The Use of Slow-Frequency Prefrontal Repetitive Transcranial Magnetic Stimulation in Refractory Neuropathic Pain

Shirlene M. Sampson, MD, MS, Simon Kung, MD, Donald E. McAlpine, MD, and Paola Sandroni, MD, PhD

Objective: A number of antidepressant medications, as well as electroconvulsive therapy, have been shown to reduce chronic pain. Slow-frequency repetitive transcranial magnetic stimulation (rTMS) applied to the right dorsolateral prefrontal cortex has also been shown to have an antidepressant effect. Given the high degree of suffering experienced by subjects with chronic neuropathic pain and the treatment resistance noted in this population, the use of slow-frequency rTMS as adjuvant therapy may be of significant clinical benefit.

Methods: Fifteen sessions of 1-Hz rTMS (1600 stimulations/session) were applied to the right dorsolateral prefrontal cortex as adjuvant treatment in 9 subjects with refractory neuropathic pain over 3 weeks. Pain and depression ratings were performed at baseline, weekly during rTMS treatment, and monthly for up to 3 months after treatment.

Results: Five males and 4 females participated, and all had long-standing refractory neuropathic pain (range, 1–19 years), with an average baseline pain rating of 7.3 and no depression (Hamilton Rating Scale for Depression average, 3.6; range, 0-8). Three subjects had a greater than 50% decline in pain ratings by the completion of rTMS treatments, and 1 subject responded more slowly with greater than 50% improvement in pain by the end of the 3-month follow-up. An improvement in pain ratings was noted in responders within the first week.

Conclusions: Although these are preliminary findings in an open treatment trial, the subjects in this trial are among the least likely to have a placebo response. Given that rTMS is a well-tolerated and noninvasive intervention, any sustained improvement in neuropathic pain with rTMS is encouraging.

Key Words: transcranial magnetic stimulation, TMS, neuropathic pain

(*J ECT* 2011;27: 33–37)

BACKGROUND AND SIGNIFICANCE

Neuropathic pain is a chronic syndrome that persists after a primary lesion or dysfunction of the peripheral or central nervous system.[1] Examples of neuropathic pain syndromes include postherpetic neuralgia, painful peripheral neuropathies from various etiologies, trigeminal neuralgia, complex regional pain syndromes, and deafferentation pain. It is common that despite multiple nonpharmacologic (ie, behavioral and physical therapies), pharmacologic (newer serotonin-noradrenaline agents or tricyclic antidepressants, anticonvulsants, etc), and interventional approaches (dorsal cord stimulators, various nerve blocks, and intrathecal drug delivery systems), some patients never achieve adequate pain control.

From the Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN.
Received for publication December 8, 2010; accepted December 8, 2010.
Reprints: Shirlene M. Sampson, MD, MS, Department of Psychiatry and Psychology, Mayo Clinic, 200 First St, Rochester, MN 55905 (e-mail: sampson.shirlene@mayo.edu).
O'Shaughnessy Foundation provided financial support for this trial, and Neuronetics, Inc, provided equipment support.

DOI: 10.1097/YCT.0b013e31820c6270

Chronic neuropathic pain is mainly due to central sensitization.[2–4] There are 2 main pain pathways: (1) the laterospinothalamic tract and (2) the medial lemniscal pathway (paleospinothalamic). The laterospinothalamic tract is the discriminative sensory pathway for accurate stimulus localization and protective reflexive responses (ie, withdrawal). It projects to the insular cortex, which plays a crucial role in visceral/homeostatic status/sensation, and to the somatosensory cortex, crucial in somatotopic representation and motor responses to pain. The medial lemniscal pathway has more complex connections, resulting in the autonomic and affective responses associated with pain. This component relays in the brainstem (ventrolateral medulla, periaqueductal gray, parabrachial nucleus, and solitary nucleus) and the mediodorsal thalamic nuclei, which project to the anterior cingulate area, the insula, and prefrontal cortex. These pathways are illustrated in Figure 1. A schematic of descending pathways modulating pain sensation is depicted in Figure 2.

The close link between pain and mood is obvious when looking at the anatomical substrates. The anterior cingulate, insular cortex, and prefrontal cortex are key structures in both systems. The concept of modulating both systems at the same time has become more and more widespread with the realization that drugs used to treat one can benefit the other and vice versa. Indeed, reclassification of "antidepressants" and "anticonvulsants" as neuromodulators has stressed the close interrelationship at the neuromatrix level.

The neuroanatomical overlap in both mood and pain pathways likely accounts for the increased risk for depression with chronic pain and the experience of worsening pain when depressed.[5] This overlap also is likely related to why antidepressant medications can be effective in treating chronic pain.

Electroconvulsive therapy (ECT) is the most effective treatment for depression and has also been shown to treat chronic pain.[6,7] A more recent development in brain stimulation techniques for treating depression is repetitive transcranial magnetic stimulation (rTMS or TMS). Transcranial magnetic stimulation is a safe, noninvasive method of "electrodeless" brain stimulation using brief magnetic pulses that pass unimpeded through the scalp and skull, to produce a current in underlying cortical tissue. Both high-frequency TMS applied to the left dorsolateral prefrontal cortex (DLPFC) and low-frequency TMS applied to the right DLPFC have been shown to have an antidepressant effect.[8]

It is also known that direct stimulation of the motor cortex with chronic electrical stimulation or rTMS can reduce chronic central pain.[9,10] A single session of high-frequency (10 Hz) rTMS applied to the motor cortex was able to reduce chronic pain for up to 8 days,[10] and monthly sessions of rTMS were able to control neuropathic pain in a patient for more than a year.[11] One meta-analysis of 149 subjects with neuropathic pain treated with rTMS applied to the motor cortex also shows significant efficacy of active TMS versus sham.[12]

To date, most studies using rTMS to reduce pain have stimulated the motor cortex using a single session of treatment, whereas most studies using rTMS to treat depression have

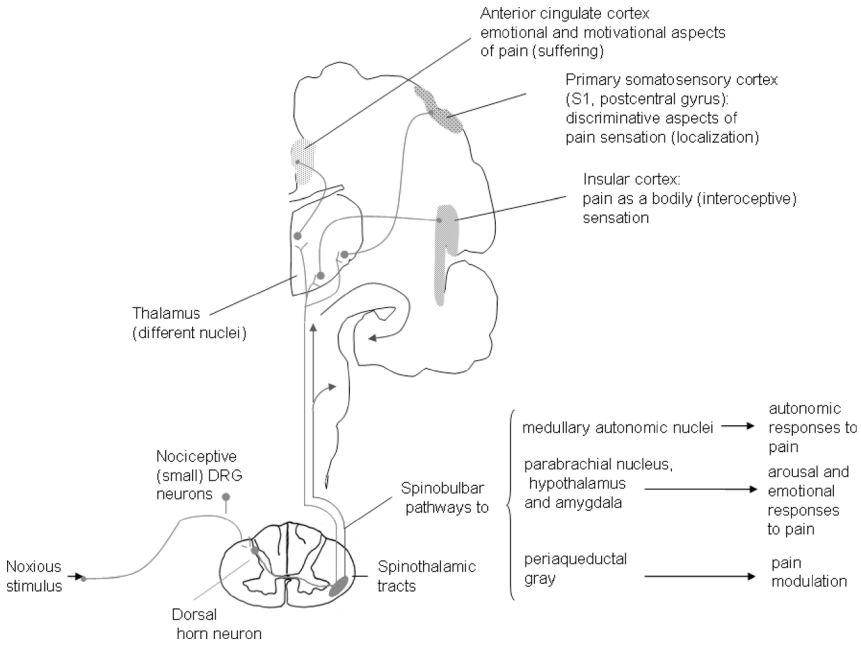

FIGURE 1. Pain sensation pathways.

stimulated the DLPFC. Pain studies using rTMS applied to the motor cortex also differ from depression studies in that only subthreshold intensities have been used. This latter difference may be significant as higher intensity is thought to be important in obtaining a more optimal therapeutic response in studies using rTMS to treat depression.[8] Another key feature that may make

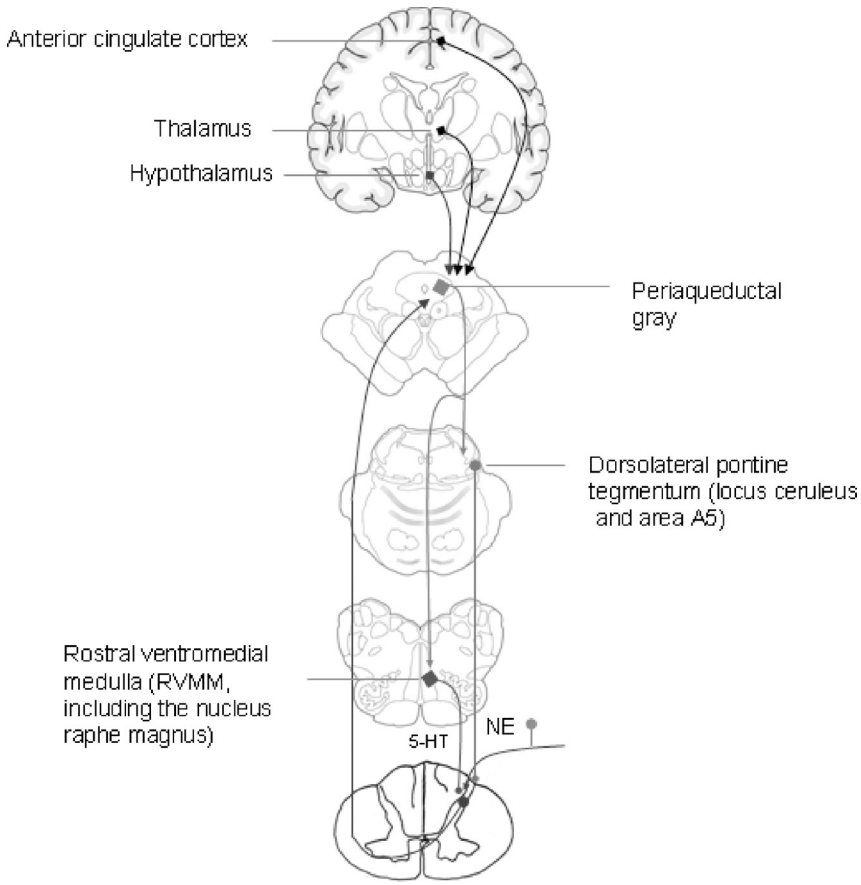

FIGURE 2. Components of the pain modulation system.

stimulation of the DLPFC more useful in treating pain is the significant connection to the anterior cingulate, which is involved in the emotional component of pain. Chronic fibromyalgia pain has been reported to improve with slow-frequency rTMS applied to the right DLPFC in subjects receiving rTMS for depression.[13] Four patients experienced significant improvement in pain with 20-rTMS treatments, and the duration of improvement ranged from 15 to 27 weeks after the acute treatment course ended. There has also been a report of pain improvement with high-frequency rTMS applied to the left DLPFC in a controlled trial for depression.[14] Three 10-Hz rTMS treatments applied to the left DLPFC have been shown to improve neuropathic pain by an average of 19% and were superior to sham.[15]

Given that rTMS has been useful in difficult-to-treat depression, and it is less invasive than ECT, it is possible that rTMS applied to the DLPFC may be a useful and more tolerable approach to the treatment of chronic neuropathic pain. Thus, this study examines the safety and feasibility of treating chronic neuropathic pain with repetitive TMS applied to the DLPFC.

METHODS

Study Design and Subjects

This study was a prospective, open trial of rTMS in 9 subjects with chronic neuropathic pain. A total of 15 TMS treatments were given (5 days per week for 3 weeks), and subjects were followed up monthly for 3 months after the TMS treatment had been completed.

Subjects aged 18 to 65 years, who met the criteria for chronic, refractory, or poorly controlled neuropathic pain (at least 6 months' duration) with subjective pain ratings of at least 5 of 10 on 4 of 7 days despite being on medications, who had a Hamilton Rating Scale for Depression (HRSD) score of less than 18 (17-item HRSD), were enrolled. Subjects were capable of providing informed consent, and a board-certified neurologist provided the diagnosis of chronic neuropathic pain. Exclusion criteria included the following: a diagnosis of depression as per HRSD greater than 18, alcohol or illicit substance dependence or abuse in the past 12 months, dementia, unprovoked seizure history, seizure disorder or family history of treatment-resistant epilepsy, pregnancy, metal in the head (except dental fillings), implanted medication pump, pacemaker, prior brain surgery, history of stroke, severe aortic stenosis (even if asymptomatic), severe angina (even if stable), class III congestive heart failure, known ejection fraction of less than 30%, significant change or increase in antidepressant or pain medications within the last 4 weeks, significant change in primary treatment interventions for pain in the past 4 weeks, or medically unstable.

Subject workup included a medical history and neurological examination, mental status examination, and a pregnancy test for women of childbearing age who could potentially become pregnant. This study was approved by our institutional review board, and written consent was obtained from all subjects.

Clinical Evaluation

All subjects were evaluated by a clinical rater using the HRSD (17 items) at baseline and at the end of each week of rTMS treatment. Subjects completed mood and pain visual analog scales (VASs) before and after all rTMS treatments. Subjects were evaluated with HRSD and pain ratings monthly for 3 months after completing the TMS treatment. After treatment, those subjects not able to be followed up in person were contacted by phone. For these subjects, Likert pain ratings were obtained instead of VAS ratings.

All medications used by study subjects and the number/frequency of rTMS treatments were recorded. No pain medication changes were permitted during the study.

TMS Procedures

Single stimuli and rTMS were provided using a Neuronetics (model 2100 CRS, Malvern, Pa) repetitive stimulator. Stimulation was performed with the coil placed tangentially to the scalp. All subjects and treaters wore earplugs to reduce the risk for hearing threshold shifts.

Motor Threshold Determination

Single-pulse TMS was applied to the right motor cortex (M1) to determine the visual motor threshold (MT) for contraction of the contralateral abductor pollicis brevis. The visual MT is defined as the lowest TMS intensity required to produce muscle contraction in at least 5 of 10 trials. The optimal site for abductor pollicis brevis activation was determined by applying single-TMS stimuli at suprathreshold intensity to scalp positions distributed in a grid over M1. After identifying this position, the visual MT estimation was obtained using the MT Assist program (Neuronetics, Inc). There was a minimum interval of 5 seconds between TMS stimuli.

rTMS Treatments

One-hertz rTMS was applied to the right DLPFC with an intensity of 110% of MT. The DLPFC location was defined as that area 5 cm anterior to the motor cortex for activation of ABP. Subjects received a total of 1600 stimuli per session (26.67 minutes). Treatment occurred 5 days per week for 3 weeks. The TMS coil was placed tangential to the scalp. Subjects were monitored during and after rTMS for any side effects or adverse events.

Data Analysis

Clinical scales for depression and subjective pain (HRSD, VAS) were recorded as numeric variables for all patients and summarized by the mean and range. These summaries were obtained from measurements made at baseline, during rTMS treatment, at the end of treatment, and 1 week and monthly after treatment for 3 months. Demographic and other information, including patient age and sex, as well as medications and the number and frequency of rTMS treatments, was recorded for each subject and summarized as appropriate for the type of data.

Treatment success, as commonly accepted, was defined as a 50% decline or greater in subjective pain ratings on a VAS.

RESULTS

Five males and 4 females, aged 24 to 62 years, were enrolled in this study. Table 1 lists the demographic data and clinical summaries of the subjects. Pain duration ranged from 1 to 20 years, and the mean pain level at study entry was 7.3 (range, 6.9–9.8). All subjects had failed multiple standard therapies and had exhausted most available options, with the exception of motor cortex and deep brain stimulation. Subjects were not depressed and had a mean HRSD of 3.6 (range, 0–8). No changes in psychiatric or pain medications occurred during the study.

Subjects experienced no unexpected side effects, and rTMS was well tolerated in general, with all subjects completing 15 rTMS treatments. Expected side effects included discomfort at the treatment site during treatment and at times a transient mild headache after the treatment session. After completing rTMS, 1 subject was lost to follow-up, and a second subject was lost after the 2-month follow-up.

TABLE 1. Summary of Subject Demographics and Clinical Information

Subject	Age, y	Sex	Neuropathic Pain Syndrome	Pain Duration, y	VAS	Clinical Details
1	50	Male	Cord pain syndrome NOS	3	6.9	Severe burning and painful spasms; failed multiple medications
2	38	Male	Chronic regional pain syndrome	2.5	8.1	Initially in right arm, spread to face and contralateral arm; severe allodynia; failed multiple medications and pain rehabilitation program
3	50	Male	Phantom limb pain	1	7.5	Failed multiple medications and dorsal cord stimulator
4	25	Male	Postherpetic neuralgia	5	7.5	Bilateral T6–T7, failed multiple regimens
5	45	Female	Phantom limb pain	19	9.8	Failed multiple medications, dorsal cord stimulator, pain rehabilitation program
6	45	Male	Deafferentation pain due to root avulsions	20	9.2	Failed multiple medications, dorsal root entry zone procedure
7	62	Female	Central pain with parkinsonism; somatoform component	4	6.9	Failed/intolerant to multiple medications
8	24	Female	Multiple congenital deformities, developed severe erythromelalgia	8	7	Medications helped some, but became intolerant
9	49	Female	Numbness on left side of the face progressing to anesthesia dolorosa (cause unknown)	10	7.2	Magnetic resonance imaging is negative, medications helped some, but became intolerant due to decreased functional capacity

Subject pain ratings are listed in Table 2. Three of 9 subjects had a 50% improvement in pain or greater, and this was noted within the first week of treatment. Two of these subjects continued to have ongoing pain improvement for the time they were available for follow-up (2–3 months). One subject had a progressive return of his/her pain, notable by 1-month follow-up. A fourth subject had a more gradual response and continued to have a slow improvement in pain after rTMS was completed, achieving a 50% decline in pain or greater by 3 months after treatment, still with no changes in her medications. Of note, this subject's chronic erythema, caused by altered vasomotor tone, also improved. A fifth subject had a 46% improvement in pain at 1-month follow-up.

DISCUSSION

One of the main findings of our study was that 4 of 9 subjects had significant improvement in pain, with 3 of 4 having rapid onset of improvement (ie, within the first week of treatment). This would suggest that although those who respond to rTMS are likely to do so early in the course of therapy, a delayed response may still occur. Compared with response times seen in treating depression, pain improvement appears to be much more rapid when present.

In terms of durability of response, 2 of the 3 responders showed ongoing improvement in pain at 2 to 3 months after treatment. One responder had his pain gradually return after TMS was discontinued, with a return to his baseline level of pain noted at the 2-month follow-up. Overall, these findings are much more durable than those noted with TMS applied to the motor cortex, where pain improvement tends to last for hours to days only. These findings suggest that targeting the DLPFC as the TMS treatment site and using a more intense treatment series may also enhance response durability.

The methods used in this study to treat chronic pain differ from most TMS pain trials in 3 ways: (1) site of stimulation (DLPFC vs motor cortex), (2) number of treatments and overall number of stimulations, and (3) intensity used (percent MT). Changing the site of stimulation may be a significant component

TABLE 2. Neuropathic Pain Ratings at Baseline, Weekly During Active TMS Treatment, and Monthly for 3 Months After Treatment

	VAS						
Subject	Baseline	Week 1	Week 2	Week 3	Month 1	Month 2	Month 3
1	6.9	8.5	9.4	9.3	9	7.9	8.6
2	8.1	9.2	8.9	9.1	8	8	9
3*	7.5	2.2	0.5	2.1	3	3	3
4*	7.5	0	0	0	4	0	—
5	9.8	9.8	9.8	9.8	7	10	10+
6*	9.2	1.3	1.7	1.3	6	9	10
7	6.9	9.4	4.1	6.4	—	—	—
8†	7	6.3	5.2	5	4	4	3
9	7.2	4.4	5.8	5.6	4	7	7

*Responder.

†Delayed responder.

in accessing and altering key limbic structures such as the anterior cingulate and the insula. Increasing the overall number of stimulations and intensity are also significant differences as these have been shown to predict increased success in treating depression[8] and thus are likely better able to alter limbic pathways.

This study is limited by being an open trial; however, given the subjects' history of treatment resistance and severity of pain and suffering, these results are quite encouraging, as any improvement in these subjects' pain is notable. Given that TMS is safe and noninvasive and has fewer adverse effects compared with medications,[16,17] it may represent a valid treatment option, but further research is warranted to quantify its efficacy in comparison to standard therapies. The total number of stimulations provided in this trial is about half that used in more recent depression trials, and the intensity used is also lower; thus, these parameters likely need further optimization. As well, maintenance TMS options need to be explored to see if durability of treatment can be enhanced, as maintenance TMS to the motor cortex has been shown to be of benefit.[11]

REFERENCES

1. Woolf C, Mannion R. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353(9168):1959–1964.
2. Woolf C. Evidence for a central component of post-injury pain hypersensitivity. *Nature*. 1983;306:686–688.
3. Woolf C, Salter M. Neuronal plasticity-increasing the gain in pain. *Science*. 2000;288:1765–1768.
4. Woolf C. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. *Life Sci*. 2004;74:2605–2610.
5. Rome H, Rome J. Limbically augmented pain syndrome (LAPS): kindling, corticolimbic sensitization, and the convergence of affective and sensory symptoms in chronic pain disorders. *Pain Med*. 2000;1(1):7–23.
6. Bloomstein J, Rummans TA, Maruta T, et al. The use of electroconvulsive therapy in pain patients. *Psychosomatics*. 1996;37:374–379.
7. Rasmussen K, Rummans T. Electroconvulsive therapy in the management of chronic pain. *Curr Pain Headache Rep*. 2002;6:17–22.
8. Gershon A, Dannon P, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. *Am J Psychiatry*. 2003;160(5):835–845.
9. Nguyen J, Lefaucher JP, LeGuerinel C, et al. Motor cortex stimulation in the treatment of central and neuropathic pain. *Arch Med Res*. 2000;31:263–265.
10. Lefaucheur J, Drouot X, Nguyen J. Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. *Neurophysiol Clin*. 2001;31:247–252.
11. Lefaucheur J, Drouot X, Menard-Lefaucheur I, et al. Neuropathic pain controlled for more than a year by monthly sessions of repetitive transcranial magnetic stimulation of the motor cortex. *Clin Neurophysiol*. 2004;34:91–95.
12. Leung A, Donohue M, Xu R, et al. rTMS for suppressing neuropathic pain: a meta-analysis. *J Pain*. 2009;10(12):1205–1216.
13. Sampson S, Rummans T, Rome J. Slow frequency rTMS reduces fibromyalgia pain. *J Neuropsychiatry Clin Neurosci*. 2003;15(2): 257–258.
14. Avery D, Holtzheimer PE, Fawaz W, et al. Transcranial magnetic stimulation reduces pain in patients with major deprssion: a sham-controlled study. *J Nerv Ment Dis*. 2007;195(5):378–381.
15. Borckardt J, Smith AR, Reeves ST, et al. A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. *Pain Med*. 2009;10(5):840–849.
16. O'Reardon JP, Blumner KH, Peshek AD, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007;62:1208–1216.
17. Janicak P, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry*. 2008;69:222–232.