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Transcranial Magnetic Stimulation for Pain, Headache, and Comorbid Depression: INS-NANS Expert Consensus Panel Review and Recommendation

Albert Leung, MD*[†]; Prasad Shirvalkar, MD, PhD[‡]; Robert Chen, MA, MBBChir, MSc, FRCPC[§]; Joshua Kuluva, MD[¶]; Michael Vaninetti, MD; Richard Bermudes, MD[††]; Lawrence Poree, MD, PhD[‡‡]; Eric Wassermann, MD[§§]; Brian Kopell, MD[¶¶]; Robert Levy, MD, PhD[***]; and the Expert Consensus Panel[†††]**

Background: While transcranial magnetic stimulation (TMS) has been studied for the treatment of psychiatric disorders, emerging evidence supports its use for pain and headache by stimulating either motor cortex (M1) or dorsolateral prefrontal cortex (DLPFC). However, its clinical implementation is hindered due to a lack of consensus in the quality of clinical evidence and treatment recommendation/guideline(s). Thus, working collaboratively, this multinational multidisciplinary expert panel aims to: 1) assess and rate the existing outcome evidence of TMS in various pain/headache conditions; 2) provide TMS treatment recommendation/guidelines for the evaluated conditions and comorbid depression; and 3) assess the cost-effectiveness and technical issues relevant to the long-term clinical implementation of TMS for pain and headache.

Methods: Seven task groups were formed under the guidance of a 5-member steering committee with four task groups assessing the utilization of TMS in the treatment of Neuropathic Pain (NP), Acute Pain, Primary Headache Disorders, and Posttraumatic Brain Injury related Headaches (PTBI-HA), and remaining three assessing the treatment for both pain and comorbid depression, and the cost-effectiveness and technological issues relevant to the treatment.

Results: The panel rated the overall level of evidence and recommendability for clinical implementation of TMS as: 1) high and extremely/strongly for both NP and PTBI-HA respectively; 2) moderate for postoperative pain and migraine prevention, and recommendable for migraine prevention. While the use of TMS for treating both pain and depression in one setting is clinically and financially sound, more studies are required to fully assess the long-term benefit of the treatment for the two highly comorbid conditions, especially with neuronavigation.

Conclusions: After extensive literature review, the panel provided recommendations and treatment guidelines for TMS in managing neuropathic pain and headaches. In addition, the panel also recommended more outcome and cost-effectiveness studies to assess the feasibility of the long-term clinical implementation of the treatment.

Keywords: acute pain, headache, neuropathic pain, pain, persistent headache, post-traumatic brain injury related headache, primary headaches, review, rTMS, TMS, transcranial magnetic stimulation, treatment recommendation

Address correspondence to: Albert Leung, MD, Department of Anesthesiology, Center for Pain Medicine, UCSD School of Medicine, Center for Pain and Headache Research, VASDHS, 9300 Campus Point Drive, #7651, La Jolla, CA 92093, USA. Email: ayleung@ucsd.edu

* Professor of Anesthesiology and Pain Medicine, Department of Anesthesiology, Center for Pain Medicine, University of California, San Diego, School of Medicine, La Jolla, CA, USA;
[†] Director, Center for Pain and Headache Research, VA San Diego Healthcare System, La Jolla, CA, USA;
[‡] Assistant Professor, Departments of Anesthesiology (Pain Management), Neurology, and Neurosurgery, UCSF School of Medicine, USA;
[§] Catherine Manson Chair in Movement Disorders, Professor of Medicine (Neurology), University of Toronto, Toronto, Ontario, Canada;
[¶] Neurologist and Psychiatrist, TMS Health Solution, San Francisco, CA, USA;
** Assistant Clinical Professor, Anesthesiology and Pain Medicine, UCSD School of Medicine, La Jolla, CA, USA;
[††] Chief Medical Officer, TMS Health Solutions, Assistant Clinical Professor- Volunteer, Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA;
[‡‡] Professor of Anesthesiology, Director, Neuromodulation Service, Division of Pain Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA, USA;
[§§] Director, Behavioral Neurology Unit, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA;
[¶¶] Professor of Neurosurgery, Mount Sinai Center for Neuromodulation, New York, NY, USA;
*** President of International Neuromodulation Society, Editor-in-Chief, Neuromodulation, Boca Raton, FL, USA; and
[†††] See Appendix for Complete List of Task Group Members

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INTRODUCTION

Transcranial magnetic stimulation (TMS) noninvasively stimulates the brain by utilizing electromagnetic coils to produce small focal electrical currents in the cortex(1,2). Repetitive TMS (rTMS) in which repeated trains of TMS are applied is currently approved by the United States Food and Drug Administration (FDA) for treating major depression and obsessive–compulsive disorder, and single pulse TMS is approved for treating migraine headaches. While more people are familiar with its use in psychiatric disorders than in pain disorders, a similar degree of effort has been applied to assess its effect in both conditions. TMS devices usually consist of an insulated electric coil that generates a dynamic magnetic field. This magnetic field can then induce an electric field through the scalp and skull to reach the first few centimeters of the brain without significant attenuation. A figure-of-eight coil is commonly used for its ability to direct stimulation with precision. Depolarization of corticospinal tracts with TMS delivered to the motor cortex occurs at about the junction of the

Table 1. Hierarchy of Studies by the Type of Design (U.S. Preventive Services Task Force) (8).

Evidence level	Study type
I	At least one controlled and randomized clinical trial, properly designed
II-1	Well-designed, controlled, nonrandomized clinical trials
II-2	Cohort or case studies and well-designed controls, preferably multicenter
II-3	Multiple series compared over time, with or without intervention, and surprising results in noncontrolled experience
III	Clinical experience-based opinions, descriptive studies, clinical observations, or reports of expert committees

Table 2. Level of Certainty Regarding Net Benefit Based on Evidence Strength (8).

Level of certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of the individual studies. Inconsistency of findings across individual studies. Limited generalizability of findings to routine practice. Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess the effects on health outcomes. Evidence is insufficient because of: • the limited number or size of the studies; • important flaws in the study design or methods; • inconsistency of finding across individual studies; • gaps in the chain of evidence; • findings not generalized to routine practice; • lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

Table 3. Meaning of Recommendation Degrees (U.S. Preventive Services Task Force) (8).

Degree of recommendation	Meaning
A	Extremely recommendable (high-level evidence that the measure is effective and benefits outweigh the harms)
B	Recommendable (at least moderate level evidence that the measure is effective and benefits exceed harms)
C	The USPSTF recommends selectively offering or providing this service based on professional judgment and patient preferences; there is at least moderate certainty that the net benefit is small
D	Inadvisable (at least moderate evidence that the measure is ineffective or that the harms exceed the benefits)
I	Insufficient, low-quality, or contradictory evidence; the balance between benefit and harms cannot be determined

gray and white matter but various other axons can also be activated by the TMS pulses within the superficial cortical layers of the precentral gyrus, such as interneurons or thalamocortical afferents (3). The application of TMS therapy has the ability to influence various neurotransmitter systems in brain networks including their receptors and associated second messengers, and to promote synaptic plasticity underlying the prolonged analgesic effect of the procedure (4–6). TMS technology has an excellent safety track record when used under the safety guidelines established in 1998(1). A more updated safety and application guideline was published in 2009(7). In light of the opioid epidemic and chronic use of psychoactive medications, noninvasive and nonpharmacological treatment modalities for pain becomes increasingly important. While emerging evidence support the use of TMS as a treatment for pain, the lack of consensus in the field regarding the quality of existing evidence, treatment recommendations and guidelines, and its costeffectiveness hinder the clinical implementation of this treatment modality. Thus, the current multi-disciplinary multi-national expert panel aims to: 1) assess and rate the quality of the existing outcome evidence of TMS in various pain and headache conditions; 2) provide TMS treatment recommendations and guidelines for various pain and headache conditions; and 3) assess the cost-effectiveness and technical issues relevant to the long-term clinical implementation of TMS for pain and headache.

Table 4. Evidence Rankings From the Centers of Disease Control and Prevention (9).

Recommendability	Meaning
IA	Strongly recommend for implementation and supported by well-designed experimental, clinical, or epidemiological studies
IB	Strongly recommended for implementation and supported by some experimental, clinical, or epidemiological studies and strong theoretical rationale
II	Suggested for implementation and supported by suggestive clinical or epidemiological studies or theoretical rationale
No recommendation/ unresolved issue	Practices for which insufficient evidence or no consensus regarding efficacy exists

PANEL ORGANIZATION AND METHODOLOGY

The panel consists of a 5-member steering committee which provided guidance and recommendation for seven task groups. Four task groups were assigned to assess the utilization of TMS in the treatment of four separate pain conditions, namely, chronic neuropathic pain, acute pain, primary headache disorders and posttraumatic brain injury headaches. Each task group consists of 3 to 5 members who reviewed the existing clinical evidence and rated the type of study design (Table 1), level of certainty regarding the net benefit based on the study design (Table 2) and meaning of recommendation degrees (Table 3) based on the criteria established by U.S. Preventive Service Task Force (8). In addition, the task groups also provided evidence ranking for clinical implementation recommendation (Table 4) based on the criteria established by the Centers for Disease Control and Prevention (9). Three separate task groups further analyzed the TMS as a treatment for both pain and comorbid depression, the cost-effectiveness and technological issues relevant to the treatment. Individual studies were also rated by the guideline established by American Academy of Neurology Classification of Evidence for Therapeutic Studies (10).

CHRONIC NEUROPATHIC PAIN

The chronic neuropathic pain (NP) task group consisted of a panel of five international experts from various disciplines including pain management, neurology, and anesthesiology. The task group members are experienced in managing patients with chronic NP and providing clinical TMS therapy for patients with NP and/or conducting related clinical or mechanistic studies.

TMS for Chronic Neuropathic Pain

Among various pain conditions treated with TMS, neuropathic pain (NP) has been the most studied one (Tables 5 and 6). The International Association for the Study of Pain (IASP) defined NP as "pain caused by damage or disease affecting the somatosensory nervous system." NP may be associated with abnormal sensations called dysesthesia or pain arising from normally nonpainful stimuli (allodynia) (16). It is estimated that close to 10% of the global population are affected by NP (17–19). Unfortunately, pharmacological interventions have not yielded robust outcomes and often carry untoward side effects and the potential for abuse when used to treat NP.

Based on previous studies, the supraspinal pain processing network is known to involve the thalamus (TH) and such brainstem structures as the pons, which relate sensory afferent signals to other supraspinal regions including: 1) sensory discriminatory regions such as primary and secondary somatosensory cortices (SSC1 and SSC2), and inferior parietal lobe (IPL); 2) affective regions such as the anterior cingulate cortex (ACC) and the insula (IN); and 3) modulatory regions involving the motor cortex and

Table 5. Summary of Reviews in TMS for Neuropathic Pain (NP).

Authors (year)	Review type	Studies included	NP conditions	Data type	Site of TMS	Number of studies	Review summary
Leung, et al. (2009) (11)	Meta-analysis	RCT	Various	Pooled Individual Data	M1	5	ssTMS can effectively reduce NP and rTMS appear to have more robust and sustainable analgesic effect than ssTMS. NP conditions with higher anatomical origins have more favorable response to the treatment than those with more peripheral origins.
Boldt et al. (2014) (12)	Cochrane Review	RCT	SCI	Study Result Summaries	M1	3	Evidence is insufficient to suggest that rTMS is effective in reducing chronic pain in people living with SCI. The benefits and harms of commonly used non-pharmacological pain treatments should be investigated in randomized controlled trials with adequate sample size and study methodology.
Jin et al. (2015) (13)	Meta-analysis	RCT	Various	Study Result Summaries	M1	29	HF-rTMS stimulation on M1 is effective in relieving pain in NP patients. Although 5 sessions of rTMS treatment produced a maximal analgesic effect and may be maintained for at least one month, further large-scale and well-controlled trials are needed to determine if this enhanced effect is specific to certain types of NP such as post-stroke related central NP.
Lefaucheur, et al. (2014) (14)	Consensus Panel	RCT	Various	Study Result Summaries	M1, LDLPFC	9(M1); 2(LDLPFC)	Level-A (Definitive) Evidence for contralateral M1 for NP
Gao et al. (2017) (15)	Meta-analysis	RCT (2), CROSS-OVER (4)	SCI	Study Result Summaries M1 Vertex		6	rTMS might reduce SCI associated neuropathic pain; Further studies are required to support our conclusions.

LDLFPC, left dorsolateral prefrontal cortex; M1, motor cortex; RCT, randomized controlled trials; rTMS, repetitive transcranial magnetic stimulation; SCI, spinal cord injury; ssTMS, single session transcranial magnetic stimulation.

various regions of the prefrontal cortices (PFCs) (20,21). These regions of the brain interact with each other via networks forming a third order system of pain matrices (22). The IN is especially implicated in the assessment of the magnitude of pain (23,24). Furthermore, the inferior parietal lobe (IPL) is also known to play an important role in spatial discriminatory functions of pain perception (25,26). NP conditions can occur as a result of maladaptation of supraspinal pain processing, which is often accompanied by diminished modulatory functional connectivity from either the prefrontal or the primary motor cortices. While high frequency (>5 Hz) TMS on either the left dorsolateral prefrontal cortex (DLPFC), or the primary motor cortex (M1) can result in an

Table 6. Assessment and Recommendation Summary of the Neuropathic Pain (NP) Task Group.

Conditions	Study design (I, II-1, II-2, II-3, III)	Level of certainty in evidence (H, M, L)	USPSTF recommendation score (A-F)	CDC recommendation score (1A, 1B, II)
TMS of M1 for NP	I	H	A	IA
TMS of F3 for NP	I	M	B	IB

Table 7. Summary of Postoperative Pain Studies.

Author (year)	Number of subjects	Description	TMS target	TMS protocol	NNG	Results	Study type	Adverse events	Study class	Comments
Borckardt et al. (2006) (39)	20	RCT- 20 mins Left DLPFC rTMS vs sham after gastric bypass surgery, measured postoperative PCA opioid use	Left DLPFC - 5 cm anterior in a parasagittal line from optimum thumb movement	10-Hz (4000 pulses) @ 100% RMT	NO	VAS (no change), but 40% decrease in mean cumulative morphine use (by 1.21 mg/2 hour) in PCA over time	RCT	Incidence of headache 50% in treatment vs 20% in sham	II	Single blinding only, mixed laparoscopic, and open cases
Borckardt et al. (2008) (40)	20 (40 for combined analysis with 2006 results)	RCT- replication and extension of Borckardt 2006 - rTMS of left DLPFC after gastric bypass	Left DLPFC - 5 cm anterior in a parasagittal line from optimum thumb movement	10-Hz (4000 pulses) @ 100% RMT	NO	36% decrease in mean cumulative morphine PCA usage; when combined with 2006 data, total 40 subjects, significant decrease in average pain and worst pain VAS (~2 points) and improved mood VAS.	RCT	Not reported	II	Single blinding only, mixed laparoscopic, and open cases
Borckardt et al. (2014) (37)	108	Double-blind, sham controlled RCT of rTMS of Left DLPFC for postoperative pain related to gastric bypass	Left DLPFC - found using EEG 10–20 coordinates (F3)	20 mins of either (1) 2 sessions of 10 Hz (4000 pulses) @ 110% RMT, (2) 2 sham sessions (3) 1 active TMS then 1 sham or (4) 1 sham then 1 active TMS	NO	MPQ affective and MPQ sensory pain scores were significantly improved for any group with rTMS treatment on POD1, which normalized by discharge day. No effect of rTMS on postoperative VAS or PCA opioid usage.	RCT	Incidence of headache 27% in treatment vs. 11% in sham	I	Large overall group with multiple treatment sequences lend more support to main effect of TMS, double blinding may not have been robust given patients guessed which arm they were on at higher than chance.

DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; M1, primary motor cortex; MPQ, McGill pain questionnaire; NNG, MRI-based neuronavigation system; NRS, numerical rating scale; OCC, occipital midline; PCA, patient controlled analgesia; POD, postoperative day; RCT, randomized controlled trial; RMT, resting rotor threshold; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation; VAS, visual analog scale.

Table 8. Summary of Experimental Pain Studies.

Author (year)	Number of subjects	Description	TMS target	tms protocol	NNG	Results	Study type	Adverse events	Study class	Comments
Tamura et al. (2004) (41)	7	Within subject Sham controlled M1 rTMS 30 mins after acute capsaicin injection	Contralateral M1	1 Hz (300 pulses)	YES	1.5–2 pt. pain VAS score reduction of capsaicin induced hyperalgesia for 2–7 min poststimulation	Experimental pain model—intradermal capsaicin	Not reported	III	Single-blinding only, Sham used TENS machine, not TMS
Brighina et al. (2011) (42)	16	rTMS of left vs right DLPFC (vs no treatment) effect on VAS, 10 or 20 min after 3% capsaicin application to left or right dorsum hand	Left vs right DLPFC	rTMS at 5 Hz (1800 pulses) @ 95% RMT	YES	Left DLPFC rTMS reduced VAS score by 20-30 mm in both hands, when delivered either 10 or 20 mins after capsaicin, lasting at least 60 mins.	Experimental pain model—intradermal capsaicin	Not reported	II	No sham, but Right DLPFC served as a robust control
Summers et al. (2004) (44)	40	Low (1 Hz) vs high (20 Hz) rTMS (or Sham) applied to contralateral motor cortex- and influence on cold sensory and pain thresholds	Contralateral M1-motor twitch	Experiment 1: 1 Hz (500 pulses); Experiment 2: 20 Hz (500 pulses)	NO	Both low and high frequency increased cold sensory thresholds, only high frequency rTMS increased cold pain threshold by −1.43 deg C.	Experimental pain model—thermal pain	Not reported	II	Good Sham control by reproducing clicking noise with second TMS coil, single blinded only
Graff-Guerrero et al. (2005) (46)	180	rTMS of Left/Right M1 or DLPFC or vertex or sham—effect on cold pressor pain, thermal pain, and pressure pain, DLPFC found 5 cm anterior to M1	L/R M1 based on thumb twitch, L/R DLPFC 5 cm anterior to M1 site, vertex or sham.	1 Hz, 15 min (900 pulses) @ 100% RMT		Right DLPFC (but not left) increased tolerance to cold pressor test in both hands, but no effect on thermal or pressure pain. M1 TMS had no effect.	Experimental pain model—cold pressor pain, thermal pain, pressure pain	No adverse events	II	No blinding, Sham involved 45 degree rotation of figure of 8 coil, 1 Hz may be inhibitory, consistent with + results from high frequency left DLPFC TMS
Borckardt et al. (2007) (45)	20	RCT-Sham controlled Left DLPFC rTMS for 15 mins to assess effect on thermal pain thresholds.	Left DLPFC - 5 cm anterior in a parasagittal line from optimum thumb movement	10 Hz (300 pulses) @100% RMT	NO	0.8 deg C, increased Thermal Pain threshold after rTMS	Experimental Pain Model - thermal pain	Incidence of headache 10% in each group	II	Unclear if thermal pain threshold is clinically meaningful
Nahmias et al. (2009) (47)	52	Double blinded, cross-over rTMS of right M1 or DLPFC—effect on thermal pain and RIII nociceptive reflex	Right M1 optimum thumb EMG response, Right DLPFC 5 cm anterior to M1, or Sham	10 Hz, 15 mins (1500 pulses) @ 80% RMT	NO	Both right M1 and DLPFC TMS increased cold (but not hot) pain thresholds on both sides of body. No effect on nociceptive reflex. No effect on subjective pain VAS with cold pain stimuli.	Experimental pain model—thermal pain, nociceptive reflex	Not reported	II	Sham stimulation delivered in separate session 2 weeks before active so unclear how effective blinding was.
Taylor et al. (2012) (48)	24	Single blinded, sham controlled rTMS of DLPFC with naloxone—effect on change in thermal pain threshold measured with QST	Left DLPFC found with beam method, targeting F3 location	10 Hz, (4000 pulses) @110% RMT	NO	Left DLPFC increased hot pain sensory thresholds (reduced pain sensation) which was abolished by Naloxone, compared to saline infusion and sham TMS controls	Experimental pain model—thermal pain	No adverse events	II	Good sham control, naloxone infusion control, and patient blinding.
Sacco et al. (2014) (43)	14	rTMS of left M1 vs left DLPFC vs midline OCC—effect on thermal pain thresholds and pain VAS	Left M1, left DLPFC, midline occipital cortex	10 Hz (2000 pulses) @ 90% RMT	NO	M1 rTMS reduced pain NRS in response to capsaicin thermal hyperalgesia compared to DLPFC or OCC TMS; TMS in no regions had effect on heat pain threshold detection	Experimental Pain Model - topical capsaicin+ thermal pain	Not reported	III	No blinding, no sham, but used brain regional TMS controls, not likely that <1 point in NRS reduction is clinically meaningful.

deg, degrees; DLPFC, dorsolateral prefrontal cortex; EMG, electromyography; L, left; M1, primary motor cortex; NNG, MRI-based neuronavigation system; NRS, numerical rating scale; OCC, occipital midline; R, right; RMT, resting rotor threshold; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation; VAS, visual analog scale.

Table 9. Assessment and Recommendation Summary of the Acute Pain Task Group.

Conditions	Study design (I, II-1, II-2, II-3, III)	Level of certainty in evidence (H, M, L)	USPSTF recommendation score (A-F)	CDC recommendation score (1A, 1B, II)
TMS of F3 for postoperative pain	I	M	C	IB
TMS of M1 for postoperative pain:	NA	L	I	NR
TMS of F3 for experimental pain	II-1	M	NR	NR
TMS of M1 for experimental pain	II-1	M	NR	NR

I, insufficient data; NR, no recommendation.

analgesic benefit, their relative mechanisms of action appear to be different. With stimulations at the M1, a strong focal activation was observed in the thalamus, insula, cingulate-orbitofrontal junction and the brain stem periaqueductal gray (PAG) area in the brainstem, suggesting that a direct top-down activation of the descending pain control system mediated via a motor-thalamus and/or motor-brainstem functional linkage (27,28). On the other hand, rTMS of the left DLPFC applied at the F3 site (according to the International 10–20 System of electrode placement) exerts a diffuse top-down inhibitory effect along the descending midbrain-thalamic-cingulate pathway through the descending fibers from the prefrontal cortex. Thus, the widespread effect of DLPFC stimulation can potentiate the motor cortex and modulate the affective circuits relevant to both pain and depression (29–32). Since NP is associated with diminished motor cortical network excitability or defects in the pain modulatory network, stimulating the motor cortex provides the most direct means of restoring motor cortical excitability and its pain modulatory functions (33). An early meta-analysis based on randomized controlled studies suggested that TMS at the M1 is more effective in suppressing central rather than peripheral NP (34). More recent meta-analyses further confirmed the efficacy of TMS in managing NP (13,35). A European consensus panel further granted Level A (Definitive) evidence for TMS at the contralateral M1 for unilateral NP, with no recommendation for cortical targets other than M1 because of insufficient data (14) based on their review of available randomized controlled studies. The NP conditions with the greatest responses to TMS include post-stroke central pain and trigeminal neuralgia, whereas NP conditions with more peripheral anatomical origins such as posttraumatic peripheral neuropathic pain responded to the treatment less favorably.

Treatment Protocol

The most utilized studied protocol consists of 5–10 treatments sessions (at >24 and < 72 hours intervals) at 10–20 Hz, 2000–3000 pulses per session and an intensity of stimulation corresponding to 80–90% of the resting motor threshold (RMT). This is then followed by biweekly to monthly maintenance treatment sessions with similar settings (14,36).

Assessment and Recommendation

Based on the evidence established from randomized controlled trials (RCTs) assessed in previously conducted meta-analyses and Cochrane reviews (Table 5), outcome of the recent panel review and the rating provided by the majority of the members, the task group rated the overall study design for TMS at M1 as I, level of certainty in evidence as High for NP of supraspinal origin, Moderate for phantom limb pain and Low for NP of spinal cord and peripheral origins. The task group also granted a USPSTF Level A recommendation and CDC Level IB recommendation supporting the adaptation of TMS for treating appropriate neuropathic pain indications including post-stroke central pain and trigeminal neuralgia. In addition to M1, left DLPFC can be considered as an alternate treatment location for patients with diffuse NP problems or comorbid severe depression. The task group also recommends the use of brain MRI-based neuronavigation guidance for treatment to ensure the consistency and reliability of the treatment location and avoid any potential adverse effect (further discussed in the technical issue section) from nonspecific stimulation.

Recommended Treatment Protocol

For patients with NP but no severe comorbid depression, the task group recommends 5–10 induction sessions (at >24 and < 72 hours intervals) at 10–20 Hz, 2000–3000 pulses per session and an intensity of stimulation corresponding to 80–90% of the resting motor threshold (RMT) at the contralateral M1 for unilateral NP or left DLPFC for diffuse neuropathic pain conditions. Is there a maintenance treatment plan for no comorbid depression? For patients with NP and comorbid severe depression, the task group recommends at least 10 induction sessions (at >24 and < 72 hours intervals) at 10–20 Hz, 2000–3000 pulses per session and an intensity of stimulation corresponding to 80–90% of the resting motor threshold (RMT) at the left DLPFC, followed by biweekly to monthly maintenance treatment sessions with similar settings based on the duration of the treatment benefits.

ACUTE PAIN

The acute pain task group consisted of three experts from disciplines including pain management, neurology, and anesthesiology. The members are experienced in managing acute pain.

The analgesic effects of TMS for postoperative or acute pain have been relatively less studied than in chronic pain syndromes. The task group identified studies from only one investigational group evaluating treatment targeting the left DLPFC for pain after surgery (37). Other investigators have studied effects of TMS in experimental models of acute pain(38). A PubMed search [keywords: (TMS) AND (postoperative pain) OR (acute pain) OR (pain threshold)] and a separate search [keywords: (TMS) AND (experimental pain)] identified 80 papers, including 3 prospective studies of postsurgical patients who received active or sham TMS to the left DLPFC, assessing opioid usage and pain intensity. The task group identified eight additional papers that evaluated the effect of active vs sham rTMS of either M1 or left DLPFC on experimental models of acute pain. The analyzed results include

Table 10. Study Summary of TMS in Primary Headaches.

Author (Year)	Class of study	Type of study	Patient type, no. of patients	Target, coil type, frequency, intensity, number of pulses/sessions/ number of sessions	Sham or comparator group	Results	Comments
Single pulse TMS studies for acute migraine							
Lipton et al. (2010) (49)	I	Randomized controlled	Migraine, 82 real/82 sham	Occiput, 2 pulses 30 sec apart within 1 hr. of aura onset	Sham stimulator	Pain free response rates after 2 hours 39% for real vs 22% for sham	Acute migraine treatment
Bhola et al. (2015) (50)	IV	Open labeled	Migraine, 331 completed at 1 survey, 190 completed 2 surveys at 12 weeks	Occiput, 1–2 pulses	None	Reduced number of monthly headache days at 12 weeks compared to baseline	Postmarketing survey. Acute migraine treatment and migraine prevention
Single pulse TMS studies for acute migraine							
Bhola et al. (2015) (50)	IV	Open labeled	Migraine, 331 completed at 1 survey, 190 completed 2 surveys at 12 weeks	Occiput, 1–2 pulses	None	Reduced number of monthly headache days at 12 weeks compared to baseline	Post marketing survey. Acute migraine treatment and migraine prevention
Starling et al. (2018) (51)	III	Prospective, open labeled	Migraine, 95 patients completed 3 month protocol	Occiput, 4 pulses 2× per day for prevention, 3 pulses repeated up to 2× for treatment	Performance goal, a statistically derived placebo response, was used as comparator	−2.75 reduction in headache days, 46% responder. Both better than performance goal	Migraine prevention
Irwin et al. (2018) (52)	IV	Open labeled	Migraine, 12 completed study	Occiput, 4 pulses 2× per day, acute treatment 3 pulses repeated up to 2×	None	Decreased number of headache days in the treatment period compared to run in period	Migraine prevention, adolescents aged 12–17
High-frequency rTMS at L-DLPFC for migraine prevention							
Brighina et al. (2004) (53)	II	Randomized, controlled	Chronic migraine, 6 real, 5 sham	L-DLPFC, F8, 20 Hz, 90% RMT, 400 pulses,12 sessions over ~ 18 days	Coil perpendicular to DLPFC	Decreased attack frequency, headache index, number of abortive in medication in real compared to sham group	
O'Readon et al. (2007) (54)	IV	Open labeled	Migraine and depression 1, psychogenic headache and depression 1	L-DLPFC, F8, 10 Hz, 120% RMT, induction and maintenance sessions	None	Reduction in migraine frequency and severity	rTMS for treatment of depression
Conforto et al. (2014) (55)	II	Randomized controlled	Migraine, 7 real, 7 sham	L-DLPFC, F8,10 Hz 110% RMT, 10 Hz, 1600 pulses, 23 sessions over 8 weeks	Coil held perpendicular to vertex	Number of headache days decreased in sham group but not in real group	
High-frequency rTMS at L-M1 for migraine prevention							
Misra et al. (2012) (56)	IV	Open labeled	Migraine, 51	L-M1, F8, 8 Hz, 70% RMT, 584 pulses, 3 sessions over 5 days	None	Improvement in migraine frequency, severity, number of recue medications taken and functional disability	
Misra et al. (2013) (57)	II	Randomized, controlled	Migraine, 50 real, 50 sham	L-M1, F8, 10 Hz, 600 pulses, 70% RMT, 3 sessions over 5 days	Sham coil	Improved headache frequency, VAS score and functional ability improved in real compared to sham group	Not realistic sham stimulation
Kalita et al. (2016) (58)	III	Randomized controlled	Chronic migraine and tension type headache, 52 3 sessions, 46 1 session	L-M1, F8,10 Hz, 70% RMT, 600 pulses, 1 or 3 sessions	Sham coil	Decreased headache frequency, severity and functional disability in both groups	Comparison of 1 vs 3 session of rTMS, method of allocation not stated
Shehata et al. (2016) (59)	III	Randomized, Open labeled	Chronic migraine, 14 rTMS/15 BTX-A	L-M1, F8, 10 Hz, 80% RMT, 2000 pulses, 12 sessions over 1 month	Btx-A treatment	Headache frequency and severity decreased in both groups, with no significant difference	
Zardouz et al. (2016) (60)	IV	Open labeled case series	Migraine, 5	L-M1, F8, 10 Hz, 80% RMT, 2000 pulses, 5 sessions over 2 months	None	Decreased intensity, frequency and duration of migraine	Migraine prevention
Misra et al. (2017) (61)	III	Non-randomized cohort study	Migraine, 24 3 sessions, 21 1 session, real, 47 sham	L-M1, F8, 70% RMT, 600 pulses, 1 or 3 sessions	Sham coil	Reduction in headache frequency and disability in 3 session vs sham	Baseline characteristics not compared
Tripathi et al.(2018) (62)	III	Randomized, unblinded	Migraine, 60 real rTMS/60 sham, 30 amitriptyline	L-M1, F8, 10 Hz, 70% MT, 600 pulses, 1 session (n = 36) or 3 sessions over 5 days (n = 24)	Amitriptyline, sham coil	Frequency of headache, VAS, migraine index decreased in both rTMS and amitriptyline groups. Result of sham group was not reported	
Low frequency rTMS at vertex for migraine prevention							
Teepker et al. (2010) (63)	III	Randomized controlled	Migraine, 13 real/14 sham	Vertex, circular coil, 1 Hz, visual motor threshold −2%, 500 pulses, 2 trains, 5 consecutive days	Sham figure of 8 coil	No significant difference between active and sham groups in headache diary	No statistics to compare baseline characteristics. Gender of subjects unmatched
Continuous theta burst stimulation at R-M1 for migraine prevention							
Chen et al. (2016) (64)	IV	Open labeled	Migraine, 9	R-M1, cTBS, 20 sessions over 4 weeks	None	Decreased number of headache days compared to baseline	
Bilateral DLPFC deep rTMS for migraine prevention							
Rapinesi et al. (2016) (65)	III	Randomized, open labeled	Chronic migraine 7/ 7 standard treatment	Bilateral DLPFC, deep TMS, 10 Hz, 600 pulses, 12 sessions in 1 months	None	Reduction in pain intensity, number of attacks, analgesic use	
High-frequency rTMS at M1 face are for cluster headache							
Hodaj et al. (2015) (66)	III	Open labeled	Cluster headache, 19	M1 face, F8, 10 Hz, 80%RMT, 2000 pulses, 12 sessions over 3 weeks	None	Reduction in pain (VAS) at 15 and 180 days after treatment initiation	Open-label, naturalistic study, included other types of facial pain

BTX-A, botulinum toxin type A; cTBS, continuous theta burst stimulation; DLPFC, dorsolateral prefrontal cortex; F8, figure of eight; L, left; M1, motor cortex; MT, motor threshold; R, right; RMT, resting motor threshold; VAS, visual analog scale.

Table 11. Assessment and Recommendation Summary of the Primary Headache Task Group.

Conditions	Study design (I, II-1, II-2, II-3, III)	Level of certainty in evidence (H, M, L)	USPSTF recommendation score (A-F)	CDC recommendation score (1A, 1B, II)
sTMS for acute migraine	I	M	B	1B
sTMS for migraine prevention	II-2	M	C	II
High-frequency rTMS at DLPFC for migraine prevention	III	L	I	None
High-frequency rTMS at M1 for migraine prevention	II-1	M	B	II
Low-frequency rTMS at vertex for migraine prevention	III	L	I	None
Continuous theta burse stimulation at M1 for migraine prevention	III	L	I	None
High-frequency deep rTMS at DLPFC for migraine prevention	III	L	I	None
rTMS for cluster headache	III	L	I	None

148 postoperative patients and 353 healthy volunteers subject to experimental pain.

Postoperative pain: Two randomized, sham-controlled trials with class II evidence were conducted to evaluate the effect of rTMS at left DLPFC on postoperative morphine usage after gastric bypass surgery (39,40). While the second article was a replication study, both separately demonstrated a 40% reduction in mean cumulative milligrams of morphine use during the hospitalization. Combining data from both studies ($N = 40$), patients who showed a significant decrease in the average pain scores also demonstrated improved mood scores (40). A follow-up larger double-blinded, sham-controlled RCT (class I evidence) of 2 sessions 10 Hz stimulation at the left DLPFC failed to replicate a prior claim of decreased opioid usage or pain score but did find improvements in McGill Pain Questionnaire (MPQ) affective and sensory pain scores (37). These results suggest that the postoperative analgesic effect of a single session of TMS at the left DLPFC is transient (Table 7) with the only type of surgery studied is gastric bypass; the effect of M1 TMS or repetitive TMS on postoperative pain has not been tested.

Experimental pain: Application of capsaicin to the skin, as a model of acute pain, induces temporary thermal hyperalgesia. Two studies evaluated the effect of TMS on alleviating acute pain following intradermal 3% capsaicin injection. One study (class III) demonstrated that 1 Hz rTMS applied to the contralateral M1 cortex produced a significant reduction in pain for 2–7 minutes post TMS treatment (41). A second study (class II) demonstrated (42) that only left hemisphere 5 Hz DLPFC rTMS stimulation provided bilateral analgesic effects. In contrast, another study (class II) found a significant reduction in topical capsaicin-induced pain following contralateral M1 TMS (but *not* contralateral, left DLPFC TMS), conflicting with prior studies (43).

Quantitative sensory testing (QST) measures patients' subjective sensation and pain responses to slow, controlled heating or cooling. The task group identified five studies that tested the influence of TMS on QST outcomes. One study (class II) using low (1 Hz) or high frequency (20 Hz) rTMS of contralateral M1 (versus sham) demonstrated that TMS at both frequencies increased cold sensory detection thresholds, suggesting that M1 TMS modifies thermal sensory processing (44). However, only 20 Hz TMS increased cold *pain* detection thresholds compared to sham, supporting possible analgesic effects of high-frequency TMS of contralateral M1. A second sham controlled RCT (class II) using 15 min of 10 Hz rTMS over the left DLPFC also resulted in increased heat pain thresholds compared to sham (45). However, it is unclear whether the reported 0.8 °C increase in pain detection threshold is clinically meaningful. Two studies directly compared the effect of M1 vs DLPFC TMS on QST measures. Right sided 1 Hz DLPFC TMS (but not left or M1) increased tolerance to cold pressor pain, without changing QST thermal or pressure pain thresholds (class II study) (46). Because 1 Hz TMS is interpreted to provide inhibition of underlying cortex, these results may be consistent with similar findings from high frequency (excitatory) stimulation of left DLPFC; reconciling these observations may imply that relative excitation of left DLPFC, compared to right, is responsible for analgesia. Contradicting previous observations, however, another study (class II) found that high frequency (10 Hz) right DLPFC and M1 TMS increased QST cold pain thresholds on both sides of the body, without changing heat pain sensation or reported pain scores(47).

Overall, evidence regarding laterality specificity of M1 or DLPFC TMS for acute pain related analgesia is conflicting, with different groups supporting analgesic effects in both hemispheres following experimental stimuli.

A mechanistic study assessing the role of endogenous opioids in mediating analgesia to painful thermal stimuli (48) showed that 10 Hz TMS of the left DLPFC was associated with a significant decrease in pain and a significant increase in pain thresholds. This effect was completely abolished after pretreatment with an intravenous bolus of 0.1 mg/kg of naloxone, an opioid antagonist, but not with saline. Because pretreatment with naloxone blocks the analgesic effects of left high-frequency DLPFC TMS, these effects appear to be mediated through endogenous opioids.

In assessing the side effects of the treatment, only three studies reported the presence or absence of adverse events: Graff-Guerrero et al. (46) and Taylor et al. (48) reported no adverse events; Borckardt et al. observed a 10% incidence of headache in each group, which was neither severe nor serious (45) (Table 8).

Assessments and Recommendations

The task group provided separate assessments of two acute pain conditions: postoperative and experimental pain, and recommendations for clinically relevant postoperative pain at two different stimulation locations (M1 vs DLPFC) (Table 9).

TMS of Left Prefrontal cortex (PFC) for Postoperative Pain

Study design meets Level I criteria supporting a possible role for 10 Hz left DLPFC TMS in reducing short-term postoperative pain after gastric bypass surgery. A moderate level of certainty suggests TMS of left DLPFC be selectively offered to individual patients based on professional judgment and patient preference (Degree of Recommendation = C). Left DLPFC rTMS for postoperative pain after gastric bypass carries a CDC recommendation score of IB. It is unclear whether these recommendations extend to surgeries other than gastric bypass.

TMS of M1 for Postoperative Pain

The task group did not identify any studies evaluating M1 TMS for postoperative pain. Therefore, the task group cannot comment on study design. Level of certainty is low, and USPSTF recommendation is class I (insufficient data) as no recommendation can be made on CDC criteria.

TMS of Left PFC for Experimental Pain

Study Design meets Level II-1 criteria with a Moderate level of certainty.

TMS of M1 for Experimental Pain

Study Design meets Level II-1 criteria with a Moderate level of certainty.

PRIMARY HEADACHE DISORDERS

The primary headache disorders task group consisted of a panel of four experts specialized in neurology and/or pain management (Tables 10 and 11). The task group members are experienced in managing patients with headaches and are involved in TMS-related studies.

Primary headache disorders include migraine, tension-type headache, and the trigeminal autonomic cephalalgias (a family which includes cluster headache). These are common disorders, which are leading causes of disability worldwide according to the World Health Organization's Global Burden of Disease (67). For example, migraine is the third leading cause of disability among under-50s worldwide (68). One-year prevalence of migraine is 17.1% among women and 5.6% among men in the United States (69). Tension-type headaches are even more common but less disabling. Cluster headaches affect about 1/1000 people and are they have been called "suicide headaches." In general, headache treatments are divided into acute treatments (previously called "abortive" treatments), which are used when one is experiencing a headache, and preventive treatments (previously called "prophylactic" treatments), which are used on a daily basis regardless of whether the individual is experiencing a headache that day. TMS has been studied for headache prevention; single-pulse TMS was studied first for acute migraine treatment and later for migraine prevention (70).

Single Pulse TMS

Several studies tested the utility of single pulse TMS to treat migraine headache pain based on the hypothesis that TMS applied at the back of the head would disrupt cortical spreading depression. These studies used a handheld TMS device that is switched on and positioned at the occiput by the patient. The single magnetic pulse has the strength of 0.9 T measured 1 cm from the device service with rise time of 180 μs and pulse duration of less than 1 ms. In this common protocol, a second pulse could be applied after the first pulse (49,50).

Acute Treatment of Migraine

A class I RCT tested occipital single pulse TMS for acute treatment of migraine with aura (49) found pain free response rates after 2 hours were 39% for real stimulation group compared to 22% for sham stimulation group. Based on the study, the United States federal drug administration (FDA) approved the single pulse TMS device for acute pain relief in migraine with aura. A postmarketing survey in the United Kingdom (class IV study) (50) in190 patients showed that 62% found the device effective in reducing or alleviating migraine pain. No serious adverse events were reported in both studies. For acute treatment of migraine with single pulse occipital TMS, based on one class I and one class IV study, the task group gives a rating of level I evidence for study design, level M for certainty of evidence, grade B for USPSTF recommendation and and grade 1B recommendation (Tables 10 and 11).

Migraine Prevention

A postmarketing survey in the United Kingdom (class IV study) (50) reported decreased number of headache days for those with episodic or chronic migraine compared to baseline. In a prospective, open-labeled, observational study that compared the results to a statistically derived placebo response (ESPOUSE study, class III), showed the treatment resulted in mean reduction of 2.75 headache days per month and 46% responder rate, which was better than the performance goal based on the statistically derived placebo response. This study led to FDA approval of single pulse TMS for preventive treatment of migraine. A small open-labeled class IV study tested single pulse TMS for migraine prevention in adolescents aged 12 to 17 (52). No serious adverse events were reported in any of the studies. In summary, one class III and two class IV studies have suggested utility of single pulse TMS in migraine prevention. The task group proposes a level II-2 evidence for study design and level M for certainty of evidence. The task group recommends selectively offering this service based on professional judgment and patient preference (Grade C, USPSTF) and grade II CDC recommendation (Tables 10 and 11).

Repetitive TMS for Migraine Prevention

The application of repeated trains of TMS pulses defines a rTMS procedure. It is currently applied in a laboratory or clinic setting by healthcare professionals.

High-Frequency rTMS to Left Dorsolateral Prefrontal Cortex (DLPFC)

Several studies applied high frequency (>5 Hz) rTMS to the left DLPFC for migraine prevention. High-frequency rTMS to the left DLPFC is an approved treatment for depression. A small, randomized controlled trial (class II study) (53) found migraine attack frequency, headache index and the use of acute medications were decreased in the real compared to the sham stimulation group. An open labeled class IV study in two patients with headaches who were receiving 10 Hz rTMS to the left DLPFC for treatment of depression reported reduction in migraine severity and frequency with the treatment (54). Another small, randomized controlled class II study (55) found the number of headaches decreased in the sham but not in the real stimulation group. Since one small class II study showed positive results but another small class II study showed negative results, there is level III evidence for study design, level L for certainty of evidence and insufficient evidence for recommendation (Grade I, USPSTF; no recommendation for CDC ranking) for high-frequency rTMS to the left DLFPC for migraine prevention (Tables 10 and 11).

High-Frequency rTMS to Motor Cortex (M1)

High-frequency rTMS to the M1 has been studied for treatment of pain and therefore a number of studies tested this approach for migraine prevention. An open labeled class IV study

stimulated the left M1 (56) demonstrated improvement in migraine frequency, with reported educations in severity, the number of rescue medications used and functional disability. A class II randomized, controlled trial (57) was conducted with 50 migraine patients randomized to real rTMS and 50 patients to sham rTMS, using similar rTMS parameters as the open-labeled study by the same group (56). However, realistic sham stimulation was not used, thus founding the result interpretation. The real rTMS group had improved headache frequency, pain severity, and functional ability compared to the sham group. A class III randomized controlled trial treated 52 patients with chronic migraine or tension type headache with three sessions of rTMS compared to 46 patients treated with one session of rTMS (58), using similar parameters in previous studies conducted by the same group (56,57). The method of randomization was not stated. Similar improvement in headache frequency, severity and functional disability was reported in both groups. A randomized but open labeled study (class III) compared 12 sessions of 10 Hz rTMS to left M1 over 1 month to botulinum toxin type A injections. Both groups showed decreased headache frequency and severity (59). An open labeled study (class IV) with five patients treated with left M1 10 Hz rTMS for five sessions and found decreased frequency, intensity, and duration of migraine (60). A non-randomized class III study tested 46 patients with real stimulation (24 patients three sessions, 22 patients one session) and 47 patients with sham stimulation (64). The main purpose of the study was to assess the relationship between β endorphin level and pain relief. There was greater reduction in headache frequency and functional disability but no difference in pain severity in the group treated with three sessions of rTMS compared to the sham-treated group. Finally, a randomized but unblinded class III study tested 30 patients with three sessions and 30 patients with one session of 10 Hz rTMS to M1, 60 patients with sham stimulation and 30 patients were treated with amitriptyline. Improvement in headache frequency, severity and migraine index was reported for all the groups studied but statistical comparisons between the groups were not reported (62). No serious adverse event was reported in the published studies.

In summary, one class II (57), one class III (61), and two class IV studies (56,60) showed efficacy of high frequency left M1 rTMS in migraine prevention compared to sham stimulation or baseline. One class III study showed that the effects of rTMS were similar to botulinum toxin type A injection, which is an approved treatment for migraine. Based on these studies, the task group provides level II-1 for study design, Level M for certainty of evidence, Grade B USPSTF recommendation, and Grade II CDC recommendation for left M1 high-frequency rTMS for migraine prevention (Tables 10 and 11).

Other rTMS Paradigms

A class III randomized, controlled trial tested 1 Hz rTMS with a circular coil placed over the vertex for five consecutive days in migraine patients randomized to real (13 patients) or sham (14 patients) stimulation. A figure-of-eight coil was used for sham stimulation. There was no significant difference in headache diary between the real and sham stimulation groups (63).

A class IV open-labeled study tested 20 sessions of continuous theta burst stimulation of the right M1 over 4 weeks in 9 migraine patients (64). There was a decreased number of headache days with the treatment compared to baseline.

Deep TMS, which allows stimulation of deeper cortical or subcortical regions of the brain using the H1 coil, was tested in a randomized but unblinded class III study. The bilateral DLPFC was stimulated at 10 Hz, 600 pulses per session with 12 sessions in 1 month. Reduction in pain intensity, number of attacks, and analgesic use was reported in seven patients treated with deep TMS compared to seven patients who received standard treatment (65).

Due to the low number of studies, the task group rates the study design at level III, certainty of evidence at level L, and no recommendation can be provided for these treatment paradigms for prevention of migraine (Grade I, USPSTF; no recommendation, CDC) (Tables 10 and 11).

rTMS for Cluster Headache

Only one open-labeled class IV study tested rTMS for cluster headache. Included in this broader study of facial pain were 19 patients with cluster headache. Ten Hz rTMS was applied to the area of facial representation in M1 with 12 sessions over three weeks (66). Reduction in pain level at 15 and 180 days after treatment initiation was reported. The task group provides level III for study design, level L for certainty of evidence, and insufficient evidence for recommendation of rTMS in the treatment of cluster headache (Grade I, USPSTF; no recommendation, CDC) (Tables 10 and 11).

POSTTRAUMATIC BRAIN INJURY RELATED HEADACHE

The posttraumatic brain injury (PTBI) related headache (PTBI-HA) task group consisted of experts from pain management, psychiatry/neuropsychology, neurology, and rehabilitation medicine, who are experienced in managing patients with traumatic brain injury (TBI), providing clinical TMS treatment for rehabilitating patients with PTBI-HA and/or conducting related clinical or mechanistic studies (Tables 12 and 13).

TMS for Posttraumatic Injury Related Headache

The U.S. Center for Disease Control and Prevention (CDC) estimated the prevalence of new TBI cases in the United States at over 1.7 million per year (74). Headache is one of the most common debilitating chronic pain conditions in patients after a TBI. This high prevalence (>60%) of persistent chronic headache is often associated with neuropsychological dysfunction in mood, attention, and memory, which has a profound negative impact on patients' quality of life and increases their givers' stress. Unfortunately, conventional pharmacological treatments for PTBI-HA have not been shown to be effective and drugs such as narcotics have many long-term side effects including the risk of abuse, addiction, and death (75–77). In assessing the underlying pathophysiology of mild TBI-related morbidities, although gross structural lesions are usually not detected by conventional anatomical brain neuroimaging techniques such as magnetic resonance imaging (MRI) or computer tomography (CT) in patients with mild TBI, studies with diffusion tensor imaging (DTI) suggest that these patients may suffer from diffuse axonal injury in the major cortical white matter tracts including corpus callosum, anterior corona radiata, corticospinal tract, and internal capsules, which are crucial for intracortical connectivity. These abnormal findings, as reflected in

Table 12. Summary of Reviewed TMS Studies for Post traumatic Brain Injury Related Headaches.

Author (year)	Number of Subjects	Description	TMS Target	TMS protocol	NNG	Results	Study type	Adverse events
Koski et al. (2014) (71)	15	Prospective study with fMRI correlation	left DLPFC	20 week day sessions at 10 hz, 110% rRMT, 1000 pulses/ session	NO	Decrease of PCS	Open label	Increase Headache (N = 3), sleep disturbance (N = 3)
Leung et al. (2015) (72)	24	RCT with sham control	left MC	3 sessions (>24 and < 72 h apart) at 80% RMT, 2000 pulses/session	YES	Decrease of persistent headache prevalence, and debilitating headache exacerbation composite scores	RCT	
Leung et al. (2017) (73)	32	RCT with sham control	Left DLPFC	4 sessions (>24 and < 72 hours apart) at 80% RMT, 2000 pulses/session	YES	Decrease of persistent headache prevalence, and debilitating headache exacerbation composite scores with transient improvement in severe depressive symptoms	RCT	Transient elevation of preservation score without any behavioral correlation

Table 13. Post traumatic Brain Injury Task Group Assessment Summary.

Conditions	Study design (I, II-1, II-2, II-3, III)	Level of certainty in evidence (H, M, L)	USPSTF recommendation score (A-F)	CDC recommendation score (1A, 1B, II)
HF TMS at M1 or F3*	I	H	A	1A

F3, left dorsolateral prefrontal cortex; HF, high frequency; M1, primary motor cortex; TMS, transcranial magnetic stimulation.
*Preferred site for patients with moderate to severe depression.

part by the diminished fractional anisotropy index found in the frontal cortices, are often directly correlated with deficits in fine motor skills, attention, mood, and memory identified by neuropsychological and motor functional assessments (78,79). Other studies with functional MRI suggest that patients with persistent PTBI-HA have significant compromised prefrontal modulatory responses to painful stimuli and their resting state connectivity to other pain-related regions are diminished in comparison to age and gender matched healthy controls (80). In addition, defects in the white matter tracts such as the superior longitudinal tract, which connects the prefrontal cortex with the somatosensory discriminatory cortices and anterior thalamic tract, which links the prefrontal with the affective cortices, are thought to play a role in these pain modulatory functional deficits (80,81).

On neurophysiological assessments, TBI patients appear to suffer from long lasting elevation of motor cortical evoked potentials, suggesting a deficiency in cortical excitability and conductivity in brain areas associated with pain modulation or adaptation. These deficits are also associated with other NP conditions (82). These structural and electrophysiological abnormalities in the TBI population correlated with the finding of a brain perfusion study, which demonstrated that TBI patients had hypoperfusion in the basal ganglia, a key relay center between cortical areas (particularly the prefrontal cortical area and parietal cortices) and the limbic system, suggesting a dissociative state between the affective (hyperactive) and modulatory (hypoactive) aspects of supraspinal activities (83). Therefore, rectifying this dissociative state by means of noninvasive brain neuromodulation such as TMS has been proposed for addressing PTBI related symptoms (84,85).

In animal models, TMS has shown to promote neurogenesis after TBI (86). In humans, two published RCTs assessing the effect of neuronavigation rTMS at the M1 (72) and left LDLPFC (73) demonstrated with a short (3–4 sessions with >24 and < 72 hours apart) course of rTMS at 10 Hz, 80% RMT, and 2000 pulses per session could significantly reduce the intensity of average daily headache, the prevalence of persistent headache, and the overall severity of the debilitating headache exacerbation up to one to two months. In addition, the left DLPFC site appears to have an overall more robust effect than the left MC for pain with an added advantage of improving mood function in the cohort of patients who are moderately to severely depressed. Although case series support the long-term use of the treatment at either location for treating PTBI-HA (87), large scale randomized studies are required to support the use of rTMS for managing PTBI-HA.

Table 14. TMS Trials Examining Effects on Depression When Treating Pain.

Author (year)	Treatment location (sample size)	Stimulation protocol (design)	Pain conditions	Effect on pain	Effect on depression	Quality of life measures	Quality of study
	Motor cortex (M1) stimulation						
Picarelli et al. (2010) (88)	M1 (NNG) (*N* = 23)	10 sessions (2 wks) at 10 Hz, 100% RMT, 2500 pulses/session (RCT)	Complex regional pain syndrome type I	Significant improvement noted in VAS scores during treatments in the active group	HDRS-21 items: no improvement in depression between active and sham groups	Significant improvement in DASH, affective subscores of SF-36, QOL and MPQ in the active group	Class II
Mhalla et al. (2011) (89)	M1 (NNG) (*N* = 40)	Induction: 5 consecutive daily sessions; Maintenance: 3 weekly sessions +3 fortnightly session +3 monthly sessions; at 10 Hz, 80% RMT, 1500 pulses/session (RCT)	Fibromyalgia	Significant improvement in BPI in the active group	HDRS 21-item: no effect; BDI: no effect	Sensory and affective subscores of MPQ QoL and PCS scores improvement in the active group	Class I
Passard et al. (2007) (90)	M1 (NNG) (*N* = 30)	10 daily sessions at 10 Hz, 80% RMT, 2000 pulses/session (RCT)	Fibromyalgia	Significant improvement in BPI pain intensity and Interference, MPQ, and FIQ at day 15 in the Active group	HDRS, BDI, HADS: no change	BPI -interference and FIQ score significantly decreased through day 30 in the Active group	Class I
Hosomi et al. (2013) (91)	M1 (NNG) (*N* = 70)	10 daily session at 5 Hz, 90% RMT, 500 pulses/session (RCT)	Neuropathic pain	Mean VAS score reduction immediately after stimulation in the active group; no cumulative effect during daily stimulation.	BDI: no change	SF-MPQL decrease in short term but no cumulative long-term effects in the active group	Class I
Boyer et al. (2014) (92)	M1 (NNG) (*N* = 38)	10 induction (2 weeks) and 4 biweekly maintenance sessions at 10 Hz, 90% RMT, 2000 pulses/session (RCT)	Fibromyalgia	Not measured	No significant change in BDI in the sham or treatment group	Patients of the active rTMS group had greater QoL improvement in the FIQ and in the mental component of the SF-36	Class I
DLPFC stimulation							
Leung et al. (2017) (73)	L-DLPFC (NNG) (*N* = 29)	4 sessions (1-2wks) at 10 Hz, 80% RMT, 2000 pulses/session (RCT)	Mild traumatic brain injury-related headaches	Active group revealed a significant decrease in average daily persistent headache intensity compared to sham	Significant improvement in HDRS score in treatment group		Class I
Lee et al. (2012) (93)	R-DLPFC (*N* = 15)	10 sessions (2 weeks) at low frequency (1 Hz), 110% RMT over R-DLPFC (1600 pulses per session) or high frequency (10 Hz), 80% RMT over the left M1 (2000 pulses/session) vs Sham (RCT)	Fibromyalgia	Pain VAS, K-FIQ improved with HF and LF stim but was maintained after 1 month only with LF TMS	Depression (BDI): Both LF and HF groups had significantly lower BDI scores but only the LF group maintained at 1 month.	FIQ, QOL improved after LF and HF TMS and was maintained after 1 month with low-frequency TMS	Class II
Short et al. (2011) (94)	L-DLPFC (*N* = 20)	10 sessions (2 weeks) at 10 Hz, 120% RMT, 4000 pulses/session (RCT)	Fibromyalgia	Pain scores improved from baseline but did not differ from sham	HDRS: no statistical difference (sham vs active).	No significant difference in BPI, FIQ	Class II

BDI, Beck Depression Inventory; BPI, brief pain inventory; DASH, disability of arm, shoulder and hand questionnaire; DLPFC, dorsolateral prefrontal cortex; FIQ, fibromyalgia impact questionnaire; HDRS, hamilton depression rating scale; HF, high frequency; ITI, inter-train interval; K-FIQ, Korean version of FIQ; LF, low frequency; MPQ, McGill pain questionnaire; NEPIQoL, neuropathic pain impact on quality of life; NRS, numerical rating scale; PCS, pain catastrophizing scale; PGI, patient global impression scale of improvement; QoL, quality of life; Rand-36/SF-36, 36-item short form health survey questionnaire.

Assessment and Recommendation

Based on the existing clinical outcome evidence for the short-term efficacy (1–2 months) in alleviating PTBI-HA symptoms, the majority of the task group members rated the study design as I for TMS at M1 or left DLPFC, level of certainty in evidence as High for mild PTBI-HA. The task group also rated USPSTF recommendation as A and CDC recommendation as IA for the clinical implementation of the rTMS at either M1 or left DLPFC for mild PTBI-HA with the latter being considered as alternate treatment location for patients with PTBI-HA and comorbid severe depression.

Target	Hz	Number of pulse per session	Protocol	Total Number of treatments
L DLPFC	10HZ	3000	4 second train at 120% RMT, 26 second ITI, 75 trains per session, 5 sessions per week	30-36

Figure 1. Conventional TMS treatment for major depressive disorder. LDLPFC, left dorsolateral prefrontal cortex; RMT, resting motor threshold; ITI, inter-train interval. [Color figure can be viewed at wileyonlinelibrary.com]

Recommended Treatment Protocols

For PTBI-HA without comorbid severe depression, the task group recommends rTMS at either left MC or left DLPFC starting with 5 induction sessions (at >24 and < 72 hours intervals) at 10–20 Hz, 2000–3000 pulses per session and an intensity of stimulation corresponding to 80–90% of the resting motor threshold (RMT). Is there a maintenance treatment plan for those without comorbid depression? For patients with PTBI-HA and comorbid severe depression, the task group recommends at least 10 treatments as induction sessions (at >24 and < 72 h intervals) at 10–20 Hz, 2000–3000 pulses per session and an intensity of stimulation corresponding to 80–90% of the resting motor threshold (RMT) at the left DLPFC. This is then followed by biweekly to monthly maintenance treatment sessions with similar settings based on the duration of the treatment benefits.

COMORBID DEPRESSION

The pain/comorbid task group consisted of experts specialized in psychiatry and neurology, who are experienced in treating depression and/or pain with TMS (Table 14, Fig. 1).

TMS for Pain and Comorbid Depression

It is well known that patients with chronic pain conditions often suffer from comorbid depression. If a clinician attempts to treat one condition, while ignoring the other, interventions are often unsuccessful in alleviating the patient's symptoms. In fact, the conditions occur so often together that authors have created the terms "depression-pain syndrome" or "depression-pain dyad" (95). One study of 300 patients referred to a pain center noted 261 (87%) of the patients met criteria for major depressive disorder (MDD). Another study of 196 private patients with MDD noted that 116 (59%) of them had benign recurring pain (96). It has also been shown that patients with multiple pain conditions are 3 to 5 times more likely to be depressed (97).

As well as being clinically related, there are significant neurobiological correlates between chronic pain and major depressive disorder. There are well described similar disturbances in biogenic amines and serotonergic systems. Substance P has been shown to be elevated in the cerebrospinal fluid in both chronic pain and depression (98).The anterior cingulate cortex has been shown to be overactive and negatively correlated to both states. Further, dysregulation in other areas of the limbic system have been implicated in both conditions (99).

Emotional state has also been shown to have a strong influence in the processing of pain. A negative emotional state increases the subjective experience of pain; whereas, a positive emotional state decreases the perception of pain(100). Therefore, it would stand to reason that when trying to treat chronic pain, it would be of benefit to also improve mood. TMS has been proven to be effective and approved by the FDA for treating MDD (101). As the task group explores the benefits of TMS in chronic pain conditions, it is logical to ask about the literature and its quality related to the treatment of chronic pain with noninvasive brain stimulation in the setting of comorbid depression.

The task group reviewed the available literature and found that the available data from well-controlled trials addressing this precise question are scarce. A PubMed search using keywords, "TMS AND depression AND pain" yielded 71 articles and "transcranial magnetic stimulation AND depression AND pain" yielded 165 articles. While there were many well-controlled studies directly studying pain, only a handful directly studied depression as well.

While treatment locations vary for chronic pain, the most common and robust pain target seems to be M1. On the other hand, the conventional and FDA-approved treatment for depression is over the left DLPFC. Thus, the first question the task group asked is if there is evidence of benefit in depression from treatment over M1. The survey did not find conclusive evidence that treatment over M1 alone in chronic pain helps with depression (Table 14).

The next question is whether treating depressive symptoms over the DLPFC can also help in chronic pain states. In fact, a conventional TMS for depression study with DLPFC as the treatment target noted additional improvement in the subjective experience of pain (102). Similarly, in some of the pain studies that used the DLPFC as the target for pain, there was noted improvement in depressive symptoms along with headache pain (73).

Further, the task group did note that many of the pain studies were able to show improvement in affective sub-scores of quality of life measures (90) but did not necessarily show significant improvement in depression (Table 14). However, due to the fact that most of these studies were of shorter duration than the conventional TMS treatment for depression, which ranges from 30 to 36 treatments, no definitive conclusion can be reached. This begs the question if had the treatment continued would there be a more robust effect on depression.

The results of the survey do point to TMS as being a useful tool when chronic pain is comorbid with depression as there is a clear connection clinically and neurobiologically; and TMS does appear to be effective in both states independently. However, if depression is a predominant symptom in a patient with chronic pain, it seems imperative to treat at least in part over the DLPFC and potentially for a more prolonged course to achieve maximal

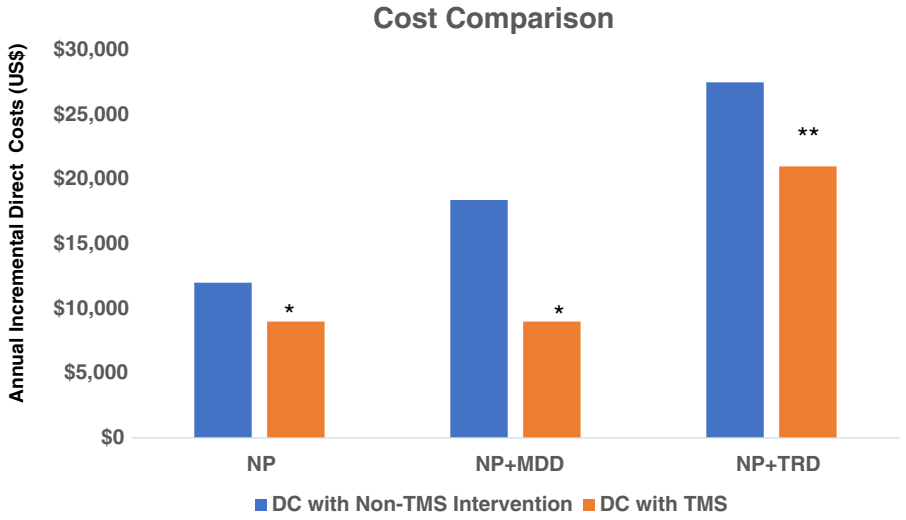

Figure 2. Annual incremental cost comparison for TMS for neuropathic pain (NP) alone, with comorbid major depressive disorder (MDD) or treatment-resistant depression (TRD); *30 sessions; **70 sessions 3. [Color figure can be viewed at wileyonlinelibrary.com]

benefit. Although there is a clear promise for the use of TMS when these two conditions are comorbid, in order to determine the best protocol for this clinical scenario, more well-controlled studies with varied treatment locations and a more prolonged course are required.

COST-EFFECTIVENESS OF TMS IN MANAGING PAIN AND COMORBID CONDITIONS

Chronic non-malignant pain affects close to 20–30% of the population and is a major socioeconomic burden worldwide(103,104) (Fig. 2). Approximately 10% of the population are specifically affected by chronic NP (17,105). In the United States, the Institute of Medicine estimates the cost of direct care expenditure and loss of productivity due to pain to be US$560–$635 billion annually. Aside from loss of work productivity, the United States spends US$17.8 billion on prescribed analgesics with US$1.9, US$3.6, and US$12.3 billions spent annually on non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant medications, respectively (106). For NP, the average annualized direct medical costs to payers, direct, and indirect costs per patient were US$6016 (95% CI 5316–6716), US$2219 (95% CI 1919–2519), and US$19,000 (95% CI 17,197–20,802), respectively, with significant differences across pain severity levels and conditions (107,108). Overall the direct cost of prescribed non-opioid analgesics for posttraumatic NP is about US$12,000 per year per patient and the cost is more than doubled if indirect cost is included (109). Despite the staggering cost of drug therapy, the results with drug therapy are suboptimal. Only 30–40% of patients with NP achieve a 50% reduction in pain with current available pharmacological agents such as tricyclics, gabapentin, and pregabalin (110). In addition, analgesic dosing is commonly limited by unwanted and burdensome side effects such as drowsiness, motor impairment, cognitive dysfunction, and substance use disorders which further increases healthcare costs (76,110–112). In patients abusing opioids, the cost of pain management is eight times higher than in nonabusers (113).

Table 15. Likely Characteristics of Non Neuronavigation-Guided vs Neuronavigation-Guided TMS for Chronic Pain.

Parameter	Nonneuronavigated TMS	Neuronavigated TMS
Initial costs	Lower	Higher
Long-term costs	Likely higher	Likely lower
Time efficiency	Higher initially, possibly lower long term	Lower initially, possibly higher long term
Location accuracy/ treatment reliability	Lower	Higher
Treatment reproducibility	Lower	Higher

Detailed cost-effectiveness analyses of rTMS in treating various pain and headache conditions have yet to be reported. However, a preliminary cost analysis of TMS for pain can be conducted incorporating costs associated with treatment such as: room utilization, TMS equipment, supplies, technician, neurologist coverage for each session and/or consultation, and administrative fees. Assuming 20–30 treatments (induction and maintenance) per year at a cost of US$300 (based on feedback from Clinical TMS Society) per session, the total indirect and direct costs for rTMS in treating pain would range from US$6000–9000 per year. For severe treatment resistant depression this has been modeled at 70 treatments per year (acute and maintenance rTMS) with a 1-year horizon cost of US$21,000 and a cost of US$105,000 over a 5-year horizon (114). In the United States, most insurance companies will not approve maintenance treatments for major depression but most insurance companies will cover 2 courses of TMS a year for patients who relapse, which are typically courses of 36 treatments. Patients with pain and major depression could have TMS treatment for both conditions at no added cost except those related to the additional time of administration (Fig. 2).

The overall economic burden of MDD in the United States is estimated to be greater than US$200 billions, and the annual incremental direct medical cost for a patient with MDD is

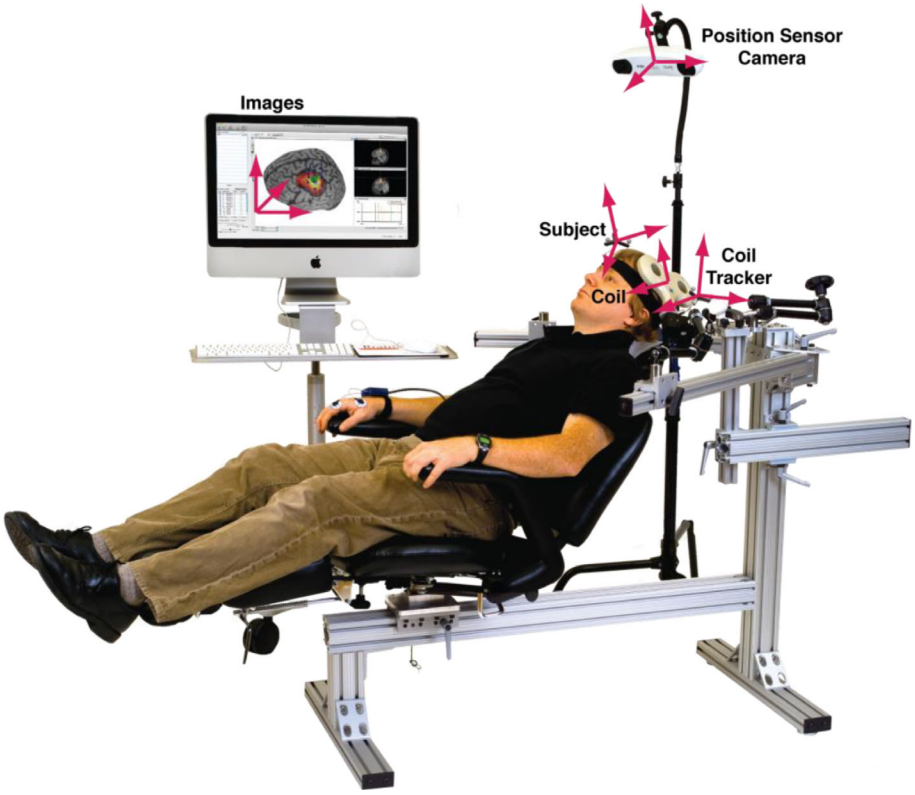

Figure 3. Set-up for neuronavigation guided transcranial magnetic stimulation. [Color figure can be viewed at wileyonlinelibrary.com]

US$6,400 (115). For patients who have failed to gain remission from two or more antidepressant medications, and meeting the criteria for treatment resistant depression (TRD), the annual incremental direct costs range from US$12,000 to US$19,000 (116). Thus, the direct annualized costs for neuropathic pain patients with MDD would be US$18,400 while for those with TRD and neuropathic pain it would range from US$24,000 to US$31,000 (average estimate of US$27,500) (Fig. 2). A 5-year treatment period would predict costs of US$120,000 to US$155,000. Treating both conditions with TMS in one setting vs treating each condition with pharmacological agents in separate settings would reduce costs over 5 years by US$15,000 to US$50,000. Treating patients currently using opioids would further reduce costs. This latter cost structure should reflect the costs of treating those with comorbid pain and depression, given that pain/headache and depression share a greater than 50% comorbid rate (117).

Previous cost benefit analysis in the setting of depression suggests that the incremental cost of TMS therapy for pain would be lower than the societal willingness-to-pay threshold (118). Compared with sham treatment, TMS at a cost of US$300 per treatment session provides an incremental cost effectiveness ratio (ICER) of US$34,999 per quality of annual live year (QALY). This cost benefit ratio is less than the "willingness-to-pay" standard of US$50,000 per QALY for a new treatment for both major depression and pain. When productivity gains due to clinical recovery were included, the ICER was reduced to US$6667 per QALY (118,119). In open-label conditions, TMS provided a net cost saving of US$1123 per QALY when compared with the current standard of care. In the open-label condition, cost savings increased further when the costs for productivity losses were included in the model with net savings of US$7,621 (119). Additional cost-effectiveness analyses supported the use of rTMS over medications and other invasive therapies (120,121). Given that the annual total number of TMS sessions are similar for treating either condition in this model and the treatment can be applied to treat both comorbid conditions in one setting, the cost-effectiveness of TMS in managing chronic pain will likely be compatible with findings of depression or conceivably even less when both conditions are being addressed simultaneously with the treatment although more definitive analyses are required.

TECHNICAL ISSUES

The technical issues task group consisted of a group of five multinational TMS experts from both clinical and research fields (Table 15, Fig. 3).

TMS Systems

There are a number of manufacturers of TMS equipment, including Magstim Inc. (Minnesota), MagVenture (Georgia), Neurosoft (Ivanovo, Russia), Mag & More (Munich, Germany), BrainsWay (Jerusalem, Israel), and Neuronetics (Pennsylvania). For a specific application, each system offers a number of distinct advantages and disadvantages. Efficacy of treatment for a specific application or disorder might be seen as the most important criteria. However, details of treatment design, patient population tested, and other factors can make direct comparison of relative efficacy between devices difficult to perform in practice. Other more easily documented factors include the speed, intensity and duration of magnetic stimulation that can be produced, and for how long.

The tendency for coils to heat during use requires either an efficient method of cooling, or down time between treatments for return to operating temperature limits, the latter limiting its efficient use. Another factor includes the ease of device use, which involves details such as the size and portability of the coils and device itself, as well as the simplicity and customizability of the user interface. Acquisition and maintenance costs to provider and treatment cost to the patient (including potential additional per-treatment charges from the vendor), patient comfort during treatment, and the quality of customer service are all important factors to consider.

Neuronavigation- vs Non-Neuronavigation-Based TMS

The fundamental task in TMS is to select and place the coil correctly over the intended cortical target for stimulation. The principles of stereotactic surgery have been incorporated into neuronavigation systems, which facilitate that task, and can be thought of as a global positioning system (GPS) for the brain (122). The map in a neuronavigator is an anatomical magnetic resonance imaging (MRI) of the subject's head and brain. A position sensor system is used to track the location of the subject's head and the TMS coil and map those locations to the homologous locations once the patients' anatomical landmarks are co-registered with the corresponding brain imaging landmarks known as fiducial points. This method allows the operator to optimally place the coil over the intended cortical target(s) with precision and vigor. On the other hand, without a neuronavigation system, coil placement is solely determined by skull landmarks, often similar to those used to place EEG electrodes or locating a functional brain region such as motor cortex then moving across at predefined paths and distances to the presumed regions of interest. However, individual variability of head size and shape limit the anatomic precision of these methods. In addition, this approach is often very time consuming and provides no live treatment location verification during the delivery of the treatment. Another non-neuronavigation guided localization method is to draw coil positions on a cap carefully positioned relative to scalp landmarks. Lycra swimming caps have traditionally been used. These caps fit tightly and are secure, but some patients find them uncomfortable so that typically manufacturers provide looser fitting cotton caps for clinical applications. The stability of these caps is enhanced with a strap under the chin, but unless they fit snuggly at the stimulation location, there is potential for movement leading to errors in targeting.

Neuronavigation Systems

Currently available neuronavigation systems include but are not limited to the ANT Visor2™ (ANT Neuro; Belgium), Neuronavigator (Brain Innovation, the Netherlands), IVS Software Engineering VoXim™ system (IVS Solutions, Germany), Localite TMS Navigator (Localite, Germany), Nexstim SmartFocus™ TMS (Nexstim, Finland), Brainsight (Rogue Research, Canada), Soterix Medical Neuronavigation (Soterix Medical) or Syneika One (Syneika, France). These systems differ in terms of the precise method of spatial navigation and 3D brain reconstruction. In addition to the navigation approach, a robotic system, such as the ANT Smartmove or Axilum Robotics TMS-Robot and TMS-Cobot (Axilum Robotics, France), can be employed to automatically position the TMS coil with some form of feedback of head movement, as opposed to manual positioning.

The technologies employed to track the position of the patient's head during TMS include infra-red light, electromagnetic field, and ultrasound wave. During infrared navigation, light reflectors are secured to the patient's head and the TMS coil. Cameras are used to discern the position of the head in real time using image processing and geometric calculation. These systems have short latency and high precision but require a clear "line of sight" from the light sources to the reflectors and the tracking cameras. Electromagnetic systems utilize a spatially varying magnetic field to locate the position and movements of coils, which are secured to the patient's head. This technology also has high precision and does not require a clear line of sight between the patient's head and the field generator. Ultrasound systems measure either the "time of flight" or phase coherence of sound waves traveling from the emitters to the receiver to localize the head and coil positions in 3 dimensions. These systems are not affected by electromagnetic interference but generally have lower accuracy than the other technologies (123).

Recommendation for TMS Neuronavigation

Neuronavigation increases precision of focal stimulation. Establishing the stimulation intensity relies on the determination of the RMT, which has been classically defined as the amount of TMS machine output (intensity) necessary to produce a motor evoked potential that exceeds a defined peak-to-peak amplitude (usually 50 μV) 50% of the time in a finite number of trials. Given that the motor cortex is somatotopically organized, identifying the precise motor cortical location for the RMT determination and subsequent treatments is most reliable using neuronavigation with electromyography (124). Focal motor stimulation and motor hot spot targeting are also more robust with the accuracy of image guidance (125,126). Neuronavigation also helps maintain the appropriate location and orientation of the coil during a session and between sessions (127).

The need for this precision in clinical applications must be balanced against whether the use is feasible in any particular setting, and whether the application shows evidence that failure to use neuronavigation would lead to inadequate outcomes. Settings without access to an MRI could use a template brain that is adapted to individuals (128); however, without a dedicated, trained staff, the technique is unfeasible. In the case of rTMS for chronic pain, the brain target with the most evidence for effectiveness is M1 contralateral to the side of pain (14,129,130). There is evidence that a clinic could ameliorate chronic pain in their patients by targeting M1 without neuronavigation (131). What is not clear is whether leveraging the somatotopic organization of M1 could enhance pain relief. One study demonstrated greater efficacy when stimulation is applied to the motor cortex region representing an area adjacent to the area in pain (132). Specifically, patients with unilateral chronic neuropathic hand pain showed significantly greater pain relief during stimulation of the motor cortex region representing face than for hand. However, again, these regions can be localized without neuronavigation using the muscle response to stimulation (motor evoked potential recording). Diffuse pain syndromes have also benefitted from TMS hence leveraging somatotopy may not be essential (89,90,92). Any benefit of targeting based on somatotopy may also vary depending on the site of pain, for example while modulating motor cortex regions represented medially such as lower limbs or back, for which localization may be more challenging without neuronavigation (133).

Clinical research data suggest that the significant advantage of TMS treatment delivered with brain MRI-based neuronavigation is in improved clinical outcome. In depression, erroneously targeting the premotor cortex instead of the left DLPFC led to treatment failures (134,135). Similarly, inaccurate M1 targeting can lead to higher machine output and erroneous stimulation of the somatosensory and/or adjacent parietal cortices. In contrast, one study demonstrated larger cognitive benefits of rTMS trials (as measured by performance on a spatial processing task) are associated with targeting accuracy, such that there were reductions in the number of subjects needed to reach a significant level of efficacy using image-guidance based on functional MRI as compared to a less accurate, EEG-based method (136). Further, TMS delivery to unintended cortical regions can result in exacerbation of pain rather than pain reduction, especially if the TMS mode being used is not suited for the unintended target (e.g., an excitatory protocol being delivered to the somatosensory cortex causing increased pain) (137).

There is evidence that stimulating DLPFC relieves pain as well as depression (94,138,139). In contrast to motor targets, the most effective DLPFC targets in depression are less well established in part because there is not an analog to the motor hot spot for nonmotor targets (other than the occipital phosphenes) in which stimulation has a clear behavioral response signifying accuracy. Identifying the optimal location within DLPFC, a large, heterogeneous brain region, is a topic of debate but several traditional approaches that locate this target using scalp landmarks completely miss this region (134,135). One of the methods used to localize the left DLPFC for TMS in pain treatment involves marking the target at the left DLPFC in a normalized brain based on the Talairach coordinates established from previous pain related functional imaging studies then reversing it back to its native state (73). While using more scalp landmarks, for example, (140–142) could potentially improves the outcome, clinical research using imaging techniques such as functional connectivity may someday lead to superior outcomes (143–145).

If, in contrast, TMS is used to predict response to invasive stimulation or guide neurosurgical procedures, for example (146), high precision in targeting is needed and therefore having neuronavigation-based target is essential for TMS to be useful. For example, TMS in the treatment of pain grew out of the early studies of surgically implanted motor cortex stimulation (MCS) (147). Since not all patients benefit from MCS (148,149), motor cortex TMS has been used to predict which patients will benefit from MCS prior to surgery such that patients who respond to rTMS have a better outcome (150–152) while those who fail to respond have poor outcomes to surgical implanted motor cortex stimulation(153). More refined trials of rTMS benefiting from neuronavigation targeting should improve its predictive value.

Time and Cost of Neuronavigation

While formal studies evaluating the time and cost considerations of TMS with and without the use of neuronavigation are lacking, some data are available from common observations. A typical TMS session without the use of neuronavigation, which requires the reestablishment of the proper target each time, takes approximately 45 min to complete. Despite the additional steps required for neuronavigation (e.g., placing the tracker on the patient, marking the fiducials, removing the tracker, etc.), because of the time savings afforded by being able to quickly navigate to the proper treatment site, a typical session of neuronavigated TMS takes approximately 20 min. Assuming a typical number of 20 to 30 treatment sessions per year and a 25 min per session time savings, we can estimate that 500 to 750 min per year can potentially be saved for both patients and providers with the use of neuronavigation. While the use of neuronavigation does require a baseline brain MRI, one can see that the time savings of using it will likely overshadow this initial cost fairly quickly. In addition, a baseline brain MRI offers the added benefit of ruling out underlying pathology, which would provide significant clinical and/or medico-legal liability advantages. Again, while these relevant factors have not been formally studied, they collectively should be considered when designing a TMS program. Future formal studies on these topics would help better characterize the time and cost variables surrounding neuronavigation.

Patient Positioning and Safety

Whereas issues of patient safety and comfort are extensively described elsewhere (7,154,155), positioning and comfort are briefly surveyed here. Pain at the point of stimulation and neck pain related to immobilization are common during TMS therapy, particularly when stimulating the frontal lobe and at the beginning of treatment (156). This pain decreases over time (157–159). Reducing the stimulator intensity in the early sessions and slowly increasing over days as stimulation is better tolerated is an effective strategy, which allows for monitoring of stimulation dosage and extending the length of treatment to compensate. This approach is preferred to the uncontrolled technique of placing layers of paper between the stimulator and scalp and removing them as the patient tolerates. A small study showed that localized, injected, anesthetic agents could also decrease stimulation-related pain intensity (160) but this approach is rarely used since adjusting intensity generally works well. Maintaining close contact between the TMS coil and a fixed location on the scalp is essential for effective treatment. Keeping the alignment between the TMS coil and head requires taking the time needed to position the patient comfortably in the chair so they can remain still. Comfortable positioning depends in part on the type of chair, device shape, and the brain location targeted and is described in more detail elsewhere (154). It is important to provide cushions and support for the head and arms and enhancing comfort.

As novel brain targets are discovered, it is important to remain vigilant for local specific discomfort issues. For example, the facial twitching associated with frontal stimulation is well known; however, less frequently discussed is the nausea associated with cerebellar stimulation (161). The loud clicking noise occurring throughout the TMS treatment is another discomfort that has been measured in several stimulators and compared to hearing safety guidelines (162). Without hearing protection such as ear plugs or muffs, the Occupational Safety and Health Administration (OSHA) restricts exposure to impulsive noise that is >140 dB. Prolonged periods (15 min) of intensities from 115 to 140 dB, and longer periods (8 hours) of noise between 90 and 115 dB is considered risky. When exceeding these levels, OSHA recommends hearing protection (163), but these levels are not reached in most cases of rTMS therapy for pain, either for operators or patients. Finally, as with all treatments that involve patients lying supine or in a reclining position, older adults and other populations vulnerable to dizziness should sit briefly to reduce the risk of dizziness and syncope upon standing.

Future Advancements and Directions of TMS for Pain

Future developments in this field may lead to the validation of new and more effective stimulation paradigms inducing long

lasting benefit. These new developments may include new coils for the stimulation of new cortical and subcortical targets, the use of devices allowing for better standardization and reproducibility of the stimulation in repeated sessions, and the identification and validation of predictors of response to treatment.

Some promising new stimulation paradigms include theta-burst stimulation (TBS) consisting of short bursts of 50 Hz rTMS repeated at a rate in the theta range (5 Hz, 500 ms), as a continuous (cTBS), or intermittent (iTBS) trains. The main potential advantage of these paradigms is related to their larger effects on synaptic plasticity involving long-term potentiation or depressive effects on cortical synapses, occurring much faster than with traditional rTMS protocols. Although data obtained in healthy volunteers suggest that TBS may induce larger analgesic effects than conventional rTMS (164–166), this approach has not been used with success in pain patients, except as a priming procedure (167). Thus, this priming effect should be further assessed in conjunction with other known clinically efficacious protocol for managing various pain or headache conditions.

To date, most of the studies related to rTMS-induced analgesia have targeted the M1 at high frequency of stimulation, but other potential cortical or subcortical targets could emerge in the future. High-frequency stimulation of the left DLPFC has been reported as efficacious in some studies (47), but other deeper structures have also been targeted. In particular, recent results have suggested that stimulation of the operculo-insular region, which plays an established role in the perception and modulation of pain, may induce analgesic effects in an experimental pain model (164). However, the safety of this target for therapeutic application deserves investigation (168). Another potential new target is the anterior cingulate cortex (ACC) (169), which also plays a major role in pain perception. Specific coils have been used in these studies, such as the butterfly double-cone coil for the insula (170) or a multicoil rTMS array for the ACC (169). Deeper brain structures can also be targeted with H-coils, which induce much larger and deeper stimulation than the classical figure-of-eight coil (171). Promising results, which have yet to be confirmed in future large-scale studies, have been reported in patients with chronic neuropathic pain (172,173). Conversely, a recent study showed negative results (no difference between active and sham conditions) in a large series of patients with central NP using high-frequency rTMS targeting the insula with a double-cone coil or to the ACC with an H-coil (174).

One objective of ongoing research studies in this field is to personalize TMS therapy. Some data suggest that changes in intracortical excitability and modulation could be predictive of long-term response to treatment (89). Other approaches for the selection of responders could be based on the identification of specific changes in brain activity, measured by EEG or fMRI before rTMS (175).

More accurate and reproducible positioning of the coil, most notably during repeated sessions over several weeks or months, should be easier with the use of robotized, image-guided rTMS. The robot coupled to a neuronavigation system can adjust the position and orientation of the coil to the predefined target when patients move their head during the stimulation sessions in real time (176,177).

One limitation of previous clinical trials is their lack of full double blinding because one of the investigators had to place the active or sham coil. The development of new active and sham coils associated with a specific software using predetermined and randomized patient and operator codes now allows for true double blinding in rTMS trials.

Another limitation of the use of rTMS in chronic pain patients is related to the necessity to administer the treatment in a specialized center. The development of at home rTMS systems could allow a large increase in the number of treated patients (178), once research has clearly identified and validated the appropriate treatment targets and stimulation protocols for a given pain state.

Aside from medical-legal concern in clinical implementation, it is imperative that future TMS investigation for pain and headache should involve neuronavigation guidance to completely eliminate the various investigational issues related to inconsistent targeting, thus optimizing the certainty of the study outcome. In addition, correlated functional imaging studies such as supraspinal pain network resting state functional connectivity assessment should be conducted when feasible to study the underlying neuronal mechanisms supporting the clinical hypotheses.

Authorship Statement

Drs. Leung, Kopell, Poree, Wassermann, and Levy are members of the steering committee who: 1) Designed the panel review process and provided support, recommendations and guidelines to the group leaders; 2) Provided feedback to the group leaders; 3) Established timeline and milestone for the task group leaders; 4) Provided critique for the groups' review results and recommendations; 5) Provide editorial support for the task groups; and 6) Participated in manuscript preparation. Drs. Leung, Saitoh, Lefaucheur, Khedr, Ciampi de Andrade, Shirvalkar, Dr. Schuster, Salmasi, Adamson, Ettenhofer, Liu, Sargent, Chen, Chai, Goadsby, Kuluva, Ault, Bermudes, Cochran, Scangos, Vaninetti, Bouhassira, Clark, Comeau, and Rosen are either task group leaders or members who: 1) Conducted Literature Review; 2) Rated the Level of Evidence; 3) Provided Recommendations and Guidelines; and 4) Participated in the final manuscript preparation.

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APPENDIX

TASK GROUPS

NEUROPATHIC PAIN TASK GROUP

Albert Leung, M.D. (Leader)
Professor of Anesthesiology and Pain Medicine, Department of Anesthesiology, Center for Pain Medicine, UCSD School of Medicine; Director, Center for Pain and Headache Research, VASDHS, USA.

Youichi Saitoh, M.D., Ph.D.
Professor, Department of Neuromodulation and Neurosurgery, Center of Medical Innovation and Translational Research, Osaka University Graduate School of Medicine, Japan.

Jean-Pascal Lefaucheur, M.D.
Professor, Unit of Clinical Neurophysiology, EA 4391, Henri Mondor Hospital, Assistance Publique—Hôpitaux de Paris, Créteil, France.

Eman Khedr
Professor, Neurology Department, Assiut University Hospital Assiut, Egypt.

Daniel Ciampi de Andrade, M.D
Professor, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Instituto do Câncer do Estado de São Paulo, Brazil.

ACUTE PAIN TASK GROUP

Prasad Shirvalkar MD, PhD (Leader)
Assistant Professor, Department of Anesthesiology (Pain Management), Department of Neurology, Department of Neurosurgery, UCSF School of Medicine, USA.

Nathaniel M. Schuster, MD
Assistant Professor, Center for Pain Medicine, Department of Anesthesiology, UC San Diego, USA.

Vafi Salmasi, MD.
Instructor, Stanford University School of Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Division of Pain Medicine, USA.

POST TRAUMATIC BRAIN INJURY HEADACHE TASK GROUP

Albert Leung, M.D. (Leader)
Professor of Anesthesiology and Pain Medicine, Department of Anesthesiology, Center for Pain Medicine, UCSD School of Medicine; Director, Center for Pain and Headache Research, VASDHS, USA.

Maheen Mausoof Adamson, Ph.D.
Senior Scientific Research Director, Defense and Veterans Brain Injury Center (DVBIC) VA, Palo Alto Health Care System, Director for Research, Headache Center for Excellence, Polytrauma, VA Palo Alto Health, Care System, Clinical Associate Professor Neurosurgery, Stanford School of Medicine, USA.

Mark L. Ettenhofer, Ph.D.
Research Scientist, Defense and Veterans Brain Injury Center, Naval Medical Center, San Diego, University of California, San Diego, and VA San Diego Healthcare System, USA.

Jie Liu, M.D
Staff Neurologist, TBI Clinic, Camp Pendleton, USA.

Paul Sargent, M.D.
Commander of U.S. Navy, Site Director, Defense and Veterans Brain Injury Center (DVBIC), Camp Pendleton Medical Center, USA.

PRIMARY HEADACHE DISORDERS TASK GROUP

Robert Chen, MA, MBBChir, MSc, FRCPC (Leader)
Catherine Manson Chair in Movement Disorders, Professor of Medicine (Neurology), University of Toronto, Toronto, Ontario, Canada.

Nu Cindy Chai, M.D.
Assistant Professor, Department of Anesthesiology (Pain Management), Department of Neurology, UC San Francisco, School of Medicine, San Francisco, CA, USA.

Peter J. Goadsby, M.D., Ph.D., D.Sc.
Professor of Neurology, UC San Francisco, School of Medicine, San Francisco, CA, USA.

Nathaniel M. Schuster, MD
Assistant Clinical Professor, Center for Pain Medicine, Department of Anesthesiology, UCSD School of Medicine, La Jolla, CA, USA

COMORBID DEPRESSION TASK GROUP

Joshua Kuluva, MD (Leader)
Neurologist and Psychiatrist, TMS Health Solution, San Francisco, CA, USA.

Jennifer Ault, D.O.
Neurologist/Pain Management, Sutter Health, Berkeley, CA, USA.

Richard A. Bermudes, M.D.
Chief Medical Officer, TMS Health Solutions, Assistant Clinical Professor- Volunteer, Department of Psychiatry, University of California, San Francisco, CA, USA

Michelle Cochran, M.D.
Past President of Clinical TMS Society, Psychiatrist, Nashville, TN, USA.

Katherine Scangos, M.D.
Interventional Psychiatry Fellow, UC San Francisco, School of Medicine, San Francisco, CA, USA

TECHNICAL ISSUE TASK GROUP

Michael Vaninetti, M.D. (Leader)
Assistant Clinical Professor, Anesthesiology and Pain Medicine, UCSD School of Medicine, La Jolla, CA, USA.

Didier Bouhassira, M.D., Ph.D.
Director of Research, Inserm U-987, CHU Ambroise Paré, APHP, Université Paris-Saclay, Boulogne-Billancourt, France

Vincent Clark, Ph.D.
Professor of Translational Neuroscience, Mind Research Network, Director, Psychology Clinical Neuroscience Center and Professor of Psychology and Neuroscience, University of New Mexico, Albuquerque, NM, USA.

Roch Comeau, Ph.D.
President, Rogue Research Inc., Montreal, Quebec, Canada.

Allyson Rosen, Ph.D.
Clinical Associate Professor (Affiliated), Stanford University School of Medicine, Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA, USA

COST-EFFECTIVENESS TASK GROUP

Richard A. Bermudes, M.D. (Leader)
Chief Medical Officer, TMS Health Solutions, Assistant Clinical Professor- Volunteer, Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA.

Joshua Kuluva, M.D.
Neurologist and Psychiatrist, TMS Health Solution, San Francisco, CA, USA.

Albert Leung, M.D.
Professor of Anesthesiology and Pain Medicine, Department of Anesthesiology, Center for Pain Medicine, UCSD School of Medicine; Director, Center for Pain and Headache Research, VASDHS, USA.

COMMENTS

This review work has summarized current status of the role of transcranial magnetic stimulation (TMS) for pain and headache, including neuropathic pain and post-traumatic brain injury related headache, which are sometimes difficult to manage. The authors are experts in this field of therapeutic use of TMS, and have provided recommendations for TMS. This paper could be one of the useful treatment guidelines in order to manage neuropathic pain and headaches using TMS. In addition, cost-effectiveness of such TMS treatments is also discussed for the long-term clinical implementation of the TMS treatments.

Masahito Kobayashi, MD, PhD
Saitama, Japan

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Non-invasive neuromodulation, especially TMS, has been applied in many aspects, however, the lack of well recognized guideline/recommendation slowed down the progression of TMS. Pain is common and complex, which means "multi-" strategy should be applied, Multidisciplinary and Multi-treatment, drugs, rehabilitation and neuromodulation. This consensus is not only the accumulation of literature review, but also the essence of clinical experiences from authors who are well-known experts in the field of pain.

Guoming Luan, MD, PhD
Beijing, China

