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Original Research

Single Session Effects of Prolonged Continuous Theta Burst Stimulation Targeting Two Brain Regions on Pain Perception in Patients with Painful Diabetic Neuropathy: A Preliminary Study

Bhushan Thakkar[1,*], Carrie L. Peterson[2], Edmund O. Acevedo[3]

[1]Department of Physical Therapy, Virginia Commonwealth University, Richmond, VA 23298, USA
[2]Department of Biomedical Engineering, Virginia Commonwealth University, Richmond, VA 23219, USA
[3]Department of Kinesiology and Health Sciences, Virginia Commonwealth University, Richmond, VA 23284, USA
*Correspondence: bthakkar001@dundee.ac.uk (Bhushan Thakkar)

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Abstract

Background: Painful diabetic neuropathy (pDN) is the most common cause of neuropathic pain (NP) in the United States. Prolonged continuous theta burst stimulation (pcTBS), a form of repetitive transcranial magnetic stimulation (rTMS), is quick (1–4 minutes) and tolerable for most individuals, compared to high frequency rTMS and can modulate pain thresholds in healthy participants. However, its effects on patients with chronic pain are still unclear. The primary purpose of this preliminary study is to investigate the effects of single session pcTBS targeted at the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) on a set of self-report measures of pain (SRMP) that assess the (a) sensory-discriminative; (b) affective-motivational; and (c) cognitive-evaluative aspects of pain experience. **Methods**: For this prospective, single-blind study, forty-two participants with pDN were randomized to receive either pcTBS targeting the M1 or the DLPFC brain regions. SRMP were completed at baseline, post pcTBS and 24h-post pcTBS. A two-way mixed model repeated measures analysis of variance (2 brain regions by 3 time points) was conducted to evaluate the effects of pcTBS stimulation at M1 and DLPFC for each subscale of each SRMP. **Results**: After a single session of pcTBS targeted at M1 or DLPFC in patients with pDN, statistically significant improvements from baseline to post pcTBS and baseline to 24 h-post pcTBS were observed for different SRMP subscales examining the (a) sensory-discriminative, (b) affective-motivational and (c) cognitive-evaluative components of the pain experience. At 24 h-post pcTBS, none of the participants reported any serious adverse events to the pcTBS treatment, thus demonstrating its feasibility. **Conclusions**: In pDN patients with NP, our study results demonstrated significant improvement in scores on self-report measures of pain (SRMP) after a single session of pcTBS targeting the M1 and DLPFC brain regions. Future studies should consider utilizing multiple sessions of pcTBS to evaluate its long-term effects on pain perception, safety and tolerability in patients with chronic pain. **Clinical Trial Registration**: This study was registered on the ClinicalTrials.gov website (NCT04988321).

Keywords: chronic pain; noninvasive brain stimulation; diabetes mellitus; neuromodulation; clinical trial

1. Introduction

Diabetic neuropathy, a type of nerve damage that can occur with diabetes, can lead to chronic pain [1–3]; one in five patients with diabetic neuropathy develop painful diabetic neuropathy (pDN), the most common cause of neuropathic pain (NP) in the United States [2,4]. pDN has debilitating consequences with a major impact on morbidity and quality of life [1,2,5]. There are no medications that target the pathophysiology of pDN to reverse the course of neuropathy [1,6]. Therefore, symptomatic treatment is the mainstay of management for pDN with only three US Food and Drug Administration approved drug therapies: pregabalin, duloxetine, and tapentadol [2,6]. These pharmacological treatments have demonstrated poor efficacy with only one in seven patients typically achieving sufficient pain relief [7] and some patients develop problematic side effects. Furthermore, the estimated increase in the prevalence of diabetes mellitus to 629 million cases by 2045 [8] and the associated pDN, highlight the urgent need to develop new therapeutic approaches.

Repetitive transcranial magnetic stimulation (rTMS), a noninvasive form of brain stimulation, has been investigated as a form of treatment for NP and has been found to be safe, well-tolerated and effective. Additionally, the pain relief obtained from a single rTMS session can last up to eight days [9–11]. rTMS involves the application of TMS pulses using an electromagnetic coil applied to the scalp. A magnetic field is directed to a specific region(s) of the brain with different patterns and frequencies that modulate brain activity to produce immediate and long-term effects through changes in neuroplasticity [12–14]. Previous studies have consistently reported its feasibility and safety with only a few contraindications [15,16]. With regards to chronic pain and specifically NP, rTMS via stimulation of the primary motor cortex (M1) has consistently demonstrated analgesic effects [11,17,18]. Another cortical target for NP that that can be targeted with rTMS is the dorsolateral prefrontal cortex (DLPFC) [19–21]; this is also the primary target site for alleviating depression [22–24]. In patients with NP, activation of DLPFC has been linked to pain perception, in partic-

ular through the modulation of the cognitive and emotional aspects of pain processing [19,25,26].

Conventional rTMS requires 20 to 30 min of stimulation time to achieve its full effect, which can make experimental and clinical applications logistically challenging. A recently developed rTMS paradigm, theta burst stimulation (TBS) [27], is more time efficient and can reduce patient discomfort. TBS requires significantly less stimulation time (1–4 minutes) and lower stimulation intensities (bursts of three pulses at 30 Hz or 50 Hz, repeated five times per second with 600 pulses in total) [27–29]. A prolonged continuous form of TBS (pcTBS) with twice the number of stimuli (1200 pulses) produces a facilitatory increase similar to that of intermittent TBS and rTMS [27–29]. The effects of pcTBS on pain modulation have been investigated only in healthy subjects targeting M1 [30–32] and DLPFC [33]. Two of these studies [32,33] found a similar increase in pain threshold compared to rTMS after one session of pcTBS. In healthy participants, a greater increase in pain thresholds was found after three sessions of pcTBS [30] compared to three sessions of rTMS and demonstrated that this greater increase continued up to 24 hours post stimulation.

The analgesic effects of pcTBS targeted at the M1 and DLPFC brain regions in patients with pDN remains unknown. The purpose of this preliminary study was to examine the effectiveness of a single session of pcTBS at the M1 and DLPFC regions of the brain to alleviate pain in patients with pDN. More specifically, utilizing a single pcTBS session, we examined the effects of pcTBS at M1 and DLPFC on the analgesic, cognitive and emotional aspects of pain perception using self-report measures of pain (SRMP) that assess the multidimensional aspects of the chronic pain experience. These SRMP, albeit subjective, are valid and reliable measures to evaluate the pain experience and are considered the gold standard [34–36]. They can assess the sensory-discriminative (location, quality and intensity), affective-motivational (unpleasantness) and cognitive-evaluative components (beliefs, attitudes, intention) [34,37,38] aspects of pain. We hypothesized that, compared to baseline, a single session of pcTBS targeted at the M1 brain region would lead to improvement in scores on SRMP that evaluate the sensory-discriminative and affective-motivational components of pain. Also, we hypothesized that pcTBS targeted at the DLPFC brain region would lead to similar improvements on SRMP, although the scores that measure the cognitive-emotional aspects of pain and quality of life would be elevated beyond the improvements demonstrated with stimulation at M1, since DLPFC is involved in the modulation of the emotional and cognitive aspects of the pain experience.

2. Materials and Methods

2.1 Participants and Randomization into M1 and DLPFC Groups

This study utilized the same participants, recruitment policies, inclusion/exclusion criteria and randomization protocol that have been published in a study [39] that examined the neural mechanisms of pcTBS targeted at M1 and DLPFC in patients with NP. Briefly, all participants provided written informed consent before study participation. Fig. 1 describes the recruitment of study participants. All the study participants were over 18 and under 75 years of age, with type 2 diabetes, pain of at least 4/10 on the visual analog scale, and a score of $>$19 on the Pain Detect Questionnaire. Patients with any active contraindications to rTMS or with any other form of NP were excluded from the study. Participants were also excluded if they were unable to read or interpret instructions due to any language barriers and women who were pregnant were also excluded. Patients randomized to Group 1 received sham pcTBS at M1 followed by active pcTBS at MI. Patients in Group 2 received sham pcTBS at DLPFC followed by active pcTBS at DLPFC. Fig. 2 describes the data collection protocol for the two groups.

Each session began with completion of SRMP and identification of cortical hotspots for DLPFC or M1. Then baseline measures of corticospinal excitability were assessed followed by sham pcTBS stimulation at DLPFC or M1. Next, active pcTBS (treatment) at DLPFC or M1 was performed. Lastly, SRMP were collected again. Each individual study session took 120–150 minutes to be completed. SRMP were measured twice for every session and collected electronically 24 hours after the study session was completed along with a pcTBS safety questionnaire to evaluate any potential side effects.

2.2 Prolonged Continuous Theta Burst Stimulation (pcTBS)

The pcTBS protocol for patients in the M1 and DLPFC group have been described in detail in another study [39]. With the patient seated comfortably, pcTBS was performed using a Magstim (Whitland, UK) Super Rapid^2 Plus^1 stimulator and a 70 mm double air film coil (P/N: 3950-00, Magstim, Whitland, UK). The pcTBS protocol consisted of three pulses at 50 Hz (i.e., 60 ms) repeated 400 times at intervals of 200 ms (total of 1200 pulses in 1 min and 44 s) [27,30,33]. For the sham condition, a sham coil looking identical to the active coil and making a similar noise but without delivering any active stimulation, was placed above the hotspot. A surface electromyography electrode was placed on the right abductor pollicis brevis muscle and monitored for evoking motor responses for the M1 cortical hotspot. Single-pulse TMS was delivered to the contralateral M1 brain region (i.e., left M1). The cortical hotspot was the location evoking the largest peak-to-peak motor evoked potential amplitude in the abductor pollicis brevis at the lowest stimulation intensity. Resting motor threshold

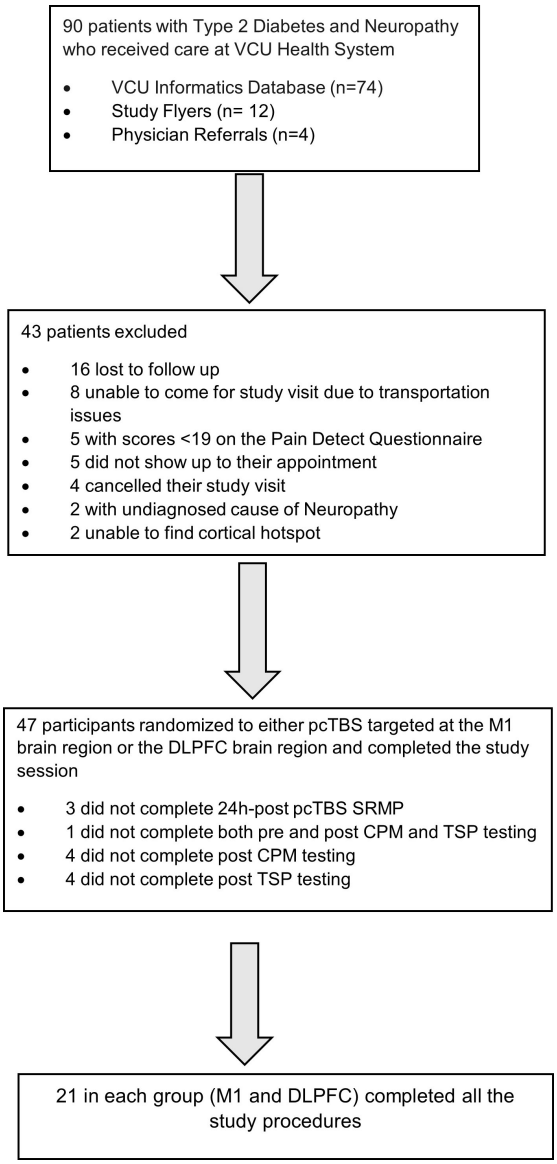

Fig. 1. Study flow chart describing the eligibility and recruitment process. pcTBS, Prolonged continuous theta burst stimulation; M1, primary motor cortex; DLPFC, dorsolateral prefrontal cortex; SRMP, self-report measures of pain; VCU, Virginia Commonwealth University; CPM, Conditioned Pain Modulation; TSP, Temporal Summation of Pain.

was determined as the lowest stimulus intensity that induces motor evoked potential with an amplitude of $\geq$50 µV in at least 5 of 10 consecutive stimuli with the muscle fully relaxed [13,40]. pcTBS stimulation intensity was set to 80% of the resting motor threshold.

2.3 Identification of the Cortical Hotspot for DLPFC

The cortical hotspot for left DLFPC was measured using the Beam F3 location system where F3 stands for hotspot location for DLPFC [41,42]. Beam F3 uses three measurements: head circumference, nasion-inion distance, and left tragus-to-right tragus distance. Once these three measurements are obtained, they are entered in to an online calculator which provides two values (X, Y) in cms that are used to locate F3. F3 is marked as the point of intersection of X and Y where X is a point along the circumference from the midline and Y is the distance from the vertex [42]. This method accounts for head size and shape and has a higher level of precision and reproducibility compared to other methods [41,43].

2.4 Self-Report Measures of Pain (SRMP)

All questionnaires were completed by the participants on an iPad (Apple, Cupertino, CA, USA) using REDCap (Virginia Commonwealth University, VCU, Richmond, VA, USA) electronic data capture tools hosted at VCU [44,45]. Participants completed SRMP at baseline (pre pcTBS), post pcTBS (after active pcTBS) and 24 h-post pcTBS (24 hours after the study session was completed). The four SRMP completed at each of the three time points included the following:

(1) The **Bodily and Emotional Perception of Pain (BEEP)** questionnaire is a self-report questionnaire measuring the impact of chronic pain on daily life [46]. It has 23 items on a 0–5 Likert scale that assess three pain dimensions, namely the emotional reaction to pain, the limitations to daily life caused by pain, and the interference caused by pain in personal and social functioning [46]. BEEP has demonstrated satisfactory internal consistency with a Cronbach's alpha of $>$0.70 both as a global scale and for its three dimensions [46]. The subscales of BEEP evaluate the sensory-discriminative, affective-motivational, cognitive-evaluative constructs of chronic that focus on both the M1 and the DLPFC brain regions.

(2) The **Brief Pain Inventory (BPI)** for patients with diabetic neuropathy (BPI-DN) is a widely used and validated numeric rating scale that measures severity of pain (4 items), and its interference (7 items) with daily function and other aspects of pain (e.g., location of pain, relief from medications) [47–49]. For the pain severity subscale, each item uses a 0–10 numeric rating scale anchored at zero for "no pain" and 10 for "pain as bad as you can imagine". For the pain interference subscale, each item uses the same 0–10 numeric rating scale with zero for "does not interfere" and 10 "completely interferes" [47]. Zelman *et al.* [48] demonstrated that both the severity and interference scales were distinct scales with sufficient construct and criterion validity. A change of 1 point on the BPI Interference Scale indicates a minimally important change [50]. A decrease of $\geq$30% appears to reflect at least moderately important differences, and lastly a decrease $\geq$50% appears to reflect substantial improvements [50]. BPI-DN primarily targets the M1 region and assesses the sensory-discriminative and affective-motivational constructs.

(3) The **Depression, Anxiety and Stress Scale (DASS-21)** is a 21-item scale comprising three, 7-item subscales that measure depression, anxiety and stress. Psychometric analyses conducted primarily with nonclinical samples has revealed strong support for the internal con-

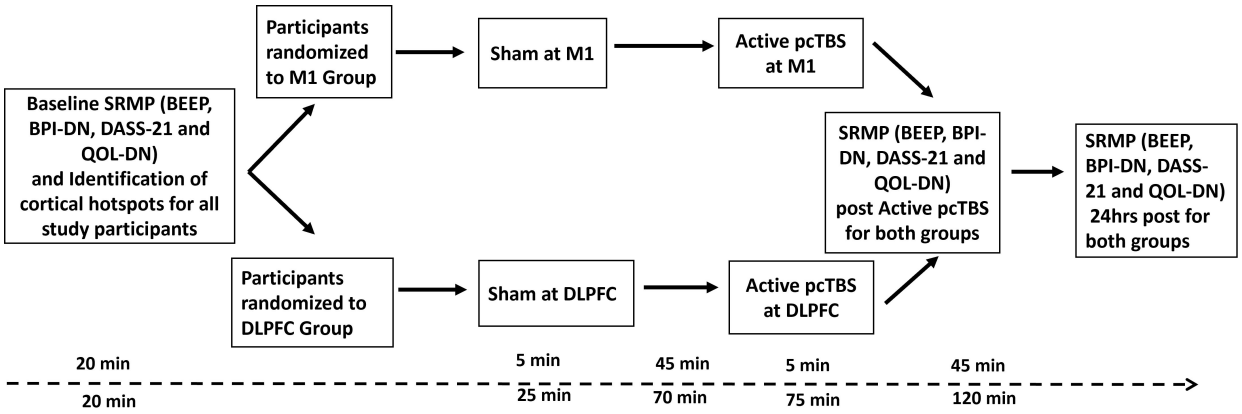

Fig. 2. Data collection protocol for the two groups. Prior to collecting data, Self-report measures of pain (SRMP) were completed by all participants and the cortical hotspots for M1 and DLPFC were identified. The timeline for the study session is described in minutes above and below the dashed line with the total time for all the study procedures described below the dashed line and time for individual procedures described above the dashed line. BEEP, Bodily and Emotional Perception of Pain; BPI-DN, Brief Pain Inventory for patients with diabetic neuropathy; DASS-21, Depression, Anxiety and Stress Scale; QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy.

sistency, convergent and discriminant validity of the three scales [51,52]. Subjects are asked to use 4-point severity/frequency scales (0—did not apply to me at all, 1—applied to me to some degree, or some of the time, 2—applied to me to a considerable degree, or a good part of time, and 3—applied to me very much, or most of the time) to rate the extent to which they have experienced each state over the past week. Scores for depression, anxiety and stress are calculated by summing the scores for the relevant items. DASS-21 has demonstrated strong internal consistency (0.96, 0.89 and 0.93 for depression, anxiety, and stress, respectively) and convergent and discriminant validity for the three scales in clinical and nonclinical samples [51,52]. DASS-21 mainly evaluates the role of the DLPFC brain region by measuring the cognitive-evaluative constructs of chronic pain.

(4) The **Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN)** questionnaire is an instrument to assess quality of life in diabetic polyneuropathy [53]. The QOL-DN is comprised of 35 items with three subscale items (symptoms, activities of daily living, and generic health status) [53]. QOL-DN has also demonstrated a satisfactory internal consistency measured by Cronbach's alpha (0.77–0.84) [53,54]. Furthermore, QOL-DN provides a quantitative evaluation of the impact of pDN on quality of life in these patients and measures the cognitive-evaluative constructs of chronic pain primarily assessing the DLPFC brain region.

BEEP, BPI-DN, DASS-21 and QOL-DN provide quantitative evaluation of pain perception and its impact on quality of life in pDN patients. Participants also completed a demographic questionnaire at baseline and a blinding questionnaire [39], in which the participants were asked to identify which treatment they thought they received first? Active or Inactive pcTBS, and how certain they were in their ability to guess the treatment?

The blinding survey and the safety questionnaire are included in the **Supplementary Material**.

2.5 Statistical Analysis

The sample size for this study was calculated based on reported standardized effect sizes of 0.50–0.65 for changes in Pain Detect Questionnaire scores [55,56], 0.55 for BEEP [46], and 0.44–0.73 for BPI-DN [48,49]. Using an effect size of 0.50 with power of 0.80 at the 0.05 level, the present study recruited 42 participants (21 in each group). Statistical Package for Social Science (SPSS®software, v. 28.1, IBM Corporation, Armonk, NY, USA) was used for all statistical analysis with significance set at $p < 0.05$. The assessment of normality and identification of outliers has been previously described in detail [39].

The dependent variables for analyses were: the BEEP, BPI-DN, DASS-21, and QOL-DN subscales and the two independent variables were the two brain regions: M1 and DLPFC. A two-way mixed model repeated measures analysis of variance (RMANOVA; 2 brain regions by 3 time points) was conducted to evaluate the effects of pcTBS stimulation at M1 and DLPFC for each subscale. The Greenhouse–Geisser approach was used to correcting for violations of sphericity if the estimated epsilon (ε) was less than 0.75. Huynh-Feldt correction was used if ε was greater than 0.75. Effect sizes (partial eta-squared [η^2]) are reported for significant effects. Where appropriate, post hoc analyses were performed using a Bonferroni multiple comparison correction.

3. Results

3.1 Demographics

Table 1 presents the participant demographic data. Forty-seven participants were randomized to receive either pcTBS at the M1 brain region (n = 23; males = 11 and fe-

Table 1. Demographic Data for all Participants.

	Total (N = 47)	pcTBS at M1	pcTBS at DLPFC	*p*-value
Sex, n (%)				0.16
Male	19 (40.42)	11 (47.7)	8 (33.33)	
Female	28 (59.38)	12 (52.2)	16 (66.67)	
Race, n (%)				0.13
• Non-Hispanic Black	24 (51.10)	12 (52.17)	12 (50.00)	
• Non-Hispanic White	18 (38.30)	8 (34.78)	10 (41.66)	
• Asian	1 (2.10)	0 (0.00)	1 (4.23)	
• Hispanic/Latino/Spanish	1 (2.10)	1 (4.30)	0	
• Mixed	2 (4.30)	1 (4.30)	0	
• Prefer not to say	1 (2.10)	1 (4.30)	1 (4.23)	
Age (years)	58.65 ± 8.82	59.65 ± 10.23	57.71 ± 7.33	0.46
Duration of pain (years)	5.59 ± 0.04	5.63 ± 4.87	5.54 ± 6.08	0.48
PD-Q score (–1 and 38 range)	22.15 ± 65.55	21.78 ± 2.58	22.50 ± 3.36	0.21
Current pain on VAS (0–10 range)	5.87 ± 1.88	5.91 ± 1.90	5.83 ± 1.90	0.44
BMI, kg/m^2	31.87 ± 6.51	33.26 ± 6.57	30.54 ± 6.30	0.08

BMI, body mass index; VAS, visual analog scale; PD-Q, Pain Detect Questionnaire. *p*-values and t-value for two sample *t*-tests for each sample characteristic.

males = 12) or pcTBS at the DLPFC brain region (n = 24; males = 8 and females = 16). There were no significant differences in demographic characteristics between the two groups. Two participants reported 0 for all the subscales on the DASS-21 at all three time-points and were removed from that analysis.

3.2 Changes in SRMP

3.2.1 BEEP Scores

Fig. 3 depicts the changes in BEEP subscale scores for the two brain regions from baseline to post pcTBS. The effects of pcTBS stimulation on the BEEP Emotional Reaction to Pain subscale revealed no significant interaction effects for brain region activation across time (F (1,38) = 1.112, $p = 0.298$); however, there was a significant main effect for time for this subscale (F [1.79, 68.11] = 15.66, $p \leq 0.001$, partial $\eta^2 = 0.004$). Post hoc analyses revealed that for the M1 group, the BEEP Emotional Reaction to Pain subscale had a significant decrease from baseline to post pcTBS and from baseline to 24 h-post pcTBS. For the DLPFC group, the BEEP Emotional Reaction to Pain scale demonstrated a significant decrease from baseline to post pcTBS. Regarding the effects of pcTBS stimulation on the BEEP Pain Interference subscale, there was no significant interaction effect for brain region activation across time (F (1,40) = 0.001, $p = 0.975$); there was a significant main effect for time on this subscale (F [2.00, 42.88] = 5.876, $p = 0.004$, partial $\eta^2 = 0.128$). Post hoc analyses revealed that for the DLPFC group, the BEEP Pain Interference scores had a significant decrease from baseline to 24 h-post pcTBS. Regarding the effects of pcTBS stimulation on the BEEP Pain Limitations subscale, there was no significant interaction effect for brain region and time (F (1,40) = 0.719, $p = 0.402$); there was a significant main effect for time on this subscale (F [2.00, 66.094] = 4.702, $p = 0.017$, partial $\eta^2 = 0.105$). Post hoc analyses revealed that for the DLPFC group, the BEEP Pain Limitations subscale approached significance ($p = 0.057$) from baseline to 24 h-post pcTBS.

3.2.2 BPI-DN Scores

Fig. 4 depicts the changes in BPI-DN subscale scores for the two brain regions from baseline to post pcTBS. The effects of pcTBS stimulation on the BPI-DN Pain Severity subscale revealed no significant interaction effects for brain region activation across time (F (1,40) = 0.044, $p = 0.835$). There was a significant main effect for time on this subscale (F [2.00, 113.597] = 5.839, $p = 0.004$, partial $\eta^2 = 0.127$). Post hoc analyses revealed that for the M1 group this subscale demonstrated a significant decrease from baseline to 24 h-post pcTBS. Regarding the effects of pcTBS stimulation on the BPI-DN Pain Interference subscale, there was no significant interaction effect for brain region activation and time (F (1,40) = 0.609, $p = 0.440$); there was a significant main effect for time on this subscale (F [2.00, 228.483] = 5.457, $p = 0.006$, partial $\eta^2 = 0.128$). Post hoc analyses of the DLPFC group revealed that the BPI-DN Pain Interference subscale demonstrated a significant decrease from baseline to 24 h-post pcTBS. The BPI-DN Pain Interference subscale approached a significant drop from baseline to post pcTBS for the DLPFC group.

3.2.3 DASS-21 Scores

Fig. 5 depicts the changes in DASS-21 subscale scores for the two brain regions from baseline to post pcTBS. The effects of pcTBS stimulation on the DASS-21 Depression subscale revealed no significant interaction effects for brain region activation across time (F (1,37) = 0.655, $p = 0.424$); there was a significant main effect for time (F [1.70, 62.77] = 18.518, $p \leq 0.001$, partial $\eta^2 = 0.334$). Post hoc analyses revealed that for the M1 group, this subscale demonstrated a significant decrease from baseline to post pcTBS, and from

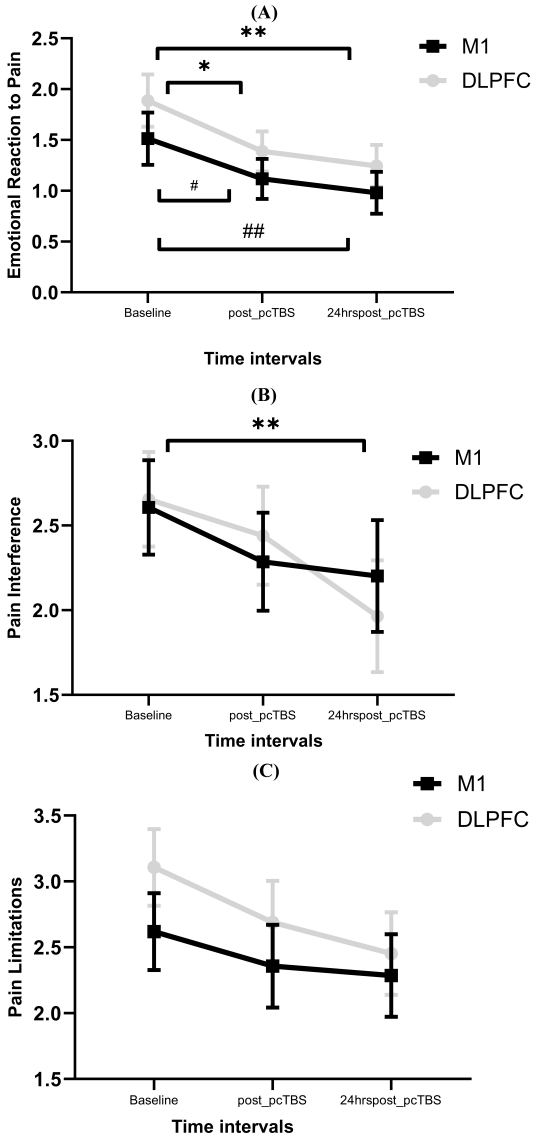

Fig. 3. Effects of pcTBS at M1 and DLPFC on BEEP scores across the three time points. For the M1 group (# indicates a significant decrease from baseline to post pcTBS; ## indicates significant decrease from baseline to 24 h-post pcTBS) and for the DLPFC group (* indicates a significant decrease from baseline to post pcTBS; ** indicates a significant decrease from baseline to 24 h-post pcTBS). (A) BEEP Emotional Reaction to Pain. (B) BEEP Pain Interference. (C) BEEP Pain Limitations. There was no interaction effect for all the three BEEP subscales but there was a statistically significant effect of time for all the three subscales. Post hoc Bonferroni analyses revealed a significant decrease for both M1 and DLPFC for the BEEP Emotional Reaction to Pain scores from baseline to post pcTBS and baseline to 24 h-post pcTBS. For the BEEP Pain Interference scores, only the DLPFC region demonstrated a significant decrease from baseline to 24 h-post pcTBS.

baseline to 24 h-post pcTBS. For the DLPFC group, the DASS-21 Depression subscale demonstrated a significant decrease from baseline to post pcTBS and from baseline to 24 h-post pcTBS. Regarding the effects of pcTBS stimulation on the DASS-21 Anxiety subscale, there was no significant interaction effect for brain region activation across time (F (1,35) = 0.792, p = 0.380); there was a significant main effect for time on the subscale (F [1.28, 44.92] = 11.752, $p \leq 0.001$, partial η^2 = 0.251). Post hoc analyses revealed that for the M1 group, the DASS-21 Anxiety subscale demonstrated a significant decrease from baseline to post pcTBS, and from baseline to 24 h-post pcTBS. For the DLPFC group, this subscale approached a significant decrease from baseline to 24 h-post pcTBS, and from post pcTBS to 24 h-post pcTBS. For the DASS-21 stress subscale, there was no significant interaction effect for brain region and time (F (1,38) = 0.002, p = 0.965); there was a significant main effect for time on this subscale (F [1.52, 58.07] = 12.972, $p \leq 0.001$, partial η^2 = 0.254). Post hoc analyses revealed that for the M1 group, the DASS-21 stress subscale demonstrated a significant decrease from baseline to post pcTBS and from baseline to 24 h-post pcTBS.

3.2.4 QOL-DN Scores

Fig. 6 depicts the changes in QOL-DN subscale scores for the two brain regions from baseline to post pcTBS. The effects of pcTBS stimulation on the QOL-DN symptoms subscale revealed a significant interaction (effect for brain region and time, F (2,76) = 1.819, p = 0.045. Subsequent simple effect analysis revealed no significant differences between groups. With regards to the effects of pcTBS stimulation on the QOL-DN activities of daily living subscale, there was no significant interaction effect for brain region and time (F (1,38) = 0.037, p = 0.848); however, there was a statistically significant main effect for time on this subscale (F [2.00, 76.00] = 8.212, $p \leq 0.001$, partial η^2 = 0.178). Post hoc analyses revealed that for the M1 group, the QOL-DN activities of daily living subscale demonstrated a significant decrease from baseline to post pcTBS, and from baseline to 24 h-post pcTBS. With regards to the effects of pcTBS stimulation on the QOL-DN generic health status scores, there was no interaction effect for brain region and time (F (1,38) = 0.125, p = 0.725); the main effect for time on this subscale approached significance (F [1.72, 65.38] = 2.737, p = 0.080).

3.2.5 Assessment of Clinically Important Differences

3.2.5.1 Changes in Pain Intensity Scores on BPI-DN. Pain intensity was assessed on a 0–10 scale response to the following question on BPI-DN: “Please rate your pain due to your diabetes by sliding to the one number that tells how much pain you have right now” for the entire study sample (n = 42). Results revealed a reduction in pain intensity of 13.53 $\pm$ 0.41% from baseline to post pcTBS, and a reduction of 15.11 $\pm$ 0.41% from baseline to 24 h-post pcTBS. Similarly, responses to the following item were assessed: “Please rate your pain due to your diabetes by sliding to the one number that best describes your pain at its worst in the last 24 hours”. Results revealed a reduction

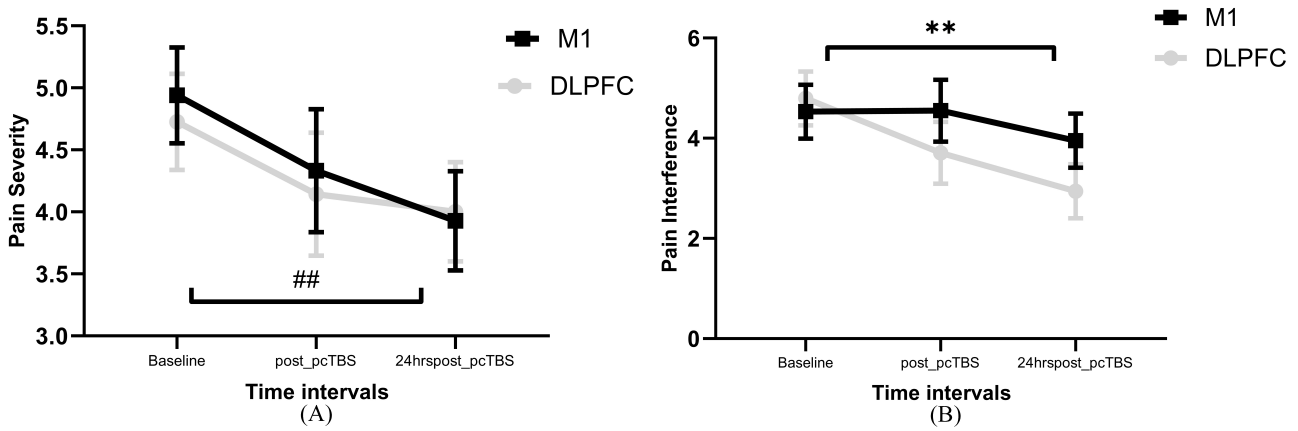

Fig. 4. Effects of pcTBS at M1 and DLPFC on BPI-DN scores across the three time points. For the M1 group (## indicates significant decrease from baseline to 24 h-post pcTBS) and for the DLPFC group (** indicates a significant decrease from baseline to 24 h-post pcTBS). (A) BPI-DN Pain Severity. (B) BPI-DN Pain Interference. There was no interaction effect for both the BPI-DN subscales but there was a statistically significant effect of time. Post hoc Bonferroni analyses revealed a significant decrease for the M1 group brain region for Pain Severity scores from baseline to 24 h-post pcTBS and for the Pain Interference scores for the DLPFC group brain region from baseline to 24 h-post pcTBS.

in pain intensity scores by 14.52 ± 0.61% from baseline to post pcTBS, and 15.60 ± 0.61% from baseline to 24 h-post pcTBS. Of note, this one-point decrease in BPI-DN pain intensity scores is considered a minimally important improvement [53,57]. Likewise, the 0.81 point decrease from baseline to post pcTBS and a 1.10 point decrease from baseline to 24 h-post pcTBS also on the question assessing current pain represents minimally important improvement in patients with chronic pain [53,57].

3.2.5.2 Changes in BPI-DN Pain Interference Scale. Our complete study sample of 42 subjects also reported a change of 1.18 points on the BPI-DN pain interference scale from baseline to 24 h-post pcTBS and 0.61 point change from baseline to post pcTBS. This magnitude of change in scores (1.18) from baseline to 24 h-post pcTBS on the interference scale represents minimally important changes [53,57].

3.3 Reporting of Adverse Events

At 24 h-post pcTBS, none of the participants reported any serious adverse events to the pcTBS treatment or the study session. Out of the 44 participants that completed the safety questionnaire, 11 (25%) participants reported an adverse event. Headache was reported by eight participants, neck pain was reported by six participants, and discomfort was reported by five participants. In addition, one participant reported a toothache, two participants reported an increase in pain, one participant mentioned that they had shoulder pain, and one participant reported nausea. None of these events required medical care and recovery was spontaneous. There were no reports of seizures or hearing impairments by the participants.

3.4 Blinding

The blinding questionnaire was completed by 40 participants. Fifteen participants (37.5%) correctly reported that they received inactive pcTBS (sham pcTBS) first with 55% certainty, whereas 25 participants (63.5%) incorrectly reported that they received active pcTBS first with 44.44% certainty.

4. Discussion

The purpose of this study was to determine the effect of a single session pcTBS targeted at the M1 and DLPFC brain regions to alleviate pain perception in pDN patients. Both pcTBS targeted at M1 and DLPFC demonstrated significant improvement in scores over time on SRMP that evaluated the sensory-discriminative, affective-motivational and cognitive-evaluative constructs of the pain experience. The magnitude of reduction in pain intensity (13–16%) on a 0–10 scale across the three time points and the one-point reduction from baseline to 24 h-post pcTBS on the BPI-DN pain interference scale revealed minimally important improvement [50,58]. In addition, the symptom subscale of QOL-DN, which measures quality of life in patients with pDN and provides a subjective perception of symptoms associated with nerve damage, revealed a significant interaction effect for brain region and time, although there were no group differences. Further investigation is needed to replicate these results, examine the effects of multiple treatment sessions, and determine whether the changes are unique to patients with pDN.

Results from the present study utilizing pcTBS demonstrated a reduction in pain scores after a single session across time on the BEEP, BPI-DN, DASS-21 and Norfolk-QOL-DN scores. These results are consistent with previous studies (two utilizing single session and one utiliz-

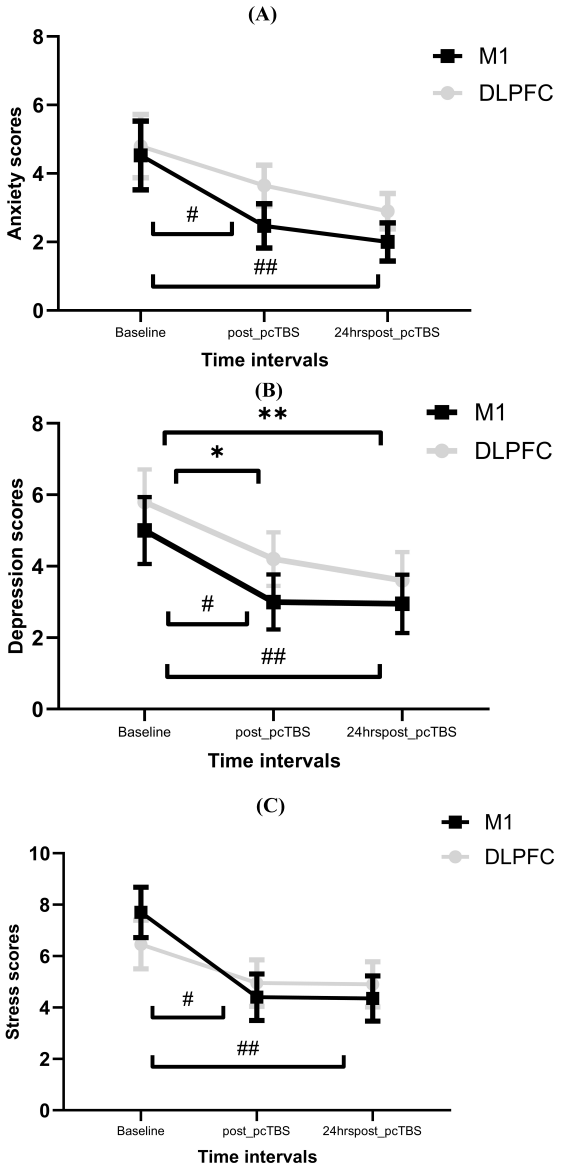

Fig. 5. Effects of pcTBS at M1 and DLPFC on DASS-21 scores across the three time points. For the M1 group (# indicates a significant decrease from baseline to post pcTBS; ## indicates significant decrease from baseline to 24 h-post pcTBS) and for the DLPFC group (* indicates a significant decrease from baseline to post pcTBS; ** indicates a significant decrease from baseline to 24 h-post pcTBS). (A) DASS-21 Depression scores. (B) DASS-21 Anxiety scores. (C) DASS-21 Stress scores. There was no interaction effect for all the three DASS-21 subscales but there was a statistically significant effect of time for all the three subscales. Post hoc Bonferroni analyses revealed a significant decrease for both M1 and DLPFC for the DASS-21 Depression scores from baseline to post pcTBS and baseline to 24 h-post pcTBS. For the DASS-21 Anxiety scores, only the DLPFC region demonstrated a significant decrease from baseline to 24 h-post pcTBS.

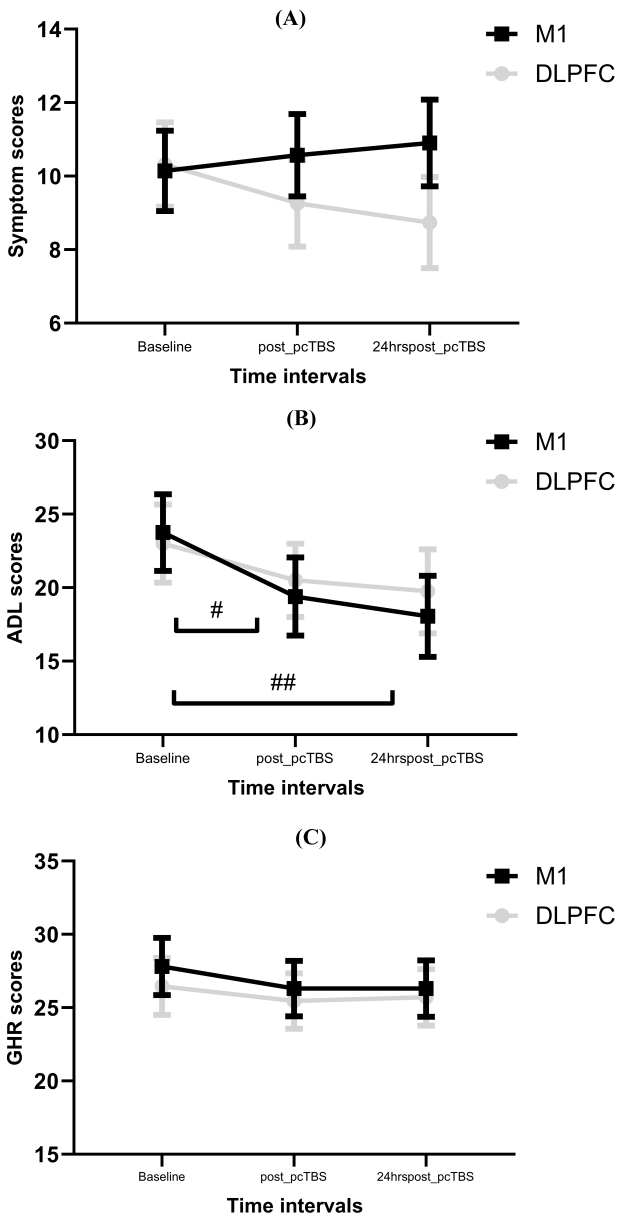

Fig. 6. Effects of pcTBS at M1 and DLPFC on QOL-DN. For the M1 group (# indicates a significant decrease from baseline to post pcTBS; ## indicates significant decrease from baseline to 24 h-post pcTBS). (A) QOL-DN Symptoms. (B) QOL-DN activities of daily living. (C) QOL-DN Generic health status. There was no interaction effect for all the three subscales but there was a statistically significant effect of time on the activities of daily living subscale. Post hoc Bonferroni analyses revealed a significant decrease for the M1 brain region group from baseline to post pcTBS and baseline to 24 h-post pcTBS.

ing three sessions) applying rTMS to the M1 and DLPFC regions in healthy participants to examine pain threshold and cortical excitability [30–32]. In addition, the current study provides unique evidence regarding the use of pcTBS at DLPFC as a possible intervention for pDN. Previous studies that have utilized rTMS in patients with pDN have only targeted the M1 brain region and have revealed short-term pain relief and improvement in quality of life [59–61]. For example, Yang *et al.* [60] randomized patients with pDN

either to an active rTMS group or a sham stimulation group where they completed five sessions that targeted the M1 brain region. Participants in the active rTMS group reported a three-point improvement in scores measured using numeric rating scale scores one day post treatment. Similarly, one-week post treatment there was a one-point decrease in scores compared to baseline [60].

Targeting the M1 and DLPFC brain regions with pcTBS, on average our results demonstrated a one-point decrease on the BPI-DN pain intensity items (from baseline to post pcTBS and from baseline to 24 h-post pcTBS) and on the BPI-DN pain interference scale (from baseline to 24 h-post pcTBS). This change in scores represents "minimally important improvement" which provides some evidence for the clinical benefit of pcTBS as an intervention targeted at the M1 and the DLPFC brain region. Although this work is a preliminary investigation assessing single session effects, our results revealed that both M1 and DLPFC brain regions exhibited significant improvement in scores across the three time points for the BEEP emotional reaction to pain subscale and the DASS-21 depression subscale. This further suggests that pcTBS targeted at the M1 and DLPFC brain regions modulates the emotional and cognitive aspects constructs of the pain experience measured using SRMP. In addition, pcTBS targeted at the DLPFC region resulted in a significant decrease on the BEEP subscales of pain interference and pain limitations that measure the sensory-discriminative and affective-motivational aspects of the pain experience. A similar decrease was observed for the BPI-DN score of pain interference from baseline to post pcTBS. This improvement in SRMP that measures the multidimensional aspects of the pain experience could suggest that pcTBS targeted at the M1 and DLPFC brain regions decreases activation of brain regions responsible for modulation of pain in pDN patients.

Neuroimaging studies have revealed that the cortical areas associated with the sensory-discriminative and affective-motivational dimensions of pain include the somatosensory cortex and the anterior cingulate cortex [38,57,62,63]. Thus, pcTBS targeted at the DLPFC brain region modulates the activation of these brain regions to decrease the sensory and affective dimensions of the pain experience. Similarly, the cortical areas associated with the cognitive-evaluative dimensions of pain experience include the DLPFC, hippocampus, limbic system and the insula [20,25,57,64]. As a result of the changes observed in SRMP subscales linked to the cognitive-evaluative dimensions of pain (emotional reaction to pain scores on BEEP, DASS-21 subscales of anxiety, depression and stress), it can be postulated that pcTBS at M1 and DLPFC resulted in improvement to the emotional and cognitive aspects of the pain experience. Previous studies where rTMS has been utilized as an intervention in patients with neuropsychiatric disorders have revealed that rTMS not only modulates the activity of the stimulation target but also alters the network activity in surrounding brain regions [65,66]. Likewise, the multidimensional experience of pain also involves numerous interconnected brain structures listed above working together [57,62,67], with rTMS and pcTBS potentially modifying the thalamocortical connectivity coupled with alterations in the descending brainstem regions to reduce pain perception in pDN patients.

The mechanism of action for pcTBS targeted at the M1 and DLPFC brain regions are unclear, although previous studies have highlighted synaptic plasticity [27,68–70]; distinct neurophysiological [71,72], neurochemical [28,68,70]; and endogenous mechanisms acting cortically, or at supraspinal or spinal levels [20,21,73–75] as possible explanations. Of note, our research group has recently published an article [39] examining neural mechanisms that have been proposed to play a role in explaining the effects of pcTBS targeted at the M1 and DLPFC brain regions utilizing the participants of the present study [39]. Resulted demonstrated a significant increase in neurophysiological mechanisms of corticospinal excitability ($p \leq 0.001$) measured using motor evoked potential amplitude [39]. A similar significant increase was also seen in measures of γ-aminobutyric acid receptor (GABA) activity measured using paired pulse TMS measures of short intracortical inhibition ($p \leq 0.001$) and long intracortical inhibition ($p = 0.024$) [39]. Although, that study did not observe any changes in the activity of the ascending ($p = 0.160$) and descending ($p = 0.834$) endogenous pain modulatory systems [39] Moisset *et al.* [30] and Klírová *et al.* [31] also observed an increase in corticospinal excitability after a single session of pcTBS targeted at the M1 region while De Martino *et al.* [33] detected an increase after three sessions of pcTBS targeted at the DLPFC region. Both these studies were performed in healthy participants only. Thus, these results suggest that the neural mechanisms of corticospinal excitability and GABA activity could potentially contribute to changes with pcTBS targeted at M1 and DLPFC.

The effects of pcTBS and rTMS are dependent on the frequency of stimulation used to induce synaptic plasticity [76–78]. In addition, the neuroplasticity induced changes in the cortical circuits outlast the period of stimulation, a characteristic of long-term potentiation (LTP) and long-term depression (LTD) [27,79,80]. TBS consists of pulses applied in bursts of three at 50 Hz with an inter-burst interval at 5 Hz and with pcTBS these pulses are repeated 400 times at intervals of 200 ms resulting in 1200 pulses. With pcTBS induced synaptic plasticity, there are specific alterations in neuronal calcium concentrations that dictate its after effects [77,79,81]. Greater calcium influx leads to LTP and a decrease in calcium influx contributes to LTD [68,69,79]. The changes in calcium concentrations are dependent on the action of the N-Methyl-D-aspartate receptors, GABA activity, glutamate receptors and the and the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor activity [27,28,69]. Each of these changes helps to explain the improvement in pain perception in response to pcTBS revealed in this study.

None of the participants in this study reported any serious adverse events during the study session or any treatment related serious adverse events 24 hours after the session was completed. The side effects that study participants reported (headache for 8 participants and neck pain for 6 participants) were similar in type and frequency to what has been reported in previous studies [15,16,82] that utilized rTMS targeted at the M1 and DLPFC brain regions.

Although this preliminary study utilized four SRMP to address the different components of the pain experience, none of the SRMP were able to identify any group differences (pcTBS at M1 and pcTBS at DLPFC) from baseline to post pcTBS, and from baseline to 24 h-post pcTBS. This highlights the need for the development of a core group of standardized SRMP with adequate psychometric properties that can detect changes in patients with chronic NP. In addition, these SRMPs should incorporate the sensory-discriminative, affective-motivational and cognitive-emotional aspects of the pain experience. The findings in this study should be considered exploratory and need to be replicated in larger future randomized controlled trials. Future studies should also utilize clinical screening tools that assess sensory function and examine its correlation with the subjective perceptions of the patients' neuropathy symptoms before and after pcTBS. Considering the short-lasting effect of a single rTMS session [83–86] a future multiple session pcTBS protocol would be expected to be more effective in alleviating pain, due to accumulated treatment responses [64,87–89].

A potential limitation is that the sham stimulation was delivered prior to active pcTBS stimulation to prevent any potential response to active pcTBS stimulation from influencing the sham response [90–92]. However, it is possible this decision resulted in an order effect. Another potential limitation is that the diabetic patients in this study were a more pathophysiologically homogenous group relative to previous studies on the treatment of neuropathic pain using rTMS. This may have limited the variability within and between groups and provided greater power and increased the likelihood of observing a true difference [88,89], although the actual population of patients with pDN is a more heterogeneous group. Furthermore, the mechanisms for different types of NP and chronic pain may result in different responses to stimulation and thus lead to differences in the analgesic and emotional aspects of the pain experience. Additionally, it is vital that future studies combine structural magnetic resonance imaging (MRI) assessments before and after pcTBS to identify and examine functional connectivity approaches in pDN patients. This will delineate the specific changes in the activation of the brain regions involved in modulation of pain perception that can provide the mechanistic link for pcTBS stimulation to different brain regions and their relationship to the multidimensional constructs of the pain experience.

5. Conclusions

pDN is largely irreversible, and management is mainly supportive with the goal of limiting progression of symptoms when medications no longer provide sufficient analgesia. pcTBS is a safe, non-invasive brain stimulation technique that can stimulate different brain regions to induce changes in brain networks that modulate the sensory, affective and emotional aspects of pain processing. We found that a single session of pcTBS targeted at either the M1 or the DLPFC brain region in patients with pDN resulted in improvement on the affective, sensory, quality of life, emotional and cognitive aspects of the pain experience. In addition, pcTBS demonstrated excellent tolerability and feasibility and future studies should consider utilizing multiple sessions of pcTBS to evaluate its long-term effects on pain perception.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Conceived and designed the experiments—BT, CP, EA. Performed the experiments and analyzed the data—BT. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All the participants provided written informed consent and this study was approved by the Virginia Commonwealth University (VCU) Institutional Review Board (HM20021531).

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2303054.

References

[1] Tesfaye S, Vileikyte L, Rayman G, Sindrup SH, Perkins BA, Baconja M, *et al*. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. Diabetes/metabolism Research and Reviews. 2011; 27: 629–638.

[2] Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, *et al*. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017; 40: 136–154.

[3] Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, *et al*. Diabetic neuropathy. Nature Reviews. Disease Primers. 2019; 5: 41.

[4] Hicks CW, Selvin E. Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. Current Diabetes Reports. 2019; 19: 86.

[5] Girach A, Julian TH, Varrassi G, Paladini A, Vadalouka A, Zis P. Quality of Life in Painful Peripheral Neuropathies: A Systematic Review. Pain Research & Management. 2019; 2019: 2091960.

[6] Alam U, Sloan G, Tesfaye S. Treating Pain in Diabetic Neuropathy: Current and Developmental Drugs. Drugs. 2020; 80: 363–384.

[7] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet. Neurology. 2015; 14: 162–173.

[8] Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besançon S, *et al*. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Research and Clinical Practice. 2020; 162: 108072.

[9] Lefaucheur JP. Cortical neurostimulation for neuropathic pain: state of the art and perspectives. Pain. 2016; 157: S81–S89.

[10] Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, *et al*. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). Clinical Neurophysiology. 2020; 131: 474–528.

[11] Moisset X, Bouhassira D, Avez Couturier J, Alchaar H, Conradi S, Delmotte MH, *et al*. Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations. Revue Neurologique. 2020; 176: 325–352.

[12] Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007; 55: 187–199.

[13] Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Annals of Physical and Rehabilitation Medicine. 2015; 58: 208–213.

[14] Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985; 1: 1106–1107.

[15] Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, *et al*. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clinical Neurophysiology. 2021; 132: 269–306.

[16] Oberman L, Edwards D, Eldaief M, Pascual-Leone A. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. Journal of Clinical Neurophysiology. 2011; 28: 67–74.

[17] O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. The Cochrane Database of Systematic Reviews. 2018; 4: CD008208.

[18] Gatzinsky K, Bergh C, Liljegren A, Silander H, Samuelsson J, Svanberg T, *et al*. Repetitive transcranial magnetic stimulation of the primary motor cortex in management of chronic neuropathic pain: a systematic review. Scandinavian Journal of Pain. 2020; 21: 8–21.

[19] Che X, Cash RFH, Luo X, Luo H, Lu X, Xu F, *et al*. High-frequency rTMS over the dorsolateral prefrontal cortex on chronic and provoked pain: A systematic review and meta-analysis. Brain Stimulation. 2021; 14: 1135–1146.

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

[21] Taylor JJ, Borckardt JJ, Canterberry M, Li X, Hanlon CA, Brown TR, *et al*. Naloxone-reversible modulation of pain circuitry by left prefrontal rTMS. Neuropsychopharmacology. 2013; 38: 1189–1197.

[22] Fitzgerald PB, Brown TL, Marston NAU, Daskalakis ZJ, De Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. Archives of General Psychiatry. 2003; 60: 1002–1008.

[23] Noda Y, Silverstein WK, Barr MS, Vila-Rodriguez F, Downar J, Rajji TK, *et al*. Neurobiological mechanisms of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex in depression: a systematic review. Psychological Medicine. 2015; 45: 3411–3432.

[24] Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, *et al*. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet. 2018; 391: 1683–1692.

[25] Seminowicz DA, Moayedi M. The Dorsolateral Prefrontal Cortex in Acute and Chronic Pain. The Journal of Pain. 2017; 18: 1027–1035.

[26] Ong WY, Stohler CS, Herr DR. Role of the Prefrontal Cortex in Pain Processing. Molecular Neurobiology. 2019; 56: 1137–1166.

[27] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005; 45: 201–206.

[28] Suppa A, Huang YZ, Funke K, Ridding MC, Cheeran B, Di Lazzaro V, *et al*. Ten Years of Theta Burst Stimulation in Humans: Established Knowledge, Unknowns and Prospects. Brain Stimulation. 2016; 9: 323–335.

[29] Chung SW, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB. Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews. 2016; 63: 43–64.

[30] 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 Stimulation. 2015; 8: 135–141.

[31] Klírová M, Hejzlar M, Kostýlková L, Mohr P, Rokyta R, Novák T. Prolonged Continuous Theta Burst Stimulation of the Motor Cortex Modulates Cortical Excitability But not Pain Perception. Frontiers in Systems Neuroscience. 2020; 14: 27.

[32] Li C, Zhang N, Han Q, Zhang L, Xu S, Tu S, *et al*. Prolonged Continuous Theta Burst Stimulation Can Regulate Sensitivity on Aβ Fibers: An Functional Near-Infrared Spectroscopy Study. Frontiers in Molecular Neuroscience. 2022; 15: 887426.

[33] De Martino E, Fernandes AM, Galhardoni R, De Oliveira Souza C, Ciampi De Andrade D, Graven-Nielsen T. 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. The Journal of Pain. 2019; 20: 1459–1469.

[34] Fillingim RB, Loeser JD, Baron R, Edwards RR. Assessment of Chronic Pain: Domains, Methods, and Mechanisms. The Journal of Pain. 2016; 17: T10–T20.

[35] Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. The Journal of Pain. 2016; 17: T70–T92.

[36] Smith SM, Dworkin RH, Turk DC, McDermott MP, Eccleston C, Farrar JT, *et al*. Interpretation of chronic pain clinical trial outcomes: IMMPACT recommended considerations. Pain. 2020; 161: 2446–2461.

[37] Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychological Bulletin. 2007; 133: 581–624.

[38] Auvray M, Myin E, Spence C. The sensory-discriminative and affective-motivational aspects of pain. Neuroscience and Biobehavioral Reviews. 2010; 34: 214–223.

[39] Thakkar B, Peterson CL, Acevedo EO. Prolonged continuous theta burst stimulation increases motor corticospinal excitability and intracortical inhibition in patients with neuropathic pain: An exploratory, single-blinded, randomized controlled trial. Neurophysiologie Clinique. 2023; 53: 102894.

[40] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, *et al*. 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. Clinical Neurophysiology. 2015; 126: 1071–1107.

[41] Mir-Moghtadaei A, Caballero R, Fried P, Fox MD, Lee K, Giacobbe P, *et al*. Concordance Between BeamF3 and MRI-neuronavigated Target Sites for Repetitive Transcranial Magnetic Stimulation of the Left Dorsolateral Prefrontal Cortex. Brain Stimulation. 2015; 8: 965–973.

[42] Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimulation. 2009; 2: 50–54.

[43] Trapp NT, Bruss J, King Johnson M, Uitermarkt BD, Garrett L, Heinzerling A, *et al*. Reliability of targeting methods in TMS for depression: Beam F3 vs. 5.5 cm. Brain Stimulation. 2020; 13: 578–581.

[44] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009; 42: 377–381.

[45] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, *et al*. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. 2019; 95: 103208.

[46] Preti A, Stocchino S, Pinna F, Deidda MC, Musu M, Sancassiani F, *et al*. BEEP-Bodily and Emotional Perception of Pain. A Questionnaire to Measure Reaction to Pain in Chronic Pain Disorders. Frontiers in Psychology. 2019; 10: 480.

[47] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Annals of the Academy of Medicine, Singapore. 1994; 23: 129–138.

[48] Zelman DC, Gore M, Dukes E, Tai KS, Brandenburg N. Validation of a modified version of the brief pain inventory for painful diabetic peripheral neuropathy. Journal of Pain and Symptom Management. 2005; 29: 401–410.

[49] Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. The Journal of Pain. 2004; 5: 133–137.

[50] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, *et al*. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. The Journal of Pain. 2008; 9: 105–121.

[51] Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales. 2nd edn. Psychology Foundation: Sydney. 1995.

[52] Brown TA, Chorpita BF, Korotitsch W, Barlow DH. Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. Behaviour Research and Therapy. 1997; 35: 79–89.

[53] Vinik EJ, Hayes RP, Oglesby A, Bastyr E, Barlow P, Ford-Molvik SL, *et al*. The development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy. Diabetes Technology & Therapeutics. 2005; 7: 497–508.

[54] Bredfeldt C, Altschuler A, Adams AS, Portz JD, Bayliss EA. Patient reported outcomes for diabetic peripheral neuropathy. Journal of Diabetes and its Complications. 2015; 29: 1112–1118.

[55] Lee YJ, Koch EMW, Breidebach JB, Bornemann R, Wirtz DC, Pflugmacher R. Diagnosis of Neuropathic Components in Patients with Back Pain Before and After Surgery. Zeitschrift Fur Orthopadie Und Unfallchirurgie. 2016; 154: 571–577.

[56] Cappelleri JC, Bienen EJ, Koduru V, Sadosky A. Measurement properties of painDETECT by average pain severity. ClinicoEconomics and Outcomes Research. 2014; 6: 497–504.

[57] Mercer Lindsay N, Chen C, Gilam G, Mackey S, Scherrer G. Brain circuits for pain and its treatment. Science Translational Medicine. 2021; 13: eabj7360.

[58] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, *et al*. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005; 113: 9–19.

[59] Onesti E, Gabriele M, Cambieri C, Ceccanti M, Raccah R, Di Stefano G, *et al*. H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy. European Journal of Pain. 2013; 17: 1347–1356.

[60] Yang S, Kwak SG, Choi GS, Chang MC. Short-term Effect of Repetitive Transcranial Magnetic Stimulation on Diabetic Peripheral Neuropathic Pain. Pain Physician. 2022; 25: E203–E209.

[61] Abdelkader AA, Gohary AME, Mourad HS, Salmawy DAE. Repetitive tms in treatment of resistant diabetic neuropathic pain. Egyptian Journal of Neurology, Psychiatry and Neurosurgery 2019; 55: 1–9.

[62] Malfliet A, Coppieters I, Van Wilgen P, Kregel J, De Pauw R, Dolphens M, *et al*. Brain changes associated with cognitive and emotional factors in chronic pain: A systematic review. European Journal of Pain. 2017; 21: 769–786.

[63] Garcia-Larrea L, Peyron R. Pain matrices and neuropathic pain matrices: a review. Pain. 2013; 154: S29–S43.

[64] Nardone R, Höller Y, Langthaler PB, Lochner P, Golaszewski S, Schwenker K, *et al*. rTMS of the prefrontal cortex has analgesic effects on neuropathic pain in subjects with spinal cord injury. Spinal Cord. 2017; 55: 20–25.

[65] To WT, De Ridder D, Hart J, Jr, Vanneste S. Changing Brain Networks Through Non-invasive Neuromodulation. Frontiers in Human Neuroscience. 2018; 12: 128.

[66] Fox MD, Halko MA, Eldaief MC, Pascual-Leone A. Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). NeuroImage. 2012; 62: 2232–2243.

[67] Zheng W, Woo CW, Yao Z, Goldstein P, Atlas LY, Roy M, *et al*. Pain-Evoked Reorganization in Functional Brain Networks. Cerebral Cortex. 2020; 30: 2804–2822.

[68] Wischnewski M, Schutter DJLG. Efficacy and Time Course of Theta Burst Stimulation in Healthy Humans. Brain Stimulation.

2015; 8: 685–692.
[69] Cárdenas-Morales L, Nowak DA, Kammer T, Wolf RC, Schönfeldt-Lecuona C. Mechanisms and applications of theta-burst rTMS on the human motor cortex. Brain Topography. 2010; 22: 294–306.
[70] Huang YZ, Lu MK, Antal A, Classen J, Nitsche M, Ziemann U, *et al*. Plasticity induced by non-invasive transcranial brain stimulation: A position paper. Clinical Neurophysiology. 2017; 128: 2318–2329.
[71] Granovsky Y, Sprecher E, Sinai A. Motor corticospinal excitability: a novel facet of pain modulation? Pain Reports. 2019; 4: e725.
[72] Goldsworthy MR, Vallence AM, Hodyl NA, Semmler JG, Pitcher JB, Ridding MC. Probing changes in corticospinal excitability following theta burst stimulation of the human primary motor cortex. Clinical Neurophysiology. 2016; 127: 740–747.
[73] Yang S, Chang MC. Effect of Repetitive Transcranial Magnetic Stimulation on Pain Management: A Systematic Narrative Review. Frontiers in Neurology. 2020; 11: 114.
[74] Moisset X, de Andrade DC, Bouhassira D. From pulses to pain relief: an update on the mechanisms of rTMS-induced analgesic effects. European Journal of Pain. 2016; 20: 689–700.
[75] 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. 2014; 155: 598–605.
[76] Rounis E, Huang YZ. Theta burst stimulation in humans: a need for better understanding effects of brain stimulation in health and disease. Experimental Brain Research. 2020; 238: 1707–1714.
[77] Huang YZ, Chen RS, Rothwell JC, Wen HY. The after-effect of human theta burst stimulation is NMDA receptor dependent. Clinical Neurophysiology. 2007; 118: 1028–1032.
[78] He W, Fong PY, Leung TWH, Huang YZ. Protocols of non-invasive brain stimulation for neuroplasticity induction. Neuroscience Letters. 2020; 719: 133437.
[79] Huang YZ, Rothwell JC, Chen RS, Lu CS, Chuang WL. The theoretical model of theta burst form of repetitive transcranial magnetic stimulation. Clinical Neurophysiology. 2011; 122: 1011–1018.
[80] Bliss TVP, Cooke SF. Long-term potentiation and long-term depression: a clinical perspective. Clinics. 2011; 66: 3–17.
[81] Li CT, Huang YZ, Bai YM, Tsai SJ, Su TP, Cheng CM. Critical role of glutamatergic and GABAergic neurotransmission in the central mechanisms of theta-burst stimulation. Human Brain Mapping. 2019; 40: 2001–2009.
[82] Jiang X, Yan W, Wan R, Lin Y, Zhu X, Song G, *et al*. Effects of repetitive transcranial magnetic stimulation on neuropathic pain: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews. 2022; 132: 130–141.
[83] Borckardt JJ, Reeves ST, Weinstein M, Smith AR, Shelley N, Kozel FA, *et al*. Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: a replication study. Brain Stimulation. 2008; 1: 122–127.
[84] Lefaucheur JP, Drouot X, Nguyen JP. Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. Neurophysiologie Clinique. 2001; 31: 247–252.
[85] Jetté F, Côté I, Meziane HB, Mercier C. Effect of single-session repetitive transcranial magnetic stimulation applied over the hand versus leg motor area on pain after spinal cord injury. Neurorehabilitation and Neural Repair. 2013; 27: 636–643.
[86] Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, *et al*. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain. 2007; 130: 2661–2670.
[87] Mhalla A, Baudic S, de Andrade DC, Gautron M, Perrot S, Teixeira MJ, *et al*. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. Pain. 2011; 152: 1478–1485.
[88] Attal N, Poindessous-Jazat F, De Chauvigny E, Quesada C, Mhalla A, Ayache SS, *et al*. Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. Brain. 2021; 144: 3328–3339.
[89] Lefaucheur JP, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. Neurology. 2006; 67: 1568–1574.
[90] Mittal N, Majdic BC, Peterson CL. Intermittent theta burst stimulation modulates biceps brachii corticomotor excitability in individuals with tetraplegia. Journal of Neuroengineering and Rehabilitation. 2022; 19: 73.
[91] Mittal N, Majdic BC, Sima AP, Peterson CL. The effect of intermittent theta burst stimulation on corticomotor excitability of the biceps brachii in nonimpaired individuals. Neuroscience Letters. 2021; 764: 136220.
[92] Mittal N, Thakkar B, Hodges CB, Lewis C, Cho Y, Hadimani RL, *et al*. Effect of neuroanatomy on corticomotor excitability during and after transcranial magnetic stimulation and intermittent theta burst stimulation. Human Brain Mapping. 2022; 43: 4492–4507.