Randomized Controlled Trial

Repetitive Transcranial Magnetic Stimulation of the Dorsolateral Prefrontal Cortex for Phantom Limb Pain

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Background: Phantom limb pain (PLP) is a prevalent and distressing occurrence in 60-80% of individuals who have undergone amputations. Recent research underscores the significance of maladaptive cortical plasticity in the genesis of PLP, emphasizing the importance of targeting cortical areas for therapeutic interventions. Repetitive transcranial magnetic stimulation (rTMS), a noninvasive tool for cortical stimulation, demonstrates effectiveness in treating various chronic pain conditions of neuropathic origin. Nevertheless, there exists a limited body of research investigating the application of rTMS as a therapeutic intervention specifically for managing PLP. Notably, the dorsolateral prefrontal cortex (DLPFC) plays a crucial role in central pain processing, suggesting its potential as a key therapeutic target in PLP treatment. There is a lack of adequate data regarding the effectiveness of DLPFC-targeting rTMS in alleviating the pain experienced by PLP patients.

Objective: In this study, our aim was to investigate the impact of 10 sessions of DLPFC-targeting rTMS on the pain status of individuals experiencing PLP.

Study Design: Randomized controlled trial.

Setting: Traumatic amputees reporting to the tertiary care center with PLP.

Methods: The study was approved by the Institute Ethics Committee (IECPG-299/27.04.2022) and registered in the Clinical Trials Registry of India (CTRI/2022/07/043938). Nineteen patients suffering from PLP were recruited and randomized into real or sham rTMS groups. In the real rTMS group, patients received 10 sessions of rTMS at the DLPFC contralateral to the amputation site. The rTMS, administered at 90% of the resting motor threshold (RMT), was delivered as 8 trains of 150 pulses per train at the rate of one Hz and an inter-train interval of 60 seconds. The total number of pulses per session was 1,200. The sham group received 10 sessions of sham rTMS through the perpendicular placement of an rTMS coil over the DLPFC. These sessions lasted for the same duration and included the same sounds as the real group but involved no active stimulation. The patients' pain status was evaluated using the Visual Analog Scale (VAS) at baseline, at the end of each session of real or sham rTMS and at the 15th, 30th, and 60th day after the the completion of real or sham therapy.

Results: A significant decrease in VAS scores was noted after 10 sessions of real rTMS that targeted the DLPFC, in contrast to the sham rTMS group. The real rTMS group's reduction in VAS scores also persisted during the follow-up.

Limitations: A few patients had to drop out due to physical restrictions and financial constraints. Consequently, only a small number of individuals were able to complete the study protocol successfully.

Conclusion: A regimen of 10 sessions of real rTMS of the DLPFC was associated with significant pain relief in patients with PLP, and the effects were sustained for 2 months. Therefore, the present study shows that rTMS of the DLPFC has potential as an effective therapeutic intervention for sustained pain relief in PLP patients.

Key words: Cortical reorganisation, cortical plasticity, DLPFC, neuropathic pain, noninvasive brain stimulation, neuromodulation, phantom limb pain, rTMS

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Phantom limb pain (PLP) is a chronic neuropathic pain affecting 40–80% of amputees (1-3).The pathophysiology of this debilitating condition has not been deciphered completely. However, reports of sensory and motor map remodeling in these patients suggest the role of maladaptive changes, involving glial and neural activity, as well as connections (4-7). Therefore, therapeutic modalities that can induce cortical modulation are being investigated. Repetitive transcranial magnetic stimulation (rTMS), a noninvasive tool for magnetic stimulation of the brain, has been shown to induce synaptic plasticity (8,9). rTMS has been successfully employed in treating various chronic pain conditions of neuropathic origin and thus shows potential as an effective treatment modality for PLP (9-12).

Very few investigations have been conducted into the effects of rTMS on PLP patients. Ahmed et al studied the effects of 5 sessions of 20 Hz rTMS over the motor cortex ipsilateral to the site of amputation in patients with PLP. The authors of the study reported that PLP patients experienced significant decreases in VAS and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scores, unlike patients who received sham treatment. These results were sustained at one month of follow-up (13). Similarly, 10 sessions of 10 Hz rTMS over the motor cortex contralateral to the site of amputation produced pain relief in PLP patients. This relief was still present at 2 months of follow-up (14). Therefore, these studies showed rTMS therapy had the potential to relieve pain.

The dorsolateral prefrontal cortex (DLPFC) has a central role in pain processing and modulation (15). Low-frequency stimulation of the DLPFC has been successful in providing sustained pain relief for chronic pain conditions of neuropathic origin, like fibromyalgia (16). However, there is a lack of data investigating the efficacy of low-frequency rTMS of the DLPFC for PLP. Two case reports have explored this matter, but the DLPFC was not the only site stimulated in either protocol (17,18). Hence, the pain relief cannot be attributed solely to rTMS of the DLPFC without a properly designed study to investigate its potential as a treatment modality for PLP.

Therefore, the present study was designed to assess the effect of DLPFC-targeting rTMS on the pain status of PLP patients and the technique's potential as a therapeutic tool with sustained analgesic effects for PLP.

Methods

The study was conducted in a the Pain Research and TMS Laboratory of the Department of Physiology at All India Institute of Medical Sciences (AIIMS), New Delhi, in collaboration with Jai Prakash Narayan Apex Trauma Centre (JPNATC) AIIMS, New Delhi, after approval from the Institute Ethics Committee (IECPG-299/27.04.2022), and registered in the Clinical Trials Registry of India (CTRI/2022/07/043938).

Traumatic amputees aged 18 to 65 years and suffering from PLP were recruited from JPNATC, after informed written consent. Patients with head deformities, pregnancy, neuropsychiatric disorders, cardiac pacemakers, medical pumps, metal implants, or any pathology that could alter the course of PLP (diagnosis of cancer, immunological disorders, renal insufficiency requiring dialysis treatment, etc.) were excluded from the study.

This was a randomized controlled trial. After screening, the patients were randomly allocated to the real (intervention) or sham (control) rTMS group in a one-to-one ratio using block randomization (block size of 4) (Fig. 1). The primary outcome measure was change in pain status as assessed by VAS score.

Pain assessment was done using the VAS scores at the baseline, after each intervention session, and at the 15th, 30th, and 60th day after the completion of the intervention.

Intervention

Ten sessions of real or sham rTMS intervention were given over 2 weeks. A Neuro MS/D (Neurosoft™) stimulator with a figure-8 coil was used for stimulation in both groups.

The patient was seated in a comfortable chair. Ag-AgCl surface electrodes (FIAB; 22*34mm) were placed on the abductor pollicis brevis (contralateral to the site of amputation) with a ground electrode on the wrist to acquire an electromyogram. The tentative hot spot was determined at 5 cm horizontally from the vertex on the scalp. Stimulation from the coil was delivered at this area to locate the point where the largest motor-evoked potentials were elicited. This area was deemed the motor hot spot. The resting motor threshold was defined as the minimal intensity required to elicit motor-evoked potentials of 50 mV peak-to-peak amplitude in 5 out of 10 consecutive trials at the motor hot spot.

The real and sham therapies were applied to the DLPFC contralateral to the site of amputation. The DLPFC was marked as 5 cm anterior to the motor hot spot (19). The area was marked in red ink for ensuring the stimulation of the same area in all sessions.

Real rTMS Therapy Protocol

Patients in this group received 10 sessions of rTMS at one Hz frequency, 90% RMT, and an intertrain interval of 60 seconds. Each session contained a total of 1,200 pulses, delivered over the course of 8 trains. The duration of the therapy was 26 minutes and 52 seconds (Fig. 2A).

Sham rTMS Therapy Protocol

Patients in this group received 10 sessions of sham rTMS stimulation though the perpendicular placement of the rTMS coil over the DLPFC so that no stimulation was delivered to the brain. The sham stimulation produced sounds like the real coil but without active stimulation of the brain. The duration of each therapy session was 26 minutes and 52 seconds, exactly as in the real rTMS group (Fig. 2B).

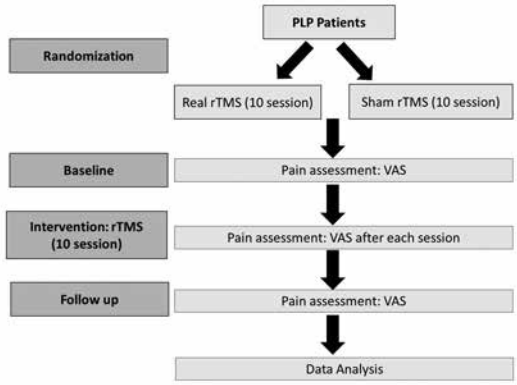

Fig. 1. *Experimental design of the study.*
The study was a randomized placebo-controlled patient blinded trial. Patients were randomly divided into real rTMS therapy (intervention group) or sham rTMS therapy (placebo control group). (PLP: phantom limb pain; rTMS: repetitive transcranial magnetic stimulation; VAS: visual analog scale.)

Fig. 2. *A. Patient set-up for real rTMS therapy.*
Figure shows patient with left leg amputated above knee, seated in a chair with stimulation coil placed over the right DLPFC, which is delivering sham real stimulation. (DLPFC: dorsolateral prefrontal cortex; rTMS: repetitive transcranial magnetic stimulation.)

B. Patient set-up for sham rTMS therapy (TMS coil in perpendicular orientation).
Figure shows patient with right arm amputated below elbow, seated in a chair with stimulation coil placed over left DLPFC, which is delivering sham rTMS stimulation. (DLPFC: dorsolateral prefrontal cortex; rTMS: repetitive transcranial magnetic stimulation.)

Statistical Analysis

Graph Pad Prism (version 9.5.0) (GraphPad Software, Inc.) was used for the data analysis. The normality of the data was checked using the Shapiro-Wilk normality test. Normally distributed data were represented as the mean ± SD. Skewed data were represented as the median (interquartile range). Intergroup comparisons were made using the Mann-Whitney test, and intragroup comparisons were made using the Friedman test. Post-hoc analysis was done using Dunn's multiple-comparisons test.

Results

Sixty patients were screened from May 2022 to November 2022. Of those patients, 19 were included in the study. Among them, complete data could be collected for 14 patients, since attrition occurred (Fig. 3). The patient characteristics are provided in Table 1. No differences between the real and the sham group were observed at the baseline (Table 1). The cause of amputation in all cases was trauma. All patients tolerated the rTMS without experiencing any adverse effects in any session.

Overall, the respective VAS ratings of the real group and the sham group showed significant differences from one another after 10 rTMS sessions and at the first and the third follow-up (Fig. 4).

After 9 sessions of rTMS therapy, the VAS scores of the patients in the real rTMS group [VAS: 1.50 (3.50-1.00)] showed a significant decline from what they were at the baseline [VAS: 6.50 (8.00-5.25)]. The significant decline in VAS scores was sustained at the end of the therapy [VAS: 0.00 (0.75-0.00)] and at days 15 [VAS: 0.00 (1.00-0.00)], 30 [VAS: 1.00 (2.00-0.00)], and 60 [VAS: 0.50 (1.75-0.00)] after the therapy. However, no significant difference from the baseline VAS scores was observed in the sham rTMS group during therapy or at any follow-up point (Fig. 5).

Discussion

In the present study, 10 sessions of low-frequency rTMS therapy of the DLPFC contralateral to the amputated limb resulted in a significant decline in the patient's subjective pain perception from the baseline, as assessed through VAS ratings. The analgesic effects were sustained during the follow-up until day 60 after the therapy.

Although the pathophysiology of PLP is still elusive, recent studies suggest that maladaptive cortical changes are the major cause of PLP (5,20). During cortical reorganization, the areas representing the amputated extremity are taken over by the neighboring areas in both the primary somatosensory and motor cortex, and the extent of the somatosensory cortex's involvement is correlated with the intensity of the phantom limb experience (2,5,21). fMRI mapping has shown cortical and colossal plasticity in the brains of amputees and found neuroplastic modifications in PLP patients (22). Several lines of evidence make it reasonable to assume that rTMS can alter synaptic strength through processes like LTP and LTD (8). Therefore, therapeutic modalities that target cortical areas, such as the version of rTMS described in this article are being explored as PLP treatments.

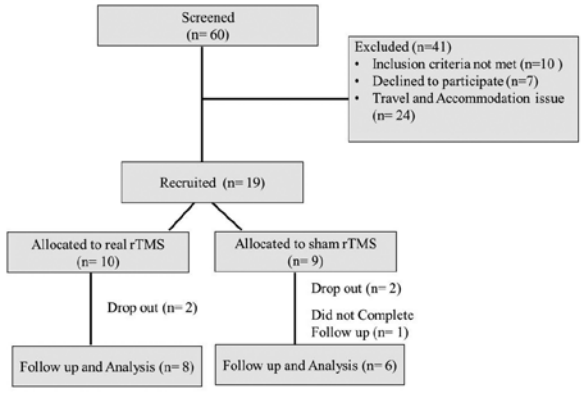

Fig. 3. *CONSORT flow diagram.*

Table 1. *Details of phantom limb pain patients in real and sham rTMS groups.*

Parameters	Real rTMS (n = 10)	Sham rTMS (n = 9)	*P* value
Age in years (mean ± SD)	28.87 ± 7.98	37 ± 13.24	0.26
Gender (Male: Female)	10:0	8:1	-
Duration of pain in weeks [median (interquartile range)]	4 (11.00-2.50)	7 (8-3)	0.98
VAS at baseline (mean ± SD)	6.5 ± 1.51	5.4 ± 1.51	0.21
Site of amputation Upper limb Lower limb	 2 8	 1 8	-

Values are expressed as mean ± SD for parametric and median (interquartile range) for nonparametric data; $P < 0.05$ is taken as significant. (rTMS: repetitive transcranial magnetic stimulation; VAS: visual analog scale.)

Not many studies have investigated the efficacy of rTMS therapy on PLP. Ahmed et al (13) have reported pain relief in 27 PLP patients after 5 sessions of 20 Hz rTMS of the ipsilateral motor cortex. Malavera et al (14) have reported similar results in 54 PLP patients after 10 sessions of 10Hz rTMS of the contralateral motor cortex. Apart from these, only a few case reports of rTMS therapy exist (17,18,23-25).

The DLPFC has received little investigation as a potential rTMS target in treatments meant to provide pain relief to PLP patients, despite DLPFC-targeting rTMS procedures' success in relieving pain caused by various chronic conditions of neuropathic origin (15). In a case report by Grammer et al, a PLP patient underwent 17 sessions of low-frequency rTMS of the primary sensory cortex (PSC) and 11 sessions of high-frequency rTMS of the DLPFC contralateral to the amputated arm. The initial PSC rTMS resulted in a VAS decrease from 5 to 2. The alternating stimulation of PSC and DLPFC resulted in a further decrease from 2 to one (17). Similarly, for a 69-year-old PLP patient whose right lower limb had been amputated, 30 sessions of rTMS over the primary sensory area (PSA), primary motor area (PMA), and DLPFC of the left hemisphere were applied, resulting in a VAS decline from 9 to 4 (18). Because, in these case reports, multiple areas were stimulated, it is difficult to ascertain how much the DLPFC-targeting rTMS contributed to the pain relief. Additionally, there is no information on whether the analgesic effects persist over the long term, despite sustained pain relief being an essential feature of any potential treatment strategy.

The present study showed that PLP patients experienced sustained pain relief after 10 sessions of low-frequency rTMS of the DLPFC and that the analgesic effects were sustained even at 60 days post-therapy.

The DLPFC has been hypothesized to play a critical role in the "top-down" mode of the inhibition of neuronal coupling along the ascending midbrain–thalamic–cingulate pathway through descending fibers from the prefrontal cortex (26). The DLPFC's gray matter has been shown to be associated with pain intensity in PLP (27). Similar findings have been reported in other chronic pain conditions (28). Furthermore, these morphological changes that are postulated to be associated with chronic pain have been shown in neuroimaging studies to be potentially reversible upon the successful treatment of pain (15,29).

We observed that the real rTMS group experienced a significant decrease in VAS scores after therapy, unlike the sham rTMS group, reflecting the role of the top-down modulation of pain processing. rTMS is speculated to induce alterations in the activity of brain structures, such as the orbitofrontal cortices, medial thalamus, anterior cingulate, and periaqueductal gray matter, that are involved in the modulation and pro-

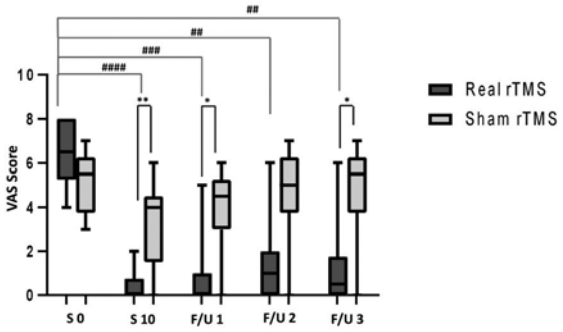

Fig. 4. *VAS rating at baseline (S0), after 10 sessions of sham (gray)/real (black) rTMS of DLPFC (S10), and at day 15 (F/U1), day 30 (F/U 2), and day 60 (F/U 3) after therapy.*
Values are expressed as median (interquartile range). # indicates a significant intra-group difference. * indicates a significant difference between sham rTMS and real rTMS group. *: $P < 0.05$; **P or ##: $P < 0.01$; ###: $P < 0.001$; ####: $P < 0.0001$. (DLPFC: dorsolateral prefrontal cortex; F/U: follow-up; rTMS: repetitive transcranial magnetic stimulation; S: session.)

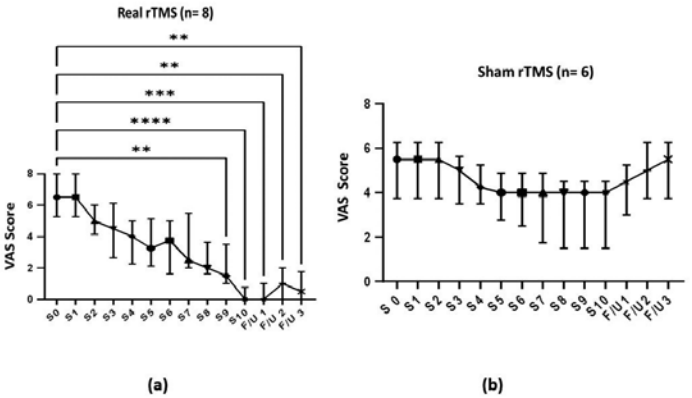

Fig. 5. *VAS rating at baseline (S0), after every session of real rTMS (a) or sham rTMS (b) of DLPFC (S1-S10), and at day 15 (F/U1), day 30 (F/U 2), and day 60 (F/U 3) after therapy.*
(*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$; ****: $P < 0.001$. DLPFC: dorsolateral prefrontal cortex; F/U: follow-up; rTMS: repetitive transcranial magnetic stimulation; S: session.)

cessing of pain (9,26,30). The DLPFC is associated with brain areas like the anterior cingulate cortex, amygdala, and anterior insula, that have roles in pain processing (15). rTMS of the DLPFC can potentially modulate the connections among these areas. Therefore, rTMS of the DLPFC may have a top-down mode of inhibition of neuronal connections along the ascending midbrain–thalamic–cingulate pathway through descending fibers from the prefrontal cortex.

Conclusion

Based on the findings of the present study, we can conclude that 10 sessions of low-frequency rTMS of the DLPFC in PLP patients produce a significant decrease in PLP, which is sustained even at 2 months after the therapy. This result encourages future exploration of this treatment protocol for providing effective and sustained relief from the debilitating condition of PLP.

Strengths and Limitations

This is the first study to report the effects of rTMS of the DLPFC on pain relief in PLP patients with a follow-up of 60 days. However, the high percentage of dropouts due to physical restrictions and financial constraint resulted in a small number of patients who could complete the study protocol. The small sample size is a limitation of the study.

Authors' Contributions

DV: Patient recruitment, data acquisition, analysis, interpretation, and preparation of the final manuscript; RB: Idea conception and study design, analysis, interpretation, and preparation of the final manuscript; SF: Data acquisition and analysis, preparation of the final manuscript; RKY: Analysis and interpretation of data, preparation of the final manuscript; SS: Clinical evaluation, screening and recruitment of patients, interpretation, and preparation of the final manuscript; NM: Clinical evaluation, screening, recruitment of patients, and preparation of the final manuscript; MAK: Data analysis and preparation of the final manuscript; AS: Idea conception and study design, data acquisition, analysis, interpretation, and preparation of the final manuscript

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