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New Developments in Non-invasive Brain Stimulation in Chronic Pain

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Abstract

Purpose of Review—The goal of this review is to present a summary of the recent literature of a non-invasive brain stimulation (NIBS) to alleviate pain in people with chronic pain syndromes. This article reviews the current evidence for the use of transcranial direct current (tDCS) and repetitive transcranial magnetic stimulation (rTMS) to improve outcomes in chronic pain. Finally, we introduce the reader to novel stimulation methods that may improve therapeutic outcomes in chronic pain.

Recent Findings—While tDCS is approved for treatment of fibromyalgia in Canada and the European Union, no NIBS method is currently approved for chronic pain in the United States. Increasing sample sizes in randomized clinical trials (RCTs) seems the most efficient way to increase confidence in initial promising results. Trends at funding agencies reveal increased interest and support for NIBS such as recent Requests for Application from the National Institutes of Health. NIBS in conjunction with cognitive behavioral therapy and physical therapy may enhance outcomes in chronic pain. Novel stimulation methods, such as transcranial ultrasound stimulation, await rigorous study in chronic pain.

Summary

Excitatory NIBS targeting motor cortex or left dorsolateral prefrontal cortex has the greatest support for ameliorating pain in chronic pain patients, particularly in Chronic Overlapping Pain Conditions, such as fibromyalgia. Confidence in the efficacy of NIBS interventions is most negatively affected by RCTs with small sample sizes. Increased attention from funding agencies to

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Conflict of Interest

Timothy Meeker, Rithvic Jupudi, Frederik Lenz and Joel Greenspan declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

the promise of NIBS and to the problem of small sample sizes in applied neuroscience is anticipated to improve confidence in these relatively side-effect free interventions.

Keywords

non-invasive brain stimulation; repetitive transcranial magnetic stimulation; rTMS; chronic pain; transcranial direct current stimulation; tDCS

Introduction

Epidural motor cortex stimulation: prelude to non-invasive neuromodulation for pain alleviation

Non-invasive brain stimulation (NIBS) protocols as adapted for intervention in chronic pain, arguably have their intellectual origins in invasive epidural motor cortex stimulation (EMCS) [1, 2]. Invasive methods requiring neurosurgery are reserved for patients presenting with intractable chronic pain with clear neuropathic signs and symptoms. While EMCS appears to be effective for central post stroke pain (CPSP), it seems ineffective for spinal cord injury pain (SCIP) leaving a vast gap in analgesic potential for many patients who may benefit from NIBS [3]. NIBS using transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS) or more recently reported methods such as transcranial alternating current stimulation (tACS) and low-intensity transcranial ultrasound stimulation (TUS) are promising avenues of research that may lead to future treatments for chronic pain of all etiologies [4-6]. However, the field of NIBS for chronic pain has been plagued by promising preliminary published reports of analgesic effects in a variety of chronic pain syndromes with little follow-up in appropriately powered, blinded, randomized and sham-controlled clinical trials [7]. Historically this was in part caused by the lack of funding and attention from major funding agencies such as the National Institutes of Health, which we note in recent years has improved substantially (Figure) [8].

In neuropathic pain caused by a lesion of the central nervous system, for example in patients with central post-stroke pain (CPSP) and spinal cord injury-related pain (SCIP), medications including morphine and pregabalin frequently have limited or no effect on the patient's pain [9-11]. In the early 1990s, Tsubokawa and colleagues pioneered EMCS for treatment of CPSP, and 9 of 12 patients experienced strongly positive long term pain relief from this invasive therapy [12]. EMCS is an invasive form of motor cortex neuromodulation, which requires neurosurgical implantation and has been reported to provide 40% to 50% pain amelioration in 45% of treated patients at one-year follow-up [13]. While early reports of pain alleviation by EMCS generally lacked periods of double blind testing, where the intracranial stimulator would be turned off or on by random determination, several later studies included double-blind test periods [14-17]. Of the four studies reporting double-blind testing, three showed generally positive pain ameliorating effects.

Short-term pain reduction produced by excitatory, high frequency M1 rTMS correlates with the clinical success of EMCS, suggesting these interventions may have similar mechanisms [18, 19]. Recent evidence in a case series of 12 patients demonstrated rTMS's improved

positive and negative predictive value for EMCS success when applied over a 4 session regime [20].

In an attempt to translate the pain alleviating effects of invasive EMCS to a wider patient population by using noninvasive techniques known to modulate cortical excitability, randomized controlled trials (RCTs) of both high frequency repetitive transcranial magnetic stimulation (rTMS) and anodal transcranial direct current stimulation (tDCS) were found to alleviate neuropathic pain [21-25]. An RCT comparing high frequency M1 rTMS to anodal M1 tDCS, and each to their own sham, found active rTMS superior to sham and active tDCS, but importantly found analgesic effects of M1 rTMS correlated positively to those of anodal M1 tDCS, suggesting individual patients respond similarly to tDCS and rTMS [26]. It is important to note that while typical courses of treatment with tDCS only reach levels of analgesia of clinical significance after at least three 20 minute once-daily sessions, temporary pain alleviation from EMCS and rTMS occurs after 10 to 20 minutes of stimulation, and these early effects predict clinical success [13, 22, 27, 28, 20]. We discuss recent studies using non-invasive neuromodulation methods for alleviation of pain perception in chronic pain syndromes.

Non-invasive Brain Stimulation: Analysis of the analgesic effect of M1-targeted rTMS in chronic pain patients

Since Lefaucheur and colleagues first reported analgesic effects of M1 rTMS in patients with neuropathic pain in hopes of using rTMS as a tool to predict efficacy of EMCS, several guidelines and meta-analyses investigating the potential analgesic effects of M1 rTMS have been published [29, 24, 7]. In general, the most frequently investigated M1 rTMS protocols generally aim to increase cortical excitability in the motor cortex. For example, the most recent Cochrane review update of NIBS for chronic pain listed that 32 published reports of 42 rTMS studies used high frequency (≥ 5 Hz) M1 rTMS, which is known to increase cortical motor excitability. In addition, a variety of sham methodologies were taken advantage of in this population of studies. Optimal sham stimulation, where somatosensory, visual and auditory perception of the verum (or true) coil is mimicked, is reported in only eight of 42 analyzed studies. Generally, suboptimal sham coils are used where only two perceptual aspects of the verum stimulation are mimicked; 14 of 42 sham coils mimicked only auditory and visual aspects. It is probable that in a crossover study there is no perfect sham for active rTMS given that sensations from verum stimulation arise from the scalp and subcutaneous tissues, as well as from the meninges and periosteum [30]. A sham coil with the ability to stimulate these targets would likely not be considered ethical. Furthermore, sham coils which stimulate the scalp may deliver neurophysiologically relevant energy which may produce neuromodulation. Therefore, for rTMS studies, sham blinding may always remain questionable.

Recent evidence-based guidelines were published by a European commission which reviewed clinical rTMS studies for several chronic disorders including chronic pain disorders, movement disorders, stroke, epilepsy, tinnitus, depression and anxiety disorders [31]. Their general conclusions included an absence of efficacy of low frequency rTMS protocols in all chronic pain disorders evaluated, and significant efficacy of high frequency,

excitatory, rTMS protocols in neuropathic pain and perhaps in some other chronic pain disorders studied. Specifically, they found evidence that 1) there is a suggestion that low frequency M1 rTMS contralateral to the side of pain is frequently ineffective in neuropathic pain, 2) there is a definite analgesic effect of high frequency M1 rTMS contralateral to the side of pain in chronic neuropathic pain, and 3) there is a suggested analgesic effect of M1 rTMS contralateral to the affected side in CRPS. This guideline did not find enough high-quality evidence to make any further evidence-based recommendations. At the time, they found a lack of high-quality evidence in non-neuropathic pain syndromes. The recent Cochrane review update was less charitable, finding the current evidence for a heterogenous small effect size favoring active high frequency M1 rTMS to be below the minimal level of clinical significance based on low quality evidence [7]. Factors that lowered the quality of evidence for clinical efficacy of high frequency M1 rTMS included suboptimal sham, small sample sizes in many studies, as well as suboptimal randomization and blinding procedures.

Recently published studies and clinical trials are more rigorous in design and have benefited from the past nearly 20 years of research. For example, a multi-center parallel RCT in 144 patients with intractable chronic neuropathic pain compared a 4 week, 20 once-daily stimulation session intervention using high frequency rTMS of M1 to an optimal sham [32]. Despite finding no significant difference between sham and verum rTMS in their primary outcome (mean visual analogue scale decreases), patients enrolled in the verum continuous weekly follow-up maintained lower pain intensity ratings compared to those experiencing sham stimulation. It is notable that this trial used a relatively low dose (500 pulses) of M1 rTMS, whereas more successful studies have used both higher frequency stimulation (20 Hz vs. 5 Hz) and a higher dose (2000 to 3000 pulses) [32]. Recently, a study has found verum neuronavigated M1 rTMS to be superior to sham or non-neuronavigated M1 rTMS consistent with clinical opinion in EMCS that accurate targeting of the painful somatotopic area of motor cortex is critical for clinically meaningful outcomes [33, 3]. Further supporting this contention is evidence reported by Shimizu and colleagues that conventional high frequency rTMS had no analgesic effect in patients with neuropathy of the lower limb, while 5 Hz M1 rTMS using a double cone coil capable of reaching the paracentral lobule was superior to both conventional and sham stimulation [34].

Non-invasive Brain Stimulation: Analysis of the analgesic effect of DLPFC-targeted rTMS in chronic pain patients and acute post-operative pain

High frequency rTMS of the left DLPFC is approved by the US Food and Drug Administration for the treatment of depression. and a recent study in patients with depression found that those depressives with widespread pain found rTMS of left DLPFC analgesic [35, 36]. More recently, studies of DLFPC rTMS have been conducted in chronic pain patients as well. These studies used high frequency rTMS targeting left DLPFC or low frequency rTMS targeted right DLPFC as an intervention [7]. Three studies from the same lab group have investigated high frequency left DLPFC rTMS to reduce post-surgical patient-controlled analgesia (PCA). While the first two studies found that treatment reduced use of PCA, the most recent study, with the largest number of subjects, found no effect of DLFPC rTMS on PCA use [37-39]. Additional studies have found analgesic and therapeutic effects of high frequency rTMS of left DLPFC in patients with central poststroke pain,

chronic widespread pain (CWP), burning mouth syndrome and fibromyalgia [40-46]. While five published studies in fibromyalgia and CWP show positive effects on pain, fatigue and physical functioning, no study show improvement in all three domains and all studies have been conducted in sample sizes of 7 to 12 per group, which significantly increases the risk of false positive results [47]. Overall there is limited, but promising evidence of the analgesic effects of high frequency rTMS of the left DLPFC in both neuropathic and non-neuropathic chronic pain syndromes. Given variability of effects of neuromodulation depending on accuracy of targeting and small effect sizes relative to investigation of all-or-none phenomena, larger sample sizes and better targeting should be goals for future studies.

Non-invasive Brain Stimulation: Analysis of the analgesic effect of rTMS of other cortical targets in chronic pain patients

In chronic pain patients the effects of cortical stimulation of targets alternate to M1 and DLPFC have been reported. Four of these studies reported high quality evidence supporting the analgesic effects of cortical neurostimulation, including the second somatosensory cortex, vertex, and dorsal anterior cingulate cortex (ACC) [48-50]. Another study, in a smaller group of migraine patients showed supporting evidence of 1 Hz rTMS to the vertex for the treatment of chronic migraine [49]. An important caveat of NIBS studies that aim to target locations deep to the cortical surface is that all neural structures between the scalp and the target receive at least as much stimulation as the target. Additionally, the scalp sensations and muscular contractions produced by deep rTMS are much more intense than those produced when aiming to stimulate the cortical surface. Tzabazis and colleagues applied H-coil 10 Hz rTMS targeting the dorsal ACC and found superior analgesic effects in fibromyalgia patients when compared to sham stimulation, which were present on follow-up 4 weeks after the intervention [50]. A recently published study used deep rTMS to target the posterior insula and anterior cingulate cortex (ACC) in an attempt to alleviate chronic central neuropathic pain after stroke or spinal cord injury [51]. This study compared the effects of deep rTMS of the ACC or insula to sham deep rTMS of either target in 98 patients suffering from central neuropathic pain in a protocol of 5 once-daily sessions followed by 11 once-weekly stimulation sessions. Neuromodulation of neither target was superior to sham stimulation on measures of pain interference, pain dimensions, neuropathic pain symptoms, medication use or quality of life. However, ACC deep rTMS reduced anxiety symptoms during the 12-week treatment period whereas posterior insula rTMS reduced sensitivity to heat pain and warmth as indicated by elevated thresholds. Finally, since S2 plays a prominent role in pain processing, Lindholm and colleagues found that active high frequency S2 rTMS was superior to both M1/S1 stimulation and sham stimulation in alleviating neuropathic orofacial pain [48]. Future exploratory studies should seek to develop these novel cortical targets in order to optimize neurostimulation for long-term analgesia and larger studies are needed to replicate these results in order to support the analgesic action of non-invasive cortical neurostimulation.

Non-invasive Brain Stimulation: Analysis of the analgesic effect of M1-targeted tDCS in chronic pain patients

The exposure of neural tissue to electric fields set up by direct currents (DC) has been known for more than 50 years to produce long-term changes in the activity of neurons [52,

53]. The rediscovery of the potential clinical applications of this technique had to await the development of an objective way of measuring the effects of neuroplasticity in humans, namely development of the TMS coil to evoke motor-evoked potentials [54]. When neurons are exposed to a DC field, the area under the anodal electrode experiences a depolarization of the resting membrane potential and endogenous neural activity is increased in rate, ultimately augmenting the baseline excitability of that population of neurons [55, 56]. Under the cathodal electrode, the neural population experiences a hyperpolarization of the resting membrane potential and endogenous neural activity is decreased in rate, ultimately suppressing the baseline excitability of that population of neurons. This dichotomy of neuromodulatory responses is oversimplified for many reasons, including the variability of the geometry of in vivo neuronal elements such as axons, dendrites and cell bodies as well as the effects of past plasticity-inducing events [55, 57]. However, for our purposes the dichotomy of anodal tDCS enhancing cortical excitability and cathodal tDCS suppressing cortical excitability remains useful [54, 56].

From 2006 until 2017, 34 studies investigated the effects of M1 tDCS in chronic pain patients with various etiologies of chronic pain [7]. In a recently published set of guidelines commissioned by the European Chapter of the International Federation of Clinical Neurophysiology, an expert panel found enough supporting evidence to make a guideline recommendation for M1 anodal tDCS for neuropathic pain secondary to spinal cord injury and for fibromyalgia [6]. M1 anodal tDCS for neuropathic pain secondary to spinal cord injury, the expert commission found, is possibly effective. Further, the panel found sufficient evidence to support that M1 anodal tDCS is probably effective for treating pain in fibromyalgia as assessed by pain intensity reports and the fibromyalgia impact questionnaire. Six studies of pain alleviation from anodal M1 tDCS in fibromyalgia reported an analgesic effect when using at least five once-daily sessions of 1 or 2 mA delivered for 20 minutes compared to sham. However, one study found no pain alleviating effect after 10 consecutive once-daily 20 minutes sessions of 2 mA stimulation compared to sham [58-63]. Three studies have studied the effects of M1 anodal tDCS on PCA during postoperative recovery, either from total knee arthroplasty or lumbar spine surgery, and found pain to be less with active stimulation compared to sham and the total amount of drug during PCA to be lower in the post-surgery period [64-66]. The positive findings of analgesia mediated by anodal M1 tDCS in fibromyalgia and in post-operative pain provide strong preliminary evidence to support an analgesic effect superior to sham stimulation in both acute and chronic pain conditions. However, the evidence is not without limitations, and the size of the superiority effect of anodal tDCS over sham stimulation is often less than a ten or twenty percent reduction in patients' self-reported pain intensity , which calls into question its clinical relevance [6].

Regarding neuropathic pain secondary to spinal cord injury (SCIP), three studies reported an analgesic effect, superior to sham, of at least one 20 minute session of 2 mA anodal M1 tDCS, while three additional studies found no significant effect compared to sham stimulation [22, 67-70]. An additional three studies of neuropathic phantom limb pain found anodal M1 tDCS to be superior to sham in its analgesic effects [71-73]. One study of neuropathic radiculopathy found only a trend of an analgesic effect with M1 anodal tDCS. But notably, this tDCS effect correlated positively with the analgesic effects of high

frequency M1 rTMS [26]. The evidence for superior analgesic effects of anodal M1 tDCS compared to sham stimulation in neuropathic pain, particularly of peripheral origin is more consistent compared to other chronic pain disorders. However, the strongest evidence relies on relatively few trials with small sample sizes ($n < 25$ per group) and therefore more work is needed to substantiate the analgesic effects of anodal M1 tDCS in neuropathic pain syndromes [47, 74, 75, 6].

Non-invasive Brain Stimulation: Analysis of the analgesic effect of DLPFC-targeted tDCS in chronic pain patients

The use of tDCS of the DLPFC has only been reported using left sided stimulation [6]. Three of these studies assessed the effects of left DLPFC tDCS in fibromyalgia, one of which found that verum stimulation reduced experimental pain sensitivity and increased heat pain tolerance, while only one of the other two studies found significant analgesic effects of stimulation on clinical pain [59, 62, 76]. While one study of post-operative pain and PCA usage found reduced PCA usage after left DLPFC tDCS compared to sham stimulation, another study in patients recovering from lumbar spine surgery found no significant difference between verum DLPFC and sham stimulation [77, 78]. More recently, post-surgical opioid use was found to be reduced more by left DLPFC than left M1 tDCS when applied at 2 mA in four 20-minute sessions after total knee arthroplasty [79].

Potential mechanisms of primary motor cortex neuromodulation for pain amelioration

M1 neuromodulation may affect multiple levels of the neuraxis to ameliorate pain. Motor cortex excitability is altered by acute and tonic noxious stimuli, and in chronic pain conditions including painful diabetic neuropathy, fibromyalgia and complex regional pain syndrome [80-87]. This modulation of cortical excitability by tonic or chronic nociceptive stimulation is remedied by pain alleviating neuromodulation [27, 88]. Among M1 neuromodulation's neurophysiological effects is the modulation of thalamic activity [89-91]. Studies in animal pain models demonstrated that EMCS decreased nociceptive driven neural activity and BOLD response in S1 [92, 93]. Additionally, high frequency M1 rTMS causes reorganization of the S1 somatotopic map and reduction in the amplitude of painful laser evoked potentials, while anodal tDCS reduces BOLD responses to painful stimuli [94-96, 73, 97]. Together these findings suggest that S1 excitability is potentially mediated through M1 corticocortical pathways.

Research during the last two decades has begun to unravel the bidirectional influences between the function of the motor system and somatosensory system [80, 98]. Lasting plasticity in M1 and S1 can be evoked by repetitive patterned stimulation originating from corticocortical fibers arising in the opposite primary cortex (S1 to M1 as well as M1 to S1) both in humans and animal models [99-102]. Acute phasic cutaneous pain as well as tonic cutaneous and muscular pain suppresses motor cortex excitability in healthy subjects [80, 82, 86, 103]. Motor cortex oscillatory activity shows enhanced coherence during acute phasic pain, while voluntary movement preparation suppresses subjective pain intensity and evoked potentials elicited by painful laser stimuli [104-106]. Acute prolonged tonic pain impairs retention of motor training without impairing performance improvements during acquisition [107]. Interestingly, TMS studies have shown decreased inhibition in the form of

reductions in cortical silent period (CSP) and short interval intracortical inhibition (SICI), GABAergic mediated measures in chronic pain syndromes such as complex regional pain syndrome and painful diabetic neuropathy, but also in fibromyalgia [27, 84, 85, 98, 108, 87, 109]. Previous healthy subject studies have shown that moderate prolonged tonic pain mediated by capsaicin suppresses MEPs, while enhancing SICI and CSP for the 60 to 80 minute duration of capsaicin mediated pain [82, 88, 110]. In fact, aberrant motor cortex excitability induced either by a prolonged tonic pain model in healthy subjects or by a chronic pain disorder in patients may be normalized by analgesic M1 neuromodulation [27, 111, 88, 112].

Descending pain modulatory network involvement in motor cortex neuromodulation

A series of studies by the Lyon group found patients with implanted EMCS had increased brain activity as measured by PET in areas including pgACC, dACC, medial thalamus, and periaqueductal grey (PAG), which correlated with magnitude of pain alleviation as well as enhanced functional connectivity between pgACC and PAG after 30 to 45 minutes of EMCS [90, 113, 114]. Further studies by this group found evidence of enhanced endogenous opioid release in anterior midcingulate cortex (aMCC) and PAG in response to EMCS, and that prestimulation opioid receptor availability positively predicted magnitude of pain alleviation [115, 116]. This pattern of responses in the ACC, medial thalamus and PAG has been found by other groups using pain alleviative EMCS in humans, and replicated in animal models of neuropathic pain and in tonic pain ameliorated by M1 tDCS [89, 117-121, 97]. Studies in healthy subjects and chronic pain patients have found evidence that high frequency rTMS targeting M1 is in part mediated by opioid- and NMDA-dependent mechanisms as well as evidence of β-endorphin release [122-124, 63]. Studies in patients and healthy controls have found variable neural responses and pain amelioration effects after excitatory, anodal transcranial direct current stimulation (M1-anodal tDCS) and excitatory M1 rTMS. Additionally, while neurophysiological responses show no clear direction of modification across studies, there is evidence of response modulation in pain-associated regions including PAG, ACC, somatomotor cortex, anterior and posterior insula, S2 cortex, dorsal medulla, and basal ganglia structures [125-130, 97]. Related evidence from rTMS studies targeting DLPFC, which has been shown to reverse the effects of prolonged tonic pain on motor cortex excitability, demonstrate a naloxone-sensitive effect that reduces activity in pgACC and PAG [88, 123, 131]. Furthermore, recent evidence in healthy subjects undergoing [^{11}C]carfentanil PET after high frequency rTMS of the somatomotor cortex found evidence of release of endogenous opiates in the ACC and medial prefrontal cortex ipsilateral to rTMS and in operculoinsular structures contralateral to rTMS [132].

Animal studies of EMCS have demonstrated naloxone-sensitive anti-nociceptive effects in acute and chronic pain models [92, 118, 119, 133, 134]. Studies in animal pain models have demonstrated that reduced nociceptive-related defensive responses associated with EMCS is accompanied by decreases in spontaneous or evoked neural activity related to nociception in the spinal dorsal horn (SDH), pontine reticular formation, PAG and parafascicular nucleus, the centromedian, ventroposterolateral and posterior nuclei of the thalamus, as well as the somatosensory and prefrontal cortex [92, 93, 118-120, 134, 1, 135]. Further, anti-nociceptive effects were associated with increased nociceptive and basal neural activity in the ACC,

basolateral and central nuclei of the amygdala, and PAG coupled with increased release of the inhibitory amino acids glycine and GABA in the PAG [118-120, 136]. The profile of neuronal activation by motor cortex stimulation in rodent studies supports the involvement of descending pain modulatory network, especially the ACC and PAG as well as modulation of SDH processing of noxious stimuli [119, 135].

Future promising directions in NIBS for chronic pain

In addition to the need for clinical trials with greater numbers of patients and better trial design, larger analgesic effects may be expected from alternative protocols using neuromodulatory methods as adjuncts to cognitive behavioral therapy or rehabilitation or from neuromodulation targeted to known neurophysiological abnormalities which accompany chronic pain. Recent studies have revealed important potential examples of alternative protocols and a novel method of neuromodulation. Increased attention from funding agencies such as the NIH, should spur future progress, particularly in response to RFAs from the BRAIN Initiative such as “Non-Invasive Neuromodulation - New Tools and Techniques for Spatiotemporal Precision (R01)" and “Non-Invasive Neuromodulation - Mechanisms and Dose/Response Relationships for Targeted CNS Effects (R01)."

Chronic pain conditions are accompanied by alterations in cortical excitability, but these alterations are thought to be caused by loss of inhibitory drive from the thalamus. The result is a phenomenon known as thalamocortical dysrhythmia (TCD) [137, 138]. The result of TCD is the well-known cortical reorganization that accompanies chronic pain as well as the lesser known reduction in alpha EEG power, oscillations in the 8 to 12 Hz range and enhancement of theta power [139-142]. Recent studies have shown this shift in peak alpha to occur not only in chronic pain patients, but to occur in response to tonic pain models and peak alpha to be predictive of individual sensitivity to such tonic pain models [142, 143]. Transcranial alternating current stimulation (tACS) at alpha frequencies, such as 10 Hz, at intensities like tDCS allows entrainment of cortical oscillations [144]. Recent studies have shown alpha tACS induced an increase in alpha EEG in chronic low back pain patients which was correlated and accompanied by a reduction in pain intensity [145]. In healthy subjects, evoked pain was reduced by alpha tACS only when the stimulus was of an uncertain intensity, perhaps reflecting enhanced threat or anxiety [4].

Several studies have evaluated the effects of NIBS combined with other therapies such mirror therapy for phantom limb pain, aerobic exercise for fibromyalgia and peripheral electrical stimulation for chronic low back pain [146, 147, 73]. Finding the optimal combinations of NIBS and complementary or traditional pain therapies will take several elaborate and sophisticated RCTs.

While electrical stimulation of the brain is a logical extension of the electrical properties of nervous tissue, recently it has been reported that transcranial ultrasound at sub-lesional intensities can lead to the modulation of neurons in both animal models as well as humans [5]. Low intensity transcranial ultrasound (TUS) has shown promising analgesic effects and improvement of mood in chronic pain patients [148]. No additional studies have reported effects of low intensity TUS in chronic pain populations.

Conclusion

The last 5 years of research activity on noninvasive brain stimulation (NIBS) has yielded promising results in the treatment of chronic pain. Studies investigating the potential mechanisms underlying the analgesic effects of NIBS has shown that both endogenous opioid releasing regions of the brain and modifications of somatomotor plasticity that accompany chronic pain syndromes are involved in the initial and lasting analgesic actions of NIBS. An exciting decade lays ahead where novel stimulation methods and modalities such as tACS and TUS should be expected to contribute more flexibility to the NIBS armamentarium. Future improvements in clinical trial protocols for devices, conduct and reporting will be necessary to further refine the precision of trial results and interpretation. Increased support and attention from funding agencies such as the NIH would encourage larger and more mechanism driven clinical trials. Much work remains, but recent developments inspire more interest in the field of NIBS for chronic pain.

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• Of importance

• Of major importance

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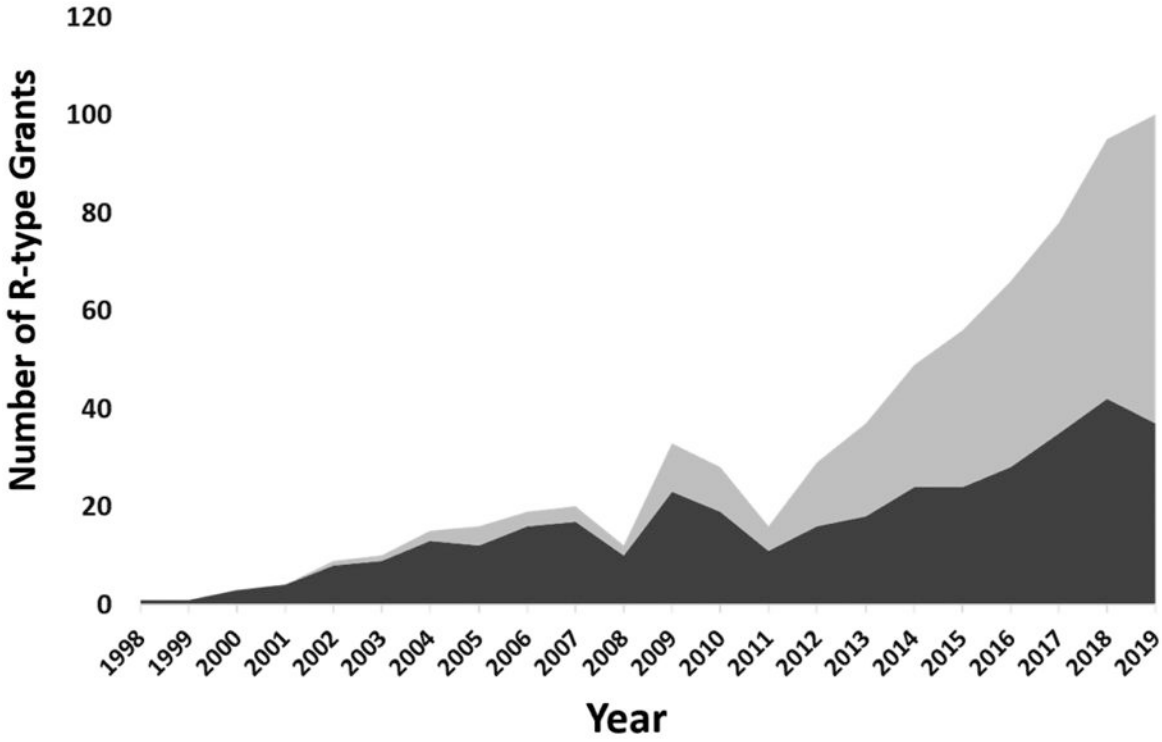

Figure.

In dark grey, R-type grants mentioning rTMS in the public abstract. In light grey, R grants mentioning tDCS in the public abstract.