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Theta Burst Stimulation of the Human Motor Cortex Modulates Secondary Hyperalgesia to Punctate Mechanical Stimuli

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ABSTRACT

Objectives: Many chronic pain conditions show evidence of dysregulated synaptic plasticity, including the development and maintenance of central sensitization. This provides a strong rationale for neuromodulation therapies for the relief of chronic pain. However, variability in responses and low fidelity across studies remain an issue for both clinical trials and pain management, demonstrating insufficient mechanistic understanding of effective treatment protocols.

Materials and Methods: In a randomized counterbalanced crossover designed study, we evaluated two forms of patterned repetitive transcranial magnetic stimulation, known as continuous theta burst stimulation (TBS) and intermittent TBS, during normal and central sensitization states. Secondary hyperalgesia (a form of use-dependent central sensitization) was induced using a well-established injury-free pain model and assessed by standardized quantitative sensory testing involving light touch and pinprick pain thresholds in addition to stimulus-response functions.

Results: We found that continuous TBS of the human motor cortex has a facilitatory (pronociceptive) effect on the magnitude of perceived pain to secondary hyperalgesia, which may rely on induction and expression of neural plasticity through heterosynaptic long-term potentiation–like mechanisms.

Conclusions: By defining the underlying mechanisms of TBS-driven synaptic plasticity in the nociceptive system, we offer new insight into disease mechanisms and provide targets for promoting functional recovery and repair in chronic pain. For clinical applications, this knowledge is critical for development of more efficacious and mechanisms-based neuromodulation protocols, which are urgently needed to address the chronic pain and opioid epidemics.

Keywords: Central sensitization, hyperalgesia, motor cortex, pain, theta burst stimulation

INTRODUCTION

Synaptic plasticity is a fundamental property of neurons that enables modification of the strength and efficacy of synaptic transmission through activity-dependent mechanisms. Two major forms of synaptic plasticity, long-term potentiation (LTP) and long-term depression (LDP), can bidirectionally modify synaptic strength,[1] and these processes are classically represented by the neural activity patterns for learning, memory formation, and behavioral adaptation.[2,3] However, studies have shown that LTP also can be induced in pain pathways[4,5] and may contribute to increased pain sensitivity.[6,7]

Pain amplification through activity-dependent synaptic plasticity has been termed central sensitization.[8] Although there are differences between central sensitization and LTP linked to memory, there also are some striking similarities.[9,10] Indeed, it has been well established that N-methyl-D-aspartate (NMDA) receptors are essential for the initiation of LTP, in the same way that they are indispensable for use-dependent central sensitization.[11,12] Other molecular mechanisms point to close parallels between

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hippocampal LTP and central (spinal) sensitization of the nociceptive system.[9] However, unlike LTP, the behavioral consequences of central sensitization can be more readily detected in humans,[13] with relevant aspects of this phenomenon extensively studied using human surrogate pain models.[14]

Central sensitization induced by electrical stimulation of primary afferent neurons has been used as a pain model to probe changes in LTP-like synaptic plasticity associated with persistent pain conditions. For example, in the spinal dorsal horn, homosynaptic and heterosynaptic LTP at A- and C-fiber synapses has been shown after high-frequency (~100 Hz) stimulation of primary afferents,[11,15] and in response to noxious peripheral stimuli.[4,12,16] Low-frequency continuous stimulation (2 Hz) also triggers LTP but only homosynaptically between peripheral C-fibers and spinal cord lamina I neurons.[12] Interestingly, conditioning with high-frequency burst-like stimulation of peripheral nerves appears more efficacious than continuous stimulation for inducing secondary hyperalgesia (heterotopic LTP) in humans.[17]

In contrast, there is limited information on the effects of stimulating centrally to directly or indirectly modulate LTP-like pain amplification. Indirect assessments from human studies using noninvasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), have shown that long-term modification of cortical function is indicated for therapeutic purposes in chronic pain.[18] rTMS can modulate not only chronic pain but also pain hypersensitivity that is experimentally induced by capsaicin in healthy volunteers.[19,20] Theta burst stimulation (TBS) is a promising alternative to standard repetitive transcranial magnetic stimulation (rTMS) and is an effective stimulus for LTP.[21,22] TBS resembles the physiological theta frequency and firing patterns of neurons that decrease the threshold of neuronal circuit activation required to induce LTP.[22–24] TBS is more efficient than continuous high-frequency stimulation at eliciting LTP in the hippocampus[22] and striatum of the rat brain.[25] However, little is still known about TBS-driven synaptic plasticity and the potential link between nociceptive LTP and the perceptual consequence (hyperalgesia) in the human nociceptive system.

In the present study, we stimulated the human motor cortex with two TBS protocols: continuous TBS (cTBS) and intermittent TBS (iTBS) to induce long-term depression (LTD)-like inhibition and LTP-like facilitation during normal and central sensitization states. Motor cortex stimulation is well known to modulate pain,[26] and the TBS protocols have been shown to be similar to the paradigms that induce LTP and LTD in animal models,[21,27] although direct effects of TBS on synaptic transmission in humans can only be measured indirectly. Secondary hyperalgesia (a type of central sensitization) was elicited by capsaicin/heat[28] and assessed using a standardized quantitative sensory testing (QST) protocol involving touch and pain thresholds in addition to stimulus-response functions.[29,30] Our hypothesis was that after the administration of cTBS, there would be an immediate change in the ability of heat/capsaicin to sustain LTP within the area of secondary hyperagesia, which experimentally would be measurable as an increase in pain thresholds to mechanical punctate stimuli, compared with iTBS.

MATERIALS AND METHODS

Subjects

Sixteen healthy subjects participated in the study [male/female 5/11; age (mean ± SD), 27 ± 10 years; body mass index, 21 ± 2.88 kg/m^2]. All participants were right-handed assessed by the Edinburgh Handedness Inventory.[31] Subjects were excluded if they had cerebrovascular disease, neurologic or psychiatric disorders, or contraindications to magnetic resonance imaging and TMS. In addition to routine screening, subjects were free of pain, medication, and caffeine at the time of testing. Informed written consent was obtained in accordance with University of Nottingham Research Ethics Committee (REC reference 457-1912).

Experimental Design

All subjects attended three separate sessions: baseline (no stimulation) and two stimulation sessions (iTBS and cTBS). After the baseline session (S1), participants were randomized into stimulation sessions (S2 and S3) using a within-subject crossover design. The session order was counterbalanced across the group, and sessions were separated by at least one week. Subjects were blinded to the type of TBS stimulation being delivered. During the three sessions, participants underwent QST across three conditions:

- condition 1 (C1): presensitization/pre-TBS
- condition 2 (C2): postsensitization/pre-TBS
- condition 3 (C3): postsensitization/post-TBS

These conditions were presented in two different ways on the left and right arm, which we called control and treated arm. The only difference between these two was the induction of central sensitization in the right arm through the application of capsaicin and heat. The left arm served as the control. The timing of the QST was performed immediately after TBS administration and was less than the known duration of the TBS effects on cortical excitability[32,33] (Fig. 1a,b).

Transcranial Magnetic Stimulation

TMS was delivered using a Magstim Rapid[2] stimulator with handheld 70-mm figure-of-eight coil (Magstim Co Ltd, UK). TBS comprised three pulses at 50 Hz repeated at 200-ms (5 Hz) intervals, with a total 600 pulses.[32] iTB was delivered by means of a 2-second train of pulses repeated every 10 seconds for a duration of 190 seconds, whereas cTBS was a 40-second train of uninterrupted pulses. The stimulation intensity was set to 80% of the resting motor threshold (RMT) and fixed across all the stimulation sessions (RMT; mean ± SD, 56% ± 9.5%).

Motor Cortex Mapping

Motor mapping was performed to delineate the hand area of the left primary motor cortex according to current practice.[34] Individuals' RMTs were determined using single-pulse TMS to the abductor digiti minimi muscle of the right hand. RMT was defined as the minimum stimulator output that induces an observable muscle twitch at the right hand for five of ten trials of TMS pulses.[35,36] The site at which stimuli of slightly suprathreshold intensity consistently produced a twitch in the target muscle was marked as the "hot spot." The motor mapping was individually assessed in each session per participant, and TBS was performed over this marked area.

Induction and Monitoring of Secondary Hyperalgesia

Secondary hyperalgesia was induced with the heat/capsaicin sensitization model.[28] Test areas were the forearms, and for each subject, two squares were drawn at symmetrical locations: an inner square (30 × 30 mm^2) matching the size of the contact thermode

(MSA Thermal Stimulator, Somedic, Sweden) and an outer square (60 × 60 mm^2) defined as the secondary area. The area between the borders of the two squares was a 270-mm^2 target area to which mechanical punctate stimuli were delivered during the experiments (Fig. 1c,d). Sensitization was produced through chemical stimulation (capsaicin cream, Axsain 0.075% w/w cream, Cephalon Ltd, UK) applied to the right arm in the middle of the inner rectangle. This topical treatment induced a selective, localized, and reversible degeneration of capsaicin-selective nociceptors located in the epidermis.[37] Hyperalgesia after capsaicin involves two primary afferent pathways: C-nociceptors for induction and Aδ-mechanonociceptors for signaling the state of pain amplification,[30,38] with C-fibers responsible for the largest contribution to secondary hyperalgesia.[39] For all subjects, the left arm served as the control. The capsaicin cream was removed after 30 minutes, and sensitization was rekindled at 90 minutes by heating the marked location to 40 °C for 5 minutes. The presence of secondary hyperalgesia was assessed using a validated standardized QST protocol.[29,30] Stimulus response functions (SRF) to punctate mechanical stimuli were defined using a series of calibrated pinprick stimulators (250-μm tip diameter, force: 32, 64, 128, 256, 512 mN) (MRC Systems GmbH, Heidelberg, Germany). In both test areas, the different intensities were applied three times each in balanced order. After each stimulus, the participants were asked to rate the pain intensity on a verbal rating scale (0 = no pain; 100 = worst pain imaginable). Pain to light touch (allodynia) was tested by light stroking with a cotton wisp (CW) (3 mN), Q-tip fixed to a plastic strip (100 mN), and a soft brush (200–400 mN). In cases in which the stroking stimuli were perceived as painful, participants were asked to give a rating (verbal rating scale; 0–100).

Statistical Analyses

The presence of secondary hyperalgesia was assessed separately for every test stimulus and every session. Ratings were transformed into decadic logarithmic values to obtain a lognormal distribution. To avoid the loss of zero values due to the logarithmic transformation, a small constant (0.1) was added to all raw data (zero and nonzero values).[29] The magnitude of differences between the various levels of light touch stimuli was tested by least squares differences (LSD) post hoc tests. Discrimination of the five intensities of punctate probes in both arms was tested by two-way repeated measures (RM) analysis of variance (ANOVA), with all data adjusted for multiple comparisons using the false discovery rate method of Benjamini-Hochberg.

RESULTS

Characterization of Secondary Hyperalgesia to Light Touch (Allodynia)

The presence of allodynia was assessed using three light touch stimuli and evaluated separately for every session (Fig. 2 and Table 1). Pain to light touch occurred only in a minority of subjects per session [baseline (7/16), cTBS (3/16), iTBS (5/16)] and with a similar incidence across the different test stimuli [baseline (19/144, 13.2%), cTBS (7/144, 4.9%), iTBS (12/144, 8.3%)]. There was a significant effect of the CW 30 minutes after sensitization under condition 2 compared with presensitization condition 1 (Fisher's LSD; $t = 2.522$, $p = 0.0235$). Pain to light touch was never reported in the control arm. The very mild level of dynamic mechanical allodynia as seen previously[30] precluded us from assessing the contribution of TBS on its induction.

Characterization of Secondary Hyperalgesia to Punctate Mechanical Stimuli

The incidence of pain and the SRFs to five different strengths of punctate stimuli were evaluated separately for each session (Fig. 3 and Table 2). Before capsaicin/heat treatment, the incidence and cumulative probability functions were similar for both arms (RM-ANOVA, main effect; baseline $p = 0.3692$, cTBS $p = 0.0455$, iTBS $p > 0.9999$) with 50% probability thresholds of pain in left/right arm interpolated as 50.2/49.2 mN (baseline), 49.2/78.0 mN (cTBS), and 37.3/43.1 mN (iTBS). The ratings of pricking pain were not significantly different for the left and right arms at each session (RM-ANOVA, main effect; baseline $p = 0.4941$, cTBS $p = 0.2471$, iTBS $p = 0.5720$).

Thirty minutes after heat/capsaicin treatment, the probability of pain reports was significantly increased in the treated arm (RM-ANOVA, main effect; baseline $p = 0.0962$, cTBS $p = 0.0038$, iTBS $p = 0.0077$), with 50% probability thresholds of pain in control/treated arms interpolated as 57.6/5.9 mN (baseline), 74.9/22.1 mN (cTBS), and 53.2/1.0 mN (iTBS). The heat/capsaicin also led to significant increases in pain ratings across all levels of stimulus force (RM-ANOVA, main effect; baseline $p = 0.0055$, cTBS $p = 0.0006$, iTBS $p = 0.0030$) with the SFR shifted to the left with slope roughly parallel to the control side [baseline, $r = 0.521/0.335$ (left/right); cTBS, $r = 0.678/0.503$; iTBS $r = 0.610/0.379$]. All experimental sessions showed reliable sensory changes in the skin area of secondary hyperalgesia.

Effect of TBS on Secondary Hyperalgesia

Sensitization was rekindled at 90 minutes to assess the effects of TBS on punctate hyperalgesia (Fig. 3). In the absence of any intervention (baseline session), the pain incidence was similar for both test sites (RM-ANOVA, main effect; control $p = 0.5760$, treated $p = 0.0567$) with 50% probability thresholds pre-/post-TBS interpolated as 57.6/59.2 mN (control) and 5.99/3.98 mN (treated). Pain ratings also were not significantly different for both sites at all stimulus levels (RM-ANOVA, main effect; control $p = 0.1780$, treated $p = 0.6893$), and the SFR remained parallel pre-/post-TBS [control, $r = 0.521/0.497$; treated, $r = 0.335/0.307$], indicating a mechanical hyperalgesia that was stable across time.

cTBS of the motor cortex caused the incidence of pain reporting to increase with 32 mN of force (RM-ANOVA, 32 mN probe; control $p = 0.0152$, treated $p = 0.0070$), and the population threshold pre-/post-TBS was interpolated as 75.0/53.2 mN (control) and 22.0/8.66 mN (treated). Preferentially around the capsaicin treated site but not the control site, pain ratings were significantly enhanced to all punctate stimuli (RM-ANOVA, main effect; control $p = 0.6121$, treated $p = 0.0297$), and the steepness of the regression line also was slightly reduced in the treated arm [control, $r = 0.678/0.658$; treated, $r = 0.503/0.417$].

After iTBS, the incidence of pain ratings remained the same for both test sites (RM-ANOVA, main effect; control $p = 0.6198$, treated $p = 0.8323$), with 50% probability thresholds pre-/post-TBS interpolated as 53.2/31.5 mN (control) and 1.03/17.6 mN (treated). Around the capsaicin-treated site, pain ratings were significantly enhanced in response to three pinprick stimulators (64 mN, 128 mN, 256 mN) and were reflected in the main effect of the repeated measures (RM-ANOVA, main effect; control $p = 0.2518$, treated $p = 0.0420$). Pain ratings also increased in the control site but only with the 512 mN probe (RM-ANOVA, 512 mN force; control $p = 0.0137$). The steepness of the regression lines was slightly increased in the

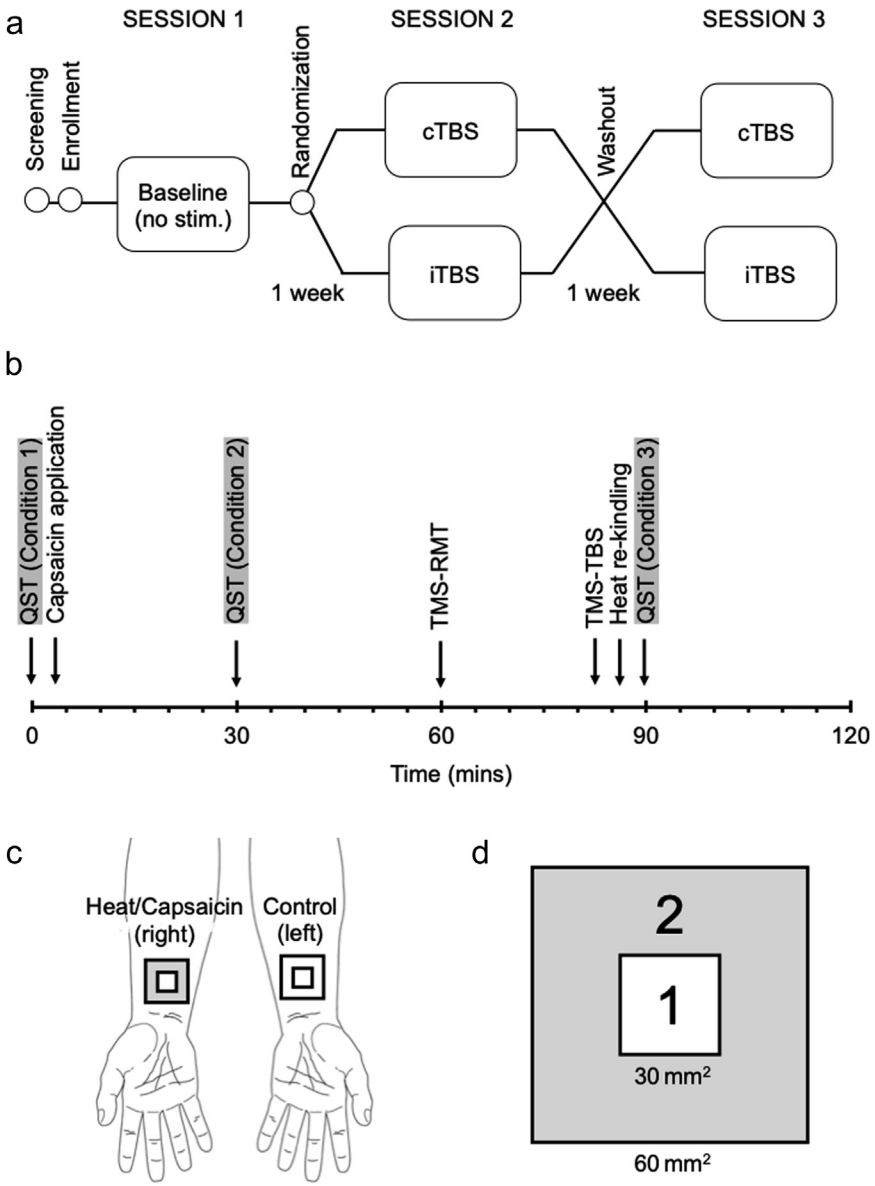

Figure 1. Experimental design. a. The study design was as a randomized within-subject crossover with respect to TBS stimulation. b. Timings of actions performed during the three sessions. QST was conducted under three experimental conditions: condition 1 (C1) (presensitization/pre-TBS), condition 2 (C2) (postsensitization/pre-TBS), and condition 3 (C3) (postsensitization/post-TBS). QST measurements were performed immediately after TBS administration and were less than the known duration of the TBS effects on cortical excitability. c. Central sensitization was induced by heat/capsaicin treatment to the right arm, with the left arm serving as the control. d. Test areas were the forearms with two squares drawn at symmetrical locations: an inner square matching the size of the contact thermode, and an outer square defined as the target area for mechanical punctate stimulation.

treated arm but not the control site [control, $r = 0.610/0.587$; treated, $r = 0.379/0.413$]. The individual effects of TBS on the magnitude of pain over the range of stimulating forces are shown in Figure 4, and the inferences from the observed changes in pain ratings to TBS are depicted in Figure 5.

Finally, to investigate the protocol-specific effects of TBS on secondary hyperalgesia, we directly contrasted the responses of iTBS and cTBS to baseline (no stimulation). The profiles used normalized changes relative to the individual's baseline assessed before any conditioning (Fig. 6). In the treated arm, changes in pain ratings were significantly higher after cTBS than in the other groups (one-way ANOVA: cTBS > iTBS $p = 0.0355$; cTBS > No Stim $p = 0.0283$; main effect; $p = 0.0482$). No significant differences were reported between the groups in the control arm (one-way ANOVA: main effect; $p = 0.8412$).

DISCUSSION

Neurogenic hyperalgesia, including enhanced pain perception to noxious pinprick stimuli (punctate mechanical hyperalgesia) and pain to non-noxious light tactile stimuli (dynamic mechanical allodynia), is a common sign of many clinical pain conditions. We replicated this phenomenon using a well-characterized experimental injury-free pain model and show that stimulation of the human motor cortex through two different TBS protocols induces

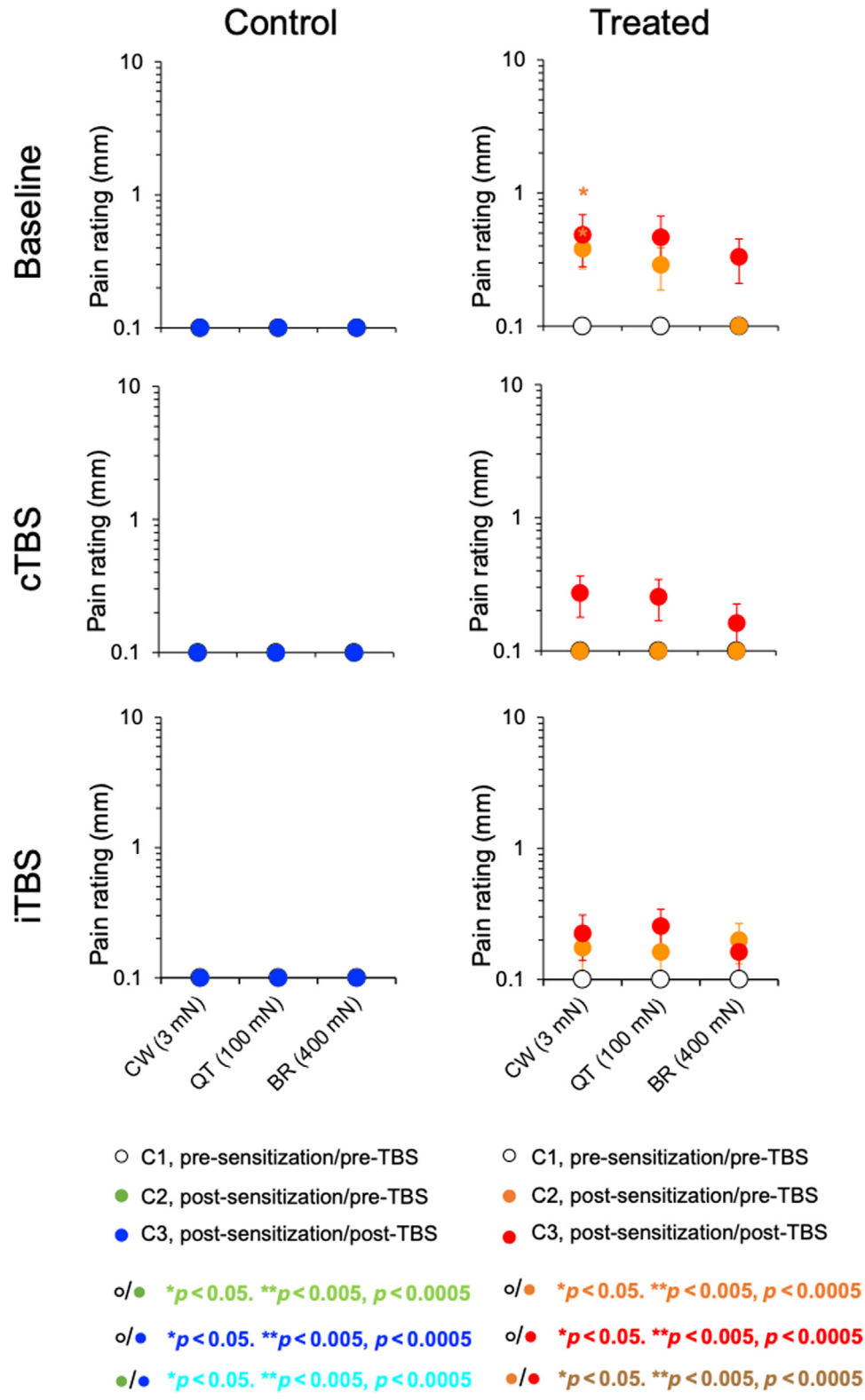

Figure 2. Secondary hyperalgesia to light touch (allodynia). QST to light touch in the heat/capsaicin-treated and control arm. At each of the three sessions, QST was conducted under three experimental conditions: condition 1 (C1), presensitization/pre-TBS; condition 2 (C2), postsensitization/pre-TBS; condition 3 (C3), postsensitization/post-TBS. Group comparisons were performed using Fisher's LSD test (*$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$). BR, soft brush; QT, Q-tip fixed to a plastic strip. [Color figure can be viewed at www.neuromodulationjournal.org]

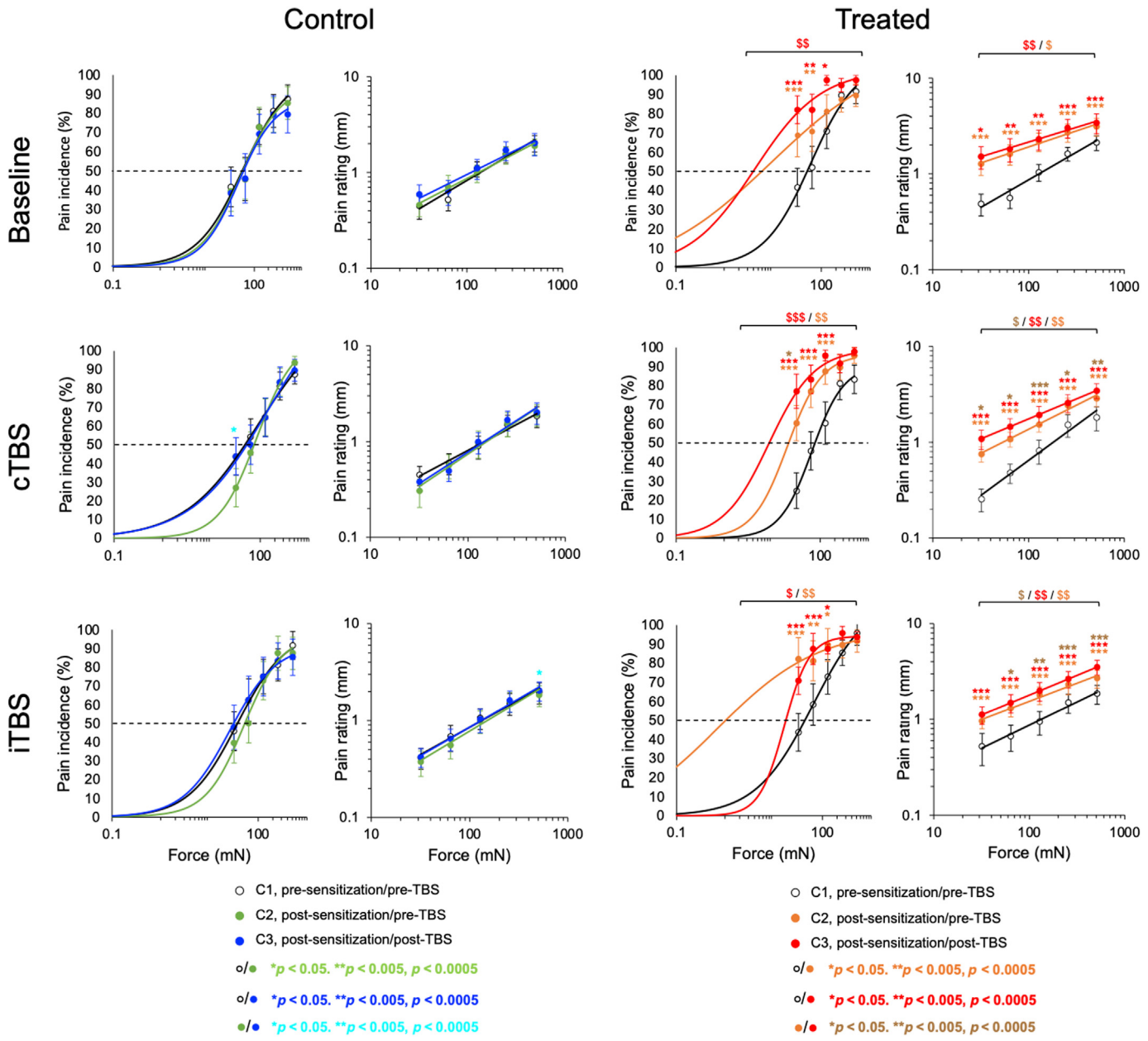

Figure 3. Secondary hyperalgesia to punctate mechanical stimuli. QST involving SRF to mechanical pinprick stimuli in the heat/capsaicin-treated and control arm. At each of the three sessions, QST was conducted under three experimental conditions: condition 1 (C1), presensitization/pre-TBS; condition 2 (C2), postsensitization/pre-TBS; condition 3 (C3), postsensitization/post-TBS. Group comparisons were performed using RM-ANOVA (*effect of individual probes: $^{*}p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0005$; $^{\$}$main effect: $^{\$}p < 0.05$, $^{\$\$}p < 0.005$, $^{\$\$\$}p < 0.0005$). All data adjusted for multiple comparisons using false discovery rate method of Benjamini-Hochberg. [Color figure can be viewed at www.neuromodulationjournal.org]

immediate changes in pain sensitivity to mechanical punctate stimuli delivered around the treated site (secondary hyperalgesia). In the following discussion, we consider the potential mechanisms underlying the effects on neuronal excitability and its potential relevance for the therapeutic effects of modulating central sensitization in patients with clinical hyperalgesia.

A major finding of this study is that cTBS of the human motor cortex facilitates secondary hyperalgesia to punctate mechanical stimuli. rTMS protocols of repeated low-frequency stimulation (ie, ~1 Hz) and cTBS have routinely shown LTD-like effects on cortical synapses,[40] although no study has ever tested this with respect to central sensitization. In general, conditioning stimuli like capsaicin that induce LTP at C-fiber synapses also cause hyperalgesia in humans.[6] Under this assumption, we hypothesized that reversing the established LTP may provide a method of stimulation-induced analgesia (hypoalgesia), which may be partially attributable to LTD. However, the intensification of secondary hyperalgesia suggests a different mechanism of action either by inhibiting LTD and/or facilitating LTP, or through modulation of cortical inhibition. The reason for this is unclear, but it has been shown that on occasion, a single TBS protocol can cause LTP in certain neurons, whereas it causes LTD in others.[41,42] In humans, the physiological effects of TBS also are highly variable, with inhibitory effects observed in some subjects and facilitatory effects observed in others.[43–45] At the behavioral level, this most

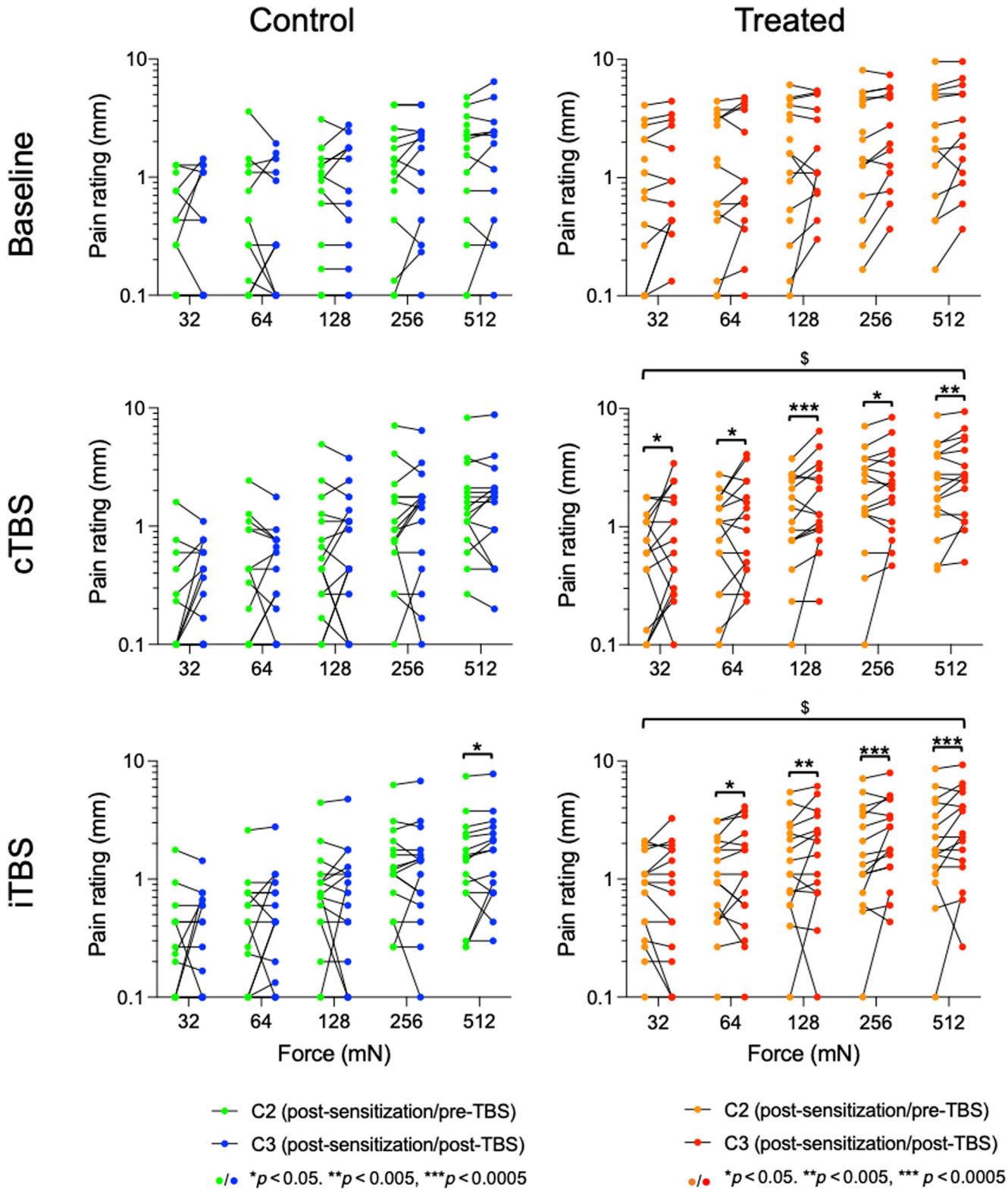

Figure 4. Individual responses to TBS during secondary hyperalgesia. The magnitude of individual responses to mechanical pinprick stimuli in the heat/capsaicin-treated and control arm. Comparisons between condition 2 (C2) (postsensitization/pre-TBS) and condition 3 (C3) (postsensitization/post-TBS) were performed using RM-ANOVA (*effect of individual probes: *$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$; $^{\$}$main effect: $^{\$}p < 0.05$, $^{\$\$}p < 0.005$, $^{\$\$\$}p < 0.0005$). All data adjusted for multiple comparisons using false discovery rate method of Benjamini-Hochberg. [Color figure can be viewed at www.neuromodulationjournal.org]

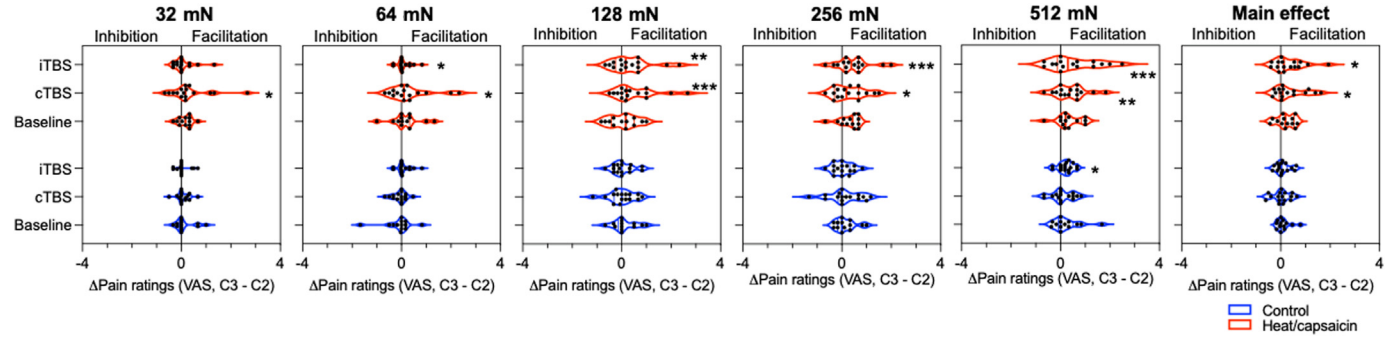

Figure 5. Excitatory and inhibitory responses to TBS. Neuromodulation was reflected as facilitatory (positive) or inhibitory (negative) changes in (Δ) (D) pain ratings between condition 2 (C2) (postsensitization/pre-TBS) and condition 3 (C3) (postsensitization/post-TBS). Zero line indicates no change to pinprick stimuli in treated (red) and control arm (blue). The black dots depict individual subjects' data. Comparisons were performed using RM-ANOVA (*main effect of punctate stimuli: *$p <$ 0.05, **$p < 0.005$, ***$p < 0.0005$). All data adjusted for multiple comparisons using false discovery rate method of Benjamini-Hochberg. [Color figure can be viewed at www.neuromodulationjournal.org]

likely relates to the different experimental conditions or parameters of stimulation and the methods used to evaluate TBS-induced plasticity.[46,47] However, therapeutic outcomes also are known to be highly variable from subject to subject, suggesting that for TMS to be effective in the treatment of chronic pain,[48] there needs to be better standardization.[26,49]

In the same individuals under identical experimental conditions, it appeared that iTBS had a similar facilitatory effect on the magnitude of perceived pain to secondary hyperalgesia. Although direct post hoc testing at the group level could not differentiate it from baseline (no stimulation). The mechanisms by which iTBS exerts its effects are not yet fully defined,[46] but there is strong evidence for inducing synaptic plasticity through LTP-like mechanisms that requires interaction with NMDA receptors.[50,51] The process of iTBS-induced plasticity and pain hypersensitivity likely share similar LTP-like signaling mechanisms, although direct modulation of central sensitization in the human nociceptive system could not be shown. LTP in the spinal cord is an fundamental mechanism underlying central sensitization,[5,15,52,53] with the induction of human secondary hyperalgesia after capsaicin believed to involve two primary afferent pathways: C-nociceptors for induction and Aδ-mechanonociceptors for signaling the state of pain amplification.[30,38] However, it is C-fiber nociceptors that are believed to be responsible for the largest contribution to induction of both homotopic and heterotopic LTP (secondary hyperalgesia).[39] Other dynamic changes in functional plasticity can occur over different temporal scales (acute to chronic) and on the molecular, synaptic, cellular, and network levels in pain processing.[7,54] For example, spinal dorsal horn neurons can be modulated by different levels of tonic and phasic inhibition, which is determined by γ-amino butyric acid (GABA)-ergic and glycinergic neurotransmission.[55,56] Interestingly, modulation of inhibition has been proposed as an alternative way to explain lasting changes in cortical excitability, with some animal data showing that iTBS interferes with distinct subgroups of inhibitory interneurons in the cortex.[57] Therefore, it is feasible that the effects in humans are mediated by changes in both glutamatergic and GABAergic signaling within local excitatory-inhibitory networks.[58] As such, we cannot exclude additional forms of activity-dependent plasticity as possible mechanisms of TBS-induced changes in pain perception.

There are several limitations and interesting questions raised by the present study that should be considered. Although it appears that TBS can influence central sensitization, it did not allow us to distinguish between the TBS protocols (iTBS and cTBS) or the functional classes of neurons affected by the stimulation. Future studies will need to dissect the relative contribution of different neurotransmitter systems and receptor subtypes to TBS effects and determine whether they also may induce adaptive or maladaptive plasticity relevant to pain hypersensitivity. Synaptic plasticity in the nociceptive system also may differ from the classical induction of plasticity in the human motor system.[34] For example, the extent to which stimulation of the motor cortex interferes with the activity in local and distributed neural circuits is complex[59,60] and unlikely to follow the exact same pattern of activity as other cortical areas. Studying TBS effects in animal models of chronic pain will be one way to further highlight the cellular mechanisms related to stimulation-induced changes in central sensitization. This also may

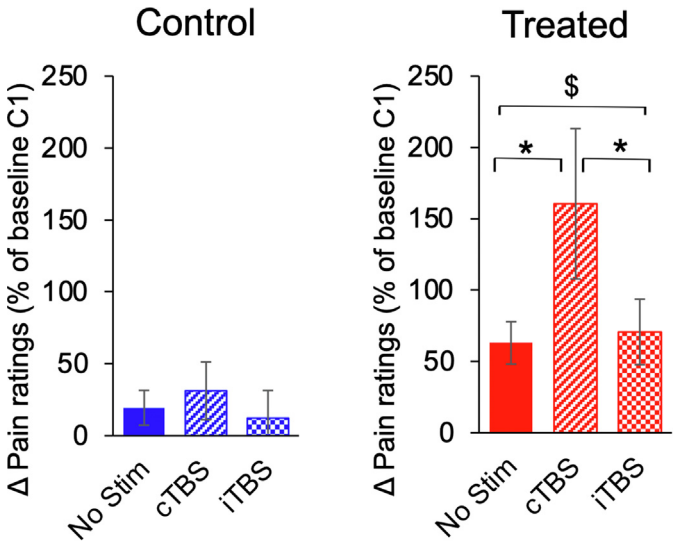

Figure 6. Protocol-specific effect of TBS on secondary hyperalgesia. Between-session comparisons of the TBS protocols across all forces of mechanical pinprick stimuli. Normalized data represent the percentage change in (Δ) (D) pain ratings between condition 2 (C2) (postsensitization/pre-TBS) and condition 3 (C3) (postsensitization/post-TBS) divided by condition 1 (C1) (presensitization/pre-TBS). Group-level comparisons were performed using one-way ANOVA (*effect of individual: variables: *$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$; $^{\$}$main effect: $^{\$}p < 0.05$, $^{\$\$}p < 0.005$, $^{\$\$\$}p < 0.0005$). No Stim, no stimulation. [Color figure can be viewed at www.neuromodulationjournal.org]

Table 1. Secondary Hyperalgesia to Light Touch.

Session	Force	Control						Treated					
		VAS (± SEM)			*p* Value (*t*-score)			VAS			*p* Value (*t*-score)		
		C1	C2	C3	C1 vs C2	C1 vs C3	C2 vs C3	C1	C2	C3	C1 vs C2	C1 vs C3	C2 vs C3
Baseline	3 mN (CW)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	–	–	–	0.00 (±0.00)	0.38 (±0.11)	0.48 (±0.21)	0.02 (2.52)	0.07 (1.97)	0.45 (0.77)
	100 mN (QT)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	–	–	–	0.00 (±0.00)	0.29 (±0.10)	0.47 (±0.21)	0.08 (1.86)	0.09 (1.87)	0.10 (1.77)
	400 mN (BR)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	–	–	–	0.00 (±0.00)	0.00 (±0.00)	0.33 (±0.12)	–	0.07 (1.99)	0.07 (1.99)
cTBS	3 mN (CW)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	–	–	–	0.00 (±0.00)	0.00 (±0.00)	0.27 (±0.09)	–	0.09 (1.84)	0.09 (1.84)
	100 mN (QT)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	–	–	–	0.00 (±0.00)	0.00 (±0.00)	0.26 (±0.09)	–	0.10 (1.78)	0.10 (1.78)
	400 mN (BR)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	–	–	–	0.00 (±0.00)	0.00 (±0.00)	0.16 (±0.06)	–	0.33 (1.00)	0.33 (1.00)
iTBS	3 mN (CW)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	–	–	–	0.00 (±0.00)	0.18 (±0.06)	0.23 (±0.09)	0.25 (1.19)	0.16 (1.46)	0.45 (0.77)
	100 mN (QT)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	–	–	–	0.00 (±0.00)	0.16 (±0.06)	0.26 (±0.09)	0.33 (1.00)	0.10 (1.78)	0.19 (1.38)
	400 mN (BR)	0.00 (±0.00)	0.00 (±0.00)	0.00 (±0.00)	–	–	–	0.00 (±0.00)	0.20 (±0.07)	0.16 (±0.06)	0.16 (1.48)	0.33 (1.00)	0.61 (0.52)

QST to light touch in the heat/capsaicin-treated and control arm. Participants across three sessions received the same QST measures under three experimental conditions: C1, presensitization/pre-TBS; C2, postsensitization/pre-TBS; C3, postsensitization/post-TBS. Group comparisons were performed using Fisher's LSD test. Dashes (–) represent no result owing to zero values (ie, no pain responses to the stimulus). BR, soft brush; QT, Q-tip fixed to a plastic strip, VAS, visual analog scale.

Table 2. Secondary Hyperalgesia to Punctate Mechanical Stimulation.

Session	Force	Control						Treated					
		VAS (± SEM)			*p* Value (*t*-score)			VAS (± SEM)			*p* Value (*t*-score)		
		C1	C2	C3	C1 vs C2	C1 vs C3	C2 vs C3	C1	C2	C3	C1 vs C2	C1 vs C3	C2 vs C3
Baseline	32 mN	0.45 (±0.12)	0.45 (±0.11)	0.59 (±0.15)	0.95 (0.06)	0.33 (1.02)	0.22 (1.29)	0.49 (±0.12)	1.27 (±0.31)	1.52 (±0.40)	<0.0001 (6.29)	0.0087 (2.71)	0.7353 (0.34)
	64 mN	0.52 (±0.12)	0.71 (±0.23)	0.64 (±0.19)	0.31 (1.05)	0.40 (0.88)	0.66 (0.46)	0.56 (±0.13)	1.62 (±0.38)	1.82 (±0.50)	<0.0001 (8.49)	0.0015 (3.34)	0.7357 (0.34)
	128 mN	1.09 (±0.20)	0.99 (±0.20)	1.11 (±0.26)	0.43 (0.82)	0.91 (0.12)	0.35 (0.97)	1.04 (±0.21)	2.18 (±0.48)	2.31 (±0.54)	<0.0001 (9.18)	0.0020 (3.23)	0.8788 (0.15)
	256 mN	1.55 (±0.29)	1.53 (±0.31)	1.70 (±0.38)	0.85 (0.20)	0.27 (1.16)	0.14 (1.57)	1.62 (±0.27)	2.71 (±0.58)	3.03 (±0.67)	<0.0001 (8.80)	0.0004 (3.75)	0.5742 (0.56)
	512 mN	2.03 (±0.40)	1.88 (±0.35)	2.02 (±0.52)	0.38 (0.91)	0.95 (0.06)	0.37 (0.93)	2.12 (±0.38)	3.13 (±0.66)	3.42 (±0.80)	<0.0001 (8.10)	0.0009 (3.51)	0.5403 (0.62)
	Main effect	1.13 (±0.13)	1.11 (±0.13)	1.21 (±0.16)	0.97 (0.35)	0.37 (1.91)	0.20 (2.46)	1.17 (±0.13)	2.18 (±0.23)	2.42 (±0.27)	0.0055 (10.51)	0.0035 (11.96)	0.6893 (0.17)
cTBS	32 mN	0.45 (±0.10)	0.31 (±0.10)	0.38 (±0.08)	0.13 (1.61)	0.45 (0.78)	0.26 (1.17)	0.26 (±0.07)	0.76 (±0.14)	1.08 (±0.25)	<0.0001 (4.76)	<0.0001 (6.99)	0.0134 (2.55)
	64mN	0.60 (±0.15)	0.57 (±0.16)	0.50 (±0.11)	0.59 (0.55)	0.12 (1.63)	0.31 (1.04)	0.48 (±0.11)	1.08 (±0.19)	1.40 (±0.31)	<0.0001 (5.69)	<0.0001 (7.80)	0.0140 (2.53)
	128 mN	0.90 (±0.24)	0.98 (±0.31)	0.99 (±0.25)	0.40 (0.86)	0.39 (0.89)	0.92 (0.10)	0.82 (±0.23)	1.55 (±0.27)	2.06 (±0.42)	<0.0001 (6.87)	<0.0001 (10.5)	0.0001 (4.09)
	256 mN	1.50 (±0.38)	1.57 (±0.44)	1.69 (±0.39)	0.69 (0.41)	0.31 (1.04)	0.48 (0.73)	1.53 (±0.41)	2.43 (±0.46)	2.72 (±0.55)	<0.0001 (8.53)	<0.0001 (10.1)	0.0281 (2.25)
	512 mN	1.85 (±0.46)	1.93 (±0.49)	2.02 (±0.52)	0.57 (0.59)	0.35 (0.97)	0.43 (0.81)	1.83 (±0.51)	2.89 (±0.55)	3.29 (±0.62)	<0.0001 (10.7)	<0.0001 (12.4)	0.0022 (3.19)
	Main effect	1.06 (±0.14)	1.07 (±0.16)	1.12 (±0.16)	0.98 (0.28)	0.61 (1.33)	0.65 (1.26)	0.98 (±0.15)	1.74 (±0.18)	2.11 (±0.22)	0.0006 (23.0)	0.0008 (17.4)	0.0297 (5.769)
iTBS	32 mN	0.41 (±0.10)	0.38 (±0.11)	0.42 (±0.09)	0.34 (0.94)	0.93 (0.09)	0.51 (0.68)	0.52 (±0.19)	0.96 (±0.17)	1.04 (±0.23)	<0.0001 (4.49)	<0.0001 (4.41)	0.4363 (0.78)
	64 mN	0.68 (±0.21)	0.56 (±0.15)	0.65 (±0.17)	0.06 (2.00)	0.68 (0.42)	0.22 (1.29)	0.67 (±0.20)	1.30. (±0.24)	1.53 (±0.33)	<0.0001 (6.46)	<0.0001 (7.26)	0.0339 (2.17)
	128mN	1.06 (±0.26)	1.00 (±0.26)	1.03 (±0.28)	0.54 (0.62)	0.74 (0.34)	0.72 (0.36)	0.95 (±0.26)	1.80 (±0.38)	2.16 (±0.44)	<0.0001 (8.70)	<0.0001 (10.2)	0.0011 (3.44)
	256mN	1.51 (±0.38)	1.59 (±0.37)	1.62 (±0.40)	0.50 (0.70)	0.45 (0.77)	0.76- (0.32)	1.50 (±0.34)	2.31 (±0.49)	2.77 (±0.51)	<0.0001 (8.21)	<0.0001 (10.7)	<0.0001 (4.42)
	512mN	1.97 (±0.49)	1.84 (±0.45)	2.04 (±0.46)	0.12 (1.64)	0.39 (0.89)	0.0137 (2.79)	1.86 (±0.41)	2.69 (±0.57)	3.25 (±0.63)	<0.0001 (8.49)	<0.0001 (11.8)	<0.0001 (5.39)
	Main effect	1.13 (±0.15)	1.07 (±0.14)	1.15 (±0.15)	0.25 (2.26)	0.84 (0.80)	0.10 (3.12)	1.10 (±0.14)	1.81 (±0.19)	2.15 (±0.22)	0.0030 (12.47)	0.0022 (13.59)	0.0420 (4.95)

QST involving SRF to mechanical pinprick stimuli in the heat/capsaicin-treated and control arm. Participants across three sessions received the same QST measures under three experimental conditions: C1, presensitization/pre-TBS; C2, postsensitization/pre-TBS; C3, postsensitization/post-TBS. Group comparisons were performed using RM-ANOVA with all data adjusted for multiple comparisons using false discovery rate method of Benjamini-Hochberg.

benefit other clinical methods of neuromodulation that at least partly may be attributable to plasticity in the spinal cord and supraspinal structures or both.[48,61]

Considering the facilitatory (pronociceptive) effects of cTBS, this finding is at odds with the recruitment of classical LTD-like mechanisms discussed in the literature and should receive further investigation. One possibility is that this is a nonspecific effect of TBS; therefore, testing with a sham-controlled stimulation may be useful for future comparisons. TBS was applied at a lower intensity (80% RMT), which is below the threshold for activating the excitatory inputs to pyramidal neurons.[62] This intensity differs from the 80% active motor threshold used in the original TBS paradigm assessing short-interval intracortical inhibition in the motor cortex.[32] We used RMT to more accurately reflect the resting state under which TBS was delivered; thus, the stimulation intensity required during voluntary motor activation may be comparatively higher in healthy subjects.[63] On the basis of this evidence, we cannot exclude the possibility that the modulating effects of TBS on secondary hyperalgesia may be mediated by changes in corticospinal and/or intracortical excitability.

Finally, the principle of metaplasticity[64–66] (higher-order plasticity) has been shown extensively in the human motor cortex for corticospinal excitatory synaptic neurotransmission[67–74] and accounts for considerable interindividual variation in the direction, magnitude, and duration of TBS responses.[43–45,75] Currently, very little is known concerning the extent to which it operates in other brain areas and ways it links to behavior such as pain hyperexcitability.[76] Given the interest in using TBS as a clinical tool to treat disorders such as chronic pain, which would benefit from the reliable and stable induction of plasticity conferred by LTP or LDP, it is important we understand how protocol parameters choices (such as pulse interval, duration, and frequency) and the nociceptive state interact and affect the outcome of stimulation.

CONCLUSIONS

In conclusion, we show cTBS modulates secondary hyperalgesia (a form of use-dependent central sensitization) that may rely on the induction and expression of neural plasticity through heterosynaptic potentiation of LTP-like mechanisms in the peripheral nociceptors, spinal cord, and supraspinal brain areas. This study provides a fundamental basis for understanding the principal mechanisms of TBS-driven synaptic plasticity in the nociceptive system and offers new methods for developing improved neuromodulation protocols that may be effective in reducing symptoms and disability in some people with chronic pain.

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Authorship Statements

Duncan J. Hodkinson, Marianne M. Drabek, JeYoung Jung, Sudheer T. Lankappa, and Dorothee P. Auer designed and conducted the study, including patient recruitment, data collection, and data analysis. Duncan J. Hodkinson prepared the manuscript draft with important intellectual input from Marianne M. Drabek, JeYoung Jung, Sudheer T. Lankappa, and Dorothee P. Auer. All authors approved the final manuscript.

Conflict of Interest

The authors reported no conflict of interest.

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REFERENCES

1. Bear MF, Malenka RC. Synaptic plasticity: LTP and LTD. *Curr Opin Neurobiol*. 1994;4:389–399.
2. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*. 1993;361:31–39.
3. Paulsen O, Sejnowski TJ. Natural patterns of activity and long-term synaptic plasticity. *Curr Opin Neurobiol*. 2000;10:172–179.
4. Sandkühler J. Understanding LTP in pain pathways. *Mol Pain*. 2007;3:9.
5. Sandkühler J. Learning and memory in pain pathways. *Pain*. 2000;88:113–118.
6. Sandkühler J. Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev*. 2009;89:707–758.
7. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science*. 2000;288:1765–1769.
8. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10:895–926.
9. Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends Neurosci*. 2003;26:696–705.
10. Sandkühler J. Central sensitization versus synaptic long-term potentiation (LTP): a critical comment. *J Pain*. 2010;11:798–800.
11. Ikeda H, Heinke B, Ruscheweyh R, Sandkühler J. Synaptic plasticity in spinal lamina I projection neurons that mediate hyperalgesia. *Science*. 2003;299:1237–1240.
12. Ikeda H, Stark J, Fischer H, et al. Synaptic amplifier of inflammatory pain in the spinal dorsal horn. *Science*. 2006;312:1659–1662.
13. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 Suppl):S2–S15.
14. Klein T, Magerl W, Rolke R, Treede RD. Human surrogate models of neuropathic pain. *Pain*. 2005;115:227–233.
15. Randić M, Jiang MC, Cerne R. Long-term potentiation and long-term depression of primary afferent neurotransmission in the rat spinal cord. *J Neurosci*. 1993;13:5228–5241.
16. Kronschläger MT, Drdla-Schutting R, Gassner M, Honsek SD, Teuchmann HL, Sandkühler J. Gliogenic LTP spreads widely in nociceptive pathways. *Science*. 2016;354:1144–1148.
17. Gousset S, Mouraux A, van den Broeke EN. Burst-like conditioning electrical stimulation is more efficacious than continuous stimulation for inducing secondary hyperalgesia in humans. *J Neurophysiol*. 2020;123:323–328.
18. Lefaucheur JP, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). *Clin Neurophysiol*. 2020;131:474–528.
19. Sacco P, Prior M, Poole H, Nurmikko T. Repetitive transcranial magnetic stimulation over primary motor vs non-motor cortical targets; effects on experimental hyperalgesia in healthy subjects. *BMC Neurol*. 2014;14:166.
20. Tamura Y, Okabe S, Ohnishi T, et al. Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin. *Pain*. 2004;107:107–115.
21. Larson J, Lynch G. Induction of synaptic potentiation in hippocampus by patterned stimulation involves two events. *Science*. 1986;232:985–988.
22. Larson J, Munkácsy E. Theta-burst LTP. *Brain Res*. 2015;1621:38–50.
23. Larson J, Wong D, Lynch G. Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. *Brain Res*. 1986;368:347–350.
24. Rose GM, Dunwiddie TV. Induction of hippocampal long-term potentiation using physiologically patterned stimulation. *Neurosci Lett*. 1986;69:244–248.
25. Hawes SL, Gillani F, Evans RC, Benkert EA, Blackwell KT. Sensitivity to theta-burst timing permits LTP in dorsal striatal adult brain slice. *J Neurophysiol*. 2013;110:2027–2036.
26. Cruccu G, Garcia-Larrea L, Hansson P, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. *Eur J Neurol*. 2016;23:1489–1499.

27. Hess G, Aizenman CD, Donoghue JP. Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex. *J Neurophysiol*. 1996;75:1765–1778.
28. Petersen KL, Rowbotham MC. A new human experimental pain model: the heat/capsaicin sensitization model. *Neuroreport*. 1999;10:1511–1516.
29. Magerl W, Wilk SH, Treede RD. Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. *Pain*. 1998;74:257–268.
30. Ziegler EA, Magerl W, Meyer RA, Treede RD. Secondary hyperalgesia to punctate mechanical stimuli. Central sensitization to A-fibre nociceptor input. *Brain*. 1999;122:2245–2257.
31. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971;9:97–113.
32. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005;45:201–206.
33. Nettekoven C, Volz LJ, Kutscha M, et al. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. *J Neurosci*. 2014;34:6849–6859.
34. Ziemann U, Paulus W, Nitsche MA, et al. Consensus: motor cortex plasticity protocols. *Brain Stimul*. 2008;1:164–182.
35. Rossini PM, Barker AT, Berardelli A, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol*. 1994;91:79–92.
36. Rothwell JC, Hallett M, Berardelli A, Eisen A, Rossini P, Paulus W. Magnetic stimulation: motor evoked potentials. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl*. 1999;52:97–103.
37. Nolano M, Simone DA, Wendelschafer-Crabb G, Johnson T, Hazen E, Kennedy WR. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. *Pain*. 1999;81:135–145.
38. Magerl W, Fuchs PN, Meyer RA, Treede RD. Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. *Brain*. 2001;124:1754–1764.
39. Henrich F, Magerl W, Klein T, Greffrath W, Treede RD. Capsaicin-sensitive C- and A-fibre nociceptors control long-term potentiation-like pain amplification in humans. *Brain*. 2015;138:2505–2520.
40. Huang YZ, Rothwell JC, Chen RS, Lu CS, Chuang WL. The theoretical model of theta burst form of repetitive transcranial magnetic stimulation. *Clin Neurophysiol*. 2011;122:1011–1018.
41. Hirsch JC, Crepel F. Use-dependent changes in synaptic efficacy in rat prefrontal neurons in vitro. *J Physiol*. 1990;427:31–49.
42. Shen KZ, Zhu ZT, Munhall A, Johnson SW. Synaptic plasticity in rat subthalamic nucleus induced by high-frequency stimulation. *Synapse*. 2003;50:314–319.
43. Hamada M, Murase N, Hasan A, Balaratnam M, Rothwell JC. The role of interneuron networks in driving human motor cortical plasticity. *Cereb Cortex*. 2013;23:1593–1605.
44. Hinder MR, Goss EL, Fujiyama H, et al. Inter- and Intra-individual variability following intermittent theta burst stimulation: implications for rehabilitation and recovery. *Brain Stimul*. 2014;7:365–371.
45. López-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-Del-Olmo M. Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain Stimul*. 2014;7:372–380.
46. Suppa A, Huang YZ, Funke K, et al. Ten years of theta burst stimulation in humans: established knowledge, unknowns and prospects. *Brain Stimul*. 2016;9:323–335.
47. Corp DT, Bereznicki HGK, Clark GM, et al. Large-scale analysis of interindividual variability in theta-burst stimulation data: results from the 'Big TMS Data Collaboration. *Brain Stimul*. 2020;13:1476–1488.
48. Knotkova H, Hamani C, Sivanesan E, et al. Neuromodulation for chronic pain. *Lancet*. 2021;397:2111–2124.
49. Cruccu G, Aziz TZ, Garcia-Larrea L, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol*. 2007;14:952–970.
50. Huang YZ, Chen RS, Rothwell JC, Wen HY. The after-effect of human theta burst stimulation is NMDA receptor dependent. *Clin Neurophysiol*. 2007;118:1028–1032.
51. Teo JT, Swayne OB, Rothwell JC. Further evidence for NMDA-dependence of the after-effects of human theta burst stimulation. *Clin Neurophysiol*. 2007;118:1649–1651.
52. Miletic G, Miletic V. Long-term changes in sciatic-evoked A-fiber dorsal horn field potentials accompany loose ligation of the sciatic nerve in rats. *Pain*. 2000;84:353–359.
53. Willis WD. Long-term potentiation in spinothalamic neurons. *Brain Res Brain Res Rev*. 2002;40:202–214.
54. Kuner R. Central mechanisms of pathological pain. *Nat Med*. 2010;16:1258–1266.
55. Derjean D, Bertrand S, Le Masson G, Landry M, Morisset V, Nagy F. Dynamic balance of metabotropic inputs causes dorsal horn neurons to switch functional states. *Nat Neurosci*. 2003;6:274–281.
56. Moore KA, Kohno T, Karchewski LA, Scholz J, Baba H, Woolf CJ. Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. *J Neurosci*. 2002;22:6724–6731.
57. Funke K, Benali A. Modulation of cortical inhibition by rTMS - findings obtained from animal models. *J Physiol*. 2011;589:4423–4435.
58. Stagg CJ, Wylezinska M, Matthews PM, et al. Neurochemical effects of theta burst stimulation as assessed by magnetic resonance spectroscopy. *J Neurophysiol*. 2009;101:2872–2877.
59. Hodkinson DJ, Bungert A, Bowtell R, Jackson SR, Jung J. Operculo-insular and anterior cingulate plasticity induced by transcranial magnetic stimulation in the human motor cortex: a dynamic casual modeling study. *J Neurophysiol*. 2021;125:1180–1190.
60. Hodkinson DJ, Jackson SR, Jung J. Task-dependent plasticity in distributed neural circuits after transcranial direct current stimulation of the human motor cortex: a proof-of-concept study. *Front Pain Res (Lausanne)*. 2022;3:1005634.
61. James ND, McMahon SB, Field-Fote EC, Bradbury EJ. Neuromodulation in the restoration of function after spinal cord injury. *Lancet Neurol*. 2018;17:905–917.
62. Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. *J Physiol*. 1996;496:873–881.
63. Goldsworthy MR, Pitcher JB, Ridding MC. The application of spaced theta burst protocols induces long-lasting neuroplastic changes in the human motor cortex. *Eur J Neurosci*. 2012;35:125–134.
64. Abbott LF, Nelson SB. Synaptic plasticity: taming the beast. *Nat Neurosci*. 2000;3(suppl):1178–1183.
65. Abraham WC. Metaplasticity: tuning synapses and networks for plasticity. *Nat Rev Neurosci*. 2008;9:387.
66. Karabanov A, Ziemann U, Hamada M, et al. Consensus paper: probing homeostatic plasticity of human cortex with non-invasive transcranial brain stimulation. *Brain Stimul*. 2015;8:993–1006.
67. Gamboa OL, Antal A, Laczo B, Moliadze V, Nitsche MA, Paulus W. Impact of repetitive theta burst stimulation on motor cortex excitability. *Brain Stimul*. 2011;4:145–151.
68. Hamada M, Terao Y, Hanajima R, et al. Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. *J Physiol*. 2008;586:3927–3947.
69. Iyer MB, Schleper N, Wassermann EM. Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. *J Neurosci*. 2003;23:10867–10872.
70. Lang N, Siebner HR, Ernst D, et al. Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. *Biol Psychiatry*. 2004;56:634–639.
71. Müller JF, Orekhov Y, Liu Y, Ziemann U. Homeostatic plasticity in human motor cortex demonstrated by two consecutive sessions of paired associative stimulation. *Eur J Neurosci*. 2007;25:3461–3468.
72. Siebner HR, Lang N, Rizzo V, et al. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *J Neurosci*. 2004;24:3379–3385.
73. Todd G, Flavel SC, Ridding MC. Priming theta-burst repetitive transcranial magnetic stimulation with low- and high-frequency stimulation. *Exp Brain Res*. 2009;195:307–315.
74. Ziemann U, Ilić TV, Pauli C, Meintzschel F, Ruge D. Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *J Neurosci*. 2004;24:1666–1672.
75. Vallence AM, Goldsworthy MR, Hodyl NA, Semmler JG, Pitcher JB, Ridding MC. Inter- and intra-subject variability of motor cortex plasticity following continuous theta-burst stimulation. *Neuroscience*. 2015;304:266–278.
76. Magerl W, Hansen N, Treede RD, Klein T. The human pain system exhibits higher-order plasticity (metaplasticity). *Neurobiol Learn Mem*. 2018;154:112–120.

COMMENTS

This is the first report that cTBS may modulate secondary allodynia and hyperalgesia after capsaicin-induced hypersensitivity. Thus, cTBS may induce LTP-like neuroplasticity.

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This is an interesting study investigating the effects of two forms of tetanic high-frequency, TBS on LTP in the spinal cord, which is a fundamental mechanism underlying central sensitization for persistence of pain. For both TBS protocols, the authors found that stimulation of the human motor cortex had a facilitatory effect on the magnitude of perceived pain to capsaicin-induced secondary hyperalgesia (a type of central sensitization), which relies on induction and expression of neural plasticity through heterosynaptic LTP-like mechanisms. The study provides a basis for improved understanding of the principal mechanisms of TBS-driven synaptic plasticity in the nociceptive system and offers new methods for developing improved neuromodulation protocols that may be effective in reducing symptoms and disability in chronic pain conditions.

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