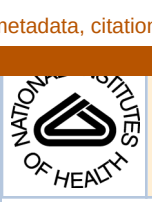

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A Randomized, Controlled Investigation of Motor Cortex Transcranial Magnetic Stimulation (TMS) Effects on Quantitative Sensory Measures in Healthy Adults: Evaluation of TMS Device Parameters

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Abstract

There is emerging evidence that transcranial magnetic stimulation (TMS) can produce analgesic effects in clinical samples and in healthy adults undergoing experimentally induced pain, and the field of minimally invasive brain stimulation for the management of pain is expanding rapidly. While, motor cortex is the most widely used cortical target for TMS in the management of neuropathic pain, few studies have systematically investigated the analgesic effects of a full range of device parameters to provide initial hints about what stimulation intensities and frequencies are most helpful (or even potentially harmful) to patients. Further, there is considerable inconsistency between studies with respect to laboratory pain measurement procedures, TMS treatment parameters, sophistication of the sham methods, and sample-sizes. The present study employed a sham-controlled, within-subject, cross-over design to examine the effects of five different TMS treatment parameters across several quantitative sensory measures in a sample of healthy adult volunteers. 65 participants underwent quantitative sensory testing procedures pre- and post- 40-minutes of real and sham motor cortex TMS. TMS was delivered at 1Hz 80% resting motor threshold (rMT), 1Hz 100%rMT, 10Hz 80%rMT, 10Hz 100%rMT, or 50Hz triplets at 90% of active motor threshold (intermittent theta-burst). The mean painfulness rating of real TMS stimulation itself was 3.0 (SE=.36) out of 10 and was significantly greater than zero ($t(64)=8.17$, $p<.0001$). The sham TMS methods used permitted matching between real and sham TMS-induced scalp sensations and participants were successfully blinded to condition (real versus sham).

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Findings suggest that the effects of motor cortex TMS on quantitative sensory tests in healthy adults vary across different treatment parameters with the smallest observed effect for intermittent theta-burst stimulation (Cohen's d=0.03) and the largest for 10Hz 100%rMT (d=.34). Overall, TMS was associated with statistically significant effects on warm and cool sensory thresholds, cold pain thresholds, suprathreshold stimulus unpleasantness ratings and wind-up pain. With respect to device parameter effects, higher frequency stimulation appears to be associated with the most analgesic and anti-sensitivity effects with the exception of intermittent theta-burst stimulation. The present findings support several clinical research findings suggesting that higher TMS frequencies tend to be associated with the most clinical benefit in patients with chronic pain.

Keywords

transcranial magnetic stimulation; pain; motor cortex; TMS; thermal; theta

Introduction

Transcrianial magnetic stimulation (TMS) is a minimally invasive brain stimulation technology that can focally stimulate the brain of an awake individual [1,2]. A localized pulsed magnetic field transmitted through a figure-8 coil (lasting only microseconds) is able to focally stimulate the cortex by inducing electrical currents in the brain [3] that depolarize superficial (a few millimeters deep) cortical neurons [4,5].

Medium-term effects of TMS (seconds to minutes) likely arise from transient changes in local neurochemistry[6] and a great deal of research has been focused on whether different TMS frequencies might have different biological effects. Repeated lower-frequency stimulation of a single neuron in culture can produce long-lasting inhibition of cell-cell communication, while higher frequency stimulation can improve communication [7]. Several studies have shown that chronic stimulation of the motor cortex can produce inhibitory or excitatory intermediate effects that last several minutes following stimulation [8,9].

There is accumulating evidence that TMS can produce analgesic effects in chronic pain conditions of various etiologies, reduce post-operative pain, and decrease laboratory-induced pain in healthy adult samples [10–40]. While some early research in this area seemed to indicate that TMS was only capable of producing short-lived effects, more recent evidence suggests that repeated TMS treatments can produce meaningful analgesic effects lasting several weeks [15,30,38] if delivered repeatedly for days to weeks. Various cortical targets have been investigated, but the results of most studies to date support the utility of motor cortex stimulation, especially for neuropathic pain [19,32–36,41]. The field of minimally invasive brain stimulation for the management of pain is expanding rapidly, and researchers have moved quickly into the clinical arena without accumulating much preliminary data regarding the most effective device parameters for managing clinical pain. While, motor cortex is the most widely used cortical target for TMS in the management of neuropathic pain, few studies have systematically investigated the analgesic effects of a full range of device parameters to provide initial hints about what stimulation intensities and frequencies are most helpful (or even potentially harmful) to patients.

Some recent findings suggest that the analgesic effects of motor cortex stimulation may be due in part to changes in activity at local cortical sites as well as at the thalamic nuclei [42]. It is possible that corticothalamic tracts may exert an inhibitory influence on thalamic pain processing and transmission [29]. High frequency rTMS may suppress pain information relayed through the spinothalamic tracts and the ipsilateral thalamic nuclei [33,36,37].

However, there is also evidence to suggest that at least a portion of motor-cortex TMS-related analgesic effects may be due to changes in prefrontal and limbic activity (associated with the affective and cognitive-evaluative dimensions of pain experience) [33,34,43].

While there are some promising findings in this literature, there is much variability with respect to the: (1) number of TMS pulses delivered per study, (2) frequency of the rTMS pulses, (3) intensity of the TMS stimulation, (4) duration of the treatment, (5) sham TMS methods, and (6) dependent measures used [43]. Recent meta-analytic and review studies suggest that at least 1000 to 1200 TMS pulses are needed to realize analgesic efficacy and repeated TMS sessions are associated with longer-term effects [43,44]. There is also evidence to suggest that higher frequency and intensity stimulation may be better for clinical applications [32,44], but the range of TMS frequency in the current clinical and laboratory research literature is large (0.5Hz to 20Hz, and in some studies 50Hz triplets (theta-burst) stimulation is used) [45]. The intensity of the stimulation varies considerably (80% of motor threshold up to 120%)[45]. When sham-control conditions have been employed, methods are often sub-optimal. TMS, especially at higher intensities and frequencies, can produce scalp sensations. These sensations can be uncomfortable or even painful for some individuals[41,44,46]. Unfortunately, many of the existing studies of TMS effects on pain perception have not employed methods to simulate and match the sensations of sham stimulation with active stimulation. However, there now exists technology to match sham TMS sensations with those of real [47,48].

The present study was designed to address these issues and employed a sham-controlled, within-subject, cross-over design to examine the effects of five different TMS treatment conditions (controlling for total number of TMS pulses (1200 per session over two sessions) and duration of stimulation) across a wide array of experimental pain-inducement methods in a sample of healthy adult volunteers. The sham TMS methods were conducted in a manner such that sham stimulation produced similar sensations to real stimulation.

Methods

Participants

Participants were 75 right-handed healthy volunteers with no history of chronic pain, depression, anxiety, seizures, closed head injuries, or metal implants above the waist. Eight participants did not complete both study visits (did not return follow-up scheduling phone calls) and were excluded from analysis. Two participants had vasovagal syncope during the motor threshold assessment and were excluded from the study. Sixty-five participants were included in the analysis (39 females and 26 males). The mean age of the sample was 29.95 (SD=11.51). Two were Asian, 11 were African American, 2 were Hispanic and 50 were Caucasian. Ten of the participants were smokers. This study was approved by the Institutional Review Board at the home institution and all participants provided written informed consent. All procedures were conducted in the Brain Stimulation Laboratory at the Medical University of South Carolina.

Measures

Screening Measures—Participants completed the Beck Depression Inventory-II (BDI), the Beck Anxiety Inventory (BAI), and the Brief Pain Inventory (BPI) and were eligible for the study if their BDI scores were less than 12, their BAI scores were less than 12 and if they reported no history of chronic pain conditions.

Hot and Cold Sensory Threshold Assessment—The Medoc PATHWAY Pain & Sensory Evaluation System (Medoc Ltd, Israel) with advanced thermal stimulator (ATS)

was used to apply 10 thermal stimuli to participants' left volar forearm, 5cm from the wrist. The thermal baseline temperature was set to 32°C. The Medoc system randomized the order of stimuli (5 warm and 5 cold) as well as the duration of the rest period between stimuli. At the start of each trial, the thermode increased or decreased in temperature at the rate of 0.25°C per second and participants were instructed to push a button the moment they detected any change in temperature. After participants pressed the button, the thermode returned to baseline temperature and the next trial began (with a random interstimulus interval ranging from 1 to 5 seconds).

Hot and Cold Pain Threshold Assessment—The Medoc PATHWAY system with ATS thermode was used to apply 10 thermal stimuli to each participant's left volar forearm, 5cm from the wrist. The thermal baseline temperature was set to 32°C and the program alternated between hot and cold stimuli. The thermode was programmed to increase or decrease from baseline at the rate of 1°C per second and participants were instructed to press a button when the sensation reached “the level that they considered to be painful.” They were further instructed “We are not interested in seeing how much you can tolerate or stand, but rather we are interested in determining exactly what temperature you consider to be painful, or stated another way, what exact temperature crosses your threshold from being hot (or cold) to being painful.” After each trial, participants used a computerized visual analogue scale (VAS) to rate the painfulness of each stimulus at its worst during the trial (anchored with “no pain” and “worst pain imaginable”) so that we could determine whether changes in pain threshold (if found) were due to changes in reaction time or a willingness to tolerate more or less pain before stopping the ramping thermode. A 30-second rest period was used between trials.

Mechanical Pain Threshold Assessment—A digital Electrovonfrey Anesthesiometer (IITC model Alemo 2290-4; Woodland Hills, CA, USA) was used with rigid plastic tips. Pressure was applied to the dorsum of the ventral pad of the digit minimi of the right hand at the rate of 10 grams per second. Participants were instructed to say “stop” as soon as the sensation reached the level they considered to be painful. They were further instructed “We are not interested in seeing how much you can tolerate or stand, but rather we are interested in determining exactly what pressure you consider to be painful, or stated another way, what exact pressure crosses your threshold from pressure to pain.” After each trial, participants used a computerized visual analogue scale (VAS) to rate the painfulness of the stimulus at its worst during the trial (anchored with “no pain” and “worst pain imaginable”) so that we could determine whether changes in pain threshold (if found) were due to changes in reaction time or a willingness to tolerate more or less pain before stopping the application of pressure. A 30-second rest period was used between trials.

Suprathreshold Magnitude Assessment—The Medoc PATHWAY system with contact heat evoked potential stimulator (CHEPS) was used to apply brief (0.75 second) thermal stimuli to the left volar forearm, 5cm from the wrist. Stimuli were provided at 3 levels (46°C, 47.5°C and 49°C) and the order of presentation was random. Three stimuli were presented for each temperature (9 trials). Participants rated the painfulness and unpleasantness of each stimulus using the computerized VAS described above. A 30-second rest period was used between trials.

Thermal Wind-Up Pain Assessment—The Medoc PATHWAY system with CHEPS thermode was used to apply 30-seconds of brief (0.5 second) heat pulses delivered at the rate of 1 per 1.5 seconds to the left volar forearm. Two practice trials were conducted using the heat pain threshold determined via methods described above. The wind-up curve was generated using the heat threshold plus 1.5°C. Participants rated the painfulness of the

stimuli in real-time using a computerized VAS. The computerized VAS program recorded the position of the VAS marker every second throughout each 30-second trial.

TMS Methods

Equipment—A Neuronetics (Model 2100, Neuronetics Inc.; Malvern, PA) was used to deliver all TMS. An iron-core, soild-state figure of 8 coil was used. The eSham system [47] was used in conjunction with a specially-design sham TMS coil from Neuronetics that matched the real TMS coil in appearance as well as the sound it generated. When combined with the eSham system, the sham TMS scalp sensations are able to be matched with the sensations produced by real TMS (see *Sham Control TMS methods* below).

Motor threshold assessment—The TMS machine was set to 40% of maximal output with a frequency of 0.5Hz and a systematic search strategy was implemented to localize the area of the motor strip associated with visible movement of the abductor pollicis brevis (APB) of the right hand. The machine intensity was adjusted until APB movement was achieved and then localized. The coil location was marked with a nontoxic felt-tipped marker on the participant's scalp for use during the motor threshold assessment and as the rTMS treatment location. A computerized Parameter Estimation by Sequential Testing (PEST) algorithm was used to estimate resting motor threshold with visual thumb movement as the criteria[49]. If the participant was assigned to the theta-burst condition (see Treatment Conditions below), an analogue hand dynomometer was used and participants applied active pressure to the device at 20% of maximal force during TMS pulses (visual detection of dynomometer needle movement was used as the criterion). The PEST seed vale was determined by the TMS administrator based on the best guess of the true threshold using information obtained during the localization process [49].

Treatment conditions—Participants were randomly assigned to one of 5 treatment conditions (1Hz at 80%rMT [n=13], 1Hz at 100%rMT [n=12], 10Hz, at 80%rMT [n=15], 10Hz at 100%rMT [n=13], theta-burst (50 Hz triplets delivered at the rate of 5Hz) at 90% of active motor threshold [n=12]). Participants received two 20-minute motor rTMS sessions per visit (separated by a 20 minute rest period) in order to ensure adequate TMS dosing to produce effects (if present) and to better approximate dosing strategies used in clinical treatments than previous laboratory studies. Total number of pulses per session was set to 1200 and on/off times were adjusted to maintain this standard. For 1Hz conditions, participants received 1 pulse per second for 20 minutes (no off-time). For 10Hz conditions, participants received 20-minutes of TMS (10 pulses per second) with a 4-second on-time and 36-second off-time. For theta-burst, participants received 2 seconds of 50Hz triplets delivered at the rate of 5 triplets per second and an off-time of 28-seconds. Thus, in all conditions, participants received a total of 2400 pulses at each visit.

Participants completed two visits and were randomly assigned to receive real rTMS at one visit and sham rTMS at the other. The methods employed at each visit were identical except for whether real or sham stimulation occurred.

Sham (Control) TMS methods—The eSham system[47] was implemented in conjunction with the specialized Neuronetics sham TMS coil. Two Thymapad Stimulus Electrodes (Somatics, LLC; Lake Bluff, Il) were placed on the scalp under the TMS coil separated by 1cm. For conditions involving 100%rMT, an additional 2 thymapad electrodes (connected to the electrical generator from the eSham system) were placed across the APB of the right hand. The electrodes were attached to the hand during both real and sham conditions. If during the sham titration procedures, stimulation produced visible movement of the hand, the generator was set to deliver TMS-synced pulses of mild electrical current

during the sham treatment in order to create subtle thumb movement so that participants would be unable to determine whether they were receiving real or sham stimulation based on whether they experienced movement. In most cases, movement was not noticed in the 100%rMT conditions (likely due to slight decreases in cortical excitability induced by the sham titration TMS pulses; see below) and thus the generator was only connected for 2 subjects in the 1Hz condition and 1 in the 10Hz condition (a total of 3 out of 65; 4.6% of participants study-wide) where TMS motor movement was deemed problematic with respect to maintaining the blind.

Next, 1-second (3-seconds if the participant was to receive 1Hz stimulation) of stimulation was applied at the frequency assigned to the participant. However, the intensity was pseudo-randomly varied around the actual intensity to be delivered during the treatment session. These brief trains were interspersed with identical sham TMS trains with pseudo-randomly varying mA values from the eSham electrical generator. Participants were asked to rate the painfulness of each stimulation train using a numeric rating scale (0=no pain at all, 10=worst pain imaginable). This procedure continued until the mA value of electrical stimulator was determined that produced identical subjective pain ratings to those of the real stimulation at the TMS intensity to which the participant was assigned.

Procedures

Participants completed all screening measures and provided written informed consent to participate. They were then taken to the laboratory and quantitative sensory testing was conducted. The order of the pain measurement procedures was randomized except that the thermal sensory threshold trials were always conducted first, followed by pain threshold assessment in order to provide the temperatures necessary for conducting the wind-up trials. The thermode was always placed on the same spot on the left arm for each participant.

After completion of the quantitative sensory assessment, a TMS motor threshold was obtained. The eSham system was set-up and titrated to match the cutaneous sensations associated with real TMS at the intensity and frequency to be delivered during the rTMS session. If motor movement was noticed in the 100%rMT conditions toward the end of the titration procedures, the eSham electrical generator was routed to mimic this movement during sham stimulation sessions (n=3). Participants underwent two 20-minute motor rTMS sessions separated by a 20-minute break, and then completed another quantitative sensory assessment. Participants came back to the laboratory 2-weeks later and underwent the exact same procedures except that if they received real TMS at the first visit, they received sham at the second visit (and vice versa). The same stimulation parameters were used for the real and sham TMS sessions at visit-one and visit-two. After completion of the second visit, participants were asked to guess which session was real and which was sham as well as provide a confidence rating using a numeric rating scale.

Analyses

For all sensory and pain threshold measurements, the first of the five trials in each series was discarded to control for novelty effects, and to reduce variability associated with suppression of a-∂ fiber activity to ensure consistency between the subsequent measured trials [50]. Hierarchical Linear Modeling (HLM) was implemented using PROC MIXED in SAS (SAS Institute Inc.; Cary, NC) in order to assess the within-subject interactions of time (pre to post TMS) and treatment type (real versus sham TMS) and the between-subject factor of TMS device-parameter condition (1Hz at 80%rMT, 1Hz at 100%rMT, 10Hz at 80%rMT, 10Hz at 100%rMT, theta-burst at 90%aMT), on quantitative sensory measurements (thereby by testing a series of 2×2×5 full factorial mixed models) [51] [52]. Prior to application of the models, baseline scores (pre-TMS) were evaluated between groups (real versus sham) and

between the 5 TMS treatment conditions. If significant baseline differences were observed for a quantitative sensory test, the baseline scores were co-varied in that model to control for baseline differences (i.e., determine if there were any significant effects over-and-above baseline differences). For all models, each individual threshold trial and suprathreshold estimation trial for each subject was entered into the model and the means and slopes were model-estimated at level-1 for each subject. Wind-up slopes were square-root transformed to achieve linearity and HLM was used to examine differences in wind-up slopes as a function of the Treatment Type × Time interaction and TMS-condition. Participants' individual intercepts and slopes were entered into the model as random effects. The covariance structure of the models was “unstructured”, the estimation method was restricted maximum likelihood (REML), and the degrees of freedom estimation method was Kenward-Roger.

Subjective procedural pain ratings for real rTMS were examined using one-sample t-tests to determine whether the TMS procedures resulted in any pain (i.e., pain ratings > 0) and to substantiate the use of the eSham system (which was titrated to match the procedural painfulness of real TMS for each participant individually).

Results

TMS Procedural Painfulness—The mean painfulness rating of real TMS stimulation was 3.0 (SE=.36) out of 10 (where 0=“no pain” and 10=“worst pain imaginable”). This mean painfulness rating was significantly greater than zero ($t(64)=8.17$, $p<.0001$). There was some variability in the painfulness across the different TMS treatment settings. The most painful TMS settings were 10Hz100% and theta-burst. TMS at 10Hz100% was associated with a mean painfulness rating of 4.6 (SE=.88; $t(12)=5.29$, $p=.002$) and theta burst was associated with a mean painfulness rating of 4.9 (SE=.81; $t(11)=6.12$, $p=.001$). TMS at 1Hz100% was associated with a mean painfulness rating of 2.3 (SE=.56; $t(11)=4.03$, $p=.005$). The least painful conditions were the ones involving 80%rMT. TMS at 10Hz80% was associated with a mean painfulness rating of 1.9 (SE=.63; $t(14)=2.98$, $p=.018$) and 1Hz80% was associated with a mean rating of 1.8 (SE=.56; $t(12)=3.13$, $p=.017$).

Overall, the mean mA value used to match the sham TMS sensations with those of real TMS was 2.81 mA (SE=0.28). The mean motor threshold value was 53.71% of machine output (SE=1.65).

Mask Validity—With respect to guesses about whether participants received real or sham TMS, 51% of the sample guessed correctly ($X^2(1)=0.019$, ns) which is not significantly different from chance, suggesting that participants were unable to determine correctly which treatment was real and which was sham. The mean guess-confidence rating in the group that guessed correctly was 5.04 out of 10 (SE=0.63) and the mean for the group that guessed incorrectly was 5.98 (SE=0.67). These values were not significantly different ($t(63)=1.03$, ns) suggesting that those guessing correctly were no more or less confident in their guess than those guessing incorrectly.

Pain Threshold Task Validity—No significant main effects or interactions were found for time (pre- to post- TMS), TMS type (real versus sham) or TMS condition on participants' subjective appraisals of the level of painfulness associated with each of the pain threshold trials (hot, cold and mechanical). Thus, if significant effects are detected for any of the pain threshold trials, it is likely due to a change in the threshold itself, and not due to changes in reaction time, task performance strategies, or other factors that might influence the behavioral patterns associated with terminating each threshold stimulus during the thresholding trial. Participants rated the mean painfulness achieved for each heat pain threshold trial as 37.87 (SE=.66) out of 100 (where 0=no pain and 100=worst pain

imaginable) suggesting that participants stopped the thermode from heating to indicate their heat pain threshold was reached when the sensation was experienced as ~3.8 out of 10. The mean subjective rating associated with the pain-level experienced during cold pain threshold trials was 32.11 (SE=.67), and the mean subjective rating associated with mechanical pain thresholding trials was 32.55 (SE=.64).

TMS and Device Parameter Effect Summary

The effect sizes (Cohen's d) across all pain modalities in this healthy adult cohort varied as a function of TMS device parameters. The largest effect size was observed for 10Hz100% rTMS (d=0.34). The smallest effect size was observed for theta-burst stimulation (d=.03). The effect sizes for 1Hz100% and 1Hz80% settings were 0.24 and 0.32 respectively, and the effect-size for 10Hz80% was 0.18.

Heat Sensory Thresholds

No significant baseline differences in heat sensory thresholds were observed between groups (real versus sham TMS; $F(1,459)=0.07$, ns) nor across TMS treatment conditions ($F(4,51.7)=0.41$, ns). There were no main effects on pre- post- TMS changes in heat sensory threshold for real versus sham TMS ($F(1,949)=0.29$, ns), nor across TMS device setting conditions ($F(4,57)=0.30$, ns). However, the pre-post × real-sham × device-parameter interaction was significant ($F(4,941)=3.76$, $p=.005$), and 10Hz100% TMS was associated with a significant increase in heat sensory threshold compared to sham ($t(941)=3.14$, $p=0.002$). Similarly, 10Hz80% was associated with a significant increase in heat sensory threshold relative to sham ($t(943)=2.69$, $p=0.0073$). No significant effects were observed for the other TMS settings on heat sensory thresholds (see Table 1).

Cold Sensory Thresholds

No significant baseline difference in cold sensory thresholds were observed between groups (real versus sham TMS; $F(1,470)=0.00$, ns) nor across TMS treatment conditions ($F(4,50.8)=1.22$, ns). There was no main effect on pre- post- TMS changes in cold sensory thresholds for real versus sham TMS ($F(1,952)=0.01$, ns), nor for TMS condition ($F(4,62.2)=1.28$, ns). However, there was a significant three-way pre-post × real-sham × device-parameter interaction effect on cold sensory thresholds ($F(4,936)=3.11$, $p=.015$). Real 10Hz100% rTMS was associated with a relative anti-hypersensitivity effect compared to sham ($t(936)=2.75$, $p=.006$) and 10Hz80% was associated with an anti-hypersensitivity effect ($t(936)=2.37$, $p=.02$) as well. No other TMS conditions were associated with significant effects on cold sensory thresholds (see Table 1).

Heat Pain Thresholds

There was a significant difference in baseline scores between the real and sham conditions ($F(1,412)=15.05$, $p<.0001$), but no difference across TMS conditions ($F(4,60.4)=0.12$, ns). After controlling for baseline differences, there was a significant main effect on pre- post-TMS changes in heat pain thresholds for real versus sham TMS ($F(1,869)=5.00$, $p=.03$), but no main effect for TMS device settings ($F(4,51.9)=0.12$, ns) nor a pre-post × real-sham × device-parameter interaction ($F(4,834)=2.21$, $p=.07$; see Table 2).

Cold Pain Thresholds

There were no baseline differences between real versus sham TMS ($F(1,409)=0.45$, ns), nor for TMS device setting conditions ($F(1,60.9)=0.57$, ns). There was no main effect for real versus sham TMS on cold pain thresholds ($F(1,867)=0.18$, ns), nor for the TMS device setting factor ($F(1,870)=15.33$, $p<.0001$), but no main effect for real versus sham TMS ($F(1,873)=0.22$, ns), nor for TMS condition ($F(4,62.8)=0.72$, ns). There was a significant

pre-post × real-sham × device-parameter interaction (F(4,864)=3.65, p=.01). Relative to sham TMS, there were an anti-hyperalgesic effects for 10Hz100% TMS (t(864)=3.09, p=.002), 10Hz80% TMS (t(865)=2.50, p=.01), and 1Hz80% TMS (t(864)=3.09, p=.002). A significant hyperalgesic effect was observed for theta-burst TMS (t(864)=2.47, p=.01). No significant effects were observed the other TMS settings (see Table 2).

Mechanical Pain Thresholds

There was a significant baseline difference in mechanical pain threshold between the real and sham conditions (F(1,234)=5.56, p=.02) but no difference across the TMS device parameters (F(4,33)=0.19, ns). After controlling for baseline differences, there was no main effect for real versus sham TMS (F(1,501)=0.09, ns), nor for TMS device-parameter condition (F(4,61)=0.12, ns). There was no significant pre-post X real-sham X device-parameter interaction effect on mechanical pain thresholds (F(4,466)=1.32, ns; see Table 2).

Suprathreshold Magnitude Estimation - Intensity

There were no significant differences between real and sham TMS conditions in baseline suprathreshold pain intensity ratings (F(1,1022)=3.08, ns), nor across TMS device settings (F(4,60.9)=0.28, ns). There were no main effects on the pre- post- TMS changes in intensity ratings between real and sham TMS conditions (F(1,2058)=2.31, ns), nor across TMS device setting conditions (F(4,62.5)=0.25, ns). There was also no pre-post X real-sham X device-parameter interaction effect (F(4,2053)=1.98, ns; see Table 2).

Suprathreshold Magnitude Estimation - Unpleasantness

There was a significant baseline difference in suprathreshold pain unpleasantness ratings between the real and sham conditions (F(1,1023)=16.31, p<.0001), but not across TMS device setting conditions (F(4,60.9)=0.25, ns). After controlling for baseline differences, there were no significant main effects on the pre-post- TMS changes in unpleasantness ratings for the real/sham condition (F(1,2074)=1.34, ns) nor for the TMS device settings condition (F(4,58.3)=0.16, ns). However, after controlling for baseline differences, the pre-post X real-sham X device-parameter interaction was significant (F(4,2044)=5.08, p=.0004). There was a significant analgesic effect for 10Hz100% TMS on unpleasantness ratings (t(2043)=2.08, p=.038) and for 1Hz80% (t(2041)=2.28, p=.023). There were no significant effects observed for other TMS device settings (see Table 2).

Wind-up Pain

Because all wind-up slope measurements were forced to start with a score of 0 for all conditions, baseline differences were not examined. There was no main effect for real versus sham TMS (F(1,19000)=2.02, ns), nor for TMS condition (F(4,63)=1.02, ns). There was a significant three-way pre-post X real-sham X device-parameter interaction effect on wind-up slopes (F(4,19000)=4.27, p=.002).

Real TMS at 10Hz80% was associated with a significant decrease in wind-up slope relative to sham (t(19000)=11.34, p<.0001) as was 1Hz80% (t(19000)=11.43, p<.0001). Real 10Hz100% TMS was associated with a significant increase in wind-up slope (t(19000)=7.42, p<.0001) compared to sham as was theta-burst TMS (t(19000)=4.68, p<.0001) suggesting hyperalgesic effects for these two settings (see Table 2).

Discussion

Findings from this randomized, sham-controlled trial wherein the procedural sensations of real TMS were matched between sham and real conditions suggest that the effects of motor cortex TMS on laboratory-induced pain in healthy adults are small and variable. Overall,

forty minutes of active motor cortex TMS was associated with significant effects on heat sensory thresholds, cold sensory thresholds, cold pain thresholds, suprathreshold thermal stimulus unpleasantness ratings and wind-up pain. No significant effects were observed for suprathreshold thermal stimulus intensity ratings, heat pain thresholds, or mechanical pain thresholds. Device-parameter specific effects were found for several of the QST measures. 10Hz stimulation (regardless of intensity) was associated with a total of 7 significant analgesic effects, anti-hyperalgesic effects, and/or decreased sensitivity to non-noxious stimuli in the present study, and only 1 hyperalgesic effect. 1Hz stimulation was associated with a total of 4 significant analgesic effects, anti-hyperalgesic effects, and/or decreased sensitivity to non-noxious stimuli, but no hyperalgesic effects. Theta-burst stimulation was associated with 2 hyperalgesic effects. In general, these findings are consistent with much of the available data from several studies suggesting that low-frequency motor rTMS and intermittent theta-burst may produce no effects or even hyperalgesic effects while higher-frequency stimulation (e.g., 10–20Hz) is associated with more robust analgesic and/or anti-sensitivity effects [19,20,32–36,41,43,44]. With respect to stimulus intensity, there did not appear to be much difference between 100% versus 80% stimulation when collapsing across frequencies. These findings suggest that some TMS device settings may be better than others to help manage pain in clinical cohorts (e.g. high frequency), and that some of the device settings available to practitioners are may be counter-therapeutic (e.g., theta-burst).

Theta-burst TMS effects on pain perception are less studied and not well-understood compared to the other settings employed in this study, and it should be clarified that theta-burst differs substantially from the other settings investigated in the present study. There is some evidence that continuous theta-burst stimulation is associated with cortical inhibition and analgesic effects, whereas intermittent theta-burst (more like the condition employed in the present study) is not [53] [54]. Findings from the present study seem to support this. More work is needed to clarify the effects of continuous and intermittent theta-burst stimulation on pain perception.

With respect to mechanisms of motor TMS action on pain perception, there is some evidence that changes in activity at local cortical sites as well as at the thalamic nuclei may be involved[42]. It is possible that corticothalamic tracts may exert an inhibitory influence on thalamic pain processing and transmission [29]. High frequency rTMS may suppress pain information relayed through the spinothalamic tracts and the ipsilateral thalamic nuclei [33,36,37]. However, there is also evidence to suggest that at least a portion of motor-cortex TMS-related analgesic effects may be due to changes in prefrontal and limbic activity [33,34,43]. The present study did not directly address the issue of mechanisms *per se*, but overall, the data seem to support the notion that higher frequency stimulation is generally associated with more suppression of spinothalamic tract activity than low frequency stimulation. Thus, differences between device settings with respect to hyperalgesic versus analgesic effects may be related to the interaction between TMS frequency and corticothalamic tract activity patterns. But, the presence of a motor TMS effect on suprathreshold *unpleasantness* ratings, and not on *intensity* ratings suggests that there may have been a TMS-related influence exerted on the processing of the emotional component of the pain experience. While 10Hz100% motor TMS was associated with mostly analgesic, anti-hyperalgesic, and decreased sensitivity effects, a hyperalgesic effect was observed for it on our wind-up pain measure. The nature of this finding is unclear, but may suggest that 10Hz100% TMS over the motor cortex ipsilateral to the side of repetitive noxious stimulation has little impact (or even counter-therapeutic effects) on receptive field expansion of wide-dynamic range neurons in the spinal cord (primarily a central pain facilitation/sensitization process). We might then speculate that 10Hz100% motor TMS produces analgesic effects by enhancing cortical inhibitory processes at the expense of resources that might otherwise be used to dampen central sensitization.

Synchronization and desynchronization of the neural patterns may play a role in perception, motor action and conscious experience [55], and it has been suggested that human rolandic oscillations originate in the anterior bank of the central sulcus (20-Hz rhythm) and the postcentral cortex (10-Hz rhythm). Tamura et al [55] found that 1-Hz rTMS over motor cortex significantly reduced movement-related rebound of the 20-Hz oscillation in association with decreased motor cortical excitability. It may be that different TMS frequencies interact with oscillations associated with different cortical structures and functions to produce observed effects on pain perception. However, data from the current study do not permit any inference with respect to such mechanisms of action. More work is needed in this area.

There are several limitations of current study including the fact that only a healthy adult cohort was employed. There is evidence that chronic pain of various etiologies is associated with changes in cortical and subcortical organization that may maintain or exacerbate pain. The area(s) of aberrant reorganization are potential targets of TMS treatment. Since this reorganization is not present in healthy adult samples, inferences about optimal device parameters and hypothetical mechanisms of TMS action may not necessarily be valid for all clinical applications. However, the findings from this study are consistent with much of the literature on the use of motor TMS to manage chronic pain as many of these studies have reported analgesic benefits associated with higher frequency stimulation. Much work is needed to determine the TMS device parameters (intensity and frequency), as well as stimulation on and off times, treatment schedules, treatment durations and maintenance schedules that optimally manage chronic pain of different types.

In the present study, the side of TMS stimulation was the same as the thermal pain target (i.e., left motor cortex and left volar forearm) but not the mechanical pain target (i.e., right hand). It is possible that the effect-sizes reported in the present study underestimate the effects that might be seen when TMS is delivered over the cortex contralaterally to the painful area (as is typically done in clinical settings). However, there was not a large discrepancy in the effects observed between hands in the present study (although the laterality of stimulation is confounded by experimental pain modality). Interestingly, significant analgesic effects were observed for thermal pain despite the ipsilateral cortical target supporting the notion that at least a portion of motor-cortex TMS-related analgesic effects may be due to changes associated with the affective and cognitive-evaluative dimensions of pain experience [33,34,43].

In summary, findings from this controlled, randomized investigation suggest that the effects of motor cortex TMS on laboratory-induced pain in healthy adults are small and vary to some extent as a function of frequency and intensity parameters. Higher frequency stimulation appears to be associated with the most analgesic effects, anti-hyperalgesic effects, as well as decreased sensitivity to non-noxious stimuli. These findings are consistent with several studies using clinical participants which suggest that higher TMS frequencies tend to be associated with the most clinical benefit [32]. Future work is needed to clarify mechanisms of action, evaluate the effects of contralateral versus ipsilateral stimulation, and to determine whether laboratory investigations in healthy adult cohorts are generalizable to different clinical pain conditions.

References

1. George MS, et al. Mechanisms and the current state of transcranial magnetic stimulation. CNS Spectr. 2003; 8(7):496–514. [PubMed: 12894031]
2. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985; 1(8437):1106–7. [PubMed: 2860322]

3. Barker, A., et al. Magnetic stimulation of the human nervous system: an introduction and basic principles. In: S, C., editor. Magnetic Stimulation in Clinical Neurophysiology. Butterworth; Boston: 1989. p. 55-72.
4. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. Arch Gen Psychiatry. 1999; 56(4):300–11. [PubMed: 10197824]
5. George, M.; Belmaker, R. Transcranial magnetic stimulation. In: MS, G., editor. Neuropsychiatry. American Psychiatric Press; Washington DC: 2000.
6. George MS, et al. Mechanisms and state of the art of transcranial magnetic stimulation. J Ect. 2002; 18(4):170–81. [PubMed: 12468991]
7. Malenka RC, Nicoll RA. Long-term potentiation--a decade of progress? Science. 1999; 285(5435): 1870–4. [PubMed: 10489359]
8. Wu T, et al. Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. Neurosci Lett. 2000; 287(1):37–40. [PubMed: 10841985]
9. Chen R, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology. 1997; 48(5):1398–403. [PubMed: 9153480]
10. Hirayama A, et al. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. Pain. 2006; 122(1–2):22–7. [PubMed: 16495011]
11. Fregni F, et al. Treatment of chronic visceral pain with brain stimulation. Ann Neurol. 2005; 58(6): 971–2. [PubMed: 16315281]
12. Fregni F, Freedman S, Pascual-Leone A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. Lancet Neurol. 2007; 6(2):188–91. [PubMed: 17239806]
13. 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)
14. Borckardt JJ, et al. 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.
15. Borckardt JJ, et al. A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. Pain Med. 2009; 10(5):840–9. [PubMed: 19594842]
16. Borckardt JJ, et al. 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]
17. Borckardt JJ, et al. Post-Operative Left Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) Reduces Patient-Controlled Analgesia Use. Anesthesiology. 2006; 105:557–562. [PubMed: 16931989]
18. Short E, et al. Non-invasive brain stimulation approaches to fibromyalgia pain. Journal of Pain Management. 2009; 2(3)
19. Andre-Obadia N, et al. 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]
20. Andre-Obadia N, et al. Pain relief by rTMS: differential effect of current flow but no specific action on pain subtypes. Neurology. 2008; 71(11):833–40. [PubMed: 18779511]
21. Amassian V, et al. Induced pain is relieved by transcranial magnetic stimulation of human parietal lobe through endorphin release. Electroencephalogr Clin Neurophysiol. 1997; 103:179.
22. Topper R, et al. Repetitive transcranial magnetic stimulation of the parietal cortex transiently ameliorates phantom limb pain-like syndrome. Clin Neurophysiol. 2003; 114(8):1521–30. [PubMed: 12888036]
23. Tamura Y, et al. Facilitation of A[delta]-fiber-mediated acute pain by repetitive transcranial magnetic stimulation. Neurology. 2004; 62(12):2176–81. [PubMed: 15210878]
24. Tamura Y, et al. Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin. Pain. 2004; 107(1–2):107–15. [PubMed: 14715396]

25. Rollnik JD, et al. Repetitive transcranial magnetic stimulation for the treatment of chronic pain - a pilot study. Eur Neurol. 2002; 48(1):6–10. [PubMed: 12138303]
26. Reid P, Pridmore S. Improvement in chronic pain with transcranial magnetic stimulation. Aust N Z J Psychiatry. 2001; 35(2):252. [PubMed: 11284914]
27. Pujol J, et al. The effect of repetitive magnetic stimulation on localized musculoskeletal pain. Neuroreport. 1998; 9(8):1745–8. [PubMed: 9665594]
28. Pridmore S, et al. Transcranial magnetic stimulation and chronic pain: current status. Australasian Psychiatry. 2005; 13(3) In press.
29. Pleger B, et al. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Neurosci Lett. 2004; 356(2):87–90. [PubMed: 14746870]
30. Owen S, Aziz TZ. Long lasting antalgic effects of daily repetitive transcranial magnetic stimulation in neuropathic pain. J Neurol Neurosurg Psychiatry. 2005; 76(6):761. [PubMed: 15897493]
31. Migita K, et al. Transcranial magnetic coil stimulation of motor cortex in patients with central pain. Neurosurgery. 1995; 36(5):1037–9. discussion 1039–40. [PubMed: 7540735]
32. 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]
33. Lefaucheur JP, et al. Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. Neuroreport. 2001; 12(13):2963–5. [PubMed: 11588611]
34. Lefaucheur JP, et al. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. Neurology. 2006; 67(9):1568–74. [PubMed: 17101886]
35. Lefaucheur JP, et al. 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]
36. Lefaucheur JP, et al. 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]
37. Lefaucheur JP, et al. Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. Neurology. 2006; 67(11):1998–2004. [PubMed: 17159107]
38. Khedr EM, et al. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry. 2005; 76(6):833–8. [PubMed: 15897507]
39. Kanda M, et al. Transcranial magnetic stimulation (TMS) of the sensorimotor cortex and medial frontal cortex modifies human pain perception. Clin Neurophysiol. 2003; 114(5):860–6. [PubMed: 12738431]
40. Johnson S, Summers J, Pridmore S. Changes to somatosensory detection and pain thresholds following high frequency repetitive TMS of the motor cortex in individuals suffering from chronic pain. Pain. 2006; 123(1–2):187–92. [PubMed: 16616419]
41. Cruccu G, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. Eur J Neurol. 2007; 14(9):952–70. [PubMed: 17718686]
42. Bestmann S, et al. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur J Neurosci. 2004; 19(7):1950–62. [PubMed: 15078569]
43. Leo RJ, Latif T. Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: a review. J Pain. 2007; 8(6):453–9. [PubMed: 17434804]
44. Rosen AC, et al. Noninvasive transcranial brain stimulation and pain. Curr Pain Headache Rep. 2009; 13(1):12–7. [PubMed: 19126365]
45. Lefaucheur JP. The use of repetitive transcranial magnetic stimulation (rTMS) in chronic neuropathic pain. Neurophysiologie Clinique. 2006; 36:117–124. [PubMed: 17046606]
46. Borckardt JJ, et al. Reducing pain and unpleasantness during repetitive transcranial magnetic stimulation. J ECT. 2006; 22(4):259–64. [PubMed: 17143157]
47. Borckardt JJ, et al. Development and Evaluation of a Portable Sham TMS System. Brain Stimulat. 2008; 1(1):52–59.

48. Hoeft F, et al. Electronically switchable sham transcranial magnetic stimulation (TMS) system. PLoS One. 2008; 3(4):e1923. [PubMed: 18398456]

49. Borckardt JJ, et al. Estimating Resting Motor Thresholds in TMS Research and Practice: A Computer Simulation Evaluation of Best Methods. J ECT. 2006; 22:169–175. [PubMed: 16957531]

50. Price DD, et al. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. Pain. 1977; 3(1):57–68. [PubMed: 876667]

51. 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.

52. Bryk A, Raudenbush S. Application of hierarchical linear models to assessing change. Psychological Bulletin. 1987; 101(1):147–158.

53. Poreisz C, et al. Attenuation of N2 amplitude of laser-evoked potentials by theta burst stimulation of primary somatosensory cortex. Exp Brain Res. 2008; 185(4):611–21. [PubMed: 18043910]

54. Csifcsak G, et al. Electrophysiological correlates of reduced pain perception after theta-burst stimulation. Neuroreport. 2009; 20(12):1051–5. [PubMed: 19590390]

55. Tamura Y, et al. Functional relationship between human rolandic oscillations and motor cortical excitability. European Journal of Neuroscience. 2005; 21(9):2555–2562. [PubMed: 15932613]

TABLE-1

Mean (StdErr) hot and cold sensory threshold values for each randomization condition (real versus sham TMS) and each device parameter condition along with statistical output examining baseline differences as well as main effects and the 3-way interaction between time (pre- post- TMS), randomization (real versus sham), and device parameters. Significant device parameter effects (p<.05) are highlighted in bold along with an indication of the direction of the observed effect.

		Cold Pain Threshold (°C)			Hot Pain Threshold (°C)			SupraThresh Intensity (VAS Points)		
TMS Settings	**Condition**	**Pre**	**Post**		**Pre**	**Post**		**Pre**	**Post**	
10hz100pct	Real	**12.38 (0.81)**	**13.17 (0.78)**	* *A*	45.10 (0.39)	44.48 (0.35)		42.20 (1.95)	40.93 (1.98)	
	Sham	**11.28 (0.88)**	**14.26 (1.00)**		45.80 (0.36)	44.66 (0.40)		39.90 (2.37)	42.72 (2.49)	
10hz80pct	Real	**18.15 (1.03)**	**18.51 (0.97)**	* *A*	44.07 (0.29)	43.77 (0.38)		51.37 (2.16)	50.54 (2.21)	
	Sham	**16.59 (0.86)**	**18.13 (0.87)**		45.05 (0.34)	43.62 (0.34)		48.95 (1.40)	42.51 (1.41)	
1hz100pct	Real	15.72 (0.81)	15.26 (0.79)		43.32 (0.33)	43.18 (0.31)		53.41 (1.93)	49.88 (2.02)	
	Sham	16.10 (0.83)	14.97 (0.83)		43.97 (0.38)	44.26 (0.34)		50.06 (1.86)	51.65 (2.06)	
1hz80pct	Real	**16.90 (0.57)**	**17.60 (0.68)**	* *A*	43.69 (0.25)	43.14 (0.25)		52.63 (1.53)	50.41 (1.56)	
	Sham	**16.38 (0.78)**	**18.99 (0.73)**		44.52 (0.31)	43.05 (0.27)		41.57 (2.00)	44.59 (1.91)	
theta90pct	Real	**13.01 (1.06)**	**16.16 (1.07)**	* *H*	43.66 (0.41)	43.38 (0.39)		48.70 (1.61)	48.96 (1.47)	
	Sham	**14.57 (0.96)**	**14.60 (0.93)**		44.88 (0.40)	44.07 (0.36)		43.85 (1.69)	44.89 (1.92)	
	Baseline Difference Real TMS/ Sham:	F(1,409)=0.45, p=.50		ns	**F(1,412)=15.05, p<.0001**		*	F(1,1022)=3.08, p=.08		ns
	Baseline Difference TMS-Settings:	F(1,60.9)=0.57, p=.68		ns	F(4,60.4)=0.12, p=.97		ns	F(4,60.9)=0.28, p=.89		ns
	Main Effect Real TMS/Sham:	F(1,867)=0.18, p=.67		ns	**F(1,869)=5.00, p=.03** †		*	F(1,2058)=2.31, p=.13		ns
	Main Effect TMS-Settings:	F(4,62.8)=0.72, p=.58		ns	F(4,51.9)=0.12, p=.97†		ns	F(4,62.5)=0.25, p=.91		ns
	Real TMS/Sham X Pre-Post X TMS-Settings:	**F(4,864)=3.65, p=.01**		*	F(4,834)=2.21, p=.07†		ns	F(4,2053)=1.98, p=.10		ns

		Suprathresh Unpleasant (VAS Points)			Mechanical Pain Threshold (g)			Wind-Up Pain Slopes (pts per second)		
TMS Settings	**Condition**	**Pre**	**Post**		**Pre**	**Post**		**Pre**	**Post**	
10hz100pct	Real	**42.45 (1.99)**	**41.33 (2.12)**	*A* *	159.03 (5.78)	154.42 (5.14)		**2.87 (0.02)**	**2.91 (0.02)**	*H* *
	Sham	**40.03 (2.37)**	**43.59 (2.70)**		148.48 (5.89)	144.78 (4.27)		**2.89 (0.02)**	**2.89 (0.02)**	
10hz80pct	Real	52.72 (2.27)	52.67 (2.32)		148.84 (5.82)	147.68 (6.63)		**2.89 (0.02)**	**2.84 (0.02)**	*A* *
	Sham	48.27 (1.49)	44.36 (1.57)		151.91 (4.71)	159.60 (5.96)		**2.89 (0.02)**	**2.86 (0.02)**	
1hz100pct	Real	53.51 (2.20)	51.17 (2.17)		162.59 (7.97)	174.31 (13.19)		**2.86 (0.02)**	**2.84 (0.02)**	
	Sham	46.15 (2.02)	47.36 (2.19)		162.95 (7.97)	159.10 (7.36)		2.83 (0.02)	2.85 (0.02)	

		Cold Pain Threshold (°C)			Hot Pain Threshold (°C)			SupraThresh Intensity (VAS Points)		
TMS Settings	**Condition**	**Pre**	**Post**		**Pre**	**Post**		**Pre**	**Post**	
1hz80pct	Real	**54.88 (1.87)**	**52.40 (2.02)**	*A* *	159.72 (3.18)	165.14 (3.04)		**2.84 (0.02)**	**2.82 (0.02)**	*A* *
	Sham	**39.26 (1.89)**	**44.57 (1.94)**		162.99 (5.07)	154.45 (4.37)		**2.90 (0.02)**	**2.88 (0.02)**	
theta90pct	Real	48.78 (1.87)	46.45 (1.82)		138.98 (4.98)	152.38 (6.83)		**2.83 (0.02)**	**2.86 (0.02)**	*H* *
	Sham	41.22 (1.93)	40.71 (2.18)		153.59 (6.32)	149.93 (6.41)		**2.86 (0.02)**	**2.83 (0.02)**	
	Baseline Difference Real TMS/ Sham:	**F(1,1023)=16.31, p<.0001**		*	**F(1,234)=5.56, p=.02**		*			
	Baseline Difference TMS-Settings:	F(4,60.9)=0.25, p=.91		ns	F(4,33)=0.19, p=.94		ns			
	Main Effect Real TMS/Sham:	F(1,2074)=1.34, p=.25†		ns	F(1,501)=0.09, p=.77†		ns	F(1,19000)=2.02, ns		ns
	Main Effect TMS-Settings:	F(4,58.3)=0.16, p=.96†		ns	F(4,61)=0.12, p=.98†		ns	F(4,63)=1.02, ns		ns
	Real TMS/Sham X Pre-Post X TMS-Settings:	**F(4,2044)=5.08, p=.0004** †		*	F(4,466)=1.32, p=.26†		ns	**F(4,19000)=4.27, p=.002**		*

*p<.05

A Decreased Sensitivity Relative to Sham

H Hyperalgesic Effect Relative to Sham

† Controlling for baseline values

TABLE-2

Mean (StdErr) hot, cold, and mechanical pain threshold values, suprathreshold pain intensity and unpleasantness ratings, and wind-up slope values for each randomization condition (real versus sham TMS) and each device parameter condition along with statistical output examining baseline differences as well as main effects and the 3-way interaction between time (pre- post- TMS), randomization (real versus sham), and device parameters. Significant device parameter effects (p<.05) are highlighted in bold along with an indication of the direction of the observed effect.

		Heat Sensory Threshold (°C)			Cold Sensory Threshold (°C)		
TMS Settings	**Condition**	**Pre**	**Post**		**Pre**	**Post**	
10hz100pct	Real	**34.08 (0.11)**	**35.74 (0.16)**	*A* *	**29.88 (0.14)**	**29.02 (0.18)**	* *A*
	Sham	**34.45 (0.13)**	**34.87 (0.14)**		**28.96 (0.28)**	**29.22 (0.17)**	
10hz80pct	Real	**34.96 (0.17)**	**36.41 (0.41)**	*A* *	29.95 (0.19)	29.32 (0.21)	
	Sham	**34.46 (0.12)**	**35.07 (0.21)**		30.56 (0.09)	30.07 (0.11)	
1hz100pct	Real	34.49 (0.10)	35.32 (0.15)		**30.34 (0.09)**	**29.42 (0.18)**	* *A*
	Sham	34.90 (0.18)	35.50 (0.23)		**29.56 (0.15)**	**29.45 (0.17)**	
1hz80pct	Real	34.67 (0.16)	34.48 (0.14)		29.26 (0.21)	28.89 (0.17)	
	Sham	35.07 (0.21)	35.33 (0.19)		29.40 (0.20)	28.78 (0.24)	
theta90pct	Real	35.17 (0.29)	35.17 (0.18)		29.45 (0.17)	29.71 (0.20)	
	Sham	34.98 (0.23)	35.65 (0.20)		30.11 (0.15)	29.51 (0.17)	
	Baseline Difference Real/Sham:	F(1,459)=0.07, p=.80		ns	F(1,470)=0.00, p=.95		ns
	Baseline Difference TMS-Settings:	F(4,51.7)=0.41, p=.80		ns	F(4,50.8)=1.22, p=.31		ns
	Main Effect Real/Sham:	F(1,949)=0.29, p=.59		ns	F(1,952)=0.00, p=.97		ns
	Main Effect TMS-Settings:	F(4,57)=0.30, p=.88		ns	F(4,62.2)=1.28, p=.29		ns
	Real/Sham X Pre-Post X TMS-Settings:	**F(4,941)=3.76, p=.005**		*	**F(4,936)=3.11, p=.01**		*

*p<.05

A A Decreased Sensitivity Relative to Sham

† Controlling for baseline values