Neuromodulatory treatments for chronic pain: efficacy and mechanisms

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Abstract

Chronic pain is common, and the available treatments do not provide adequate relief for most patients. Neuromodulatory interventions that modify brain processes underlying the experience of pain have the potential to provide substantial relief for some of these patients. The purpose of this Review is to summarize the state of knowledge regarding the efficacy and mechanisms of noninvasive neuromodulatory treatments for chronic pain. The findings provide support for the efficacy and positive side-effect profile of hypnosis, and limited evidence for the potential efficacy of meditation training, noninvasive electrical stimulation procedures, and neurofeedback procedures. Mechanisms research indicates that hypnosis influences multiple neurophysiological processes involved in the experience of pain. Evidence also indicates that mindfulness meditation has both immediate and long-term effects on cortical structures and activity involved in attention, emotional responding and pain. Less is known about the mechanisms of other neuromodulatory treatments. On the basis of the data discussed in this Review, training in the use of self-hypnosis might be considered a viable 'first-line' approach to treat chronic pain. More-definitive research regarding the benefits and costs of meditation training, noninvasive brain stimulation and neurofeedback is needed before these treatments can be recommended for the treatment of chronic pain.

Introduction

Chronic pain is a common problem worldwide that incurs substantial individual and social costs.[1–5] Estimates of the prevalence of chronic pain in the population vary from about 20–40%, depending on how it is measured.[1,6] Chronic pain of all types is known to have a negative impact on quality of life, and costs hundreds of billions of dollars in the USA alone (US$560–635 billion per year in 2010 constant dollars, according to one estimate[4]). Chronic

pain of neuropathic origin tends to be more severe and to have larger negative effects on sleep, psychological functioning and employment functioning than non-neuropathic chronic pain.[3,7]

The most common treatments for chronic pain are medications, and a variety of classes of pharmaceuticals have been recommended as first-line, second-line and third-line treatment options for chronic neuropathic pain.[8,9] By contrast, nonpharmacological treatments tend to be mentioned as treatments of last resort or treatments to 'consider', if they are mentioned at all. However, most patients with chronic pain do not experience clinically meaningful pain relief with medication management alone. A recent meta-analysis of the efficacy of opioids —considered by many to be the most powerful analgesic class available—for chronic pain concluded that these drugs result in only small improvements in pain intensity relative to placebo.[10] Even among individuals who do experience some benefit with medications, complete pain relief is extremely rare.[8,11] Perhaps in part because of the lack of efficacy of available pharmacological treatments, as well as a recognition of the multiple physiological and psychological factors that contribute to the severity of chronic pain, experts are increasingly examining the potential benefits of psychological and electrical neuromodulatory interventions for the treatment of various pain conditions.[11]

The strongest rationale for considering neuromodulatory approaches as treatments for chronic pain is the growing understanding that all pain is ultimately the result of supraspinal cortical processing;[12] that is, our experience of pain results from what the brain does with sensory input, rather than from the sensory input itself. Therefore, any intervention that targets pain-related brain activity has the potential to influence pain.[13] A number of interventions target brain activity as a primary focus of treatment. These include hypnosis, which first seeks to alter the individual's brain state via 'hypnotic trance' before making suggestions for changes; meditation practices, which teach and encourage states such as 'mindfulness'; neurofeedback, including both functional MRI (fMRI) and EEG biofeedback; and cortical electrical stimulation procedures, including transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS).

The purpose of this Review is to summarize the state of knowledge regarding the efficacy and mechanisms of these neuromodulatory interventions as treatments for chronic pain. Each approach will be discussed sequentially, beginning with a brief description, followed by a review of available evidence regarding the treatment's efficacy and its potential mechanisms of action. The article concludes with a discussion of the clinical and research implications of the findings.

Hypnotic analgesia

Definition and description

Hypnosis has been defined as "a social interaction in which one person, designated the subject, responds to suggestions offered by another person, designated the hypnotist, for experiences involving alterations in perception, memory, and voluntary action."[14] Standard hypnotic treatments usually begin with an induction that involves an initial set of suggestions for patients to focus their attention on a single stimulus (for example, a spot on

the wall, sensations associated with breathing) and to experience initial changes in perceptions (for example, relaxation).[15] The hypnotic induction is thought to increase the subject's openness or willingness to respond to the suggestions that follow—an idea that is supported by experimental evidence.[16,17]

The hypnotic induction is followed by suggestions that target changes in the presenting problem. For individuals with pain, these might include suggestions for greater comfort or ability to function well in the presence of pain. The suggestions that are provided following the hypnotic induction can be of many types (examples are provided in Box 1). Hypnosis for chronic pain also usually includes 'post-hypnotic' suggestions provided at the end of the session that the benefits experienced during the session will continue, and that the patient can practice self-hypnosis by using a cue to re-experience the benefits from treatment.[18] Sessions are often recorded, and patients are encouraged to practice self-hypnosis by listening to the recordings regularly. In this way, patients are given considerable control over the process: hypnosis is taught as a skill for patients to practice and use on their own, as opposed to a treatment given to the patient.

Box 1

Hypnotic suggestions for chronic pain management

The following are examples of hypnotic suggestions that can be used for the management of chronic pain.

Direct suggestion for comfort

"You are noticing where in the body you feel the greatest comfort, and allowing this sense of comfort to expand…"

Indirect suggestion for treatment benefits

"I don't know how you will find the most benefit from today's session … perhaps you will experience a sense of relaxation and increased ability to ignore uncomfortable sensations … but I do know that you will find yourself experiencing more and more comfort and control…"

Use of metaphors

"You might experience any uncomfortable sensations as an image or object, such as a fire or tightly knotted rope … that's right … and now notice how that object changes … and as you notice these changes, your experience changes … becoming more and more comfortable…"

Post-hypnotic suggestions for maintenance of gains

"And the comfort, useful insights, and other benefits you achieved for yourself in today's session will last beyond the session … automatically … for as long as they are useful to you … for minutes, for hours, days, years, and decades…"

Effects

Several narrative and systematic reviews have examined the efficacy of hypnosis for reducing pain in individuals with a variety of chronic pain conditions.[19–22] Each of these reviews has come to the same conclusion: hypnotic treatments reduce pain intensity effectively, and do so for a wide variety of pain problems. Moreover, the beneficial effects are specific, occurring over and above any effects due to time, therapist attention and outcome expectancy. Thus, hypnosis is more than a type of placebo treatment.

These reviews do not usually examine or discuss the variability in treatment response; that is, the fact that hypnosis may not necessarily be universally effective for all patients. A closer examination of outcome variability might be useful to clinicians and their patients for understanding what they can expect from hypnosis treatment. We have begun to examine these issues in our clinical trials by performing responder analyses,[23] and have indeed found a great deal of variability in individual response to this treatment.[24–26] Interestingly, hypnosis seems to be more effective for some types of pain problems than for others. For example, in individuals with chronic pain associated with spinal cord injury—a chronic pain problem that is refractory to many pain treatments—the response rate (as defined by a 30% or greater reduction in pain[27]) varies from 22% to 27%.[25,26] The response rate is higher (33–47%) in individuals with multiple sclerosis, and even higher (60%) in patients with amputation-related pain.[25] Analyses also suggest that individuals with neuropathic pain might be more likely to respond to hypnosis than are individuals with non-neuropathic pain.[26]

Perhaps in part because of early research demonstrating moderate to strong associations between trait hypnotizability and response to hypnotic analgesia suggestions in the laboratory setting,[28] an impression persists that only individuals who score highly on trait hypnotizability tests can benefit from hypnosis treatment for chronic pain. The evidence, however, indicates weak associations between trait hypnotizability and response to hypnosis in individuals with chronic pain,[24–26] suggesting that patients should not be excluded from hypnosis treatment on the basis of low hypnotizability scores alone.

Findings regarding the possible adverse and beneficial 'side effects' of hypnosis treatment also deserve attention. Although problems have been reported when hypnosis is administered by stage hypnotists where the goal is to entertain an audience, often at the expense of the hypnotic subject,[29] the inherent risk is minimal when hypnosis is provided by trained clinicians.[30] In fact, research indicates that hypnotic treatment of pain can have a large number of beneficial effects on symptoms and conditions that are not necessarily the target of treatment. These effects include such diverse outcomes as improvements in sleep quality,[31–35] creativity,[33] self-efficacy and confidence,[33,34] mood,[31,32,34,35] and socializing.[34,35] We are not aware of any clinical trials that have reported notable adverse effects associated with clinical hypnosis, consistent with the conclusion that hypnosis treatment has an extremely positive side-effect profile.[36–38]

Mechanisms

A growing number of studies are examining the effects of hypnotic analgesia on brain areas and neurophysiological processes that underlie the experience of pain. Three general conclusions can be drawn from this body of work. First, hypnosis and hypnotic analgesia suggestions have been shown to affect virtually all of the neurophysiological processes that underlie the experience of pain, from those in the periphery to those in the spinothalamic tract and numerous cortical areas.[39,40] Second, the specific effects of hypnosis on brain activity depend on the wording of the hypnotic suggestions.[41,42] Last, although people can respond to suggestions for pain relief without a hypnotic induction, the efficacy of analgesia suggestions is enhanced when they are preceded by this step.[16,17,43] This latter finding might be related to neurophysiological changes that occur with a hypnotic induction, which are thought to reduce overall monitoring and executive functioning activities.[44]

Over 50 years ago, Chapman and colleagues examined the effects of suggestions for one arm being 'normal' or 'vulnerable' and the other being 'numb' or 'wooden' on the response to a heated rod applied to the skin of each arm.[45] The researchers found more-severe lesions, higher skin temperatures, and other indications of greater inflammatory responses in the 'vulnerable and normal' arm than in the 'analgesic' arm following noxious heat stimulation (see also Hammond *et al.*[46]). Hypnotic analgesia has also been shown to affect spinal cord reflexes,[47,48] and imaging studies have shown that hypnotic analgesia can reduce activity in virtually all of the supraspinal areas that have been identified as components of the 'pain matrix', including the thalamus,[16,17] sensory cortices,[16,17,42] insula,[16,17] anterior cingulate cortex (ACC),[41] and frontal attentional control systems.[49]

The changes produced by hypnosis seem to depend in large part on the wording of the hypnotic suggestions.[15] For example, suggestions to reduce the unpleasantness of pain that result in a decrease in the extent to which the pain bothers the individual, but not in the intensity of the pain, are associated with reductions in activity in the anterior cingulate cortex (a structure in the limbic system that is thought to process the affective response to pain) but not in the sensory cortices (the structures associated with the processing of the sensory components of pain, such as intensity).[41] By contrast, hypnotic suggestions for reductions in pain intensity result in decreased activity in the sensory cortices, but not in the anterior cingulate cortex.[42] Similarly, hypnotic suggestions for decreased pain can result in reduced connectivity between different cortical sites—a type of neurophysiological dissociation.[50] On the other hand, hypnotic suggestions to relive a pleasant autobiographical event that results in decreased pain results in increases in connectivity between brain areas.[51]

We speculate that the hypnosis-related decreases in connectivity might represent a disruption in the 'pain matrix', and that hypnosis-related increases in connectivity might represent a strengthening of and a focus on what might be referred to as a 'pleasure' or 'comfort' matrix. Either approach can result in a decrease in the subjective experience of pain. Whether or not our speculation regarding the dissociation versus association effects of hypnotic suggestions ultimately proves to be accurate would not detract from the general conclusion supported by these findings; namely, that differences in the wording of hypnotic analgesia suggestions have different effects on the brain. Thus, it seems to make sense to talk about hypnotic analgesia in terms of multiple mechanisms.

A final note about the research on the mechanisms of hypnosis and hypnotic analgesia merits consideration. There has been some controversy in the field regarding whether or not a formal hypnotic induction is necessary for suggestions to be effective. One camp views hypnotic responses as having very few differences, if any, from ordinary day-to-day cognitive processes and responses. In this view, the same factors that contribute to all human behaviour—motivation, attributions and beliefs, cultural and role expectations—influence hypnotic responses via the same underlying mechanisms.[52] Another camp views hypnotic processes and hypnotic responding as having unique characteristics that are separate from normal day-to-day cognitive processes, and view the hypnotic induction as facilitating qualitative changes in cognitive processes that facilitate the response to subsequent suggestions.[53]

A definitive conclusion to this debate has not yet been reached, because the available evidence can be interpreted as being consistent with both views. For example, evidence reported by Derbyshire and colleagues indicates that people can respond to suggestions to experience more or less pain even without a hypnotic induction.[16,17] However, they also found that responses to suggestions are enhanced to some degree following a hypnotic induction. Similarly, evidence indicates some consistent differences in neurophysiological measures between individuals who score highly on hypnotizability tests ('highs') and those who obtain low scores on these tests ('lows'). Specifically, compared with lows, highs tend to have higher baseline levels of theta activity (relatively slow oscillations, 4–7 Hz) as measured by EEG.[54] Theta brain waves are associated with a number of processes and states, including focused and sustained concentration, reduced anxiety and sympathetic autonomic nervous system activity, and enhanced memory functions.[55] Interestingly, both highs and lows also exhibit an increase in theta activity with hypnotic inductions.[54]

The fact that theta oscillations are present to some degree in all individuals, and the possibility that they might facilitate the response to suggestions, could explain why many people can respond to suggestions even outside the hypnotic context or without a hypnotic induction. Consequently, the response to suggestions can be viewed as an 'ordinary' response. Alternatively, because hypnotic inductions might enhance brain patterns that facilitate the response to suggestions, the hypnotic context can also be viewed as contributing to states and responses that differ from ordinary day-to-day experiences.

Meditation

Definition and description

Meditation has historical roots across an array of religious contexts, including Christianity, Judaism, Shintoism, Taoism, Sufism and Buddhism. As such, many forms of meditation exist. The various forms of meditation can, however, be viewed as falling on a continuum between two primary types: mindfulness meditation and concentrative practice. Lutz and colleagues have provided an excellent discussion of these various forms of meditation.[56] Given the different aims and emphases of the various forms of meditation, it is possible that each type could have different effects. To date, however, the greatest amount of research in the context of pain management has focused on mindfulness-based meditation. Furthermore, a recent review concluded that while concentrative practices are not particularly effective for

pain management, mindfulness meditation seems to have positive influences on both sensory and affective components of the experience of pain.[57] Hence, we focus the remainder of our discussion primarily on mindfulness meditation.

Jon Kabat-Zinn, the founder of mindfulness-based approaches within the Western medical community, describes mindfulness as "the awareness that emerges through paying attention on purpose, in the present moment, and non-judgementally to the unfolding of experience, moment by moment."[58] Shapiro and Carlson operationally define mindfulness as both an outcome (mindful awareness) and a process (mindful practice).[59] Under this dually defined model, mindful awareness represents steadfast attention to—and presence with—each moment; mindful practice (meditation) encapsulates the systematic training of the mind to intentionally attend in an open, accepting and discerning way.

Mindfulness meditation for pain management is typically delivered within a structured 8-week Mindfulness-Based Stress Reduction (MBSR) programme in which a series of mindfulness practices are taught in a group setting. The various techniques often begin by inviting patients to hold as the primary object of awareness various sensations (of tastes, sounds or physical sensations, for example), movements (as with yoga and walking meditation), and the breath as it enters and leaves the body. Over time, trainees also learn to focus on and be aware of the arising and passing away of thoughts. Invariably during meditation, distraction arises in a number of forms (for example, thoughts, sounds, painful sensations); however, the premise of mindfulness is simply to notice whatever arises without reacting with attachment or aversion. Patients are instructed to simply label the phenomenon (for example, "thinking"), and then return to the focus (for example, the movements of the breath). In this way, distraction is viewed not as a problem but, rather, as a component of the mindfulness meditation training itself. It provides an opportunity to notice that the mind has wandered, and then, calmly and non-judgementally, to return attention to the focal object. Patients are usually given a series of guided mindfulness audio files, and are instructed to practice meditation for 45 min each day between sessions. Thus, as with hypnosis, mindfulness meditation is taught as a skill in which patients actively engage to develop and use independently, rather than as a treatment that the patient passively receives.

Effects

Research on mindfulness-based treatments for chronic pain is still in its infancy, but there is a small but growing literature of controlled trials on mindfulness-based pain and stress reduction and other mindfulness meditation therapies for chronic illnesses. Several reviews of controlled studies of mindfulness-based treatments for a wide range of clinical populations (including but not limited to chronic pain) have reported significant and moderate improvements on standardized measures of physical health and mental well-being.[60–62] The number of randomized and nonrandomized controlled trials investigating the efficacy of this approach for heterogeneous chronic pain conditions is also steadily increasing.

Although the benefits of mindfulness as a stand-alone treatment compared with—or in combination with—pharmaceutical approaches has not been systematically investigated, most studies have compared group meditation training with standard care, and have found

statistically significant and clinically meaningful improvements in pain intensity with mindfulness meditation. Mindfulness approaches applied to chronic pain conditions are also typically beneficial with respect to disability, pain acceptance, pain catastrophizing, self-efficacy, and measures of affect, both immediately post-treatment and at follow-up.[60–63]

Mechanisms

A rapidly growing body of research is examining the specific neural mechanisms of mindfulness-based treatments for pain relief. It has been hypothesized that mindfulness-related changes in the cortical structures underlying attention and emotional responding,[64,65] in conjunction with the cultivation of mindfulness and pain acceptance, underlie improved pain outcomes.[66] Correlational research has provided tentative evidence in support of this hypothesis. One study within a clinical population with various medical problems, for example, reported that mindfulness meditation corresponded to increased mindfulness, which in turn led to symptom reduction and improved well-being.[67] Mindfulness was also found to mediate treatment gains during an MBSR intervention for irritable bowel syndrome pain.[68] Studies utilizing fMRI and EEG technology in healthy individuals and long-term meditators have demonstrated significant concurrent correlations between mindfulness meditation and brain structure in cortical areas associated with pain perception (see Table 1 for a summary of the findings).[64,69–72]

Neuroimaging results are beginning to identify additional cortical areas associated with meditation practice. For example, among healthy individuals, active mindfulness meditation is generally associated with increased brain activity in the bilateral insula, the rostral ACC, and the dorsomedial prefrontal cortex (PFC).[71,73] The PFC findings are thought to be associated with heightened attention during meditation, whereas activity in the insula and ACC are postulated to be involved in interoceptive awareness.[74,75]

Using fMRI and a thermal pain paradigm, Grant and colleagues found that compared with controls, experienced practitioners of mindfulness meditation (in a non-meditative state) showed reduced activation in executive, evaluative and emotion areas (PFC, amygdala and hippocampus) and concurrent increased activation in primary pain-processing regions (ACC, thalamus and insula) during painful stimulation.[70] Moreover, the higher pain thresholds in the expert meditators that were found in this study were associated with reduced functional connectivity between the midcingulate cortex (MCC) and dorsolateral PFC, suggesting a decoupling of cognitive-evaluative and sensory-discriminative brain networks—a finding and interpretation that is consistent with mindfulness theory.

Using a similar thermal pain paradigm, Lutz and colleagues conducted an fMRI study of expert meditators (in a meditative state), and found that, compared with novices, experts showed enhanced activation in the 'salience network' (the dorsal anterior insula and the anterior MCC) during pain, indicating faster neural habitation.[76] This increased activity correlated with reduced baseline activity in the same areas before the painful stimulus was administered, and enhanced neural habituation in the amygdala and pain-related regions, suggesting a downregulation of anticipatory processes associated with pain. Of note, an experimental pain study among healthy individuals reported that even brief mindfulness meditation training (20 min of mindfulness practice per day for 4 days) can result in reduced

pain ratings and decreased pain-related activity in the bilateral insula and primary and secondary somatosensory cortices.[65] This latter study has important implications with regard to the potential effectiveness of mindfulness meditation training in patients with chronic pain, many of whom may be novice meditators.

Evidence suggests that mindfulness can also elicit enduring, trait-related brain changes—an important consideration in the context of treatment of chronic pain conditions. Compared with controls, long-term, expert meditators show increased grey matter and cortical thickness in the hippocampus, brainstem, posterior and anterior insula, MCC, and parietal cortex and PFC.[71] One study showed that thickness in these regions correlated positively with number of years or hours spent in mindfulness practice, and correlated inversely with sensitivity[77] to an experimentally induced pain stimulus. Importantly, the MCC is involved in pain inhibition,[78] and reduced grey matter volume in this region is often found in individuals with chronic pain.[79] Of note, even brief mindfulness meditation training has been associated with structural brain changes including increased grey matter in the hippocampus and parietal regions,[71] a finding that again speaks to the potential benefits of providing mindfulness training to novice meditators for chronic pain management. To the best of our knowledge, fMRI research systematically investigating the neural correlates of learned meditation for chronic pain management in novice practitioners has yet to be conducted.

Reviews of EEG meditation studies (predominantly conducted with healthy individuals) converge with the fMRI findings described above to provide further evidence that mindfulness meditation produces relatively short-term brain state changes, as well as potential long-term changes in neurophysiological function. For example, research has consistently shown a state-related slowing of alpha rhythm and increased state-related and trait-related alpha power with mindfulness meditation;[80] these effects do not seem to depend on the type of meditation or relative experience of the meditator.[72] The effects of mindfulness meditation on alpha activity might be associated with reduced anxiety, and feelings of calm and positive affect.[80] Increased theta activity is also consistently found during some meditation practices.[80] Associations between increased theta activity and meditation proficiency have been observed, with this effect more likely to occur in advanced practitioners.[81] Reported findings of increased power coherence and gamma band effects with meditation are emerging.[79] Some research suggests that increased gamma band activity might only be seen in advanced, long-term mindfulness practitioners.[72]

An additional study pertaining to the potential benefit of long-term meditation practice examined event-related potentials during anticipation of pain, and found that long-term practice alters anticipatory evaluation and processing of pain in the MCC and other pain regions.[69] This finding is consistent with those of Lutz and colleagues.[76] Finally, a review of the literature reported an effect of mindfulness meditation on prefrontal alpha asymmetry in different populations,[82] and a shift towards left-sided anterior activation,[83,84] a pattern associated previously with positive emotions.[85]

Although there are limitations to the research discussed above (see Cahn and Polich[80] for an excellent overview of the limitations most commonly noted), taken together, the degree of

concordance between fMRI and EEG studies conducted with healthy individuals and long-term meditators suggests that mindfulness meditation can instigate state-related and trait-related brain changes in areas associated with attention, emotional responding, and pain perception. The evidence is consistent with a view that mindfulness modulates experimentally induced pain through enhancement of the frontal attentional control systems, and reductions in evaluative and emotional responses and arousal.[64,65,80] The extent to which these findings translate into an understanding of the mechanisms of mindfulness for alleviation of chronic pain in the clinical setting is unclear. Overall, however, the evidence to date implicates mindfulness meditation in eliciting neuroprotective structural and functional brain changes that hold potential for reducing the pain and suffering associated with chronic pain conditions.

Noninvasive brain stimulation

Definition and description

Noninvasive brain stimulation techniques provide electrical stimulation of the brain via direct current or pulses of magnetic fields (Figure 1a,b). The two techniques that have been studied the most with respect to pain management are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS stimulates cortical tissue via a magnetic coil that is placed near the scalp above the targeted area. When a current is passed through the coil, a magnetic field is produced that penetrates the skull. The current can be provided in pulses of different frequencies. High-frequency stimulation (5 Hz) lowers neuronal firing thresholds so that they can fire with less stimulation from other neurons, thereby increasing brain excitability, whereas low-frequency stimulation (usually 1 Hz) increases firing thresholds, thereby inhibiting excitability. Stimulation is provided in 'trains' of pulses of varying lengths, and can also vary in intensity as well as overall duration.

tDCS provides a weak current (usually 1–2 mA) directly to the scalp via large electrodes, usually for 20 min per session. Standard treatment involves one session of stimulation per day for 5 days (a total of 1 h 40 min of stimulation). The current provided via the positive electrode (anode) lowers the firing threshold of the neurons that lie in the cortex immediately below the electrode and, therefore, results in greater neuronal excitability of these neurons. Negative current (provided via the cathode) increases the firing threshold of the neurons below the electrode, resulting in greater inhibition of those neurons.

A common target for chronic pain treatment with both rTMS and tDCS is to stimulate the motor cortex contralateral to the painful area; for example, for right shoulder pain, the rTMS magnet or tDCS anode would be placed over the left motor cortex. Motor cortex activity is thought to limit the processing of nociceptive signals by sending inhibitory signals directly to the thalamus, thereby reducing the perceived intensity of the pain.[86,87]

Effects

A number of reviews summarizing findings regarding the efficacy of rTMS and tDCS for the treatment of various chronic pain conditions have been published over the past 3 years.[86–90]

These reviews have noted a great deal of variability in outcome between studies: most report weak to strong effects on pain reduction, but a small minority report increases in pain with stimulation.

The heterogeneity in findings suggests the probable existence of factors that moderate treatment effects. For rTMS, one of these factors seems to be stimulation frequency; that is, low-frequency stimulation (<5 Hz) does not appear to result in meaningful reductions in pain intensity.[87] For both rTMS and tDCS, the stimulation site seems to be important, with stimulation of the motor cortex eliciting greater reductions in pain intensity than stimulation at other sites.[87,88] The type of pain might also be a contributing factor. For example, a 2009 study reported that rTMS was more effective in improving central neuropathic pain than peripheral neuropathic pain.[91] In addition, rTMS providing high-frequency stimulation over the motor cortex in individuals with chronic neuropathic pain seems to result in more pain reduction than does this same stimulation protocol in individuals with non-neuropathic pain.[87] Finally, recent research suggests that the efficacy of high-frequency stimulation might be enhanced by first 'priming' the motor cortex with intermittent bursts of low-frequency (theta) stimulation.[92]

Very few studies have examined the long-term effects of cortical stimulation in patients with chronic pain, but the findings that are available suggest a lack of long-term benefit.[86–88,93] Both rTMS and tDCS are associated with transitory minor adverse events in some individuals, which include transient headache, fatigue, scalp irritation, sleep problems, and dizziness.[86–88] However, neither procedure seems to increase the risk of any serious or lasting adverse effects.

Mechanisms

At the most basic level, like any neuromodulatory treatment, noninvasive brain stimulation strategies are thought to reduce pain through alterations in the activity of brain areas that are involved in pain processing.[87] Consistent with this possibility, research findings support an impact of both tDCS and rTMS on cortical excitability.[94,95] However, the mechanisms through which reductions in pain result from stimulation of the motor cortex—the stimulation site with evidence for the greatest efficacy in pain reduction—are not yet entirely clear.

Researchers note that motor cortex stimulation has widespread effects on multiple cortical (cingulate, frontal cortices, thalamus and striatum) and subcortical (periaqueductal grey matter) structures.[88] This observation raises the possibility that stimulation may operate via more-general effects: just as a loud noise that could disrupt the work being done in a meeting, electrical brain stimulation might simply 'interrupt' the processing of pain across a number of different areas. One hypothesis is that stimulation of the γ-aminobutyric acid-expressing (GABAergic) inhibitory neurons in the motor cortex directly inhibits activity in thalamic nuclei, thereby blocking all somatosensation, including nociception.[86] However, the evidence shows that tDCS, for example, results in a large cascade of changes at multiple levels, and instigates changes not only in GABAergic activity, but also in glutamatergic, dopaminergic, serotonergic and cholinergic activity.[89] At this point in time, the issue of which of these changes—in isolation or in combination—produces salutary pain effects has

yet to be clarified. Furthermore, the possibility remains that treatment-induced changes associated with brain stimulation that are not currently fully elucidated (for example, changes in brain gamma activity)[96] could be core underlying mechanisms of these procedures.[97]

Neurofeedback

Description

Neurofeedback is a type of biofeedback in which patients are provided with direct information regarding brain activity, as determined by either the amplitude (also known as 'power') of EEG-assessed brain oscillations measured from electrodes placed on the scalp (Figure 1c), or the amount of blood flow in specific areas of the brain as measured by fMRI. Reinforcing feedback regarding the extent to which training criteria are being met is provided to patients in real time via both visual (that is, a computer screen) and auditory modalities. The goal of training is to decrease brain activity thought to be associated with the processing of nociceptive information (for example, beta wave patterns in the 13–21 Hz frequency range or blood flow in the anterior cingulate cortex), and to increase activity hypothesized to be associated with reduced pain information processing and increased relaxation (for example, alpha patterns in the 8–12 Hz frequency range). Training (electrode) sites used for EEG neurofeedback treatment of pain often include sites that are near the sensory cortices (for example, T3 and T4 in the 10–20 system),[98,99] as well as a central site that could exert more-global effects on brain activity (for example, Cz in the 10–20 system),[98,100] although other electrode training sites have also been used.

Effects

To our knowledge, no large-scale clinical trial has been completed to test the efficacy of neurofeedback for any chronic pain problem. However, a number of pilot studies and case series have been published, which provide a preliminary sense of the potential of this treatment to benefit patients with chronic pain. One early pilot trial in a small ($n = 12$) sample of patients with headache demonstrated that patients who received 20 sessions of alpha enhancement neurofeedback reported more reduction in headache activity than did patients who received standard care.[101] Another study found that patients who received any one of four different biofeedback interventions (including one designed to increase alpha power) reported significant reductions in headache activity.[102] One study comparing two biofeedback treatments (one to increase hand warmth and the second to increase alpha power) and a self-hypnosis training intervention in a sample of 33 individuals with migraine headache found positive effects for all three treatments that did not differ significantly between conditions.[103] These preliminary findings suggest that neurofeedback—specifically, alpha enhancement neurofeedback—has the potential to reduce headache frequency and severity, and that this approach might have similar efficacy to other forms of biofeedback (or hypnosis) for the treatment of headache pain. Studies with larger sample sizes are needed to determine whether this conclusion holds when tested more definitively.

A more recent study in patients with fibromyalgia randomly assigned 18 patients to receive either 20 sessions of neurofeedback to enhance the sensory motor rhythm frequency

bandwidth (12–15 Hz) or 10 mg of escitalopram per day for 8 weeks.[104] Although both treatment groups reported significant improvements across all outcome measures, the participants receiving the neurofeedback training reported significantly greater improvement than did those who received escitalopram. Interestingly, no significant pre-treatment to post-treatment changes in the mean amplitudes of any EEG-assessed bandwidth were observed.

In 2013, we published an uncontrolled case series examining the effects of 12 sessions of EEG neurofeedback in 10 individuals with spinal cord injury and chronic pain.[105] Three protocols (four sessions each) were used for all participants, although they each involved reinforcement of the amplitude of slower oscillations (alpha and sensory motor rhythm frequencies) and suppression of both beta and theta power. The participants reported modest pre-treatment to post-treatment reductions in worst pain and pain unpleasantness, which were maintained at 3-month follow-up. Pre-treatment to post-treatment changes in EEG-assessed oscillations were observed that were consistent with the training protocols for theta and alpha power (decreases and increases, respectively), but not beta power. However, EEG activity returned to baseline levels by the 3-month follow-up assessment, even though pain intensity did not, suggesting that the observed changes on EEG could have reflected brain states that facilitate change in pain but do not underlie the pain experience *per se.*

Another study testing the effects of real-time fMRI biofeedback to teach patients to gain control over activity in the anterior cingulate cortex (a brain area consistently associated with the experience of pain) demonstrated marked decreases in pain—five of eight patients studied reported pain reductions of 50% or greater—with this treatment.[106]

In summary, the available evidence indicates that neurofeedback may be beneficial for patients with chronic pain, but its specific effects, relative to appropriate control conditions, have yet to be tested in methodologically sound clinical trials.

Mechanisms

The traditional rationale underlying neurofeedback treatment for chronic pain has been based on two critical assumptions.[13,107] The first assumption is that brain oscillations in certain bandwidths reflect neurophysiological processes that underlie the experience of pain. The second assumption is that neurofeedback training effectively alters the amplitude of those pain-related oscillations, shifting them from patterns associated with the experience of pain to patterns associated with the experience of comfort. Although early studies provided some limited support for these assumptions, the relationships between EEG-assessed brain patterns and pain are likely to be more complicated than was originally thought.

Findings from studies of acute (induced) pain models have shown fairly consistent patterns of effects of pain on brain oscillations. Specifically, more-intense pain stimuli produce an increase in power across all bandwidths, suggesting global excitability. Moreover, beta frequencies tend to increase more than other bandwidths, and the power of alpha, relative to overall power, tends to decrease.[108–110]

Research examining differences between individuals with and without chronic pain on EEG measures is scarce. However, the findings from the few clinical studies that have been

performed to date are generally consistent with those from acute (induced) pain studies. In one study, for example, individuals with chronic pain were shown to have elevations in all EEG frequency bandwidths, and more relative beta activity and less relative alpha activity, compared with those without chronic pain.[111] In contrast to the findings from acute pain research, however, patients with chronic pain in this study exhibited more very slow theta activity (both absolute and relative) than did those without chronic pain. The authors of this study hypothesized that these EEG differences might have been the result of a thalamocortical dysrhythmia. Specifically, they hypothesized that increased thalamic theta activity resulting from decreased input into the thalamus contributes to an increase in theta activity throughout the cortex, which interferes with cortical inhibition of pain. Subsequently, this results in increased cortical activity in the beta bandwidth, and leads to positive symptoms, including pain.[112]

The results from a number of recent studies call into question the assumption that EEG-assessed oscillations directly reflect pain intensity or the neurophysiological processes that underlie the experience of pain. A study published in 2013, which compared EEG measures between groups of individuals with spinal cord injury who did and did not have chronic pain, replicated the previous findings of increased theta and reduced alpha activity in individuals with chronic pain.[113] Among those with chronic pain, however, few significant associations were found between EEG brain activity measures and pain severity, except that more alpha activity, as measured from frontal electrode sites (perhaps reflecting less inhibitory activity), was associated with more pain.[113] Moreover, in a case series examining the effects of single sessions of four neuromodulatory approaches (hypnosis, meditation, motor cortex tDCS, and neurofeedback designed to inhibit beta and increase alpha activity), pre-session to post-session changes in EEG activity were not associated with changes in pain.[96] Thus, although some evidence suggests that neurofeedback can be effective in reducing chronic pain, the question of whether it produces these benefits by reducing brain oscillations specifically associated with the experience of pain, by increasing oscillations associated with the experience of comfort, or via other as yet unidentified mechanisms, remains to be answered.

Summary and conclusions

Overall, this Review indicates that the level of evidence for various noninvasive neuromodulatory treatments for chronic pain varies across treatment modalities. Much more is known about effects and mechanisms for hypnosis than for the other treatments, but each of the other treatments has shown some promise to benefit individuals with chronic pain. Table 2 lists the advantages and disadvantages of the neuromodulatory pain interventions reviewed in this article.

The efficacy of hypnosis treatment for reducing chronic pain is supported by fairly consistent evidence. Although more research with larger numbers of participants would be welcomed to test the efficacy and mechanisms of this approach, the available evidence supports its specific effects on many—if not all—of the identified neurophysiological processes involved in the experience of pain. Moreover, once people learn self-hypnosis strategies, they tend to continue to use them, and the benefits of treatment tend to last (for at

least 12 months). In addition, the side-effect profile of hypnosis is excellent, and patients who learn to use hypnosis report a large variety of beneficial effects on well-being. However, like all other extant pain treatments including analgesic medications, treatment outcome with hypnosis is variable, and not everyone responds. Nevertheless, in our view, given its potential for pain reduction and positive side-effect profile, hypnosis might be considered as a reasonable 'first-line' treatment for chronic pain.

To date, too few studies of mindfulness meditation have been conducted to enable firm conclusions to be drawn regarding its effects on chronic pain. A growing body of research, however, supports the effects of mindfulness meditation on the brain structures and processes involved in attention and pain control, providing an indication of how ongoing mindfulness practice could help individuals to control pain. The limited available evidence regarding efficacy is promising, and provides a rationale for full clinical trials with adequate sample sizes to determine the benefits of mindfulness meditation, and to identify the subgroups of patients for whom the benefits are likely to be greatest.

Preliminary evidence also supports the potential for noninvasive brain stimulation techniques that increase activity in the motor cortex to reduce chronic pain, at least in the short term. These treatments might benefit individuals with neuropathic pain to a greater extent than those with non-neuropathic pain. However, even within samples of individuals with neuropathic pain, outcomes are highly variable, suggesting that additional moderating factors may be operating. Research is needed to determine whether changes in treatment parameters (for example, more sessions, longer sessions, stronger stimulation, addition of regular 'booster' treatment sessions, 'priming' with theta stimulation before treatment) increase the maintenance of benefits of these treatments.

Evidence that neurofeedback can reduce the severity of chronic pain is also emerging. However, the benefits reported to date seem to be moderate at best, and knowledge regarding long-term maintenance of these benefits is lacking. Given the importance of the problem of chronic pain, research into any treatment that could potentially alleviate chronic pain in even a subset of individuals would be useful. On the basis of the available evidence for the treatments reviewed in this article, neurofeedback approaches currently hold the least promise in terms of providing significant benefits to large numbers of individuals with chronic pain. The possibility remains, however, that neurofeedback, which has good evidence for altering brain activity in ways consistent with training parameters, might work synergistically with other treatments to enhance their overall efficacy. For example, given that individuals with higher theta power are more responsive to hypnotic suggestions, neurofeedback protocols that teach individuals to increase theta power on command could potentially make them more receptive to hypnotic treatments. Similarly, as higher levels of activity in the motor cortex are associated with greater ability to suppress pain, neurofeedback protocols that teach individuals to enhance activity in the motor cortex could, in turn, enhance the efficacy of tDCS or rTMS treatments.

Ultimately, the primary goal for most patients is to experience the most relief possible from treatments that are effective yet have minimal adverse effects (and, ideally, maximum

positive 'side effects'). As we have highlighted in this article, neuromodulatory treatments should clearly be conceptualized as tools that could contribute to this goal.

Acknowledgments

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Key points

- Chronic pain is common and has substantial negative consequences for individuals and society

- As the brain is ultimately the organ that processes pain information, treatments that target brain activity have the potential to provide pain relief

- Solid evidence indicates that hypnosis has short-term and long-term benefits for a variety of pain problems, and should be considered as a first-line treatment given its demonstrated efficacy and positive side-effect profile

- Training in meditation shows promise for reducing chronic pain, although more research is needed to confirm the initial findings

- Noninvasive brain stimulation is potentially effective for reducing chronic pain in the short term, but preliminary evidence suggests that brain stimulation alone might not have long-term benefits

- Neurofeedback has some potential for reducing chronic pain, although the research findings suggest weak effects when this technique is used alone

Review criteria

We searched the MEDLINE and PsychINFO databases between January 1990 and December 2013 using the search terms "chronic pain" or "neuropathic pain" with "epidemiology", "hypnosis", "meditation", "brain stimulation", "tDCS", "tTMS" and "neurofeedback". We focused primarily on systematic reviews and meta-analyses for the key summary conclusions, but also identified key empirical articles (mostly randomized controlled trials, when available), both through the reference lists of the review articles and through the original search, that would be useful for providing information regarding treatment mechanisms.
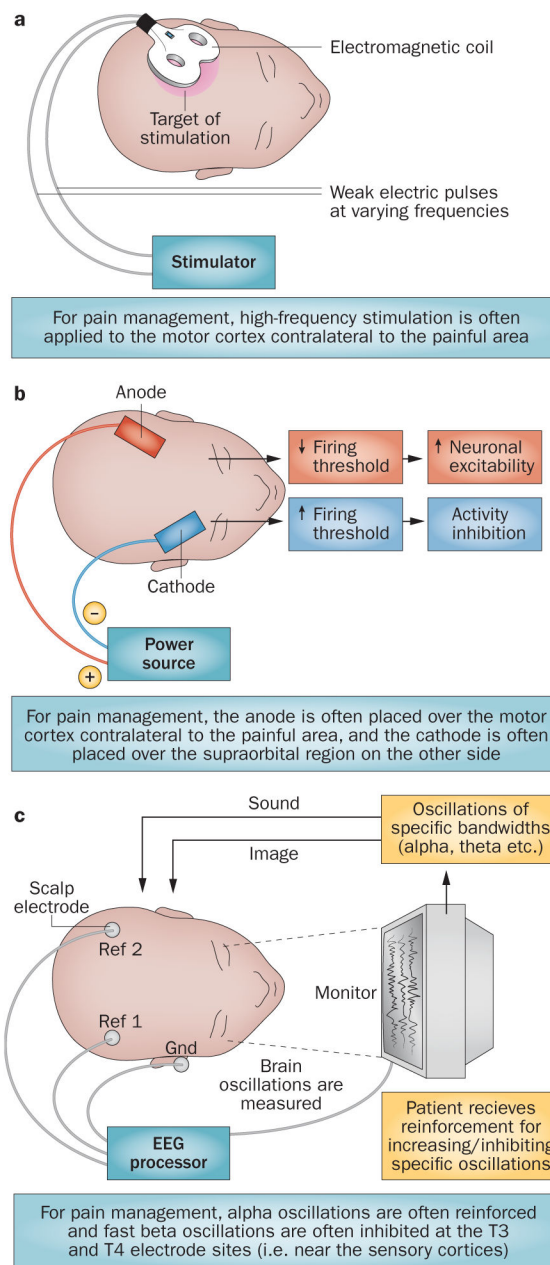
Figure 1.
Noninvasive brain stimulation and neurofeedback techniques for the treatment of chronic pain. **a** | Repetitive transcranial magnetic stimulation. **b** | Transcranial direct current stimulation. **c** | EEG biofeedback (neurofeedback). Abbreviations: Gnd, ground electrode; Ref, reference electrode.

Table 1

Effects of meditation in patients with chronic pain

Brain area or bandwidth	Effect	Hypothesized function and/or behavioural correlate
Primary and secondary somatosensory cortices	Decreased pain-related activation (post-meditation)	Decreased pain processing, associated with lower self-reported pain intensity [*]
Insula	Increased activation	Increased control over sensory processing among experienced meditators [‡]
Bilateral insula	Increased activation (during meditation) Decreased pain-related activation (post-meditation)	Increased interoceptive awareness [§] Decreased pain processing, associated with lower self-reported pain intensity [*]
Posterior and anterior insula	Increased grey matter	Thickness inversely correlated with pain sensitivity [‡]
Dorsal anterior insula	Increased activation	Faster neural habituation and downregulation of pain anticipation [‡]
PFC	Reduced activation Increased grey matter	Decreased executive and evaluative processing; that is, decreased negative judgements and memories about pain [‡] Thickness inversely correlated with pain sensitivity [‡]
Dorsomedial PFC	Increased activation	Heightened attention [§]
Dorsolateral PFC and MCC	Reduced functional connectivity	Decoupling of cognitive-evaluative and sensory-discriminative functions [‡]
MCC	Increased grey matter	Thickness inversely correlated with pain sensitivity [‡]
Anterior MCC	Increased activation	Faster neural habituation and downregulation of pain anticipation
Parietal cortex	Increased grey matter [*‡]	Thickness inversely correlated with pain sensitivity [‡]
Anterior cingulate cortex	Increased activation	Increased interoceptive awareness [2]
		Increased pain processing among experienced meditators [‡]
Hippocampus	Reduced activation	Decreased evaluative processing; that is, decreased negative judgements and memories about pain [‡]
	Increased grey matter [*‡]	Thickness inversely correlated with pain sensitivity [‡]
Thalamus	Increased activation	Increased pain processing among experienced meditators [‡]
Amygdala	Reduced activation	Decreased anticipation of pain negative emotional processing; that is, decreased negative emotions in response to pain [‡]
Brainstem	Increased grey matter	Thickness inversely correlated with pain sensitivity [‡]
Alpha activity (8–13 Hz)	Increased power in this relatively slow (inhibitory) oscillation	Alpha activity associated with reduced anxiety and greater feelings of calm and positive affect [‖]
Theta activity (4–8 Hz)	Increased power in this very slow (inhibitory) oscillation	Theta activity associated with heightened attention, reduced anxiety and sympathetic autonomic nervous system activity, and enhanced memory functions [‡§]

[*] Among healthy individuals (following brief training in mindfulness meditation) during experimental pain stimulation.

[‡] Among experienced meditators during painful stimulation.

[§] During meditation among healthy individuals.

[‖] State and trait effects, not dependent on meditation expertise.

Abbreviations: MCC, midcingulate cortex; PFC, prefrontal cortex.

Table 2

Neuromodulatory chronic pain treatments: advantages and disadvantages

Treatment	Advantages	Disadvantages
Hypnosis	Moderate evidence supports short-term and long-term efficacy Encourages self-management and self-efficacy Few (if any) negative side effects Numerous beneficial side effects (for example, increased global well-being) Evidence supports effects on most neurophysiological processes involved in pain processing—supports potential benefits for a wide variety of pain problems	Outcome is variable: not everyone benefits Treatment requires patient involvement and motivation
Meditation	Preliminary evidence is promising Encourages self-management and self-efficacy Few (if any) negative side effects Reported beneficial side effects include increased well-being Preliminary evidence supports effects on brain structures involved in attention, emotional processing and pain	Evidence for efficacy not yet well-established Treatment requires patient involvement and motivation fMRI and EEG studies examining the neural correlates of meditation training among novices with chronic pain is lacking
Noninvasive brain stimulation (repetitive transcranial magnetic stimulation and transcranial direct current stimulation)	Preliminary evidence for short-term effects is promising Treatment requires minimal patient effort	Requires equipment Must be provided in the clinic (home practice not yet possible) Passive treatment (does not encourage self-efficacy) Evidence for long-term benefits is lacking; preliminary evidence suggests that benefits may be temporary Associated with minor transitory side effects (for example, fatigue, scalp irritation, dizziness) Mechanisms not yet understood
Neurofeedback (EEG and real-time functional MRI biofeedback)	Preliminary evidence for short-term benefits is promising Encourages self-management and self-efficacy	Requires equipment Effects appear to be weak Evidence for long-term benefits is lacking Mechanisms not yet understood Treatment requires patient involvement and motivation