Transcranial Magnetic Stimulation

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➲ Instructions for Use

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Coverage Rationale

The following are unproven and not medically necessary due to insufficient evidence of efficacy:
- Transcranial magnetic stimulation (TMS) for treating all medical (i.e., non-behavioral) conditions including but not limited to:
  - Alzheimer's disease
  - Chronic neuropathic pain
  - Dystonia
  - Epilepsy
  - Headaches
  - Parkinson's disease
  - Stroke
  - Tinnitus
  - Traumatic brain injury (TBI)
- Navigated transcranial magnetic stimulation (nTMS) for treatment planning or for diagnosing motor neuron diseases or neurological disorders
- Theta-burst stimulation including accelerated and/or MRI guided protocols

For Behavioral Disorders, refer to the Optum Behavioral Clinical Policy titled Transcranial Magnetic Stimulation at Optum Provider Express > Clinical Resources > Guidelines/Policies & Manuals > Behavioral Clinical Policies.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0858T	Externally applied transcranial magnetic stimulation with concomitant measurement of evoked cortical potentials with automated report
0889T	Personalized target development for accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation derived from a structural and resting-state functional MRI, including data preparation and transmission, generation of the target, motor threshold-starting location, neuronavigation files and target report, review and interpretation

CPT Code	Description
0890T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including target assessment, initial motor threshold determination, neuronavigation, delivery and management, initial treatment day
0891T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent treatment day
0892T	Accelerated, repetitive high-dose functional connectivity MRI-guided theta-burst stimulation, including neuronavigation, delivery and management, subsequent motor threshold redetermination with delivery and management, per treatment day
90867	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
90868	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent delivery and management, per session
90869	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management

Description of Services

Transcranial magnetic stimulation (TMS) is a non-invasive method of delivering electrical stimulation to the brain. In general, single-pulse TMS is used to explore brain functioning and repetitive TMS (rTMS) is used to induce changes in brain activity that lasts beyond the stimulation period (Klomjai et al. 2015). Single-pulse TMS was originally introduced in 1985 as a noninvasive and safe way to stimulate the cerebral cortex. Activation of the motor cortex by TMS produces contralateral muscular-evoked potentials (MEPs), thus providing a valuable tool for functional mapping of the motor cortex. Technological advances introduced generators capable of producing rapid, repetitive pulses of magnetic stimulation. The magnetic field pulses pass unimpeded through the hair, skin, and skull and into the brain where they induce an electrical current to flow inside the brain without seizures or need for anesthesia. The amount of electricity created is very small and cannot be felt by the individual, but the electric charges cause the neurons to become active and are thought to lead to the release of neurotransmitters such as serotonin, norepinephrine, and dopamine. rTMS is currently under investigation as a treatment for several disorders originating in the cerebral cortex including pain, dystonia, epilepsy, headaches, Parkinson's disease, stroke, and tinnitus. TMS is delivered by various available devices, and treatment has been tested using a variety of protocols, including high frequency delivered over the left dorsolateral prefrontal cortex, low frequency delivered over the right or left dorsolateral prefrontal cortex, bi-lateral delivery and deep TMS in which deeper prefrontal regions are stimulated.

Navigated transcranial magnetic stimulation (nTMS) is being studied as a diagnostic tool to stimulate functional cortical areas at precise anatomical locations to induce measurable responses. This technology is being investigated to map functionally essential motor areas for diagnostic purposes and for treatment planning.

Theta burst stimulation (TBS), is a non-invasive form of rTMS where short bursts of 3 to 5 pulses per second are administered at a higher frequency but with a specific interburst level that generates an overall lower frequency. There are accelerated TMS protocols that provide the benefit of a shorter treatment duration, which speeds up the alleviation of targeted symptoms and improves the individual's adherence to the treatment plan. There is also a new approach being studied that uses functional magnetic resonance imaging neuronavigated connectivity-guided intermittent theta burst stimulation (cgiTBS) to treat treatment-resistant depression (Morriss et al. 2024).

Clinical Evidence

Therapeutic Transcranial Magnetic Stimulation (TMS)

The current evidence is insufficient to determine the efficacy of TMS for treating conditions such as Alzheimer's disease, epilepsy, headaches, pain, Parkinson's disease, stroke, and tinnitus. Due to small sample sizes, short-term follow-ups, and variability in technique and outcome measures, there is insufficient data to conclude that transcranial magnetic stimulation is beneficial for treating these conditions.

Alzheimer's Disease (AD)

Moussavi et al. (2024) conducted a large, multisite, randomized controlled trial (RCT) to evaluate the effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) in treating Alzheimer's disease (AD). This double-blind, placebo-controlled study included 156 participants with mild to moderate AD. Participants were assigned to receive either 2 or 4 weeks of rTMS treatment or a sham treatment. The findings revealed significant cognitive improvements in both the active and sham rTMS groups up to two months post-treatment. However, there were no significant differences in cognitive outcomes between the two groups. These results indicate potential benefits of rTMS but highlight the necessity for further research to understand its mechanisms and long-term effects.

Ozer et al. (2024) conducted a double-blind, placebo-controlled study to assess the efficacy of dTMS targeting the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) in patients with OCD. There were 29 participants, with 14 receiving active TMS and 15 receiving a placebo. The active group underwent stimulation twice daily at 20 Hz for three weeks, while the placebo group received sham stimulation. The active TMS group experienced significant reductions in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores (from 25.36 ±5.4 to 18.43 ±6.86) and Hamilton Anxiety Rating Scale (HAM-A) scores (from 10.6 ±3.5 to 6.7 ±2.7) compared to the placebo group. Accelerated dTMS with a double-cone coil proves to be an effective adjunctive treatment for treatment-resistant OCD, though it did not significantly reduce symmetry-related OCD symptoms. This study included limitations: a small sample size, specificity of symptoms, limited follow-up, there was some placebo effect and there could be treatment burden with twice daily sessions for three weeks. Additional research is needed with larger samples and longer follow-up periods to fully understand the treatment's efficacy and safety.

Yan et al. (2023) conducted a systematic review and meta-analysis evaluating the effectiveness of different components of TMS on improving cognitive function in individuals with AD There were a total of 21 studies and 25 trials were included in this meta-analysis. The findings revealed a significant overall cognition improvement of real stimulation compared with sham stimulation (short-term effects: SMD, 0.91; 95% CI 0.44-1.38; p < 0.01; long-lasting effects: SMD, 0.91; 95% CI 0.27-1.55; p < 0.01). Subgroup analysis demonstrated that stimulation of the left dorsolateral prefrontal cortex and bilateral cerebellums, as well as moderate frequency stimulation (5 Hz and 10 Hz) on mild and moderate cognitive impairment patients, were more effective than other TMS protocols. However, the additional application of cognitive training showed no significant improvement. Study limitations included a small sample size even though 21 studies and 25 trials were included; global outcomes were assessed but additional research is needed for behavioral and cognitive impairment as well as heterogeneity of the subjects, Last there were some findings that were from a single small sample size study leaving a need for larger robust studies. The author's concluded that cognitive improvement effect of TMS was demonstrated in MCI and AD patients in both short-term assessment and long-lasting outcomes, and the efficiency of TMS is affected by the stimulation frequency, stimulation site, and participant characteristics. Additional RCTs are needed to support these promising findings.

Yao et al. (2022) conducted a RCT to evaluate rTMS to the cerebellum and how it effects cognitive recovery in patients with AD. Applying rTMS and brain imaging techniques would help identify the role of the cerebellum in regulating cortical cognitive networks in AD and better describe the cerebellum rTMS effects. 27 patients with AD were included in this randomized, double-blind, sham-controlled trial and were randomly assigned to one of the two groups: rTMS-real or rTMS-sham. They investigated the efficacy of a four-week treatment of bilateral cerebellum rTMS to promote cognitive recovery and alter specific cerebello-cerebral functional connectivity. Results showed that cerebellum rTMS significantly improves multi-domain cognitive functions, directly associated with the observed intrinsic functional connectivity between the cerebellum nodes and the dorsolateral prefrontal cortex (DLPFC), medial frontal cortex, and the cingulate cortex in the real rTMS group. The sham stimulation showed no significant impact on the clinical improvements and the cerebello-cerebral connectivity. The authors note that while the results are promising, there are limitations that included the approach used to identify the target areas of stimulation. They recognized that the lack of a neuronavigation system interferes with precision therapy from our sample; the International Federation of Clinical Neurophysiology recommended using rTMS as an add-on instrument to enhance cognitive training effects and induce a comprehensive cognitive improvement in AD patients. The clinical efficacy of rTMS treatments could be improved by combining neuronavigation rTMS with cognitive training. Additional studies are needed to further investigate the impact of cerebellar stimulation as an innovative target to improve cognitive functions in AD to understand the potential clinical implications of this approach.

Zhang et al. (2021) conducted a meta-analysis of RCTs of the effects of TMS on mild cognitive impairment (MCI). MCI has a high risk of progression in patients with AD. RTMS (rTMS) is a non-invasive brain stimulation technique used to improve cognitive deficits in patients with MCI and AD. Although previous meta-analyses included studies carried on patients with MCI and AD, few studies have analyzed patients with MCI independently. This meta-analysis aimed to evaluate the effects and safety of rTMS on cognition function in patients with MCI and factors that may influence such effects. Results included a total of 12 studies involving 329 patients with MCI were included in the present meta-analysis. The analyses results revealed that rTMS improved cognitive function [standardized mean difference (SMD) = 0.83, 95% confidence interval (CI) = 0.44-1.22, p = 0.0009] and memory function (SMD = 0.73, 95% CI = 0.48-0.97, p < 0.00001) in the MCI + rTMS active group when compared to the sham stimulation group. The showed that: (1) cognitive improvement was more pronounced under high-frequency rTMS stimulation of multiple sites, such as the bilateral dorsolateral prefrontal cortex and (2) more than 10 rTMS stimulation sessions produced higher improvement on cognition function in patients with MCI. Study limitations include, a limited number of studies, small sample size, the duration of rTMS was not assessed, heterogeneity with stimulation parameters and last the study only evaluated cognition. The authors note that rTMS can improve cognitive function in patients with MCI, especially when applied at high frequency, multi-site, and for a prolonged period. However, based on limitations, further studies are needed to confirm these findings and discover more effective stimulation protocols and targets.

Xie et al. (2021) conducted a systematic review and meta-analysis to provide up-to-date evidence on the effects of rTMS (rTMS) treatment on cognitive function in patients with mild cognitive impairment (MCI) and early stage of Alzheimer's disease (AD). The effectiveness of this therapy is still under deliberation due to the variety of rTMS parameters and individual differences including distinctive stages of AD in the previous studies. This meta-analysis is aiming to assess the cognitive enhancement of rTMS treatment on patients of MCI and early AD. Twelve studies with 438 participants (231 in the rTMS group and 207 in the control group) in thirteen randomized, double-blind, and controlled trials were included. Random effects analysis revealed that rTMS stimulation significantly introduced cognitive benefits in patients of MCI and early AD compared with the control group (mean effect size, 1.17; 95% CI, 0.76 - 1.57). Most settings of rTMS parameters (frequency, session number, stimulation site number) significantly enhanced global cognitive function, and the results revealed that protocols with 10 Hz repetition frequency and DLPFC as the stimulation site for 20 sessions can already be able to produce cognitive improvement. The cognitive enhancement of rTMS could last for one month after the end of treatment and patients with MCI were likely to benefit more from the rTMS stimulation. This study added important evidence to the cognitive enhancement of rTMS in patients with MCI and early AD and discussed potential underlying mechanisms about the effect induced by rTMS. The limitations included a limited number of trials, small sample size, inability to assess the change of treatment relative to the baseline of all studies and high heterogeneity of stimulation parameters (frequency, session number, stimulation site). Additional randomized controlled studies are needed with larger sample sizes and better design to identify the optimal parameters of rTMS intervention on cognition of AD patients.

Holczer et al. (2020) conducted a systematic review to examine the presence and extent of methodological issues confounding non-invasive brain stimulation (NIBS) studies attempting to alleviate the cognitive symptoms of demented individuals. However, serious methodological limitations appear to affect the estimates of their efficacy. The focus was on rTMS or tDCS, i.e., the two most frequent NIBS techniques. Patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) were included. The study reviewed the stimulation parameters and methods of studies that used TMS or tDCS to alleviate the cognitive symptoms of patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI). The risk of bias was also included in these studies. There were 36 studies identified of which 23 were randomized-controlled trials. More than 75% of randomized-controlled trials involved some levels of bias in at least one domain. Stimulation parameters were highly variable with some ranges of effectiveness emerging. Studies with low risk of bias indicated TMS to be potentially effective for patients with AD or MCI while questioned the efficacy of tDCS. This was the first time the presence and extent of methodical issues affecting TMS and tDCS research involving patients with AD and MCI were examined. The risk of bias frequently affected the domains of the randomization process and selection of the reported data while missing outcome was rare. Unclear reporting was present involving randomization, allocation concealment, and blinding. Methodological awareness can potentially reduce the high variability of the estimates regarding the effectiveness of TMS and tDCS. Studies with low risk of bias delineate a range within TMS parameters seem to be effective but question the efficacy of tDCS. The study also had limitations including the lack of quality assessment of the non-RCTs as well as a quantitative analysis. Only the measurements of cognitive domain were considered, and most neuropsychiatric symptoms are considered to be closely linked with cognitive disturbances causing reduced quality of life in neurodegenerative disorders. Author's note that based on the current literature, it is difficult to conclude the effectiveness of NIBS methods in dementia research.

Lin et al. (2019) conducted a systematic review and meta-analysis to evaluate the effects of rTMS (rTMS) on cognitive function in patients with AD. A total of 12 studies with 231 patients were included, with 8 randomized controlled studies and 4 self-controlled studies. Eleven studies used high frequency rTMS (≥ 5 Hz), but only one study directly compared the difference between low-frequency (1 Hz) and high-frequency (20 Hz). Random-effects analysis showed that rTMS could significantly improve cognition compared with sham-rTMS (SMD: 0.60, 95% CI: 0.35-0.85, $p < .0001$). In subgroup analyses, the effect for stimulation at a single target was 0.13 (95% CI: -0.35-0.62) and multiple targets 0.86 (95% CI: 0.18-1.54). Treatment for ≤ 3 sessions produced an effect of 0.29 (95% CI: -1.04-1.62), whereas treatment for ≥ 5 sessions produced an effect of 2.77 (95% CI: 2.22-3.32). No differences were found for rTMS combined with medication or cognitive training. The authors concluded that rTMS can significantly improve cognitive ability in patients with mild to moderate AD. According to the authors, several limitations of this meta-analysis should be considered. First, the number of studies and sample size in the meta-analysis were small. Second, although the efficacy of rTMS was evaluated, there was no assessment of the effect of duration due to inadequate data. Third, the presence of heterogeneity between studies was inevitable and this inconsistency may have influenced the results. Further trials with larger samples are needed to explore the optimal parameters and verify the effect of rTMS on cognition in AD patients.

Hayes (2019) published a report on neuroAD Therapy System for Alzheimer disease. Hayes concluded that there is not enough evidence to draw firm conclusions regarding the efficacy of the neuroAD device in patients with mild to moderate AD.

Dong et al. (2018) conducted a systematic review and meta-analysis to evaluate the efficacy and safety of rTMS in AD. Five RCTs involving 148 participants were included in this review. Compared with sham stimulation, high-frequency rTMS led to a significant improvement in cognition as measured by Assessment Scale-cognitive subscale (ADAS-cog), but not (Mini-Mental State Examination) MMSE. High frequency rTMS also improved the global impression in comparison to the placebo. There was no significant difference in mood and functional performance between high frequency rTMS and sham groups. Only one trial included low frequency rTMS reported no significant improvement in cognition, mood, and functional performance. Few mild adverse events were observed in both the rTMS and sham groups. The authors concluded that rTMS is relatively well tolerated, with some promise for cognitive improvement and global impression in patients with AD. According to the authors, a limitation of this meta-analysis is that the sample size was too small to ensure adequate power to detect a significant difference in primary outcomes among groups.

According to the National Institute for Health and Care Excellence (NICE) guideline for dementia: assessment, management and support for people living with dementia and their carers' (2018), non-invasive brain stimulation (includingTMS) should not be offered to treat mild to moderate Alzheimer's disease, except as part of a randomized controlled trial.

Epilepsy

In a Cochrane review, Walton et al. (2021) assessed the evidence for the use of TMS in individuals with drug-resistant epilepsy compared with other available treatments in reducing seizure frequency, improving quality of life, reducing epileptiform discharges, antiepileptic medication use, and side effects. Included were randomized controlled trials were double-blinded, single-blinded, or unblinded, and placebo controlled, no treatment, or active controlled, which used rTMS without restriction of frequency, coil, duration, or intensity on participants with drug-resistant epilepsy. The eight included studies (241 participants) were all randomized trials; seven of the studies were blinded. Methodological and design information in the included studies was unclear, mostly relating to randomization and allocation concealment. They were not able to combine the results of the trials in analysis due to differences in the studies' designs. For the current update, two of the eight studies analyzed showed a statistically significant reduction in seizure rate from baseline (72% and 78.9%) reduction of seizures per week from the baseline rate, respectively), while the other six studies showed no statistically significant difference in seizure frequency following rTMS treatment compared with controls (low-certainty evidence). One study assessed quality of life and found that more participants showed improvement in quality-of-life scores with active treatments compared to the sham treatment, but this only involved seven participants (very low-certainty evidence). Four studies evaluated our secondary endpoint of mean number of epileptic discharges, three of which showed a statistically significant reduction in discharges after active rTMS treatment. Adverse effects were uncommon in the studies and typically involved headache, dizziness, and tinnitus; however increased seizure frequency did occur in a small number of individuals. The included trials reported no substantial changes in medication use. Authors note the risk of bias was either low or unclear, and the certainty of the evidence was low to very low. The certainty of evidence for the primary outcomes of this review to be low to very low. There was some evidence to suggest that rTMS is safe, but some adverse events were experienced. The inconsistency in technique and outcome prevented meta-analysis, and the evidence for efficacy of rTMS for seizure reduction is still lacking, even though there is reasonable evidence that indicates it is effective at reducing epileptiform discharges. The use of rTMS is still a fairly new therapy for seizures, and future studies should aim to methodically establish a standard technique for its use.

In a Cochrane review, Chen et al. (2016) assessed the evidence for the use of TMS in individuals with drug-resistant epilepsy compared with other available treatments in reducing seizure frequency and improving quality of life. Seven randomized controlled trials that were double-blinded, single-blinded or unblinded, and placebo, no treatment, or active controlled were included in the analysis. The total number of participants in the seven trials was 230. Two of the seven studies analyzed showed a statistically significant reduction in seizure rate from baseline (72% and 78.9% reduction of seizures per week from the baseline rate, respectively). The other five studies showed no statistically significant difference in seizure frequency following rTMS treatment compared with controls. The authors judged the quality of evidence for the primary outcomes of this review to be low. According to the authors, there is evidence that rTMS is safe and not associated with any adverse events, but given the variability in technique and outcome reporting that prevented meta-analysis, the evidence for efficacy of rTMS for seizure reduction is still lacking despite reasonable evidence that it is effective at reducing epileptiform discharges.

Headaches

Zhong et al. (2022) conducted a meta-analysis on the effect of rTMS on chronic migraine with or without aura by examining the effect of rTMS on pain intensity and frequency of headaches in addition to the relationship between the stimulation site and efficacy. Eight studies were included which resulted in a random effects analysis showed an effect size of -1.13 [95% confidence interval (CI): -1.69 to -0.58] on the frequency of migraine attacks, indicating that rTMS was more effective for decreasing migraine attacks than the sham rTMS. The author's indicated that the results provide some direction for further research, and they believe that rTMS can aid in the prevention of migraines. But, this study does have limitations which includes: the efficacy of the rTMS on chronic migraine was preliminary and inconclusive because of the heterogeneity in study designs of rTMS stimulation (including the frequency of stimulation the number of pulse, pulse intensity, and the number of session); lack of outcomes homogeneity and long-term real world efficacy data; the sample size is small because of the non-randomized sham-controlled designs, case-reports, had incomplete outcomes, and small sample size (n < 4) were excluded, therefore, only eight studies were eligible; the diagnose criteria used in some studies varied; and lastly, there were no multicenter trials, and the overall focus was therefore limited. Consequently, further robust, and multicenter trials are necessary to confirm these results.

Cheng et al. (2022) in a network meta-analysis of RCTs aimed at comparing treatment approaches with respect to their effectiveness (with specific respect to migraine prophylaxis) and their acceptability in patients with migraine. Nineteen RCTs were included (n = 1493; mean age = 38.2 years; 82.0% women). We determined that the high frequency rTMS over C3 yielded the most decreased monthly migraine days among all the interventions [mean difference = - 8.70 days, 95% confidence intervals (95%CIs): - 14.45 to - 2.95 compared to sham/control groups]. Only alternating frequency (2/100 Hz) transcutaneous occipital nerve stimulation (tONS) over the Oz (RR = 0.36, 95%CIs: 0.16 to 0.82) yielded a significantly lower drop-out rate than the sham/control groups did. This study confirmed that the hf-TMS-C3 and hf-tONS-Oz were associated with the most efficacy in outcomes of monthly migraine days and response rate, respectively. Also, c-tDCS-CP4 + a-tDCS-arm, in addition to improving monthly migraine days, were most effective among the interventions in improving migraine pain severity. Because of the limitations of the small sample sizes, heterogeneous primary outcomes, and study design among the included RCTs, and short follow-up periods, the results suggest the need for future large-scale RCTs with longer follow-up which would help determine the preventive effects of noninvasive brain/nerve stimulation in patients with migraine.

Moisset et al. (2020) conducted a systematic review with meta-analysis of RCTs focusing on neurostimulation techniques for migraine treatment. Several non-invasive and even invasive neurostimulation methods have been proposed for acute or preventive migraine treatment. The target population was patients of any age, including children, with migraine according to the international classification of headache disorders (ICHD) criteria. The migraine conditions considered included both episodic and chronic migraine, either with or without aura. Studies focusing on other headache types, especially tension-type headaches or cluster headaches, were excluded. Outcomes for the quantitative synthesis were 2 hours pain free for acute treatment and headache days per month for preventive treatment. Subgroup analyses was done by treatment (stimulation method and site of application). Estimates were pooled using random-effects meta-analysis. Thirty-eight articles were included in the qualitative analysis (7 acute, 31 preventive) and 34 in the quantitative evaluation (6 acute, 28 preventive). Remote electrical neuromodulation (REN) was effective for acute treatment. Data were insufficient to draw conclusions for any other techniques (single studies). Invasive occipital nerve stimulation (ONS) was effective for migraine prevention, with a large effect size but considerable heterogeneity, whereas supra-orbital transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS), and high-frequency rTMS over the primary motor cortex (M1) were effective, with Vagus-nerve stimulation, left prefrontal cortex rTMS, and cathodal transcranial direct current stimulation (tDCS) over the M1 had no significant effect and heterogeneity was high. Six studies tested repetitive TMS. There are several neuromodulation methods that are of potential interest for migraine management, but the quality of the evidence is very poor. This review had several limitations. The meta-analysis was based on a very limited number of articles for each study sub-group and the estimation of effect size may not be accurately driven. The methodological quality of the studies was heterogenous. The follow-up period was very short, and long-term benefits of neuromodulation are yet to be proven. Future large and well-conducted studies are needed and could improve on the present results.

Stilling et al. (2019) performed a systematic review on the use of TMS and (tDCS for the treatment of specific headache disorders (i.e., migraine, tension, cluster, posttraumatic). Studies were selected by inclusion criteria for participants (adults 18-65 with primary or secondary headaches), interventions (TMS and tDCS applied as headache treatment), comparators (sham or alternative standard of care), and study type (cohort, case-control, and randomized controlled trials [RCT]). Thirty-four studies were included: 16 rTMS, 6 TMS (excluding rTMS), and 12 tDCS. The majority investigated treatment for migraine (19/22 TMS, 8/12 tDCS). The quality of the studies ranged from very low to high. The authors concluded that rTMS is the most promising with moderate evidence that it contributes to reductions in headache frequency, duration, intensity, abortive medication use, depression, and functional impairment. However, only a few studies reported changes greater than sham treatment. Further high-quality RCTs with standardized protocols are required for each specific headache disorder to validate a treatment effect.

Reuter et al. (2019) performed a systematic review of 71 clinical trials to inform clinical decisions about non-invasive neuromodulation for migraine and cluster headaches. Non-invasive vagus nerve stimulation (nVNS), single-transcranial magnetic stimulation (sTMS) and external trigeminal nerve stimulation (all with regulatory clearance) were well studied compared with the other devices, for which studies frequently lacked proper blinding, sham controls, and sufficient population sizes. sTMS which includes the Cerena Transcranial Magnetic Stimulator (eNeural Therapeutics) and the SpringTMS device (eNeural Therapeutics) was evaluated in three published studies for the acute and preventive treatment of migraine. According to the authors, nVNS studies demonstrated the most consistent adherence to available guidelines. According to the authors, the scope of this systematic review was limited by the heterogeneity among the clinical trials analyzed and the unavailability of many of the study results, which precluded a formal systematic meta-analysis of all identified studies.

In a systematic review of controlled clinical trials, Shirahige et al. (2016) evaluated the efficacy of noninvasive brain stimulation (NIBS) on pain control in migraine patients. Eight studies were included in the quantitative analysis with 153 migraine patients who received NIBS and 143 patients who received sham NIBS. In the overall meta-analysis, the authors did not find significant results for pain intensity, for migraine attacks, and for painkiller intake. However, subgroup analysis considering only tDCS effects demonstrated a decrease for pain intensity, migraine attacks, and painkiller intake. Subgroup analysis for TMS did not reveal significant effects for any outcome. The authors concluded that this review failed to find support for the superiority of NIBS over sham treatment. According to the authors, there is a need for larger controlled trials with methodological rigor, which could increase the power of result inference.

According to the National Institute for Health and Care Excellence (NICE) Guideline for transcranial magnetic stimulation for treating and preventing migraine (2014), evidence on the efficacy of TMS for the treatment of migraine is limited in quantity and for the prevention of migraine is limited in both quality and quantity. Evidence on its safety in the short and medium term is adequate but there is uncertainty about the safety of long-term or frequent use of TMS. Therefore, according to NICE, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

Clinical Practice Guidelines

European Headache Federation

In a position statement for neuromodulation of chronic headaches, the European Headache Federation states that application of the noninvasive rTMS in chronic headaches is not yet evidence based, given the poor amount of controlled data (Martelletti et al. 2013).

Parkinson's Disease (PD)

Romero et al. (2024) conducted a randomized, four-arm controlled trial to investigate the effects of bilateral repetitive Transcranial Magnetic Stimulation (rTMS) and EEG-guided neurofeedback (NFB) on motor and non-motor symptoms in Parkinson's disease (PD). The study included 40 participants, divided into four groups: rTMS, NFB, a combination of both, and a control group with no intervention. The participants (27 males, average age 63 ±8.26 years, baseline UPDRS-III score 15.63 ±6.99 points, Hoehn and Yahr stages 1-3) were assessed for various outcomes. Group C (combination of rTMS and NFB) showed the most significant improvements in motor symptoms, health-related quality of life, and cortical silent periods, followed by Group A (rTMS) and Group B (NFB). There were negligible differences between Groups A-C and Group D (control) in terms of functional mobility and limits of stability. The combination group exhibited the greatest enhancement in motor symptoms and health-related quality of life, along with significant changes in cortical silent periods, indicating increased cortical excitability. No significant differences were observed in functional mobility or postural stability across the groups. The study's limitations included a small sample size, single-center design, short follow-up period, and lack of examination of individual differences in response to rTMS and NFB. These limitations highlight the need for further research with larger, multi-center trials and longer follow-up to better understand the efficacy and safety of combining rTMS and NFB for treating Parkinson's disease.

Deng et al. (2022) conducted a systematic review with meta-analysis to assess the therapeutic effects of rTMS on FOG and cognition in patients with Parkinson's disease (PD) and provide updated evidence on the role of rTMS therapy in patients with PD. Sixteen randomized controlled studies with a total of 419 patients were included. Fixed-effects analysis revealed that rTMS was effective in improving freezing of gait questionnaire scores (short-term effect: WMD = -0.925, 95% CI: -1.642 to -0.209, p = .011; long-term effect: WMD = -2.120, 95% CI: -2.751 to -1.489, p = .000), 10-m walking time (short-term effect: WMD = -0.456, 95% CI: -0.793 to -0.119, p = .008; long-term effect: WMD = -0.526, 95% CI: -0.885 to -0.167, p = .004), Timed Up-and-Go scores (short-term effect: WMD = -1.064, 95% CI: -1.555 to -0.572, p = .000;

long-term effect: WMD = -1.097, 95% CI: -1.422 to -0.772, p = .000), Montreal cognitive assessment (WMD = 3.714, 95% CI: 2.567 to 4.861, p = .000), and frontal assessment battery (WMD = -0.584, 95% CI: -0.934 to -0.234, p = .001). In conclusion, RTMS showed a positive effect on FOG and cognitive dysfunction in Parkinson's disease. Unfortunately, due to the limited number of studies, no subgroup analysis of the rTMS stimulation parameters could be conducted to assess the effects of different stimulation parameters on the motor and cognitive outcomes. To be able to translate rTMS into a viable form of clinical treatment, a better understanding of how different rTMS parameters affect motor and cognitive function is necessary to induce optimal improvements in the functioning of patients with PD. Additional high-quality studies are needed to determine the optimum rTMS protocol.

Xie et al. (2020) systematically assessed the effectiveness of rTMS intervention on gait in individuals with PD. The inclusion criteria for this review were RCTs, exploring the effect of rTMS in patients diagnosed with idiopathic PD. Among 14 eligible studies, including 298 participants were analyzed in this meta-analysis. Walking time was improved with rTMS compared with sham rTMS (standardized mean difference [SMD] -0.30; 95% confidence interval [CI], -0.57 to -0.03; p = .03). The score for the freezing of gait questionnaire did not differ significantly between rTMS and no intervention. Four studies compared Timed Up and Go (TUG) test between the 2 treatment groups and no significant differences were found between the rTMS and control group (SMD -0.45; 95% CI, -1.32 to 0.41; p = .30). During the off-state, there were no significant differences in estimated effect sizes (SMD = -0.29; 95% CI, -0.79 to 0.21; p = .25), which is significantly different in on-state (SMD -0.98; 95% CI, -1.78 to -0.18; p = .02) evaluation. The authors concluded that the results of the meta-analysis propose the favorable effect of rTMS on walking performance in the short term but not over the long term. The limitations of this meta-analysis may be that the unclear risk of bias on certain domains constrained the results due to incomplete data in a few studies. In addition, the sample size of the included studies was relatively small. Larger RCTs with improved study methodology are needed to evaluate the effectiveness of rTMS for patients with PD.

Yang et al. (2018) performed a meta-analysis to evaluate the optimal rTMS parameters for motor recovery of PD. Electronic databases were searched for studies investigating the therapeutic effects of rTMS on motor function in patients with PD. Twenty-three studies with a total of 646 participants were included. The pooled estimates of rTMS revealed significant short-term and long-term effects on motor function improvement of PD. Subgroup analysis observed that high-frequency rTMS (HF-rTMS) was significant in improving motor function, but low-frequency rTMS (LF-rTMS) was not. In particular, when HF-rTMS targeted over the primary motor cortex (M1), in which the bilateral M1 revealed a larger effect size than unilateral M1. Compared to single-session, multi-session of HF-rTMS over the M1 showed significant effect size. In addition, HF-rTMS over the M1 with a total of 18,000-20,000 stimulation pulses yielded more significant effects than other dosages. According to the authors, these results suggest that rTMS might be helpful in improving the motor deficits of PD patients. The authors stated that there are limitations of this meta-analysis. First, the experimental designs of the included studies were not homogenous (e.g., randomized controlled trials versus crossover design). Second, the selected participants varied in age, disease stage, and other biological characteristics that may have confounded the results.

Goodwill et al. (2017) conducted a meta-analysis that quantified the effectiveness of rTMS to improve motor and cognitive dysfunction in PD. A total of24 rTMS with a sham control group were included in the analyses. The results showed an overall positive effect in favor of rTMS compared with sham stimulation on motor function. The use of rTMS did not improve cognition. No effects for stimulation parameters on motor or cognitive function were observed. The authors acknowledged several limitations. Studies evaluating rTMS demonstrated modest effect sizes (0.4–0.6) and large heterogeneity between studies. Clinical and lifestyle variables including PD-related comorbidity, physical activity levels and other mental health conditions were not accounted for in the subgroup analyses, which may have influenced the responsiveness to non-invasive brain stimulation (NBS).

In a systematic review and meta-analysis, Wagle Shukla et al. (2016) reviewed the literature on clinical repetitive rTMS trials in Parkinson's disease to quantify the overall efficacy of this treatment. Prospective clinical trials were included that had an active arm and a control arm and change in motor scores on Unified Parkinson's Disease Rating Scale as the primary outcome. The authors pooled data from 21 studies that met these criteria and analyzed separately the effects of low- and high-frequency rTMS on clinical motor improvements. rTMS therapy demonstrated benefits at short-term follow-up (immediately after a treatment protocol) with a pooled mean difference of 3.4 points as well as at long-term follow-up (average follow-up 6 weeks) with mean difference of 4.1 points. The authors concluded that rTMS therapy results in mild-to-moderate motor improvements and has the potential to be used as an adjunct therapy for the treatment of Parkinson's disease. According to the authors, future large, sample studies should be designed to isolate the specific clinical features of Parkinson's disease that respond well to rTMS therapy. The authors indicated that the literature on the use of rTMS for levodopa-induced dyskinesia, objective bradykinesia, and gait measures is sparse and that on the basis of the current available information, the results are conflicting, and no clear treatment protocol has yet been defined.

Pain

Mori et al. (2024) conducted a randomized, sham-controlled parallel trial to assess the efficacy and safety of navigation-guided rTMS over the primary motor cortex in patients with upper limb neuropathic pain. The study included 30 participants who were assigned to either an active rTMS group or a sham stimulation group. The primary outcome was the reduction in pain intensity, measured using a numerical rating scale. Although the active rTMS group experienced a greater reduction in pain intensity compared to the sham group, the difference was not statistically significant. However, the active rTMS group did show improvements in pain-related disability scores. No serious adverse events were reported, indicating that rTMS is a safe treatment option. While the study did not demonstrate significant pain relief from rTMS, it suggested potential benefits in reducing pain-related disability. The study's limitations included a small sample size, short follow-up period, subjective pain rating scale, and being a single study. Further research with larger sample sizes, a more diverse population, and longer follow-up is needed to confirm these findings.

Saleh et al. (2022) in a systematic review examined the effectiveness of rTMS in neuropathic pain secondary to spinal cord injury (SCI). The search identified a total of 203 potential articles. Of these, 8 RCTs met the eligibility criteria for qualitative synthesis providing the total data of 141 patients. All studies employed high-frequency rTMS. In 7 studies, rTMS was applied over the motor cortex, and in 1 study over the left dorsolateral prefrontal cortex; 5 studies reported a significant improvement in baseline pain scores after treatment, and 3 studies found a significant difference between sham versus non-sham stimulation at any time; 6 RCTs were included in the quantitative synthesis and showed a significant overall reduction of pain intensity in the rTMS groups compared with the sham groups (MD - 0.81, 95 % CI: - 1.45 to - 0.17). The authors concluded that these findings indicated that high-frequency rTMS of the primary motor cortex and left dorsolateral prefrontal cortex might be promising stimulation targets for neuropathic pain in SCI.

Yang et al. (2022) in a RCT evaluated intended to evaluate the effect of high-frequency (10 Hz) rTMS on the left primary motor cortex (M1) for neuropathic pain in the lower extremities due to diabetic peripheral neuropathy (DPN). In this randomized trial, 22 patients in an outpatient clinic of a single academic medical center with DPN were randomly assigned to either the rTMS group (10 Hz stimulation, five sessions) or the sham group. A numeric rating scale (NRS) was used to measure pain intensity before treatment and after 1 day and 1 week of the treatment. Physical and mental health status was used to evaluate using the Short Form 36-Item Health Survey (SF-36), comprising two subscales (physical and mental component scores [PCSs and MCSs]), at 1-week post-treatment. Of the 22 included patients, 20 (10 patients in each group) completed the study. In the rTMS group, the NRS score at one day and one week posttreatment was significantly lower than that at pretreatment. The SF-36 PCS and SF-36 MCS were significantly increased one week after the rTMS sessions. The NRS score, SF-36 PCS, and SF-36 MCS did not significantly change after the rTMS sessions in the sham group. Two limitations included a small number of included patients and no long-term follow-up. In conclusion, high-frequency rTMS on the left M1 may be useful for managing pain in the lower extremities due to DPN and may improve a patient's the quality of life. Larger studies with long-term follow up is needed to confirm these results.

Che et al. (2021) conducted a systematic review and meta-analysis to investigate the analgesic efficacy of rTMS over the dorsolateral prefrontal cortex (DLPFC) on chronic and provoked pain. A total of 626 studies were identified in a systematic search. Twenty-six eligible studies were included for the quantitative review, among which 17 modulated chronic pain and the remaining investigated the influence on provoked pain. The left side DLPFC was uniformly targeted in the chronic pain studies. While data identified no overall effect of TMS across chronic pain conditions, there was a significant short-term analgesia in neuropathic pain conditions only (SMD = -0.87). In terms of long-lasting analgesia, there was an overall pain reduction in the midterm (SMD = -0.53, 24.6 days average) and long term (SMD = -0.63, 3 months average) post DLPFC stimulation, although these effects were not observed within specific chronic pain conditions. Surprisingly, the number of sessions was demonstrated to have no impact on rTMS analgesia. In the analysis of provoked pain, data also indicated a significant analgesic effect following HF-rTMS over the DLPFC (SMD = -0.73). A publication bias was identified in the studies of provoked pain but not for chronic pain conditions. Other limitations included small study size in each category, no consensus in the definition of long-lasting rTMS analgesia. Overall, the findings support that HF-DLPFC stimulation is able to induce an analgesic effect in chronic pain and in response to provoked pain. While the results are promising, larger more robust studies are needed to validate the findings.

Yu et al. (2020) conducted a meta-analysis examining the effectiveness of the effects of overall noninvasive brain stimulation (NIBS) on post- spinal cord injury (SCI) neuropathic pain (NP). A meta-analysis on pain intensity, depression, and anxiety levels was conducted to evaluate the effect of noninvasive brain stimulation on neuropathic pain in individuals with spinal cord injury.

Eleven studies were selected including eight RCT's and three cross-over RCTs. All studies compared and active NIBS group with a sham group. The intervention of these studies included rTMS (four trials), tDCS (six trials), and CES (one trials). The pooled analysis demonstrated no significant effect of rTMS, transcranial direct current stimulation, or cranial electrotherapy stimulation on neuropathic pain reduction after spinal cord injury. In addition, noninvasive brain stimulation showed no beneficial effect over sham stimulation on the improvement of depression, while it yielded a significant reduction of anxiety levels immediately after treatment. Subgroup analysis showed that only cranial electrotherapy stimulation had a significant effect on the reduction of anxiety levels among the three types of noninvasive brain stimulation. There are limitations with the study including the small number evaluated for each type of stimulation, most subjects were male and only studies that contained pain were included whereas those only examined anxiety, and depression may have been missed. The overall findings indicated that noninvasive brain stimulation had no significant effect on pain reduction in individuals with post-SCI NP, but cranial electrotherapy stimulation might be useful in the management of anxiety in these individuals. These findings do not support the routine use of noninvasive brain stimulation for NP in individuals with SCI. Further studies are needed with larger sample size to support this technology.

Gatzinsky et al. (2020) conducted a systematic review to evaluate the effects of high frequency TMS of M1 in the treatment of chronic neuropathic pain (NP) based on the magnitude of relative pain reduction (active vs sham stimulation) and to investigate the applicability the accuracy to predict a positive response to epidural motor cortex stimulation (MCS) which is supposed to give a more longstanding pain relief. There were 32 articles included twenty-four RCTs and eight case series. Data on 5-20 Hz (high-frequency) rTMS vs. sham was extracted from 24 blinded randomized controlled trials which varied in quality, investigated highly heterogeneous pain conditions, and used extremely variable stimulation parameters. The difference in pain relief between active and sham stimulation was statistically significant in 9 of 11 studies using single session rTMS, and in 9 of 13 studies using multiple sessions. Baseline data could be pulled out from 6 single and 12 multiple session trials with a weighted mean pain reduction induced by active rTMS, compared to baseline, of -19% for single sessions, -32% for multiple sessions with follow-up < 30 days, and -24% for multiple sessions with follow-up ≥ 30 days after the last stimulation session. For single sessions, the weighted mean difference in pain reduction between active rTMS and sham was 15 percentage points, for multiple sessions the difference was 22 percentage points for follow-ups < 30 days, and 15 percentage points for follow-ups ≥ 30 days. Four studies reported data that could be used to evaluate the precision of rTMS to predict response to MCS, showing a specificity of 60-100%, and a positive predictive value of 75-100%. There were no serious adverse events reported. rTMS targeting M1 can result in significant reduction of chronic NP which, however, is transient and shows a great heterogeneity between studies; very low certainty of evidence for single sessions and low for multiple sessions. Multiple sessions of rTMS can sustain a longer effect. rTMS seems to be a fairly good predictor of a positive response to epidural MCS and may be used to select patients for implantation of permanent epidural electrodes. Additional studies on the efficacy of rTMS for different types of NP is needed. Major knowledge gaps remain concerning the long-term effects of rTMS on HRQoL and the use of analgesic medication. These vital conclusion variables need to be addressed more consistently in future studies to validate the routine use of rTMS in chronic pain management.

Hamid et al. (2019) systematically reviewed and evaluated the current literature on TMS for patients suffering from chronic pain, assessed its efficacy, and estimated the best stimulation protocol. Twelve RCTs were included involving 350 patients with focal and generalized chronic pain. An existing proof showed a null response of low frequency rTMS stimulation, rTMS delivered to the dorsolateral prefrontal cortex in chronic pain patients. However, a witnessed pain-killing response was documented when applying active high- frequency TMS on the motor cortex M1 area compared to sham. Pain relief was detected for a short time following the application of active high-frequency motor cortex stimulation in nine clinical trials, and the long-lasting analgesic effect was proved. No side effects were mentioned for the technique. The authors concluded that although TMS is a safe, promising technique to reduce long-lasting refractory pain, the evidence is hampered and influenced by multifactorial stimulation parameters. Additional research efforts are needed to highlight the best optimal stimulation protocol and to standardize all parameters to promote the long-term efficacy of rTMS as a noninvasive alternative in the management of chronic refractory pain.

Galhardoni et al. (2019) compared the analgesic effects of stimulation of the anterior cingulate cortex (ACC) or the posterior superior insula (PSI) against sham deep (d) rTMS in patients with central neuropathic pain (CNP) after stroke or spinal cord injury in a randomized, double-blinded, sham-controlled, 3-arm parallel study. Participants were randomly allocated into the active PSI-rTMS, ACC-rTMS, sham-PSI-rTMS, or sham-ACC-rTMS arms. Stimulations were performed for 12 weeks, and a comprehensive clinical and pain assessment, psychophysics, and cortical excitability measurements were performed at baseline and during treatment. The main outcome of the study was pain intensity (numeric rating scale [NRS]) after the last stimulation session. Ninety-eight patients (age 55.02 ±12.13 years) completed the study. NRS score was not significantly different between groups at the end of the study. Active rTMS treatments had no significant effects on pain interference with daily activities, pain dimensions, neuropathic pain symptoms, mood, medication use, cortical excitability measurements, or quality of life. Heat pain threshold was significantly increased after treatment in the PSI-dTMS group from baseline (1.58, 95% confidence interval [CI] 0.09-3.06) compared to sham-dTMS (-1.02, 95% CI -2.10 to 0.04, p = 0.014), and ACC-dTMS caused a significant decrease in anxiety scores (-2.96, 95% CI -4.1 to -1.7) compared to sham-dTMS (-0.78, 95% CI -1.9 to 0.3; p = 0.018). The authors concluded that ACC- and PSI-dTMS were not different from sham-dTMS for pain relief in CNP despite a significant antinociceptive effect after insular stimulation and anxiolytic effects of ACC-dTMS.

In an updated version the Cochrane review published in 2014, O'Connell et al. (2018) evaluated the efficacy of non-invasive brain stimulation techniques in chronic pain. The update included a total of 42 rTMS studies. The meta-analysis of rTMS studies versus sham for pain intensity at short-term follow-up (0 to < 1-week postintervention), (27 studies, involving 655 participants), demonstrated a small effect with heterogeneity. This equates to a 7% reduction in pain, or a 0.40-point reduction on a 0 to 10 pain intensity scale, which does not meet the minimum clinically important difference threshold of 15% or greater. The authors concluded that there is very low-quality evidence that single doses of high frequency rTMS of the motor cortex may have short-term effects on chronic pain and quality of life. However, multiple sources of bias exist that may have influenced the observed effects. The authors stated that they did not find evidence that low frequency rTMS or rTMS applied to the dorsolateral prefrontal cortex are effective for reducing pain intensity in chronic pain. According to the authors, there remains a need for substantially larger, rigorously designed studies, particularly of longer courses of stimulation.

Saltychev and Laimi (2017) investigated whether there is evidence of rTMS being effective in decreasing the severity of pain among patients with fibromyalgia. Seven trials were included in the meta-analysis. The risk of bias was considered low for seven studies. Pain severity before and after the last stimulation decreased by -1.2 points on 0-10 numeric rating scale. Pain severity before and 1 week to 1 month after the last stimulation decreased by -0.7 points. Both pooled results were below the minimal clinically important difference of 1.5 points. The authors did not find evidence of clinically significant effectiveness of rTMS in decreasing the severity of fibromyalgia pain immediately after the treatment as well as in short-term follow-up.

Goudra et al. (2017) evaluated the role of rTMS in the treatment of chronic pain. Studies comparing rTMS and conventional treatment for chronic pain were searched. The comparison was made for decrease in the pain scores with and without (sham) the use of rTMS after a follow-up interval of 4-8 weeks. All reported pain scores were converted into a common scale ranging from "0" (no pain) to "10" (worst pain). Nine trials with 183 patients in each of the groups were included in the analysis. The decrease in pain scores with rTMS was 1.12 and in sham-rTMS was 0.28. The pooled mean drop in pain scores with rTMS therapy was higher by 0.79. The duration and frequency of rTMS were highly variable across trials. Publication bias was unlikely. The authors concluded that the use of rTMS improves the efficacy of conventional medical treatment in chronic pain patients. This treatment is not associated with any direct adverse effects. However, according to the authors, the duration and frequency of rTMS therapy is presently highly variable and needs standardization. According to the authors, availability of a limited number of trials examining the usefulness of rTMS is an important drawback of the current meta-analysis.

Clinical Practice Guidelines

European Academy of Neurology (EAN)

Cruccu et al. (2016) conducted a systematic review and meta-analysis of trials to update previous European Federation of Neurological Societies guidelines on neurostimulation for neuropathic pain. The GRADE system was used to assess quality of evidence and propose recommendations. Weak recommendations were given for the use of primary motor cortex (M1) rTMS in neuropathic pain and fibromyalgia and inconclusive recommendations were given regarding complex regional pain syndrome (CRPS). There were inconclusive recommendations regarding rTMS of the dorsolateral prefrontal cortex (DLPFC) in fibromyalgia and neuropathic pain.

Stroke

Chen at al. (2024) conducted a randomized controlled trial to evaluate the effectiveness of low-frequency rTMS in treating poststroke neurogenic bladder. A total of 100 patients were divided into two groups: one receiving active rTMS and the other receiving sham stimulation. The active rTMS group showed significant improvements in bladder function compared to the sham group, as measured by urodynamic studies and patient-reported outcomes. Patients in the active rTMS group reported a better quality of life related to urinary symptoms. The treatment was well-tolerated with no serious adverse events reported. Limitations included a single center study, small sample size due to the covid pandemic, rTMS was used as a single treatment, future studies might want to add pelvic floor exercises. Investigating the underlying mechanisms of how rTMS affects bladder function can provide insights into optimizing treatment parameters and improving efficacy. The authors note that study suggests that low-frequency rTMS may be a promising non-invasive treatment for improving bladder function and quality of life in patients with poststroke neurogenic bladder. Future research is needed to confirm these promising results.

In a systematic review, Vabalaite et al. (2021) aimed to assess the effect of high-frequency rTMS for upper extremity motor function recovery after a first-time ischemic stroke. A total of 6440 studies were found in the databases and four trials were included in the review. Three of the studies were randomized control trials (RCT), and one was a pseudo-RCT. Three of the studies showed good methodological quality and one was rated as excellent. Fugl-Meyer Assessment (FMA) was performed in three out of four studies and the score significantly increased in the HF-rTMS treatment group compared with sham stimulation in all trials. Other measures used in the studies were handgrip strength, shoulder abduction, Motricity Index, Wolf Motor Function Test (WMFT), and Box and Block, although these tests did not show unanimous results. All four studies showed significantly better results in at least one test that was performed for hand motor function evaluation in a 10 Hz stimulation group while none of the tests showed any advantage for sham stimulation groups. Two studies reported headache as an adverse event (six patients in total). Limitations of the study included differences in design due to poorly defined rTMS protocols and small sample size. Despite the limitations, the overall results showed that HF-rTMS may increase impaired upper extremity motor function better than sham stimulation in stroke patients. Additional larger randomized controlled groups are needed to better confirm and evaluate the efficacy and safety of HF-rTMS for upper extremity motor function recovery in stroke patients. (Dionisio et al. 2017 included in this study)

Xie et al. (2021) conducted a systematic review and network meta-analysis (NMA) looking at the different modalities of TMS on lower extremity motor function and corticospinal excitability in patients with stroke. This systematic review and NMA of TMS for patients with stroke included data from 26 RCTs, including 943 participants who were randomized to one of four rTMS interventions (deep, high frequency, low-frequency, and intermittent theta-burst rTMS or sham stimulation. Only LF-rTMS was superior to sham stimulation for motor function improvement, as measured by the FMA. Although direct evidence suggested that HFrTMS was more effective than sham stimulation for speed, this result was not replicated in the NMA. In addition, HFrTMS appeared to be more effective than LF-rTMS for MEP amplitudes. Network meta-analysis results of 18 randomized controlled trials regarding lower extremity motor function recovery revealed that low frequency rTMS had better efficacy in promoting lower extremity motor function recovery than sham stimulation. Network meta-analysis results of five randomized controlled trials demonstrated that high-frequency rTMS led to higher amplitudes of motor evoked potentials than low-frequency rTMS or sham stimulation. These findings suggest that rTMS can improve motor function in patients with stroke, and that low-frequency rTMS mainly affects motor function, whereas high-frequency rTMS increases the amplitudes of motor evoked potentials. This study had limitations including an unclear risk of bias on allocation. Also, some nodes were not connected which may have led to inaccurate results. Additional high-quality randomized controlled trials are needed to confirm this conclusion and support the effects of rTMS in stroke patients. This study is registered in PROSPERO (registration No. CRD42020147055).

Ghayour-Najafabadi et al. (2019) conducted a systematic review with meta-analysis to investigate the effectiveness of rTMS in recovery of lower limb dysfunction in patients poststroke. Fifteen trials with 385 patients were included. Results showed that rTMS had a significant effect on balance (standard mean difference [SMD] = .38; 95% confidence interval [CI], .07: .69; I2 = 51%) and mobility (SMD: -.67; 95% CI, -1.08: -.26; I2 = 72%). However, rTMS had no significant immediate effects on the lower limb subscale of the Fugl-Meyer Assessment (FMA-L) (SMD = .01; 95% CI, -.29: .31; I2 = 0%). Continued effects of rTMS was also found to be significant during the follow-up period (SMD = .46; 95% CI, .09: .84; I2 = 14%). According to the authors, this study suggests that rTMS may be more effective than no treatment or sham for improving lower limb motor function in the immediate post-therapy to 30-day follow-up period. Although there are large effect sizes that support a recommendation for rTMS intervention, the existing level of evidence is poor, and further trials are needed to strengthen this preliminary finding.

In a systematic review, Cotoi et al. (2019) evaluated the effectiveness of theta-burst stimulation for the treatment of stroke-induced unilateral spatial neglect. Nine studies met the inclusion criteria, generating a total of 148 participants. Eight studies evaluated a continuous stimulation protocol, and one study investigated an intermittent stimulation protocol. Overall, both protocols significantly improved neglect severity when compared against placebo or active controls ($p < 0.05$). This systematic review found that theta-burst stimulation seems to improve post-stroke unilateral spatial neglect, but because the evidence is limited to a few small studies with varied and inconsistent protocols and use of terminology, no firm conclusion on effectiveness can be drawn.

In a systematic review, Sebastianelli et al. (2017) summarized the evidence for the effectiveness of low-frequency (LF) rTMS in promoting functional recovery after stroke. Sixty-seven studies were included in the review. The authors observed considerable heterogeneity across studies in the stimulation protocols. According to the authors, the use of different patient populations, regardless of lesion site and stroke etiology, different stimulation parameters and outcome measures means that the studies were not readily comparable, and estimating real effectiveness or reproducibility was very difficult. The authors concluded that LF rTMS over unaffected hemisphere may have therapeutic utility, but the evidence is still preliminary, and the findings need to be confirmed in further randomized controlled trials.

Dionísio et al. (2017) conducted a systematic review to provide information regarding the application of rTMS in stroke patients and to assess its effectiveness in clinical rehabilitation of motor function. Seventy trials were included in the review. The majority of the articles reported rTMS showing potential in improving motor function, although some negative reports, all from randomized controlled trials, contradicted this claim. According to the authors, future studies are needed because there is a possibility that a bias for non-publication of negative results may be present.

In a meta-analysis and systematic review, McIntyre et al. (2017) evaluated the effectiveness of rTMS in improving spasticity after stroke. A literature search of multiple databases was conducted for articles published in English from January 1980 to April 2015 using select keywords. Studies were included if: 1) the population included was > 50% stroke patients; 2) the sample size included ≥ 4 subjects; 3) the intervention applied was rTMS; and 4) upper extremity spasticity was assessed pre and post intervention. Randomized controlled trials (RCTs) were assessed for methodological quality using the Physiotherapy Evidence Database (PEDro) tool. The main outcome measurement was the Modified Ashworth Scale (MAS). Ten studies met the inclusion criteria: two RCTs (PEDro scores 8-9) and eight pre-post studies. Meta-analyses of primarily uncontrolled pre-post studies found significant improvements in MAS for elbow, wrist, and finger flexors. However, a meta-analysis of the two available RCTs failed to find a significant rTMS treatment effect on MAS for the wrist. The authors concluded that there is limited available evidence to support the use of rTMS in improving spasticity post stroke. Despite the positive findings reported, better powered and appropriately controlled trials are necessary.

Tinnitus

Yin et al. (2021) conducted an updated meta-analysis from a 2016 meta-analysis (Soleimani included below) to obtain more evidence from randomized controlled trials (RCTs) to assess the efficacy of rTMS for the treatment of tinnitus. The analysis included 12 randomized sham-controlled clinical trials with a total of 717 participants. Active rTMS was superior to sham rTMS in terms of the short-term and long-term effects (6 months) on the tinnitus handicap inventory scores, but an immediate effect was not significant. There was no significant immediate effect on the tinnitus questionnaire (TQ) and Beck depression inventory (BDI) scores. In conclusion, this meta-analysis was consistent and extended the findings of the previous meta-analysis. This study confirmed that rTMS improved tinnitus-related symptoms, but the TQ and BDI scores demonstrated a minimal initial benefit. Additional studies with larger sample sizes in multi-center setting are needed looking at long term outcomes.

Liang et al. (2020) conducted a systematic review and meta-analysis to examine the effects of the effects of rTMS to evaluate its clinical efficacy and safety. After database selection, twenty nine randomized studies involving 1228 chronic tinnitus patients were included. Compared with sham-rTMS, rTMS exhibited significant improvements in the tinnitus handicap inventory (THI) scores at 1 week (mean difference [MD]: −7.92, 1 month (MD: -8.52,), and 6 months (MD: -6.53), post intervention; there were significant mean changes in THI scores at 1 month (MD: -14.86) and 6 months (MD: -16.37) post intervention, and the tinnitus questionnaire (TQ) score at 1 week post intervention (MD: -8.54). Nonsignificant efficacy of rTMS was found regarding the THI score 2 weeks post intervention (MD: -1.51); the mean change in TQ scores 1-month post intervention (MD: -3.67); TQ scores 1 (MD: -8.97) and 6 months (MD: -7.02) post intervention; and adverse events (odds ratios [OR]: 1.12). Egger's and Begg's tests indicated no publication bias. There were several study limitations, including, there were a limited number of subjects which limits a more accurate analysis, and some results were nonsignificant, the studies only analyzed the English language, which could have lost data from other languages and due to the limited number of studies, the possibility of false negatives could not be excluded. This meta-analysis established that rTMS is effective for chronic tinnitus; however, its safety needs more proof from large sample size, multi-center studies are needed for validation.

Soleimani et al. (2016) conducted a systematic literature review and meta-analysis on the effect of rTMS compared with sham in chronic tinnitus patients. For the meta-analysis weighted mean differences (and standard deviations) of Tinnitus Questionnaire (TQ) and Tinnitus Handicap Inventory (THI) scores were determined. Therapeutic success was defined as difference of at least 7 points in the THI score between baseline and the follow-up assessment after treatment. Results from 15 RCTs were analyzed. For THI, the data of mean difference score in two groups, 1 and 6 months after intervention, was 6.71 and 12.89, respectively. According to the authors, these data underscore the clinical effect of rTMS in the treatment of tinnitus. The authors reported that there is high variability of studies design and reported outcomes. Replication of data in multicenter trials with a large number of patients and long-term follow-up is needed before further conclusions can be drawn.

Traumatic Brain Injury

Neville et al. (2019) investigated the effects of repetitive transcranial magnetic stimulation (rTMS) on cognitive function in patients with traumatic brain injury (TBI). A single-center study was conducted using a randomized, double-blind, placebo-controlled design to investigate rTMS in patients aged 18–60 years with chronic diffuse axonal injury (DAI) lasting more than 12 months post-injury. Participants were randomly assigned in a 1:1 ratio to either a sham group or a real treatment group. The authors note the following results: Thirty patients with chronic DAI met the study criteria. Between-group comparisons of performance on TMT Part B at baseline and after the 10th rTMS session did not differ between groups ($p = 0.680$ and $p = 0.341$, respectively). No significant differences were observed on other neuropsychological tests. No differences in adverse events between treatment groups were observed. Limitations included the following: small sample size, heterogeneity of TBI, short term follow-up, single blind design and limits of the cognitive assessments used. These limitations suggest that while the study provides valuable insights, further research with larger sample sizes, longer follow-up periods, and more advanced methodologies are needed to fully understand the potential of rTMS in treating cognitive deficits in TBI individuals.

Clinical Practice Guidelines

American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)

In a clinical practice guideline for tinnitus, the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) Guideline Development Panel indicated that clinicians should not recommend TMS for the treatment of patients with persistent, bothersome tinnitus (Tunkel et al., 2014).

Other Conditions

Clinical Practice Guidelines

American Academy of Neurology (AAN)

The AAN published an evidence-based practice guideline on the treatment of restless legs syndrome (RLS) in adults (Winkelman et al., 2016, Reaffirmed on October 12, 2019). The guideline states that rTMS is possibly effective in the treatment of primary moderate to severe RLS (level C). This recommendation is based on one Class II study.

In 2019, the AAN published a guideline on the treatment of tics in people with Tourette syndrome and chronic tic disorders (Pringsheim et al., 2019). According to the guideline, there is insufficient evidence to determine whether people with tics receiving the following interventions are more or less likely than those receiving an alternate intervention to have reduced tic severity:

- Continuous theta burst transcranial magnetic stimulation of the supplementary motor area vs sham transcranial magnetic stimulation, 1 Class II study; confidence in evidence downgraded due to imprecision
- rTMS of the supplementary motor area vs sham stimulation, 1 Class II study, confidence in evidence downgraded due to imprecision (adults only)
- rTMS of the left motor or prefrontal cortex vs sham stimulation, 1 Class III study

Navigated Transcranial Magnetic Stimulation (nTMS)

Due to limited studies, small sample sizes, weak study designs and heterogenous study population characteristics, there is insufficient data to conclude that navigated transcranial magnetic stimulation (nTMS) is effective for treatment planning and/or diagnostic evaluation. Larger randomized controlled studies with larger populations are needed to evaluate how this technology can reduce clinical diagnostic uncertainty and/or impact treatment planning.

Schiavao et al. (2022) conducted a systematic review of the literature regarding the use of these techniques to improve the planning and safety of brain tumor surgeries. New techniques that provide functional information regarding the motor cortex include TMS, direct cortical stimulation (DCS), and nTMS. These tools can be used to plan a customized surgical strategy, and the role of motor evoked potentials (MEPs) is well described during intra-operative, using intraoperative neuromonitoring. MEPs can aid in localizing primary motor areas and delineate the cut-off point of resection in real-time, using direct stimulation. In the post-operative, the MEP has increased your function as a predictive marker of permanent or transitory neurological lesion marker. The inclusion criteria included were studies presenting confirmed diagnosis of brain tumor (primary or metastatic), patients > 18 y/o, using TMS, Navigated TMS, and/or Evoked Potentials as tools in preoperative planning or at the intra-operative helping the evaluation of the neurological status of the motor cortex, and articles published in peer-reviewed journals that were written in English or Portuguese. A total of 38 studies were selected for this review, of which 14 investigated the potential of nTMS to predict the occurrence of motor deficits, while 25 of the articles investigated the capabilities of the nTMS technique in performing pre/intraoperative neuro mapping of the motor regions. The use of transcranial navigated techniques to aid surgeons performing brain tumor surgeries has increased in the last decade, with the improvement of both TMS equipment and software/hardware, however, the true impact of the TMS in improving surgical and clinical outcomes continues to be a debate. Raffa et al. 2013 previously cited in this policy, performed a systematic review and meta-analysis where they showed that the use of TMS in brain surgery resulted in an increased odds of obtaining gross total resection (GTR) and a reduced craniotomy extent. In conclusion, TMS is a respected means to enhance the safety and effectiveness of brain tumor resection, by performing a high accurate preoperative mapping of the motor area and its connection with the tumor. Also, intra/ postoperative TMS is a valuable tool to predict the occurrence or duration of motor deficits, helping the surgeon to better align the postoperative recovery expectation for the patient. Further studies and new protocols are needed, as well as standardized protocols for MEP need to be defined.

Jeltema et al. (2020) published a systematic review to provide an overview of the literature on the comparison of nTMS as a mapping tool to the current gold standard, which is (intraoperative) direct cortical stimulation (DCS) mapping. of articles that compared nTMS to intraoperative DCS for mapping of motor or language function. Thirty-five publications were included in the review, describing a total of 552 patients. All studies concerned either mapping of motor or language function. No comparative data for nTMS and DCS for other neurological functions were found. For motor mapping, the distances between the cortical representation of the different muscle groups identified by nTMS and DCS varied between 2- and 16-mm. Regarding mapping of language function, solely an object naming task was performed in the comparative studies on nTMS and DCS. Sensitivity and specificity ranged from 10 to 100% and 13.3-98%, respectively, when nTMS language mapping was compared with DCS mapping. The positive predictive value (PPV) and negative predictive value (NPV) ranged from 17 to 75% and 57-100% respectively. Limitations include, studies are prospective or retrospective, there is only data available for nTMS motor and language mapping compared to DCS. There is no other literature that includes other neurological functions between both techniques. nTMS mapping is a relatively new mapping technique for cortical function localization and can be a helpful and informative preoperative diagnostic tool. Additional more robust studies are needed that should highlight the validation of nTMS mapping for other neurological functions, as well as other language tasks to that compared to the "gold standard" direct cortical stimulation mapping.

Raffa et al. (2019) conducted a systematic review and meta-analysis on studies that analyzed the impact of nTMS-based motor mapping on surgery of patients affected by motor-eloquent intrinsic brain tumors, in comparison with series of patients operated without using nTMS. The impact of nTMS mapping was assessed analyzing the occurrence of postoperative new permanent motor deficits, the gross total resection rate (GTR), the size of craniotomy and the length of surgery. Only eight observational studies were considered eligible and were included in the quantitative review and meta-analysis. The pooled analysis showed that nTMS motor mapping significantly reduced the risk of postoperative new permanent motor deficits (OR = 0.54, p = 0.001, data available from eight studies) and increased the GTR rate (OR = 2.32, p < 0.001, data from seven studies). Moreover, data from four studies documented the craniotomy size was reduced in the nTMS group (-6.24 cm2, p < 0.001), whereas a trend towards a reduction, even if non-significant, was observed for the length of surgery (-10.30 min, p = 0.38) in three studies. Collectively, currently available literature provides data in favor of the use of nTMS motor mapping: its use seems to be associated with a reduced occurrence of postoperative permanent motor deficits, an increased GTR rate, and a tailored surgical approach compared to standard surgery without using preoperative nTMS mapping. The authors indicated that nonetheless, there is a growing need of high-level evidence about the use of nTMS motor mapping in brain tumor surgery. Well-designed randomized controlled studies from multiple Institutions are needed to continue to clarify this emerging topic. (Raffa et al. (2018) and Frey et al. (2014), which were previously cited in this policy, are included in the Raffa et al. (2019) systematic review and meta-analysis).

Sollmann et al. (2018), which was not included in the above systematic review and meta-analysis, evaluated a novel multimodal setup consisting of preoperative navigated nTMS and nTMS-based diffusion tensor imaging fiber tracking (DTI FT) as an adjunct to awake surgery. Sixty consecutive patients suffering from highly language-eloquent left-hemispheric low- or high-grade glioma underwent preoperative nTMS language mapping and nTMS-based DTI FT, followed by awake surgery for tumor resection. Both nTMS language mapping and DTI FT data were available for resection planning and intraoperative guidance. Clinical outcome parameters, including craniotomy size, extent of resection (EOR), language deficits at different time points, Karnofsky Performance Scale (KPS) score, duration of surgery, and inpatient stay, were assessed. According to postoperative evaluation, 28.3% of patients showed tumor residuals, whereas new surgery-related permanent language deficits occurred in 8.3% of patients. KPS scores remained unchanged. According to the authors, this is the first study to present a clinical outcome analysis of this modern approach, which is increasingly applied in neuro-oncological centers worldwide. The authors indicated that although human language function is a highly complex and dynamic cortico-subcortical network, the presented approach offers excellent functional and oncological outcomes in patients undergoing surgery of lesions affecting this network. According to the authors, a limitation of this study is that it analyzed clinical outcome without a control group; thus, follow-up studies that include randomized controlled trials are needed to prove the optimized outcome in comparison to patients who do not undergo such an extensive preoperative workup.

Theta-Burst Stimulation Including Accelerated and/or MRI Guided Protocols

Studies demonstrating the clinical use and safety of accelerated, repetitive, mri-guided theta-burst stimulation are lacking. Therefore, it is not possible to conclude whether accelerated, repetitive, mri-guided theta-burst stimulation has a beneficial effect on health outcomes.

Chen at al. (2022) investigated the used theta burst stimulation (TBS) guided by diffusion MRI-guided theta burst stimulation (TBS) to enhance memory and functional connectivity in individuals with MCI. MCI is often a precursor to Alzheimer's disease, making early intervention crucial. They measured the effects on memory performance and RSFC. The authors found that TBS improved associative memory performance. It also increased RSFC was observed in the hippocampus and other regions, including the occipital fusiform, frontal orbital cortex, putamen, posterior parahippocampal gyrus, and temporal pole. The study emphasized the transmission of TBS effects from the superficial cortex to the hippocampus. Limitations include small sample size, variability in how the participants responded, the non-selective effects of the regions that were affected, the author's note that the results suggest that excitatory iTBS is more effective for memory enhancement compared to inhibitory cTBS and sham TBS. The findings support the potential of TBS as a therapeutic tool for cognitive enhancement in MCI. Further research with larger sample sizes and more controlled conditions are necessary to expand on these preliminary findings.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The FDA has approved a number of devices for use in Transcranial Magnetic Stimulation. Refer to the following websites for more information (use product codes GWF, HAW, IKN, OBP, OCI, and OKP):

- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

(Accessed October 15, 2024)

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