



# Transcranial magnetic stimulation of the brain: guidelines for pain treatment research

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## Abstract

Recognizing that electrically stimulating the motor cortex could relieve chronic pain sparked development of noninvasive technologies. In transcranial magnetic stimulation (TMS), electromagnetic coils held against the scalp influence underlying cortical firing. Multiday repetitive transcranial magnetic stimulation (rTMS) can induce long-lasting, potentially therapeutic brain plasticity. Nearby ferromagnetic or electronic implants are contraindications. Adverse effects are minimal, primarily headaches. Single provoked seizures are very rare. Transcranial magnetic stimulation devices are marketed for depression and migraine in the United States and for various indications elsewhere. Although multiple studies report that high-frequency rTMS of the motor cortex reduces neuropathic pain, their quality has been insufficient to support Food and Drug Administration application. Harvard's Radcliffe Institute therefore sponsored a workshop to solicit advice from experts in TMS, pain research, and clinical trials. They recommended that researchers standardize and document all TMS parameters and improve strategies for sham and double blinding. Subjects should have common well-characterized pain conditions amenable to motor cortex rTMS and studies should be adequately powered. They recommended standardized assessment tools (eg, NIH's PROMIS) plus validated condition-specific instruments and consensus-recommended metrics (eg, IMMPACT). Outcomes should include pain intensity and qualities, patient and clinician impression of change, and proportions achieving 30% and 50% pain relief. Secondary outcomes could include function, mood, sleep, and/or quality of life. Minimum required elements include sample sources, sizes, and demographics, recruitment methods, inclusion and exclusion criteria, baseline and posttreatment means and SD, adverse effects, safety concerns, discontinuations, and medication-usage records. Outcomes should be monitored for at least 3 months after initiation with prespecified statistical analyses. Multigroup collaborations or registry studies may be needed for pivotal trials.

**Keywords:** Neuropathic pain, Neuromodulation, Treatment, Human, Device

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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PAIN 156 (2015) 1601–1614

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<http://dx.doi.org/10.1097/j.pain.0000000000000210>

## 1. Transcranial magnetic stimulation: principles and applications

Transcranial magnetic stimulation (TMS) is being explored as a noninvasive alternative to invasive neurostimulation techniques (such as deep brain stimulation (DBS) and epidural cortical stimulation) for treating neurological disorders and exploring brain function. First demonstrated in 1985,<sup>13</sup> TMS uses electromagnetic induction to electrically influence nearby cells. Strong effects can depolarize neurons sufficiently to trigger action potentials. Low-intensity TMS seems to mostly stimulate low-threshold inhibitory interneurons, whereas higher intensities excite projection neurons.<sup>92</sup> Transcranial magnetic stimulation pulses can be applied singly, but for therapeutic use, multiple pulses are rapidly applied (repetitive transcranial magnetic stimulation [rTMS]).

### 1.1. Insights from studies of invasive brain stimulation for treating pain

Transcranial magnetic stimulation emerged from experience with invasive brain stimulation. Neurosurgical motor cortex stimulation (MCS) and DBS are proven effective for treating chronic pain (typically defined as more than 40% reduction of pain scores for at least 12 months after implantation). Epidural MCS involves surgically opening the skull to attach an electrode array to dura directly above the motor cortex. Subdural

electrodes, although still used, convey additional risk from breaching the dura.

A 2009 systematic review reported evidence from 14 studies that intracranial MCS is safe and effective for treating neuropathic pain (NP). Half of the patients reported at least 40% to 50% pain reduction with best outcomes for central poststroke pain and neuropathic facial pain.<sup>31</sup> A systematic review by the European Federation of Neurological Societies also found MCS efficacious for central poststroke and facial pain.<sup>21</sup> In a series of 100 consecutive patients, 80% with poststroke pain and 56% with pain from spinal cord injury (SCI) benefited.<sup>78</sup> In the 4 small randomized controlled trials (RCTs) of MCS for central and peripheral NP with at least 12-month follow-up, approximately 60% were responders.<sup>60,62,66,116</sup> Not surprisingly, a meta-analysis found that intracranial MCS is more effective than extracranial stimulation, therefore patients with partial pain relief after rTMS should consider implanted MCS,<sup>70</sup> especially because pain relief from high-frequency rTMS predicts success of later MCS.<sup>11,67</sup>

Deep brain stimulation is a more-invasive technique in which electrodes are implanted through the skull, dura, and brain to stimulate deep targets. Stimulation sites for treating pain include the periventricular and periaqueductal gray matter (PVG, PAG), internal capsule, and sensory thalamus. A meta-analysis indicated that long-term success is most common after DBS of the PVG or PAG (79%) or the PVG or PAG plus sensory thalamus or internal capsule (87%); stimulating the thalamus alone was less effective (58%).<sup>15</sup> Two controlled nonrandomized prospective studies,<sup>42,90</sup> multiple uncontrolled retrospective studies, and a recent large retrospective study<sup>101</sup> together indicate that more than 80% of patients with intractable low back pain (failed back surgery) and 58% of patients with poststroke pain achieved long-lasting relief, with even higher rates for phantom limb pain and polyneuropathies.<sup>15</sup>

Motor cortex stimulation and DBS should be more effective than rTMS because they directly contact target neurons and can be administered continually, but their use is limited in part by cost and complications, which include infections in 5% to 15% of cases<sup>31,109</sup> and technical failures (eg, electrode migration, fractures, skin erosion) in 1/4 of cases.<sup>31,87</sup> Deep brain stimulation, which conveys risk of brain hemorrhage, causes permanent harm in less than 1% of patients.<sup>105</sup> Minor side effects (eg, muscle contraction or tingling) are common and often ameliorated by changing stimulation parameters. Epidural hematomas are a rare concern, and other complications are minor and transient, including a seizure during programming trials in 12%, infections in 6%, and technical failures in 5%.<sup>31</sup> This combination of demonstrated efficacy but high cost and significant risk drove the development of noninvasive modalities such as rTMS.

### 1.2. Technical basis of transcranial magnetic stimulation

A summary of how TMS works follows: Capacitors in a pulse generator are rapidly charged and then discharged by a thyristor trigger switch to send brief currents through coils of conductive wire to produce brief rapidly changing magnetic fields. These induce local electric fields that cause current to flow in any conducting structures within a few centimeters according to Faraday's law (**Fig. 1A**). The characteristic click of discharging TMS coils is caused by Lorentz forces that mutually repel adjacent windings. Thus, TMS coils must be tightly encapsulated to hold together, which imposes limits on the design and use. Also, coils heat during prolonged repeated use, so they may need to be cooled or interchanged with a spare coil to prevent overheating. Other design considerations include focality and depth of

penetration. The most common figure-of-8 coils (2 adjacent circular coils with counter-rotatory currents [**Fig. 1**]) provide more focal stimulation than single-circle coils,<sup>49</sup> and newer configurations, such as the double cone or H coil reportedly deepen penetration.<sup>27</sup>

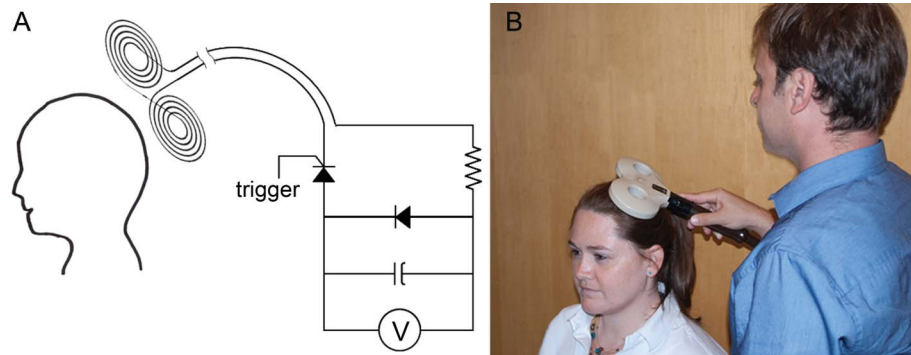
### 1.3. Using repetitive transcranial magnetic stimulation for medical therapy

The rationale for applying rTMS to treat neurological or psychiatric disorders is that it can change the brain to produce effects that last beyond the duration of stimulation. Such "plasticity" underlies normal brain functions such as learning, adaptation to changes, and recovery from brain injury. Different TMS application patterns have different effects. Generally, early changes involve altering synaptic strength, whereas longer exposures trigger longer-lasting anatomical changes such as sprouting and alterations of dendritic spines. By analogy to basic synaptic physiology, strengthening synaptic strength is often referred to as long-term potentiation and reducing synaptic strength is called long-term depression.

Depending on how it is applied, rTMS can induce either long-term potentiation or long-term depression,<sup>100</sup> because high-frequency rTMS (5 Hz or faster) increases excitability, whereas slow rTMS at approximately 1 Hz decreases it. The mechanism of increased excitability after rapid rTMS may involve weakened intracortical inhibition.<sup>53</sup> "Theta burst TMS" is delivery of 5-Hz trains of clusters of 3 TMS stimuli at 50-millisecond intervals. Long trains of theta burst TMS lead to depression, whereas periodic short trains increase excitability.<sup>48</sup> Quadripulse TMS involves delivering clusters of 4 pulses at different intervals. Short intervals of approximately 5 milliseconds in the cluster lead to facilitation, whereas longer intervals (eg, 50–100 milliseconds) cause depression.

Psychiatric applications of rTMS include obsessive compulsive disorder and suppressing hallucinations, but use for medication-resistant depression is currently most successful and approved for clinical marketing in multiple countries (see section 4.3; Regulatory considerations). A recent systematic review found level A evidence supporting this use.<sup>58</sup> The rationale comes from the success of electroconvulsive therapy and observations that depressed patients have hypometabolism of the left dorsolateral prefrontal cortex (DLPFC). This is ameliorated (along with the depression) by repeated rapid rTMS delivered to the left DLPFC, which affects a corticosubcortical network involved in mood regulation.<sup>33</sup>

At present in the United States, the only neurological indication approved by the Food and Drug Administration (FDA) for TMS is acute migraine with aura.<sup>33,71</sup> In Europe, other devices, eg, from Magstim, MagVenture, Nexstim, and Neuronix, have also obtained CE Mark and are applied clinically for multiple neurological disorders including pain, dementia, stroke recovery, epilepsy, and movement disorders. Parkinson's disease research followed a similar logic to depression, namely because motor cortex excitability is low, increasing it with rapid rTMS might improve movement, but so far, benefits have been too mild for clinical approval. Of note, motor cortex rTMS augments dopamine release in the striatum.<sup>111</sup> Although it is probably not its major mechanism, this illustrates that the mechanisms of TMS effects are still not fully understood. Because tinnitus involves overactivity of the auditory cortex, slow rTMS is used to suppress it,<sup>112</sup> but clinical utility is uncertain. Epilepsy is also treated with suppressive TMS. Improving recovery from stroke is complex and may require increasing and decreasing different types of cortical excitability.<sup>58</sup>



**Figure 1.** (A) Schematic of the electrical circuits that underlie transcranial magnetic stimulation (TMS): A capacitor or group of capacitors is charged by a high-voltage power supply (V). They are then discharged by a thyristor trigger switch to send a rapidly changing current through the coil, which produces a transient magnetic field locally. This penetrates through the scalp, skull, meninges, and cerebrospinal fluid to induce a current pulse that transiently changes the polarization across the cell membrane of underlying cells. Specific conditions can depolarize some neurons sufficiently to trigger an action potential that propagates along that neuron's pre-existing anatomical connections. (B) Depiction of TMS administration using a figure-of-8 coil to stimulate the primary (M1) motor cortex.

#### 1.4. Parameters of transcranial magnetic stimulation administration

Multiple technical parameters contribute to the effects of TMS, and those described in **Table 1** should be specified in publications. *Pulse intensity* influences safety and is usually tailored to individual subjects' threshold for inducing a motor response (muscle twitch). Regarding *pulse frequency*, 10 or 20 Hz have been most common in pain research. However, because prolonged high-frequency stimulation increases seizure risk (see section 1.5), rTMS is usually applied in "trains" of pulses interspersed with rest periods. *Train length* and *intertrain interval* thus also need to be specified. Most previous studies did not fully report these technical parameters, hindering reproducibility and meta-analysis. Improving *sham TMS*<sup>23</sup> is another technical priority. Double blinding researchers and subjects, as expected

for medication trials, is exceedingly difficult with devices. Parameters pertinent to blinding TMS subjects include: (1) the *auditory* click of coil discharge, (2) the *visual* stimulation including coil location and orientation, (3) the *touch* of the coil tapping, (4) the *sensation* associated with activating scalp muscles, and (5) *avoiding brain stimulation*. Hardly any previous studies addressed these fully. Future studies should consider reporting to what extent their sham meets each consideration. For instance, inert sham coils offer visual, tactile, and sometimes auditory stimuli, but the lack of electrical sensations unblinds experienced subjects. An active coil angled so that only 1 wing touches the scalp,<sup>51</sup> or nonconductive spacers between the coil and scalp, satisfy requirement (1) and partially satisfy requirements (2), (3), and (4). Adding electrodes for electrical stimulation can satisfy requirement (4).<sup>17,47</sup> Criterion (5) is better met by a spacer of appropriate thickness than by coil angling, which is also hard to standardize. Another strategy for sham is to stimulate the cortex expected to lack relevant effect, such as the vertex,<sup>23</sup> which controls for criteria 1 to 4. However, pain processing is highly distributed throughout the brain. A small study recently demonstrated a trend towards reduction of acute pain after rTMS application to the occipital cortex,<sup>104</sup> and this approach was considered unacceptable in a recent systematic review.<sup>58</sup> Blinding TMS administrators is even more difficult and currently best addressed by coils that can be remotely programmed to deliver sham or true pulses, for instance, by opposing current flow within the loops to cancel their magnetic fields<sup>46</sup> or with a commercially available sham-capable system such as a MagVenture MagPro.

**Table 1**  
**Minimum technical parameters to describe a transcranial magnetic stimulation study.**

Category	Parameters
Coil design	Shape Size
Coil placement	Coil orientation Stimulation site Method for locating stimulation site
Stimulation parameters	Pulse intensity (as % resting motor threshold) Pulse frequency Train length Train duration Number of trains Intertrain interval
Session parameters	Total pulses per session Total number of sessions Between session intervals (eg, weekday, every consecutive day) Maintenance session parameters
Sham conditions	Strategies for allocation concealment Extent of blinding of subjects and administrators Control of auditory, visual, tactile, electrical effects Were subjects asked to identify real vs sham? Were subjects asked to rate sensory and/or auditory and visual sensations?

#### 1.5. Safe administration of repetitive transcranial magnetic stimulation

As for most trials of potential therapies, benefit to research subjects is assumed to be nil, thus even relative risks acceptable for some medical uses will usually disqualify subjects for research study. Single-pulse TMS has no long-lasting effects but rTMS conveys a few risks that must be minimized by proper patient selection and technique. A 2009 international consensus meeting established safety precautions that are universally endorsed.<sup>103</sup> The most important potential adverse event (AE), heating, moving, or damaging ferromagnetic implants including electronic devices in or near the head, is managed by strictly excluding patients with such devices or ferromagnetic fragments. These restrictions are similar to those for magnetic resonance imaging

(MRI). Patients with pain should be queried specifically about previous neurosurgical procedures and the presence of neural stimulators or pumps.

For the majority of people without implants, the only known significant risk is inducing a single seizure during TMS. The risk is small, estimated at  $\leq 1/10,000$ <sup>103</sup> among all rTMS studies to date. Only 2 seizures have been reported among more than 30 published studies of rTMS for pain<sup>56,82,97</sup> in which safety recommendations were followed.<sup>103</sup> The total number of pulses, pulse intensity, and frequency must be carefully chosen, particularly for high-frequency (>10 Hz) rTMS. A single induced seizure does not increase the risk for epilepsy (recurrent seizures), and 1 seizure in a monitored medical setting is unlikely to cause serious harm, but all TMS facilities need explicit plans for providing rapid medical response in the event of an induced seizure. Because risk is higher in people with previous seizures or brain lesions, or with use of medications that reduce the seizure threshold (see section 4.2; Use of concomitant medications, therapies, and other environmental factors), these are considered relative contraindications to medical use of TMS (Table 2). The possibility of inducing cognitive changes is a valid concern that requires further study. The limited data so far show no cognitive changes after 3 months of motor cortex rTMS for treating pain.<sup>14</sup>

The most common AE of TMS is headache, reported in 1 study in up to 42% of participants having active rTMS and 33% having sham TMS.<sup>82</sup> These may be caused by pressing the coil against subjects' heads for extended periods or by the muscle contractions induced. Most are mild and respond to over-the-counter treatments. Other reported AEs include pain at the stimulation site, neck pain, muscle aches, dizziness, nausea, tiredness, and tinnitus.<sup>74</sup> Of note, meta-analysis reveals that AEs are no more common after real TMS than after sham TMS.<sup>82</sup> Lastly, as for MRI, patients should wear earplugs to minimize noise exposure from coil discharge and thus reduce the risk of transient threshold shifts or hearing loss.

## 2. What is already established about repetitive transcranial magnetic stimulation for treating pain?

Transcranial magnetic stimulation activates short intracortical interneurons and long axons connected with distant structures.<sup>60,62</sup> Passing axons—particularly those with bends—are more easily excited than cell bodies,<sup>79</sup> and therefore, rTMS has remote effects. Motor cortex rTMS oriented posteroanteriorly and parallel to the midsagittal plane preferentially activates horizontal cortical axons running parallel to the surface.<sup>11,65</sup> Early studies of dural MCS implicated antidromic activation of thalamocortical pathways,<sup>114</sup> and recent studies show that integrity of the

thalamocortical tracts is required to treat pain.<sup>88</sup> Imaging shows that MCS additionally affects structures involved in affective, cognitive, and emotional aspects of pain, such as the cingulate and orbitofrontal cortices,<sup>37</sup> perhaps by influencing opioidergic or gamma-aminobutyric acid transmission.<sup>73</sup>

For treatment, research has established that a figure-of-8 coil delivering biphasic pulses should be placed over the precentral gyrus (primary motor cortex) contralateral to the painful side with a posteroanterior orientation (Fig. 1B). High frequency (10 or 20 Hz) should be used to activate projecting axons and local interneurons.<sup>11</sup> It should be applied below the threshold for motor activation to avoid triggering muscle contractions. Proof-of-principle studies demonstrate that repeated rTMS sessions can produce cumulative pain reductions for at least several weeks after 10 consecutive weekday sessions,<sup>51</sup> but the optimal timing for long-term efficacy and safety are undefined. Many laboratories empirically use 10 consecutive weekday “induction” sessions followed by a “maintenance” phase comprising 3 sessions a week apart, 3 sessions a fortnight apart, then 3 sessions a month apart.<sup>77</sup> It is also largely unexplored whether rTMS should also be considered for acute pain, such as postoperative, and whether efficacy might be augmented by combining rTMS with medications or physical therapy.<sup>97</sup> Regarding where best to administer rTMS to relieve pain, it is still debated whether the cortical representation of the painful body region should be targeted, or the adjacent cortex in the precentral gyrus.<sup>64</sup> If precise targeting is important, it needs to be clarified whether or not image-guided navigation systems,<sup>5</sup> which are expensive and require that subjects obtain MRI, improve efficacy. There may also be other potential cortical targets such as the posterior insula, the right secondary somatosensory cortex (SII), or the DLPFC, although 1 study finds DLPFC stimulation ineffective for poststroke pain.<sup>25,107</sup>

Two 2014 systematic reviews synthesize the results of published rTMS studies for chronic pain. Both find rTMS efficacious, but the evidence for NP seems strongest. The Cochrane meta-analysis of all pain indications stated that “the pooled estimate approaches the threshold of minimal clinical significance.”<sup>82</sup> However, a consortium of European experts found level A evidence of “definite efficacy” of high-frequency rTMS of the primary motor cortex for NP.<sup>58</sup> Both reviews emphasize the need to improve the quality of future trials.

## 3. Which conditions are most suitable for studies of repetitive transcranial magnetic stimulation for treating pain?

Some pain syndromes are more appropriate for research than others. Repetitive transcranial magnetic stimulation has not

**Table 2**  
Contraindications to medical use of transcranial magnetic stimulation.

	Absolute contraindications	Very strong contraindications	Relative contraindications
Regarding ferromagnetic metal	Ferromagnetic metal in the head (eg, plates or pins, bullets, shrapnel)		Ferromagnetic metal in the neck or chest
Regarding microprocessors	Microprocessor implants in the head (eg, cochlear implants) or life-sustaining microprocessor implants anywhere in the body (eg, prosthetic cardiac valves)	Microprocessor implants in the neck (eg, vagus nerve stimulator)	Microprocessor implants below the neck (eg, spinal pumps, stimulators)
Regarding seizure risk		Epilepsy or previous induced seizures	Prior brain lesions, major head trauma, medications that lower seizure threshold, recent withdrawal from sedative medications that raise seizure risk (eg, alcohol, barbiturate)
Miscellaneous		Pregnancy	Hearing loss, tinnitus

usually been considered for treating acute or nociceptive/inflammatory pain, presumably because the standard of care is to resolve its underlying cause. However, not all causes can be cured, and there is evidence of efficacy of rTMS for chronic visceral pain including cancer<sup>110</sup> and even for transient syndromes such as postoperative pain<sup>16</sup> and aborting migraine headache with aura.<sup>71</sup> Neuropathic pain syndromes are reported to benefit most from rTMS of the motor cortex,<sup>58</sup> but some chronic pain syndromes labeled as “nonneuropathic”<sup>58</sup> include conditions such as CRPS I and fibromyalgia (FM) that have been associated with nerve injury.<sup>7,38,84–86</sup> Focal lesions with defined onset, for instance from shingles or trauma, have the advantage of known localization and time of onset, but early cases often improve spontaneously, which complicates the outcome; therefore, established cases, for instance of more than a year’s duration, are preferable.

### 3.1. Central pain from lesions of the brain or spinal cord

Neuropathic pain is common in multiple sclerosis (MS) affecting between 14% and 28% of patients.<sup>113</sup> A survey of more than 10,000 patients with MS reported some evidence of NP in 75%, rated by half as severe.<sup>41</sup> A long-term prospective study of 15,754 stroke patients identified central pain (CP) in 2.7%.<sup>83</sup> There are few trials of any treatments for CP, so guidelines come from studies of peripheral NP, despite uncertain relevance.<sup>12</sup> The highest quality study found that pregabalin is not superior to placebo for poststroke pain.<sup>52</sup> The only adequately powered drug trial with positive results for CP found pregabalin efficacious for SCI.<sup>108</sup> The only trial for MS pain found uncertain benefit of cannabinoids.<sup>55</sup>

In contrast, most among the small RCTs report efficacy of rTMS in CP,<sup>10,11</sup> but stimulation location and frequency seem to matter. For SCI, which causes predominantly torso and leg pain, a sham-controlled trial in 111 patients showed benefits for overall and worst pain when the motor cortex representation of the hand was targeted at 10 Hz,<sup>50</sup> whereas a double-blinded placebo-controlled study of 17 patients with SCI stimulated at 10 Hz at the vertex (closer to the leg cortex) was negative,<sup>121</sup> as was a study of 5-Hz vertex stimulation.<sup>26</sup> Ten sessions of 5-Hz rTMS applied to the cortex innervating the painful area in 64 patients with predominantly central NP had intermediate results, namely transient reduction in mean pain.<sup>47</sup> For poststroke CP, 5 sessions of MRI-guided 10-Hz rTMS applied to the motor cortex innervating the painful area gave modest pain relief in 14 patients for up to 4 weeks.<sup>44</sup> Pain relief correlated with improved warmth perception in the painful area.<sup>44,62</sup> Single 10-Hz rTMS sessions applied to the hand site (regardless of the site of pain) gave short-term relief and suggested that pain caused by brainstem strokes responds less than pain from supratentorial strokes.<sup>63</sup> A well-designed, double-blind placebo-controlled study found that 10 sessions of 10-Hz rTMS applied to the left DLPFC did not relieve poststroke pain.<sup>25</sup>

### 3.2. Facial neuropathic pain

There are effective pharmacological and surgical treatments for classic trigeminal neuralgia, but these are not universally efficacious, and there are few treatments for other types of facial NP. The overall prevalence of facial NP is unknown, but causes other than classical trigeminal neuralgia are common. Significant proportions of patients with idiopathic facial pain have evidence of neuropathic mechanisms.<sup>32</sup> Systematic reviews of case series report moderate to good outcomes from epidural MCS in facial NP, with 68% responding initially, and 50% of implanted patients benefiting at 1 year.<sup>21,31</sup> For rTMS, multiple studies suggest that

facial NP responds better than other types of NP,<sup>63,68</sup> making it a leading candidate for rTMS trials.

### 3.3. Postherpetic neuralgia

Postherpetic neuralgia (PHN) is the second most common NP condition for pain medication trials because it is so common (1/3-1/2 lifetime prevalence<sup>91</sup>) and its etiology, localization, and onset are evident. Postherpetic neuralgia is dermatome-centered pain caused by damage to sensorineural cell bodies within 1 trigeminal or spinal ganglia caused by shingles (zoster). Early PHN improves spontaneously, which complicates trials. Risk for PHN is age dependent, with patients aged above 70 years having more than a 50% risk of pain lasting at least a year.<sup>24</sup> It can affect any location, but the torso and first trigeminal ganglion are most common. Many studies evaluating rTMS included patients with PHN.

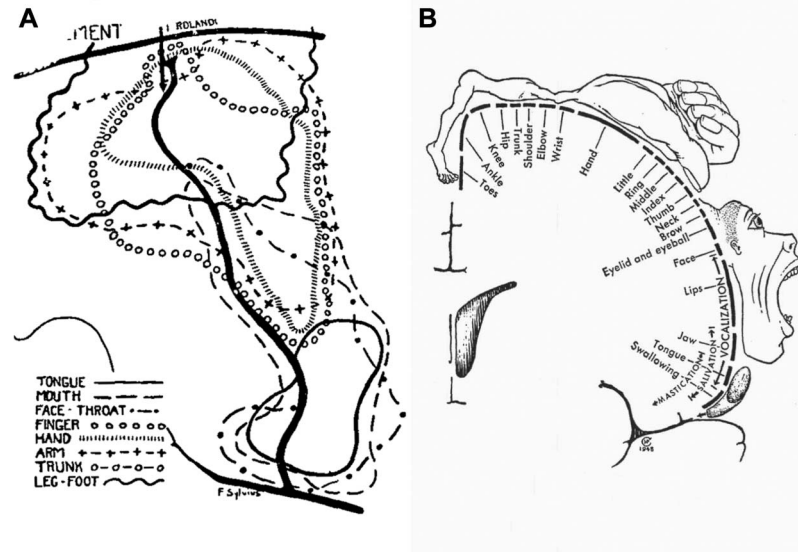
### 3.4. Fibromyalgia and painful small-fiber polyneuropathy

Fibromyalgia is a globally prevalent, well-studied, widespread-pain syndrome affecting 1% to 5% of the population. Recent consensus criteria for diagnosis and scoring are useful for trials.<sup>119</sup> Several well-designed studies, including one reporting long-term efficacy of maintenance rTMS, require external confirmation.<sup>14,77,93</sup> A systematic review in 2013 found high-frequency rTMS to the motor cortex efficacious for FM,<sup>76</sup> but a small study in 2014 did not find benefit for average daily pain.<sup>18</sup> Multiple new studies report evidence of small-fiber polyneuropathy among patients with FM, eg,<sup>85</sup> meaning this population may be heterogenous.

Small-fiber polyneuropathy is highly prevalent although most cases remain undiagnosed and complex tests are required to confirm diagnosis.<sup>8</sup> Diabetic polyneuropathy is overall the most-trialed NP condition. Advantages for trials include high and increasing prevalence, global relevance, and widespread availability of inexpensive blood tests for hyperglycemia. Cancer chemotherapy, another common cause of painful polyneuropathy, has unique advantages because it is preplanned and temporal precise. Pretreatment data can be obtained. Research tools for diabetic polyneuropathy are well developed, less so for other causes. A potential disadvantage is that the motor cortex representation of the feet is not easily accessible transcranially (**Fig. 2**), although evidence from patients with central causes of foot pain (see section 3.1) supports efficacy of off-site stimulation. The cooled, Heschl (H)-coil, that reportedly allows deeper penetration of TMS is reported as efficacious for painful diabetic polyneuropathy.<sup>89</sup>

### 3.5. Less-studied conditions

Back and neck pain must be considered because of their prevalence, although there are no rTMS studies so far. Potential disadvantages include the fact that their causes are usually mixed, the torso has less cortical representation (**Fig. 2**), and there are strong psychosocial influences.<sup>19</sup> Focal or regional pain disorders have the advantage of being common but the disadvantage of being heterogenous in location and cause. The most common cause of unilateral distal neuropathy is trauma—often medical or military—with occasional internal causes, for instance in carpal tunnel syndrome. Posttraumatic neuralgias with additional visible signs, termed “complex regional pain syndrome,” have been studied in 2 small trials of motor cortex rTMS totaling 32 patients.<sup>97,98</sup> Spinal radicular pain, usually from osteoarthritis, is very common and a likely future target. There is preliminary evidence of efficacy of motor cortex rTMS for brachial plexus



**Figure 2.** Pictorial representations of the anatomical targets of neurons within the primary motor cortex located in the precentral gyrus in the brain's frontal lobe. The amount of the cortex devoted to each body region is proportional to how richly innervated that region is, not to its actual size, which creates a distorted representation of the body called a "homunculus." Neurosurgeon Wilder Graves Penfield (1891-1976), a trainee of Osler, Cushing, and Sherrington, mapped brain functions while developing neurosurgical treatments for epilepsy as the founding director of the Montreal Neurological Institute at McGill University. While operating, he used electrical stimulation to map "eloquent" portions of each patient's exposed brain to minimize surgical damage.<sup>99</sup> (A) A map of the motor cortex published in 1937 by Penfield and Boldrey based on electrical exploration of the cortex of 163 awake, cooperative patients with craniotomies.<sup>95</sup> The lines enclose the areas within which electrical stimulation of the exposed cortex triggered a movement in that part of the body. (B) This anatomical homunculus based on the work of Penfield et al. was drawn for illustrative purposes by medical artist Hortense Cantile.<sup>96</sup> Although oversimplified and criticized, the motor and sensory homunculi continue to be widely reproduced to educate about brain function.

lesions.<sup>61</sup> Phantom limb pain is associated with cortical reorganization, making rTMS an attractive option that has not yet been studied.

#### 4. Designing clinical trials of repetitive transcranial magnetic stimulation for pain

Many previous studies not only often fail to report all technical parameters (see section 1; Transcranial magnetic stimulation: principles and applications) but also lack the details needed to measure effect sizes, to permit calculating sample sizes for future studies and to perform meta-analysis. Minimum required elements should include baseline plus posttreatment means and SD for all primary outcomes. Exact sample sizes, full inclusion and exclusion criteria, methods of allocation concealment, subjects' demographic and medical characteristics, the source of subjects (eg, community vs hospital), and recruitment methods should be specified. Studies should document ethical approval and monitor safety and should report all AEs and reasons for subject withdrawal or discontinuation,<sup>28</sup> but a meta analysis of 30 trials of rTMS for pain revealed that 17 did not report any information regarding AEs.<sup>82</sup> For chronic pain, it is important that benefits and risks be assessed for long enough, meaning that primary outcomes should usually be monitored for at least 3 months after treatment initiation. All statistical analyses should be prespecified. The field is not yet mature enough to know the utility of biomarkers (eg, gene sequences or imaging) as outcomes, but banking this information for future evaluation should be encouraged.

##### 4.1. Outcome measures

The literature describing rTMS for pain indications resembles that for interventional pain therapies in that few patients are

studied, often in uncontrolled case series, with nonuniform case definitions and outcomes, as summarized in **Table 3**. Research standards have progressed towards increased rigor and objectivity, and using recommended outcomes would strengthen the field. The usual *primary outcome* (*end point*) is treatment efficacy or effectiveness (which incorporates tolerability and ease of use as well as efficacy) for reducing pain. Pain intensity scales such as the Numeric Pain Rating Scale (NPRS) or Visual Analog Scale (VAS) are validated and universally accepted. The mean change from baseline and responder analyses (30% and 50%) may also be appropriate.

*Secondary outcomes* are encouraged to provide added information, such as effects on activities of daily living, disability, quality of life, decreases in medication use, and subject satisfaction. Secondary outcomes now often include patient-reported health-related quality of life (HRQOL). Another patient-centered trend influencing outcome measures is shared medical decision making.<sup>117</sup> Effects of treatment on health care utilization are an outcome of increasing relevance given the importance of reducing medical costs. Section 4.2 "Use of concomitant medications, therapies, and other environmental factors" discusses monitoring concomitant medications. We recommend active capture questionnaires for more sensitive and detailed monitoring than passive capture or general inquiry. These should include participant ratings of frequency, severity, importance, and associated distress.

The proceedings of the "Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)" meetings provide consensus guidelines about outcomes of pain treatment trials. These identified 6 core domains to consider: pain, physical functioning, emotional functioning, participant ratings of improvement and

**Table 3**  
**Outcome measures used in published studies of multiday repetitive transcranial magnetic stimulation applied to the primary motor cortex to treat chronic neuropathic pain.**

Study (see references below)	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
General pain															
Numeric Pain Rating Scale (NPRS)		×		×										×	
Visual Analog Scale (VAS) for pain	×		×		×		×	×	×	×	×		×		×
Brief Pain Inventory (BPI)				×		×						×			
McGill Pain Questionnaire (MPQ)		×	×		×					×					
Short-form McGill Pain Questionnaire (SF-MPQ)									×						
Brazilian Profile of Chronic Pain: Screen (B-PCP:S)													×		
Pain Impact questionnaire (PIQ-6)					×										
Neuropathic pain															
Douleur Neuropathique en 4 Questions (DN4)										×			×		
Neuropathic Pain Symptom Inventory (NPSI)										×					
The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)	×	×													
Depression/anxiety															
Beck Depression Inventory (BDI)		×	×			×	×		×	×			×	×	
Hamilton Depression Rating Scale (HDRS)		×			×										
Hospital Anxiety and Depression Scale (HAD)		×				×						×			
Hamilton Anxiety Rating Scale (HARS)					×										
State-Trait Anxiety Inventory (STAI)													×		
Pain Catastrophizing Scale (PCS)						×							×		
Disability															
Disabilities of the Arm, Shoulder, and Hand (DASH)					×										
The 36-Item Short-Form Health Survey (SF-36)					×	×								×	
General															
Satisfaction with treatment (Likert Scale)															×
Patient Global Impression of Change (PGIC)									×			×			
Sleep															
Pittsburgh Sleep Quality Index (PSQI)													×		
Disease specific															
Fibromyalgia Impact Questionnaire (FIQ)		×				×	×							×	

A, Khedr et al.<sup>51</sup>; B, Passard et al.<sup>93</sup>; C, Defrin et al.<sup>26</sup>; D, Kang et al.<sup>50</sup>; E, Picarelli et al.<sup>97</sup>; F, Mhalla et al.<sup>77</sup>; G, Lee et al.<sup>56</sup>; H, Lefaucheur et al.<sup>59</sup>; I, Hosomi et al.<sup>47</sup>; J, Onesti et al.<sup>89</sup>; K, Fricová et al.<sup>36</sup>; L, Hasan et al.<sup>44</sup>; M, Dall'Agnol et al.<sup>22</sup>; N, Boyer et al.<sup>18</sup>; O, Yilmaz et al.<sup>121</sup>

satisfaction with treatment, symptoms, and AEs, participant disposition,<sup>115</sup> and proposed specific core outcome measures (Table 4) to be considered in designing studies of chronic pain treatments.<sup>28</sup> The balance between generic and focused instruments is important. Generic instruments facilitate comparison with data from other healthy or ill cohorts and facilitate collaboration (see section 4.4; Resources for multicenter networks and trials), whereas condition-specific instruments may better capture disease-specific concerns.<sup>118</sup> For example, the 36-item Medical Outcomes Study Short-Form Questionnaire (SF-36) was designed to assess overall health of populations in which no one disease is excessively prevalent. Unless supplemented by questions targeting mental health, physical function, and other domains important for assessing HRQOL, the SF-36 lacks the sensitivity necessary for decisions about whether a specific treatment is working at the N-of-1 level.<sup>102</sup> The voluminous array of generic and specific HRQOL assessment instruments is summarized in monographs and Web-based repositories of open-access questionnaires and other instruments.<sup>102</sup> The IASP suggests that “for future NP trials, pain relief scales, patient and clinician global impression of change, the proportion of responders (50% and 30% pain relief), validated NP quality measures and assessment of sleep, mood, functional capacity and quality of life are recommended.”<sup>40</sup> A recent high-quality trial of motor cortex rTMS included most of these outcomes and also measured depression.<sup>47</sup> This approach to outcome assessment can help demonstrate that any pain relief is not merely a nonspecific correlate of treating depression.

Because TMS and other device trials study fewer subjects than drug trials, information provided by each enrollee should be maximized. Descriptions of enrollees’ demographics and TMS parameters must meet or surpass recent consensus recommendations.<sup>20</sup> Variables such as gender, age, and ethnicity should always be reported. As discussed above, studying homogenous groups of patients with at least moderate pain intensity can maximize the signal-to-noise ratio,<sup>29</sup> and training subjects at enrollment may reduce variability and reporting errors.

**Table 4**  
**IMMPACT II recommendations for core outcome measures to be considered in clinical trials of chronic pain treatment efficacy and effectiveness (reprinted with permission from Deng et al.<sup>27</sup>).**

Pain
11-point (0-10) numerical rating scale of pain intensity
Usage of rescue analgesics
Categorical rating of pain intensity (none, mild, moderate, and severe) in circumstances in which numerical ratings may be problematic
Physical functioning (either 1 of 2 measures)
Multidimensional Pain Inventory Interference Scale
Brief Pain Inventory interference items
Emotional functioning (at least 1 of 2 measures)
Beck Depression Inventory
Profile of Mood States
Participant ratings of global improvement and satisfaction with treatment
Patient Global Impression of Change
Symptoms and adverse events (AE)
Passive capture of spontaneously reported AE and symptoms and use of open-ended prompts
Participant disposition
Detailed information regarding participant recruitment and progress through the trial, including all information specified in the CONSORT guidelines

#### 4.2. Use of concomitant medications, therapies, and other environmental factors

Medication use is a common secondary outcome that must be monitored in trials of rTMS because medications (and other therapies and environmental conditions) can modify effectiveness and safety (Table 4).<sup>28</sup> Also, a goal of many nonpharmacological pain treatments is to enable patients to reduce or discontinue high doses of undesirable pain medications (namely opioids). Because of ethical considerations, studies of rTMS for pain have primarily been conducted in patients using other (insufficient or poorly tolerated) pain therapies, which often include multiple neuroactive medications. Patients with chronic pain often use multiple classes of pain medications, more than 1 medication in a class, and even multiple formulations of the same medication (eg, long- and short-acting opioids); in addition, medications are taken variably according to the need, so accurate documentation is difficult.

One simple metric is to quantify the use of approved “rescue” analgesics; another is to track the proportions of subjects taking various classes of pain medications.<sup>30</sup> It is possible to quantitate overall opioid consumption using morphine equivalents, but conversion tables do not accommodate individual differences in pharmacokinetics and pharmacodynamics, and in any case are applicable only to opioids. Real-time documentation using medication diaries may improve the depth and accuracy of data collection. The Medication Quantification Scale combines drug class, dose, and detriment (risk) to compute a single numeric medication profile value.<sup>43</sup> There are few metrics for other pain cotreatments including alternative, over-the-counter, herbal, and folk remedies and physical medicine treatments. At a minimum, rTMS studies should include detailed records of all medication use, including specific doses, and recording of nonmedical pain therapies. Large registry studies may be needed to analyze these complex variables. Because cotreatments add “noise” to clinical trials that can obscure signals, consideration should be given to trials of “stand-alone” rTMS.

Monitoring recent and current consumption as well as nonprescribed and prescribed medications is required to screen for study eligibility and ensure subject safety. Potentially problematic prescription medications used by some patients having pain include tricyclics (eg, nortriptyline, amitriptyline), antiviral medications, and antipsychotic medications (eg, chlorpromazine, clozapine), but there are no analyses measuring how each medication alters seizure risk and few TMS publications even fully describe subjects’ medications and doses. Consuming or discontinuing commonly abused substances can increase cortical excitability and risk of a TMS-induced seizure (Table 2).<sup>103</sup> Withdrawal from sedatives (eg, alcohol, barbiturates, benzodiazepines, meprobamate, and chloral hydrate) increases seizure risk, so patients must be asked about recent and current use, and recent substance abuse should be an exclusion criterion. Other potentially problematic drugs of abuse include phencyclidine, amphetamines, ketamine, and gamma-hydroxybutyrate. Establishing a national or a global registry to report and fully document every case of TMS-induced seizures is recommended to better characterize specific risk factors because these are far too rare for individual centers to acquire enough cases to study.

There are yet additional parameters to consider recording for potential future use, including state of mind and health at the time of the study, and use of nonprescription neuroactive substances such as caffeine.<sup>20</sup> Sleep deficits alter cortical excitability, and given the efficacy of ketogenic diets in suppressing the cortical



excitability that causes seizures,<sup>72</sup> low-carbohydrate diets could conceivably influence the outcomes of rTMS. One study coupled rTMS with behavioral training to increase benefit for tinnitus.<sup>120</sup> However, rTMS studies have not been designed or powered to assess these added variables, and there are currently no validated methods for data collection and analysis. Large collaborative studies or registries (section 4.4; Resources for multicenter networks and trials) and real-time data entry by subjects or passive capture by monitoring devices will be necessary. “Health connectivity” is an emerging trend in medicine and public health, so these parameters may soon become available.

### 4.3. Regulatory considerations

Authorization processes vary in different countries and influence the pace of clinical application of TMS. There are differences in risk classification, transparency, and rigor of assessment of safety and effectiveness. For medical devices, the US FDA, the Canadian Therapeutic Products Directorate (TPD), and the Australian Therapeutic Goods Administration (TGA) require evidence of clinical efficacy, device quality and performance, and safety, whereas Europe has emphasized safety and performance over efficacy, thus European CE marking typically precedes US clearance by 2 to 5 years.<sup>54</sup> For a device to be legally marketed in the European Union (EU), the requirements of the European Medical Device Directives must be met and a CE Mark obtained from the European Commission. Directive 93/42/EEC and its subsequent amendments regulate medical devices such as TMS.

The US FDA’s Center for Devices and Radiological Health (CDRH) and the European Commission have approved TMS devices for several indications. The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) requires compliance with the Pharmaceutical and Medical Device Law (PMDL), and in 2013, Brainsway announced plans to seek permission to market their Deep TMS system in Japan for major depression. The most widely approved TMS application is major depression, for which rTMS has been approved in Canada, Australia, New Zealand, the EU, Israel, and the United States.

In the United States, the FDA’s CDRH has tiered risk-based requirements, with class I defined as low to moderate risk, class II as moderate to high risk, and class III as high risk. For class I devices, adherence to general controls (eg, good manufacturing processes, registration, medical device reporting, labeling) is considered sufficient to reasonably ensure safety and effectiveness. For class II devices, adherence to general and special controls (eg, performance standards, postmarket surveillance, patient registries, special labeling requirements) is required. Class III devices must additionally undergo premarket approval. Transcranial magnetic stimulation devices have been classified as class II as they are not implanted, nor do they have long-lasting or potentially fatal AE, so the investigational device exemptions (IDE) process is not required. The 510(k) process, typical for class II devices, requires demonstrating substantial equivalence in safety, efficacy, intended use, and technological characteristics to a legally marketed “predicate” device. The de novo pathway is used for low to moderate risk devices such as TMS devices without predicates. This establishes a new regulation and allows this device to serve as a predicate subsequently. For instance, in 2008, the first TMS device was authorized by the CDRH through the de novo classification process for treatment-resistant major depression (Neuronetics’ NeuroStar),<sup>1</sup> and in 2013, Brainsway’s H1 System was approved for marketing after demonstrating

substantial equivalence.<sup>2</sup> And, de novo classification was granted in 2013 to eNeura’s single-pulse CerenaTMS device for treating acute pain in migraine with aura; and then in 2014 their portable device, SpringTMS<sup>3</sup> was approved using 510(k) with CerenaTMS as the predicate. Both were CE-marked in the EU before FDA application.

For devices to treat pain, prospective sham-controlled RCTs are preferred for the pivotal trials that establish device safety and effectiveness when seeking regulatory approval. This is due to the subjective nature of pain and significant placebo effects. Pivotal trials generally have prespecified hypotheses, inclusion and exclusion criteria, and description of device-specific attributes, end points, and statistical analyses. In pain trials, suboptimal shams and blinding are problematic because of the subjective nature of pain assessment. A blinding assessment that requires forced choice of group assignment and the reason for the choice can help assess the integrity of blinding as discussed in the CDRH’s “Guidance for Industry and FDA Staff—Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems.”<sup>4</sup> Although randomized sham-controlled trials have historically been used to support TMS applications to the FDA, other study designs can be considered if they provide reasonable assurances of device safety and effectiveness for intended purpose, including randomized comparative trials (with previously cleared or approved treatments), comparison with usual treatment, crossover designs, and prospective nonrandomized observational trials (propensity analyses).

The FDA often determines the indication for use of a device based on the adequacy of trial design and the collected data. Considerations for designing pain trials include: Will the device be used to treat acute and/or chronic pain? What type and etiology of pain will be treated? Will it be used as an adjunct to medications or as monotherapy? Will it be used in adults and/or children? Will it be used to treat mild, moderate, and/or severe pain?

### 4.4. Resources for multicenter networks and trials

Given the difficulty of assembling sufficient numbers of homogeneous subjects to sufficiently power studies of rTMS, multicenter research consortia that provide infrastructure and standardized metrics are increasingly recognized to add efficiency and lower cost. Collaborative TMS studies face additional difficulties regarding acquisition of identical expensive TMS devices and standardization of TMS administration, but a recent multicenter, randomized, double-blind, sham-controlled, crossover study of rTMS for NP was successfully conducted at 7 Japanese centers.<sup>47</sup> Global collaboration offers added difficulties pertaining to language, such as the need to validate study instruments in different languages, and variations in national medical and regulatory practices.

Some collaborations originate from within communities of researchers focusing on specific conditions, others are organized by governmental agencies. An example of a disease-based consortium is the United States’ Northeast amyotrophic lateral sclerosis (NEALS) consortium (<http://www.alsconsortium.org/>) created in 1995 to coordinate collaborative clinical research on amyotrophic lateral sclerosis. Membership grew to more than 100 centers comprising more than 500 personnel with varying roles. Clinical data and biosamples are banked and shared, and clinical research training is offered. An example of a government-funded organization is the NIH-funded consortium of Clinical and Translational Science Award Centers at more than 60 US academic medical institutions (<https://www.ctsacentral.org/>).

This offers resources to enhance general clinical research, some accessible to non-US investigators. For instance, NIH supports a free public domain resource called the Patient-Reported Outcomes Measurement System (PROMIS; www.nihpromis.org) that contains outcome assessments applicable to a wide variety of chronic diseases and conditions. It currently has 3 items pertaining to pain intensity, 39 items measuring pain behaviors, and 40 items pertaining to pain interference.<sup>9</sup> It is not yet clear whether these pain-related items are sufficiently comprehensive for clinical analgesic trials, and whether they can exclusively support regulatory applications for new drug approval.

The NIH National Institute for Neurological Disorders and Stroke funds an initiative specifically designed for neurological disorders, called “NeuroNEXT” (Network for Excellence in Neuroscience Clinical Trials; <http://www.neuronext.org/>). It was created to more efficiently ready promising neurological therapies for phase II testing. A Clinical Coordinating Center at the Massachusetts General Hospital manages the 27 participating research institutions using master research service subcontracts and a central institutional review board, so that individual member institutions do not need to separately approve each study. A Data Coordinating Center at University of Iowa provides a centralized repository and resource for data collection and statistical analysis. NeuroNEXT accepts applications and funds trials from industry and academic groups; to date, no TMS or pain studies have been conducted.

## 5. Technological advances that might improve efficacy of repetitive transcranial magnetic stimulation for treating pain

Technological improvements might also yield more-conclusive studies, so we reviewed emerging technologies that might potentially improve outcomes.

### 5.1. Using anatomical magnetic resonance imaging to guide coil placement

For localized brain functions, the stimulation site determines the type and magnitude of the effect. To maximize therapeutic effects of rTMS for pain, one would ideally know where the neuronal representation regulating pain is located, select a cortical portion that is accessible to TMS, and target it as precisely and selectively as possible. However, pain is widely distributed, and individual differences in cortical anatomy, white-matter connectivity, and structure-to-function mappings make this challenging. A basic prerequisite for precise rTMS is being able to repeatedly place the coil over a patient-specific cortical target. This is improved by commercially available MRI-guided navigation systems that use infrared cameras to coordinate the relative 3-dimensional location of subjects' heads and TMS coil, and user-selected landmarks from each subject's head MRI.<sup>39</sup> Magnetic resonance imaging-guidance is required to accurately compare the effects of stimulating different cortical targets. There is some evidence that MRI-guided rTMS is more efficacious for pain,<sup>45,57</sup> but this is not conclusive. Given the added cost and effort of obtaining MRIs for each subject, the value of MRI-navigation should be clarified before undertaking large clinical trials.

### 5.2. Mapping transcranial magnetic stimulation electric fields on cortical surfaces

Current TMS navigators localize the TMS coil, but not its predicted cortical activations, yet this refinement is within reach.

Each person's individual cortical surface can be automatically extracted from their MRI, eg, with FreeSurfer software.<sup>34</sup> This also permits parsing of possible cortex orientation-specific influences. Individual cortical surfaces can also be nonlinearly morphed to other brain surfaces (eg, group averages), to facilitate group-level studies and meta-analyses, as recently published.<sup>6</sup> Estimating the primary electric fields induced in the brain by specific TMS parameters requires volume conductor models. Present-day commercial navigation devices either omit these or use simplified less-accurate spherical models.<sup>81</sup> Realistically shaped models using Finite Element Methods and Boundary Element Models have already been used in at least 1 group-level TMS study.<sup>6</sup> Using them in practical TMS navigation systems seems feasible and might improve further targeting accuracy at modest computational and labor cost.

### 5.3. Measuring distant effects of transcranial magnetic stimulation using magnetic resonance imaging tractography

Transcranial magnetic stimulation activations spread to secondary areas through white-matter tracts<sup>94</sup> including spread to deep subcortical targets,<sup>69</sup> and these secondary activations correlate with therapeutic potency.<sup>33</sup> Thus, cortical TMS targets can be considered as windows to networks extending throughout the brain. Once these are characterized, it becomes possible to apply TMS using parameters designed to maximize network-level activations. Diffusion MRI tractography allows identifying individual-specific white-matter pathways. Once TMS-induced electric field distributions on each subject's cortex is computed as above, the resulting binary mask can be used to seed tractography and estimate distant effects. These can be further refined by considering axonal orientation and bending relative to the electric field.<sup>49</sup> Advances in diffusion MRI<sup>106</sup> bring this within reach.<sup>80</sup>

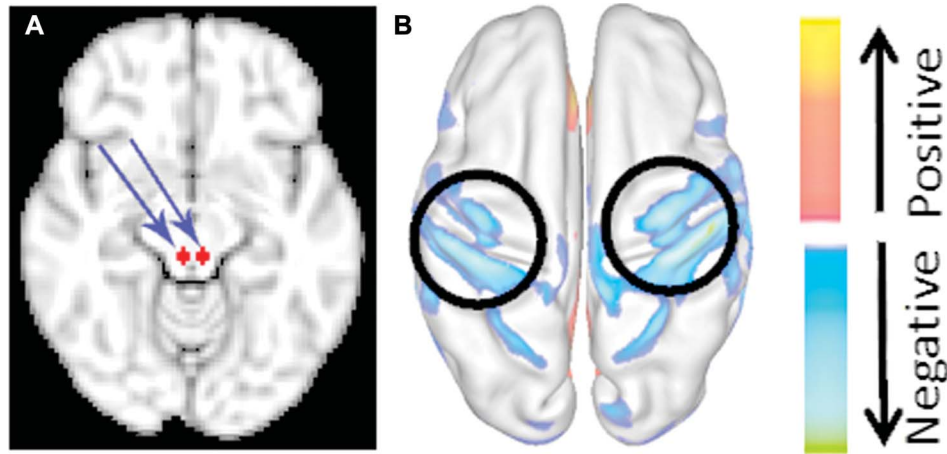
### 5.4. Resting-state functional connectivity magnetic resonance imaging

Resting-state functional connectivity MRI uses correlations in spontaneous fluctuations in blood oxygenation to reveal brain networks. This has helped identify network abnormalities correlated with chronic pain symptoms.<sup>75</sup> Recent work suggests that resting-state functional connectivity MRI may predict the propagation of focal brain stimulation, facilitate visualization of TMS-induced network changes, and lend insight into therapeutic mechanisms.<sup>34</sup> Resting-state functional connectivity MRI is now sufficiently robust and reproducible to help identify patient-specific targets based on their connectivity.<sup>35</sup> For pain, it can test whether efficacy of rTMS application to specific motor cortex targets is due to connectivity with deeper regions implicated in pain perception (**Fig. 3**).<sup>33</sup> If confirmed, this might improve targeting and perhaps efficacy.

Today, we recommend transition from the still-widespread practice of applying rTMS without imaging guidance, where resources permit it. Even basic navigators recording coil position relative to each subject's MRI document the precise cortical areas activated needed to clarify which specific sites offer best efficacy, and off-line tools available today may augment their scientific utility.

## 6. Future considerations

Most research studies provide proof-of-concept that rTMS can improve some chronic pain syndromes, but they have been insufficient to confirm specific indications and best methods.<sup>82</sup>



**Figure 3.** Magnetic resonance imaging (MRI) depicting deep and cortical sites most efficacious to stimulate for treating chronic pain. (A) The periaqueductal gray (PAG), the primary control center for descending pain modulation, and the most effective target for deep brain stimulation for pain (arrows). (B) Mean resting-state functional MRI connectivity mapping of 1000 normal subjects. Spontaneous modulations in the fMRI signal are extracted from the PAG. Fluctuations in the primary sensory and motor cortices (circles) are most correlated with those of the PAG. Modified with permission from.<sup>33</sup>

Most published studies have been small and unblinded, with exceptions (eg, Ref. 47). Study designs, subjects, technical parameters, and outcomes have been inconsistent with full details only rarely fully reported, hindering confirmation or meta-analysis. Several recent studies are of higher quality, demonstrating a commitment to improvement. Funding agencies should support research designed to build towards clinical trials of sufficient quality to support regulatory approval of rTMS for clinical use in chronic pain. We suggest a round of studies to optimize design and methods for clinical trials for pain indications. Transcranial magnetic stimulation administration parameters, subject populations, and outcome measures should be standardized and optimized. Other important goals include identifying the best location for MCS relative to the subjects' painful body area and clarifying whether MRI-guided localization is cost effective. Guidelines for accreditation and expertise need improvement.

Given the difficulties inherent in recruiting large numbers of well-characterized subjects with homogenous pain syndromes, multisite collaborations between teams using identical equipment, parameters, and methods should be established and supported, along with bioinformatic resources for securely collecting and analyzing complex data. These could provide foundations for the postmarketing surveillance probably necessary to power analysis of very rare side effects and potential complex consequences for memory, learning, or personality. Global registries, passive electronic collection of TMS administration parameters, patient-reported outcomes, and information technology applications would permit data accrual with less effort required from TMS administrators.

We suggest that the suffering and disability associated with uncontrolled chronic pain, the common and serious adverse effects associated with pain medications, and the preliminary evidence of efficacy and safety of TMS for treating some types of pain mandate greater investment in developing this therapy.

### Conflict of interest statement

A. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab, Neuroelectrics, Axilum Robotics, Magstim, and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of TMS with

EEG and MRI. None of these patents is currently licensed or generating any license fees. M. Hallett may accrue revenue on US Patent #7,407,478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil); and he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. M. Fox is listed as an inventor in issued patents or patent applications on functional connectivity and guidance of TMS. The other authors have no conflicts of interest to declare. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, the National Institutes of Health or the Sidney R. Baer Jr Foundation.

### Acknowledgements

Supported in part by the Radcliffe Institute for Advanced Study and the Samuels Family Foundation, the Public Health Service (K24NS059892, K23NS083741, NS38493, R01HD069776, R01NS073601, R21 MH099196, R21 NS082870, R21 NS085491, R21 HD07616, and U01NS077179) and NINDS intramural support to M. Hallett, the UK National Institute of Health Research (PB-PG-0110-20321) to T. Nurmikko, the Hopkins Neurosurgery Pain Research Institute, the American Academy of Neurology/American Brain Foundation, the Sidney R. Baer Foundation, the Harvard Catalyst—Clinical and Translational Science Center (UL1 RR025758).

### Article history:

Received 22 August 2014

Received in revised form 30 March 2015

Accepted 17 April 2015

Available online 25 April 2015

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