Case Series

rTMS in Alleviating Mild TBI Related Headaches – A Case Series

Albert Leung, MD, Amir Fallah, BS, Shivshil Shukla, BS, Lisa Lin, MD, Alice Tsia, DO, David Song, MD, Gregory Polston, MD, and Roland Lee, MD

From: Department of Anesthesiology, University of California, San Diego, School of Medicine, Veterans Administration San Diego Healthcare System, La Jolla, CA

Address Correspondence:
Albert Leung, M.D.
Department of Anesthesiology
University of California, San Diego
School of Medicine;
Veterans Administration San Diego Healthcare System
9300 Campus Point Drive #7651
La Jolla, CA 92073-1300
E-mail: ayleung@ucsd.edu

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 04-27-2015
Revised manuscript received: 06-03-2015
Accepted for publication: 08-07-2015

Free full manuscript: www.painphysicianjournal.com

Background: Headache is one of the most common debilitating chronic pain conditions in patients with mild traumatic brain injury. Conventional pharmacological treatments have not been shown to be effective in alleviating debilitating mild traumatic brain injury related headaches (MTBI-HA). Therefore, the development of an innovative non-invasive therapy in managing MTBI-HA is needed in the field of pain management. Repetitive transcranial magnetic stimulation (rTMS) utilizes a basic electromagnetic coupling principle in which a rapid discharge of electrical current is converted into dynamic magnetic flux, allowing the induction of a localized current in the brain for neuromodulation. The treatment is currently FDA approved for treating depression in the United States. Recent meta-analysis studies have implicated its usage in chronic pain management.

Objective: The objective of the prospective case series is to assess the potential application of rTMS in alleviating MTBI-HA.

Study Design: A prospective evaluation was conducted in patients with established diagnoses of MTBI-HA and treated with neuronavigational guided rTMS.

Setting: The study was conducted at the Veteran Administration San Diego Healthcare System where over 400 patients with MTBI were being evaluated annually by the Rehabilitation Medicine Service. A fraction of this patient population was referred and evaluated in the Anesthesia Pain Clinic for the consideration of rTMS for their headaches.

Methods: A prospective case series was conducted with human subject protection committee approval. Patients with established diagnoses of MTBI and constant headaches rated at ≥ 4 on a 0 – 10 Numerical Rating Pain Scale (NRPS), and on stable headache medication regimens were selected to receive the treatment. Four sessions of rTMS were delivered to specific areas of cortices over a 2-month period. Patients' average intensities of lingering constant headaches (defined as duration of headache lasting more than 48 hours), and the average frequency (number of severe headache episodes per day), intensity (NRPS), and duration (hours) of headache exacerbations were assessed before and after the rTMS treatment protocol.

Results: Six men (average age of 50) with MTBI-HA received the rTMS treatment protocol. Average pre and post-rTMS constant headache scores (± SD) on the NRPS were 5.50 (± 1.38) and 2.67 (± 1.75), respectively, with an average post-rTMS headache intensity reduction of 53.05% (± 19.90). The average headache exacerbation frequency (episodes per week) was reduced by 78.97% (± 19.88) with 2 patients reporting complete cessation of severe headache episodes. For those (N = 4) with persistent headache exacerbations, the average duration and intensity of these exacerbations were reduced by 50.0% and 31.7%, respectively.

Limitations: This prospective evaluation provides the initial insight that rTMS may be beneficial in alleviating a debilitating chronic pain condition in patients with MTBI-HA. More controlled randomized studies should be conducted to validate its efficacy. Other co-existing cognitive and mood dysfunction should be assessed as well.

Conclusions: rTMS offers a non-invasive treatment option for MTBI-HA. The tested treatment protocol was well tolerated by the patients and can be adopted for future randomized controlled studies in further validating the treatment efficacy.

Key words: Transcranial magnetic stimulation, MTBI, mild traumatic rrain injury, headaches, pain neuromodulation

Pain Physician 2016; 19:E347-E353

Chronic post-traumatic injury headache (HA) is the most debilitating clinical symptom in patients with mild traumatic brain injury (MTBI) (1). Unfortunately, conventional pharmacological treatments have not been shown to be effective in alleviating headaches in this patient population. Drug regimens often contain many long-term untoward psychosomatic and abusive side effects (2). Therefore, a non-invasive means of neuromodulation may offer an excellent alternate therapeutic option for this debilitating chronic pain problem. Recently, the use of non-invasive brain stimulation such as repetitive transcranial magnetic stimulation (rTMS) has yielded favorable clinical outcomes in a few chronic central pain conditions including post-stroke central pain and headaches (3-4). Among the various locations of cortical stimulation, the motor and the prefrontal cortices, especially the left dorsal lateral prefrontal cortex (LDLPFC), appear to have the most profound analgesic benefit. The LDLPFC is also known to have a mood enhancing effect. This option of headache management has not been assessed in patients with MTBI related HA (MTBI-HA). Here we reported a prospective case series in which 6 patients with established diagnoses of chronic MTBI-HA responded favorably to this non-invasive treatment. Prior to each treatment session, a magnetic resonance image (MRI) of the brain was obtained and reviewed by a neuroradiologist to ensure no brain abnormality would exclude the patient from the rTMS treatment. The image obtained was then used for neuronagvigational guided (NNG) rTMS. Each patient's average intensity of lingering constant headache (defined as duration of headache lasting more than 48 hours) was assessed with a 0 – 10 numerical rating pain scale (NRPS). In addition, the average frequency (number of headache episode per day), intensity (NRPS), and duration (hours per each exacerbation episode) of headache exacerbation were assessed before (pre) and after (post) the rTMS treatment protocol. All patients were advised to maintain their HA analgesics during the course of the treatment but were allowed to adjust the medications after the treatment protocol was completed.

Case Series

Case #1

A 41 year-old man with no prior history of headache suffered a concussion after a fall. He remembered hitting the bottom of the stairs prior to a brief period (less than a minute) of loss of consciousness (LOC). He developed constant headache on the left side of his head behind the eye with a throbbing sensation, photophobia, phonophobia, tinnitus, visual disturbances, and nausea shortly after the injury. Relief from non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin was minimal. He rated the average intensity of his constant headache at 6/10 (NRPS) with an average frequency, duration, and intensity of exacerbation at 3 episodes/week, 3 hours/episode, and 10/10 (NPRS), respectively, before the treatment. He received the rTMS treatment protocol uneventfully. He reported the average intensity of constant headache was reduced to 1/10 (NRPS) and the average frequency, duration, and intensity of headache exacerbations were changed to one episode per week, one hour per episode, and 2/10 (NRPS), respectively, at the completion of the treatment protocol. He no longer required aspirin or other NSAIDS for his headache.

Case #2

A 52 year-old man with no prior history of headache suffered a fall while working on his truck with LOC for a few minutes. He developed a global headache with photophobia and phonophobia immediately after the fall. He also reported an occasional ringing sensation in his ears and difficulty with short-term memory and attention. He subsequently suffered from several blast-related head injuries while in active military duty without confusion or LOC. His headache relief from prescribed Topiramate 100 mg BID and oral Sumatriptin was minimal. His pre-rTMS headache intensity was 5/10 (NRPS), and the average frequency, duration, and intensity of headache exacerbations were 2 episodes per week, 4 hours per episode, and 7/10 (NRPS), respectively. He underwent the rTMS treatment protocol uneventfully. He reported the average constant headache intensity was decreased to 2/10 (NRPS), and the average frequency, duration, and intensity of headache exacerbations were one episode per week, 4 hours per episode, and 7/10 (NRPS), respectively, after the treatments. He was subsequently lost follow-up due to other medical problems. His rTMS session was resumed 2 years later. With an ongoing monthly rTMS maintenance schedule, his average constant headache intensity has been around 3/10 (NRPS), and the average frequency, duration, and intensity of headache exacerbations were one episode per week, 4 hours per episode, and 7/10 (NRPS), respectively. He no longer takes Sumatriptin and requires only scheduled Topiramate for his headache.

Case #3

A 56 year-old man with a 4-year history of constant headache precipitated by a fall was referred for TMS evaluation by the Tramatic Brain Injury (TBI) clinic with the diagnosis of HA. The location of his headache has been global but concentrated in his right hemisphere extending from the forehead to the occipital region. On average the patient has been on a stable regimen of headache medications consisting of 4 tablets of hydrocodone 10 mg/acetaminophen 650 mg (Vicodin) per day and 3 to 4 tablets of Tramadol 50 mg a day for at least one year prior to the rTMS treatments. Due to his prior drug problem and concern of addiction, he was reluctant to increase his headache medication. He received 2 occipital nerve blocks which relieved his occipital headaches but provided no relief for the frontal and temporal headaches. He rated his pre-rTMS constant headache intensity at 8/10 (NRPS), and the average frequency, duration, and intensity of headache exacerbations at 14, 9, and 10/10, respectively. He rated his post-rTMS average constant headache intensity level at 6/10 (NRPS). The average frequency, duration, and intensity of headache exacerbations were 2, 3, and 7/10, respectively. The patient subsequently received monthly maintenance treatment and continued to have adequate headache relief with only occasional use of Vicodin.

Case #4

A 60 year-old man presented with a 7-year history of headache and neck pain after suffering a concussion in a motor vehicle accident (MVA) with no loss of consciousness. His headache was primary felt in the left occipital region with frequent radiation to the neck and back. He was diagnosed with HA and treated with Bupropion, Naproxen, Zolpidem, and Ultram with no significant relief in headaches or improvement in his mood. His neck pain improved after several trigger point injections. Pre-rTMS headache assessments indicated that he suffered from a constant headache at an average intensity of 5/10, and the average frequency, duration, and intensity of headache exacerbations were 3 episodes per week, 3 hours per episode, and 6/10 (NRPS), respectively. Subsequent to the rTMS treatment protocol, he reported an average constant headache of 2/10 (NRPS) without any exacerbation. His headache was subsequently well controlled with maintenance rTMS every 6 weeks with only occasional use of Naproxen for his arthritic pain.

Case #5

A 54 year-old man with no prior history of headache developed a 7-year history of headache after bluntly hitting his head in a fall. He suffered a brief period of LOC during the falling incidence and developed a persistent headache in the occipital and frontal regions with photophobia, phonophobia, dizziness, nausea, and tremors afterwards. Past failed treatments for his headache included Amitriptyline, Tramadol, Diclofenac, and Naproxen. Prior to the rTMS, he reported an average constant headache intensity of 5/10 (NRPS), with an average frequency, duration, and intensity of headache exacerbations at 5½ episodes per week, 4 hours/episode, and 6/10 (NRPS), respectively. The patient received the rTMS treatment protocol uneventfully. Subsequent to the treatment protocol, the patient reported a change of average constant headache level to 3/10 (NRPS), and no longer experienced any headache exacerbations. He subsequently was placed on a monthly maintenance rTMS protocol with adequate headache control.

Case #6

A 38 year-old man with no prior history of headache developed constant headache after a MVA in 2008. He rated his average constant headache intensity at 4/10 (NRPS), and an average frequency, duration, and intensity of headache exacerbations at 7 episodes per week, 4 hours per episode, and 8/10 (NRPS), respectively. His headache was accompanied with gait balance problem, photophobia, phonophobia, and extreme irritability during the exacerbations. Regular BOTOX injections helped his neck myofascial pain but not his headache. Previous failed therapies for headaches included Topiramate, Tramadol, Zolmitriptan, and Sumatriptan. The patient completed the rTMS treatment protocol uneventfully. He reported a post-treatment average constant headache intensity of 2/10 (NRPS), and his average frequency, duration, and intensity of headache exacerbations were 2 episodes per week, 2 hours per episode, and 4/10 (NRPS), respectively. the patient continued to receive monthly rTMS maintenance treatment and reported a cessation of his constant headache. In addition, the average frequency, duration, and intensity of his headache exacerbations were reduced to 2 episodes/week, 2 hours/episode, and 8/10 (NRPS), respectively. He used Sumatriptan occasionally to control the exacerbations.

rTMS Treatment

To be consistent with each patient, a standardized treatment protocol was adopted. Prior to rTMS

treatment, the motor threshold was determined using electromyography (5). The location for the established motor threshold was marked on the stereotaxic NNG software and used as the treatment location for motor cortex stimulation (see Fig. 1). To consistently stimulate the LDLPFC across the patients, we have adopted a standardized algorithm in localizing the treatment target based on functionally established coordinates for the LDLPFC. Active-rTMS consists of 20 trains with each train containing 100 pulses delivered at 10 Hz and 80% of the motor threshold via the figure eight (Magpro B65) coil over the area as determined above. For a single location treatment, a total of 2000 pulses per session were delivered. For sequential dual location treatment, 1500 pulses were delivered per site. All patients received the first treatment at the LMC, the second treatment at the LDLPFC, and the third and fourth treatments sequentially at the LDLPFC and LMC. Each treatment setting was within the treatment safety guidelines recommended by the FDA (6).

Result

Six men (average age of 50) with MTBI-HA received the rTMS treatment protocol. Pre-treatment brain MRI showed no gross abnormality in all 6 patients. Average pre and post-rTMS constant headache scores (± SD) on the NRPS were 5.50 (± 1.38) and 2.67 (± 1.75), respectively, with an average post-rTMS headache intensity reduction of 53.05% (± 19.90). The average headache exacerbation frequency (episodes per week) was reduced by 78.97% (± 19.88) with 2 patients reporting complete cessation of severe headache episode. For those (N = 4) with persistent headache exacerbations, the average duration and intensity of these exacerbations were reduced by 50.0% and 31.7%, respectively (see Table 2). In addition, 3 of the 6 patients were able to completely eliminate their headache abortive medications and the other 3 were able to reduce their medications at the completion of the initial treatment series (see Table 1).

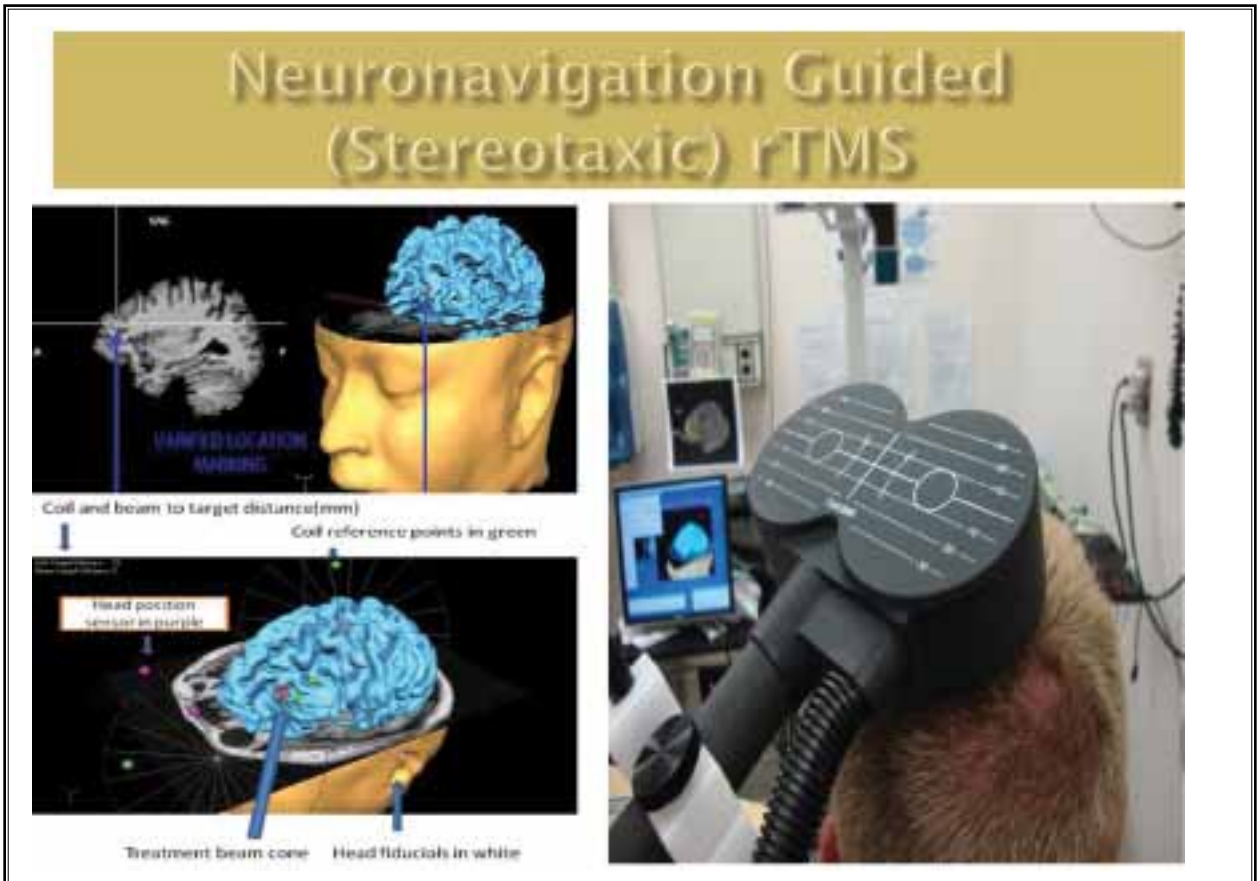

Fig. 1. *Repetitive transcranial magnetic stimulation (rTMS) with stereotaxic neuronavigation guidance.*

Table 1. *Pre and post-rTMS difference in the average constant headache intensity (NPRS), and headache exacerbation intensity (NPRS), frequency (number of episode per week) and duration (number of hours per episode.*

Case	Age	Sex	History of CPTH (Years)	Cause	Pre-rTMS Average Intensity of Constant Headache	Pre-rTMS Headache Exacerbation			Post-rTMS Average Intensity of Constant Headache	Post-rTMS Headache Exacerbation		
						Intensity	Frequency	Duration		Intensity	Frequency	Duration
#1	41	M	3	Fall	6.0	10.0	3.0	3.0	1.0	2.0	1.0	1.0
#2	52	M	4	Fall	5.0	7.0	2.0	4.0	2.0	7.0	1.0	4.0
#3	56	M	1.5	Fall	8.0	10.0	14.0	9.0	6.0	7.0	2.0	3.0
#4	60	M	7	MVA	5.0	6.0	3.0	3.0	2.0	0	0	0
#5	54	M	7	Fall	5.0	6.0	5.5	4.0	3.0	0	0	0
#6	38	M	4	MVA	4.0	8.0	7.0	4.0	2.0	4.0	2.0	2.0
Average (±SD)	50.2 (±4.4)		4.4 (±2.2)		5.5 (±1.4)	7.8 (±1.8)	5.8 (±4.4)	4.5 (±2.3)	2.6 (±1.8)**	3.3 (±3.2)*	1.0 (±0.9)*	1.7 (±1.6)*

rTMS: Repetitive Transcranial Magnetic Stimulation; NPRS: Numerical Rating of Pain Scale; MVA: Motor Vehicle Accident; CPTH: Chronic Post-traumatic Headache; **: $P < 0.01$; *: $P < 0.05$

Discussion

While the prevalence of HA in the general TBI population is estimated to be around 57.8% (7), the incidence of persistent HA in veterans with MTBI is even higher (over 70%) than the general population. This high prevalence of chronic HA and neuropsychological dysfunction casts a profound negative impact on TBI patients' quality of life and becomes a major obstacle in their effort to resume normal activities after the head injury. Unfortunately, conventional medical therapies for HA rely heavily on psychotropic and opioid medications, and are deficient in both reducing MTBI-HA and improving associated neuropsychological dysfunction. A recent study showed that many individuals with mild TBI may be self-treating their headaches by utilizing over-the-counter pain relief medications for abortive therapy. These medications, however, are only providing effective treatment for a minority of this patient population and have potential systemic side effects (8). Prescribed medications such as anticonvulsants, tricyclics, and narcotics also have many side effects and abusive risks and do not serve as effective preventive treatment for MTBI-HA (2). This lack of treatment efficacy from existing pharmacological interventions calls for the development of a different prevention and treatment strategy for managing MTBI-HA and associated functional impairment. In assessing the underlying pathophysiology of MTBI related morbidities, recent studies with diffusion tensor imaging suggest that MTBI patients suffer from diffuse axonal injury in the major cortical white matter tracts including the corpus callosum, anterior corona radiata, corticospinal tract, and internal capsules, which are crucial for intracortical connectivity. These abnormalities can lead to a dissociative state between the affective (hyperactive) and modulatory (hypoactive) aspects of the pain network (9). Thus, therapies that enhance the supraspinal modulatory functions can potentially correct this dissociative state, and improve MTBI-HA and associated neuropsychological dysfunction.

rTMS uses electromagnetic principles to produce a small electrical current in the cortex without the requirement of anesthesia (10). Currently devices developed from similar electromagnetic principles are approved for treating depression and migraine headaches in the United States (11,12). While both dorsolateral prefrontal cortex (DLPFC) and motor cortex (MC) high frequency (> 1 Hz) rTMS can result in an analgesic benefit, their relative mechanisms appear to be different. With stimulation at the motor cortex, a strong focal activation was observed in the thalamus, insula, cingulate-orbitofrontal junction, and periaqueduct grey (PAG) area in the brainstem, suggesting a top-down activation of the descending pain control system mediated via a motor-thalamus and/or motor-brainstem functional linkage (13). On the other hand, rTMS at the DLPF exerts a top-down inhibitory effect along the ascending midbrain-thalamic-cingulate pathway through the descending fibers from the prefrontal cortex (14,15). One recent important finding is that left DLPFC stimulation can potentiate the excitability of motor cortices (16). In addition substantial evidence indicates high frequency rTMS at the LDLPFC is known to

Table 2. *Pre and post-rTMS usage of headache related preventive and abortive medications.*

Case Series	Pre-rTMS Headache Medications		Post-rTMS Headache Medications	
	Preventive	**Abortive**	**Preventive**	**Abortive**
#1	None	NSAIDS	None	None
#2	Topiramate 100mg, 2 tablets per day	Sumatriptan 50 mg , averaged 2 tablets per day	Topiramate 100mg BID	None
#3	Tramadol 50 mg, 4 tablets per day	Hydrocodone 10mg/Acetaminophen 650 mg, averaged 4 tablets per day	None	Hydrocodone 10mg/Acetaminophen 650 mg, averaged less than one tablets per day
#4	Tramadol 50 mg, 4 tablets per day	Naproxen 250mg, averaged two to 3 tablets per day	None	Naproxen 250mg, averaged less than one tablet per day
#5	Failed Tramadol and amitriptyline	Failed Diclofenac and Naproxen	None	None
#6	Topiramate 50mg , 2 tablets per day;	Zolmitriptan 2.5 mg, averaged one tablet per day, Sumatriptan 50mg, averaged 3 tablets per day.	None	Sumatriptan 50 mg, averaged less than one per day

NSAIDS: Non-steroidal anti-inflammatory; rTMS: Repetitive Transcranial Magnetic Stimulation

enhance attentional cognitive function with associated antidepressant benefit. Increasing evidence from randomized studies with sham control demonstrated the efficacy of rTMS in providing pain relief for a variety of neuropathic pain conditions (5,17-20). A recent meta-analysis study further suggests the neuroanatomical origin of neuropathic pain may impact the rTMS-induced analgesic effect at the motor cortex with centrally originated pain being more responsive to treatment, suggesting a differential top-down treatment effect and the potential application of rTMS in treating centrally originated MTBI-HA and neuropsychological dysfunction (3). While a preliminary study indicates rTMS at the DLPFC may help reduce post-concussive symptoms, the long-term effect of the treatment at both locations for headache relief has yet to be assessed (21). Therefore, the current case series demonstrates it is feasible and potentially beneficial to sequentially treat both LMC and LDLPFC in patients with MTBI-HA. The observation from the current case series provides the initial evidence of this therapeutic approach as rTMS effectively reduces the intensity of the constant MTBI-HA by more than 50% and the treatment is effective in reducing the frequency, duration, and intensity of headache exacerbations. In addition, all patients tolerated the treatment protocol well without any significant side effects.

While the current case series provides the initial clinical evidence suggesting rTMS at the both LMC and LDLPFC can safely modulate MTBI-HA with reduction in overall intensity, frequency, and duration, controlled randomized studies are required to further validate this treatment modality and relative location effects.

Acknowledgment

The authors thank Melanie Valentin, N.P., and Jennifer Peters, N.P., for their assistance in patient evaluation and treatment scheduling.

References

1. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med* 2008; 358:453-463.
2. Patil VK, St Andre JR, Crisan E, Smith BM, Evans CT, Steiner ML, Pape TL. Prevalence and treatment of headaches in veterans with mild traumatic brain injury. *Headache* 2011; 51:1112-1121.
3. Leung A, Donohue M, Xu R, Lee R, Lefaucheur JP, Khedr EM, Saitoh Y, Andre-Obadia N, Rollnik J, Wallace M, Chen R. rTMS for suppressing neuropathic pain: A meta-analysis. *J Pain* 2009; 10:1205-1216.
4. Misra UK, Kalita J, Bhoi SK. High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: A randomized, placebo-controlled study. *J Neurol* 2013; 260:2793-2801.
5. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. *J Neurol Neurosurg Psychiatry* 2005; 76:833-838.
6. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol* 1998; 108:1-16.
7. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: A systematic review. *JAMA* 2008; 300:711-719.
8. DiTommaso C, Hoffman JM, Lucas S, Dikmen S, Temkin N, Bell KR. Medication usage patterns for headache treatment after mild traumatic brain injury. *Headache* 2014; 54:511-519.
9. Lewine JD, Davis JT, Bigler ED, Thoma R, Hill D, Funke M, Sloan JH, Hall S, Orrison WW. Objective documentation of traumatic brain injury subsequent to mild head trauma: Multimodal brain imaging with MEG, SPECT, and MRI. *J Head Trauma Rehabil* 2007; 22:141-155.
10. Pascual-Leone A, Pridmore H. Transcranial magnetic stimulation (TMS). *Aust N Z J Psychiatry* 1995; 29:698.
11. Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, Fischell RE, Ruppel PL, Goadsby PJ. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: A randomised, double-blind, parallel-group, sham-controlled trial. *Lancet Neurol* 2010; 9:373-380.
12. George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. *Curr Opin Psychiatry* 2013; 26:13-18.
13. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B. Electrical stimulation of motor cortex for pain control: A combined PET-scan and electrophysiological study. *Pain* 1999; 83:259-273.
14. Lorenz J, Cross D, Minoshima S, Morrow T, Paulson P, Casey K. A unique representation of heat allodynia in the human brain. *Neuron* 2002; 35:383-393.
15. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: The role of the dorsolateral prefrontal cortex in pain modulation. *Brain* 2003; 126:1079-1091.
16. Paus T, Castro-Alamancos MA, Petrides M. Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. *Eur J Neurosci* 2001; 14:1405-1411.
17. Andre-Obadia N, Peyron R, Mertens P, Mauguiere F, Laurent B, Garcia-Larrea L. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. *Clin Neurophysiol* 2006; 117:1536-1544.
18. Hirayama A, Saitoh Y, Kishima H, Shimokawa T, Oshino S, Hirata M, Kato A, Yoshimine T. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. *Pain* 2006; 122:22-27.
19. Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipovic SR, Hummel FC, Jaaskelainen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schonfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol* 2014; 125:2150-2206.
20. Pleger B, Janssen F, Schwenkreis P, Volker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. *Neurosci Lett* 2004; 356:87-90.
21. Koski L, Kolivakis T, Yu C, Chen JK, Delaney S, Ptito A. Noninvasive brain stimulation for persistent postconcussion symptoms in mild traumatic brain injury. *J Neurotrauma* 2014; 32:38-44.