American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 00, No 00 (), 2019: pp 1–11
Available online at www.jpain.org and www.sciencedirect.com

# Original Reports

## Sessions of Prolonged Continuous Theta Burst Stimulation or High-frequency 10 Hz Stimulation to Left Dorsolateral Prefrontal Cortex for 3 Days Decreased Pain Sensitivity by Modulation of the Efficacy of Conditioned Pain Modulation

Enrico De Martino,* Ana Mércia Fernandes,† Ricardo Galhardoni,†,‡,§ Carolina De Oliveira Souza,¶ Daniel Ciampi De Andrade,†,‡,‖ and Thomas Graven-Nielsen*,[a]

*Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark, †Pain Center, LIM-62, Department of Neurology, University of São Paulo, São Paulo, Brazil, ‡Service of Interdisciplinary Neuromodulation (SIN), Laboratory of Neuroscience (LIM27) and National Institute of Biomarkers in Neuropsychiatry (INBioN), Department and Institute of Psychiatry, University of São Paulo School of Medicine, São Paulo, Brazil, §School of Medicine, University of City of São Paulo (UNICID), São Paulo, Brazil, ¶Movement Disorders Clinic, Department of Neurology, Hospital das Clinicas of the University of São Paulo School of Medicine, São Paulo, Brazil, ‖Pain Center, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil

**Abstract:** **The 10 Hz repetitive transcranial magnetic stimulation (10 Hz-rTMS) to the left dorsolateral prefrontal cortex produces analgesia, probably by activating the pain modulation system. A newer rTMS paradigm, called theta burst stimulation (TBS), has been developed. Unlike 10 Hz-rTMS, prolonged continuous TBS (pcTBS) mimics endogenous theta rhythms, which can improve induction of synaptic long-term potentiation. Therefore, this study investigated whether pcTBS to the left dorsolateral prefrontal cortex reduced pain sensitivity more efficiently compared with 10 Hz-rTMS, the analgesic effects lasted beyond the stimulation period, and the reduced pain sensitivity was associated with increased efficacy of conditioned pain modulation (CPM) and/or intracortical excitability. Sixteen subjects participated in a randomized cross-over study with pcTBS and 10 Hz-rTMS. Pain thresholds to heat (HPT), cold, pressure (PPT), intracortical excitability assessment, and CPM with mechanical and heat supra-pain threshold test stimuli and the cold pressor test as conditioning were collected before (Baseline), 3 (Day3) and 4 days (Day4) after 3-day session of rTMS. HPTs and PPTs increased with 10 Hz-rTMS and pcTBS at Day3 and Day4 compared with Baseline ($P = .007$). Based on pooled data from pcTBS and 10 Hz-rTMS, the increased PPTs correlated with increased efficacy of CPM at Day3 ($P = .008$), while no correlations were found at Day4 or with the intracortical excitability.**

***Perspective:*** ***Preliminary results of this comparative study did not show stronger pain sensitivity reduction by pcTBS compared with 10 Hz-rTMS to the L-DPFC. Both protocols maintained increased pain thresholds up to 24-hours after the last session, which were partially associated with modulation of CPM efficacy but not with the intracortical excitability changes.***



***Key words:*** *Pain, repetitive transcranial magnetic stimulation, dorsolateral prefrontal cortex, conditioned pain modulation, intracortical excitability, diffuse noxious inhibitory control.*

Received January 29, 2019; Revised April 29, 2019; Accepted May 22, 2019.
[a]http://www.cnap.hst.aau.dk/~tgn
Conflict of interest: The authors have no conflicts of interest to declare.
Support to Center for Neuroplasticity and Pain (CNAP) is provided by the Danish National Research Foundation (DNRF121). R.G. is supported by São Paulo Research State Foundation (FAPESP 2017/03002-5).
Trial registration number: NCT03733015

Address reprint requests to Thomas Graven-Nielsen, DMSc, PhD, Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Fredrik Bajers Vej 7D-3, 9220 Aalborg E, Denmark. E-mail: tgn@hst.aau.dk

1526-5900/$36.00



https://doi.org/10.1016/j.jpain.2019.05.010

Noninvasive brain stimulation has received a lot of attention as a potential pain therapy.[1,2] For instance, 10 Hz repetitive transcranial magnetic stimulation (rTMS) applied to the left dorsolateral prefrontal cortex (L-DLPFC) decreased pain sensitivity in healthy subjects[3,4] and reduced experimental,[5,6,4] postoperative,[7–9] and chronic pain.[10–12] Although several studies demonstrated pain relief effects of daily 10 Hz L-DLPFC rTMS sessions in chronic[10–12] and in experimental pain,[5] no studies have proven whether the decreased pain sensitivity in healthy subjects could be maintained for several hours by repetitive sessions of rTMS, which may have a clinical relevance if one considers rTMS to be potentially useful before painful procedures.

Although still unclear, the mechanism underlying 10 Hz rTMS-induced analgesia may be mediated by the activation of descending pain control systems[6,4] or the neuro-modulatory effects on the intracortical excitability.[13] For instance, a recent study demonstrated an anatomical circuitry from the periaqueductal gray and the nucleus cuneiformis to the L-DLPFC,[14] and 10 Hz L-DLPFC rTMS increased the L-DLPFC activity and attenuated the brainstem and medulla responses to painful stimuli,[6] indicating that L-DLPFC rTMS may drive top down analgesia by modulating the descending nociceptive control pathways.[6] An alternative explanation can be the modulation on the intracortical excitability. Indeed, short intracortical inhibition (SICI) was reduced in chronic pain[15,16] and in healthy subjects during experimental pain.[13,17,18] Using 5 Hz L-DLPFC rTMS during experimental pain, SICI normalization and pain reduction have been shown,[13] indicating a possible intracortical modulatory action of L-DLPFC rTMS.

A newer paradigm of rTMS, called theta burst stimulation (TBS), has been recently developed,[19–21] which is much shorter than "classical" 10 Hz rTMS and appear to have stronger and more reproducible clinical and neuromodulatory effects.[20,22,23] The application of theta burst patterns of stimulation to induce synaptic long-term potentiation comes from the burst discharge at theta rhythms (ranges 4–7 Hz) described in hippocampus of animals during exploratory behavior.[23] In humans, continuous (cTBS) with 600 pulses have been demonstrated to induce long-term depression.[24,23] However, when cTBS is prolonged to 1,200 pulses (pcTBS), the cortical effect becomes facilitatory,[25] similar to what it has been described following intermittent TBS (iTBS). Although pcTBS and iTBS are both facilitatory paradigms, a stronger analgesic effect has been recently reported by pcTBS compared with the iTBS and 10 Hz rTMS to the primary motor cortex (M1).[22] In addition, in patients with treatment-resistant depression, a similar antidepressant effect between 10 Hz and iTBS to the LDPFC has been recently demonstrated.[26] To date, no studies have compared whether L-DLPFC pcTBS would reduce pain sensitivity more efficiently compared with the "classical" 10 Hz-LDPFC rTMS. Therefore, this study aimed to compare the analgesic effects of 3-day consecutive sessions of 2 rTMS protocols and investigated whether 1) L-DLPFC pcTBS produced stronger reduction in pain sensitivity compared with 10 Hz L-DLPFC rTMS, 2) the effects lasted beyond the last day of stimulation, and 3) the increase of pain thresholds were associated with changes in the descending pain control system and/or in the intracortical excitability.

# METHODS

## Participants

Based on a previous study showing the strongest analgesic effect of pcTBS compared with 10 Hz rTMS to the primary motor cortex (M1) on 13 healthy subjects,[22] 16 participants were recruited in this preliminary randomized cross-over study at Hospital das Clínicas (University of São Paulo, Brazil), between September and November 2018. The study was approved by the local Ethics Committee (54271916.8.0000.0068), registered at ClinicalTrials.gov (NCT03733015), and performed in accordance with the Helsinki Declaration. Written informed consent was obtained prior to study commencement. All participants were naÿve to TMS, and without any history of chronic pain or neuropsychiatric disorders. At the day of the recruitment, participants completed the following questionnaires 1) Pain Catastrophizing Scale,[27] 2) Beck Depression Inventory,[28] 3) Positive and Negative Affective Schedule,[29] and 4) insomnia questionnaire.[30] Also, participants filled out a screening questionnaire to screen for potential contraindications for rTMS.[31]

## Study Design

Participants were randomly assigned to 2 intervention sequences of four experimental sessions on consecutive days (Day1–Day4; Fig. 1). A researcher prepared the concealed allocation schedule by computer randomization of these 2 intervention sequences to a consecutive number series without any involvement on the data collection. Both participants and the investigator involved in the data collection were blind to intervention sequences. Sequence 1 consisted of active pcTBS + sham 10 Hz rTMS (7/16 participants) and Sequence 2 of sham pcTBS + active 10 Hz rTMS (9/16 participants). Participants received the opposite protocol with an interval of 16 ± 4 days (min 11 days, max 26 days).

Each experimental session at Day1 and Day3 began with cortical excitability assessment by TMS. After this, mechanical and thermal pain thresholds (PTs) were collected in a randomized order. Subsequently, mechanical and heat supra-pain threshold stimulations as test-stimuli (TS) were evaluated in a randomized order. Finally, the cold pressor test was used as conditioning stimulus, and mechanical and heat supra-pain threshold test stimuli, and mechanical pain thresholds were repeated in the randomized order as used before the conditioning stimulus. At Day4, PTs, TS, and conditioned TS were repeated.

## Pain Sensitivity

Pressure (PPT), cold (CPT), and heat pain thresholds (HPT) were recorded. The PPT was measured using a

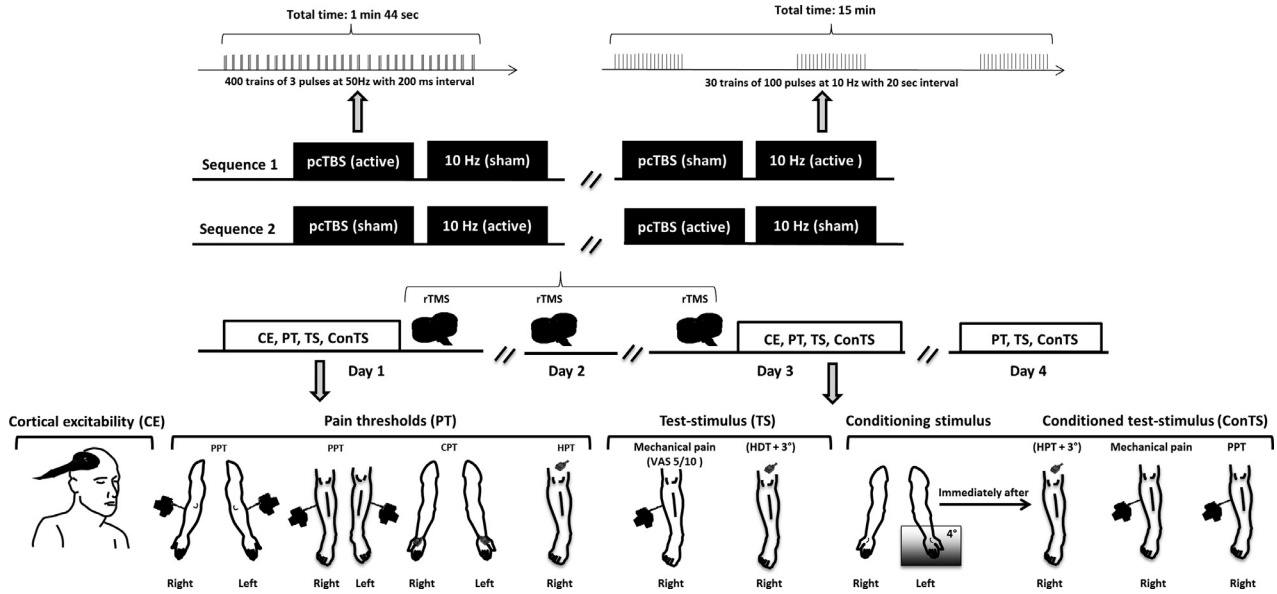


**Figure 1.** Three consecutive sessions of rTMS interventions (pcTBS and 10 Hz rTMS) to L-DLPFC were performed at Day1 (immediately after the measurements), Day2 and Day3 (before the measurements). CE was assessed at Day1 and Day3. Mechanical and thermal PT, TS, and ConTS were assessed on Day1, Day3, and Day4. Abbreviations: CE, cortical excitability; PT, pain thresholds; TS, Test-Stimulus; ConTS, conditioned pain stimuli.

handheld pressure algometer (1-cm$^2$ probe, Algometer type II, SBMEDIC Electronics, Solna, Sweden), applying pressure at a rate of 30 kPa/s perpendicular to the skin. The pain sensitivity to thermal stimuli was recorded using a Medoc (TSA II Neurosensory Analyzer, Ramat Yishai, Israel), using a standard thermode of $30 \times 30$ mm.[32] The PPT, CPT, and HPT were defined as the point where the stimulus perception changed to a perception of pain. The participants were instructed to press a button as soon as the stimulation became painful. The interval between each measure was 30 seconds and the mean of 3 successive measures were used for the analyses.

Four different sites were assessed for the PPT 1) Right extensor carpi radialis brevis (ECRB), 2) left ECRB, 3) right tibialis anterior (TA), and 4) left TA muscles.[33] The recordings were made at the right and left thenar eminences for the CPT, and over the right mid-thigh for HPT.[32] The mean value of PPT and CPT across different sites was used for the statistical analysis.

## Conditioned Pain Modulation

For the conditioned pain modulation (CPM), supra-pain threshold TS were collected before and immediately after the cold pressor test. Participants rated the pain intensity using a visual analogue scale (VAS, "no pain" = 0 to "worst imaginable pain" = 10 cm). The heat supra-pain threshold TS (HTS) was delivered for 5 seconds at 3° C above the HPT over the right mid-thigh. The pain intensity was scored on the VAS immediately after the HTS. The mechanical supra-pain threshold TS (MTS) was applied over the right TA muscle. The MTS intensity was estimated by applying increasing pressure (30 kPa/s) until the participants pressed a button as soon as the stimulation reached 5 cm on the VAS; subsequently this intensity was used as the MTS with a fast increase to the target intensity, applied for 5 seconds and rated on the VAS.

According to CPM recommendations,[34] participants immersed the left hand in a bucket of water and ice at 4° C for up to 60 seconds (cold pressor test). Immediately after they withdrew their hand, HTS and MTS were reassessed over the right thigh and TA muscle, respectively. In addition, 3 measures of PPT over the right TA were repeated. CPM was calculated as a relative difference to the TS before conditioning (eg, HTS during conditioning − HTS before conditioning). The mean value of VAS reduction across HTS and MTS was used for the statistical analysis.

## Cortical Excitability

Participants were comfortably seated and instructed to maintain their hand completely relaxed. Magnetic stimulation was applied (MagPro ×100, MagVenture A/S, Farum, Denmark) with a circular coil (MCF-125) to the left M1. Motor-evoked potentials (MEPs) were recorded using surface disposable recording electrodes (Kendall Electrode, Danlee Medical Products, NY) located on the right first dorsal interosseous muscle. MEP signals were filtered at 5 Hz to 1 kHz and sampled at 1 kHz (Neuro-MEP-Micro, 2-channel Ultraportable EMG, Ivanovo, Russia). The optimal cortical site (hotspot) was determined as the coil position that provoked a maximal peak-to-peak MEP for a given stimulation intensity. Seven measures were collected at the hotspot: Resting motor threshold (rMT), MEPs at 120%, MEPs at 140%, SICI at 2 and 4 milliseconds, and intracortical facilitation (ICF) at 10 and 15 milliseconds.[35]

The rMT was defined as the lowest intensity eliciting an MEPs of at least 50 $\mu$V in 50% of trials.[36] MEPs were recorded at 120% (MEP120) and 140% (MEP140) of the rMT at rest to evaluate the corticomotor excitability,[36]

and the stimulus-response gain (ratio of the amplitudes: MEP140/MEP120) was extracted.[35] Paired pulses were delivered randomly at 2, 4, 10, and 15 milliseconds inter-stimulus interval, with the intensity of the first stimulus set at 80% of the rMT and the intensity of the second stimulus at 120% of the rMT.[35,13,15,16] For each measurement, the results of 4 trials were averaged, and the changes in test MEP induced by conditioned stimuli (paired pulses) were expressed as a percentage of the unconditioned MEP amplitude at 120%.[37,35,16] The mean percentage inhibition with inter-stimulus interval 2 and 4 milliseconds and facilitation with the inter-stimulus interval 10 and 15 milliseconds were used for the statistical analysis.[22]

### Repetitive Transcranial magnetic Stimulation

rTMS was applied (MagPro ×100, MagVenture A/S, Farum, Denmark) with a double coil (MCF-B65 Butterfly Coil), with the main phase of the induced current in the anterior-posterior direction.[35,16,22] The coil was fixed to an arm, positioned over the L-DLPFC, according to the BeamF3 algorithm,[38,39] and stimulation intensity was set at 90% of the rMT of the FDI muscle.

pcTBS consisted of 3 pulses at 50 Hz repeated 400 times with inter-stimulus intervals of 200 milliseconds.[19,22] The total pulses of pcTBS were 1,200 delivered in 1 minute and 44 seconds. The 10 Hz rTMS consisted of 30 trains of 10 seconds with an interval of 20 seconds between trains.[7,40] Each train included 100 pulses and the total number of pulses was 3,000 given in 15 minutes.

Sham stimulation was performed with a sham coil of identical size, color and shape, emitting the same sound of the active coil.[35,16,22] In each stimulation session, participants received 2 sequential rTMS applications, one active and one sham stimulation (either sham-10 Hz rTMS or sham-pcTBS). Both types of stimulation were delivered sequentially one immediately after the other, so that participants received a total of 16 minutes 44 seconds (15 min + 1 min 44 s) of stimulation in each stimulation session. This design was chosen because both stimulation methods have durations that are too different and this could affect blinding if sham stimulation was not added to equalize the total amount of stimulation duration.

Because the rTMS procedure is known to be slightly painful,[41] pain ratings of the procedure was acquired at the end of the study, using a numerical rating scale for pain intensity, where 0 was no pain and 10 was most intense pain imaginable. Besides, blinding was assessed at the end of the study, by asking the participants whether they could guess the correct sequence of rTMS administered.

### Statistics

All data are presented as mean and standard deviations. Statistical significance was set at $P < .05$. All data were assessed for normality using visual inspection.

The effects of the 2 interventions on pain sensitivity, neurophysiological and CPM measures were assessed by 3-way mixed-model analysis of variance (ANOVA) with *Days* (Day1, Day3, and Day4) and *Interventions* (pcTBS and 10 Hz rTMS) as within subject factors and *Sequence* (Sequence-1 and Sequence-2) as a between subject factor. In case of significant differences, post hoc analyses were performed using Bonferroni to correct for multiple comparisons.

To investigate whether the cold pressor test produced a CPM effect and the paired-pulses produced an SICI and ICF, a 3-way mixed-model ANOVA with *Days* (Day1, Day3 and Day4), *Condition* (unconditioned and conditioned stimulus), and *Interventions* (pcTBS and 10 Hz rMT) as within subject factors and *Sequence* (Sequence-1 and Sequence-2) as between subjects were performed on TS and PPT, as well as single pulses MEPs and paired-pulses MEP (SICI and ICF).

Association between changes in pain thresholds (HPT, CPT, and PPT), the intracortical excitability (SICI and ICF) and CPM (supra-pain threshold TS and PPTs) were explored as the differences at Day3 and Day4 (only CPM), relative to Day1 using Pearson correlations. Whether changes in pain thresholds were stable from Day3 to Day4 were investigated as the differences from Day1 to Day3 and Day4, respectively, which were correlated using Pearson correlation. To compensate for multiple correlations, the *P*-value was Bonferroni corrected.

## RESULTS

The morphology and questionnaires are shown in Table 1 and they were within the normal ranges.[28,30,27,29] All participants performed all sessions and no data were missing.

### Pain Sensitivity

A main effect of Days was found for the PPT (Table 2; $F_{2,28} = 24.69$; $P < .001$), CPT ($F_{2,28} = 5.86$, $P = .008$), and HPT ($F_{2,23.9} = 7.54$, $P = .007$). Post hoc testing demonstrated increased PPTs and HPTs at Day3 (increased by 39.1 ± 46.1 kPa and 1.3 ± 1.6 °C; $P < .016$) and at Day4 (71.7 ± 41.7 kPa and 1.5 ± 2.2 °C; $P < .039$) compared with Day1. A tendency toward decreased CPT was found at Day3 (−1.5 ± 2.1 °C; $P = .059$) and at Day4 (−1.9 ± 2.6 °C; $P = .060$) compared with Day1. No significant main effects or interactions of Intervention and Sequence were found for the PPT, HPT, and CPT, indicating

**Table 1. Participant Characteristics**

| | |
|---|---|
| Sample size (females) | 16 (9) |
| Age (y) | 30.9 ± 8.8 |
| Height (cm) | 168 ± 7.2 |
| Weight (kg) | 72 ± 17.1 |
| BDI-II | 4.6 ± 5.7 |
| PCS | 2.3 ± 3.8 |
| PANAS-negative | 14.7 ± 4.6 |
| PANAS-positive | 40.1 ± 7.5 |
| Insomnia questionnaire | 6.3 ± 5.4 |

**Table 2. Mean (±SD, N = 16) PPTs on ECRB and TA muscles, CPT on right and left hand, and HPT on the right thigh recorded before (Day1) and after (Day3, Day4) rTMS protocols (10 Hz and pcTBS) to the L-DLPFC. Significantly increased compared with Day1 within the group (*, $P < .05$)**

| Modality | Site | Intervention | Day1 | Day3 | Day4 |
|---|---|---|---|---|---|
| PPT (kPa) | Right ECRB | 10 Hz | 256.3 ± 59.2 | 315.6 ± 67.7* | 324.9 ± 63.3* |
| | | pcTBS | 251.2 ± 42.5 | 302.5 ± 78.7* | 334.5 ± 75.9* |
| | Left ECRB | 10 Hz | 278.6 ± 83.6 | 304.6 ± 63.1* | 315.3 ± 65.6* |
| | | pcTBS | 257.2 ± 52.0 | 305.4 ± 86.2* | 331.9 ± 93.3* |
| | Right TA | 10 Hz | 564.8 ± 162.2 | 569.5 ± 177.9* | 628.2 ± 173.5* |
| | | pcTBS | 520.1 ± 176.4 | 559.5 ± 191.6* | 636.4 ± 170.5* |
| | Left TA | 10 Hz | 507.4 ± 167.2 | 537.2 ± 135.9* | 551.9 ± 199.9* |
| | | pcTBS | 474.4 ± 131.0 | 528.7 ± 148.9* | 560.3 ± 139.1* |
| CPT (°C) | Right hand | 10 Hz | 12.9 ± 5.7 | 11.1 ± 5.0 | 11.7 ± 5.1 |
| | | pcTBS | 11.9 ± 4.8 | 11.2 ± 5.7 | 10.3 ± 4.9 |
| | Left hand | 10 Hz | 14.0 ± 6.1 | 12.5 ± 5.3 | 12.2 ± 4.4 |
| | | pcTBS | 15.8 ± 3.5 | 14.0 ± 4.0 | 12.9 ± 5.1 |
| HPT (°C) | Right thigh | 10 Hz | 44.5 ± 2.9 | 45.4 ± 2.4* | 46.1 ± 1.7* |
| | | pcTBS | 45.1 ± 2.3 | 46.4 ± 1.5* | 46.2 ± 1.4* |

that both protocols produced similar decrease in pain sensitivity.

## CPM

Three-ways mixed-model ANOVA did not show any statistical changes in perceived pain intensity for HTS and MTS across Day, Intervention, or Sequence. Similarly, the conditioned painful stimuli were not significantly modified by the 2 interventions (Table 3). The conditioning stimulation led to a decrease in pain VAS scores of 1.0 ± 1.7 cm for the HTS ($F_{1,14} = 17.96$; $P < .001$), 1.6 ± 1.8 cm for the MTS, and an increase of 98.8 ± 110.4 kPa for the PPT ($F_{1,14} = 46.87$; $P < .001$) across all days. No statistical changes across Day, Intervention, or Sequence were found (Table 4).

## Cortical Excitability

All raw data are reported in Table 5 and there were no significant ANOVA factors or interactions across Day, Intervention, or Sequence. The paired pulses led to a modulation of the single pulse MEP ($F_{2,28} = 37.73$; $P < .001$). Indeed, the average 2 and 4 milliseconds inter-stimulus interval (SICI) produced an MEP inhibition of 57.9 ± 22.6% ($P < .001$) compared with MEP at 120% rMT. In contrast, average 10 and 15 milliseconds inter-stimulus interval (ICF) produced an MEP increase of 48.3 ± 73.4% ($P = .008$) compared with the single pulse MEP at 120%. A Day*Intervention interaction was found in the SICI at 2 milliseconds interval ($F_{1,14} = 6.65$, $P = .022$), but post hoc testing did not show any statistical difference (all $P > .15$).

## Associations Between Pain Sensitivity, Intracortical Excitability, and CPM

Since no group effect was found for the 2 rTMS protocols the data were pooled for the correlations. No significant association were revealed between the relative differences (Day1−Day3) of HPT, CPT, and PPT with SICI, ICF (Pearson $r > -.287$; $P = 1$).

A significant association between the differences (Day1−Day3) of PPT with supra-pain thresholds CPM (average of MTS and HTS CPM; Pearson $r = -.578$; $P = .008$; Fig. 2), but not with PPT CPM (Pearson $r = -.215$; $P = .713$). No statistical correlations were found between CPT or HPT with supra-pain thresholds

**Table 3. Mean (±SD, N = 16). HTS and MTS before and after the cold pressor test. Recorded before (Day1) and after (Day3, Day4) rTMS protocols (10 Hz and pcTBS) to the L-DLPFC**

| Test Stimuli | Intervention | Condition | Time | | |
|---|---|---|---|---|---|
| | | | Day 1 | Day 3 | Day 4 |
| HTS VAS | 10 Hz | Test-stimulus | 6.4 ± 2.1 | 5.5 ± 2.1 | 6.3 ± 2.0 |
| | | Conditioned test-stimulus | 5.4 ± 2.4 | 4.7 ± 2.3 | 5.1 ± 2.5 |
| | pcTBS | Test-stimulus | 6.4 ± 2.2 | 7.0 ± 2.5 | 6.2 ± 2.3 |
| | | Conditioned test-stimulus | 5.7 ± 2.8 | 5.4 ± 2.8 | 5.4 ± 2.8 |
| MTS VAS | 10 Hz | Test-stimulus | 5.0 ± 0.0 | 5.0 ± 0.0 | 5.0 ± 0.0 |
| | | Conditioned test-stimulus | 3.5 ± 1.9 | 3.1 ± 1.9 | 3.3 ± 1.7 |
| | pcTBS | Test-stimulus | 5.0 ± 0.0 | 5.0 ± 0.0 | 5.0 ± 0.0 |
| | | Conditioned test-stimulus | 3.7 ± 1.8 | 3.6 ± 1.7 | 3.2 ± 1.8 |

**Table 4. Mean (±SD, N = 16). CPM effects (conditioned test-stimulus − unconditioned test-stimulus) of HTS, MTS, and PPTs. Recorded before (Day1) and after (Day3 and Day4) repeated TMS protocols (10 Hz, and pcTBS) on the L-DLPFC**

| CPM | Intervention | Day 1 | Day 3 | Day 4 |
|---|---|---|---|---|
| HTS VAS (cm) | 10 Hz | −1.2 ± 1.2 | −.9 ± 1.6 | −1.1 ± 1.4 |
| | pcTBS | −.7 ± 1.6 | −1.5 ± 2.3 | −.8 ± 2.1 |
| MTS VAS (cm) | 10 Hz | −1.5 ± 1.9 | −1.9 ± 1.9 | −1.7 ± 1.7 |
| | pcTBS | −1.3 ± 1.8 | −1.5 ± 1.7 | −1.8 ± 1.8 |
| PPTs (kPa) | 10 Hz | 105.8 ± 96.5 | 108.6 ± 94.0 | 73.5 ± 153.7 |
| | pcTBS | 118.4 ± 101.9 | 121.5 ± 113.0 | 64.2 ± 96.6 |

CPM (average of MTS and HTS CPM) or PPT CPM (Pearson r < −.349; $P > .585$). No statistical changes were found between the differences (Day1−Day4) of PPT, CPT, or HPT with supra-pain thresholds CPM or PPTs CPM (Pearson r < −.438; $P > .121$).

### Maintained Reduced Pain Sensitivity at Day4

A correlation between the difference relative to Day1 at Day3 and at Day4 were found for the PPT (Pearson r = .64, $P < .001$), CPT (Pearson r = .62, $P < .001$), and HPT (Pearson r = .75, $P < .001$), indicating the analgesic effect was steadily maintained up to 24 hours (Fig. 3).

### Adverse Effects and Blinding

No adverse effects occurred in the study. The mean pain VAS during the stimulations was .8 ± 1.3 cm. Only one volunteer was able to identify the correct sequence of the stimulation administered.

## DISCUSSION

The present study assessed, for the first time, the temporal profile and nature of the reduced pain sensitivity of 2 different patterns of multiple sessions of rTMS to the same cortical target in healthy subjects. Opposite to the first hypothesis, the 10 Hz-rTMS and the pcTBS to the L-DLPFC produced a similar increase of the pain thresholds. Besides, the pain threshold modulation induced by rTMS lasted up to 24 hours after the last stimulation. Finally, a correlation between the changes in PPT and CPM was found at Day3, indicating that both pain modulations could be a consequence of the short-lasting effect of repeated magnetic stimulation to the L-DLPFC.

### Temporal Profile of Increased Pain Thresholds

Recently, L-DLPFC iTBS has been successfully tested in major depression[26] and approved by the Food and Drug Administration for patients with medication-resistant depression. In pain research, no studies have investigated the effect of L-DLPFC pcTBS on pain thresholds or during experimental and chronic pain. The results of the present study indicate that L-DLPFC pcTBS did not show any stronger analgesic effect compared with 10 Hz L-DLPFC rTMS. Previously, Moisset et al reported a CPT decrease of ∼3 °C after pcTBS to the M1,[22] while in the current study, L-DLPFC pcTBS and L-DLPFC 10 Hz-rTMS showed a CPT decrease of ∼1.5 °C. Besides, a CPT decrease from 2 to 3 °C has been reported in response to 10 Hz-rTMS to right DLPFC[37,35] and M1,[37,35,22,42] indicating a less effective effect of L-DLPFC stimulation compared with M1,[37,35,22,42] and slightly lower effect compared with the right DLPCF.[37,35] However, since the HPT and PPT have not evaluated in these previous studies, it is impossible to know whether this stronger analgesic effect is specific to CPT or generalized to all pain sensation. Indeed, Nahmias et al reported that neither 10 Hz-rTMS to M1 or right DLPFC modified the HPT,[42] while Taylor et al showed a HPT increase of 1 to 2 °C after 10 Hz L-DLPFC rTMS[4] as the present study. Globally, these studies indicate that CPT and HPT are differently affected by rTMS to M1, right or left DLPFC,[42,6,4] probably because diverse brain regions or mechanisms are involved in different types of pain.[43]

Experimental[5] and chronic pain studies[44,16,45] showed that the peak of analgesic effect induced by rTMS required few days after the beginning of the treatment (3−5 d), and can last few days after the last rTMS sessions (3 d−2 wk),[44,16,45,12] suggesting a cumulative analgesic effect of rTMS. In healthy subjects, previous studies reported that a single session of 10 Hz L-DLPFC rTMS increased the HPT of around 1 to 2 °C up to 1 hour.[3,4] The results of the present study expanded on this knowledge by demonstrating that the increase of pain thresholds lasted at least up to 24 hours after the last session. Importantly, a similar effect on pain thresholds after both stimulations was found, though the number of pulses was different. However, previous studies showed that increasing or reducing the number of TBS pulses does not extend the excitatory effects and might produce an opposite effect.[19,20] Future studies are needed to evaluate whether 1) repeated L-DLPFC rTMS sessions produce an increase of pain thresholds longer than 24 hours, 2) repeated daily sessions of pcTBS before a clinical painful procedure can reduce the pharmacological-controlled analgesia in the following days[9] and may prevent the development of chronic pain following acute injury or surgery. In fact, high pain intensity in the early stage of acute pain appears to be one of the strongest predictors of chronic pain development.[46,47] Therefore, interventions like left DLPFC rTMS, able to increase pain thresholds with minimal side

**Table 5. Mean (±SD, N = 16) cortical excitability parameters before (Day1) and after (Day3) rTMS on the L-DLPFC with either pcTBS or 10 Hz rTMS (10 Hz)**

| rTMS | Days | rMT (% MSO) | MEP 120% (mV) | MEP 140% (mV) | MEP Ratio (140/120%) | MEP 2 ms Interval (mV) | MEP 4 ms Interval (mV) | MEP 10 ms Interval (mV) | MEP 15 ms Interval (mV) |
|---|---|---|---|---|---|---|---|---|---|
| 10 Hz | Day 1 | 43.8 ± 8.1 | 1.7 ± 1.1 | 3.1 ± 1.6 | 1.9 ± 0.6 | 0.4 ± 0.3 | 0.7 ± 0.6 | 2.2 ± 1.7 | 2.3 ± 1.4 |
| | Day 3 | 42.9 ± 7.1 | 1.5 ± 0.9 | 2.8 ± 1.8 | 1.9 ± 0.8 | 0.5 ± 0.5 | 0.7 ± 0.8 | 1.8 ± 1.2 | 2.1 ± 1.3 |
| pcTBS | Day 1 | 42.7 ± 6.7 | 1.4 ± 0.9 | 3.1 ± 2.1 | 2.2 ± 1.1 | 0.5 ± 0.5 | 0.9 ± 0.7 | 2.2 ± 1.4 | 2.2 ± 1.1 |
| | Day 3 | 43.3 ± 7.8 | 1.7 ± 1.0 | 3.2 ± 2.1 | 1.9 ± 0.6 | 0.6 ± 0.5 | 1.0 ± 8.8 | 2.3 ± 1.7 | 2.1 ± 1.4 |

Abbreviations: MSO: maximum stimulator output.

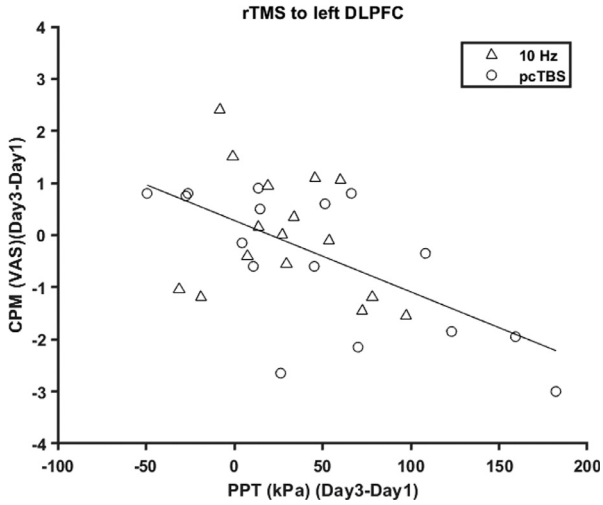


**Figure 2.** Correlations between changes in PPT and CPM (mean value of VAS reduction across heat and pressure test stimuli) at Day3. Data expressed as the difference relative to Day1. The triangle represents the 10 Hz stimulation and the circle the prolonged continuous theta burst stimulation (pcTBS). Abbreviations: PPT, pressure pain thresholds; CPM, conditioning pain modulation; VAS, visual analogue scale.

effects, may have the potential future clinical application of reducing pain sensitivity. Finally, the main practical advantage of TBS is the shorter stimulation time (below 2 min) and fewer number of pulses (1,200) compared with the "classical" 10 Hz-rTMS (1,500–4,000 pulses in 15–20min).[22,4]

## *Descending Pain Modulation System*

Neuroimaging studies reported that 10 Hz L-DLPFC rTMS induced local cortical activity changes, but also in distant brain regions, such as the medulla and the brainstem.[48,49,6] Naloxone pretreatment abolished the medulla and the brainstem response induced by 10 Hz L-DLPFC rTMS, as well as the analgesic effect, suggesting that L-DLPFC stimulation drive a top-down opioidergic analgesia thought the diffuse inhibitory pain system.[6] To test this hypothesis, CPM was systematically measured before and after 3-day sessions L-DLPFC rTMS. The results of the current study did not show any facilitation of the CPM, however a correlation between the increase in PPT and the increase in CPM was found, suggesting that both adaptations could be a consequence of a common driving factor. Similar to the current study, previous studies investigated whether a single session of 10 Hz-rTMS and pcTBS to M1 and right DLPCF were able to modulate the CPM, but no correlation between the changes in CPT and the changes in CPM was found.[22,42] A possible explanation of the different findings may be the cortical target. Indeed, M1 and right DLPFC 10 Hz-rTMS may induce analgesic effect by means of different brain mechanisms.[50,51] However, based on PPT measures, previous studies showed that transcranial direct current stimulation to M1 potentiated CPM in healthy subjects,[52,53] indicating that M1 stimulation may modulate the pain descending modulatory systems. It is interesting to note that only the PPT changes from Day1

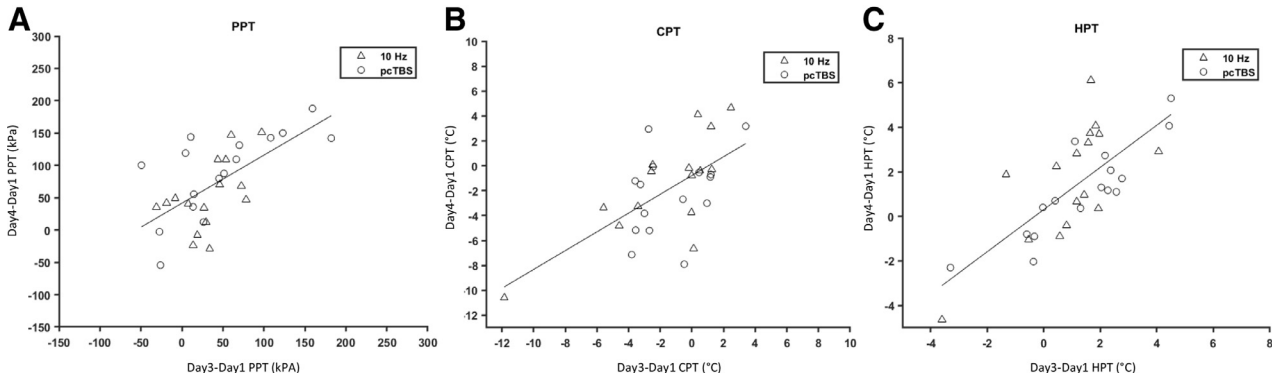


**Figure 3.** Correlations between changes in pain thresholds at Day3 and Day4 (data expressed as the difference relative to Day 1). Effects on pressure (A, PPT), cold (B, CPT), and heat (C, HPT) pain thresholds are illustrated. The triangle represents the 10 Hz stimulation and the circle the pcTBS. Abbreviations: pcTBS, prolonged continuous theta burst stimulation.

were associated with CPM in the current study, while the thermal pain threshold changes did not correlate with CPM as shown in previous studies.[22,42] This may suggest that descending modulation could act differently on diverse pain stimulations.[42] An alternative explanation may be the number of rTMS sessions. Indeed, when multiple sessions of rTMS are delivered, cumulative neuroplastic and therapeutic effects have been demonstrated,[54–56,20] indicating long-lasting and more robust effects induced by multiple daily sessions of rTMS compared with a single session. Finally, no correlation was found between PPTs and CPM at Day 4, suggesting a short-lasting effect of the neuromodulation of the descending pain modulation system.

### *Intracortical Excitability*

Similar to previous studies applying 10 Hz-rTMS to right DLPFC[35] and M1[22], SICI was not influenced by either L-DLPFC rTMS protocols in the current study. Reduced SICI have been described in several chronic pain condition, such as neuropathic[57,15,58,59] and musculoskeletal pain.[60,61] Besides, when prolonged experimental pain was applied in healthy subjects, reduced SICI has been also demonstrated.[13,17] Chronic pain studies demonstrated that several sessions of 10 Hz-rTMS to M1 produced pain relief[44,16,45] and normalized the SICI.[57,15,16] In line with these clinical findings, applying topical capsaicin in healthy subjects, 5Hz L-DLPFC rTMS reduced the pain intensity and normalized the SICI.[13] Yet, in the chronic[15,16] and experimental pain studies,[13] the changes observed after the rTMS treatment showed a normalization of the reduced SICI, suggesting that rTMS modulation of SICI may depend upon the presence of baseline continuous pain and subsequent altered cortical excitability to occur. Indeed, others have also reported lack of effect of rTMS on cortical excitability parameters, despite significant analgesic effects on pain thresholds.[35,22,42]

### *Limitations*

There are some notable limitations to the current study. First, a sham group has not been included in this study, since the aims were to investigate the pain sensitivity difference between the 2 active protocols and the association between the analgesic effect and the intracortical excitability or CPM, rather than the efficacy of rTMS versus sham rTMS in healthy subjects. Several previous studies showed that 10 Hz L-DLPFC rTMS produced analgesic effects in healthy subjects and in patients compared with a sham stimulation.[7,10,9,11,12,6,4] Importantly, the changes in HPT in the current study are similar to those described in previous active 10 Hz L-DLPFC rTMS groups,[3,4] but the effect on CPT are lower compared with M1 and right DLPCF stimulations, indicating an unlikely placebo effect.

Several complementary mechanisms associated with pain relief by rTMS have not been investigated in the current study. In fact, 10 Hz L-DLPFC rTMS provokes secondary changes in several brain areas, such as orbitofrontal cortex, the insula and the anterior cingulate cortex.[48,49] All these areas are implicated, for instance, in reward, emotion, sympathetic and parasympathetic activity and, consequently, in the regulation of pain perception. Further specific studies are needed to determine these changes in adjacent cortical areas.

A third limitation in the current study is the TBS protocol selected. Recent studies have reported excellent effects with 30 Hz (rather than 50 Hz) bursts repeated at 10 Hz (rather than 5 Hz).[62,63]

Finally, the study has not been performed in patients where additional factors play a crucial role in pain sensitivity, such as stress, anxiety, and medical expectations.[64]

## Conclusions

Preliminary results of this comparative study showed that the increase of the pain thresholds after 3-day sessions of pcTBS and 10 Hz-rTMS to the L-DLPFC were similar for both protocols, lasted at least up to 24 hours after the last rTMS session, and were correlated with modulation of the CPM efficacy at Day3. Thus, the less extensive pcTBS protocol may be attractive for future studies clarifying its clinical potential.

## Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2019.05.010.

## References

1. Galhardoni R, Correia GS, Araujo H, Yeng LT, Fernandes DT, Kaziyama HH, Marcolin MA, Bouhassira D, Teixeira MJ, De Andrade DC: Repetitive transcranial magnetic stimulation in chronic pain: A review of the literature. Arch Phys Med Rehabil 96:S156-S172, 2015

2. Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipović SR, Hummel FC, Jääskeläinen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schönfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L: Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 125:2150-2206, 2014

3. Borckardt JJ, Smith AR, Reeves ST, Weinstein M, Kozel FA, Nahas Z, Shelley N, Branham RK, Thomas KJ, George MS: Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. Pain Res Manag 12:287-290, 2007

4. Taylor JJ, Borckardt JJ, George MS: Endogenous opioids mediate left dorsolateral prefrontal cortex rTMS-induced analgesia. Pain 153:1219-1225, 2012

5. Seminowicz DA, de Martino E, Schabrun SM, Graven-Nielsen T: Left DLPFC rTMS reduces the development of long-term muscle pain. Pain 159:2486-2492, 2018

6. Taylor JJ, Borckardt JJ, Canterberry M, Li X, Hanlon CA, Brown TR, George MS: Naloxone-reversible modulation of pain circuitry by left prefrontal RTMS. Neuropsychopharmacology 38:1189-1197, 2013

7. Borckardt JJ, Reeves S, Weinstein M, Smith A, Shelley N, Kozel FA, Nahas Z, George MS: Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: A replication study. Brain Stimul 1:122-127, 2008

8. Borckardt JJ, Reeves ST, Kotlowski P, Abernathy JH, Field LC, Dong L, Frohman H, Moore H, Ryan K, Madan A, George MS: Fast left prefrontal rTMS reduces post-gastric bypass surgery pain: Findings from a large-scale, double-blind, sham-controlled clinical trial. Brain Stimul 7:42-48, 2014

9. Borckardt JJ, Weinstein M, Nahas Z, George MS: Postoperative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. Anesthesiology 557-562, 2006

10. Borckardt JJ, Smith AR, Reeves ST, Madan A, Shelley N, Branham R, Nahas Z, George MS: A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. Pain Med 10:840-849, 2009

11. Nardone R, Höller Y, Langthaler PB, Lochner P, Golaszewski S, Schwenker K, Brigo F, Trinka E: RTMS of the prefrontal cortex has analgesic effects on neuropathic pain in subjects with spinal cord injury. Spinal Cord 55:20-25, 2017

12. Short EB, Borckardt JJ, Anderson BS, Frohman H, Beam W, Reeves ST, George MS: Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: A randomized, controlled pilot study. Pain 152:2477-2484, 2011

13. Fierro B, De Tommaso M, Giglia F, Giglia G, Palermo A, Brighina F: Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) during capsaicin-induced pain: Modulatory effects on motor cortex excitability. Exp Brain Res 203:31-38, 2010

14. Hadjipavlou G, Dunckley P, Behrens TE, Tracey I: Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: A diffusion tensor imaging study in healthy controls. Pain 123:169-178, 2006

15. Lefaucheur JP, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP: Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. Neurology 67:1568-1574, 2006

16. Mhalla A, Baudic S, De Andrade DC, Gautron M, Perrot S, Teixeira MJ, Attal N, Bouhassira D: Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. Pain 152:1478-1485, 2011

17. Schabrun SM, Christensen SW, Mrachacz-Kersting N, Graven-Nielsen T: Motor cortex reorganization and impaired function in the transition to sustained muscle pain. Cereb Cortex 26:1878-1890, 2016

18. Schabrun SM, Hodges PW: Muscle pain differentially modulates short interval intracortical inhibition and intracortical facilitation in primary motor cortex. J Pain 13:187-194, 2012

19. Gamboa OL, Antal A, Moliadze V, Paulus W: Simply longer is not better: Reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res 204:181-187, 2010

20. 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 35:125-134, 2012

21. Nyffeler T, Wurtz P, Lüscher HR, Hess CW, Senn W, Pflugshaupt T, Von Wartburg R, Lüthi M, Müri RM: Extending lifetime of plastic changes in the human brain. Eur J Neurosci 24:2961-2966, 2006

22. Moisset X, Goudeau S, Poindessous-Jazat F, Baudic S, Clavelou P, Bouhassira D: Prolonged continuous theta-burst stimulation is more analgesic than "classical" high frequency repetitive transcranial magnetic stimulation. Brain Stimul 8:135-141, 2015

23. Suppa A, Huang YZ, Funke K, Ridding MC, Cheeran B, Di Lazzaro V, Ziemann U, Rothwell JC: Ten years of theta burst stimulation in humans: established knowledge, unknowns and prospects. Brain Stimul 9:323-335, 2016

24. Di Lazzaro V, Dileone M, Pilato F, Capone F, Musumeci G, Ranieri F, Ricci V, Bria P, Di Iorio R, de Waure C, Pasqualetti P, Profic P: Modulation of motor cortex neuronal networks by rTMS: Comparison of local and remote effects of six different protocols of stimulation. J Neurophysiol 105:2150-2156, 2011

25. Gamboa OL, Antal A, Laczo B, Moliadze V, Nitsche MA, Paulus W: Impact of repetitive theta burst stimulation on motor cortex excitability. Brain Stimul 4:145-151, 2011

26. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, Knyahnytska Y, Kennedy SH, Lam RW, Daskalakis ZJ, Downar J: Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation

in patients with depression (THREE-D): A randomised non-inferiority trial. Lancet 391:1683-1692, 2018

27. Sullivan MJL, Bishop SR, Pivik J: The Pain Catastrophizing Scale: development and validation. Psychol Assess 7:524-532, 1995

28. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J: An inventory for measuring depression. Arch Gen Psychiatry 4:561-571, 1961

29. Watson D, Clark LA: Development and validation of brief measures of positive and negative affect: The PANAS scales. J Pers Soc Psychol 54:1063-1070, 1988

30. Morin CM, Belleville G, Bélanger L, Ivers H: The insomnia severity index: Psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 34:601-608, 2011

31. Rossi S, Hallett M, Rossini PM, Pascual-Leone A: Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120:323-330, 2012

32. Aparecida da Silva V, Galhardoni R, Teixeira MJ, Ciampi de Andrade D: Not just a matter of pain intensity: Effects of three different conditioning stimuli on conditioned pain modulation effects. Neurophysiol Clin 1-7, 2018

33. De Martino E, Petrini L, Schabrun SM, Graven-Nielsen T: Cortical somatosensory excitability is modulated in response to several days of muscle soreness. J Pain 1-36, 2018

34. Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, Landau R, Marchand S, Matre D, Nilsen K, A S, Treede R, Wilder-Smith O: Recommendations on practice of conditioned pain modulation (CPM) testing. Eur J Pain 19:805-806, 2014

35. Ciampi De Andrade D, Mhalla A, Adam F, Texeira MJ, Bouhassira D: Repetitive transcranial magnetic stimulation induced analgesia depends on N-methyl-d-aspartate glutamate receptors. Pain 155:598-605, 2014

36. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, Di Lazzaro V, Ferreri F, Fitzgerald PB, George MS, Hallett M, Lefaucheur JP, Langguth B, Matsumoto H, Miniussi C, Nitsche MA, Pascual-Leone A, Paulus W, Rossi S, Rothwell JC, Siebner HR, Ugawa Y, Walsh V, Ziemann U: Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application: An updated report from an I.F.C.N. Committee. Clin Neurophysiol 126:1071-1107, 2015

37. Ciampi De Andrade D, Mhalla A, Adam F, Texeira MJ, Bouhassira D: Neuropharmacological basis of rTMS-induced analgesia: The role of endogenous opioids. Pain 152:320-326, 2011

38. Beam W, Borckardt JJ, Scott T, Reeves MD, Mark S, George MD: An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul 1:50-54, 2009

39. Mir-Moghtadaei A, Caballero R, Fried P, Fox MD, Lee K, Giacobbe P, Daskalakis ZJ, Blumberger DM, Downar J: Concordance between beamF3 and MRI-neuronavigated target sites for repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex arsalan. Brain Stimul 1848:3047-3054, 2016

40. Borckardt JJ, Smith AR, Hutcheson K, Johnson K, Nahas Z, Anderson B, Schneider MB, Reeves ST, George MS: Reducing pain and unpleasantness during repetitive transcranial magnetic stimulation. J ECT 22:259-264, 2006

41. Borckardt JJ, Nahas ZH, Teal J, Lisanby SH, Mcdonald M, Avery D, Durkalski V, Pavlicova M, Long J, Sackeim HA, George MS: The painfulness of active, but not sham, transcranial magnetic stimulation decreases rapidly over time: Results from the double-blind phase of the OPT-TMS trial. Brain Stimul 6:1-8, 2013

42. Nahmias F, Debes C, de Andrade DC, Mhalla A, Bouhassira D: Diffuse analgesic effects of unilateral repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers. Pain 147:224-232, 2009

43. Baumgärtner U, Iannetti GD, Zambreanu L, Stoeter P, Treede R-D, Tracey I: Multiple somatotopic representations of heat and mechanical pain in the operculo-insular cortex: A high-resolution fMRI study. J Neurophysiol 104:2863-2872, 2010

44. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC: Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 76:833-838, 2005

45. Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, Perrot S, Januel D, Bouhassira D: Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain 130:2661-2670, 2007

46. Fassoulaki A, Melemeni A, Staikou C, Triga A, Sarantopoulos C: Acute postoperative pain predicts chronic pain and long-term analgesic requirements after breast surgery for cancer Acute postoperative pain predicts chronic pain and long-term analgesic requirements after breast surgery for cancer. Acta Anaesthesiol Belg 59:241-248, 2008

47. Katz J, Seltzer Z: Incidence and risk factors for chronic pain after caesarean section under spinal anaesthesia. Anaesth Intensive Care 37:748-752, 2009

48. Cho SS, Strafella AP: rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex. PLoS One 4:2-9, 2009

49. Sibon I, Strafella AP, Gravel P, Ko JH, Booij L, Soucy JP, Leyton M, Diksic M, Benkelfat C: Acute prefrontal cortex TMS in healthy volunteers: Effects on brain11C-$\alpha$Mtrp trapping. Neuroimage 34:1658-1664, 2007

50. Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J: Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur J Neurosci 19:1950-1962, 2004

51. Seewoo BJ, Etherington SJ, Feindel KW, Rodger J: Combined rTMS/fMRI studies: An overlooked resource in animal models. Front Neurosci 12:180, 2018

52. Flood A, Waddington G, Cathcart S: High-definition transcranial direct current stimulation enhances conditioned pain modulation in healthy volunteers: A randomized trial. J Pain 17:600-605, 2016

53. Reidler JS, Mendonca ME, Santana MB, Wang X, Lenkinski R, Motta AF, Marchand S, Latif L, Fregni F: Effects of motor cortex modulation and descending inhibitory

systems on pain thresholds in healthy subjects. J Pain 13:450-458, 2012

54. Abraham WC, Logan B, Greenwood JM, Dragunow M: Induction and experience-dependent consolidation of stable long-term potentiation lasting months in the hippocampus. J Neurosci 22:9626-9634, 2002

55. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, Anderson B, Nahas Z, Bulow P, Zarkowski P, Holtzheimer PE, Schwartz T, Sackeim HA: Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder. Arch Gen Psychiatry 67:507, 2010

56. Goldsworthy MR, Pitcher JB, Ridding MC: Spaced noninvasive brain stimulation: Prospects for inducing long-lasting human cortical plasticity. Neurorehabil Neural Repair 29:714-721, 2015

57. Lefaucheur JP, Ayache SS, Sorel M, Farhat WH, Zouari HG, Ciampi De Andrade D, Ahdab R, Ménard-Lefaucheur I, Brugières P, Goujon C: Analgesic effects of repetitive transcranial magnetic stimulation of the motor cortex in neuropathic pain: Influence of theta burst stimulation priming. Eur J Pain 16:1403-1413, 2012

58. Mhalla A, de Andrade DC, Baudic S, Perrot S, Bouhassira D: Alteration of cortical excitability in patients with fibromyalgia. Pain 149:495-500, 2010

59. Schwenkreis P, Janssen F, Rommel O, Pleger B, Maier C, Tegenthoff M: Bilateral somatosensory cortex disinhibition in complex regional pain syndrome type I. Neurology 61:515-519, 2003

60. Burns E, Chipchase LS, Schabrun SM: Altered function of intracortical networks in chronic lateral epicondylalgia. Eur J Pain 20:1166-1175, 2016

61. Massé-Alarie H, Flamand VH, Moffet H, Schneider C: Corticomotor control of deep abdominal muscles in chronic low back pain and anticipatory postural adjustments. Exp Brain Res 218:99-109, 2012

62. Jacobs MF, Tsang P, Lee KGH, Asmussen MJ, Zapallow CM, Nelson AJ: Brain stimulation 30 Hz theta-burst stimulation over primary somatosensory cortex modulates corticospinal output to the hand. Brain Stimul 7:269-274, 2014

63. Nyffeler T, Cazzoli D, Wurtz P, Luthi M, von Wartburg R, Chaves S, Deruaz A, Hess CW, Muri RM: Neglect-like visual exploration behaviour after theta burst transcranial magnetic stimulation of the right posterior parietal cortex. Eur J Neurosci 27:1809-1813, 2008

64. Carr E, Nicky Thomas V, Wilson-Barnet J: Patient experiences of anxiety, depression and acute pain after surgery: A longitudinal perspective. Int J Nurs Stud 42:521-530, 2005