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Non-invasive brain stimulation approaches to fibromyalgia pain

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Abstract

Fibromyalgia is a poorly understood disorder that likely involves central nervous system sensory hypersensitivity. There are a host of genetic, neuroendocrine and environmental abnormalities associated with the disease, and recent research findings suggest enhanced sensory processing, and abnormalities in central monoamines and cytokines expression in patients with fibromyalgia. The morbidity and financial costs associated with fibromyalgia are quite high despite conventional treatments with antidepressants, anticonvulsants, low-impact aerobic exercise and psychotherapy. Noninvasive brain stimulation techniques, such as transcranial direct current stimulation, transcranial magnetic stimulation, and electroconvulsive therapy are beginning to be studied as possible treatments for fibromyalgia pain. Early studies appear promising but more work is needed. Future directions in clinical care may include innovative combinations of noninvasive brain stimulation, pharmacological augmentation, and behavior therapies.

Keywords

Fibromyalgia; transcranial magnetic stimulation; transcranial direct current stimulation; noninvasive brain stimulation; chronic pain; electroconvulsive therapy; prefrontal cortex; primary motor cortex

Introduction

The American College of Rheumatology defines fibromyalgia criteria to include pain of at least three months duration above and below the waist bilaterally, axial skeletal pain, and 11 of 18 discrete tender points (1). Historically, fibromyalgia was often termed fibrositis and categorized as an inflammatory musculoskeletal disease. However investigators have not

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found significant pathology in the muscle or connective tissue regions where fibromyalgia patients complain of pain, thus the focus has shifted to the central nervous system to explain the pain perception abnormalities. Central sensitization or augmentation is one of the more common pain models for fibromyalgia.

Central sensitization likely involves a cascade of events which culminates in the release of excitatory agents, such as glutamate and substance P, at A and C afferent pain fibers at the synapses of dorsal horn neurons and secondarily prolong the excitability of second-order dorsal horn neurons that drive pain states (2). Spinal glial cells may play a role as they can release proinflammatory cytokines, prostaglandins, glutamate, substance P, and calcitonin gene-related peptides, which can precipitate hyperexcitable dorsal horn neurons. As supporting evidence, AV-411, a glial cell modulation drug, decreased pain sensitivity to mechanical pressure in an animal model of neuropathic pain (3). In both animal and human models of central sensitization, the source of sensory input (e.g., nerve injury) is known and pain sensitivity is reduced if the source of sensory input is removed. However, the source of sensory input among patients with fibromyalgia is unknown. Therefore, many fibromyalgia researchers refer to central augmentation of sensory input rather than central sensitization when they discuss the pathophysiology of fibromyalgia (4). In conjunction with the central sensitization or augmentation model of pain, there is a constellation of other biopsychosocial factors that play a role in fibromyalgia.

Biopsychosocial abnormalities

Familial associations

Arnold et al (5) reported that the first-degree relatives of patients with fibromyalgia, compared with those of patients with rheumatoid arthritis (RA), were more likely to meet diagnostic criteria for fibromyalgia or major depressive disorder (MDD) and exhibited a greater number of sensitive tender points. The frequency of fibromyalgia among the first-degree relatives of probands with fibromyalgia and those with RA was 6.4% and 1.1%, respectively. The frequency of lifetime MDD diagnoses within these two groups of relatives was 29.5% and 18.3%.

Bradley et al (6) assessed pain thresholds for mechanical pressure, thermal and ischemic stimulation as well as blood serum serotonin levels among the siblings of fibromyalgia probands and healthy controls. Preliminary data showed that the fibromyalgia probands and their siblings displayed significantly lower pain threshold levels in response to the 3 forms of pain stimulation compared to healthy controls and their siblings, respectively. Interestingly, none of the proband siblings reported persistent or recurrent musculoskeletal pain. These findings, in conjunction with those of Arnold et al (5) suggested that both fibromyalgia probands and their first-degree relatives display enhanced pain sensitivity to multiple nociceptive stimuli.

Genetic associations

The enhanced pain sensitivity in fibromyalgia may be attributed is the serotonin transporter (5-HTT) gene (7). Offenbaecher et al (8) and Cohen et al (9) in independent samples, reported that a single nucleotide polymorphism in the regulatory region of the 5-HTT gene occurs significantly more often in patients with fibromyalgia than in healthy controls. These findings are consistent with Bradley et al (6) wherein both the fibromyalgia probands and their siblings exhibit significantly lower blood serum levels of 5-HT than healthy controls and their siblings, respectively. This particular polymorphism is found more frequently not only in fibromyalgia but patients with MDD (10), and diarrhea-predominant irritable bowel syndrome (11,12) compared with healthy controls. This data lends support to the hypothesis that fibromyalgia may be a part of a group of affective spectrum disorders (ASD) that share

1 or more physiologic abnormalities important to their etiology (13). The ASD grouping contains 10 psychiatric disorders, including major depression, and 4 medical disorders, including migraine and irritable bowel syndrome.

Environmental factors

Environmental triggers including, physical trauma and psychosocial stressors, may be involved in the pathophysiology of fibromyalgia (14,15). Harkness et al (16) reported that both physical and psychosocial stressors predict the development of chronic widespread body pain, and psychosocial factors may, in fact, initiate the development of widespread pain. Davis (17) and Okonkwo et al (18) independently found evidence that inducing negative mood and stress exposure could worsen pain ratings in patients with fibromyalgia.

Stress response dysregulation

Stress response abnormalities are present in fibromyalgia primarily involving the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous systems. McCain and Tilbe (19) observed patients with fibromyalgia or RA for 3 days and found that fibromyalgia patients exhibited higher peak and trough levels of plasma cortisol compared with those with RA. Furthermore, fibromyalgia patients displayed significantly higher overall plasma cortisol levels than RA patients. In response to dexamethasone, 35% of patients with fibromyalgia had unsuppressed plasma cortisol levels compared with only 5% of patients with RA. They also found patients with fibromyalgia lost diurnal cortisol response. Crofford (20) revealed a decreased response to corticotropin releasing hormone, which is released to enact a stress response. Hence, there is emerging support that fibromyalgia may involve neuroendocrine abnormalities.

Patients with fibromyalgia also have autonomic nervous system dysfunction that includes hypotension (21–23), variations in heart rate (22), decreased microcirculatory vasoconstriction (24), and sleep disturbance (25,26). A dysregulated autonomic nervous system may contribute to enhanced pain and other clinical problems associated with fibromyalgia through alterations of physiologic responses required for effective stress management (e.g., blood pressure increases) and pain inhibition (e.g., neurotransmitter availability).

Monoamines

Several lines of evidence suggest that both serotonin and norepinephrine systems are dysfunctional in fibromyalgia patients (27–29). Wolfe et al (7)., found that fibromyalgia subjects had lower serotonin levels even after adjusting for age and sex than those without fibromyalgia p-chlorophenylalanine, a centrally acting serotonin synthesis inhibitor, can induce symptoms similar to those associated with fibromyalgia (30). Tricyclic antidepressants and selective serotonin-norepinephrine reuptake inhibitors may also reduce pain independent of their antidepressant actions as a result of their serotonin- and norepinephrine-mediated effects on the descending pain inhibitory pathways in the brain and spinal cord (31).

While serotonin and norepinephrine have been studied more extensively, there is possibly a role for dopamine in fibromyalgia pathophysiology (32). Wood and Holman (33) using positron emission tomography found reductions in 6-[(18)F]fluoro-L-DOPA uptake on in several brain regions that involve pain perception, suggesting a disruption of presynaptic dopamine activity wherein dopamine plays an important role in endogenous analgesia.

Cytokines

Inflammatory cytokines play a role in diverse clinical processes and phenomena such as fatigue, fever, sleep, pain, depression, stress, and aching (34). Cytokines related to acute or repetitive tissue injuries may be responsible for long-term activation of spinal cord glia and dorsal horn neurons, thus resulting in central sensitization. Cytokines might cause depressive symptoms through modulation of the HPA axis or they may cause downregulation of the synthesis of serotonin; both of these effects might contribute to the development of depression and enhanced pain perception (35–37). Cytokines can directly induce pain sensitization (38) and the inflammatory cytokines IL-1, IL-6, and IL-8 may be dysregulated in FM (39).

Neuroanatomic abnormalities

Multiple brain regions are involved in pain processing. Sensory components include thalamus and sensory cortices, but affective and cognitive components to pain involving other limbic, prefrontal and associative cortices (40). There have been several neuroanatomic abnormalities observed in patients with fibromyalgia. In a single-photon emission computed tomography study, patients with fibromyalgia (compared to healthy controls) showed a decrease in regional cerebral blood flow in the thalamus, caudate nucleus, and pontine tegmentum (41). Gracely et al (42) used functional magnetic resonance imaging (fMRI) to examine the pattern of cerebral activation during the application of painful pressure in patients with fibromyalgia compared with controls. The fMRI results revealed that when moderate levels of pressure were applied to the patients and the controls, no common regions of activation were observed and a greater effect was noticed in patients. When the stimulation was increased to deliver a subjective level of pain in the control group similar to that experienced by fibromyalgia patients, similar activation patterns were seen in patients and controls. Hence, fibromyalgia patients exhibited enhanced sensory processing. This enhanced sensory processing may be nonspecific to fibromyalgia as similar brain regions (contralateral primary [S1] and secondary [S2] somatosensory cortices, inferior parietal lobule, cerebellum, and ipsilateral S2) were activated in idiopathic chronic back pain and fibromyalgia in comparison to healthy controls (43). Additional functional neuroimaging studies have suggested that fibromyalgia is associated with changes in the activity of brain structures involved in pain processing (44–46).

Morbidity and cost burden with conventional treatments

Fibromyalgia has a prevalence range of 0.5 to 5.0% in the general population and up to 15% in medical clinics. Females are 7 times more likely than males to have the disorder (47,48). Age-adjusted incidence rates were 6.88 cases per 1000 person-years for males and 11.28 cases per 1000 person-years for females in a retrospective cohort study of 62,000 enrollees in nationwide sample (48). Current treatment strategies include treating targeted symptoms of pain and depression with pharmacological and non-pharmacological treatments (49). Pharmaceutical pain management with anti-inflammatory agents, antidepressants and opiates can offer some pain relief but can have significant side effects and adverse reactions (50–52). Despite current treatment, patients with fibromyalgia still incur significant medical utilization, work absence and disability (53). In a prospective cohort study of 34,100 employees, an excess rate of absence due to sickness was 61 episodes/100 person-years among people with fibromyalgia alone (54). In a retrospective cohort including 4,699 persons with fibromyalgia, total annual costs for fibromyalgia claimants were $5,945 versus $2,486 for the typical beneficiary. Six percent of these costs were attributable to fibromyalgia-specific claims but did not include indirect costs. The prevalence of disability was twice as high among employees with fibromyalgia compared to overall employees. For every dollar spent on fibromyalgia-specific claims, the employer spent another $57 to $143 on additional direct and indirect costs (55). Patients with fibromyalgia from 6 rheumatology

centers had higher lifetime and current rates of medical service utilization with mean disability rates at 16% (56,57). In the same sample of 538 patients, measures of pain, fatigue, sleep disturbance, depression, and health status did not significantly change over seven years despite treatment (58).

To date, there are limited effective treatment options available to patients with fibromyalgia. Better therapeutic options are needed to reduce fibromyalgia morbidity and costs. Given that fibromyalgia involves abnormal central pain processing, noninvasive brain stimulation techniques are being studied as a means of modulating central nervous system pain processing.

Rationale for non-invasive brain stimulation for fibromyalgia

Noninvasive brain stimulation techniques, such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), have more evidence in psychiatric disorders. ECT and rTMS are both effective for the treatment of depression and rTMS was approved for the treatment of major depressive disorder in 2008. Other noninvasive brain stimulation methods, such as transcranial direct current stimulation (tDCS) have been less well studied in mood disorders but may be useful in both depression (59) and pain disorders (60–62).

The relationship between depression and pain is of significant interest in fibromyalgia and other disorders. When rigorous criteria are applied to diagnose depression, the prevalence of depression and concurrent chronic pain varies from 30–54% (63). The prevalence rate is higher in the general population than for either disorder alone (64). While many believe that depression is secondary to a loss of functioning due to persistent pain, there is some evidence to suggest that depressed individuals are more susceptible to developing pain disorders and they tend to have lower pain thresholds (65–67). Significant research has been done to better understand the biological and psychosocial mechanisms underlying pain and depression. There is significant overlap in the neurochemical processes and neuroanatomical structures thought to be involved in both biological and psychosocial explanations (63,68–72). Since fibromyalgia pain and depression frequently co-exist and there is overlap in terms of neurological substrates between the two conditions, investigators have begun to study noninvasive brain stimulation interventions that have potential to impact affective and sensory dimensions of the pain experience. Currently ECT, rTMS, tDCS have been employed in attempt to modulate fibromyalgia pain.

Electroconvulsive therapy

ECT was introduced in 1938 and remains one of the most effective treatments in psychiatry. ECT has developed into a technically sophisticated procedure with a proven record of safety. The procedure involves passing electrical pulses of approximately 1 ampere into the brain in order to provoke an epileptic seizure. The mechanism is action is not fully known but literature supports ECT may increase Brain Derived Neurotrophic Factor (BDNF) (73,74). BDNF likely plays a critical role in the action of antidepressants through neuronal plasticity.

Many studies, dating back to the 1940s, have reported the beneficial effects of ECT upon a variety of pain states. Several studies have demonstrated the clinical effectiveness of ECT treatment for neuropathic pain with low-blood flow in one side of the thalamus (75–77). However, some other reports have not resulted in demonstrable pain relief following ECT (78,79). In addition, there is one report that describes the use of ECT to effectively treat depression associated with fibromyalgia, but had no effect upon pain or other physical symptoms associated with fibromyalgia (80).

Usui and colleagues (81) prospectively designed an ECT study to assess changes in fibromyalgia pain that excluded patients that were diagnosed with concomitant organic disorders or mental disorders as classified by the Diagnostic and Statistical Manual of Mental Disorders. The study group consisted of 15 patients, seven men and eight women, aged 22–76 years (mean age = 42.1, SD = 13.1). The mean duration of fibromyalgia was 4.6 years (SD = 1.2). Fourteen patients had been taking antidepressant medication (milnacipran or paroxetine or amitriptyline) for fibromyalgia. Two patients were on low-dose steroid therapy. The medication was kept constant during the research trial. All patients received bilateral ECT set at 110 volts for 5 seconds. Twelve patients received six sessions, while three patients received only four sessions due to excellent responses. The number of tender points and the pain score (according to Visual analogue scale (VAS)) were significantly improved after ECT. Tender points dropped from a mean of 16.47 ± 0.59 to 6.73 ± 1.04 three days post-ECT. VAS pain scores increased at 3 months and returned to baseline in two patients. Beck Depression Inventory (BDI) scores did not reveal the presence of clinical depression and there were not significant changes in depression ratings post-ECT. The ECT treatment effect on fibromyalgia pain reduction appeared independent of mood changes in the study. Regional cerebral blood flow (rCBF) was also assessed (using single photon emission computed tomography [SPECT]) in each patient before and three days after the course of ECT. For quantitative SPECT analysis, they measured rCBF by using a three-dimensional stereotaxic region of interest template (3DSRT) (82) in addition to regional quantitative analysis. The mean thalamus-to-cerebellum ratio was significantly increased ($P < 0.01$) post-ECT in comparison to before ECT. The SPECT results suggest that improvement of rCBF in the thalamus may correlate with ECT analgesia. It has been shown that improvement in mood following administration of ECT is associated with an increase in rCBF (83). ECT may activate inhibitory pathways via the activation of serotonergic, noradrenergic, and dopaminergic neurotransmission systems in the brain (84). Abnormal sensory processing in fibromyalgia may be modulated by ECT treatment for fibromyalgia. Small sample size, open labeled design, and no other fibromyalgia quality of life instruments limited this study. Further work is needed to understand if ECT can reduce fibromyalgia pain and whether co-morbid depression would be suitable for treatment given a prior study showing no difference in fibromyalgia pain despite reduction in depression. A complicating factor of further ECT research with fibromyalgia is the “invasiveness” (i.e. anesthetic induction, seizure induction, potential cognitive side effects) of this noninvasive brain stimulation technique. Thus less invasive techniques may be more likely to gain ground in fibromyalgia research.

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is the application of weak electrical currents (1–2 mA) to modulate the activity of neurons in the brain. Neuronal firing increases when the positive pole (anode) is located near the cell body or dendrites. Neuronal firing is inhibited when cathode stimulation is applied (85,86). However, when the electrodes are placed on the scalp, the current density produced in the brain is exceedingly small, changing membrane potentials only by a fraction of a millivolt (87). The mechanism of action is unknown but pharmacological studies hint at ionic channel modulation. Sodium and calcium channel blockers eliminate both the immediate and long-term effects of anodal stimulation while blocking NMDA (glutamate) receptors prevents the long-term effects of tDCS, regardless of direction (88). Nitsche et al (89) investigated the short- and long-term effects of anodal and cathodal tDCS on the motor cortex by measuring intracortical inhibition and facilitation as well as indirect-wave (I-wave) interactions. The effects on cortical inhibition suggested that tDCS modulates the excitability of both inhibitory interneurons as well as excitatory neurons. Furthermore, anodal stimulation had a significant positive effect on I-wave facilitation. I-waves are modified by GABAergic drugs and ketamine, an NMDA

receptor antagonist, but not by ion channel blockers, thus implicating effects on inhibitory synaptic pathways in the mechanism of action of anodal stimulation (90,91).

There are limited parameters that can be set with tDCS, primarily involving locations of the cathode and anode, voltage intensity, electrode size, and time per session. The typical levels administered are 1 or 2 milliamperes of direct current applied for a maximum of 20 minutes in a given session. In contrast to TMS, this technique does not produce a strongly localized effect; however, increasing the size of the reference electrode and reducing the size of the stimulation electrode allows for more focal treatment effects (92). A feeling of tingling under the electrodes is the most common side effect, although there have been some reports of mild skin burning associated with repeated daily tDCS sessions (93).

Currently tDCS is being studied in a variety of disease processes including stroke recovery (94), depression (59), and pain (60,61). There are two published studies applying tDCS for fibromyalgia pain and sleep disturbance. Fregni et al (95) conducted tests to determine whether active stimulation of the primary motor cortex (M1) or the dorsolateral prefrontal cortex (DLPFC) is associated with a reduction of pain and other symptoms of fibromyalgia as compared with sham stimulation. The primary motor cortex and the DLPFC were chosen as targets, because stimulation of the primary motor cortex induces a significant anti-nociceptive effect using rTMS (62,96), and stimulation of the DLPFC using tDCS is associated with a significant antidepressant effect (97). Thirty-two female patients participated in this study. Patients were on stable doses of analgesics for at least two months prior to the beginning of the study and were included in the analysis in an attempt to address it as confound. Subjects underwent a two week observation period during which baseline levels of pain were established, followed by a randomization and implementation of double-blinded treatment, during which patients received daily treatment with sham tDCS, tDCS of the primary motor cortex, or tDCS of the DLPFC for five consecutive days, with a 21 day followup. Subjects underwent assessment with clinical visual analogue scale (CVAS), Fibromyalgia Impact Questionnaire (FIQ), Short-Form 36 Health Survey (SF-36), Clinical Global Impression Scale (CGI), Beck Depression Inventory (BDI), and an anxiety visual analog scale. Using the 10/20 system of electrode placement, the anode was placed over C3 for primary motor cortex, F3 for DLPFC with the cathode over contralateral supraorbital area. Electrodes were 35 cm^2. The sham group received thirty seconds of stimulation over M1 so subjects felt the initial itching sensation but received no current for the rest of the session. A constant current of 2-mA intensity was applied for 20 minutes. Eleven enrolled in each treatment arm, ten in the sham group with one drop out in the M1 group due to minor skin irritation at the site of stimulation. Pain VAS revealed that DLFPC was not statistically different from sham regarding pain change over time. M1 had beta coefficient of .31, thus a . 31 mean reduction in pain with each evaluation. CGI differences in repeated-measures ANOVA revealed a group effect difference. Post hoc comparisons showed a significant difference between M1 and DLPFC stimulation, M1 and sham stimulation, and DLPFC and sham stimulation. There was no time effect with CGI, suggesting pain improvement was constant throughout the trial. There was a significant difference across the three groups in regards to percent change in the tender point scores after five days of treatment. Post hoc tests revealed a significant difference between the M1 group and the sham group but not between the sham group and the DLPFC group. On day 5, tender point scores decreased by 17.1+/−11.8% in the M1 group, by 11.8+/−8.3% in the DLPFC group, and by 2.3+/−10.9% in the sham group. The 3 groups had a decrease in FIQ scores over the course of the trial. The decrease in the M1 group was significantly different from that seen in the sham group and the DLPFC group. There was no significant difference in Beck Depression Inventory scores across the 3 groups of treatment, but the DLPFC group had absolute mean change of 3 points. There was no cognitive impairment associated with tDCS. In this study, anodal

tDCS of the primary motor cortex in fibromyalgia patients induced a significant reduction in pain compared to sham and DLFPC that lasted for several weeks after treatment had ended.

As an extension of the Fregni study, Roizenblatt and colleagues investigated correlations of sleep modulation with decreases in pain with fibromyalgia patients receiving tDCS at M1, DLPFC, or sham. There are sleep disturbances in fibromyalgia and whether alterations of alpha sleep patterns play an etiologic role are unclear (98,99). Interestingly, slow wave sleep (SWS) fragmentation by alpha rhythm or extrinsic stimuli (100–103) is connected to non-restorative sleep and musculoskeletal pain. Prior work (104) has shown subjects had deeper sleep in the end of active tDCS and during the subsequent 15 minutes after stimulation when compared to placebo conditions. Hence, the work of Roizenblatt (105) is relevant. The methods were essentially the same for all elements other than sleep assessment with polysomnography (PSG). A baseline pretreatment PSG and post-treatment PSG was acquired in addition to the other phases previously described. A minimum of 7 hours of PSG recording was obtained. Total sleep time (TST) was defined as the time elapsed between the first and last recorded sleep period. Sleep efficiency corresponded to the percentage of TST in relation to the total recording time. Sleep latency was considered the time period measured from lights going out to the beginning of sleep and REM sleep latency, as the time interval from sleep onset to the first appearance of REM sleep. There was a statistically significant sleep efficiency modulation. Post-hoc comparisons showed that sleep efficiency was improved by 11.8% after M1 tDCS and significantly worsened by 7.5% after DLPFC stimulation. Additionally, DLPFC stimulation led to a significant worsening in other parameters of sleep such as an increase in sleep latency by 133.4% and REM latency by 47.7%. Conversely, M1 stimulation led to decrease in arousals by 35%. Finally, the alpha/delta index significantly increased after M1 tDCS and decreased after DLPFC tDCS. Thus tDCS at M1 increased sleep efficiency, decreased arousals and increased delta activity in non-REM sleep. DLPFC stimulation was associated with a decrease in sleep efficiency and an increase in REM and sleep latency. Additional, alpha activity increased and delta activity decreased in non-REM sleep after DLPFC stimulation. There was a significant correlation of quality of life improvement as assessed by FIQ changes with a decrease in sleep latency and with an increase in sleep efficiency after M1 stimulation. Finally, patients in whom DLPFC stimulation did not induce a worsening of sleep efficiency were those who obtained the largest pain improvement as indexed by VAS. The authors hypothesized the excitatory effects of anodal tDCS at M1 led to improvement of sleep architecture as a result of a normalization of the dysfunctional neural network activity that is associated with pain and sleep. The alpha/delta index decrease after DLPFC anodal stimulation is in accordance with rTMS and sleep deprivation which lead to an increase in DLPFC activity (106). Interestingly, ECT is associated with an alpha-EEG sleep pattern in depressed patients that is observed at the end of the ECT series (107). In this sense, the sleep alterations observed after DLPFC stimulation in the current study correlate with the Fregni study showing that a 5-day anodal tDCS of the left DLPFC improves mood in major depression (62).

Repetitive transcranial magnetic stimulation

One of the early uses of TMS in the treatment of pain grew out of the surgical implantation of motor cortex stimulation (MCS) (108). With TMS, current is rapidly turned on and off in the electromagnetic coil through the discharge of capacitors. The end result of TMS is thus electrical stimulation of the brain, and some refer to TMS as ‘electrodeless electrical stimulation’. The electrical energy stored in a capacitor discharges and creates about 3,000 Amps. Through Maxwell’s equations and Faraday’s law, this creates a powerful magnetic field, on the order of 2 Tesla. This rapidly changing magnetic field (~30KT/s) then travels across the scalp and skull and induces an electric field within the brain (~30V/m). This induces current to flow in the brain by creating a transmembrane potential (for a thorough

discussion see (109)). This localized pulsed magnetic field over the surface of the head depolarizes underlying superficial neurons (110,111), which then induces electrical currents in the brain. TMS therefore differs from techniques where direct electrical or magnetic energy is applied to the brain or body (such as ECT). TMS can induce varying brain effects depending on: 1) the cortical region stimulated, 2) the activity that the brain is engaged in, and 3) the TMS device parameters (particularly frequency, time-interval and intensity). TMS has been shown to produce immediate effects (e.g., thumb movement, phosphenes, temporary aphasia) (112) that are thought to result from direct excitation of inhibitory or excitatory neurons. TMS at different intensities, frequencies and coil angles excites different elements (e.g., cell bodies, axons) of different neuronal groups (e.g., interneurons, neurons projecting into other cortical areas) (113–115). Intermediate effects of TMS (seconds to minutes) likely arise from transient changes in local pharmacology (e.g., gamma-aminobuteric acid, glutamate) (116) and much research has focused on whether different TMS frequencies might have different intermediate biological effects. Repeated low-frequency stimulation of a single neuron in culture produces long-lasting inhibition of cell-cell communication (117,118) while high frequency stimulation can improve communication (119).

It has been hypothesized that TMS can produce sustained inhibitory or excitatory effects in a way analogous to single-cell electrical stimulation (120). Several studies have shown that chronic stimulation of the motor cortex can produce inhibitory or excitatory intermediate effects (lasting several minutes) following stimulation (121,122). Investigations of the intermediate effects of TMS have been used to develop a better understanding of brain functioning with respect to movement, vision, memory, attention, speech, neuroendocrine hormones and mood (123–129). Longer term effects of TMS (days to weeks) are not well understood at a neurobiological level, but there is evidence to support longer-term effects on mood, seizure activity and pain (96,130–134). With respect to mood, it is hypothesized that chronic repetitive stimulation of the prefrontal cortex initiates a cascade of events in the prefrontal cortex and in connected limbic regions (135). TMS/fMRI interleaved studies as well as PET studies by Paus and others provide evidence to support this hypothesis. Prefrontal TMS sends information to important mood-regulating regions including the cingulate gyrus, orbitofrontal cortex, insula and hippocampus, and there is PET evidence that prefrontal TMS causes dopamine release in the caudate nucleus (and reciprocal activity with the anterior cingulate gyrus) (132,133,135). rTMS is currently been studied for a variety of pain conditions including laboratory induced, neuropathic pain, postoperative pain, and fibromyalgia.

Neuroimaging studies (136,137) have shown that hemodynamic changes induced in the brain by epidural electrical stimulation are not confined to the motor system, but instead involve a set of cortical (e.g. cingulate, orbitofrontal and prefrontal cortices, thalamus and striatum) and subcortical (e.g. periaqueductal gray matter) areas, involved in pain processing and modulation (138–140). Similar changes in brain activity have been demonstrated after the application of rTMS to the motor cortex (141–143), suggesting that rTMS can also modulate the activity of brain structures involved in pain perception. In particular, the analgesic effects of rTMS may involve the pain modulation systems of the diencephalon and/or descending from the brainstem to the spinal cord (144) although other mechanisms such as changes in intracortical inhibitory mechanisms have also been suggested (145). Consistent with these hypotheses, rTMS of the motor cortex, has been shown to reduce experimental pain both in healthy volunteers and in patients with chronic pain (96,30,146–151).

To date there have been three published studies involving rTMS and fibromyalgia (152,153). (See References on additional text attached for subsequent citation numbering)

Sampson (152) examined the effect of slow-frequency (1 Hz) rTMS in subjects with treatment-resistant depression and borderline personality disorder (BPD). Four subjects in this study also had a previous diagnosis of fibromyalgia. Low-frequency rTMS (1 Hz) applied to the right DLPFC was shown to increase bilateral pain tolerance in healthy volunteers (154) and has reduced depressive symptoms (155). The design was sham-controlled, double-blinded. rTMS was produced using a Magstim Super Rapid repetitive stimulator and a 70-mm figure-of-eight coil. Single transcranial magnetic stimuli were used to identify motor threshold (MT). One-hertz rTMS was applied 5 cm anterior to the optimal motor cortex stimulation site to approximate localization of the R-DLPFC. rTMS was applied using a frequency of 1 Hz, intensity of 110% MT, and two 800 second trains with an intertrain interval of 60 seconds, for a total of 1,600 stimuli per session. One of the four subjects with FM received 10 sham rTMS treatments using a 90-degree coil rotation before receiving active rTMS. Subjects received active rTMS over 4 weeks, and one subject received an additional 12 treatments over 6 weeks as part of a taper protocol for those who had remission of depression (> 50% decline and <10 on the Hamilton Rating Scale for Depression (HRSD)). Although improvement on HRSD and ratings were statistically significant, only one subject had a remission of depression. All subjects noted an improvement in fibromyalgia pain, with two subjects reporting complete resolution of pain. One subject received sham rTMS for 2 weeks with no pain improvement during that time. One subject noted improvement in pain during the first week of treatment, and two noted improvement during week 3 of treatment. Two subjects provided pain ratings during treatment and two described changes in pain retrospectively when contacted after it was noted that rTMS might be altering pain. The subjects were contacted repeatedly after finishing the acute series of treatment to assess the recurrence of pain. The subjects were defined as having recurrence of pain when reported ratings increased by at least 1.5 points. The duration of pain improvement ranged from 15 to 27 weeks. Given the limited reduction in depression ratings, the reduction in fibromyalgia pain cannot be explained by the treatment of depression alone. Notably, the subjects' pain improvement was sustained for a number of weeks after rTMS, and suggests the possibility that rTMS applied to the R-DLPFC may be clinically useful in reducing fibromyalgia pain. This study was not prospectively designed or powered to assess changes in fibromyalgia pain and hence there is only 4 subjects reported. Half the subject data was retrospectively gathered. Furthermore it is unclear what sham system was implemented. Nonetheless this is the first rTMS publication detailing prefrontal cortical stimulation in fibromyalgia with rTMS.

Carretero and colleagues (154) recently published a replication study using similar parameters as Sampson but in a larger sample with randomization and a placebo controlled arm. There were 14 subjects that underwent real TMS and 12 that received sham TMS. The real rTMS was employed with DANTEC TMS equipment at the same R-DLPFC location as with Sampson's work. Subjects received 1 Hz 60 seconds on and 45 seconds off at 110% MT for approximately 30 minutes for a total of 1200 pulses per session. Subjects received 20 daily sessions in total. Both groups improved in fatigue and CGI but there was no improvement in pain and depression. Furthermore there was no significant difference between real and sham TMS in this sample. However, the sham system was suboptimal with simply a shift in the TMS coil to 45 degrees so that sound is heard but no cutaneous sensation was experienced. More importantly subjects received 400 fewer pulses per session for a total of 8000 fewer pulses than the Sampson group. Thus subjects may have been relatively "underdosed" in comparison.

Passard and colleagues (153), hypothesized that rTMS of the motor cortex might reduce chronic widespread pain in patients with fibromyalgia. They employed a randomized, double blind, sham-controlled parallel group study analyzing the analgesic effects of repeated daily sessions of unilateral rTMS in patients with widespread pain, quality of life,

mood, and anxiety due to fibromyalgia. Tender point pain threshold was a secondary outcome. A Super-Rapid Magstim Stimulator (Magstim Co., Whitland, UK) with a figure-of-eight-shaped coil was employed. Each treatment session consisted of 25 series of 8-second pulse trains, with 52 seconds interval between series, at a stimulation frequency of 10 Hz and 80% resting motor threshold intensity, giving a total of 2000 pulses per session. The resting motor threshold (MT) was determined before each session, using a single-pulse stimulation over the left primary motor cortex. The primary outcome measure was self-reported average pain intensity over the last 24 hours using the 11-point numerical scale of the BPI. Average pain intensity was reported for 1 week as a baseline, during treatment (days 1–14) and until the first followup visit to make it possible to determine the onset of treatment effects, then was assessed at each follow-up visit on days 15, 30, and 60. Changes between the baseline and the endpoint after treatment in the BPI average pain severity score and all secondary efficacy variables (BPI-Interference scores, number of tender points, scores for the FIQ, HAD, BDI and HDRS, pressure pain thresholds) were compared between the active and sham stimulation groups. A repeated measures analysis of variance (ANOVA) was carried out in which the dependent variable was one of the outcome measures and the factors were treatment group (active or sham rTMS) and time (baseline, day 15, day 30 and day 60). Four patients (two per treatment group) withdrew from the trial between days 30 and 60. Pain intensity was similar in the two groups at baseline and rTMS had a significant effect on average pain intensity score between baseline and day 15 in comparison with sham stimulation. This effect was not maintained on days 30 and 60. Average pain intensity was significantly lower in the active rTMS group than in the sham stimulation from day 5 to day 14. On day 15, McGill Pain Questionnaire total score and the sensory and affective subscores were significantly lower in the active rTMS group than in the sham-stimulation group. The difference in affective subscore persisted until day 30, whereas the sensory subscore did not. Subjective global pain relief over the last week, as reported by the patients, was significantly greater in the active than in the sham-stimulation group up to day 30. Mean depression and anxiety scores were similar in the two treatment groups at baseline and were not significantly changed by active or sham stimulation. rTMS had no significant effect on the number of tender points. This study showed that rTMS of the primary motor cortex induced a long-lasting decrease in pain and improved quality of life in patients with fibromyalgia, without affecting mood or anxiety levels. The analgesic effects of rTMS differed for the sensory and affective dimensions of pain with the affective dimension change lasting 15 days longer. One critique of this study is the design of the sham system. Per description, it makes similar sounds as active rTMS, however there is no form of superficial stimulation to the scalp, which can be problematic as otherwise the active and sham are easily discerned when compared.

Our laboratory is currently investigating the effects of rTMS in left DLPFC with the following TMS parameters: 10 Hertz - pulse train duration (on time) 5 seconds, power (intensity) level 120% of motor threshold, and inter-train interval (off time) 10 seconds (15 second cycle time). The rationale for high frequency left prefrontal is related to current work with similar parameters for the treatment of depression and findings from implanted motor cortex stimulator research, and laboratory and clinical studies conducted in our laboratory. Much of the variance in clinical response to implanted motor cortex stimulation seems to be explained by limbic activity (136,156). If one of the mechanisms by which cortical stimulation alleviates pain is by modulating the processing of the affective dimension of pain experience, the prefrontal cortex might be a more efficient cortical target for pain management (135). Consistent with this notion, a few studies have demonstrated acute and transient anti-nociceptive effects with prefrontal cortex TMS (154,157).

We are employing a double blind (rater blinded to condition) sham-controlled design. In order to maintain study blind, the length of treatment and the number of pulses on the head

is the same for all subjects. What differs is whether they receive active or sham. The sham group only receives sham at all treatments. Our sham system incorporates a transcutaneous electrical nerve stimulator (TENS) that does not appreciably penetrate through the skull, yet does elicit uncomfortable stimuli similar to the cutaneous sensation from rTMS. Additionally the TENS unit is triggered in concert with rTMS pulses. Subjects receive 4000 pulses per session, 10 sessions over 2 weeks for a total of 40,000 pulses. Early interim analysis, using Hierarchical Linear Modeling and a 0–10 Likert pain scale, (3 active TMS participants, 1 placebo TMS participant) suggested main effects of treatment versus placebo by time (P=.0479), a decrease of 0.16 points in average pain-per-day in the treatment arm (P=.0006), and an average pain reduction of 1.79 at the end of treatment (P<.0001). The treatment arm maintained a reduction in average pain of 1.12 at the end of the last assessment in week 4 (P = .0164). Statistical significance of change per day from baseline began at day 8 and ended at day-20. The baseline HRSD mean score was 18.75 and there was an insignificant decrease in depression from baseline to end of treatment (week 2). There was a decrease in depression from baseline to last followup (P = .0307) of 4.3 points. These interim analyses are tentative at best and more confident statements can be made upon completing enrollment and full analysis. If the interim results are maintained, then fast rTMS stimulation to the LDLPFC may significant lower fibromyalgia pain and be observed before any improvement in mood.

Future directions

Noninvasive brain stimulation is in its infancy, particularly related to chronic pain disorders such as fibromyalgia. Although there are few studies to date, there are potentially promising results of at least three noninvasive techniques (ECT, tDCS, rTMS) in the treatment of fibromyalgia. More work is needed on the site of stimulation and optimal stimulation parameters. Neurophysiological markers may be useful to discern optimal parameters. Applying TMS and tDCS with event-related potentials (ERPs) may assist in describing the underlying neurophysiologic mechanisms of normal and abnormal pain responses. The laser-evoked potential is the ERP response secondary to a mild laser stimulus. Depending on the manner in which this stimulation is performed, it is possible to stimulate A delta fibers or C fibers, and TMS can be applied to modulate these evoked potentials (158). LEP changes and subjective relief on VAS were also observed after tDCS treatments (61,159).

These brain stimulation techniques do not necessarily have to occur separately. tDCS has been used for rTMS “priming” (86). Noninvasive brain stimulation techniques might be used to locate the optimum sites for pain relief and possibly to aid in the implantation process of permanent devices for more constant stimulation. Additionally, pharmacological agents have the potential to act synergistically with brain stimulation techniques (160). Specific medications eventually might be given before or after stimulation to enhance neuroplasticity changes associated with stimulation. Mental activities during stimulation may also enhance neuroplasticity changes. Gracely (161) found that catastrophizing influences pain perception through altering attention and anticipation, and heightening emotional responses to pain. Potentially, other techniques of altering attention and cognitive processing, such as hypnosis, mindfulness, or cognitive therapy in conjunction with brain stimulation may be fruitful. The wide range of techniques and parameters of brain stimulation in conjunction with pharmacological and behavioral methods makes this area of research quite innovative. All three noninvasive brain stimulation techniques are readily available, thus more clinical trial work is needed to confer evidence for employing them for the treatment of fibromyalgia.

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