2019 | 15 | 43 ± 13 (active group) | 4/11 | 8.4 ± 8.2 y (active group) | Left and right DLPFC | 10 Hz left, 120 % RMT 5-sec trains, 4000 pulses 1 Hz right, 1000 pulses | 20 | MADRS sgACC-DMN connectivity |
| Rao et al., 2019 | 13 | 40.2 ± 14.6 | 7/5 | 3 (3 m-1 y) 5 (1−5 y) 3 (5−10y) 2 (> 10) | Right DLPFC | 1 Hz, 110 % RMT 1200 pulses/session | 20 | HAM-D, CGI-I, BSSI, GAD, DTS PSQI, ESS, NBRS, RPQ, FSS STC, SWLS, MoCA, WCST BVMT |
| **Cognitive impairment** | | | | | | | | |
| Pachalska et al., 2011 | 1 | 26 | 0/1 | 2 y | Frontotemporal bilateral | 5 Hz right, 1 Hz left | 20 | WAIS-R, WAIS-III, WMS III, CVTL, TMT, Stroop |
| Bonni et al., 2013 | 1 | 20 | ? | 2 y | Left PPC | cTBS | 20 | BIT-C, BIT-B |
| Koski et al., 2015 | 15 | 34.3 ± 10.8 | 6/9 | 0,5−8 y | Left DLPFC | 10 Hz, 110 % RMT 20 × 5-sec. trials | 20 | PSC Symptom Scale, DS SD, TMT-A, TMT-B |
| Neville et al., 2019 , 2015 | 30 | 32.6 ± 12.8 | 3/27 | 17.6 m (13−26) | Left DLPFC | 10 Hz, 110 % RMT 2000 pulses in 40 trials | 10 | TMT-B |
| **Disorders of consciousness** | | | | | | | | |
| Manganotti et al., 2013 | 3 | 48 ± 19.4 | 0/2 | 26.2 ± 2.1 | Motor cortex | 20 Hz, 100 % of RMT 1000 pulses in 10 trains | 1 | DRS, JFK CRS-R |
| Louise-Bender Pape et al., 2014 | 2 | 54.32 | 0/2 | 188 d, 9 y | Right and left DLPCF | 110 % RMT 300 paired pulse | 30 | Safety indicators |
| Cincotta et al., 2015 | 2 | 47.65 | 0/2 | 3.,85 m | Left M1 | 20 Hz, 90 % RMT 1000 pulses | 5 | CGI-I, JFK CRS-R |
| He et al., 2018 | 6 | 39.5 ± 15.5 | 4/2 | 8.1 ± 9.3 | Left M1 | 20 Hz, 100 % RMT 1000 pulses | 5 | JFK CRS-R Resting state EEG |
| **Auditory function** | | | | | | | | |
| Cosentino et al., 2010 | 1 | 63 | 0/1 | 20 y | Right PTC | 1 Hz, 110 % RMT 1200 pulses for 30 min | 1 | PET scans |
| Kreuzer et al., 2013 | 1 | 53 | 0/1 | 4 y | Left PAC | 1 Hz, 110 % RMT 2000 pulses | 10 | NRS loudness |
| **Pain** | | | | | | | | |
| Choi et al., 2018 | 12 | 42.7 ± 8.7 | 6/6 | 20 y | Right PTC | 1 Hz, 90 % RMT | 10 | NRS, SF-36 |
| **Motor function** | | | | | | | | |
| Martino Cinnera et al., 2016 | 1 | 25 | 0/1 | 43 m | Right cerebellum | iTBS | 6 | FMA, BBS, JHFT, GA |
| **Chronic dizziness** | | | | | | | | |
| Paxmann et al., 2018 | 1 | 61 | 0/1 | 5 y | Left DLPFC | 10 Hz, 70 % RMT 600 pulses/sess | 10 | DHI |
| **Headache** | | | | | | | | |
| Leung et al., 2016 | 24 | 14.3 ± 12.6 | 3/21 | 187 ± 176 m | Left M1 | 10 Hz, 80 % RMT 20 trains of 10 pulses | 3 | NRS, CPT II, HRDS M-PTSD, BPI |
| Leung et al., 2018 | 29 | 34 ± 8 6/23 | | 95 ± 83 m | Left PFC | 10 Hz, 80 % RMT 20 trains of 10 pulses | 4 | NRS, CPT II, WAIS IV HVTL, HRSD, BPI, CAPS |

(*continued on next page*)

**Table 1** (*continued*)

| Studies | Patients | A (y) | G(F/M) | Time since | Target | rTMS parameters | No sessions | Clinical assessment |
|---|---|---|---|---|---|---|---|---|
| Stilling et al., 2020 | 20 | 40.3 ± 11.6 (active group) | 18/2 | 29.2 ± 14.8 m (active group) | Left DLPFC | 10 Hz, 70 % RMT 600 pulses/sess | 10 | NPRS, MoCA, PCS, RPSQ BCPSI, HIT-6, PHQ-9, GAD-7, PLC-5, QOLIBRI |

A = age, G = gender; M = male; F = female; h = hour, w = week, m = month, y = year; M1 = primary motor cortex; PFC = prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; PPC = posterior parietal cortex; RMT = resting motor threshold; AMT = active motor threshold; cTBS = continuous theta burst stimulation; iTBS = intermittent theta burst stimulation; EMG = electromyography; PTC = posterior temporal cortex; PAC = primary auditory cortex; FMA = Fugl-Meyer Assessment scale, BBS = Berg Balance Scale; JHFT = Jebsen-Taylor Hand Function test ; GA = gait analysis; WMS = Wechsler Memory Scale ; TMT = Trail Making Test; JFK CRS-R = JFK Coma Recovery Scale-Revised; MADRS = Montgomery–Åsberg Depression Rating Scale; SSI = Beck Scale of Suicidal Ideation; HAM-D = Hamilton Depression Rating Scale; CGI-S = Clinical Global Impression-Severity; GAD = Generalized Anxiety Disorder; DTS = Davidson Trauma Scale; PSQI = Pittsbourgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; NBRS = Neurobehavioral Rating Scale; RPQ and RSPQ = Rivermead Post-Concussion Symptoms Questionnaire, FSS = Fatigue Severity Scale, STC = Social Ties Checklist; SWLS = Satisfaction With Life Scale; MoCA = Montreal Cognitive Assessment, WCST = Wisconsin Card Sorting Test, BVMT = Brief Visual Memory Test; VAS = Visual Analogue Scale; PHQ-9 = Patient Health Questionnaire-9; SCWT = Stroop Color Word Test; IDS-CR = Inventory of Depressive Symptomatology - Clinician Rated version; IDS-SR = Inventory of Depressive Symptomatology - Self Rated version; sgACC-DMN = subgenual anterior cingulate cortex default mode network; NRS = numeric rating scale; SF-36 = short Form 36 Health Survey; M- PTSD = Mississippi scale for Posttraumatic Stress Disorder, HRSD = Hamilton Rating Scale for Depression ; CPT II = Conner's Continuous Performance Test; BPI = Brief Pain Inventory; CAPS = Clinician-Administered PTSD Scale; HVLT = Hopkins Verbal Learning Test ; WAIS-IV = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale – Revised; DRS = Disability Rating Scale; SSI = Suicidal Scale Inventory; BIT = Behavioural Inattention Test with conventional (BIT-C) and behavioral (BIT-B) scales; IDS-CR = Inventory of Depressive Symptomatology-Clinical Rated; DS = Digit Span; SD = Symbol Digit; DHI = Dizziness Handicap Inventory; NPRS = numeric rating pain scale; PCS = post-concussion symptoms; BCPSI = British Columbia Post-Concussion Symptom Inventory; HIT-6 = Headache Impact test; GAD-7 = generalized anxiety disorder scale; PLC-5 = post-traumatic stress disorder checklist for DMS-5; QOLIBRI = quality of life after brain injury questionnaire.

neurologic patients (Miniussi et al., 2008).

cTBS applied to the left hemisphere has been administered in a 20-year-old male patient with severe hemispatial neglect following TBI [Behavioral Inattention Test-Conventional (BIT-C) scale ~28] sustained 2 years prior to intervention (Bonni et al., 2013). Neuropsychological tests also revealed mild attentional and executive deficits and minimal memory impairment. Three pulse bursts were applied to the left posterior parietal cortex (PPC) at 80 % active MT (50 Hz, 600 pulses/session; 40 s train interval, 200 ms inter-train interval) twice daily (15 min inter-session interval) for 2 weeks. Functional MRI (fMRI) revealed decreased excitability of PPC-M1 connections in the left hemisphere and a bilateral increase of functional connectivity in the frontal-parietal network. These fMRI findings were accompanied by marked cognitive and clinical improvements lasting 2 weeks following intervention (BIT-C ~ 58).

In another case study, rTMS was applied to a 26-year-old male who had previously suffered a severe TBI which left him in a coma for 2 months (Pachalska et al., 2011) The patient exhibited anosognosia, executive dysfunction, behavioral changes sporadic aggressivity and impulsivity, perseverations, fits of uncontrolled laughter. Brain imaging revealed diffuse atrophy and enlarged lateral ventricle in the right hemisphere. The patient had previously shown little progress following "traditional rehabilitation" and relative beta training. Twenty sessions of LF (1 Hz) rTMS were administered over left frontal and temporal regions along with HF (5 Hz) rTMS to right frontal and temporal regions. Following rTMS, neuropsychological assessments revealed improvements in executive functioning (general intelligence, attention, visuospatial ability, logical memory) as well as in all categories of the frontal behavioral inventory (social conduct, personal conduct, mood disorders, and control disorders). Although EEG spectra were no different post-rTMS, but NO-GO event-related potential recordings showed improvement compared to pre-rTMS. No seizure events or significant adverse side effects were reported.

The effects of HF rTMS was assessed on individuals experiencing post-concussion syndrome (PCS) at least 6 months post-TBI (Koski et al., 2015). Fifteen patients with a score of 22 or greater on the PCS Scale received 20 daily sessions of rTMS over the left DLPFC. The 12 patients who completed treatment showed an improvement in symptoms (> 5 point decrease on PCS scale), in particular participants also reported positive outcomes such as less sleep disturbance and better mental focus. Moreover, an increase in the fMRI task-related activation peaks in the DLPFC was observed after rTMS.

In a recent ingle-center, randomized, double-blind, placebo-controlled study of rTMS conducted in patients aged with chronic (> 12 months postinjury) diffuse axonal injury (DAI), cognitive executive functions (as assessed by means of Trail Making Test Part B) was not improved by HF rTMS over the left DLPFC, though it appears safe and well-tolerated in this population (Neville et al., 2019).

### 5.3. Depression

There is a sufficient body of evidence to accept with level A (definite efficacy) the antidepressant effect of HF-rTMS of the left DLPFC (Lefaucheur et al., 2020). Several studies also investigated the effects of rTMS in post-traumatic depression (for a review, see Reti et al., 2105; Gertler et al., 2015).

rTMS treatment has been reported in a pharmacotherapy-resistant 41-year-old female patient with severe recurrent depression [Montgomery–Åsberg Depression Rating Scale (MADRS) = 34; Inventory of Depressive Symptomology-Clinical Rated (IDS-CR) = 49] persisting for 14 years with onset following a mild closed-head TBI and no prior history of brain injury (Fitzgerald et al., 2011). MRI and diffusion tensor imaging (DTI) demonstrated no presence of diffuse axonal injuries. Desvenlafaxine was held at a constant dosage 8 weeks prior to treatment and throughout the course of rTMS. Sequential bilateral rTMS was administered to the DLPFC: right-sided LF (1 Hz) rTMS followed by left-sided HF (10 Hz) rTMS. The patient showed a positive response to treatment with a significant (> 50 %) reduction in depressive symptoms (MADRS = 14; IDS-CR = 21). Attention, concentration, working memory, speed of information processing, verbal and visual memory, perceptual ability, and executive functioning were assessed by means of neuropsychological tests, and an impairment of any cognitive performance was detected. No adverse side effects of treatment were reported.

In a randomized, sham-controlled study (34 George et al., 2014). HF rTMS was administered over the left PFC to suicidal inpatients (Beck Scale of Suicidal Ideation [SSI] score ≥12 and ≥3 on Question #3 of the Hamilton Depression Rating Scale). Forty-one patients with a diagnosis of either post-traumatic stress disorder (PTSD) or mild TBI (mTBI) were recruited for this study (20 active and 21 sham). The protocol was generally well tolerated with no major side effects. A trend toward a more rapid change in SSI in the active rTMS group compared

to the sham group was observed, but there was no overall difference in the change in SSI between groups. Patients showed a reduction in how much they were bothered by thoughts of suicide, but they demonstrated no difference in future intent of suicide, thoughts of suicide, self-rated sadness, tiredness, or happiness. Since the patients continued to receive standard inpatient care, including changes in medication, throughout the study, so the observed results cannot be separated from any non-specific hospitalization effect. Results were not broken down between patients with PTSD and TBI, so conclusions cannot be drawn regarding the efficacy of this protocol specifically in relation to TBI. Anyway, the fact that this rather aggressive protocol was generally well tolerated demonstrates its feasibility.

A review article identified six randomized controlled trials (RCTs) of non-pharmacological interventions for depression in adults and children who had a TBI, with a total of 334 adult participants, none of these studies that included children as participants (Gertler et al., 2015).

A high risk of bias was identified in all studies due to a lack of blinding of participants and personnel and five studies due to a lack of blinding of outcome assessors. Because of the very-low quality evidence, the small effect sizes and the wide variability of results, no comparisons showed a reliable effect for any intervention.

A case report study also provided evidence for successful treatment of refractory depressive symptoms after severe TBI with the addition of rTMS to psychotherapy and mood-stabilizing medications, supporting the safety and tolerability of this novel therapeutic approach (Iliceto et al., 2018).

A recent study investigated the use of rTMS targeted with individualized resting-state network mapping (RSNM) of dorsal attention network (DAN) and default mode network (DMN) in subjects with treatment-resistant depression associated with concussive or moderate TBI (Siddiqi et al., 2019). MADRS improvement was inversely correlated with functional connectivity between the right-sided stimulation site and the subgenual anterior cingulate cortex (sgACC). RSNM-targeted rTMS is feasible in TBI patients with depression.

Another study was conducted to investigate the effects of LF rTMS of the right DLPFC on both depression and cognition in patients with TBI (Lee and Kim, 2018). A significant decrease in MADRS, Trail Making Test (TMT), and Stroop Color Word Test (SCWT) was observed after the intervention in the experimental group ($P < 0.01$), and there was a significant difference in the change value of MADRS, TMT and SCWT compared to the control group ($P < 0.01$). Therefore, the application of LF rTMS to the right DLPFC of patients with TBI seems to have a positive effect on depression and cognition.

A more recent study assessed specifically the safety, tolerability and efficacy of TMS for the treatment of post TBI depression (Hoy et al., 2019). rTMS was shown to be safe and well tolerated in patients who had developed depression after a TBI. After sequential bilateral rTMS (to the left and right DLPFC) there was no significant effect of rTMS on post-TBI depression, while there were significant improvements in cognition following active rTMS in the areas of working memory ($p = 0.021$) and executive function ($p = 0.029$).

In another recent pilot study the effect size of LF rTMS over the right DLPFC has been explored in 30 patients with TBI depression and co-occurring neuropsychiatric symptoms. Small (Hedge's $g = 0.19$) and highly variable effects were observed for treatment of depression and comorbid neuropsychiatric symptoms (Rao et al., 2019).

### 5.4. Auditory dysfunction

The rTMS treatment of severe tinnitus [tinnitus questionnaire (TQ) = 53] lasting for 4 years following a severe TBI has been reported in a complex 53-year-old male patient (35 Kreuzer et al., 2013). The patient presented with co-morbid post-injury onset depression, associated severe sleep disturbances, alcohol and benzodiazepine abuse, as well as a single symptomatic seizure immediately following TBI but no subsequent seizures. Prior treatments for tinnitus, including acupuncture, osteopathy, hyperbaric oxygen therapy, intravenous application of steroids, and acoustic stimulation were unsuccessful. Through the course of rTMS alcohol and benzodiazepine intake were excluded via laboratory tests. Antidepressant (75 mg amitriptyline) and antiepileptic (150–300 mg pregabalin) dosage kept constant throughout treatment. Trains of stimulation at 110 % resting MT (1 Hz, 2000 stimuli/session) applied to the left primary auditory cortex for 10 sessions demonstrated a positive effect lasting 3 months after the first treatment series (TQ = 38). Four subsequent treatment series over the course of 3 years demonstrated effects lasting 6 months (TQ = 26 after third session, no ratings taken after fourth session). The fifth and final series followed a modified protocol targeted at the right DLPFC (1 Hz, 1000 pulses/session) followed by stimulation applied to the left primary auditory cortex (1 Hz, 1000 pulses/session) for a duration of 5 days (beginning of fifth session TQ = 50; following treatment TQ = 33). The patient remained abstinent from alcohol and benzodiazepines throughout treatment. The patient reported a reduction in loudness of tinnitus, and treatment was reported to be well tolerated without adverse effects or seizures as a result of rTMS intervention.

The use of rTMS in the treatment of musical hallucinosis (a form of auditory hallucination) with an onset of 10 months following right temporal injury has been evaluated in a 63-year-old male patient with prior moderate–severe hearing loss (hearing loss remained constant throughout and following treatment) from chronic daily noise exposure over 20 years (Cosentino et al., 2010). EEG scans showed an absence of epileptiform abnormalities. MRI revealed a contusion of the right temporal pole and PET scans demonstrated hypoactivity in the corresponding temporal lesion as well as increased metabolic activity in the right posterior temporal cortex (PTC). However, neurological and neuropsychological status was normal for age and education level as assessed by memory, attention, language, apraxia, and visuospatial tests. The patients were unsuccessfully treated in the months prior to rTMS with antiepileptics (gabapentin and carbamazepine) and antipsychotics (risperidone and paroxetine). rTMS was administered to the right PTC at 90 % MT (1 Hz, 1200 pulses/session; 20 min train duration) for 2 weeks. On a 10-point scale the severity of musical hallucinations decreased from 5 to 8 points prior to treatment to 2 points post-treatment. PET scans during 5 months of follow-up sessions demonstrated decreased hyperactivity and decreased metabolic activity of the right PTC. Cognitive abilities pre- and post- rTMS intervention have not been examined. No adverse effects were reported.

### 5.5. Chronic dizziness

In a case report study a patient with chronic dizziness following mTBI underwent 10 sessions of 10 Hz at 70 % of resting MT. Dizziness symptom severity and frequency were reduced by greater than 50 % at 3 months post rTMS treatment applied over the DLPFC bilaterally, with a clinically significant reduction of dizziness disability on the Dizziness Handicap Inventory from 40 to 21 points. Even if this is a one case report, rTMS could represent an effective and cost-effective treatment option for patients who experience persistent post-traumatic dizziness secondary to mTBI (Paxman et al., 2018). The results of this one case report should be replicated in RCTs on large patient samples.

### 5.6. Motor dysfunction

The case of a 25-year-old man with chronic bilateral cortico-subcortical parieto-occipital traumatic lesion, who underwent three weeks of cerebellar iTBS, combined with neurorehabilitation treatment, has been reported (Martino-Cinnera et al., 2016). The results showed significant improvements in balance performance (as assessed by the Berg Balance Scale), motor recovery (as assessed by the Fugl-Meyer Assessment), step length, and walking speed.

### 5.7. Pain

Non-invasive brain stimulation techniques aim to induce an electrical stimulation of the brain in an attempt to reduce chronic pain by directly altering brain activity (O'Connell et al., 2013). A unique study aimed at determining whether HF (10 Hz) rTMS, applied over the M1 of the affected hemisphere, can be used to alleviate chronic central pain after mild TBI (Choi et al., 2018).

The numerical rating scale (NRS) score of the group assigned to the rTMS group was significantly lower than the sham group score at all clinical evaluation time-points during and after rTMS sessions. The rTMS group's SF-36 PCS score was significantly higher at post2, post3, post4, and post5 compared with the sham group. HF rTMS may thus be used to manage chronic central pain and improve quality of life in patients with mild traumatic brain injury. It should be considered that this is a pilot study and further research is needed.

### 5.8. Headache

Persistent mTBI related headache (MTBI-HA) represents a neuropathic pain state.

The effects of rTMS in posttraumatic headache has been assessed in veterans which were randomized to receive either HF (10 Hz) real rTMS or sham rTMS over the left M1 with brain MRI neuronavigation guidance (Leung et al., 2016). The group who received real rTMS demonstrated a significantly higher reduction in persistent headache intensity than the sham group. At least a 50 % headache intensity reduction at post-treatment one-week assessment as well as a significant reduction of the composite score of functionally debilitating headache exacerbation were found in real group at the post-treatment four-week assessment in comparison with the sham group.

The same research group also examined the hypothesis that rTMS at the left prefrontal cortex (PFC) can relieve persistent mild TBI related headache and associated neuropsychological dysfunctions (Leung et al., 2018). A significant reduction in the prevalence of persistent headache at the one-week and four-week assessments, as well as a significant improvement in the Hamilton Rating Scale for Depression score were found in the active group. This trend of improvement was also present at the post-treatment four-week assessment, even if it was not anymore statistically significant. More recently, a double-blind, randomized, sham-controlled, pilot clinical trial was performed on 20 participants with persistent post-traumatic headache (PTH) and persistent post-concussion symptoms (Stilling et al., 2020). Ten sessions of rTMS therapy (10 Hz, 600 pulses, 70 % resting motor threshold amplitude) were delivered to the left DLPFC. There was a significant overall time effect for average headache severity and a reduction in headache frequency at 1 month post-treatment. Secondary outcomes revealed an overall time interaction for headache impact, depression, post-concussion symptoms, and quality of life. In the REAL group, 60 % returned to work whereas only 10 % returned in the SHAM group. Since there was a 100 % response rate, no dropouts, and minimal adverse effects, a larger phase II study is warranted.

## 6. Discussion

The neurometabolic and cytoskeletal changes that occur after TBI (including mTBI) are known to impair structural and functional connectivity. Combined TMS and EEG (TMS-EEG) may offer several advantages over traditional approaches for studying connectivity changes post TBI (Coyle et al., 2018).

After TBI occur, in addition to the effects that are related to the primary site of damage, the resulting functional outcomes depend highly on changes that occur in regions that are remote but functionally connected to the site of injury. Excitatory rTMS can promote neuroplasticity, and when combined with task performance training, has the potential to promote adaptive plasticity (Villamar et al., 2012).

The reviewed studies in experimental animals explored the potential of rTMS as an anti-apoptotic and anti-inflammatory treatment, and showed that rTMS induced a significant improvement in neurobiological scores after TBI. These studies thus suggest that TMS might be as a promising tool for reversing the adverse neuronal mechanisms activated post-TBI, and that this approach could be translated to intervention in humans (Lu et al., 2015).

In rats combining noninvasive TMS with rehabilitative training in an EE can facilitate post-TBI recovery in rats via cortical excitability and reorganization (Shin et al., 2018).

However, although several research groups have proposed the use of rTMS to enhance neuroprotection and recovery in patients with TBI, few studies have obtained sufficient evidence regarding its effects in this population. To date, noninvasive neurostimulation techniques have been used alone or in combination with rehabilitation therapy to treat the neurological sequelae of traumatic brain damage in a rather limited number of studies (often only single case studies, only eleven RCTs) with rather variable therapeutic outcomes. One potential factor limiting a consistent success for these techniques may be the limited number of sessions carried out in patients, despite reports that their accrual may play a key role in the reversal of neurological deficits long-term.

Nonanoxic individuals whose disease process is within 3 months are more likely to benefit from rTMS treatment (He et al., 2018). rTMS has shown good results in treating major depression and may be promising for patients with post-traumatic depression. Indeed, several studies provided support for the safe and effective clinical use of rTMS for refractory depression in post-TBI patients, without significant side effects. Interestingly, rTMS may represent a promising approach also to reduce suicidal ideation in subjects with post-traumatic depression (George et al., 2014; Rao et al., 2019; Siddiqi et al., 2019).

This approach may have some utility predominantly in improving cognitive function in subjects with post-TBI depression. In particular, LF rTMS to the right DLPFC has proven to be effective in improving depression and also cognitive function in TBI patients. Given the dearth of existing evidence-based treatments for depression in this patient population, these preliminarily encouraging results indicate that larger controlled trials are warranted.In a recent study, no improvements were found in the cognitive executive functions of 30 patient with severe, chronic DAI patients in the real group compared to the sham group (Neville et al., 2019). These findings are due to the nature of DAI, which affects widespread cortical neural networks, leading to primary and secondary axotomy and microhemorragies (Adams et al., 1989). Therefore, the authors argue that TMS may not be the best option for this target population due to its focality. On the other hand, the cognitive enhancement induced by rTMS has been reported mostly in depressive patients (Lefaucheur et al., 2020). Since HF rTMS applied over the left DLPFC has proven to effectively treat depression, it is conceivable that this kind of rTMS can lead to cognitive improvement as a consequence of mood amelioration, but the pathophysiology of TBI and depression are markedly different.

The therapeutic mechanisms of rTMS in post-traumatic depression have been suggested to include neurogenesis and plasticity mechanisms. In fact, when rats with TBI received rTMS, they exhibited significantly greater proliferation in the subventricular zone, significantly higher rates of neuron survival, and significantly reduced rates of apoptosis than similarly injured control rats (Lu et al., 2017), thus suggesting that HF rTMS could promote neurogenesis. rTMS-induced plasticity, including the induction of LTP and LTD, has been confirmed in animal rTMS studies (Tang et al., 2017). Furthermore, dysregulation of neural brain-derived neurotrophic factor (BDNF) has been reported in TBI (Kaplan et al., 2010), and studies have demonstrated that HF rTMS enhances BDNF expression levels (Baek et al., 2018).

No major adverse events occurred in all the reviewed studies and overall no significant difference in the frequency of mild adverse events has been observed between groups. The most frequent adverse effects included headache, twitching and site discomfort, more rarely

tenderness, tinnitus, dizziness, pre-syncopal episodes, worsening mood and elevation of perseveration score. The occurrence of seizure in TBI patients is uncommon, especially when sub-threshold stimulation intensities are used. On the other hand, HF rTMS, including iTBS, can improve the excitability of the target cortex, thus improving the function. From this point of view, there must be glial scar formation in the target cortex after TBI, and if local excitability is improved, epilepsy may be induced.

In fact, daily administration of rTMS could produce increasing afterdischarges, triggered seizures and finally spontaneous epileptic seizures (Cavinato et al., 2012). Even if the stimulation parameters are considered "safe" according to the 2009 safety guidelines (Rossi et al., 2009), safety standards in patients with brain disorders might not operate in each case. Nevertheless, LF TMS are less likely to trigger a seizure than HF rTMS, and can thus be proposed as a safer option in TBI patients (Reti et al., 2015). Interestingly, extremely low-frequency electromagnetic fields were also found to have beneficial effects (Yang et al., 2012).

Long-term disabilities following TBI include mostly cognitive and emotional derangements, but also sensory and motor impairments. It has been demonstrated that contralesional iTBS applied during recovery from cortical injury in rats improves the recovery of motor function (Barry et al., 2014)

TBS delivered through implanted electrodes may thus be a promising avenue to explore for augmenting rehabilitation from TBI.

TMS and other noninvasive brain stimulation techniques are still not widely used and remain poorly understood in neurorehabilitation. Concerns remain regarding the safety and longevity of rTMS therapy, given that the physiologic effects of the treatment and the extent of stimulation that may be administered without seizure induction are not fully understood.

It should be considered that standard coils used in research and the clinic for rTMS are not capable of directly stimulating deep brain regions. Conversely, the Heased coil (H-coil) is likely to have the ability of deep brain stimulation without the need of increasing the intensity to extreme levels (Zangen et al., 2005). Deep TMS (dTMS) thus enables deeper non-invasive cortical stimulation at an effective depth of approximately 3 cm depending on the coil's design and the stimulation intensity. Surprisingly, dTMS has never been performed in subjects with TBI.

The reviewed studies had some limitations. Most of them are single case studies, 34 % of the reviewed human literature originates from single case reports. Overall, the relatively small sample size results in a lower statistical analysis power, limits the generalizability of the conclusions and the reliability of the therapeutic effects of rTMS in TBI patients. Moreover, the stimulation protocols, with respect to total number of pulses, duration frequency and intensity of stimulation, location and number of sessions delivered, timing of the concomitant neurorehabiltation, are highly heterogeneous. Therefore, since only a few trials have used a similar study design, estimating the real effectiveness and reproducibility is very difficult. On the other hand, due to the remarkable clinical disability, controlled clinical trials, which often involve the use of a placebo, are challenging to perform, because of the ethical issues linked to the severe nature of their clinical conditions and to the inability of the pessimistic subjects' legal guardians to provide informed consent. Another limitation is that the follow-up assessment and wash-out period were mostly rather limited. It is therefore difficult to appreciate possible prolonged effects may last following treatment. Therefore, it is useful to conduct follow-up testing at longer intervals. Furthermore, the operators who delivered the rTMS were often blind to the type (real or sham) of rTMS application, so the performance bias could not be excluded.

A short-course rTMS at the left DLPFC can alleviate MTBI-HA symptoms and provide a transient mood enhancing benefit. Further studies are required to establish a clinical protocol balancing both treatment efficacy and patient compliance.

EEG represents a potential biomarker for the therapeutic efficacy of rTMS. EEG recordings serve as a direct measure of neuronal activity, and TMS combined with high-density EEG (TMS-EEG) has allowed to study connectivity within brain networks (Miniussi and Thut, 2010; Ilmoniemi and Kicic, 2010) Such recordings have facilitated the integration of structural and functional cerebral changes, enabling a greater understanding of the variation between different states.

In conclusion, whether provided in isolation or in combination, rTMS and neurorehabilitation are synergistic in the potential to transform clinical practice. However, in humans a few pilot studies have been performed and these were limited by the small sample size and methodological concerns. In order to reach definitive conclusions, further large sample and well-designed clinical studies with appropriate patient selection are required to verify the possible positive effects of rTMS and to determine the optimal stimulation protocols, including target, stimulation intensity/duration and number of sessions.

## Declaration of Competing Interest

None.


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