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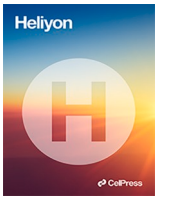

Case report

Thalamic stimulation modulated neural oscillations in central post-stroke pain: A case report

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ABSTRACT

The characterization of neural signatures within the somatosensory pathway is essential for elucidating the pathogenic mechanisms of central post-stroke pain (CPSP) and developing more effective treatments such as deep brain stimulation (DBS). We explored the characteristics of thalamic neural oscillations in response to varying pain levels under multi-day local field potential (LFP) recordings and examined the influences of continuous DBS on these thalamic activities. We recorded LFPs from the left ventral posterolateral thalamus (VPL) of a patient with CPSP in the resting state under both off- and on-stimulation conditions. We observed significant differences in the power spectral density (PSD) of different pain levels in the delta, theta and gamma frequency bands of the left VPL; 75Hz DBS significantly increased the PSD of delta and decreased the PSD of low-beta, while 130Hz DBS significantly reduced the PSD of theta and low-beta. Thalamic stimulation modulated the neural oscillations related to pain, and the changes in neural activities in response to stimulation could serve as quantitative indicators for pain relief.

1. Introduction

Central post-stroke pain (CPSP) is a neuropathic pain syndrome developing after cerebrovascular accidents and is often medically refractory. Characterization of neural signatures within the somatosensory pathway is essential for elucidating the pathogenic mechanisms of CPSP and developing more effective treatments. In our previous studies, we found two distinct oscillatory networks that were responsible for pain perception and pain modulation in the sensory thalamus [1]. However, it remains unclear how deep brain stimulation (DBS) modifies these thalamic activities during CPSP treatment. We report a case of a patient with medically refractory CPSP who received DBS modulation in the left ventral posterolateral thalamus (VPL) and right central lateral thalamus (CL). Specifically, we explored the characteristics of thalamic neural oscillations associated with different pain levels under multi-day local field

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potential (LFP) recordings, in addition to the influence of DBS on thalamic activities.

2. Case report

2.1. Participant

A 61-year-old female developed progressive and persistent right-sided neuropathic pain after a left thalamic hemorrhagic stroke 13 years ago. The pain was described as stabbing, cramping, and burning, and the highest pain intensity was on the right side of the face and the right upper limb. The pain level varied between 6 and 9 on a numerical rating scale (NRS) in the range of 0–10 (0 = no pain, 10 = maximal pain). The Brief Pain Inventory (BPI) intensity and interference scores were 8 and 6.14, respectively. She experienced this unpredictable pain 2–4 times a day, lasting 1–2 hours each time. A diagnosis of CPSP was thus clinically established. Besides the pain, the patient reported allodynia causing discomfort from light contact. No other neurological issues, such as muscle weakness or atrophy in the affected limbs, were observed. Chronic pain was also comorbid with depression [17-item Hamilton Depression Rating Scale (HAMD-17) score of 21) and anxiety [14-item Hamilton Anxiety Rating Scale (HAMA-14) score of 14]. Pharmacotherapy, including pregabalin, amitriptyline, duloxetine, and traditional Chinese medicine, was unsatisfactory. Transcutaneous electrical nerve stimulation was also unsuccessful. On admission, the patient was receiving no long-term drug treatment.

Because the CL [2] and VPL [1,3] are the two preferred targets for chronic pain treatment in lesional and DBS procedures, respectively, two DBS electrodes (Model 1200–40; SceneRay, Suzhou, China) were implanted in the left VPL and right CL (Fig. 1A) and externalized for 1 week. The location of the DBS lead was verified on the merged images of the postoperative CT scan and the preoperative MR images in the thalamic functional atlas using the lead-DBS toolbox (Fig. 1B) [4–7].

2.2. Stimulation and local field potential recordings

The implanted DBS electrodes were externalized for 1 week. The left VPL LFPs were recorded in a bipolar manner between contacts 1 and 4. Resting-state LFP recordings began around 9:30 a.m. on four consecutive days from the second day postoperatively, and the recording lasted 1–5 hours. The LFPs were recorded during 30 minutes of stimulation at frequencies of 15, 75, and 130Hz with a 30-min washout period between adjacent stimulations. The sampling frequency was 1000Hz. Stimulation began at 10:30 a.m. on the third and fourth days. Unipolar stimulation was used with contact 2 as negative and the shoulder as positive. Stimulation frequencies of 75,

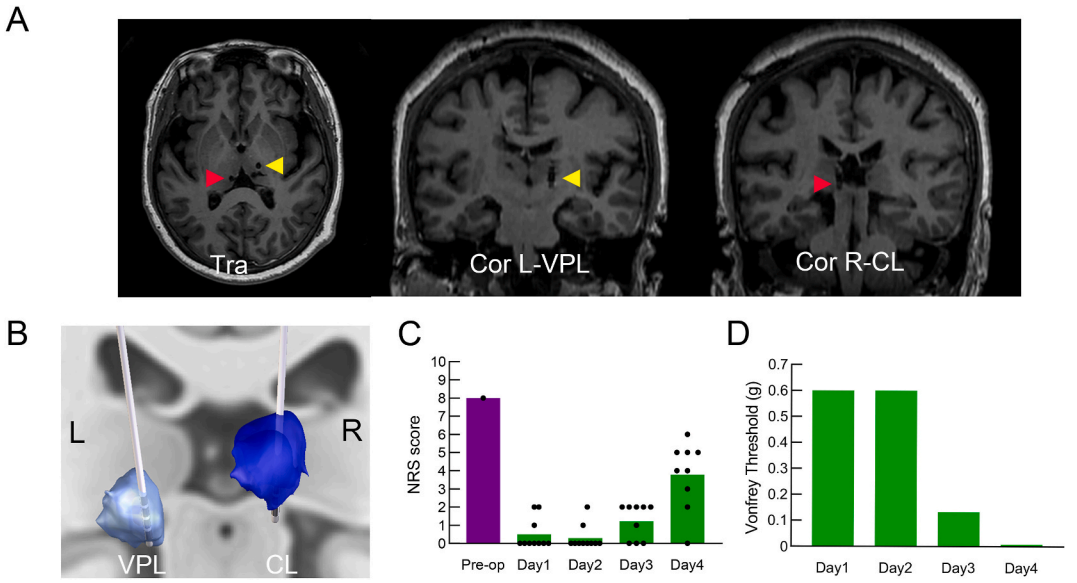

Fig. 1. Lead location, pain quantification, and characteristics of thalamic neural oscillations (A) Electrode location in transverse and coronal views. The patient underwent Leksell frame-based staged DBS surgery under general anesthesia. Stereotactic computed tomography (CT) scans were co-registered to the preoperative 3.0 T high-resolution MR images in SurgiPlan for surgical planning. Initial coordinates of the right CL target were on the anterior commissure-posterior commissure (AC-PC) line, 0–2 mm anterior to the PC and 7–8 mm lateral to the AC-PC line. The left VPL target was 3–5 mm anterior to the PC and 12–15 mm lateral to the AC-PC line. The coordinates were then adjusted in a T2-weighted sequence. A conventional frontal approach was applied, and trajectories were adjusted to avoid blood vessels. A postoperative CT scan was performed immediately after DBS lead implantation to exclude intracranial hemorrhage and then fused with preoperative MR images to ensure a satisfactory lead placement [17,18]. The coordinate of the most ventral contact of the lead targeting the right CL was 2.3 mm below the AC-PC line, 2.7 mm anterior to the PC, and 8.7 mm lateral to the AC-PC line. The coordinate of the most ventral contact of the lead targeting the left VPL was 0.4 mm below the AC-PC line, 5.5 mm anterior to the PC, and 10.2 mm lateral to the AC-PC line. (B) The electrodes were visualized in 3-D using the lead-DBS toolbox. (C) The pain level was assessed preoperatively and 1–4 days postoperatively with NRS scores. (D) The pain threshold was assessed using the von Frey approach.

130, and 15Hz were randomly applied with more than 30 minutes washout period.

2.3. Assessments

Multidimensional assessments were conducted before the operation and at the sixth and seventh month of follow-up. We measured the therapeutic effectiveness of the stimulation using the BPI and the short form of the McGill Pain Questionnaire (SF-MPQ) to determine the improvement in the patient's subjective feeling. The SF-MPQ subscales include the Pain Rating Index (PRI), Visual Analog Scale (VAS), and Present Pain Pntensity (PPI). We used the 17-item version of the HAMD-17 and the 14-item version of the HAMA-14 to record mood changes. The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate the patient's quality of sleep. During resting-state LFP recordings in the externalization period, the NRS was assessed every 10 minutes. Additionally, mechanical sensitivity was objectively assessed each day with the "up-down" method of the von Frey test on the right cheek, where the pain level was highest. The test employs a set of calibrated monofilaments or hairs, known as von Frey hairs, which exert specific forces when applied perpendicularly to the skin until they bend. The threshold for a response is determined by the force at which a patient reports

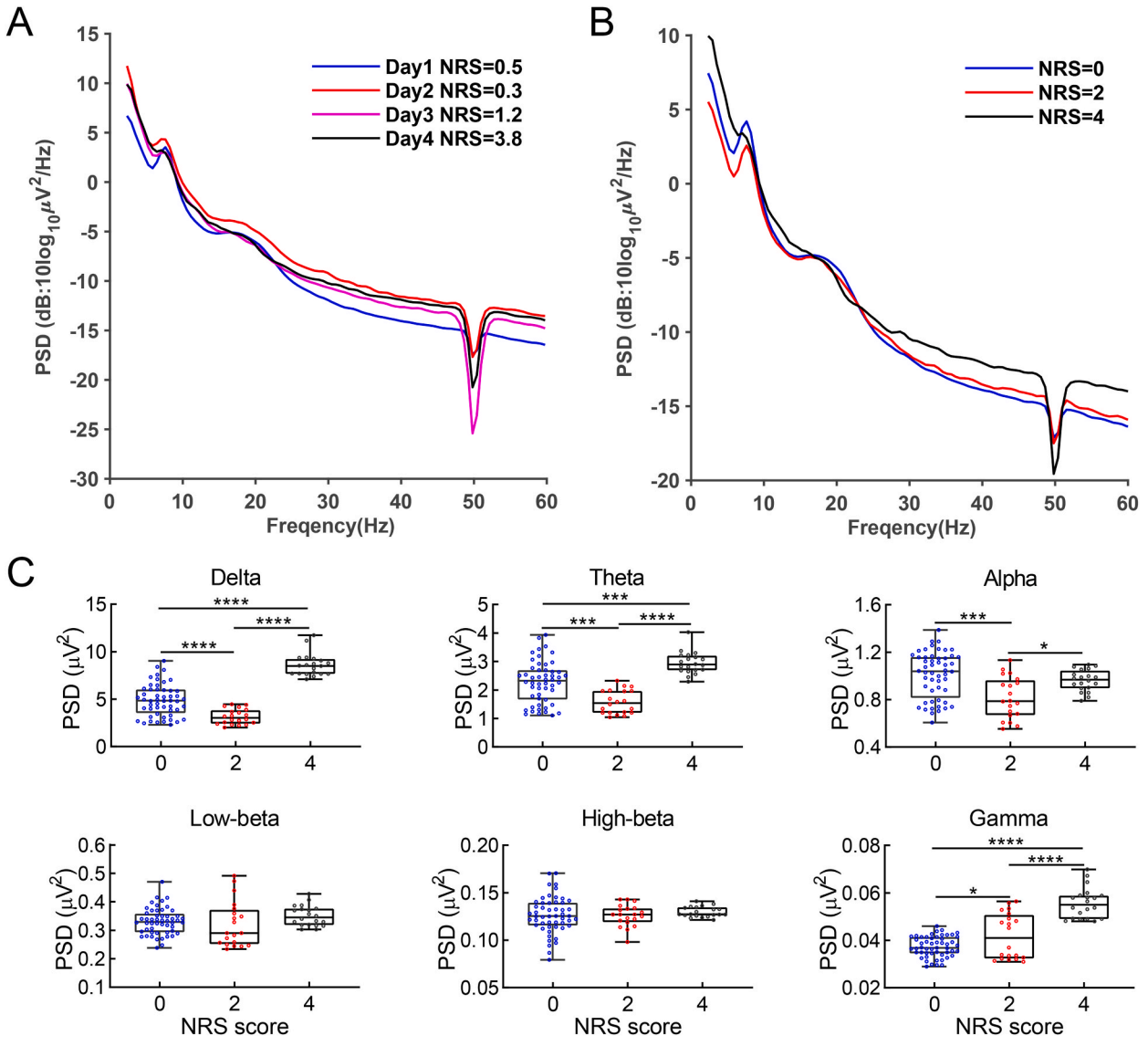

Fig. 2. Characteristics of thalamic neural oscillations at different pain levels in resting state (A) Averaged power spectra of LFPs of the VPL were calculated on each day of the trial. (The number of 60-s epochs for analysis: N-day 1 = 73; N-day 2 = 31; N-day 3 = 25; N-day 4 = 27. The NRS scores in the legend are daily averages.) (B) Averaged PSD of LFPs of the VPL were calculated at different pain levels. (N [NRS = 0] = 52; N [NRS = 2] = 20; N [NRS = 4] = 20.) (C) PSDs at each frequency band were computed at each pain level, and the delta, theta, and gamma oscillations increased significantly with increasing pain level. (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; ****, $p < 0.0001$).

the beginning of pain sensation.

The study protocol was approved by the ethics committee at Ruijin Hospital, and the patient provided written informed consent for both the surgery and the publication of this case report and any accompanying de-identified data.

2.4. Signal process and analysis

During LFP recording, the pain level was assessed with a NRS score every 10 minutes; 10-min LFP segments were extracted, centered on each pain assessment. These LFP segments were preprocessed with a low-pass filter at 90 Hz, a high-pass filter at 2 Hz to eliminate baseline shifting, an adaptive notch filter to remove 50 Hz line noise, and down-sampling to 300Hz. Each segment was then divided into ten 1-min segments, and 1-min segments with interference or artifacts were excluded. The power spectra were calculated using the Welch method with a 1-s window and a 0.75-s overlap for each 1-min LFP segment. The power was calculated at each frequency band: delta (δ, 2–4 Hz), theta (θ, 4–8 Hz), alpha (α, 8–12 Hz), low-beta (lβ, 12–20 Hz), high-beta (hβ, 20–30 Hz), and gamma (γ, 30–60 Hz), and then averaged for all segments at each assessment. Comparisons between different pain levels were conducted via ANOVA and Bonferroni multiple comparison tests. Comparisons between different stimulation stages were conducted via mixed-effects model and Bonferroni multiple comparison tests.

3. Results

The patient underwent the DBS lead implantation uneventfully. The average NRS score was 8 before surgery. This decreased to <1 on the first and second day after the surgery, then increased to 4 on the fourth day (Fig. 1C). The von Frey test showed an opposite trend, with the threshold decreasing from 0.6 to 0.008 g postoperatively (Fig. 1D). The differences between the NRS scores and Von Frey thresholds represented the patient's increase in subjective pain perception and increase in objective pain sensitivity, respectively.

Fig. 2A shows the averaged power spectral density (PSD) of the LFPs of the VPL on each day of the trial. Due to the variability in the level and duration of pain, the power spectra of consecutive days had no obvious regularity. Therefore, we classified LFP epochs according to different pain levels and plotted the average power spectra (Fig. 2B). The power spectra of VPL LFPs at different frequency

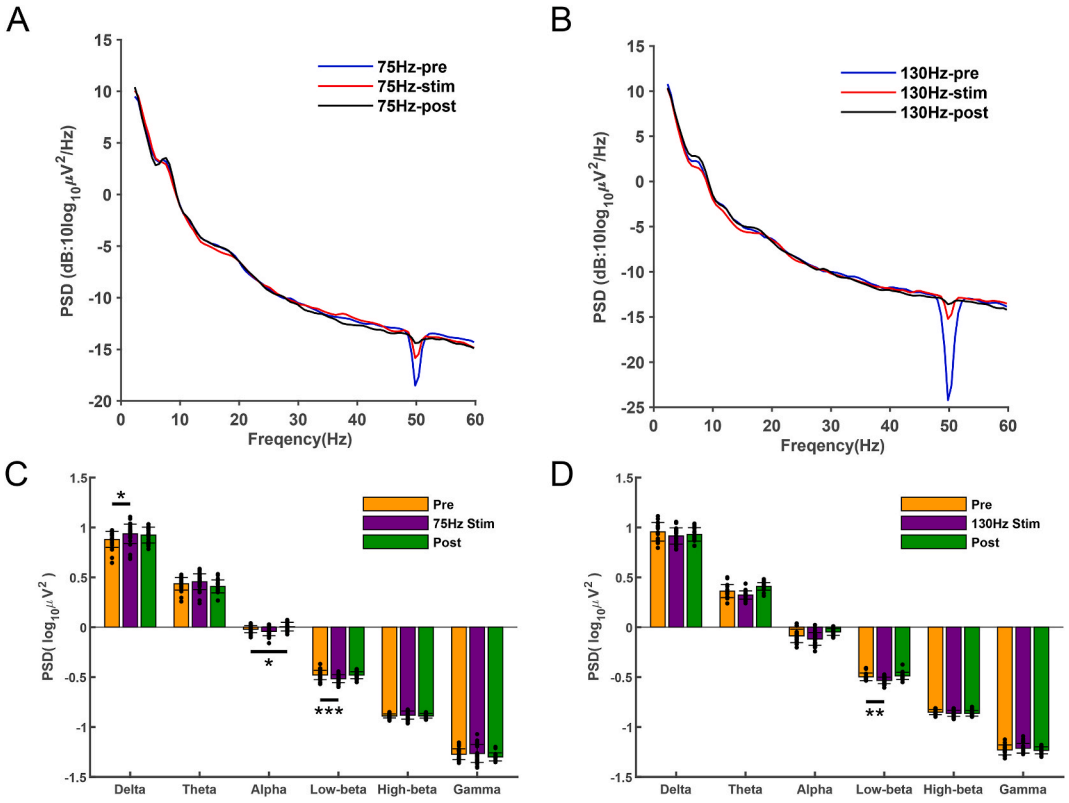

Fig. 3. Characteristics of thalamic neural oscillations indifferent stimulation states (A) PSDs of LFPs of the VPL were computed at pre-, mid, and post-stimulation states of 75Hz stimulation. (N-pre = 26; N-stim = 31; N-post = 19.) (B) PSDs of LFPs of the VPL were computed at pre-, mid, and post-stimulation states of 130Hz stimulation. (N-pre = 17; N-stim = 30; N-post = 22.) (C) Influence of 75Hz thalamic stimulation on the power spectra of LFPs (mean ± SEM). (D) Influence of 130Hz thalamic stimulation on the power spectra of LFPs (mean ± SEM). (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; ****, $p < 0.0001$).

bands were compared between the pain-free (NRS = 0), mild (NRS = 2), and moderate (NRS = 4) levels (Fig. 2C). Gamma oscillations were significantly higher at the moderate pain level than at the pain-free and mild pain level ($F [2, 89] = 62.32$, $p < 0.0001$). Both the theta ($F [2, 89] = 24.62$, $p < 0.0001$) and delta ($F [2, 89] = 77.78$, $p < 0.0001$) oscillations showed a similar pattern of oscillations that was significantly higher at the moderate level (ANOVA, $p < 0.001$). Conversely, alpha oscillation showed no significant difference between pain-free and moderate pain levels ($F [2, 89] = 8.988$, $p = 0.0003$). Additionally, low-beta ($F [2, 89] = 1.684$, $p = 0.1915$) and high-beta ($F [2, 89] = 0.3754$, $p = 0.6881$) oscillations had similar distributions at different pain levels.

Mean PSDs of different stimulation stages at 75 Hz and 130 Hz are shown in Fig. 3A and B. Mixed-effects model and Bonferroni multiple comparison tests (control: pre-stimulation) were conducted to compare oscillations at different stimulation stages. The mean PSD of pre-stimulation DBS at 75 Hz suppressed low-beta oscillations and increased delta and alpha oscillations (Fig. 3C; delta, $F [1.789, 65.29] = 3.743$, $p = 0.0334$; theta, $F [1.979, 72.24] = 3.111$, $p = 0.0511$; alpha, $F [1.894, 40.72] = 11.09$, $p = 0.0002$; low-beta, $F [1.697, 36.49] = 11.56$, $p = 0.0003$; high-beta, $F [1.435, 52.38] = 0.8907$, $p = 0.3855$; gamma, $F [1.263, 27.15] = 0.4258$, $p = 0.5659$). DBS at 130 Hz suppressed low-beta oscillations (Fig. 3D) (delta, $F [1.492, 27.61] = 1.290$, $p = 0.2828$; theta, $F [1.682, 55.52] = 20.52$, $p < 0.0001$; alpha, $F [1.562, 28.90] = 11.61$, $p = 0.0005$; low-beta, $F [1.881, 34.80] = 11.67$, $p = 0.0002$; high-beta, $F [1.972, 65.07] = 1.018$, $p = 0.3661$; gamma, $F [1.873, 34.65] = 1.706$, $p = 0.1978$).

The stimulator was internalized after the externalized trial phase. The initial parameters were defined after a monopolar review (60 μs, 130 Hz) before discharge. The goal of programming was to achieve satisfactory anticipated pain relief without intolerable stimulation-related side effects (e.g., strong paresthesia or muscle contraction). No severe adverse and unanticipated events were documented. Table 1 shows the postoperative parameters. We further compared the efficacy of thalamic DBS on pain relief, mood, and quality of sleep over 6 months of follow-up. Each side was stimulated for 1 month, and evaluation was performed at the end of each period. Left VPL stimulation (C+1-2-, 3.45 V, 50 μs, 160 Hz) led to considerable improvement, with the VAS score decreasing from 8 to 5. The mean BPI interference score improved by 27.9 %, from 6.14 to 4.43. Moreover, the HAMD-17 and HAMA-14 scores decreased by 47.6 % and 57.9 %, respectively, and the quality of sleep evaluated by the PSQI improved by 23.5 %. Table 2 shows the clinical outcomes. The patient was generally satisfied with the efficacy of the current stimulation regimen in terms of pain relief, anti-anxiety, and sleep improvement. Right CL (C+5-6-, 4.75 V, 90 μs, 180 Hz) stimulation did not have a clinically relevant impact on the pain level, suggesting that unilateral sensory thalamus DBS (ipsilateral to the stroke lesion side) should be sufficient for pain relief. Thereafter, only the left VPL DBS was turned on. The patient took levetiracetam 1g/d, flupentixol 1 mg/d and melitracen 20mg/d postoperatively.

4. Discussion

A previous study found that 43 % of patients showed a substantial reduction (60%–100 %) in their pain scores immediately after the insertion of the electrodes in the absence of stimulation, and the absence of these effects indicated unsuccessful surgery [8]. Such microlesional effects can be an intervention that helps relieve the pain, and the current study further investigated the simultaneous correlations between changes in pain level and electrophysiological activities. The causal relationship will be explored in long-term wireless LFP recordings with a PINS G106RS DBS stimulator.

Our previous studies investigated the relationship between thalamic activities and perception of neuropathic pain [1,9]. An increase in thalamic alpha oscillations has been correlated with subjective pain intensity in patients with neuropathic pain [9]. Our further research on dynamic neural states revealed the involvement of thalamic delta, theta, and gamma oscillations in pain perception [1]. With the LFP recordings in this study, we found an increase in delta, theta, and gamma oscillations with increasing pain levels. Basha et al. reported the coincidence of phantom sensations and thalamic gamma oscillatory discharges [10]. This evidence suggests thalamic gamma oscillations may be essential to pain perception.

The influence of DBS on thalamic neural oscillations has not been extensively investigated. Our previous work suggested theta, alpha, beta, and gamma oscillations were correlated with levels of pain relief, with low-beta playing a key role [3]. This study further demonstrates the direct effect of high-frequency thalamic stimulation on the suppression of low-beta oscillation. The clinical relevance of the findings needs further research, especially the changing of beta oscillations due to stimulation showed small effects. The postoperative pain relief and effect of thalamic stimulation on LFPs may be influenced by the postoperative microlesion effect, and long-term recording of LFPs with an implantable device is desirable and essential for future research in this field [11,12].

CPSP treatment remains challenging [13], and chronic thalamic stimulation only achieved moderate pain relief in this case. Despite

Table 1
Postoperative programming of the patient.

Time	Target	Contact	Pulse width/μs	Frequency/Hz	Amplitude/V
Post-op	L-VPL	1-2+	60	130	2
	R-CL	5-6+	60	130	3
1 month	L-VPL	C+1-	60	180	3
		0-1+	60	180	3
	R-CL	C+6-	90	215	4
		C+5-	90	215	3.5
6 months	R-CL	C+5-6-	90	180	4.75
7 months	L-VPL	C+1-2-	50	160	3.45

Note: C, Case; -, negative; +, positive; CL, central lateral thalamus; VPL, ventral posterolateral thalamus; L, left; R, right.

Table 2
Summary of the clinical outcomes over time.

Items	Pre-op	6-month follow-up	7-month follow-up
BPI			
Intensity	8	5	5
Interference	6.14	4.43	4.43
SF-MPQ			
PRI	18	11	11
VAS	8	7	5
PPI	3	3	2
HAMA-14	19	4	8
HAMD-17	21	17	11
PSQI	17	12	13

Abbreviation: BPI, brief pain inventory; SF-MPQ, short form of McGill pain questionnaire; PRI, pain rating index; VAS, visual analog scale; PPI, present pain intensity; HAMD-17, the 17-item version of the Hamilton Depression Rating Scale; HAMA-14, the 14-item version of the Hamilton Anxiety Rating Scale; PSQI, Pittsburgh sleep quality index.

a significant increase in delta, theta, and gamma oscillations with increasing pain levels, thalamic stimulation only suppressed the low-beta oscillations. Novel closed-loop stimulation strategies specifically targeting the modulation of these key oscillations could provide more effective treatment for neuropathic pain [14–16].

5. Conclusions

The refractory CPSP patient achieved moderate pain relief by chronic thalamic stimulation. DBS modulated the neural oscillations related to pain, and the response of neural activities to the stimulation could be taken as quantitative indicators of pain relief. Oscillation-based closed-loop stimulation strategies could be promising future methods to improve the treatment effect on neuropathic pain.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Qiyu Niu: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Zhengyu Lin:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Wenying Xu:** Writing – review & editing, Investigation, Data curation. **Kejia Hu:** Investigation, Formal analysis. **Yingnan Nie:** Investigation, Funding acquisition. **Dianyou Li:** Writing – review & editing, Supervision, Resources. **Shouyan Wang:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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