The Use of Repetitive Transcranial Magnetic Stimulation (rTMS) following Traumatic Brain Injury (TBI): A Scoping Review

Aimee E Pink[a,b], Claire Williams[a*], Nick Alderman[a,c], & Martine Stoffels[d]

[a]Department of Psychology, Swansea University, Swansea, UK, [b]Independent Neurorehabilitation Providers Alliance, UK, [c]Elysium Neurological Services, Elysium Healthcare, Badby Park, Daventry, UK, [d]Priory Neurobehavioural Brain Injury Services, Burton Park Brain Injury Hospital, Priory Group, Warwick Road, Melton Mowbray, Leicestershire, UK

A.E.Pink@swansea.ac.uk (https://orcid.org/0000-0003-1516-7922),

Claire.Williams@swansea.ac.uk (https://orcid.org/0000-0002-0791-744X),

nick.alderman@elysiumhealthcare.co.uk, MartineStoffels@priorygroup.com

Corresponding Author: Assoc. Prof. Dr Claire Williams

Email Address: Claire.Williams@swansea.ac.uk

Abstract Word Count: 195 words

Manuscript Word Count (excluding title page, abstract, references, tables and figures):

7,422 words

Abstract

There is continued interest in developing effective and innovative treatment approaches to manage and improve outcomes after traumatic brain injury (TBI). Included in this, is the potential use of repetitive Transcranial Magnetic Stimulation (rTMS), a neuromodulatory tool currently recommended by the National Institute for Health and Care Excellence as a treatment for depression. This review considers the application of rTMS after TBI, focussing on its therapeutic efficacy for a broad range of sequalae, whether an optimal and safe rTMS protocol can be determined, and recommendations for future clinical and research work. Five research databases (MEDLINE, CINAHL, PsychINFO, SCOPUS, and Web of Science) were electronically searched, identifying thirty empirical studies (single and multiple subject case reports; randomised controlled trials) for full review. Evidence suggest that rTMS has the potential to be an efficacious therapeutic intervention for multiple symptoms after TBI, including depression, dizziness, central pain, and visual neglect. However, the picture is less encouraging for prolonged disorders of consciousness and mixed for cognitive outcomes. Overall, rTMS was well-tolerated by patients, although some incidents of side effects and seizures have been reported. Recommendations are made for more comprehensive guidelines and sufficient reporting of rTMS parameters and procedures.

Keywords: Repetitive Transcranial Magnetic Stimulation, rTMS, Traumatic Brain Injury, Rehabilitation

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability, with Dewan et al. (2018) estimating that 69 million new cases of TBI will occur worldwide each year. Occurring along a continuum of severity and affecting a diverse set of cortical and sub-cortical structures (Aharon-Peretz & Tomer, 2007; Bigler, 2001, 2007), TBI is largely heterogeneous, with no two cases presenting the same symptoms despite seemingly similar injuries. Chronic and enduring problems with cognition, executive function, behavioural control, and emotion regulation are common (McMillan & Wood, 2016; Williams & Wood, 2010; Williams, Wood & Howe, 2018), imposing serious constraints on psychosocial recovery (Alderman & Wood, 2013). Given this, there is continued interest in developing effective and innovative treatment approaches to manage and improve outcomes after TBI.

Included in this, is the potential use of repetitive Transcranial Magnetic Stimulation (rTMS), a neuromodulatory tool which can induce neural activity through rapidly alternating magnetic fields (Dhaliwal, Meek, & Modirrousta, 2015; Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Brief electrical currents run through a coil creating a magnetic field at the focal point of the coil, stimulating cortical neurons below (Dhaliwal et al., 2015). rTMS is versatile, and depending on location and frequency, can be used to either inhibit or induce local and remote brain activity (Ziad, 2002). Standard rTMS is typically delivered as a train of repetitive pulses with an identical stimulus interval (Sandrini, Umilta, & Rusconi, 2011). High-frequency (≥5 Hz) stimulation is thought to facilitate neuronal excitability, whilst low-frequency (<1Hz) stimulation shows inhibitory effects (Mansur et al., 2005; Peinemann et al., 2004; Rossi et al., 2009). In contrast, patterned forms of rTMS (which are typically shorter in duration and linked to sustained changes in cortical activity; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Oberman, Edwards, Eldaief, & Pascual-Leone, 2011) normally involve a burst of three pulses applied at 50Hz and with an inter-burst interval of 200ms (Oberman et al., 2011), with a

decrease or increase in cortical excitability depending on the temporal application of the bursts. For example, continuous theta burst stimulation (cTBS) to decrease excitability consists of a 40s train of uninterrupted theta burst stimulation (TBS) with a total of 600 pulses, whereas intermittent theta burst stimulation (iTBS) to increase cortical excitability involves a 2s train of TBS repeated every 10s for a total of 190s and 600 pulses (see Schicktanz et al., 2015). Overall, rTMS paradigms are relatively easy to administer, are non-invasive, and are typically well-tolerated by patients (Choi, Kwak, Lee, & Chang, 2018). Indeed, one of the major advantages of rTMS is its relative safety and the absence of serious adverse side-effects (Dhaliwal et al. 2015), although there have been some reports of increased seizure risk (Hufnagel et al. 1990; Wassermann et al., 1996). However, even though initial evidence suggests that standard and patterned forms of rTMS confer similar risk of adverse events occurring, it remains unclear what mechanisms or combinations thereof correspond to increased risk, such as frequency, duration, stimulus intensity or total number of pulses. For this reason, there is on-going need to thoroughly examine the safety of rTMS, including any potential increased risk resulting from the application of higher frequency bursts with patterned rTMS.

Despite this, rTMS is currently recommended by the National Institute for Health and Care Excellence (National Institute for Health Care Excellence (NICE), 2015) and is approved by the U.S Food and Drug Administration (FDA approval K083538) as a treatment for depression. In addition, there has been growing interest in the potential use of rTMS as a therapeutic intervention for a variety of neurological disorders and conditions, including Parkinson's disease (Boggio et al., 2005), stroke (Hara, Abo, Kakita, Masuda, & Yamazaki, 2016), and Alzheimer's disease (Haffen et al., 2012). Insight gained from such studies has led to a number of reports documenting the use of single- and paired-pulse transcranial magnetic stimulation for prognostic and diagnostic purposes after TBI (Bagnato et al., 2012; Chistyakov

et al., 1999; Rosanova et al., 2012). Further, the potential therapeutic efficacy of rTMS after TBI has started to be explored.

Herrold et al. (2014) identified seven case studies and one non-randomised pilot study using rTMS to treat a specific neurological sequelae following mTBI. Different sites of stimulation and rTMS parameters were employed, with large heterogeneity across samples. Herrold et al. concluded that rTMS may be well suited for the treatment of mTBI, but noted the need for larger-scale studies to be conducted before firm conclusions could be drawn. Subsequently, Dhaliwal et al. (2015) identified eight case-studies and four multi-subject reports concerning the efficacy of rTMS in the treatment of symptoms following TBI. They too concluded that rTMS showed potential in the treatment of TBI related symptoms (e.g. hemispatial neglect, executive dysfunction), with rTMS generally well tolerated by patients. However, the authors noted that the literature was in its infancy, with not enough data available to draw conclusions regarding the definite efficacy of rTMS following TBI. In addition, they also noted a need for further improvement of safety guidelines to minimize the risk of adverse events, including seizure and syncope.

Since these initial reviews, there has been a sharp increase in the number of published trials and reported case studies exploring the efficacy of rTMS after TBI. Consequently, we review the literature to consider the application of rTMS after TBI, and specifically, its efficacy for the remediation and rehabilitation of a broad range of symptoms and neurological sequelae. We place particular emphasis on exploring a broad range of sequelae, documenting short- and long-term outcomes, and whether an optimal and safe therapeutic rTMS protocol can be determined. We conclude by making a number of recommendations for future clinical and research work.

Method

Records were identified by searching five electronic databases, including MEDLINE, CINAHL, PsychINFO, SCOPUS and Web of Science. A comprehensive list of keywords and search terms for two key concepts (repetitive transcranial magnetic stimulation; traumatic brain injury) were developed using a preliminary search by author AP (Table 1). The search was conducted on 18 October 2018, and screening of results and study selection was performed independently in an unblinded standardised manner by two reviewers (AP and CW). Reviewers were aware of manuscript authorship, institution, and journal. Disagreements between reviewers were resolved by consensus. Mendeley was used to manage citations and manuscripts (https://www.mendeley.com).

[Table 1 here]

The search strategy (see Figure 1) identified a combined total of 792 records (electronic database results; handsearching; reference lists; unpublished literature - conference abstracts, trial reports), with automatic screening processes subsequently removing duplicate entries (n = 276), as well as non-English language (n = 9) and/or non-human/s subject (n = 71) focussed articles. Remaining records (n = 436) were screened against the eligibility criteria based on title and abstract only, followed by a full-text review where applicable (n = 110). At this stage, records were excluded if they did not use rTMS or only used it for diagnostic and/or prognostic purposes. In addition, records with mixed samples (e.g. non-traumatic aetiologies) where data for participants with TBI could not be distinguished with confidence were excluded. Similarly, trial protocols, commentaries, conference abstracts, and records without an accessible and/or corresponding full-text were excluded.

[Figure 1 Here]

Results

Thirty empirical studies involving the use of rTMS (standard rTMS = 28, patterned rTMS = 2) as a therapeutic or rehabilitative intervention for symptoms and sequelae following TBI were retained for full review. Fourteen studies concern single- or multiple-case reports, with the remaining 16 involving multiple patients (e.g. randomised controlled trials). The majority of studies review rTMS as a stand-alone treatment, although some examine its effectiveness alongside existing rehabilitation practices and/or combined with a complementary designed therapy. Varied symptoms and sequelae are also addressed. Relevant methodological details from the reviewed rTMS papers are summarised in Table 2. Owing to the heterogeneity of TBI, detailed information concerning patient descriptions, rTMS protocols, and stimulation parameters are also captured. Relevant methodological details from the reviewed rTMS papers are summarised in Table 2. This was jointly developed by AP and CW, and owing to the heterogeneity of TBI, detailed information concerning patient descriptions, rTMS protocols and stimulation parameters were captured for each eligible article. AP initially charted the information and subsequently discussed and reviewed the captured details with CW. Any disagreements or inconsistencies in the charting process were resolved through discussion between the two reviewers.

[Table 2 Here]

Post-concussion Syndrome (PCS)

Koski et al. (2015) examined the safety and efficacy of 20 sessions of rTMS over the left dorsolateral pre-frontal cortex (left-DLPFC) for alleviating persistent PCS arising from mTBI (*n* = 15). The majority (80%) of patients completed the full rTMS protocol, but allowance was made to gradually increase stimulation intensity across sessions. Side effects were minimal and

at one to two weeks post-rTMS, severity of PCS had declined by an average of 14.6 points. Using a PCS scale change score of five points or more as indicative of change over time, nine of twelve completers improved, whereas one patient worsened. However, even though mean change scores for individual PCS symptoms showed a decline in ratings across a number of areas (e.g. headache, fatigue), none reached statistical significance. At three-month follow-up, PCS treatment gains were either stable or improved for three of eight patients assessed. For the remaining patients, treatment gains had dissipated or returned to baseline or worse, suggesting that the effects of rTMS may be of limited duration, such that maintenance sessions may be needed. In contrast, Rutherford et al. (2017) found no immediate benefit of 13 sessions of rTMS to the left-DLPFC one-month post-intervention, but a significant reduction in PCS symptoms in an active (n = 7) versus sham (n = 7) group at two-month follow-up. Therefore, the time course and stability of rTMS remains uncertain. Further, the mechanistic action by which rTMS may exert its effects on PCS symptoms remains unclear, although Koski et al. found preliminary evidence to suggest that patterns of neural activity in the DLPFC and anterior cingulate cortex (increase and decrease, respectively) consequent to rTMS may underlie its effects.

Headaches

As rTMS has proven effective for relieving pain with central nervous system aetiologies (Leung et al., 2009), a series of studies explored the efficacy of rTMS in alleviating mTBI headaches (mTBI-HA). In a prospective case series (n = 6), Leung, Fallah, et al. (2016) found that four sessions of rTMS (delivered over DLPFC and/or left motor cortex - LMC) reduced the intensity, frequency and duration of mTBI-HA symptoms, with notable improvements observed for five of six patients. Similarly, two randomised control trials have also found alleviation of mTBI-HA symptoms after relatively short courses of rTMS. Leung, Shukla, et

al. (2016) allocated patients with mTBI-HA to receive either three sessions of active (n = 12) or sham (n = 12) rTMS over the LMC. Compared to sham, the active group reported a significant percentage reduction in persistent headache intensity one-week post intervention (50% vs. 16.6%). However, these differences were no longer evident four weeks post-intervention. In contrast, debilitating headache exacerbation scores were significantly lower in the active group four weeks post-intervention, while scores for the sham group remained unchanged. In a subsequent RCT of similar design and sample size, Leung et al. (2018) found that four neuronavigated sessions of rTMS over the left-DLPFC could alleviate mTBI-HA symptoms over a longer time course. A significantly higher percentage of patients in receipt of active rather than sham rTMS no longer experienced persistent headache at one- (50% vs. 7%) and four-weeks (57% vs. 20%) post-intervention. Additionally, patients in the active group also reported lower debilitating headache and average daily persistent headache intensity scores one- and four-weeks post-intervention.

Such findings support the clinical feasibility and efficacy of a short-duration of rTMS for alleviating mTBI-HA, paving the way for morphological and mechanistic assessments of the treatment. However, the potential influence of comorbidities (e.g. depression, PTSD) on initial symptom perception or treatment response has yet to be explored. Stimulation of the DLPFC has been shown to have antidepressant effects, and consequently, the alleviation of mTBI-HA symptoms reported in Leung et al. (2018) may have been attributable to changes in the severity of depression rather than a direct effect of rTMS. In addition, neither RCT examined outcomes by mechanism of injury even though there is some evidence that clinical and functional outcomes may differ following blast versus non-blast related TBI (Greer et al., 2017; Lange, Iverson, Brubacher, Mädler, & Heran, 2012; Wilk et al., 2010). It also remains unclear whether there are any significant differences in the short- and long-term efficacy of rTMS for alleviating mTBI-HA between the LMC versus DLPFC.

Dizziness

Some patients with TBI experience persistent idiopathic post-traumatic chronic dizziness, leading to reduced quality of life (Chamelian & Feinstein, 2004). In a near-identical protocol to Koski et al. (2015), Paxman et al. (2018) explored the efficacy of ten sessions of high frequency rTMS delivered over the DLPFC in a 61-year-old male with persistent (>5 years) dizziness following mTBI. In addition to a clinically meaningful reduction in the adverse impact of dizziness on quality of life (Tamber, Wilhelmsen, & Strand, 2009), pre-intervention dizziness severity and frequency were reduced by more than 50% three-months post-intervention, with notable improvements observed between one- and three-months; possibly suggesting a delayed response to rTMS. Additionally, with a cost of $C300 per session, they argued that ten sessions of rTMS represents a low-cost burden compared to conventional therapies. However, studies focussing on pathophysiology and long-term follow-up are needed to determine the mechanistic action of rTMS and longevity of symptom relief.

Central Pain

Building on existing evidence concerning the efficacy of rTMS for managing various chronic pain conditions (Galhardoni et al., 2015), one study has examined the effects of high intensity rTMS for the management of medically intractable chronic pain after mTBI. Choi et al. (2018) found that ten sessions of high-intensity rTMS applied over the primary cortex (M1) resulted in a significant reduction in self-reported pain intensity and improved physical health-related quality of life compared to a sham group, with treatment gains sustained for at least four-weeks. Speculating on the potential mechanisms underpinning the observed effect, they argued that rTMS applied to the M1 could have provided an analgesic effect by improving blood flow, influencing the endogenous opioid system, or by modifying abnormal thalamocortical excitation of the sensory system.

Depression

Given the reported efficacy of rTMS for treating refractory depression in patients without TBI and that response rates to antidepressants have been reported to be lower following TBI than found in non-TBI depressed populations (Fann, Hart, & Schomer, 2009), several studies have explored whether rTMS can also improve mood after TBI. Fitzgerald et al. (2011) found a 50% reduction in Montgomery-Asperg Depression Rating Scale (MDRS; Montgomery & Asberg, 1979) scores after applying sequential low and high frequency stimulation to the right and left-DLPFC in a 41-year-old female 14-years post-TBI. Similarly, Nielson et al. (2015) found that 30 sessions of low frequency rTMS over the DLPFC improved mood in a 48-year-old male who had sustained a severe TBI five years prior. Specifically, baseline Hamilton Depression Rating Scale (Hamilton, 1986) scores had decreased by 49% at three-month follow-up, representing an improvement from severe to minor depressive symptoms. A similarly large effect was found by Iliceto et al. (2018) who reported a 70.8% reduction in self-reported mood symptoms from the start (assessment at one-week) to the end of a six-week (30 sessions; DLPFC) high-frequency rTMS protocol in a 37-year-old male with severe TBI. However, it should be noted that no true baseline quantitative assessment of the patient's depressive symptoms was taken before the onset of the rTMS protocol. In addition, there were also several changes to the patient's psychiatric medication regimen that commenced around the start of the protocol. Consequently, determining the specific contribution of rTMS to the patient's self-reported change in mood is not possible.

Even so, a number of pilot RCTs have also reported significant reductions in depressive symptoms in medically stable TBI samples after rTMS. Leung et al. (2018) reported slightly improved mood one-week post-assessment following active rTMS, and Siddiqi et al. (2018) found that MDRS scores had improved by an average of 56% following 20 sessions of bilateral rTMS applied to the left- (high frequency) and right-DLPFC (low frequency) (n = 9) compared

to 27% following sham (n = 5) stimulation (Cohen's d = 1.43). Likewise, Lee and Kim (2018) found that ten sessions of low-frequency rTMS applied over the right-DLPFC (n = 7) resulted in a 29.29% pre- to post-intervention decrease in MDRS scores compared to only 1.4% after sham stimulation (n = 6; effect size = 1.44). However, the active group also performed significantly better post-intervention on the Trail Making Test (TMT) and the Stroop Colour Word Test (effect size = 1.49 and 1.24 respectively). Consequently, it remains unclear whether the reported effect of rTMS on depressive symptomology was direct, or indirect via improved neurocognitive performance. In addition, none of the RCTs described above evaluated whether treatment gains persisted several months beyond the cessation of the rTMS protocol and all involved relatively small sample sizes, thereby limiting the generalisability of results. Finally, it should also be noted that Rutherford et al. (2017) found no significant active versus sham group differences in mood when assessed immediately post-intervention and at two-month follow-up. Instead, a likely placebo effect was noted, where MDRS scores improved slightly pre- to post-intervention in both groups.

Cognitive

In a case study of a 67-year-old male presenting with severe cognitive impairment following traumatic diffuse axonal injury, Hara et al. (2017) examined the treatment efficacy of 12 sessions of high frequency rTMS applied to the anterior cingulate gyrus combined with goal-oriented cognitive rehabilitation. Very small improvements on the Mini-Mental State Examination and TMT were found immediately post-treatment. These gains remained at three-month follow-up, but performance on measures of memory remained unchanged from baseline. In a similar vein, Pachalska et al. (2011) examined the therapeutic effectiveness of behavioural training combined with two differentiated neurotherapy programmes delivered in crossover design (Programme A - 20 sessions of relative beta training; Programme B - 20 sessions of

rTMS) in a 26-year-old male with severe TBI and frontal syndrome. Over the course of the neurotherapy programme, the patient's verbal and non-verbal IQ improved significantly, with memory functions also improving from baseline. However, most improvement occurred following completion of Programme B, suggesting greater efficacy of rTMS over relative beta training. However, given the cross over design, it is not possible to definitely ascribe treatment gains to rTMS alone.

That said, improved cognitive performance has been reported when rTMS has been used in isolation. In addition to the findings of Lee and Kim (2018; see previous section), Fitzgerald et al. (2010) reported small improvements after rTMS in verbal fluency and speed of information processing; although they did not examine whether gains were primary or secondary to concurrent improvements in mood. However, both Koski et al. (2015) and Rutherford et al. (2017) reported no significant changes in cognitive function following rTMS. However, in the latter study, as most patients performed near to the maximum score on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) at baseline, there was little room for improvement following the rTMS intervention.

Aphasia

Chantsoulis et al. (2017) examined the efficacy of two differentiated neurotherapy programmes (see Pachalska et al., 2011) in a 29-year-old female with severe TBI and chronic crossed aphasia. Small improvements were seen across a number of neuropsychological domains (e.g. executive, language, memory) following relative beta training (programme A), whereas most of the patients cognitive dysfunctions had resolved (including language) after low and high frequency rTMS (programme B) was sequentially applied to the left or right frontal and temporal brain regions, respectively. Western Aphasia Battery (Kertsez, 1982) quotient scores improved from 21 at baseline, to 37 after Programme A and 93 after Programme

B. Statistically reliable changes in the physiological parameters of brain functioning were also recorded, including increased event-related potentials (ERPs; P1 and P2 components) from the first (baseline) to the second (Programme A) and third recordings (Programme B), as well as greater activation over the right frontal area at the third recording. However, and similar to Pachalska et al. (2011), given the crossover design, lack of details concerning time between each neurotherapy programme and the presence of behavioural training in both programmes, the distinct therapeutic effect of rTMS in this instance is unclear.

Visuo-Spatial Attention and Neglect

Bonni et al. (2013) demonstrated how continuous theta burst stimulation (cTBS; chosen because of its ability to induce "powerful long-lasting changes in the excitability of the stimulated cortex", page 1) delivered over the left posterior parietal cortex (l-PPC), could improve symptoms of hemispatial neglect in a 20-year-old patient with severe TBI. A two-week course of cTBS (administered twice daily) significantly improved performance on the Behavioural Inattention Test (Wilson, Cockburn, & Halligan, 1987), with clinical gains still evident two weeks post-intervention. These clinical gains were accompanied by decreased excitability of the PPC-M1 connections in the left hemisphere and a bilateral increase in functional connectivity in the frontal parietal network. Such findings appear to lend support to the model of hemispheric competition as the basis of neglect (Nowak et al., 2009), and suggest that both micro- and macro-structural damage could have contributed to the patients hemispatial neglect. However, given the lack of a sham condition, and that neglect may originate from several cortical and subcortical sites, more rigorous systematic approaches (e.g. prospective controlled studies; RCTs) are needed to determine the efficacy of rTMS for such impairments.

Recovery from Disorder of Consciousness (DOC)

Using paired pulse rTMS, which incorporates excitation and cortical rest to enhance safety, Pape et al. (2009) found that a six-week rTMS protocol (30 sessions over the right-DLPFC) led to incremental neurobehavioural gains in a 36-year-old male who remained in a vegetative state (VS) 287 days after severe TBI. The patient progressed clinically from VS at baseline to a Minimally Conscious State (MCS) by the 15th session of rTMS (mid-point), with further improvements up to the 25th session. However, neurobehavioural decline almost equivalent to baseline was observed between the 25th and 30th rTMS sessions; likely reflecting increased levels of fatigue and sleepiness observed at the time of assessment. Neurobehavioural follow-up at six-weeks also indicated decline in functioning compared to the 25th session, but was still higher than baseline and the 30th session (when fatigued). In addition, incremental behavioural changes were also observed, including improved ability to focus on and/or track objects/movement/people, vocalising single words, and using an eyes-open/closed system to answer yes/no questions. Moreover, the patient's primary caregiver reported maintenance of neurobehavioural status one year after post-rTMS. On this basis, the authors concluded that at least 15 sessions of rTMS appear to be required to elicit a clinically significant change from VS to MCS, although noted that changing the dose and/or combining with another intervention could alter the time frame and therapeutic effect.

A handful of additional studies have also examined the efficacy of rTMS for DOC, but they have done so in mixed samples where treatment outcomes are inconsistently examined by aetiology (e.g. anoxia, stroke, TBI). However, even though reported outcomes do not exclusively concern TBI, they nevertheless warrant discussion here as they still provide useful information concerning the application, and potential therapeutic efficacy, of rTMS for DOC after TBI. With this caveat in mind, Xia, Bai, et al. (2017) conducted a single-blinded prospective study with 16 patients (TBI n = 2) with MCS or UWS/VS, finding no significant

improvement in CRS-R scores following 20 sessions of rTMS over the left-DLPFC. Consistent with this, Xia, Liu, et al. (2017) also found no therapeutic effect of either a single or 20 consecutive sessions of rTMS over the left-DLPFC in 13 patients (TBI *n* = 2) with DOC or UWS/VS. Similarly, Manganotti et al. (2013) found no significant improvements in CRS-R scores for three patients with TBI (VS *n* = 1, MSC *n* = 2) following a single session of high frequency rTMS over the left/right M1. However, significant increases in motor-evoked potential (MEP) amplitude were noted. Lui et al. (2016) also found no significant CRS-R changes following a single-session of rTMS (left M1) in patients with VS (TBI *n* = 2) or MCS (TBI *n* = 2) compared to a sham condition, although they noted increased peak systolic and mean flow velocity in patients with MCS.

In addition, Cincotta et al. (2015) found no therapeutic effect of high frequency rTMS at M1 (*n* = 11; 2 with traumatic aetiologies) in the first randomised, sham-controlled, cross-over study of VS. A later study by He et al. (2018) also found no significant changes in EEG parameters, CRS-R or Clinical Global Impression Improvement scale scores in their randomised, sham-controlled, cross-over study of six patients with VS, MCS/Emerging MCS, including four patients with traumatic aetiologies. Although, they noted that CRS-R scores showed slight improvement in response to both active (left M1 stimulation) and sham sessions, with one patient with traumatic aetiology emerging from MCS one week after active rTMS treatment and during a sham rTMS session. Overall, they argued that the differential response to rTMS reported across studies may be attributable to varying CRS-R scores on admission, duration of DOC, and varying aetiology. Indeed, a comparative analysis of Cincotta et al. and He et al. suggests that a lower admission CRS-R score, longer duration (> 9 months), and anoxic-ischemic encephalopathy is perhaps predictive of poorer functional outcomes and rTMS treatment response.

Even so, it should also be noted that there is generally wide variation in rTMS protocols (intensity, frequency, duration and site – see Table 2 for further details), existing studies are limited by small sample sizes, duration of DOC varies substantially, 'awakening' drugs are inconsistently terminated during rTMS protocols, and determining whether disease recovery is attributable to natural recovery or the rTMS intervention delivered is difficult. Further, there is also variation across studies concerning the assessment of minor clinical and behavioural responses indicative of DOC recovery, with several relying on either clinician or caregiver reports despite a lack of concordance often evident between the two (e.g. Cincotta et al., 2015; Schnakers et al., 2009). Finally, even though carry over effects were excluded in one study with cross-over design, it is possible that the prolonged effects of rTMS treatment may extend to several weeks; thus, follow-up testing is required at longer intervals.

Visual and Auditory Impairments

Cosentino et al. (2010) found preliminary evidence of a therapeutic role of rTMS in reducing the frequency and intensity of post-traumatic complex auditory musical hallucinosis, with treatment effects persisting for at least five months. Similarly, in a 53-year-old male experiencing severe tinnitus after TBI with comorbid depression and alcohol abuse, Kreuzer et al. (2013) found that five series of low-frequency rTMS delivered over three years resulted in a significant reduction in tinnitus severity (i.e. loudness, subjective annoyance, tinnitus handicap), with treatment effects lasting three-six months each time. In the latter case study, rTMS was delivered over the left primary auditory cortex in the first four treatment series (ten sessions each) and the right-DLPFC in the final series (five sessions). The patient remained abstinent from alcohol and benzodiazepines during the protocol. However, as the patient was in receipt of antidepressant (amitriptyline) and antiepileptic (pregabalin) medication alongside the protocol, a beneficial indirect effect of these on tinnitus cannot be ruled out. Although, this

seems unlikely as they were prescribed several months prior to the rTMS protocol and their efficacy for tinnitus is either controversial or undocumented (Bayar, Böke, Turan, & Belgin, 2007; Kreuzer et al., 2013).

Jones et al. (2018) also documented a beneficial effect of four sessions of neuronavigated low-frequency rTMS over pharmacological interventions for the treatment of post-TBI refactory binocular oscillopsia. One- to two-weeks following the second trial of rTMS in which visual area V5/MT was targeted bilaterally, symptomatic improvement in large-amplitude oscillations was observed which remained at 12-month follow-up. However, the patient subjectively reported experiencing no benefit from subsequent rTMS trials in terms of visual acuity, visual function (e.g. reading), or other functional abilities, and they continued to experience small-amplitude oscillations. Overall, this suggests that large- and small-amplitude oscillations may reflect different mechanisms, and thus, warrant different rTMS treatment approaches.

Quality of Life

Mańko et al. (2013) examined the effectiveness of two neurotherapy programmes in patients aroused from prolonged coma after TBI, finding some support for improved quality of life after rTMS. However, a robust conclusion is limited due to methodological limitations and insufficient detail presented in the original paper.

Motor Recovery

Cinnera et al. (2016) presented the case of a 25-year-old male who underwent 20 sessions of cerebellar iTBS combined with ten sessions of occupational/physical therapy, 43 months after sustaining a severe TBI. In this instance, iTBS was chosen as it has been previously shown to be effective in improving ataxic gait and posture symptoms following a cerebellar stroke

(Bonni, Ponzo, Caltagirone, & Koch, 2014). Improved motor and balance functions were recorded after rTMS, including increased walking speed (attributed to increase in right step length), improved balance (upper and lower limb), and improved right-sided fine and gross motor hand skills.

Side effects/tolerability

TBI has generally been regarded as a contradiction for rTMS due to its association with increased neural excitability and subsequent seizure risk (Herman, 2002). However, the majority of studies reviewed here report good levels of tolerability, noting only transient and minimal side effects, such as headache (Koski et al., 2015), dizziness (Leung, Shukla et al., 2016), and fatigue (Paxman et al., 2018), or none at all (e.g. Choi et al., 2018; Fitzgerald et al., 2010; Neilson et al., 2013). Additionally, some studies report positive side effects of rTMS beyond the primary outcome being assessed, such as reports of less mental 'fog', irritability, and increased energy (Koski et al., 2015). Although, it should be noted that some studies did not explicitly address safety or confirm an absence of adverse events (e.g. Bonni et al., 2013; He et al., 2018; Rutherford et al., 2017).

In contrast, a small number of studies reported more serious side effects, resulting in adaptation or termination of the rTMS protocol (e.g. Pape et al. 2014). Cavinto, Iaia, and Piccione, (2012) reported a partial and secondarily generalised tonic-clonic seizure three hours after the fourth daily session of an rTMS protocol conforming to existing safety guidelines (Wasserman, 1998). Consequently, even though occurrence of seizure is uncommon when using sub-threshold stimulation, it is possible that daily administration of rTMS could result in a long-lasting physiological cumulative effect. Namely, increasing after-discharges, triggered seizures, and eventually, spontaneous epileptic seizures. However, they equally noted that the safety guidelines did not address the maximum amount of repetitive stimulation in a single

treatment or procedures for inter-train intervals, with subsequent research finding that rTMS trains may increase the risk of seizure in patients with brain lesion, irrespective of seizure history (Rossi et al. 2009).

Given such concerns, attempts have been made to monitor the occurrence or non-occurrence of adverse events following rTMS in the context of TBI, with a view of establishing effective Data Safety Monitoring Plans (DSMP) to ensure both the safety of participants and validity of outcome data. Specifically, Pape et al. (2009) explored the efficacy (see Recovery from Disorders of Consciousness section) and safety of an rTMS protocol applied to a 26-year-old male with DOC after severe TBI, developing a comprehensive DSMP including coverage of: (1) safety procedures (e.g. rTMS to be provided only after completion of a daily medical examination; EEGs conducted before and after every rTMS session); (2) safety factors (e.g. daily monitoring of clinical and medical variables, such as sweating, skin integrity and hyper/hypotension; comparison to baseline); (3) safety response plans (e.g. action to be taken if any safety factor changes from baseline; seizure response plan), and (4) oversight by a data safety monitoring board (e.g. all safety and efficacy data reported to independent experts for monitoring). In the case of Pape et al. (2009), no adverse events were recorded that were attributable to the rTMS procedure. However, the benefits of such a rigorous DSMP were highlighted in a subsequent study (Pape et al. 2014), where EEG recording showed an electrographically seizure without clinical accompaniment 40 minutes after the 21st rTMS session in a patient in VS. Consequently, an appropriate safety response was implemented (seizure medication, daily monitoring, EEG assessment) which allowed completion of an adapted (e.g. 19 additional rTMS sessions; 2% lower stimulation intensity 100 fewer impulses per session) rTMS protocol one week later. No further adverse events were noted, highlighting that if steps are taken to minimize risks, rTMS can be applied successfully after TBI.

Finally, supplementary to DSMP and generic safety guidelines (e.g. Rossi et al., 2009), Nielson et al. (2015) also recommended adoption of rigorous pre-screening criteria for safely administering rTMS in in the context of moderate to severe TBI; including exclusion of patients with a history of seizure; review of neuroimaging reports to ensure that stimulation can be safely delivered to the target region; and exclusion of those taking medications that lower seizure threshold and/or have metallic implants. In addition, they also advised using low-frequency stimulation (owing to its antiepileptic effects; Hsu et al., 2011), although acknowledged that high-frequency stimulation may be appropriate if combined with more stringent eligibility criteria if anticipated treatment benefits sufficiently outweigh any increased risk. Further, restricting TBI patients to low-frequency stimulation protocols may be unduly restrictive in some instances, especially where high-frequency stimulation may be the preferred and most efficacious option.

Discussion

The 30 studies reviewed here suggest that rTMS has the potential to be an efficacious therapeutic intervention after TBI. Consistent improvements were documented across both single- and multiple-case reports and controlled trials for the treatment of depression (e.g. Fitzgerald et al., 2010; Iliceto et al., 2018; Siddiqi et al., 2018) and mTBI-HA (e.g. Leung et al., 2018; Leung, Shukla et al., 2016). There was also some promising initial evidence for a therapeutic effect of rTMS for the management of dizziness (Paxman et al., 2018), central pain (Choi et al., 2018), Aphasia (Chantsoulis et al., 2017), and visual neglect (Bonni et al., 2013) after TBI. However, and consistent with previous reviews (Dhaliwal et al., 2015; Herold et al., 2014), results were less encouraging for improving states of altered consciousness (e.g. He et al., 2018; Manganotti et al., 2013) and mixed for cognitive outcomes (e.g. Hara et al., 2017).

There are a variety of factors that may have hypothetically contributed to the varied effectiveness of rTMS across studies and domains of outcome. For example, the diversity and questionable adequacy of measures used to evaluate similar outcomes across studies makes comparison and evaluation of results difficult, ultimately hindering understanding of which rTMS parameters lead to the best rehabilitation outcomes and treatment response. In addition, rTMS treatment protocols and stimulation parameters vary greatly across studies, with intervention protocols often poorly defined and lacking sufficient detail to allow full replication. Nevertheless, given the heterogeneous nature of TBI, it is perhaps unrealistic to anticipate a single, optimum or even a relatively standardised rTMS protocol across studies even if targeting similar symptomology. One of the advantages of rTMS is its versatility, arguably making it an excellent match for TBI; it allows for a personalised protocol to address specific clinical needs. However, this heterogeneity, especially when combined with small sample sizes, limits the evaluation and generalisability of results. Further, even with a similar protocol, one patient may respond differently to rTMS parameters and biochemical processes compared to another. Indeed, the influence of inter-individual variables (e.g. time post-injury; injury location; severity of injury; comorbidities) on treatment outcomes remains largely unknown. Although, even if elucidated and positive treatment gains materialise, it would still be difficult to determine whether observed effects are a primary or secondary response to rTMS. For instance, given the known antidepressant action of rTMS, it remains unclear whether reported cognitive improvements would persist regardless of changes in mood, or whether cognitive gains correlate with concurrent improvements in mood (i.e. Fitzgerald et al., 2010). Consistent with this, previous research has provided some support for a cognitive neuropsychological hypothesis of antidepressant action in rTMS treatment (Boggio et al., 2005; Schutter, Van Honk, Laman, Vergouwen, & Koerselman, 2010).

The varied effectiveness of rTMS across studies may also be attributable to two additional factors: (a) variation in cortical target, and (b) protocols for positioning the rTMS coil (see McClintock et al. 2018). First, proportionally, a greater number of studies opted to apply rTMS to normalize frontal dysfunction associated with TBI, with many choosing to stimulate the left/right DLPFC. For example, the DLPFC was consistently chosen as the cortical target for the alleviation of depressive symptomology, with consistent and favourable treatment responses noted. Thus, it appears that the DLPFC may be a promising target region for the alleviation of depressive symptomology after TBI. Presumably, rTMS applied to the left DLPFC for example, induces dynamic changes throughout the central executive network, and in turn, alterations in connectivity with the salience and default mode networks. Specifically, previous research (i.e. Anderson et al., 2016) exploring the use of rTMS for the treatment of depression suggests that the mechanistic action is a decrease in over-activity of the default mode network, and enhanced activity of the salience and central executive networks, leading to relief of the cognitive, emotional and psychomotor symptoms that represent the cardinal features of depression. However, there was ultimately large variation in cortical targets across studies overall, with large variation sometimes evident within a single domain of outcome (e.g. DOC - left /right DLPFC, left/right M1; Cognitive – cingulate gyrus, left and right frontal and temporal; right DLPFC). Consequently, the varied effectiveness of rTMS noted here may be attributable, at least in part, to variation in cortical targets across studies. Therefore, at this stage it is difficult to draw systematic conclusions concerning what the most efficacious rTMS cortical targets may be to address specific symptoms/sequelae following TBI.

Second, in the current set of reviewed studies, the use of neuronavigated guidance technologies was determinable in 28 studies, with some indication of enhanced efficacy when such technologies were utilised (15/16 versus 9/11). Of course, without a formal analysis of

such data, only a tentative conclusion can be drawn. It should also be noted that in other samples, there is only limited evidence suggesting that neuronavigated guidance position technologies confer higher efficacy rates (Fitzgerald et al., 2009). Additionally, such technologies are expensive, add complexity to rTMS procedures, and place additional burden on patients and clinical resources. However, they also allow greater precision in locating cortical targets (McClintock et al., 2018), are already recommended for the treatment of depression (Fitzgerald et al., 2009), and may also help to avoid direct stimulation of potential hazards (e.g. lesions or plates that could unpredictably alter the path of rTMS currents; Neilson et al., 2015); thereby lowering risk.

In relation to this, the need to develop more comprehensive safety guidelines to maximise safe administration of rTMS in TBI remains. In addition to DSMP (Pape et al. 2009), generic safety guidelines (e.g. Rossi et al., 2009), rigorous pre-screening criteria (Nielson et al., 2015), and compensatory steps that could be taken to mitigate risk when exceeding and/or not adhering to standard safety protocols (e.g. when expected potential benefits to the patient outweigh associated costs) should be developed. In line with some of the recommendations of McClintock et al. (2018), we also recommend that reports concerning the use of rTMS after TBI consistently document the following basic procedural elements: coil selection, location, method and placement; motor threshold (e.g. site and determination method); number, time course and duration of sessions, and basic treatment parameters (e.g. intensity and how it was determined from motor threshold, pulse frequency, train duration, inter-train interval, number of stimulations and pulses per session). Importantly, such information would promote consistency in the clinical application of rTMS in TBI, provide knowledge that can facilitate further evidence-based care, promote greater rigour in rTMS designs, and allow the potential effectiveness of rTMS as a therapeutic intervention after TBI to be more thoroughly evaluated. Finally, based on the clinical application of rTMS in other neurological populations, we also

recommend consideration of the use of neuroimaging and electrophysiological methods to document the specific effects of rTMS by identifying biomarkers that could hypothetically predict a patient's response to rTMS interventions (Dionísio, Duarte, Patrício, & Castelo-Branco, 2018). This would also support the adoption and execution of rigorous pre-screening criteria as recommended previously, ensuring that patients set to gain most are identified and receive a personalised rTMS protocol.

Additionally, important aspects for future work include the need to examine the longevity and time-course of rTMS effects. The majority of studies reviewed here assessed treatment outcomes immediately after the last session of rTMS and up to one month following, with only a handful extending beyond this time-frame (Illiceto et al., 2018; Pape et al., 2009). Given the life-long, debilitating nature of TBI and its higher prevalence in younger populations (Barker-Collo, Wilde, & Feigin, 2009; Kraus & Chu, 2005), examining whether rTMS interventions can result in lasting therapeutic benefits is a particularly important consideration. It would also be of clinical and research value to explore the stability of treatment effects, and specifically, maintenance strategies following response or remission with rTMS. This may take the form of pre-determined sessions (e.g. monthly booster sessions) or adoption of a relapse treatment approach (e.g. re-introduce rTMS as needed based on worsening symptoms; McClintock et al., 2018; Mennemeier et al. 2013). As with other clinical populations, further research is needed to systematically develop evidence-based maintenance strategies, including RCT based studies comparing various approaches.

The relative effectiveness of rTMS when used in isolation or when combined with conventional rehabilitation methods also remains uncertain. Based on the concept that rTMS elicits changes to brain plasticity that can help facilitate additional functional improvements, Hara et al. (2017) argued that rTMS should be used to complement current rehabilitative methods. Consistent with this, rTMS was commonly delivered in the reviewed studies

alongside traditional cognitive rehabilitation, pharmacological interventions, neurodevelopmental therapy, or other differentiated neurotherapy programmes. However, we did not evaluate the relative effectiveness of one combination of treatments compared to another here, as there were typically only singular instances of each combination. Further, given the complex and varied needs of survivors, as well as the multifaceted nature of neurobehavioural rehabilitation, it is unlikely that rTMS will ever be used in complete isolation. Therefore, distinguishing the unique treatment effects of rTMS from those of conventional rehabilitation methods is always going to be difficult. To address this, rigorously designed RCTs are needed that include appropriate control groups. However, interpretation of treatment outcomes would still be difficult given the heterogeneous nature of TBI and subsequent inter-individual variation likely to occur across groups. Consequently, it is likely that naturalistic studies will continue to dominate and shape the field for the foreseeable future.

Finally, limitations with our scoping review should also be acknowledged. First, our results are only up to date as of 18th October 2018. Second, whilst every effort was made to locate all relevant studies that met our eligibility criteria, it is possible that some relevant literature was missed (e.g. grey literature; alternative database searches). Third, whilst the focus of our scoping review process was to provide a descriptive overview of a large and diverse body of literature, it nevertheless means that we were unable to critically synthesise outcomes from the different studies, rigorously assess the methodological quality of individual studies, or rule out the possibility of publication bias. Therefore, whilst the studies reviewed here indicate that rTMS has the potential to be an efficacious therapeutic intervention after TBI, systematic analysis of reported treatment outcomes and effect sizes need to occur before firmer conclusions can be drawn. However, the breadth of coverage achieved via a scoping review methodology, also means that we likely addressed a greater range of study designs and methodologies than would ordinarily have been included in a meta-analysis or systematic

review. Therefore, our current methodological approach arguably allowed for greater breadth of coverage and insight into a rapidly evolving research and clinical area.

Conclusion

Whilst there is not enough data to draw firm conclusions regarding the definite efficacy of rTMS after TBI, the studies reviewed here suggest that rTMS holds promise as a well-tolerated intervention for a broad range of symptoms and neurological sequalae after TBI. However, appropriate safety, pre-screening criteria and data monitoring guidelines need to be developed and consistently adopted. However, key questions remain and further naturalistic, as well as larger blinded, randomised, controlled trials need to be conducted. Encouragingly, our screening criteria identified several conference abstracts (pre-publication data), pre-trial registrations and RCT protocols that, when complete, will allow further systematic evaluation of the efficacy, safety and feasibility of applying rTMS therapeutically after TBI.

References

Adamson, M., Siddiqi, S., Swaminath, G., Wu, L., McNerney, W., Wortman, K., … Yesavage, J. (2019). Repetitive transcranial magnetic stimulation for improving cognition in veterans with TBI: Results from pilot clinical trial. *Brain Stimulation*, *12*(2), 551. doi:10.1016/j.brs.2018.12.820

Alderman, N., & Wood, R. L. (2013). Neurobehavioural approaches to the rehabilitation of challenging behaviour. *NeuroRehabilitation*, *32*(4), 761–770. doi:10.3233/NRE-130900

Anderson, R. J., Hoy, K. E., Daskalakis, Z. J., Fitzgerald, P. B. (2016). Repetitive transcranial magnetic stimulation for treatment resistant depression: Re-establishing connections. *Clinical Neurophysiology*, *127*(11), 3394-405.

Bagnato, S., Boccagni, C., Sant'Angelo, A., Prestandrea, C., Rizzo, S., & Galardi, G. (2012). Patients in a vegetative state following traumatic brain injury display a reduced intracortical modulation. *Clinical Neurophysiology: Official Journal Of The International Federation Of Clinical Neurophysiology*, *123*(10), 1937–1941. doi:10.1016/j.clinph.2012.03.014

Barker-Collo, S. L., Wilde, N. J., & Feigin, V. L. (2009). Trends in Head Injury Incidence in New Zealand: A Hospital-Based Study from 1997/1998 to 2003/2004. *Neuroepidemiology*, *32*(1), 32–39. doi:10.1159/000170090

Bayar, N., Böke, B., Turan, E., & Belgin, E. (2007). Efficacy of Amitriptyline in the Treatment of Subjective Tinnitus. *The Journal of Otolaryngology*, *30*(05), 300. doi:10.2310/7070.2001.19597

Bigler, E. D. (2001). The lesion(s) in traumatic brain injury: implications for clinical neuropsychology. *Archives of Clinical Neuropsychology*, *16*(2), 95–131. doi:10.1093/arclin/16.2.95

Bigler, E. D. (2007). Anterior and middle cranial fossa in traumatic brain injury: Relevsnt

neuroanatomy and neuropathology in the study of neuropsychological outcome. *Neuropsychology*, *21*(5), 515.

Boggio, P. S., Fregni, F., Bermpohl, F., Mansur, C. G., Rosa, M., Rumi, D. O., … Araujo Silva, M. T. (2005). Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. *Movement Disorders*, *20*(9), 1178–1184. doi:10.1002/mds.20508

Bonni, S., Mastropasqua, C., Bozzali, M., Caltagirone, C., Koch, G., Bonnì, S., … Koch, G. (2013). Theta burst stimulation improves visuo-spatial attention in a patient with traumatic brain injury. *Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *34*(11), 2053–2056. doi:10.1007/s10072-013-1412-y

Bonni, S., Ponzo, V., Caltagirone, C., & Koch, G. (2014). Cerebellar theta burst stimulation in stroke patients with ataxia. *Functional neurology*, *29*(1), 41.

Chamelian, L., & Feinstein, A. (2004). Outcome after mild to moderate traumatic brain injury: The role of dizziness. *Archives of Physical Medicine and Rehabilitation*, *85*(10), 1662–1666. doi:10.1016/J.APMR.2004.02.012

Chantsoulis, M., Półrola, P., Góral-Półrola, J., Hajdukiewicz, A., Supiński, J., Kropotov, J. D., & Pachalska, M. (2017). Application of ERPs neuromarkers for assessment and treatment of a patient with chronic crossed aphasia after severe TBI and long-term coma - Case Report. *Annals Of Agricultural And Environmental Medicine: AAEM*, *24*(1), 141–147

Chistyakov, A. V, Hafner, H., Soustiel, J. F., Trubnik, M., Levy, G., & Feinsod, M. (1999). Dissociation of somatosensory and motor evoked potentials in non-comatose patients after head injury. *Clinical Neurophysiology*, *110*(6), 1080–1089. doi:10.1016/S1388-2457(99)00029-2

Choi, G.-S., Kwak, S. G., Lee, H. Do, & Chang, M. C. (2018). Effect of high-frequency repetitive transcranial magnetic stimulation on chronic central pain after mild traumatic brain injury: A pilot study. *Journal of Rehabilitation Medicine, 50*(3), 246–252. doi:10.2340/16501977-2321

Cincotta, M., Giovannelli, F., Chiaramonti, R., Bianco, G., Godone, M., Battista, D., … Rossi, S. (2015). No effects of 20 Hz-rTMS of the primary motor cortex in vegetative state: A randomised, sham-controlled study. *Cortex, 71*, 368–376. doi:10.1016/j.cortex.2015.07.027

Cosentino, G., Giglia, G., Palermo, A., Panetta, M. L., Lo Baido, R., Brighina, F., & Fierro, B. (2010). A case of post-traumatic complex auditory hallucinosis treated with rTMS. *Neurocase*, *16*(3), 267–272

Defrin, R. (2014). Chronic post-traumatic headache: clinical findings and possible mechanisms. *Journal of Manual & Manipulative Therapy*, *22*(1), 36–43. doi:10.1179/2042618613Y.0000000053

Dewan, M. C., Rattani, A., Gupta, S., Baticulon, R. E., Hung, Y.-C., Punchak, M., … Park, K. B. (2018). Estimating the global incidence of traumatic brain injury. *Journal of Neurosurgery*, *130*(4), 1–18. doi:10.3171/2017.10.JNS17352

Dhaliwal, S. K., Meek, B. P., & Modirrousta, M. M. (2015). Non-invasive brain stimulation for the treatment of symptoms following traumatic brain injury. *Frontiers in Psychiatry*, *6*

Dionísio, A., Duarte, I. C., Patrício, M., & Castelo-Branco, M. (2018). The Use of Repetitive Transcranial Magnetic Stimulation for Stroke Rehabilitation: A Systematic Review. *Journal of Stroke and Cerebrovascular Diseases*, *27*(1), 1–31. doi:10.1016/J.JSTROKECEREBROVASDIS.2017.09.008

Fann, J. R., Hart, T., & Schomer, K. G. (2009). Treatment for Depression after Traumatic

Brain Injury: A Systematic Review. *Journal of Neurotrauma*, *26*(12), 2383–2402. doi:10.1089/neu.2009.1091

Fitzgerald, P. B., Hoy, K. E., Maller, J. J., Herring, S., Segrave, R., McQueen, S., … Daskalakis, Z. J. (2011). Transcranial magnetic stimulation for depression after a traumatic brain injury: a case study. *The Journal Of ECT*, *27*(1), 38–40

Galhardoni, R., Correia, G. S., Araujo, H., Yeng, L. T., Fernandes, D. T., Kaziyama, H. H., … de Andrade, D. C. (2015). Repetitive Transcranial Magnetic Stimulation in Chronic Pain: A Review of the Literature. *Archives of Physical Medicine and Rehabilitation*, *96*(4), S156–S172. doi:10.1016/J.APMR.2014.11.010

Haffen, E., Chopard, G., Pretalli, J.-B., Magnin, E., Nicolier, M., Monnin, J., … Vandel, P. (2012). A case report of daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) as an adjunctive treatment for Alzheimer disease. *Brain Stimulation*, *5*(3), 264–266. doi:10.1016/j.brs.2011.03.003

Hamilton, M. (1986). The Hamilton Rating Scale for Depression. In *Assessment of Depression* (pp. 143–152). Berlin, Heidelberg: Springer Berlin Heidelberg. doi:10.1007/978-3-642-70486-4_14

Hara, T., Abo, M., Kakita, K., Masuda, T., & Yamazaki, R. (2016). Does a combined intervention program of repetitive transcranial magnetic stimulation and intensive occupational therapy affect cognitive function in patients with post-stroke upper limb hemiparesis? *Neural Regeneration Research*, *11*(12), 1932–1939. doi:10.4103/1673-5374.197134

Hara, T., Abo, M., Sasaki, N., Yamada, N., Niimi, M., Kenmoku, M., … Saito, R. (2017). Improvement of higher brain dysfunction after brain injury by repetitive transcranial magnetic stimulation and intensive rehabilitation therapy: case report. *Neuroreport*, *28*(13), 800–807. doi:10.1097/WNR.0000000000000830

He, F., Wu, M., Meng, F., Hu, Y., Gao, J., Chen, Z., … Pan, G. (2018). Effects of 20Hz Repetitive Transcranial Magnetic Stimulation on Disorders of Consciousness: A Resting-State Electroencephalography Study. *Neural Plasticity*. doi:10.1155/2018/5036184

Herman, S. T. (2002). Epilepsy after brain insult: targeting epileptogenesis. *Neurology*, *59*(9 Suppl 5), S21-6. doi:10.1212/WNL.59.9_SUPPL_5.S21

Herrold, A. A., Kletzel, S. L., Harton, B. C., Chambers, R. A., Jordan, N., & Pape, T. L.-B. (2014). Transcranial magnetic stimulation: potential treatment for co-occurring alcohol, traumatic brain injury and posttraumatic stress disorders. *Neural Regeneration Research*, *9*(19), 1712–1730. doi:10.4103/1673-5374.143408

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron*, *45*(2), 201-206.

Iliceto, A., Seiler, R. L., & Sarkar, K. (2018). Repetitive Transcranial Magnetic Stimulation for Treatment of Depression in a Patient With Severe Traumatic Brain Injury. *Ochsner Journal*, *18*(3), 264–267. doi:10.31486/toj.17.0075

Jones, W., Silkworth, W., Dusto, N., Pelak, V. S., Berliner, J., Buard, I., & Kluger, B. (2018). Central visual oscillopsia: Case report and review of the literature. *Cognitive and Behavioral Neurology*, *31*(2), 86–95. doi:10.1097/WNN.0000000000000151

Kalmar, K., & Giacino, J. (2005). The JFK coma recovery scale—revised. *Neuropsychological Rehabilitation*, *15*(3–4), 454–460. doi:10.1080/09602010443000425

Kertsez, A. (1982). *Western Aphasia Battery Test Manual*. Psychological Corp.

Khedr, E. M., & Fetoh, N. A.-E. (2010). Short- and long-term effect of rTMS on motor function recovery after ischemic stroke. *Restorative Neurology and Neuroscience*, *28*(4), 545–559. doi:10.3233/RNN-2010-0558

Koski, L., Kolivakis, T., Yu, C., Chen, J.-K., Delaney, S., & Ptito, A. (2015). Noninvasive brain stimulation for persistent postconcussion symptoms in mild traumatic brain injury. *Journal Of Neurotrauma*, *32*(1), 38–44

Kraus, J. F., & Chu, L. D. (2005). *Epidemiology of Traumatic Brain Injury. Tetxbook of Traumatic Brain Injury*.

Kreuzer, P. M., Landgrebe, M., Frank, E., & Langguth, B. (2013). Repetitive transcranial magnetic stimulation for the treatment of chronic tinnitus after traumatic brain injury: a case study. *The Journal of Head Trauma Rehabilitation*, *28*(5), 386–389. doi:10.1097/HTR.0b013e318254736e

Lange, R. T., Iverson, G. L., Brubacher, J. R., Mädler, B., & Heran, M. K. (2012). Diffusion Tensor Imaging Findings Are Not Strongly Associated With Postconcussional Disorder 2 Months Following Mild Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation*, *27*(3), 188–198. doi:10.1097/HTR.0b013e318217f0ad

Lee, S. A., & Kim, M.-K. (2018). Effect of Low Frequency Repetitive Transcranial Magnetic Stimulation on Depression and Cognition of Patients with Traumatic Brain Injury: A Randomized Controlled Trial. *Medical Science Monitor*, *24*, 8789–8794. doi:10.12659/MSM.911385

Leung, A., Donohue, M., Xu, R., Lee, R., Lefaucheur, J. P., Khedr, E. M., … Chen, R. (2009, December 1). rTMS for Suppressing Neuropathic Pain: A Meta-Analysis. *Journal of Pain*. Churchill Livingstone. doi:10.1016/j.jpain.2009.03.010

Leung, A., Fallah, A., Shukla, S., Lin, L., Tsia, A., Song, D., … Lee, R. (2016). rTMS in Alleviating Mild TBI Related Headaches-A Case Series. *Pain Physician*, *19*(2), E347–E354

Leung, A., Metzger-Smith, V., He, Y., Cordero, J., Ehlert, B., Song, D., … Lee, R. (2018). Left Dorsolateral Prefrontal Cortex rTMS in Alleviating MTBI Related Headaches and

Depressive Symptoms. *Neuromodulation*, *21*(4), 390–401. doi:10.1111/ner.12615

Leung, A., Shukla, S., Fallah, A., Song, D., Lin, L., Golshan, S., … Lee, R. (2016). Repetitive Transcranial Magnetic Stimulation in Managing Mild Traumatic Brain Injury-Related Headaches. *Neuromodulation : Journal of the International Neuromodulation Society*, *19*(2), 133–141. doi:10.1111/ner.12364

Manganotti, P., Formaggio, E., Storti, S. F., Fiaschi, A., Battistin, L., Tonin, P., … Cavinato, M. (2013). Effect of high-frequency repetitive transcranial magnetic stimulation on brain excitability in severely brain-injured patients in minimally conscious or vegetative state. *Brain Stimulation*, *6*(6), 913–921. doi:10.1016/j.brs.2013.06.006

Mańko, G., Olszewski, H., Krawczyński, M., & Tłokiński, W. (2013). Evaluation of differentiated neurotherapy programs for patients recovering from severe TBI and long term coma. *Acta Neuropsychologica*, *11*(1), 9–18

Mansur, C. G., Fregni, F., Boggio, P. S., Riberto, M., Gallucci-Neto, J., Santos, C. M., … Pascual-Leone, A. (2005). Neurology. *Neurology*, *48*(5), 1398–1403. doi:10.1212/01.wnl.0000161839.38079.92

Martino Cinnera, A., Bonnì, S., Iosa, M., Ponzo, V., Fusco, A., Caltagirone, C., … Koch, G. (2016). Clinical effects of non-invasive cerebellar magnetic stimulation treatment combined with neuromotor rehabilitation in traumatic brain injury. A single case study. *Functional Neurology*, *31*(2), 117–120

McClintock, S. M., Reti, I. M., Carpenter, L. L., McDonald, W. M., Dubin, M., Taylor, S. F., … American Psychiatric Association Council on Research Task Force on Novel Biomarkers and Treatments. (2018). Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. *The Journal of Clinical Psychiatry*, *79*(1). doi:10.4088/JCP.16cs10905

Mennemeier, M., Munn, T., Allensworth, M., Lenow, J. K., Brown, G., Allen, S., …

Williams, D. K. (2013). Laterality, frequency and replication of rTMS treatment for chronic tinnitus: pilot studies and a review of maintenance treatment. *Hearing Research*, *295*(1–2), 30–7. doi:10.1016/j.heares.2012.03.010

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry*, *134*(4), 382–389. doi:10.1192/bjp.134.4.382

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., … Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–9. doi:10.1111/j.1532-5415.2005.53221.x

National Institute for Health Care Excellence (NICE). (2015). *Repetitive transcranial magnetic stimulation for depression | Guidance | NICE*. NICE. Retrieved from https://www.nice.org.uk/guidance/IPG542

Neville, I. S., Gomes-Osman, J., Amorim, R. L. O., Hayashi, C. Y., Galhardoni, R., Zaninotto, A. L., … Paiva, W. S. (2018). How can transcranial magnetic stimulation change the way we treat traumatic brain injury? *International Journal of Clinical and Experimental Medicine*, *11*(8), 7643–7650.

Nielson, D. M., McKnight, C. A., Patel, R. N., Kalnin, A. J., & Mysiw, W. J. (2015). Preliminary Guidelines for Safe and Effective Use of Repetitive Transcraniat Magnetic Stimulation in Moderate to Severe Traumatic Brain Injury. *Archives of Physical Medicine and Rehabilitation*, *96*(4), S138–S144. doi:10.1016/j.apmr.2014.09.010

Oberman, L., Edwards, D., Eldaief, M., & Pascual-Leone, A. (2011). Safety of theta burst transcranial magnetic stimulation: A systematic review of the literature. Journal of Clinical Neuroscience, 28(1), 67-74. doi: 10.1097/WNP.0b013e318205135f

Pachalska, M., Łukowicz, M., Kropotov, J. D., Herman-Sucharska, I., & Talar, J. (2011). Evaluation of differentiated neurotherapy programs for a patient after severe TBI and

long term coma using event-related potentials. *Medical Science Monitor: International Medical Journal Of Experimental And Clinical Research*, *17*(10), CS120-CS128.

Pape, T. L-B., Rosenow, J., Lewis, G., Ahmed, G., Walker, M., Guernon, A., … Patil, V. (2009). Repetitive transcranial magnetic stimulation-associated neurobehavioral gains during coma recovery. *Brain Stimulation*, *2*(1), 22–35.

Pape, T. L.-B., Rosenow, J. M., Patil, V., Steiner, M., Harton, B., Guernon, A., … Sarkar, K. (2014). RTMS safety for two subjects with disordered consciousness after traumatic brain injury. *Brain Stimulation*, *7*(4), 620–622.

Patil, V. K., St. Andre, J. R., Crisan, E., Smith, B. M., Evans, C. T., Steiner, M. L., & Pape, T. L. (2011). Prevalence and Treatment of Headaches in Veterans With Mild Traumatic Brain Injury. *Headache: The Journal of Head and Face Pain*, *51*(7), 1112–1121. doi:10.1111/j.1526-4610.2011.01946.x

Paxman, E., Stilling, J., Mercier, L., & Debert, C. T. (2018). Repetitive transcranial magnetic stimulation (rTMS) as a treatment for chronic dizziness following mild traumatic brain injury. *Case Reports*, *2018*, bcr-2018-226698. doi:10.1136/BCR-2018-226698

Peinemann, A., Reimer, B., Löer, C., Quartarone, A., Münchau, A., Conrad, B., & Roman Siebner, H. (2004). Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 Hz repetitive TMS to the primary motor cortex. *Clinical Neurophysiology*, *115*(7), 1519–1526. doi:10.1016/J.CLINPH.2004.02.005

Ren, C.-L., Zhang, G.-F., Xia, N., Jin, C.-H., Zhang, X.-H., Hao, J.-F., … Cai, D.-L. (2014). Effect of Low-Frequency rTMS on Aphasia in Stroke Patients: A Meta-Analysis of Randomized Controlled Trials. *PLoS ONE*, *9*(7), e102557. doi:10.1371/journal.pone.0102557

Rosanova, M., Gosseries, O., Casarotto, S., Boly, M., Casali, A. G., Bruno, M.-A., … Massimini, M. (2012). Recovery of cortical effective connectivity and recovery of

consciousness in vegetative patients. *Brain: A Journal of Neurology*, *135*(4), 1308–1320

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*(12), 2008–2039. doi:10.1016/J.CLINPH.2009.08.016

Rutherford, G., Lithgow, B., Mansouri, B., Sulieman, A., Pouya, O. R., Dastgheib, Z., … Moussavi, Z. (2017). Repetitive Transcranial Magnetic Stimulation (RTMS) as a Treatment for Post-concussion Syndrome. *CMBES Proceedings*, *40*

Sandrini, M., Umiltà, C., & Rusconi, E. (2011). The use of transcranial magnetic stimulation in cognitive neuroscience: a new synthesis of methodological issues. *Neuroscience & Biobehavioral Reviews*, *35*(3), 516-536.

Schicktanz, N., Fastenrath, M., Milnik, A., Spalek, K., Auschra, B., Nyffeler, T., ... & Schwegler, K. (2015). Continuous theta burst stimulation over the left dorsolateral prefrontal cortex decreases medium load working memory performance in healthy humans. *PLoS One*, *10*(3), e0120640.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., … Laureys, S. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology*, *9*(1), 35. doi:10.1186/1471-2377-9-35

Schutter, D. J. L. G., Van Honk, J., Laman, M., Vergouwen, A. C., & Koerselman, F. (2010). Increased sensitivity for angry faces in depressive disorder following 2 weeks of 2-Hz repetitive transcranial magnetic stimulation to the right parietal cortex. *International Journal of Neuropsychopharmacology*, *13*(9), 1155–1161. doi:10.1017/S1461145710000660

Siddiqi, S. H., Trapp, N. T., Hacker, C. D., Laumann, T. O., Kandala, S., Hong, X., … Brody,

D. L. (2018). REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION WITH RESTING STATE NETWORK TARGETING FOR TREATMENT-RESISTANT DEPRESSION IN TBI. *Journal of Neurotrauma*, *35*(16), A15–A15.

Tamber, A.-L., Wilhelmsen, K. T., & Strand, L. I. (2009). Measurement properties of the Dizziness Handicap Inventory by cross-sectional and longitudinal designs. *Health and Quality of Life Outcomes*, *7*(1), 101. doi:10.1186/1477-7525-7-101

Wassermann, E. M., Grafman, J., Berry, C., Hollnagel, C., Wild, K., Clark, K., & Hallett, M. (1996). Use and safety of a new repetitive transcranial magnetic stimulator. *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control*, *101*(5), 412–417. doi:10.1016/0924-980X(96)96004-X

Wilk, J. E., Thomas, J. L., McGurk, D. M., Riviere, L. A., Castro, C. A., & Hoge, C. W. (2010). Mild Traumatic Brain Injury (Concussion) During Combat. *Journal of Head Trauma Rehabilitation*, *25*(1), 9–14. doi:10.1097/HTR.0b013e3181bd090f

Wilson, B., Cockburn, J., & Halligan, P. W. (1987). *Behavioural Inattention Test*. Titchfield, UK: Thames Valley Test Company.

Xia, X., Bai, Y., Zhou, Y., Yang, Y., Xu, R., Gao, X., … He, J. (2017). Effects of 10 Hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in disorders of consciousness. *Frontiers in Neurology*, *8*(MAY), 182. doi:10.3389/fneur.2017.00182

Xia, X., Liu, Y., Bai, Y., Liu, Z., Yang, Y., Guo, Y., … He, J. (2017). Long-lasting repetitive transcranial magnetic stimulation modulates electroencephalography oscillation in patients with disorders of consciousness. *NeuroReport*, *28*(15), 1022–1029. doi:10.1097/WNR.0000000000000886

Table 1. Search Strategy: Keywords, Phrases and Search Terms.

CINAHL, MEDLINE, PsychINFO	**SCOPUS**	**Web of Science**
Concept 1: Traumatic Brain Injury		
(CINAHL: MM "Brain Injuries+") (MEDLINE: MM "Brain Injuries, Traumatic") (PsychINFO: MM "Traumatic Brain Injury")	N/A	N/A
(traumatic brain injur* OR TBI)	(traumatic brain injur* OR TBI)	(traumatic brain injur* OR TBI)
Concept 2: Repetitive Transcranial Magnetic Stimulation		
(MM "Transcranial Magnetic Stimulation")	N/A	N/A
(repetitive transcranial magnetic stimulation* OR rTMS OR transcranial magnetic stimulation* OR TMS)	(repetitive transcranial magnetic stimulation* OR rTMS OR transcranial magnetic stimulation* OR TMS)	(repetitive transcranial magnetic stimulation* OR rTMS OR transcranial magnetic stimulation* OR TMS)

*Controlled Vocabulary Terms: CINAHL = CINAHL Headings, MEDLINE = Medical Subject Headings (MeSH) terms, PsychINFO = Thesaurus.

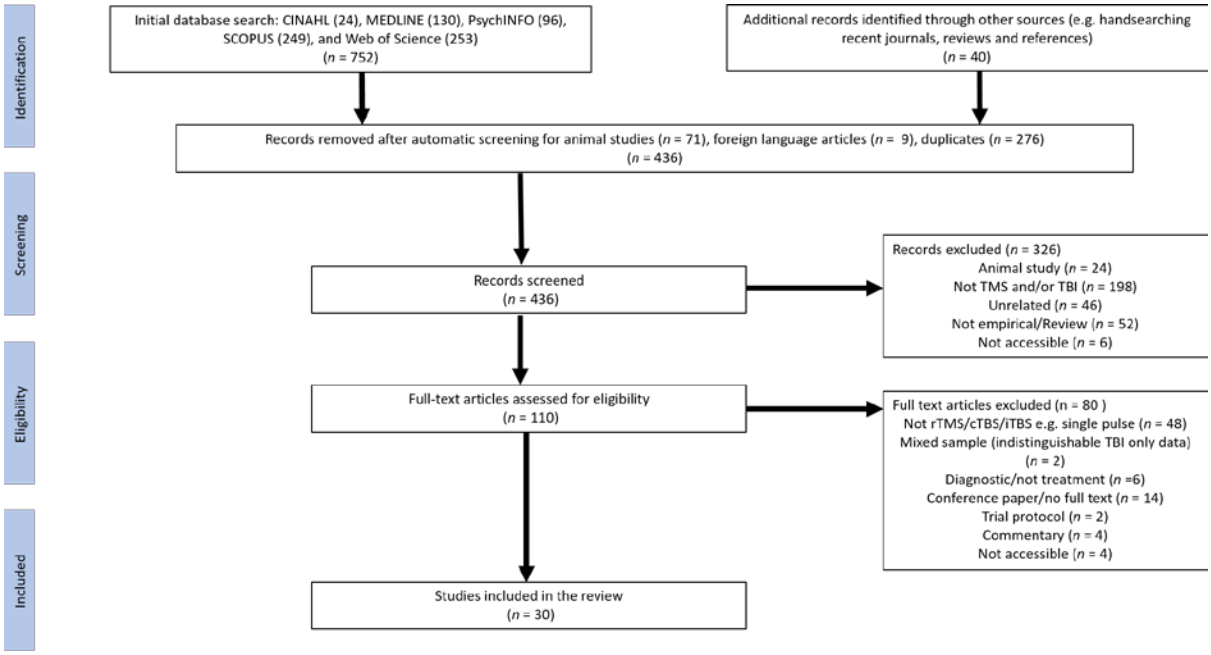

Figure 1. Study Selection Flow Diagram in-line with PRISMA guidelines.

Table 2. Summary of studies using rTMS following TBI

Citation	Participant Descriptions	Time since injury (mths)	Site/Neuro-navigation	Coil/ TMS Parameters	Outcome (Sig. improvement)	Assessment/ Follow-up	Side effects
Bonni et al (2013)[+]	20yo M, 1 week coma following severe TBI	24	Left PPC NN: 10-20 IS	Coil: 70mm Figure-8 2 sessions cTBS daily (15min interval) over 2 weeks. 3 pulse bursts at 50Hz/80% aMT repeated every 200ms for 40s.	Visual Neglect (✓)	Immediately and 2 weeks after	NI
Cavinto et al. (2012)[+]	31yo M, state of coma following severe TBI	8	Left DLPFC NN: X	Coil: 70mm Figure-8 10 daily sessions. 10min 20Hz/90% MT, 1s TD, 1min ITI	PDOC Recovery (T)	N/A	Yes
Chantsoulis et al. (2017)[+^]	29yo F, 2 month coma following severe TBI	NI	Left and right front./temp. NN: X	Coil: NI 20 sessions with 25 stimulations. Left: 1Hz, right: 5Hz.	Cognition (✓) Aphasia (✓)	Immediately after	NI
Choi et al. (2018)*	A: 3 M, 3 F, 43.2 (9.7)yrs, S: 3 M, 3 F, 42.0 (8.4)yrs	A: 17 (7.5), S: 14.3 (7.2)	Precentral Gyrus NN: TMS	Coil: Figure-8 70mm air cooled 10 sessions. A: 20 stimulations 10 Hz/90% MT, 5s TD, 55s ITI. S: as above, coil faced away	Central Pain (✓)	Immediately (5^{th}/10^{th}), 1, 2 and 4 weeks after	No
Cinnera et al. (2016)[+]	25yo M, 2 month coma following TBI	43	Right cerebellum NN: X	Coil: 70mm Figure-8 2 itBS daily for 3 weeks. 20 stimulations, 8s ITI. Train = 10 bursts (5Hz; 200ms int.). Burst = 3 pulses (50hz/80% aMT; 20ms int.)	Motor Recovery (✓)	Immediately after	NI
Cincotta et al. (2015)*^	[α]2 M in VS, 47 & 65 yo.	31 & 85	Left M1 NN: X	Coil: Figure-8 coil 5 sessions, 1-month washout. A: 10min stimulation, 20Hz/90%	PDOC Recovery (X)	Immediately, 1 week and 1 month after	No

				rMT, 1s TD, 5s ITI, 30s pause. S: mimic coil			
Cosentino et al., (2010)[+]	63yo M, progressive deafness (>20yrs),	10	Right posterior temp. NN: PET, MRI, TMS	Coil: Focal 10 sessions. 20 mins, 1200 stimuli 1Hz/90% MT	Music Hallucinations (✓)	Immediately (5^{th}/10^{th}), 4 and 5 months after	No
Fitzgerald et al. (2010)[+]	41yo F, severe TBI, 1hr loss of consciousness	168	Left and right DLPFC NN: MRI/DTI	Coil: Figure-8 cooled 4 weeks, 5 daily sessions. R: 1 train 900 pulses, 1Hz/110% rMT. L: 30 trains 5s TD, 10Hz/110% rMT, 25s ITI	Depression (✓) Cognition (✓/X)	Immediately after	No
Hara et al. (2017)[+]	67yo M	13	ACG NN: TMS	Coil: 80mm Double cone 12 sessions (6 days, 2 weeks). 24 stimulations, 10s TD (100 pulses), 1Hz/90% MT, 50s ITI	Cognition (✓/X) ADL (✓)	Immediately and 3 months after	No
He et al. (2018)*^	[α]2 M, 2 F, 29-49 yo, 2 VS, 1 MCS, 1 EMCS	1-28	Left M1 NN: X	Coil: Figure-8 5 sessions, 1 week washout. A: 20Hz/100% rMT, 20 trains, 50 pulses, 2.5s TD, 28s pause. S: coil positioned away.	PDOC Recovery (✓[θ])	Immediately after and 1 week	NI
Iliceto et al. (2018)[+]	37yo M, history of anxiety and BD, severe TBI, 11-12 day coma	10	Left DLPFC NN: X	Coil: NI 30 sessions (5 days, 6 weeks). 62 mins, 6Hz/120% sMT, 4s TD, 26s ITI, 3000 pulses	Depression (✓)	Immediately and 2 years after	No
Jones et al. (2018)[+]	57yo M	>240	1: Left V5/MT, 2 & 4: Bilateral V5/MT, 3: Bilateral V1 NN: TMS	Coil: Figure-8 air cooled 1: 5 sessions (1 week) 1Hz/90% PT. 2 & 3: 10 sessions (2 weeks) 1Hz/ 90% PT, 4: 5 sessions (1 week) 1Hz/110% PT. 30 mins, 900 stimulations per hemisphere	Oscillopsia (✓/X)	Immediately after	No

Koski et al. (2015)*	9 M, 6 F 34.3 (1.8)yrs, 1-3 concussions, 60% severe depression	6-336	Left DLPFC NN: X	Coil: Figure-8 20 sessions (5 days, 4 weeks). 20 5s TDM, 10Hz/110% rMT with 25s ITI	PCS (✓) Cognition (X)	Immediately and 3 months after	Yes
Kreuzer et al. (2013)$^{+}$	53yo M, 10 days unconscious, 1 epileptic seizure	Est. 60	1-4: Left PAC, 5: Left PAC/right DLPFC^{-} NN: X	Coil: Figure-8 90mm water cooled 1-4: 10 sessions (12 days), 2000 stimuli 1Hz/110% rMT. 5: 5 sessions (5 days), 1000 stimuli 1Hz/110% rMT	Tinnitus (✓)	3-6 months	No
Lee & Kim (2018)*	A: 5 M, 2 F, 42.42 (11.32)yrs. S: 4 M, 2 F, 41.33 (11.02)yrs.	<6	Right DLPFC NN: X	Coil: 70mm figure-8 10 sessions (5 sessions, 2 weeks), A: 50 stimulations, 1Hz/100% rMT, 40 pulses per train, 25s ITI. S: no stimulation	Depression (✓) Cognition (✓)	Immediately after	No
Leung, Shukla et al. (2016)*	A: 10 M, 2 F, 41.2 (14)yo. S: 11 M, 1 F, 41.4 (11.6)yo	NI	Left MC NN: TMS	Coil: Figure-8 3 sessions. A: 20 trains, 100 pulses 10Hz/80% rMT, 1s ITI. S: as above, coil faced away	Headache (✓)	1 week and 4 weeks	Yes
Leung, Fallah et al. (2016)*	6 M, 38-60yo	48-84 (not full data)	1: Left MC, 2: Left DLPFC, 3 & 4: both NN: Sterotaxic NNG	Coil: Figure-8 4 sessions. 100 pulses 10Hz/80% MT, 20 trains. Sequential sessions = 1500 pulses.	Headache (✓)	Immediately after	No
Leung et al. (2018*	A: 12 M, 2 F, 33 (8)yo. S: 11 M, 4 F, 35 (8)yo.	NI	Left DLPFC NN: TMS	Coil: Figure-8 4 sessions. A: 20 trains, 100 pulses 10Hz/80% rMT, 1s ITI. S: as above, coil faced away	Headache (✓)	1 week; 4-week follow-up	No

Pape et al. (2009)[+]	26yo M,	<10	Right DLPFC NN: TMS	Coil: 70mm Figure-8 30 sessions (5 days, 6 weeks). 300 paired pulse trains, 100ms inter-pulse interval, 5s ITI, 110% MT	PDOC Recovery (✓)	Immediately; 6-week follow-up	No
Pape et al. (2014)[+]	1: 54yo M, VS; 2: & 32yo M,	1: 6-7; 2: 108	1: right DLPFC 2: Left DLPFC NN: MRI	Coil: Figure-8 70mm 30 sessions of 300 paired pulse trains, 100ms inter-pulse interval, 5s ITI, 110% MT	PDOC Recovery (✓)	NI	Yes
Lui et al. (2016)*	[α]2 F in VS, 2 M in MCS, 45-63 yo	2-28	Left M1 NN: X	Coil: Figure-8 coil 1 session. A: 20 trains, 20Hz/100% MT, 2.5s TD, 28s ITI. S: Coiled faced away.	PDOC Recovery – (✓[β])	Immediately after	No
Manganotti et al. (2013)*	[α]2 M in MCS, 1 F in VS, 29-38 yo	34-94	Left and right M1 NN: MEPs	Coil: figure-8 coil 1 session. 1000 stimulations, 20Hz/MT, 10 trains, 5s TD, 20s ITI.	PDOC Recovery (X)	Immediately after	NI
Manko et al. (2013)*^	40 patients severe TBI	NI	NI	NI	Quality of Life (✓)	NI	NI
Nielson et al. (2015)[+]	48yo M, severe TBI resulting in coma (undefined)	60	Right DLPFC NN: MNI	Coil: NI 30 sessions (5 days, 6 weeks). 30 mins, 1Hz/110% MT	Depression (✓)	Immediately after, monthly for 3 months	
Pachalska et al. (2011)*^	26yo M, 2 month coma following severe TBI	Est. 36	Left/right front. and temp. NN: MRI	Coil: NI 20 sessions. Left: 1Hz. Right: 5Hz	Cognition (✓) Behavioural (✓)	Immediately after	NI
Paxman et al. (2018)[+]	61yo male, mTBI	60	Left DLPFC NN: TMS	Coil: NI	Dizziness (✓)	Immediately; 1 and 3	Yes

				10 sessions (2 weeks). 10 trains, 60 pulses 10Hz/70% rMT, 45s intertrain pause		month follow-up	
Rutherford et al. (2017)*	14 participants with concussion in the last 5yrs	<60	Left DLPFC NN: X	Coil: Figure-8 13 sessions (3 weeks). 25 bursts, 30 1.5s TD pulses, 20Hz/100% rMT, 28.5s intertain pause	PCS (✓) Cognition (X)	Immediately after; 1 and 2 month follow-up	NI
Siddiqi et al. (2018)*	A: 7 M, 2 F, 43 (13)yo. S: 4 M, 2 F, 50 (18)yo.	A:8.4 (8.2), S: 8.1 (11.3)	Left and Right DLPFC NN: RSN	Coil: 70mm Double air cooled A: 20 sessions. L: 4000 pulses, 10Hz/ 20% rMT, 5s TD, 20s ITI. Right: 1 train of 1000 pulses, 1Hz.	Depression (✓)	Immediately after	Yes
Xia, Bai et al. (2017)*	[α]1: 23yo M in MCS. 2: 40yo M in VS	1: 13. 2: 16.	Left DLPFC NN: X	Coil: Figure-8 20 sessions daily. 1000 pulses, 10Hz/90% rMT, 10s TD, 60s ITI.	PDOC Recovery (X)	Immediately after and 10 days after	No
Xia, Liu et al. (2017)*	[α]2 M, 1 F in VS, 1 M in MCS, 23-60 yo	7-13	Left DLPFC NN: 10-20 IS	Coil: Figure-8 1(/20) session. 1000 pulses, 10Hz/90% rMT, 10s TD, 60s ITI.	PDOC Recovery (X)	Immediately after	No

[+] = case study, ^ = cross over design, [α] = TBI identified from mixed sample, [θ] = 1 patient had an improved EEG, [β] = MCS only (full sample), 10-20 IS = 10-20 International System, ACG = anterior cingulate cortex, ADL = activities of daily living, aMT = active motor threshold, BD = bipolar personality disorder type 1, cTBS = continuous theta burst stimulation, DLPFC = dorsal lateral prefrontal cortex, DTI = diffusion tensor imaging, EMCS = emerged from minimally conscious state, front. = frontal lobe, ITI = inter-train interval, MC = motor cortex, MCS = minimally conscious state, MEP = motor-evoked potential, MRI = magnetic resonance imaging, NI = no information provided, NN = X = no neuronavigation available, PPC = posterior parietal cortex, RSN = resting-state networks, sMT = standard motor threshold (1.62), T = treatment terminated, temp. = temporal lobe, TD = train duration, VS = vegetative state