Published in final edited form as:

Pain. 2011 January ; 152(1): 182–187. doi:10.1016/j.pain.2010.10.018.

Fast Left Prefrontal rTMS Acutely Suppresses Analgesic Effects of Perceived Controllability on the Emotional Component of Pain Experience

Jeffrey J. Borckardt, Ph.D.^{1,2}, Scott T. Reeves, M.D.², Heather Frohman, B.S.², Alok Madan, Ph.D., M.P.H.¹, Mark P. Jensen, Ph.D.³, David Patterson, Ph.D.³, Kelly Barth, D.O.¹, A. Richard Smith, M.D.², Richard Gracely, Ph.D.⁶, and Mark S. George, M.D.^{1,4,5,7}

¹ Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina (MUSC)

² Department of Anesthesiology and Perioperative Medicine, MUSC

³ Department of Rehabilitation Medicine, University of Washington School of Medicine

⁴ Department of Neurology, MUSC

⁵ Department of Radiology, MUSC

⁶ Center for Neurosensory Disorders, Department of Endodontics, School of Dentistry, University of North Carolina Chapel Hill

⁷ Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC

Abstract

The prefrontal cortex may be a promising target for transcranial magnetic stimulation (TMS) in the management of pain. It is not clear how prefrontal TMS affects pain perception, but previous findings suggest that ventral lateral and medial prefrontal circuits may comprise an important part of a circuit of ‘perceived controllability’ regarding pain, stress and learned helplessness. While the left dorsolateral prefrontal cortex is a common TMS target for treating clinical depression as well as modulating pain, little is known about whether TMS over this area may affect perceived controllability. The present study explored the immediate effects of fast TMS over the left dorsolateral prefrontal cortex on the analgesic effects of perceived pain controllability. Twenty-four healthy volunteers underwent a laboratory pain task designed to manipulate perception of pain controllability. Real TMS, compared to sham, suppressed the analgesic benefits of perceived-control on the emotional dimension of pain, but not the sensory/discriminatory dimension. Findings suggest that, at least acutely, fast TMS over the left dorsolateral prefrontal cortex may interrupt the perceived-controllability effect on the emotional dimension of pain experience. While it is not clear whether this cortical area is directly involved with modulating perceived controllability or whether downstream effects are responsible for the present findings, it appears possible that left dorsolateral prefrontal TMS may produce analgesic effects by acting through a cortical ‘perceived control’ circuit regulating limbic and brainstem areas of the pain circuit.

Conflict of Interest Statement: None of the authors have any equity ownership in any brain stimulation device company. The present study was funded by the National Institute for Neurological Disorders and Stroke at the National Institutes of Health.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Control can be defined as “the belief that one has at one’s disposal a response that can influence the aversiveness of an event.” [50] (pg. 89). The relationship between perceived control and pain experience is quite complex and analgesic benefits of perceived controllability appear to depend upon the type of control one has as well as when the control is exercised relative to the aversive. Knowing that one has a behavioral response available that can reduce event aversiveness lessens pre-event anxiety and anticipatory physiological arousal [21], and can enhance tolerance to noxious stimuli [26]. In general, pain is perceived as less intense when someone can exercise some form of control over it [41,45,52,53]. Pain that is perceived to be controllable results in altered activation in the anterior cingulate, insular, secondary somatosensory, and prefrontal cortices (including Brodmann Areas 9, 10, and 46)[39,44]. Wiech[53] found that perceived control over pain was associated with less pain and higher activation in dorsal anterior cingulate, right dorsolateral, and bilateral anterolateral prefrontal cortices. The role of the left prefrontal cortex in pain control is unclear [22]. However, there is evidence to support the concept that left prefrontal activation is negatively correlated with pain unpleasantness[35] suggesting a possible governing role of the prefrontal cortex on the affective dimension of pain.

Transcranial magnetic stimulation (TMS) is a minimally invasive brain stimulation technology that can alter cortical excitability in humans [6,23]. As a whole, most TMS-pain studies have focused on stimulation of the motor cortex and have found significant, but short-lived alterations in pain perception. [3,19,29–33] However, the dorsolateral prefrontal cortex may be a promising cortical target for the management of certain types of pain as well. [4,9,11–13,15,25,47] To date, little is known about mechanisms of action of prefrontal TMS effects on pain perception. Krummenacher et al[28] recently employed 1Hz rTMS to transiently disrupt left and right dorsolateral prefrontal cortex function before inducing expectation-based placebo analgesia. Krummenacher et al [28] found that treatment expectation increased pain threshold and tolerance, but that low-frequency rTMS blocked this analgesia. Given the recent accumulation of studies showing that fast left dorsolateral prefrontal rTMS may be associated with decreased pain, investigation of its effects on perceived controllability might lead to a better understanding of possible neurocognitive mechanisms of action.

The present study explores the immediate effects of fast left dorsolateral prefrontal rTMS on the analgesic effects of perceived pain controllability. We hypothesized that rTMS would improve perceived-controllability over painful stimuli. If dorsolateral prefrontal TMS impacts the controllability circuit, then both real TMS and having the perception of control might act synergistically. Alternatively, dorsolateral prefrontal TMS could ‘knock out’ the perceived controllability, as with speech arrest. [43] Because the left dorsolateral prefrontal cortex has been implicated in the modulation of negative emotion, modulation of pain unpleasantness, and is a cortical target for rTMS-treatment of depression, we also hypothesized that the effects of fast rTMS of the left prefrontal cortex would be predominantly focused on the affective dimension of the pain experience.

Methods

Participants

Twenty-eight participants enrolled in the present study. Four participants during screening failed to experience pain at the level of “7 out of 10” within the safe temperature limits of the thermode using 2.5-second stimuli and were excluded from the rest of the study. Thus, 24 healthy volunteers (13 women) with a mean age of 30.42 were included. 19 participants were Caucasian, 4 were African American, and 1 was of Hispanic ethnicity.

Participants did not have a personal or family history of seizure, or personal history of chronic pain of any etiology, depression or anxiety, significant head trauma, current pregnancy, heart disorder, and were not taking any medications. All patients signed a written informed consent document, approved by the Institutional Review Board for the Protection of Human Subjects at the Medical University of South Carolina.

Thermal Pain Threshold Assessment

Cutaneous heat stimuli were delivered via the Medoc Pathway System (Medoc, Durham, NC) using a 30 × 30-mm Contact Heat Evoked Potential (CHEPS) thermode attached to each subject's left volar forearm 5 cm from the wrist. First, the temperature that reliably induced pain rated as "7 out of 10" was assessed for each participant. To accomplish this, the CHEPS thermode was programmed to emit various temperatures for 2.5 seconds duration each, and subjects verbally rated the pain using a Numeric Ratings Scale (NRS) where 0="no pain" and 10="worst pain imaginable". Parameter Estimation by Sequential Testing was used to determine the temperature that reliably resulted in a report of "7" out of "10" for each participant. This temperature was used for the duration of the experiment.

TMS Procedures

All subjects (regardless of group assignment) underwent a standard resting motor threshold assessment using a Neuronetics (Malvern, PA) Neopulse TMS machine with a figure-8 coil. The TMS machine was set initially to 40% of maximal output and a frequency of 0.5 Hz. The TMS administrator located the area of the scalp that produced visible thumb movement upon TMS stimulation by systematically making adjustments to the TMS intensity and while shifting the TMS head coil over the participants scalp, proximal to the motor cortex. Adaptive Parameter Estimation by Sequential Testing (PEST) [10] procedures were conducted to determine the amount of machine output necessary to produce visible thumb movement 50% of the time (resting motor threshold; rMT).

The TMS machine was set to 110% output of the subject's motor threshold at a frequency of 10 Hz for 5-second stimulation periods. Off-time varied from 10–15 seconds, depending on the efficiency of task completion by the subject. Treatment lasted approximately 20 minutes (4000 Pulses). The F3 location from the EEG 10–20 system was used to target the left prefrontal cortex for all participants[7]. Participants were randomized to receive either real or sham rTMS for all trials and were not crossed over (12 participants in the real TMS group and 12 in the sham group).

Sham TMS

Sham rTMS was conducted with a specially-designed Neuronetics sham-coil that looks and sounds identical to the active coil except that a hidden aluminum plate blocks actual stimulation from occurring. The eSham system[14] was implemented in conjunction with this specialized sham TMS coil. Two Thymapad Stimulus Electrodes (Somatics, LLC; Lake Bluff, IL) were placed on the scalp under the TMS coil separated by 3mm. Next, 1-second of real stimulation was applied at 10Hz over the prefrontal cortex, however, the intensity was pseudo-randomly varied around the actual intensity to be delivered during the treatment session. Each of these brief trains were paired with an identical sham TMS trains with pseudo-randomly varying mA values from the eSham electrical generator (randomly ordered). For each sham titration train, the TMS coil was turned 90°, the wide portion of the side of the coil was laid flat on the scalp and the electrical generator was turned on. After each pair of 10Hz stimulation trains (1 real and 1 sham), participants were asked to indicate "which of the two trains they felt more." We chose to ask the perceptual intensity question in this manner (rather than asking which stimulus "hurt" more) to avoid overtly suggesting that either stimulus would be painful *per se*. This procedure continued and the intensities of

real and sham stimulation were varied until the mA value of the electrical stimulator was determined that produced identical sensation intensity to real TMS at 110% of rMT. A previous study on this sham system suggests that the quality of the sensations produced by real TMS and the eSham system are virtually indistinguishable with respect to the sensory dimensions of painfulness, tingling, sharpness, piercing quality, electrical quality, tugging, pinching and tolerability. [14] Note that all participants underwent this titration procedure regardless of group assignment so that both groups underwent identical procedures during the study. After this titration procedure (i.e., during the perceived pain control trials), subjects in the sham group underwent TMS with the Neuronetics sham-coil and the electrical stimulator was turned on to release the brief electrical pulses in sync with the audible TMS clicks. [14] The electrical stimulator was turned-off for participants in the real TMS group.

Perceived Pain Control Paradigm

Participants were seated in front of a 24-inch computer monitor with a keyboard in front of their right hand. The CHEPS thermode was placed 5 cm from the wrist on the underside of the subjects left forearm. The TMS coil was placed over the F3 position[7].

Participants were instructed that they would be completing a reaction time task. [44] An arrow of random directionality (up, down, left or right) appeared on the computer screen in front of the subject. The subject pressed the corresponding arrow on the keyboard as quickly as possible. After each trial, the CHEPS thermode delivered a heat stimulus that varied in duration from 1 second to 4 seconds. The 1- and 2-second stimuli were low-pain stimuli (i.e., shorter duration than the stimuli used by the investigators to establish each participant's target temperature), and the 3- and 4-second stimuli were high-pain stimuli (i.e., longer than the duration used to establish the target temperature and high enough to trigger negative affectivity and the experience of unpleasantness). Each participant received 10Hz of TMS over F3 for 5 seconds at the same time as each thermal stimuli. Participants then rated the painfulness or unpleasantness of each thermal stimulus on a computerized visual analogue scale (100-points) of "no pain" to "worst pain imaginable" (for pain intensity) or "not unpleasant at all" to "extremely unpleasant" (for pain unpleasantness ratings). Participants underwent 10 practice trials during which they received real or sham TMS in order to allow them an opportunity to acclimate to the procedures. The actual task lasted 60 trials. See Figure 1 for an illustration of the perceived-controllability paradigm.

Investigators told participants that when the arrow prompt appeared on a green background, if they reacted faster than a random-sampling of their previous green-screen trials, then the duration of the thermal stimulus administered following that trial would be shortened. Thus, response speed (which they could control) would decrease the duration of the thermal stimulus (perceived pain control condition). In contrast, when the arrow prompt appeared on a red background, reaction time would not influence the duration of thermal stimulus and the thermal stimulus duration would be completely random (no perceived pain control condition). In actual fact, the durations of all thermal stimuli were pseudo-randomly ordered and matched for total duration between red and green screen trials. That is, only the order of thermal stimulus delivery was manipulated as needed to correspond with participants' reaction time performance without disrupting the balance of thermal stimulus duration between red and green screen trials. This paradigm is adapted from Salomons et al. [44]

After they completed the experiment, participants rated their level of perceived control over the thermal pain stimuli (0=no control to 10=complete control). They also guessed whether they received real or sham rTMS and rated their confidence in their guess (0=completely guessing to 10=absolutely sure).

Participants provided ratings for a total of 22 high-pain stimuli (i.e., 3- and 4-second) trials (8 intensity ratings and 14 unpleasantness ratings). Participants provided 4 of the pain intensity ratings for green-screen trials (perceived control condition) and 4 for red-screen trials (no control condition). They provided 7 unpleasantness ratings for green-screen trials and 7 unpleasantness ratings for red screen trials. The low pain stimuli (i.e., 1- and 2-second) trials were randomly intermixed during the study to help create the illusion of control (e.g., when they occurred following a particularly fast reaction time on a green screen trial), but the intensity and unpleasantness ratings for the low pain trials were not analyzed.

Statistical Analysis

A mixed model was implemented using PROC MIXED in SAS[48] to examine the within-subject effect of perceived-control condition (perceived-control versus no-control trials), the between-subject effect of TMS condition (real versus sham) and the interaction effect on both pain intensity and pain unpleasantness ratings while controlling for stimulus order (i.e., stimulus duration) and time for all high-pain stimuli. Participants' intercepts and slopes were entered into the model as subject-level random effects, the estimation method was REML, and the covariance matrix was unstructured. Chi-Square and t-tests were used to examine the mask (sham) validity and participants' overall ratings of perceived control.

Results

Overall, participants appear to have been successfully blinded to TMS condition assignment. Participants had a 50% chance of correctly guessing whether they received real or sham stimulation. 10 participants failed to correctly guess which group they were in, and 14 guessed correctly ($X^2(1)=0.67$, ns). Of the 12 participants in the sham TMS group, 5 guessed correctly regarding their group assignment, and of those in the real TMS group 9 guessed correctly ($X^2(1)=0.75$, ns). The mean confidence rating of those that guessed correctly was 5.07 (SD=3.56) out of 10, and of those guessing incorrectly, the mean confidence was 5.70 (SD=2.83; $t(22)=0.65$, ns).

There was a significant main effect of perceived-pain-controllability on pain intensity ($F(1,165)=7.33$, $p=.008$) and pain unpleasantness ($F(1,309)=5.23$, $p=.023$) such that thermal stimulation delivered after green-screen trials (perceived control condition) were rated less painful by 5.50 (SE=2.62) points and less unpleasant by 6.96 (SE=2.05) points on average. There were no main effects for TMS condition on pain intensity or unpleasantness ratings ($F(1,18.9)=1.62$, ns; $F(1,21.1)=1.56$, ns). While there was no significant TMS-condition by perceived-control interaction on pain intensity ratings ($F(1,165)=0.04$, ns), there was a significant TMS-condition by perceived-control interaction on pain unpleasantness ratings ($F(1,309)=6.55$, $p=.011$). The perceived-controllability effect on pain unpleasantness ratings was present in the sham TMS group but was suppressed in the real TMS group (see figure 2). The effect-size for this TMS-condition (real versus sham) effect on perceived-control-related analgesia is moderate to large (Cohen's $d=1.02$).

Most interestingly, participants in the sham group rated their overall perceived control over the thermal pain stimuli as 7.21 (SD=2.13) out of 10 while those in the real TMS group rated their perceived control significantly lower at 5.13 (SD=2.07) out of 10 ($t(22)=2.43$, $p=.024$). That is, in volunteers who were not aware of whether they were getting real or sham TMS, those getting real TMS felt they had less control over the stimuli, even though the study design was identical in the two cells. The effect-size for this contrast is also moderate to large (Cohen's $d=.98$). Fast left prefrontal TMS appeared to 'knock-out' the sense of perceived control.

Discussion

In this sham-controlled trial of the effects of fast left dorsolateral prefrontal rTMS on perceived pain controllability, rTMS appeared to acutely interrupt the analgesic benefit of participants' perception of control. Specifically, left dorsolateral prefrontal rTMS suppressed the benefits of perceived control on the emotional dimension (pain unpleasantness ratings) of the pain experience, but not the sensory/discriminatory dimension (intensity ratings). This effect was seen when fast rTMS was delivered *during* the brief period of time that perceived pain-controllability likely exerts its analgesic effect. This suggests that, at least acutely, rTMS might have suppressed the perceived-controllability effect. It is not clear whether this was due to direct manipulation of perceived control circuits in the dorsolateral prefrontal cortex that might exist but have not been well-established, or whether stimulation of the dorsolateral prefrontal cortex has downstream effects on anterolateral and medial prefrontal pathways which appear to be better established areas with respect to perceived control.

In 1967 Seligman and Maier developed the now classic learned helplessness (LH) model in dogs, which is an animal model that bears resemblance to depression, repeated stress, or chronic pain. [38] The conclusions from this work – that people do better when they are given more control, or at least perceive that they have control – have revolutionized approaches to teaching, treating patients, or even training soldiers. In a more recent LH paradigm, normal healthy rats are yoked or paired, and subjected to intermittent stressors, typically a painful tail shock. One animal is provided a wheel in its cage that, when turned, terminates each of the shocks. For the other yoked animal turning the wheel has no consequence and the duration of each of the shocks is yoked to that determined by its partner whose behavior terminates each of the shocks. Both animals receive the identical amount of shock, but only the yoked animal that does not have control over the shocks develops behaviors that resemble the “depression” (and social isolation) often seen in individuals with chronic pain. [36] The animal that has ‘the sense of control’ does not develop these behaviors. Recently Maier and colleagues have completed a series of studies that fairly convincingly demonstrate that this ‘sense of control’ is actually a signal from the ventral-medial prefrontal cortex (vmPFC) to the dorsal raphe nucleus (DRN). [1,2,5,16,37] Thus, one can temporarily inactivate the prefrontal cortex in the animal that has behavioral control, and even though they learn to abort the shocks, they still go on to develop behaviors typical of rats that do not have control. Interestingly, if the investigator does not allow behavioral control, but instead pharmacologically activates the vmPFC during uncontrollable shock, the animal does not develop ‘depression’. [17] [16] They speculate that ‘*...pharmacological activation of the vmPFC appeared to give rats the ‘illusion of control.’*’ [17] Growing evidence regarding the psychosocial concomitants of chronic pain suggests that patients with chronic pain resemble, in some ways, the previously yoked rat in the learned helplessness model, where repeated inescapable life stress (pain) leads to a feeling of ‘loss of control’ and despair. [22]

In the present study, real TMS was associated with a directional outcome suggestive of analgesia, but this effect was not statistically significant. Previous dorsolateral prefrontal rTMS and pain studies have found analgesic effects, but most have focused on changes in pain perception pre- to post- rTMS and not what happens while rTMS is being delivered [11–13,15]. The present design permits examination of the shorter-term mechanisms that might contribute to the pre- to post-rTMS analgesic effects. It may be that fast stimulation of the left dorsolateral prefrontal cortex acutely and temporarily interrupts circuit activity involved with classic cognitively-mediated analgesic effects (e.g., perceived controllability, expectation placebo analgesia), and that subsequently, this circuitry becomes hyper-excitabile as some type of over-correction for the temporary lesion occurs. This hypothetical process might produce the temporary analgesic rTMS effect that is observed

when examining changes in pain perception pre- (before simulation) to post- (during the hyper-excitability/over-correction period) stimulation.

With respect to mood and chronic pain, chronic repetitive stimulation of the dorsolateral prefrontal cortex likely initiates a cascade of events in the prefrontal cortex and in connected limbic regions. [24] Interleaved TMS/fMRI and TMS/PET studies provide evidence to support this hypothesis. Prefrontal TMS sends information to important mood and pain 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). [49] Daily dorsolateral prefrontal rTMS for several weeks has antidepressant effects and the FDA has recently approved it as a standard treatment for depression. Further, repeated dorsolateral prefrontal rTMS treatments appear to have net analgesic effects (pre- to post- stimulation), but this is the first study to date suggesting that the immediate effects may involve interference with perceived-control-circuit activity, and that the longer-term effects (anti-depressant and/or analgesic) may be due to a homeostatic brain mechanism (i.e., increased activity to correct for a temporary lesion).

Thoughts, expectations and beliefs affect perception and influence behavior, and the research base addressing the neural circuitry mediating expectation-related analgesia is growing. The placebo response is likely a learning phenomenon [8,18] that involves both subcortical and cortical mechanisms [27,40]. Placebo analgesia is reportedly dependent on reward-related dopaminergic activity [46], may share a common neural network with opioid analgesia [42], and may reduce neural transmission within common pain pathways [51]. Nonetheless, a growing body of evidence [8,20,34] suggests that the prefrontal cortex is involved with what has been classically termed “placebo” analgesia, as the prefrontal cortex has repeatedly been shown to be involved in cognitive, attention, and expectation-related analgesia [22,28,35,51,54].

The present study suggests that the decreases in the experience of the affective dimension of pain that are typically seen in response to the perception of control over noxious stimuli are modulated by the prefrontal cortex, and that concurrent prefrontal TMS can ‘knock out’ this behavior likely by interacting with this circuit. Krummenacher et al[28] found that expectation-related analgesia could similarly be knocked-out with 1Hz rTMS over both the left and right dorsolateral prefrontal cortex, however, the present study only examined the immediate effects of “excitatory” rTMS over the left dorsolateral prefrontal cortex (a common treatment strategy for depression and some types of pain). More work is needed to establish the time course of prefrontal cortical activation and deactivation patterns in response to high-frequency rTMS (both during stimulation and after) in order to better establish neurocognitive mechanisms of action of prefrontal rTMS for chronic pain.

Summary

Despite evidence that prefrontal TMS can have analgesic effects, fast left prefrontal TMS appears to acutely suppress analgesia associated with perceived-control. This effect may be limited to the emotional dimension of pain experience.

References

1. Amat J, Baratta M, Paul E, STB, Watkins L, Maier S. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nature Neuroscience* 2005;8:365–371.

2. Amat J, Paul E, Zarza C, Watkins L, Maier S. Previous experience with behavioral control over stress blocks the behavioral and dorsal raphe nucleus activating effects of later uncontrollable stress: role of the ventral medial prefrontal cortex. *Journal of Neuroscience* 2006;26:13264–13272. [PubMed: 17182776]
3. Andre-Obadia N, Peyron R, Mertens P, Manguiere 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(7):1536–44. [PubMed: 16753335]
4. Avery DH, Holtzheimer PE 3rd, Fawaz W, Russo J, Neumaier J, Dunner DL, Haynor DR, Claypoole KH, Wajdik C, Roy-Byrne P. Transcranial magnetic stimulation reduces pain in patients with major depression: a sham-controlled study. *J Nerv Ment Dis* 2007;195(5):378–81. [PubMed: 17502802]
5. Baratta M, Christianson J, Gomez D, Zarza C, Amat J, Masini C, Watkins L, Maier S. Controllable versus uncontrollable stressors bi-directionally modulate conditioned but not innate fear. *Neuroscience* 2007;146(4):1495–1503. [PubMed: 17478046]
6. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985;1(8437):1106–7. [PubMed: 2860322]
7. Beam W, Borckardt J, Reeves S, George M. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimulation* 2009;2(1):50–54. [PubMed: 20539835]
8. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annu Rev Pharmacol Toxicol* 2008;48:33–60. [PubMed: 17666008]
9. Borckardt J, Reeves S, George M. The potential role of brain stimulation in the management of postoperative pain. *Journal of Pain Management* 2009;2(3)
10. Borckardt JJ, Nahas Z, Koola J, George MS. Estimating Resting Motor Thresholds in TMS Research and Practice: A Computer Simulation Evaluation of Best Methods. *J ECT* 2006;22:169–175. [PubMed: 16957531]
11. Borckardt JJ, Reeves ST, Weinstein M, Smith AR, Shelley N, Kozel FA, Nahas Z, Byrne KT, Morgan K, George MS. Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: A replication study. *Brain Stimulat* 2008;1(2):122–127.
12. Borckardt JJ, Smith AR, Reeves ST, Madan A, Shelley N, Branham R, Nahas Z, George MS. A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. *Pain Med* 2009;10(5):840–9. [PubMed: 19594842]
13. Borckardt JJ, Smith AR, Reeves ST, Weinstein M, Kozel FA, Nahas Z, Shelley N, Branham RK, Thomas KJ, George MS. Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. *Pain Res Manag* 2007;12(4):287–90. [PubMed: 18080048]
14. Borckardt JJ, Walker J, Branham RK, Rydin-Gray S, Hunter C, Beeson H, Reeves ST, Madan A, Sackeim H, George MS. Development and Evaluation of a Portable Sham TMS System. *Brain Stimulat* 2008;1(1):52–59.
15. Borckardt JJ, Weinstein M, Reeves ST, Kozel FA, Nahas Z, Smith AR, Byrne KT, Morgan K, George MS. Post-Operative Left Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) Reduces Patient-Controlled Analgesia Use. *Anesthesiology* 2006;105:557–562. [PubMed: 16931989]
16. Christianson J, Benison A, Jennings J, Sansmark E, Amat J, Kaufman R, Baratta M, Paul E, Campeau S, Watkins L, Barth D, Maier S. The Sensory Insular Cortex Mediates the Stress-Buffering Effects of Safety Signals But Not Behavioral Control. *Behavioural Brain Research* 2008;193:87–93. [PubMed: 18554730]
17. Christianson JP, Thompson BM, Watkins LR, Maier SF. Medial prefrontal cortical activation modulates the impact of controllable and uncontrollable stressor exposure on a social exploration test of anxiety in the rat. *Stress* 2009;12(5):445–50. [PubMed: 19051125]
18. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. *Pain* 2006;124(1–2):126–33. [PubMed: 16701952]

19. Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, Simpson BA, Taylor RS. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* 2007;14(9): 952–70. [PubMed: 17718686]
20. Faria V, Fredrikson M, Furmark T. Imaging the placebo response: a neurofunctional review. *Eur Neuropsychopharmacol* 2008;18(7):473–85. [PubMed: 18495442]
21. Gatchel R, Proctor J. Physiological correlates of learned helplessness in man. *Journal of Abnormal Psychology* 1976;85:27–34. [PubMed: 1245644]
22. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull* 2007;133(4):581–624. [PubMed: 17592957]
23. George MS, Nahas Z, Kozol FA, Li X, Yamanaka K, Mishory A, Bohning DE. Mechanisms and the current state of transcranial magnetic stimulation. *CNS Spectr* 2003;8(7):496–514. [PubMed: 12894031]
24. George MS, Stallings LE, Speer AM, Spicer KM, Cheng KT, Molloy M, Risch SC, Vincent DJ, Bohning DE. Prefrontal rTMS Reduces Relative Perfusion Locally and Trans-synaptically. *Human Psychopharmacology* 1999;14:161–1170.
25. Graff-Guerrero A, Gonzalez-Olvera J, Fresan A, Gomez-Martin D, Mendez-Nunez JC, Pellicer F. Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex increases tolerance to human experimental pain. *Brain Res Cogn Brain Res* 2005;25(1):153–60. [PubMed: 15935625]
26. Kanfer F, Seider M. Self-control and the tolerance of noxious stimulation. *Journal of Personality and Social Psychology* 1973;25:381. [PubMed: 4705671]
27. Koshi EB, Short CA. Placebo theory and its implications for research and clinical practice: a review of the recent literature. *Pain Pract* 2007;7(1):4–20. [PubMed: 17305673]
28. Krummenacher P, Candia V, Folkers G, Schedlowski M, Schonbachler G. Prefrontal cortex modulates placebo analgesia. *Pain* 148(3):368–74. [PubMed: 19875233]
29. Lefaucheur JP. New insights into the therapeutic potential of non-invasive transcranial cortical stimulation in chronic neuropathic pain. *Pain* 2006;122(1–2):11–3. [PubMed: 16564623]
30. Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP. Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. *Neuroreport* 2001;12(13):2963–5. [PubMed: 11588611]
31. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS in chronic neuropathic pain: pain relief is associated with thermal sensory perception improvement. *J Neurol Neurosurg Psychiatry* 2008;79(9):1044–9. [PubMed: 18223016]
32. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. *Neurology* 2006;67(9): 1568–74. [PubMed: 17101886]
33. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib B, Cesaro P, Keravel Y, Nguyen JP. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. *J Neurol Neurosurg Psychiatry* 2004;75(4):612–6. [PubMed: 15026508]
34. Lidstone SC, Stoessl AJ. Understanding the placebo effect: contributions from neuroimaging. *Mol Imaging Biol* 2007;9(4):176–85. [PubMed: 17334853]
35. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain* 2003;126(Pt 5):1079–91. [PubMed: 12690048]
36. Maier SF. Learned helplessness and animal models of depression. *Prog Neuro -Psychopharmacol Biol Psychiatr* 1984;8:435–446.
37. Maier SF, Ryan SM, Barksdale CM, Kalin NH. Stressor controllability and the pituitary-adrenal system. *Behav Neurosci* 1986;100(5):669–74. [PubMed: 3022767]
38. Miller WR, Sligman MEP. Depression and learned helplessness in man. *Journal of Abnormal Psychology* 1975;84:228–238. [PubMed: 1169264]
39. Mohr C, Binkofski F, Erdmann C, Buchel C, Helmchen C. The anterior cingulate cortex contains distinct areas dissociating external from self-administered painful stimulation: a parametric fMRI study. *Pain* 2005;114(3):347–57. [PubMed: 15777860]
40. Peck C, Coleman G. Implications of placebo theory for clinical research and practice in pain management. *Theor Med* 1991;12(3):247–70. [PubMed: 1721730]

41. Pellino TA, Ward SE. Perceived control mediates the relationship between pain severity and patient satisfaction. *J Pain Symptom Manage* 1998;15(2):110–6. [PubMed: 9494309]
42. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia-- imaging a shared neuronal network. *Science* 2002;295(5560):1737–40. [PubMed: 11834781]
43. Rorden C, Davis B, George MS, Borckardt J, Fridriksson J. Broca's area is crucial for visual discrimination of speech but not non-speech oral movements. *Brain Stimulat* 2008;1(4):383–385.
44. Salomons TV, Johnstone T, Backonja MM, Davidson RJ. Perceived controllability modulates the neural response to pain. *J Neurosci* 2004;24(32):7199–203. [PubMed: 15306654]
45. Scharff L, Turk DC, Marcus DA. The relationship of locus of control and psychosocial-behavioral response in chronic headache. *Headache* 1995;35(9):527–33. [PubMed: 8530276]
46. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Individual differences in reward responding explain placebo-induced expectations and effects. *Neuron* 2007;55(2):325–36. [PubMed: 17640532]
47. Short E, Borckardt J, George M, Beam W, Reeves S. Non-invasive brain stimulation approaches to fibromyalgia pain. *Journal of Pain Management* 2009;2(3)
48. Singer J. Using SAS PROC MIXED to Fit Multilevel Models, Hierarchical Models, and Individual Growth Models. *Journal of Educational and Behavioral Statistics* 1998;24(4):232–355.
49. Teneback CC, Nahas Z, Speer AM, Molloy M, Stallings LE, Spicer KM, Risch SC, George MS. Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left prefrontal TMS. *J Neuropsychiatry Clin Neurosci* 1999;11(4):426–35. [PubMed: 10570754]
50. Thompson S. Will it hurt less if I can control it? A complex answer to a simple question. *Psychological Bulletin* 1981;90(1):89–101. [PubMed: 7267899]
51. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* 2004;303(5661):1162–7. [PubMed: 14976306]
52. Weisenberg M, Wolf Y, Mittwoch T, Mikulincer M, Aviram O. Subject versus experimenter control in the reaction to pain. *Pain* 1985;23(2):187–200. [PubMed: 4069720]
53. Wiech K, Kalisch R, Weiskopf N, Pleger B, Stephan KE, Dolan RJ. Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. *J Neurosci* 2006;26(44):11501–9. [PubMed: 17079679]
54. Zubieta JK, Bueller JA, Jackson LR, Scott DJ, Xu Y, Koeppe RA, Nichols TE, Stohler CS. Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J Neurosci* 2005;25(34):7754–62. [PubMed: 16120776]

Figure 1.
Illustration of a single trial of the perceived pain controllability task.

Figure 2.
Mean (StdErr) pain intensity and unpleasantness ratings under conditions of perceived-control and no-control with simultaneous real or sham prefrontal 10Hz rTMS.