Transcranial Magnetic Stimulation for Treating Physical Health Conditions (for Nebraska Only)

Policy Number: CS124NE.P
Effective Date: March 1, 2026

Instructions for Use

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Related Policies

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- Vagus and External Trigeminal Nerve Stimulation (for Nebraska Only)

Related Optum Guideline

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Application

This Medical Policy only applies to the State of Nebraska.

Coverage Rationale

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- Transcranial magnetic stimulation for treating all medical (i.e., non-behavioral) conditions, including but not limited to:
  - Alzheimer disease
  - Chronic neuropathic pain
  - Dystonia
  - Epilepsy
  - Headaches
  - Parkinson disease
  - Stroke
  - Tinnitus
  - Traumatic brain injury
- Navigated transcranial magnetic stimulation for treatment planning or for diagnosing motor neuron diseases or neurological disorders
- Theta-burst stimulation, including accelerated and/or magnetic resonance imaging-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
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 noninvasive method of delivering electrical stimulation to the brain. In general, single-pulse TMS is used to explore brain functioning, and repetitive transcranial magnetic stimulation (rTMS) is used to induce changes in brain activity that last 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, 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, in which 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 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, bilateral delivery, and deep TMS, in which deeper prefrontal regions are stimulated.

Navigated TMS 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, is a noninvasive form of rTMS, in which short bursts of three to five pulses per second are administered at a higher frequency but with a specific interburst level that generates an overall lower frequency. Accelerated TMS protocols exist 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. Additionally, a new approach is being studied that uses functional magnetic resonance imaging neuronavigated connectivity-guided intermittent theta-burst stimulation to treat treatment-resistant depression (Morriss et al., 2024).

Clinical Evidence

Therapeutic Transcranial Magnetic Stimulation

The current evidence is insufficient to determine the efficacy of transcranial magnetic stimulation (TMS) for treating conditions, such as Alzheimer disease (AD), epilepsy, headaches, pain, Parkinson disease (PD), stroke, and tinnitus. Due

to small sample sizes, short-term follow-ups, and variability in technique and outcome measures, data to conclude that TMS is beneficial for treating these conditions are insufficient.

Alzheimer Disease

Yang et al. (2024) conducted a systematic review and meta-analysis to evaluate the cognitive effects of combining non-invasive brain stimulation (NIBS) with cognitive training (CT) in patients with AD and mild cognitive impairment (MCI). Analyzing 15 randomized controlled trials involving 685 participants, the study found that NIBS combined with CT significantly improved global cognition, particularly in AD patients. Repetitive transcranial magnetic stimulation (rTMS) paired with CT showed the most consistent benefits, including improvements in attention and working memory. Transcranial direct current stimulation (tDCS) combined with CT was notably effective in enhancing language function. Study limitations included the following: the use of varied assessment scales for global and domain-specific cognition introduced considerable heterogeneity across studies. Additionally, the inability to obtain raw data from three potentially eligible studies limited the comprehensiveness of the analysis. Due to insufficient data, the specific cognitive effects of rTMS combined with cognitive training in AD and MCI could not be fully evaluated. Furthermore, subgroup analysis based on treatment parameters and cognitive training characteristics was challenging, contributing to variability in the results. These findings suggest that integrating NIBS with CT offers promising short- and long-term cognitive benefits for individuals with AD and MCI, although further research is needed to explore its effects on other cognitive domains.

Moussavi et al. (2024) conducted a large, multisite, randomized controlled trial (RCT) to evaluate the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in treating AD. This double-blinded, 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 2 months post treatment. However, no significant differences in cognitive outcomes were observed 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.

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. A total of 21 studies were included, and 25 trials were included in this meta-analysis. The findings revealed a significant overall cognition improvement with real stimulation compared with sham stimulation [short-term effects: standardized mean difference (SMD), 0.91; 95% CI, 0.44-1.38; $p < 0.01$; long-lasting effects: SMD, 0.91; 95% CI, 0.27-1.55; $p < 0.01$]. A subgroup analysis demonstrated that stimulation of the left dorsolateral prefrontal cortex (DLPFC) and bilateral cerebellums as well as moderate-frequency stimulation (5 Hz and 10 Hz) in individuals with mild or moderate cognitive impairment, were more effective than other TMS protocols. However, the additional application of cognitive training showed no significant improvement. Study limitations include 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 individuals. Lastly, some findings were from a single study with a small sample size, leaving a need for larger, robust studies. The authors concluded that the effect of improved cognition with TMS was demonstrated in individuals with MCI and AD in both short-term assessment and long-lasting outcomes, and the efficiency of TMS is affected by the stimulation frequency, stimulation site, and patient characteristics. Additional RCTs are needed to support these promising findings.

Yao et al. (2022) conducted an RCT to evaluate rTMS to the cerebellum and how it effects cognitive recovery in participants 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. Overall, 27 participants with AD were included in this randomized, double-blinded, sham-controlled trial and randomly assigned to one of the two groups: rTMS-real or rTMS-sham. They investigated the efficacy of a 4-week treatment of bilateral cerebellum rTMS to promote cognitive recovery and alter specific cerebello-cerebral functional connectivity. Results showed that cerebellum rTMS significantly improved multidomain cognitive functions, which was directly associated with the observed intrinsic functional connectivity between the cerebellum nodes and DLPFC, medial frontal cortex, and 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 noted that while the results are promising, limitations exist, including the approach used to identify the target areas of stimulation. They recognized that the lack of a neuronavigation system interferes with precision therapy from their 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 individuals with AD. 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 focused on the effects of TMS on MCI. MCI has a high risk of progression in individuals with AD. rTMS is a noninvasive brain stimulation (NIBS) technique used to improve cognitive

deficits in individuals with MCI and AD. Although previous meta-analyses included studies in individuals with MCI and AD, few studies have analyzed individuals with MCI independently. This meta-analysis aimed to evaluate the effects on and safety of rTMS in cognition function in individuals with MCI and factors that may influence such effects. Results included a total of 12 studies that involved 329 individuals with MCI, who were included in the present meta-analysis. The analyses results revealed that rTMS improved cognitive function (SMD, 0.83; 95% 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 plus rTMS active group compared with the sham stimulation group. The results showed that (1) cognitive improvement was more pronounced under high-frequency repetitive transcranial magnetic stimulation (HF-rTMS of multiple sites, such as the bilateral DLPFC, and (2) more than 10 rTMS sessions produced higher improvement in cognition function in individuals with MCI. Study limitations include the limited number of studies, small sample size, and heterogeneity with stimulation parameters; additionally, the duration of rTMS was not assessed, and the study only evaluated cognition. The authors noted that rTMS can improve cognitive function in individuals with MCI, especially when applied at high frequency, at multiple sites, 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 treatment on cognitive function in individuals with MCI and early-stage AD. The effectiveness of this therapy is still under deliberation due to the variety of rTMS parameters and individual differences, including the distinctive stages of AD in the previous studies. This meta-analysis aimed to assess the cognitive enhancement with rTMS treatment in individuals with MCI and early AD. Twelve studies with 438 individuals (231 in the rTMS group and 207 in the control group) in 13 randomized, double-blinded, and controlled trials were included. Random-effects analysis revealed that rTMS stimulation significantly introduced cognitive benefits in individuals with 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, and 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 with rTMS could last for 1 month after the end of treatment, and individuals with MCI were likely to benefit more from the rTMS stimulation. This study added important evidence to the cognitive enhancement with rTMS in individuals with MCI and early AD and discussed potential underlying mechanisms of the effect induced by rTMS. The limitations include 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, and stimulation site). Additional RCTs are needed, with larger sample sizes and better design, to identify the optimal parameters of rTMS intervention in the cognition of individuals with AD.

Holczer et al. (2020) conducted a systematic review to examine the presence and extent of methodological issues confounding NIBS studies attempting to alleviate the cognitive symptoms in individuals with dementia**.** However, serious methodological limitations appear to have affected the estimates of their efficacy. The focus was on rTMS or tDCS, i.e., the two most frequent NIBS techniques. Individuals with MCI and AD were included. The study reviewed the stimulation parameters and methods of studies that used TMS or tDCS to alleviate cognitive symptoms in individuals with AD and MCI. The risk of bias was also included in these studies. Overall, 36 studies were identified, of which 23 were RCTs. More than 75% of RCTs 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 individuals with AD or MCI, while they questioned the efficacy of tDCS. This was the first time the presence and extent of methodological issues affecting TMS and tDCS research involving individuals 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 a 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 that delineate a range within TMS parameters seem to be effective but question the efficacy of tDCS. The study also has 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. The authors noted that based on the current literature, it is difficult to conclude on 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 on cognitive function in individuals with AD. A total of 12 studies, with 231 individuals, were included, with eight RCTs and four self-controlled studies. Eleven studies used HF-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 < 0.0001). In subgroup analyses, the effect for stimulation at a single target was 0.13 (95% CI, -0.35 to 0.62) and at multiple targets was 0.86 (95% CI, 0.18-1.54). Treatment for three or fewer sessions produced an effect of 0.29 (95% CI, -1.04 to 1.62), whereas treatment for at least

five 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 individuals 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, the effect of duration was not assessed 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 individuals with AD.

Hayes (2019) published a report on the neuroAD Therapy System for AD. Hayes concluded that there is not enough evidence to draw firm conclusions regarding the efficacy of the neuroAD device in individuals 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 individuals were included in this review. Compared with sham stimulation, HF-rTMS led to a significant improvement in cognition, as measured by the Assessment Scale-Cognitive Subscale, but not on the Mini-Mental State Examination. HF-rTMS also improved the global impression compared with the placebo. No significant difference in mood and functional performance was observed between the HF-rTMS and sham groups. Only one trial that included low-frequency repetitive transcranial magnetic stimulation (LF-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 individuals 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, for the assessment of, management of, and support for people living with dementia and their carers (2018), NIBS (including TMS) should not be offered to treat mild to moderate AD, except as part of an RCT.

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; and reducing epileptiform discharges, antiepileptic medication use, and side effects. Included were RCTs that were double blinded, single blinded, or unblinded and placebo controlled, no treatment, or active controlled and used rTMS without restriction of frequency, coil, duration, or intensity in individuals with drug-resistant epilepsy. The eight included studies (241 individuals) 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 unable to combine the results of the trials in the 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 in 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 individuals had improvement in quality-of-life scores with active treatments compared with the sham treatment, but this only involved seven individuals (very-low-certainty evidence). Four studies evaluated our secondary end point 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. The authors noted that 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 was determined to be low to very low. Some evidence suggested 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 that 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 RCTs that were double blinded, single blinded, or unblinded and placebo, no treatment, or active controlled were included in the analysis. The total number of individuals 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

In a randomized controlled trial, Song et al. (2025) explored the therapeutic potential of high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) targeting the left dorsolateral prefrontal cortex (DLPFC) in individuals with migraine. Using TMS-EEG techniques, they demonstrated that HF-rTMS significantly reduced headache symptoms and enhanced frontal-temporal brain connectivity, suggesting modulation of nociceptive circuits and cortical excitability. These findings support HF-rTMS as a promising non-invasive intervention for migraine management. Future research should aim to strengthen these results by incorporating larger sample sizes, refined assessment tools, and more advanced stimulation protocols.

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 that showed an effect size of -1.13 (95% CI, -1.69 to -0.58) on the frequency of migraine attacks, indicating that rTMS was more effective in decreasing migraine attacks than the sham rTMS. The authors indicated that the results provide some direction for further research, and they believe that rTMS can aid in the prevention of migraines. However, this study does have limitations, including that (1) the efficacy of rTMS in treating chronic migraine was preliminary and inconclusive because of the heterogeneity in the study designs of rTMS stimulation (including the frequency of stimulation, number of pulses, pulse intensity, and number of sessions); (2) outcomes homogeneity and long-term real-world efficacy data were lacking; (3) the sample size was small because the nonrandomized, sham-controlled designs and case reports, which had incomplete outcomes and a small sample size ($n < 4$), were excluded, resulting in only eight studies being eligible; (4) the diagnosis criteria used in some studies varied; and (5) no multicenter trials were included, and the overall focus was therefore limited. Consequently, further robust, multicenter trials are necessary to confirm these results.

Cheng et al. (2022), in a network meta-analysis of RCTs, aimed to compare treatment approaches with respect to their effectiveness (with specific respect to migraine prophylaxis) and their acceptability in individuals with migraine. Nineteen RCTs were included (n = 1,493; mean age, 38.2 years; 82.0% women). It was determined that the HF-rTMS over C3 yielded the most decreased monthly migraine days among all the interventions [mean difference (MD), -8.70 days; 95% CI, -14.45 to -2.95, compared with sham/control groups]. Only alternating frequency (2/100 Hz) transcutaneous occipital nerve stimulation (tONS) over the Oz (relative risk, 0.36; 95% CI, 0.16-0.82) yielded a significantly lower dropout 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 and 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, 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 individuals with migraine.

Moisset et al. (2020) conducted a systematic review with meta-analysis of RCTs focusing on neurostimulation techniques for migraine treatment. Several noninvasive and even invasive neurostimulation methods have been proposed for acute or preventive migraine treatment. The target population was individuals of any age, including children, who had migraine according to the International Classification of Headache Disorders 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 of the quantitative synthesis were 2 hours pain free for acute treatment and headache days per month for preventive treatment. Subgroup analyses were done by treatment (stimulation method and site of application). Estimates were pooled using random-effects meta-analysis. Overall, 38 articles were included in the qualitative analysis (seven acute, 31 preventive) and 34 in the quantitative evaluation (six acute, 28 preventive). Remote electrical neuromodulation was effective for acute treatment. Data were insufficient to draw conclusions for any other techniques (single studies). Invasive occipital nerve stimulation was effective for migraine prevention, with a large effect size but considerable heterogeneity, whereas supraorbital transcutaneous electrical nerve stimulation, percutaneous electrical nerve stimulation, and HF-rTMS over the primary motor cortex (M1) were effective, with vagus nerve stimulation, left prefrontal cortex rTMS, and cathodal tDCS over the M1 having no significant effect; additionally, heterogeneity was high. Six studies tested rTMS. Several neuromodulation methods are of potential interest for migraine management, but the quality of the evidence is very poor. This review has several limitations. The meta-analysis was based on a very limited number of articles for each study subgroup, and the estimation of effect size may not be accurately driven. The methodological quality of the studies was heterogeneous. The follow-up period was very short, and the 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 (in addition to tDCS for the treatment of specific headache disorders, including migraine, tension, cluster, and posttraumatic). Studies were selected by inclusion criteria for individuals (adults aged 18-65 years 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, or RCT). Overall, 34 studies were included: 16 rTMS, six TMS (excluding rTMS), and 12 tDCS. The majority investigated treatment for migraine (19 of 22 TMS; eight of 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 those with 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 noninvasive neuromodulation for migraine and cluster headaches. Noninvasive vagus nerve stimulation, single-transcranial magnetic stimulation, 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. Single-transcranial magnetic stimulation, which includes the Cerena Transcranial Magnetic Stimulator (eNeura Therapeutics) and SpringTMS device (eNeura Therapeutics), was evaluated in three published studies for the acute and preventive treatment of migraine. According to the authors, noninvasive vagus nerve stimulation 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 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 NIBS on pain control in individuals with migraine. Eight studies were included in the quantitative analysis, with 153 individuals with migraine receiving NIBS and 143 individuals receiving sham NIBS. In the overall meta-analysis, the authors did not find significant results for pain intensity, migraine attacks, and painkiller intake. However, a subgroup analysis considering only tDCS effects demonstrated a decrease in pain intensity, migraine attacks, and painkiller intake. A 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, larger, controlled trials with methodological rigor, which could increase the power of result inference, are needed.

According to the NICE guideline for TMS for treating and preventing migraine (2014), evidence of the efficacy of TMS for the treatment of migraine is limited in quantity, and evidence of the prevention of migraine is limited in both quality and quantity. Evidence on its safety in the short and medium terms is adequate, but the safety of long-term or frequent use of TMS is uncertain. Therefore, according to the 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 Disease

Romero et al. (2024) conducted a randomized, four-arm, controlled trial to investigate the effects of bilateral rTMS and electroencephalogram-guided neurofeedback (NFB) on motor and nonmotor symptoms in 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 male participants; average age, 63 ±8.26 years; baseline Unified Parkinson Disease Rating Scale-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) had 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). Negligible differences were observed between groups A to C and group D (control) in terms of functional mobility and limits of stability. The combination group had 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 include 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, multicenter trials and longer follow-up to better understand the efficacy and safety of combining rTMS and NFB for treating PD.

Deng et al. (2022) conducted a systematic review with meta-analysis to assess the therapeutic effects of rTMS on freezing of gait and cognition in individuals with PD and provide updated evidence on the role of rTMS therapy in individuals with PD. Overall, 16 RCTs, with a total of 419 individuals, were included. Fixed-effects analysis revealed that rTMS was effective in improving Freezing of Gait Questionnaire scores [short-term effect: weighted mean difference (WMD), -0.925; 95% CI, -1.642 to -0.209; p = 0.011; long-term effect: WMD, -2.120; 95% CI, -2.751 to -1.489; p = 0.000], 10-m walking time (short-term effect: WMD, -0.456; 95% CI, -0.793 to -0.119; p = 0.008; long-term effect: WMD, -0.526; 95% CI, -0.885 to -0.167; p = 0.004), Timed Up and Go scores (short-term effect: WMD, -1.064; 95% CI, -1.555 to -0.572; p = 0.000; long-term effect: WMD, -1.097; 95% CI, -1.422 to -0.772; p = 0.000), Montreal Cognitive Assessment (WMD, 3.714; 95% CI, 2.567-4.861; p = 0.000), and Frontal Assessment Battery (WMD, -0.584; 95% CI, -0.934 to -0.234; p = 0.001). In conclusion, rTMS showed a positive effect on freezing of gait and cognitive dysfunction in PD. 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 individuals with PD. Additional high-quality studies are needed to determine the optimal 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 individuals diagnosed with idiopathic PD. Among 14 eligible studies, 298 individuals were analyzed in this meta-analysis. Walking time was improved with rTMS compared with sham rTMS (SMD, -0.30; 95% CI, -0.57 to -0.03; p = 0.03). The score for the Freezing of Gait Questionnaire did not differ significantly between rTMS and no intervention. Four studies compared the Timed Up and Go test between the two treatment groups, and no significant differences were found between the rTMS and control groups (SMD, -0.45; 95% CI, -1.32 to 0.41; p = 0.30). During the off state, no significant differences in estimated effect sizes (SMD, -0.29; 95% CI, -0.79 to 0.21; p = 0.25) were observed, which is significantly different in on-state (SMD, -0.98; 95% CI, -1.78 to -0.18; p = 0.02) 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 in 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 in individuals with PD.

Yang et al. (2018) performed a meta-analysis to evaluate the optimal rTMS parameters for motor recovery in PD. Electronic databases were searched for studies investigating the therapeutic effects of rTMS on motor function in individuals with PD. Overall, 23 studies, with a total of 646 individuals, were included. The pooled estimates of rTMS revealed significant short-term and long-term effects on motor function improvement in PD. A subgroup analysis observed that HF-rTMS was significant in improving motor function, but LF-rTMS was not. When HF-rTMS targeted over the M1, the bilateral M1 revealed a larger effect size than unilateral M1. Compared with single-session, multisession HF-rTMS over the M1, this showed a significant effect size. In addition, HF-rTMS over the M1, with a total of 18,000 to 20,000 stimulation pulses, yielded more significant effects than other doses. According to the authors, these results suggest that rTMS might be helpful in improving the motor deficits in individuals with PD. The authors stated that there are limitations of this meta-analysis. First, the experimental designs of the included studies were not homogenous (e.g., RCTs vs, crossover design). Second, the selected individuals 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 of 24 rTMS studies 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 existed. 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 NIBS.

In a systematic review and meta-analysis, Wagle Shukla et al. (2016) reviewed the literature on clinical rTMS trials in PD to quantify the overall efficacy of this treatment. Prospective clinical trials were included that had an active arm and control arm, and change in motor scores on the Unified Parkinson Disease Rating Scale was the primary outcome. The authors pooled data from 21 studies that met these criteria and analyzed separately the effects of LF- and HF-rTMS on clinical motor improvements. rTMS therapy demonstrated benefits at the short-term follow-up (immediately after a treatment protocol), with a pooled MD of 3.4 points, as well as at the long-term follow-up (average follow-up, 6 weeks), with an MD 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 PD. According to the authors, future large sample studies

should be designed to isolate the specific clinical features of PD 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 based on 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 M1 in participants 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 numeric rating scale (NRS). Although the active rTMS group experienced a greater reduction in pain intensity than the sham group, the difference was not statistically significant. However, the active rTMS group did have 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 include a small sample size, a short follow-up period, a 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.

In a systematic review, Saleh et al. (2022) 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, eight RCTs met the eligibility criteria for qualitative synthesis, providing the total data from 141 individuals. All studies used HF-rTMS. In seven studies, rTMS was applied over the motor cortex, and in one study, it was applied over the left DLPFC. Five studies reported a significant improvement in baseline pain scores after treatment, and three studies found a significant difference between sham vs non-sham stimulation at any time. Six RCTs were included in the quantitative synthesis and showed a significant overall reduction in 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 indicate that HF-rTMS of the M1 and left DLPFC might be promising stimulation targets for neuropathic pain in SCI.

In an RCT, Yang et al. (2022) evaluated the effect of HF-rTMS (10 Hz) on the left M1 for neuropathic pain in the lower extremities due to diabetic peripheral neuropathy (DPN). In this randomized trial, 22 participants with DPN in an outpatient clinic of a single academic medical center were randomly assigned to either the rTMS group (10-Hz stimulation, five sessions) or the sham group. An NRS was used to measure pain intensity before treatment and after 1 day and 1 week of the treatment. Physical and mental health statuses were evaluated with the 36-Item Short Form Survey (SF-36), comprising two subscales [physical and mental component scores (PCSs and MCSs)], at 1 week post-treatment. Of the 22 included participants, 20 (10 participants in each group) completed the study. In the rTMS group, the NRS score at 1 day and 1 week post treatment was significantly lower than that prior to treatment. The SF-36 PCS and SF-36 MCS were significantly increased 1 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 include a small number of included participants and no long-term follow-up. In conclusion, HF-rTMS on the left M1 may be useful for managing pain in the lower extremities due to DPN and may improve an individual's quality of life. Larger studies, with long-term follow up, are 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 DLPFC in chronic and provoked pain. A total of 626 studies were identified in a systematic search. In total, 26 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 DLPFC was uniformly targeted in the chronic pain studies. While data identified no overall effect of TMS across chronic pain conditions, significant short-term analgesia was observed in neuropathic pain conditions only (SMD, -0.87). In terms of long-lasting analgesia, an overall pain reduction was observed 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 in 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 of chronic pain conditions. Other limitations included a small study size in each category and 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 NIBS on post-SCI neuropathic pain. A meta-analysis on pain intensity, depression, and anxiety levels was conducted to evaluate the effect of NIBS on neuropathic pain in individuals with SCI. Eleven studies were selected, including eight RCTs and three crossover RCTs. All studies compared an active NIBS group with a sham group. The interventions in these studies

included rTMS (four trials), tDCS (six trials), and cranial electrotherapy stimulation (CES; one trial). The pooled analysis demonstrated no significant effect of rTMS, tDCS, or CES on neuropathic pain reduction after SCI. In addition, NIBS showed no beneficial effect over sham stimulation in the improvement of depression, while it yielded a significant reduction in anxiety levels immediately after treatment. A subgroup analysis showed that only CES had a significant effect on the reduction of anxiety levels among the three types of NIBS. There are limitations of the study, including the small number evaluated for each type of stimulation; additionally, most individuals were male, and only studies that contained pain were included, whereas those that only examined anxiety and depression may have been missed. The overall findings indicate that NIBS had no significant effect on pain reduction in individuals with post-SCI neuropathic pain, but CES might be useful in the management of anxiety in these individuals. These findings do not support the routine use of NIBS for neuropathic pain in individuals with SCI. Further studies are needed, with larger sample sizes, to support this technology.

Gatzinsky et al. (2020) conducted a systematic review to evaluate the effects of high-frequency TMS of the M1 in the treatment of chronic neuropathic pain based on the magnitude of relative pain reduction (active vs. sham stimulation) and to investigate the accuracy to predict a positive response to epidural motor cortex stimulation, which is supposed to give more long-standing pain relief. Overall, 32 articles were included: 24 RCTs and eight case series. Data on 5 to 20 Hz (high frequency) rTMS vs. a sham were extracted from 24 blinded RCTs, 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 nine of 11 studies using single-session rTMS and in nine of 13 studies using multiple sessions. Baseline data could be pulled out from six single- and 12 multiple-session trials, with a weighted mean pain reduction induced by active rTMS compared with baseline of -19% for single sessions; -32% for multiple sessions, with a follow-up of < 30 days; and -24% for multiple sessions, with a follow-up of ≥ 30 days after the last stimulation session. For single sessions, the WMD in pain reduction between active rTMS and the sham was 15 percentage points; for multiple sessions, the difference was 22 percentage points for follow-ups of < 30 days and 15 percentage points for follow-ups of ≥ 30 days. Four studies reported data that could be used to evaluate the precision of rTMS to predict response to motor cortex stimulation, showing a specificity of 60% to 100% and a positive predictive value of 75% to 100%. No serious adverse events were reported. rTMS targeting the M1 can result in significant reduction of chronic neuropathic pain, which, however, is transient; shows great heterogeneity between studies; and has very-low certainty of evidence for single sessions and low certainty of evidence 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 motor cortex stimulation and may be used to select individuals for implantation of permanent epidural electrodes. Additional studies on the efficacy of rTMS for different types of neuropathic pain are needed. Major knowledge gaps remain in relation to the long-term effects of rTMS on health-related quality of life and 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 individuals with chronic pain, assessed the efficacy of TMS, and estimated the best stimulation protocol. Twelve RCTs were included, which involved 350 individuals with focal and generalized chronic pain. An existing proof showed a null response with LF-rTMS stimulation, rTMS delivered to the DLPFC in individuals with chronic pain. However, a witnessed pain-killing response was documented when applying active high-frequency TMS on the motor cortex M1 area compared with the 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 ACC or the posterior superior insula (PSI) against sham deep (d) rTMS in participants with central neuropathic pain after stroke or SCI in a randomized, double-blinded, sham-controlled, three-arm, parallel study. Participants were randomly allocated into the active PSI-rTMS, ACC-rTMS, sham-PSI-rTMS, or sham-ACC-rTMS arm. 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 (NRS) after the last stimulation session. Overall, 98 participants (aged 55.02 ±12.13 years) completed the study. The 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. The heat pain threshold was significantly increased after treatment in the PSI-dTMS group from baseline (1.58; 95% CI, 0.09-3.06) compared with that with 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 with 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 central neuropathic pain, despite a significant antinociceptive effect after insular stimulation and the anxiolytic effects of ACC-dTMS.

In an updated version of the Cochrane review published in 2014, O'Connell et al. (2018) evaluated the efficacy of NIBS techniques in chronic pain. The update included a total of 42 rTMS studies. The meta-analysis of rTMS studies vs. a sham for pain intensity at the short-term follow-up (0 to < 1 week post intervention; 27 studies involving 655 individuals) 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 minimal clinically important difference threshold of 15% or greater. The authors concluded that there is very low-quality evidence that single doses of HF-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 LF-rTMS or rTMS applied to the DLPFC is effective for reducing pain intensity in chronic pain. According to the authors, substantially larger, rigorously designed studies are needed, particularly with longer courses of stimulation.

Saltychev and Laimi (2017) investigated whether there is evidence of rTMS being effective in decreasing the severity of pain in individuals 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 a 0 to 10 NRS. 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 to 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 individuals in each of the groups were included in the analysis. The decrease in pain scores with rTMS was 1.12 and with 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 individuals with chronic pain. This treatment is not associated with any direct adverse effects. However, according to the authors, the duration and frequency of rTMS therapy are presently highly variable and need 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 the previous European Federation of Neurological Societies guidelines on neurostimulation for neuropathic pain. The GRADE system was used to assess the quality of evidence and propose recommendations. Weak recommendations were given for the use of M1 rTMS in neuropathic pain and fibromyalgia, and inconclusive recommendations were given regarding complex regional pain syndrome. Recommendations regarding rTMS of the DLPFC in fibromyalgia and neuropathic pain were inconclusive.

Stroke

Chen at al. (2024) conducted an RCT to evaluate the effectiveness of LF-rTMS in treating poststroke neurogenic bladder. A total of 100 participants were divided into two groups: one received active rTMS, and the other received sham stimulation. The active rTMS group had significant improvements in bladder function compared with the sham group, as measured by urodynamic studies and patient- reported outcomes. Participants 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 include a single-center study and small sample size due to the COVID-19 pandemic; additionally, rTMS was used as a single treatment, and 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 noted that the study suggests that LF-rTMS may be a promising noninvasive treatment for improving bladder function and quality of life in individuals 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 HF-rTMS on upper extremity motor function recovery after a first-time ischemic stroke. A total of 6,440 studies were found in the databases, and four trials were included in the review. Three of the studies were RCTs, and one was a pseudo-RCT. Three of the studies showed good

methodological quality, and one was rated as excellent. The Fugl-Meyer Assessment was performed in three of four studies, and the score significantly increased in the HF-rTMS treatment group compared with the sham stimulation group in all trials. Other measures used in the studies were handgrip strength, shoulder abduction, Motricity Index, Wolf Motor Function Test, 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 the sham stimulation groups. Two studies reported headache as an adverse event (six individuals in total). Limitations of the study include differences in design due to poorly defined rTMS protocols and a 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 individuals with stroke. 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 individuals with stroke. (Dionisio et al., 2017, is included in this study.)

Xie et al. (2021) conducted a systematic review and network meta-analysis to observe the different modalities of TMS on lower extremity motor function and corticospinal excitability in individuals with stroke. This systematic review and network meta-analysis of TMS for individuals with stroke included data from 26 RCTs, which included 943 individuals who were randomized to one of four rTMS interventions (d-, HF-, LF-, or intermittent theta-burst rTMS or sham stimulation). Only LF-rTMS was superior to sham stimulation for motor function improvement, as measured by the Fugl-Meyer Assessment. Although direct evidence suggested that HF-rTMS was more effective than sham stimulation for speed, this result was not replicated in the network meta-analysis. In addition, HF-rTMS appeared to be more effective than LF-rTMS for motor-evoked potential (MEP) amplitudes. Network meta-analysis results for 18 RCTs regarding lower extremity motor function recovery revealed that LF-rTMS had better efficacy in promoting lower extremity motor function recovery than sham stimulation. Network meta-analysis results for five RCTs demonstrated that HF-rTMS led to higher amplitudes of MEPs than LF-rTMS or sham stimulation. These findings suggest that rTMS can improve motor function in individuals with stroke and that LF-rTMS mainly affects motor function, whereas HF-rTMS increases the amplitudes of MEPs. This study has 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 RCTs are needed to confirm this conclusion and support the effects of rTMS in individuals with stroke. 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 the recovery of lower limb dysfunction in individuals post stroke. Fifteen trials with 385 individuals were included. Results showed that rTMS had a significant effect on balance (SMD, .38; 95% CI, .07-.69; I^2, 51%) and mobility (SMD, -.67; 95% CI, -1.08 to -.26; I^2, 72%). However, rTMS had no significant immediate effects on the lower limb subscale of the Fugl-Meyer Assessment (SMD, .01; 95% CI, -.29 to .31; I^2, 0%). The continued effects of rTMS were also found to be significant during the follow-up period (SMD, .46; 95% CI, .09-.84; I^2, 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 posttherapy to 30-day follow-up period. Although large effect sizes that support a recommendation for rTMS intervention exist, 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 and included a total of 148 individuals. Eight studies evaluated a continuous stimulation protocol, and one study investigated an intermittent stimulation protocol. Overall, both protocols significantly improved neglect severity when compared with placebo or active controls ($p < 0.05$). This systematic review found that theta-burst stimulation seems to improve poststroke 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 LF-rTMS in promoting functional recovery after stroke. Overall, 67 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 populations of individuals, regardless of lesion site and stroke etiology, and different stimulation parameters and outcome measures means that the studies were not readily comparable, and estimating the real effectiveness or reproducibility was very difficult. The authors concluded that LF-rTMS over the unaffected hemisphere may have therapeutic utility, but the evidence is still preliminary, and the findings need to be confirmed in further RCTs.

Dionísio et al. (2017) conducted a systematic review to provide information regarding the application of rTMS in individuals with stroke and to assess its effectiveness in clinical rehabilitation of motor function. Overall, 70 trials were included in the review. The majority of the articles reported that rTMS showed potential in improving motor function, although some negative reports, all from RCTs, contradicted this claim. According to the authors, future studies are needed because a bias for nonpublication 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 that was included had > 50% individuals with stroke; (2) the sample size included ≥ 4 individuals; (3) the intervention applied was rTMS; and (4) upper extremity spasticity was assessed prior to and post intervention. RCTs were assessed for methodological quality using the Physiotherapy Evidence Database tool. The main outcome measurement was the Modified Ashworth Scale (MAS). Ten studies met the inclusion criteria: two RCTs (Physiotherapy Evidence Database scores of 8-9) and eight pre-post-studies. Meta-analyses of primarily uncontrolled pre-post studies found significant improvements in MAS for the 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 evidence to support the use of rTMS in improving spasticity post stroke is limited. 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 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 individuals. Active rTMS was superior to sham rTMS in terms of the short-term and long-term effects (6 months) on Tinnitus Handicap Inventory (THI) scores, but an immediate effect was not significant. No significant immediate effect on the tinnitus questionnaire (TQ) and Beck Depression Inventory scores was observed. 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 TQ and Beck Depression Inventory scores demonstrated a minimal initial benefit. Additional studies, with larger sample sizes, in multicenter settings are needed and should observe long-term outcomes.

Liang et al. (2020) conducted a systematic review and meta-analysis to examine the effects of rTMS to evaluate its clinical efficacy and safety. After database selection, 29 randomized studies involving 1,228 individuals with chronic tinnitus were included. Compared with sham-rTMS, rTMS exhibited significant improvements in THI scores at 1 week (MD, −7.92), 1 month (MD, -8.52,), and 6 months (MD, -6.53) post intervention; significant mean changes in THI scores were observed at 1 month (MD, -14.86) and 6 months (MD, -16.37) post intervention and in TQ scores 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); 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 ratio, 1.12). Egger and Begg tests indicated no publication bias. Several study limitations exist: (1) a limited number of individuals were included, which limits a more accurate analysis, and some results were nonsignificant; (2) the studies only analyzed the English language and could have lost data from other languages; and (3) 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 a large sample size, and multicenter studies are needed for validation.

Soleimani et al. (2016) conducted a systematic literature review and meta-analysis on the effect of rTMS compared with that of sham in individuals with chronic tinnitus. For the meta-analysis, WMDs (and SDs) of TQ and THI scores were determined. Therapeutic success was defined as a 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 MD score in two groups, 1 and 6 months after intervention, were 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 in study designs and reported outcomes. Replication of data in multicenter trials, with a large number of participants and long-term follow-up, is needed before further conclusions can be drawn.

Traumatic Brain Injury

Neville et al. (2019) investigated the effects of rTMS on cognitive function in participants with traumatic brain injury (TBI). A single-center study was conducted using a randomized, double-blinded, placebo-controlled design to investigate rTMS in participants aged 18 to 60 years with chronic diffuse axonal injury that has lasted 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 noted that 30 participants with chronic diffuse axonal injury met the study criteria; between-group comparisons of performance on the Trail Making Test Part B at baseline and after the tenth 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 include a small sample size, heterogeneity of TBI, a short-term follow-up, a 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, is needed to fully understand the potential of rTMS in treating cognitive deficits in individuals with TBI.

Other Conditions

Clinical Practice Guidelines

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

In a clinical practice guideline for tinnitus, the AAO-HNS Foundation Guideline Development Panel indicated that clinicians should not recommend TMS for the treatment of patients with persistent, bothersome tinnitus (Tunkel et al., 2014).

Clinical Practice Guidelines

American Academy of Neurology (AAN)

The AAN published an evidence-based practice guideline on the treatment of restless legs syndrome 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 restless legs syndrome (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 TMS of the supplementary motor area vs. sham TMS, one class II study; confidence in evidence downgraded due to imprecision
- rTMS of the supplementary motor area vs. sham stimulation, one class II study; confidence in evidence downgraded due to imprecision (adults only)
- rTMS of the left motor or prefrontal cortex vs. sham stimulation, one class III study

Navigated Transcranial Magnetic Stimulation

Due to limited studies, small sample sizes, weak study designs, and heterogeneous study population characteristics, data to conclude that navigated transcranial magnetic stimulation (nTMS) is effective for treatment planning and/or diagnostic evaluation are insufficient. Larger RCTs, 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 MEPs is well described in the intraoperative period using intraoperative neuromonitoring. MEPs can aid in localizing primary motor areas and delineate the cutoff point of resection in real time using direct stimulation. In the postoperative period, the MEP has increased the individual's function as a predictive marker of a permanent or transitory neurological lesion marker. The inclusion criteria were (1) studies presenting a confirmed diagnosis of a brain tumor (primary or metastatic); (2) age > 18 years; (3) use of TMS, nTMS, and/or evoked potentials as tools in preoperative planning or at the intraoperative period, helping the evaluation of the neurological status of the motor cortex; and (4) 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 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, in which they showed that the use of TMS in brain surgery resulted in 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 highly 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 individual. Further studies and new protocols are needed, and 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) DCS mapping. Of articles that compared nTMS with

intraoperative DCS for mapping of motor or language function. 35 publications were included in the review, describing a total of 552 individuals. 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% to 98%, respectively, when nTMS language mapping was compared with DCS mapping. The positive predictive value and negative predictive value ranged from 17% to 75% and 57% to 100%, respectively. Limitations include that the studies are prospective or retrospective, and data are only available for nTMS motor and language mapping compared with 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 those compared with the gold-standard DCS 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 in individuals affected by motor-eloquent intrinsic brain tumors compared with a series of individuals who underwent operation without using nTMS. The impact of nTMS mapping was assessed by analyzing the occurrence of postoperative, new, permanent motor deficits; GTR rate; size of craniotomy; and length of surgery. Only eight observational studies were considered eligible and 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 (odds ratio, 0.54; $p = 0.001$; data available from eight studies) and increased the GTR rate (odds ratio, 2.32; $p < 0.001$; data from seven studies). Moreover, data from four studies showed that the craniotomy size was reduced in the nTMS group (-6.24 $cm^{2;}$; $p < 0.001$), whereas a trend toward a reduction, even if nonsignificant, 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, increased GTR rate, and tailored surgical approach compared with standard surgery without using preoperative nTMS mapping. The authors indicated that nonetheless, the need for high-level evidence about the use of nTMS motor mapping in brain tumor surgery is growing. Well-designed RCTs from multiple institutions are needed to continue to clarify this emerging topic. [Raffa et al. (2018) and Frey et al. (2014), previously cited in this policy, are included in the Raffa et al. (2019) systematic review and meta-analysis.]

Sollmann et al. (2018), who were not included in the above systematic review and meta-analysis, evaluated a novel, multimodal setup consisting of preoperative nTMS and nTMS-based diffusion tensor imaging fiber tracking (DTI FT) as an adjunct to awake surgery. Overall, 60 consecutive participants with 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, language deficits at different time points, Karnofsky Performance Scale score, duration of surgery, and inpatient stay, were assessed. According to a postoperative evaluation, 28.3% of participants had tumor residuals, whereas new surgery-related, permanent language deficits occurred in 8.3% of participants. Karnofsky Performance Scale 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 corticosubcortical network, the presented approach offers excellent functional and oncological outcomes in participants undergoing surgery of lesions affecting this network. According to the authors, a limitation of this study is that it analyzed the clinical outcome without a control group; thus, follow-up studies that include RCTs are needed to prove the optimized outcome in comparison with that in participants 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, magnetic resonance imaging (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.

Rymaszewska et al. (2025) in an RCT, investigated the efficacy of theta burst stimulation (TBS) as an add-on therapy for individuals with treatment-resistant OCD. Of 87 individuals screened, 32 met eligibility criteria, and 27 completed the initial treatment phase. Participants (59.3% male, mean age 35.1) were randomized to either sham stimulation (n = 13) or active TBS (n = 14), which included continuous (cTBS, n = 7) and intermittent (iTBS, n = 7) protocols. By the 3-month follow-up, 20 participants remained. All continued stable pharmacological treatment throughout the study, with no changes in medication or psychotherapy, ensuring consistent conditions across groups. While improvements in OCD symptom severity were observed in the active group, results were inconclusive due to small sample size, high dropout rates, and

symptom heterogeneity. The therapeutic setting may have also influenced outcomes. The authors emphasized the need for further research to validate these findings, refine stimulation protocols, and assess long-term effects.

Chen at al. (2022) investigated the use of TBS guided by diffusion MRI-guided theta-burst stimulation to enhance memory and functional connectivity in participants with MCI. MCI is often a precursor to AD, making early intervention crucial. They measured the effects on memory performance and resting-state functional connectivity. The authors found that theta-burst stimulation improved associative memory performance. An increase in resting-state functional connectivity was also 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 theta-burst stimulation's effects from the superficial cortex to the hippocampus. Limitations include a small sample size, variability in how the participants responded, and the nonselective effects of the regions that were affected; the authors also noted that the results suggest that excitatory intermittent theta-burst stimulation is more effective for memory enhancement than inhibitory continuous theta-burst stimulation and sham theta-burst stimulation. The findings support the potential of theta-burst stimulation as a therapeutic tool for cognitive enhancement in MCI. Further research, with larger sample sizes and more controlled conditions, is 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 14, 2025)

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Policy History/Revision Information

Date	Summary of Changes
03/01/2026	**Title Change** • Previously titled *Transcranial Magnetic Stimulation (for Nebraska Only)* **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version CS124NE.O

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.