

## ABSTRACT

**Objective:** This study aims to investigate the link between the neurophysiological activity from the sensory thalamus and periventricular gray / periaqueductal gray (PVAG) and the pain relief by deep brain stimulation (DBS).

**Methods:** Local field potentials (LFPs) were recorded from the sensory thalamus and PVAG post-operatively from ten patients with neuropathic pain. The LFPs were quantified using spectral and time-frequency analysis, the relationship between the LFPs and pain relief was quantified with nonlinear correlation analysis.

**Results:** The theta oscillations of both sensory thalamus and PVAG negatively correlated with pain relief. The high beta oscillations in the sensory thalamus and the alpha oscillations in the PVAG positively correlated with pain relief. Moreover, the ratio of high-power duration to low-power duration of theta band activity in the sensory thalamus and PVAG negatively correlated with pain relief. The duration ratio at the high beta band in the sensory thalamus positively correlated with pain relief.

**Conclusions:** Our results reveal distinct neuronal oscillations at the theta, alpha, and beta frequencies correlating with pain relief by DBS.

**Significance:** The study provides quantitative measures for predicting the outcomes of neuropathic pain relief by DBS as well as potential biomarkers for developing adaptive stimulation strategies.

Characteristics of local field potentials correlate with pain relief by deep brain stimulation

Yongzhi Huang<sup>a,b</sup>, Huichun Luo<sup>a,b</sup>, Alexander L. Green<sup>c</sup>, Tipu Z. Aziz<sup>c</sup>, Shouyan Wang<sup>a,\*</sup>

<sup>a</sup>Suzhou Institute of Biomedical Engineering and Technology, Chinese Academy of Sciences, Suzhou, China

<sup>b</sup>University of Chinese Academy of Sciences, Beijing, China

<sup>c</sup>Nuffield Department of Surgery, John Radcliffe Hospital, University of Oxford, Oxford, UK

Shouyan Wang, \*Corresponding author.

Address: 88 Ke Ling Lu, Ke Ji Cheng, SND, Suzhou, Jiangsu Province, China, 215163

Tel: +86 (512) 6958 8242

Fax: +86 (512) 6958 8088

E-mail address: Shouyan Wang (swang@sibet.ac.cn)

Yongzhi Huang (huangyz@sibet.ac.cn), Huichun Luo (364418022@qq.com), Alexander L. Green (alex.green@nds.ox.ac.uk), Tipu Z. Aziz (tipu.aziz@nds.ox.ac.uk)

## Highlights

- An approach to screen the quantitative neurophysiological characteristics correlated to pain relief provided by deep brain stimulation.
- The  $\theta$ ,  $\alpha$  and  $\beta$  oscillations in thalamus or periventricular grey were significantly correlated to the pain relief.
- The dynamics of these neural oscillations could potentially be the biomarkers for predicting and modulating the pain relief.

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(PVAG) and the pain relief by deep brain stimulation (DBS).

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**Keywords** Deep brain stimulation; Neuropathic pain; Local field potentials; Neural oscillations; Spectra; Time-frequency

## 1. Introduction

Neuropathic pain is one of the most debilitating diseases and it usually responds poorly to conventional pharmacological treatment (Dworkin et al. , 2007, Dworkin et al. , 2010, Smith, 2012). In recent years, deep brain stimulation (DBS) of the sensory thalamus, periventricular gray / periaqueductal gray (PVAG) and anterior cingulate cortex have been used to treat neuropathic pain (Hosobuchi et al. , 1973, Mazars, 1975, Bittar et al. , 2005, Owen et al. , 2006a, Boccard et al. , 2014, Russo et al. , 2015). DBS has long-term efficacy in pain relief and improvement of emotional well-being and quality of life (Boccard et al. , 2013, Gray et al. , 2014). However, there are still great challenges in routinely conducting DBS for neuropathic pain because of the variability of outcome and unpredictability of success in individual subjects (Bittar et al. , 2005, Hamani et al. , 2006, Levy et al. , 2010, Boccard et al. , 2013). Also, there is a lack of objective guidance for optimizing the neuromodulation parameters, for instance, the stimulation frequency. In addition, clear understanding of the underlying mechanisms of stimulation response remains elusive.

Neurophysiological investigation of the targeted nuclei may reveal their roles in pain perception and modulation, and provide rationales for optimizing the deep brain stimulation for neuropathic pain.

Neurophysiological recordings in vivo in both animals and patients have demonstrated that there are different patterns of neuronal activity in the sensory thalamus and PVAG related to pain perception. There are increased spontaneous discharges, enlarged pain receptive fields, and rhythmic oscillatory firing in neurons in the ventral posterolateral nucleus of the thalamus (VPL) in animal models of neuropathic pain (Hains et al. , 2005, 2006, Jhaveri et al. , 2008, Iwata et al. , 2011). Effective therapies such as opioids and motor cortex stimulation were found to

increase the firing activity of PAG neurons (Chiou et al. , 1999, Sohn et al. , 2000, Pagano et al. , 2012). A recent study identified a direct correlation between the magnitude of evoked field potentials in the PAG and pain-related behavior in rats, suggesting that the PAG displays electrophysiological modulations related to the subjective experience of pain (Butler et al. , 2011). Significant increases in burst firing of thalamic neurons have been reported in patients with different forms of neuropathic pain (Lenz et al. , 1989, Lenz et al. , 1994, Lenz et al. , 1998, Radhakrishnan et al. , 1999).

Recording the deep brain local field potentials (LFPs) of sensory thalamus and PVAG provides unique opportunities to explore the function of these nuclei in patients with neuropathic pain. Our previous studies have started to elucidate the oscillatory neural activities and how they correlate to pain perception, and potentially a mechanistic link between PVAG DBS and opioidergic (Pereira et al. , 2013) or autonomic function (Green et al. , 2006). It has been found that an 8-14 Hz spindle-shaped neural signal in both the sensory thalamus and PVAG correlates to the subjective reporting of pain intensity (Green et al. , 2009). Moreover, there is a power increase at 17-30 Hz in the sensory thalamus and 8-12 Hz in the PAG due to painful ice-cold stimulus in patients with neuropathic pain (Green et al. , 2009). Further work has indicated reciprocal interactions between the sensory thalamus and PVAG (Wu et al. , 2014), and naloxone switches the low frequency and gamma activities in PVAG, which enhances awareness of worsening pain with opioid blockade (Pereira et al. , 2013). LFPs have been used to provide biomarkers for movement disorders, such as Parkinson's disease. Increasing evidence suggests that beta oscillations in the LFPs correlate with motor impairment and reduce with treatment (Kuhn et al. , 2005, Kuhn et al. , 2006, Little et al. , 2012), and have been shown to be suitable for feedback control of DBS therapy

(Little et al. , 2013).

The present study aimed to quantify the oscillatory neural activity and its time-variant changes of the LFPs in sensory thalamus and PVAG in the frequency and time-frequency domains, and identify the relationship between the quantitative measures of neural oscillations and pain relief by DBS.

## **2. Methods**

### ***2.1 Subjects***

Ten patients with chronic neuropathic pain were recruited (age,  $46 \pm 9$  years; mean  $\pm$  SD). All patients underwent unilateral implantation of DBS electrodes into both the sensory thalamus and PVAG at the John Radcliffe Hospital, Oxford. The study was performed according to the Declaration of Helsinki and approved by the Oxford Local Ethics Committee (OxRec B), and informed written consent was given by all patients.

### ***2.2 Surgical technique***

The surgical procedures of targeting and implantation of DBS electrodes (model 3387<sup>TM</sup>, Medtronic<sup>®</sup>) have been previously described (Bittar et al. , 2005, Owen et al. , 2006b, Boccard et al. , 2013, Wu et al. , 2014). In brief, the DBS target structures were localized on the fused CT/MRI images using Radionics Image Fusion<sup>TM</sup> and Stereoplan<sup>TM</sup> (Radionics, Burlington, MA, USA) pre-operatively and electrode implantation was then performed under local anesthesia. Intraoperative electrode localization was aided by eliciting feelings of warmth in the area of pain during PVAG stimulation, and paresthesia during thalamic stimulation. The final electrode placement and localization of each electrode contact were confirmed for all patients on fused imaging of post-operative CT or MRI scan and the pre-operative MRI. In all patients, the DBS electrodes were externalized for one week of trial stimulation to

assess the degree of pain relief, and the LFPs were recorded between three to five days after electrode implantation.

The sensory thalamus targets (VPL/VPM) are based on coordinates relative to the midcommissural point (MCP). For VPM, this is 5–8 mm posterior ( $y$ ), 10–12 mm lateral ( $x$ ) and at the level of the AC–PC plane ( $z = 0$ ). For VPL,  $y$  and  $z$  are the same, but  $x = 12$ –14 mm and just medial to the posterior limb of the internal capsule. Awake intraoperative testing confirms that the stimulation is somesthetically correct and the electrode can be re-sited if necessary. The PVAG is targeted at the level of the superior colliculus but with the electrode tip in the ventrolateral PAG region, 3–5 mm from the midline and just anterior to the aqueduct. The anterior and posterior commissures were identified on the axial images. The intended target for placing the deepest electrode contact was marked at the PAG at a level of <10 mm below the anterior commissure/ posterior commissure line; between the dorsal part of the red nucleus and the superior colliculus in the anteroposterior plane; and approximately 5 mm lateral to the lateral boundary of the aqueduct and the third ventricle. The trajectory is such that the proximal contacts are 2–3 mm lateral to the third ventricle at the level of the posterior commissure, approximately 10 mm posterior to the MCP (Wu et al. , 2014).

### ***2.3 Pain assessment***

All patients were asked to rate their pain on a visual analog scale (VAS, 0-10, 0 = no pain, 10 = worst pain ever experienced) pain diary twice daily (am and pm) over a period of 7 days both before the DBS surgery and within one year after the surgery (Owen et al. , 2006b, Pereira et al. , 2010). In this study, the post-operative VAS assessment was performed between 6 and 12 months after surgery according to previous study (Boccard et al. , 2013). The 14 VAS scores of each measurement were

averaged to give the mean pain scores at pre-operative and post-operative stages. Pain relief by DBS was computed as the post-operative percentage change of the VAS against the pre-operative score of each patient.

#### ***2.4 Deep brain LFPs recording***

The LFPs were recorded simultaneously from the sensory thalamus and PVAG post-operatively *via* the externalized DBS electrodes. The LFPs were recorded while the patient was off medication and before the stimulation was turned on for trial stimulation or after the stimulation was turned off over-night. Bipolar LFPs were recorded from three adjacent pairs of deep brain electrode contacts (contacts 0-1, 1-2, and 2-3) with a common electrode placed on the surface of the mastoid. The recordings were made when patients were seated at rest and any artefacts were carefully identified and excluded. The LFPs were amplified using isolated CED 1902 amplifiers ( $\times 10\,000$ , Cambridge Electronic Design, Cambridge, UK), filtered between 0.5 Hz and 500 Hz, and digitized using CED 1401 mark II at a sampling rate of 2000 Hz, displayed on-line and saved onto a hard disk using a custom-written program in Spike2 (Cambridge Electronic Design).

#### ***2.5 Spectral analysis and nonlinear correlation analysis***

The resting LFPs simultaneously recorded from both the sensory thalamus and the PVAG in 50-s segments were extracted and recordings from the contacts used for post-operative chronic stimulation were selected for further analysis. The selected LFPs were bandpass filtered between 2 and 40 Hz and down-sampled to 500 Hz.

Power spectral density was calculated using the windowed fast Fourier transform with 2-s of sliding-window and 1-s of overlap. To reduce the influence of inter-subject variability, the power spectra were normalized by dividing by the integral power



between 2 Hz and 40 Hz.

The relationship between the quantitative spectral power measures of LFPs and pain relief was quantified with nonlinear correlation analysis based on the Boltzmann regression model. The Boltzmann model constrained the range of the pain relief between 0% and 100% and was more properly suitable for the clinical outcome assessment than the linear correlation model. The Boltzmann models for positive or negative correlation are

$$\text{pain relief (\%)} = \left(1 - \frac{1}{1 + e^{(\text{Ind}_{\text{LFP}} - x)/d}}\right) \times 100\% \text{ or}$$

$$\text{pain relief (\%)} = \frac{1}{1 + e^{(\text{Ind}_{\text{LFP}} - x)/d}} \times 100\%$$

Where  $\text{Ind}_{\text{LFP}}$  is the quantitative measure of the LFP, for instance, the power at each frequency or the power of theta, alpha, or beta components within the specific frequency ranges, and  $x$  and  $d$  are the model parameters to be estimated. The model parameters were estimated iteratively using the Levenberg-Marquardt algorithm and the statistical significance of the correlation was evaluated using the F-test.

The nonlinear correlation analysis was first performed between the power at each frequency of LFPs in the sensory thalamus or PVAG and the percentage change in VAS. The frequency ranges with significant correlation were then determined. The power of theta, alpha, and high beta components was obtained by calculating the integrals of the power spectra over the specific frequency ranges around 8, 10, and 25 Hz. The nonlinear correlation between these integral powers and the pain relief was further evaluated using Boltzmann nonlinear regression analysis. To assess the relationship between these neural components, a linear correlation was performed between the power of theta and that of alpha or high beta in all patients.

## ***2.6 Time-variant dynamic analysis of LFPs***

The time-frequency representation of LFPs was obtained using the short-time Fourier transform (STFT) as described in our previous study on the dynamic variation of deep brain LFPs (Wang et al. , 2005). In the present study, a 0.3-s Hanning window with 0.28-s overlap was determined to detect rapid changes of LFPs activity over time and transient dynamic modulation between different frequency bands. These parameters provided a time resolution of 0.3 s and a frequency resolution of ~3 Hz. After obtaining the STFT spectrogram, the time-variant power was computed by averaging the spectrogram over a frequency band of interest. The time-variant power of the frequency range was normalized by dividing by the time-variant power between 2 Hz and 40 Hz. The time-variant high- or low-power of the frequency range was segregated with a threshold. The threshold was computed by averaging the normalized time-variant powers across all patients. The high-power duration and low-power duration were then computed when the time-variant power was above or below the threshold, respectively. Then, the ratio of high-power duration to low-power duration was calculated. All of signal processing, data analysis, and statistical analysis was performed in Matlab (Version 7.1, MathWorks Inc., Natick, MA, USA).

### **3. Results**

#### ***3.1 Deep brain LFPs show oscillatory characteristics***

Patient demographics are detailed in Table 1. Pain relief ranged from 6% to 64% ( $23 \pm 18\%$ , mean  $\pm$  SD). An example of LFPs recorded simultaneously from the sensory thalamus and the PVAG is shown in Fig. 1B; slowly and rapidly changing oscillations in patient #3 are displayed. The power spectra showed dominant power peaks in the alpha band ~10 Hz both in the sensory thalamus and the PVAG (Fig. 1C).

### 3.2 Significant correlation between theta and beta oscillations and pain relief

The power spectra of LFPs in the sensory thalamus and PVAG were normalized for each patient and the averaged spectra are presented (bold line, Figs 2A and 3A). Peaks were visually identifiable in the theta range ~8 Hz and the alpha range ~10 Hz.

The correlation between pain relief and the normalized power spectra of thalamic LFPs at each frequency was evaluated using the nonlinear regression model. The correlation coefficients were computed at each frequency (thin line, Fig. 2A), and the frequency range was marked when the correlation coefficients reached specified statistical significance level ( $p < 0.01$ ) (bold colored line, Fig 2A). A significant negative correlation was identified within the 6-9 Hz range (blue line, Fig 2A) and the theta power within this range negatively correlated with the percentage change in VAS ( $R = -0.61$ ,  $p = 0.005$ , Fig. 2B). A significant positive correlation was identified within the 22-33 Hz range (red line, Fig 2A). High beta power within this range was also positively correlated with the percentage change in VAS ( $R = 0.56$ ,  $p = 0.007$ , Fig. 2C). Moreover, a significant negative correlation was found between the power at 6-9 Hz and the power at 22-33 Hz ( $R = -0.88$ ,  $p < 0.001$ , Fig. 2D).

A significant negative correlation between pain relief and the normalized power spectra of PVAG LFPs was identified within the 6-9 Hz range (blue line, Fig 3A) and the theta power within this frequency range was negatively correlated with the percentage change in VAS ( $R = -0.69$ ,  $p = 0.003$ , Fig. 3B). A significant positive correlation was identified within the alpha range of 10-12 Hz (red line, Fig 3A). In addition, the alpha power was positively correlated with the percentage change in VAS ( $R = 0.51$ ,  $p = 0.009$ , Fig. 3C). There was no significant correlation between the alpha and theta power ( $R = 0.19$ ,  $p = 0.607$ , Fig. 3D).

### ***3.3 Dynamic characteristics of theta and beta oscillations correlate to pain relief***

After identifying the LFP components significantly correlated with pain relief, we analyzed the dynamic characteristics of these neural oscillations using STFT. The time-variant power of the LFPs in identified frequency ranges both in the sensory thalamus and PVAG exhibited a fluctuating pattern across time (Fig. 4A and C). A ratio of high-power duration to low-power duration was derived. The correlation between the ratio of each neural activity and the pain relief was performed using Boltzmann nonlinear regression analysis.

In sensory thalamus, the ratio of high- power duration to low-power duration at 6-9 Hz was negatively correlated with pain relief ( $R = -0.62$ ,  $p = 0.004$ , Fig. 4B), while there was a weak but significant correlation between the timing ratio at 22-33 Hz and pain relief ( $R = 0.45$ ,  $p = 0.011$ , Fig. 4B). In the PVAG, the duration ratio at 6-9 Hz was negatively correlated with pain relief ( $R = -0.43$ ,  $p = 0.012$ , Fig. 4D), while there was no significant correlation between the duration ratio at 10-12 Hz and pain relief ( $R = -0.12$ ,  $p = 0.82$ , Fig. 4D).

## **4. Discussion**

This study quantifies the relationship between pain relief treated by DBS and the neural oscillations in the sensory thalamus and PVAG. Distinct neural oscillations at theta, alpha, and high beta frequencies were correlated with pain relief. The theta power and the ratio of high- to low-power duration in both sensory thalamus and PVAG LFPs were negatively correlated with pain relief. The high beta power and the duration ratio in the sensory thalamus were positively correlated with pain relief. The alpha oscillations in the PVAG were positively correlated with pain relief.

**The efficacy of DBS is directly associated with the neurophysiological function of**

**the stimulated targets.** The oscillatory neural activities of sensory thalamus and PVAG are related to pain perception (Green et al. , 2009). There are varied outcomes in pain relief ranging from 6% to 64%, which is similar to previous studies (Bittar et al. , 2005, Boccard et al. , 2013). This study reveals that the distinct neural oscillations correlate with pain relief by deep brain stimulation. Low-frequency bursting has been recorded from single neurons in the thalamus of patients with neurogenic pain (Lenz et al. , 1989, Rinaldi et al. , 1991, Jeanmonod et al. , 1993, 1996). Thalamic neurons hyperpolarize sufficiently to deactivate calcium channels, resulting in the production of low-threshold calcium-spike bursts (Lenz et al. , 1989). The threshold calcium-spike bursts have been found to appear as rhythmic bursting activity with an average inter-burst interval of  $263 \pm 46$  ms (Jeanmonod et al. , 1996). Such a burst discharge is proposed to correlate with the delta and theta oscillations in thalamic LFPs. Thalamic relay neurons are thought to exert influence over thalamo-cortical loops, particularly in the theta frequency range, which may reflect the pathophysiology of neuropathic pain (Llinas et al. , 1999, Sarnthein et al. , 2006). The over-active theta thalamic activity is regarded as the trigger for cortical dysfunction resulting in thalamocortical dysrhythmia (Llinas et al. , 1999, Sarnthein et al. , 2006). Suppression of the theta oscillation might lead to pain relief. There is some evidence that the theta oscillation in thalamus are suppressed with PVAG stimulation at useful frequencies (Wu, 2014). Alpha oscillations in the PVAG and beta oscillations in the sensory thalamus have also been found to be closely related to pain relief suggests that, in lines with previous findings (Green et al. , 2009, Zhang et al. , 2013), these activities may be related to the pain perception. Moreover, within the sensory thalamus, theta power and high beta power were found to be strongly negatively correlated, suggesting that these oscillations are mutually inhibitory within the

sensory thalamus.

**The stimulation frequency could be optimized according to the oscillatory characteristics of the neural activity.** The findings in this study may partially explain the varied outcomes due to different stimulation parameters. There is no objective guidance for optimizing neuromodulation in neuropathic pain. Clinically, both low- and high-frequency stimulation have been used (Kumar et al. , 1997, Hamani et al. , 2006, Keifer et al. , 2014). The range of stimulation frequencies is 5-30 Hz for PVG stimulation, and 10-50 Hz for sensory thalamus stimulation (Owen et al. , 2006b). In some studies, even higher frequencies up to 100 Hz have been used (Levy et al. , 1987, Kumar et al. , 1997). In our experience, a low frequency consistently achieves therapeutic effects and a high frequency worsens the pain. DBS appears to simultaneously modulate theta, alpha, and beta neural oscillations and the relationship of each individual frequency to pain is difficult to determine. This may be a cause for the variation in clinical outcomes. Low-frequency stimulation may excite the neural oscillations while a high frequency may suppress them (Lozano et al. , 2013). The local field potentials in the current study represent the baseline condition in these patients and it remains unclear how the stimulation affects these neural activities. The excitatory and inhibitory effects of low or high frequency stimulation on the oscillatory neural activities needs further investigation.

There are some noteworthy limitations in this study. Firstly, the number of patients is relatively small. While there has been little research on the neurophysiological function in the deep brain related to pain relief provided by deep brain stimulation in these patients over the last decade (Pereira et al. , 2014), it also reflects the challenging situation in this field due to the limited number of patients implanted and

the cautious clinical healthcare. However, investigation in these patients could possibly provide unique insights and advance our understanding. Secondly, the clinical outcomes in this study had a large variation. This large variation allows us to investigate the relationship between the different level of pain relief and the neurophysiological measures, so that significant measurements correlated to pain relief could be identified. We believe that a larger number of patients and even more variation in outcome would further consolidate the results. Moreover, the variability in implant localization might cause the variation of neural signals among patients. For this reason we have carefully assessed the clinical and neuroimaging information, and LFP recordings were selected from a similar location in each patient with normalization applied to minimize the individual variation.

The effects of the power spectra normalization should be carefully examined. Increased power in one frequency band will increase corresponding normalization factor, reducing the normalized power in other frequency bands. As a consequence, the significant correlation identified in one frequency band could be an interference of other frequency bands. To account this, in this study there was no significant correlation between the pain relief and the absolute powers. It may be due to the individual variation in signal recording. Besides the normalization by the total power, we also normalized the power spectra by the power between 2 Hz and 4 Hz. The significant correlation were still found between the theta and high beta power and the pain relief in sensory thalamus. Together with the evidence from previous studies that theta, alpha and beta oscillations are involved in pain circuits (Jeanmonod et al. , 1996, Llinas et al. , 1999, Sarnthein et al. , 2006, Green et al. , 2009), it is more likely that both theta and beta oscillations were related to the pain relief.

In summary, this study developed an approach to screen the quantitative neurophysiological characteristics in deep brain local field potentials, and it found that the  $\theta$ ,  $\alpha$  and  $\beta$  oscillations in thalamus or periventricular grey were significantly correlated to the pain relief. The dynamics of these neural oscillations could potentially provide objective biomarkers for predicting and modulating the pain relief.

## Disclosure

None of the authors have potential conflicts of interest to be disclosed.

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Table 1. Demographics, etiologies, stimulation parameters, and pain assessment of patients.

No.	Age/Sex	Etiologies	Targets	Electrode pair used for analysis	Stimulation Parameters			VAS		
					A( V)	F(Hz)	PW(μs)	Pre-op.	Post-op.	Relief (%)
1	60/M	Poststroke	PVAG	1-2	0.5	20	360	9.2	8.2 (12m)	11

		pain	VPL	0-1	2.0	20	450			
2	39/M	Trigeminal	PVAG	2-3	3.0	20	330	7.5	6.0 (12m)	20
		neuralgia	VPM	2-3	3.4	20	330			
3	40/F	Intractable	PVAG	1-2	4.8	20	240	5.0	3.0 (12m)	40
		forehead pain	VPL	2-3	1.7	20	180			
4	38/M	Phantom	PVAG	2-3	2.5	30	120	8.0	6.0 (12m)	25
		limb pain	VPL	2-3	2.4	30	120			
5	43/M	Phantom	PVAG	0-1	1.5	7	210	5.6	2.0 (6m)	64
		limb pain	VPL	1-2	4.0	25	60			
6	53/M	Brachial plexus	PVAG	1-2	2.1	20	240	4.8	4.5 (12m)	6
		injury	VPL	1-2	0.7	20	270			
7	54/M	Poststroke	PVAG	2-3	1.2	10	270	6.7	5.1 (12m)	24
		pain	VPL	1-2	2.0	10	180			
8	58/M	Facial	PVAG	0-1	3.0	40	120	9.0	7.5 (12m)	17
		pain	VPL	2-3	0.8	40	120			
9	42/M	Radiculo-	PVAG	2-3	-	-	-	10.0	8.0 (12m)	20
		plexopathy	VPL	1-2	-	-	-			
10	35/M	Facial	PVAG	2-3	1.8	50	330	9.0	8.5 (6m)	6
		pain	VPL	2-3	1.6	50	210			

Figure 1. The deep brain local field potentials shows oscillatory characteristics. The localization of deep brain stimulation electrodes was confirmed on post-operative MRI scans (A). Local field potentials (LFPs) from the sensory thalamus (B, upper) and periventricular gray / periaqueductal gray (PVAG) (B, lower) in patient #3. The non-normalized and normalized power spectra of LFPs from sensory thalamus (C, upper) and PVAG (C, lower) across all patients. The darkness of the lines denoted the pain relief level in each patient, and the darker lines indicates the better pain relief. The LFPs exhibited oscillatory activity at low and high frequencies and their spectra showed peaks, particularly prominent at ~10 Hz.

Figure 2. Significant correlation between theta and beta oscillations of sensory thalamus and pain relief. The normalized power spectra of sensory thalamic LFPs across all patients (bold line and

shadowed region, mean  $\pm$  SD), and the correlation coefficients between pain relief and the normalized power at each frequency (A). The frequency range is marked by a bold colored line where the correlation is statistically significant ( $p < 0.01$ ). The nonlinear correlation between pain relief and the power at 6-9 Hz ( $R = -0.61$ ,  $p = 0.005$ ) (B). The nonlinear correlation between pain relief and the power at 22-33 Hz ( $R = 0.56$ ,  $p = 0.007$ ) (C). The linear correlation between the power at 6-9 Hz and the power at 22-33 Hz ( $R = -0.88$ ,  $p < 0.001$ ) (D). Thin lines indicate 95% confidence intervals (B, C, and D).

Figure 3. Significant correlation between theta and alpha oscillations of PVAG and pain relief. The normalized power spectra of PVAG LFPs across all patients (bold line and shadowed region, mean  $\pm$  SD), and the correlation coefficients between pain relief and the normalized power at each frequency (A). The frequency range is marked with a bold colored line where the correlation is statistically significant ( $p < 0.01$ ). The correlation between pain relief and the power at 6-9 Hz ( $R = -0.69$ ,  $p = 0.003$ ) (B). The correlation between pain relief and the power at 10-12 Hz ( $R = 0.51$ ,  $p = 0.009$ ) (C). The correlation between the power at 6-9 Hz and the power at 10-12 Hz ( $R = 0.19$ ,  $p = 0.607$ ) (D). Thin lines indicate 95% confidence intervals (B, C, and D).

Figure 4. Dynamic characteristics of theta and beta oscillations correlate to pain relief. The spectrogram of thalamic LFPs and the time-variant power at 6-9 Hz and 22-33 Hz (A). The correlation between pain relief and the time ratio at 6-9 Hz and 22-33 Hz in the sensory thalamus ( $R = -0.62$ ,  $p = 0.004$ ;  $R = 0.45$ ,  $p = 0.011$ , respectively) (B). The spectrogram of PVAG LFPs and the time-variant power at 6-9 Hz and 10-12 Hz (C). The correlation between the pain relief and the time ratio at 6-9 Hz and 10-12 Hz in the PVAG ( $R = -0.43$ ,  $p = 0.012$ ;  $R = -0.12$ ,  $p = 0.82$ , respectively) (D).

Figure 1  
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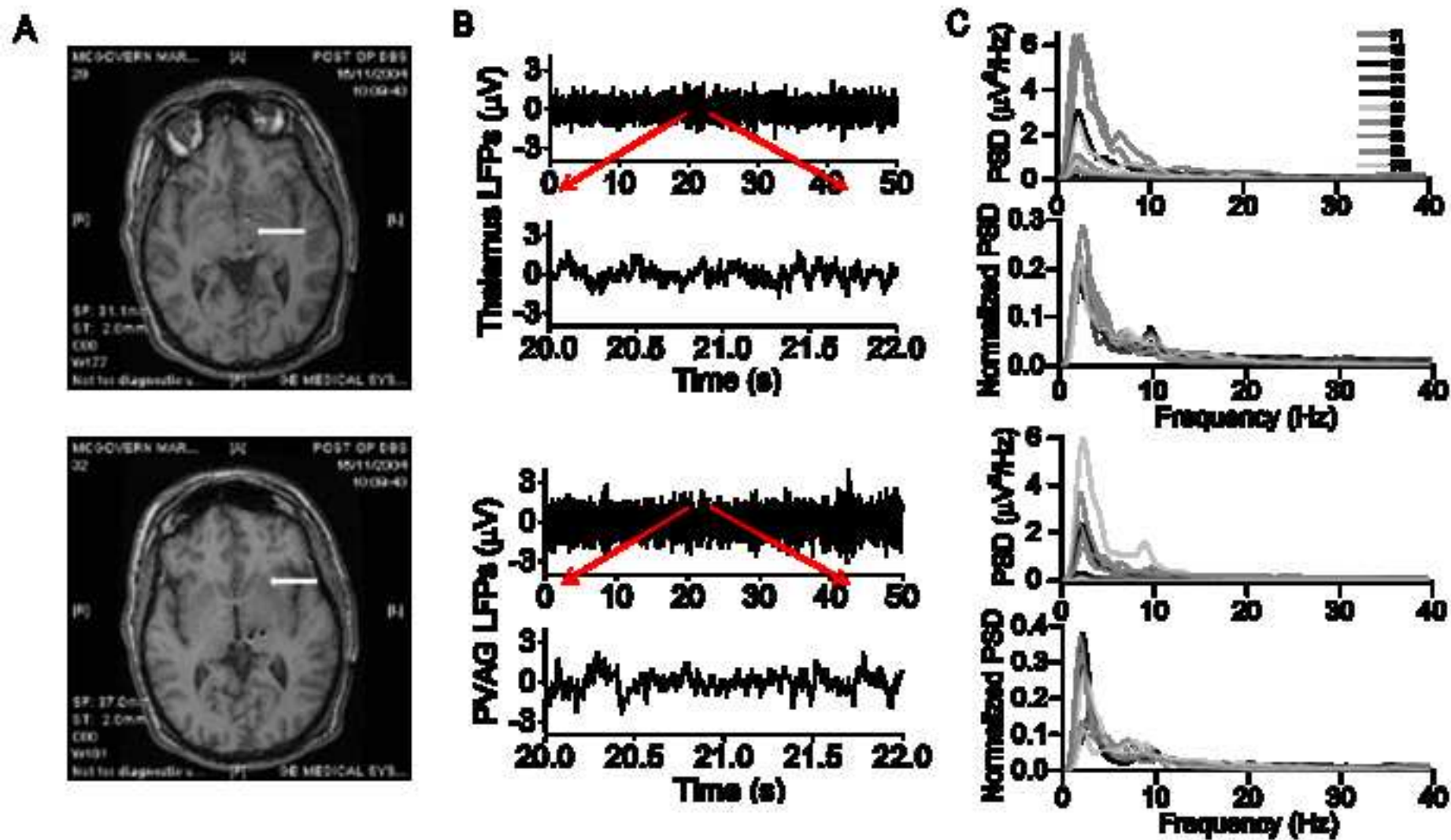




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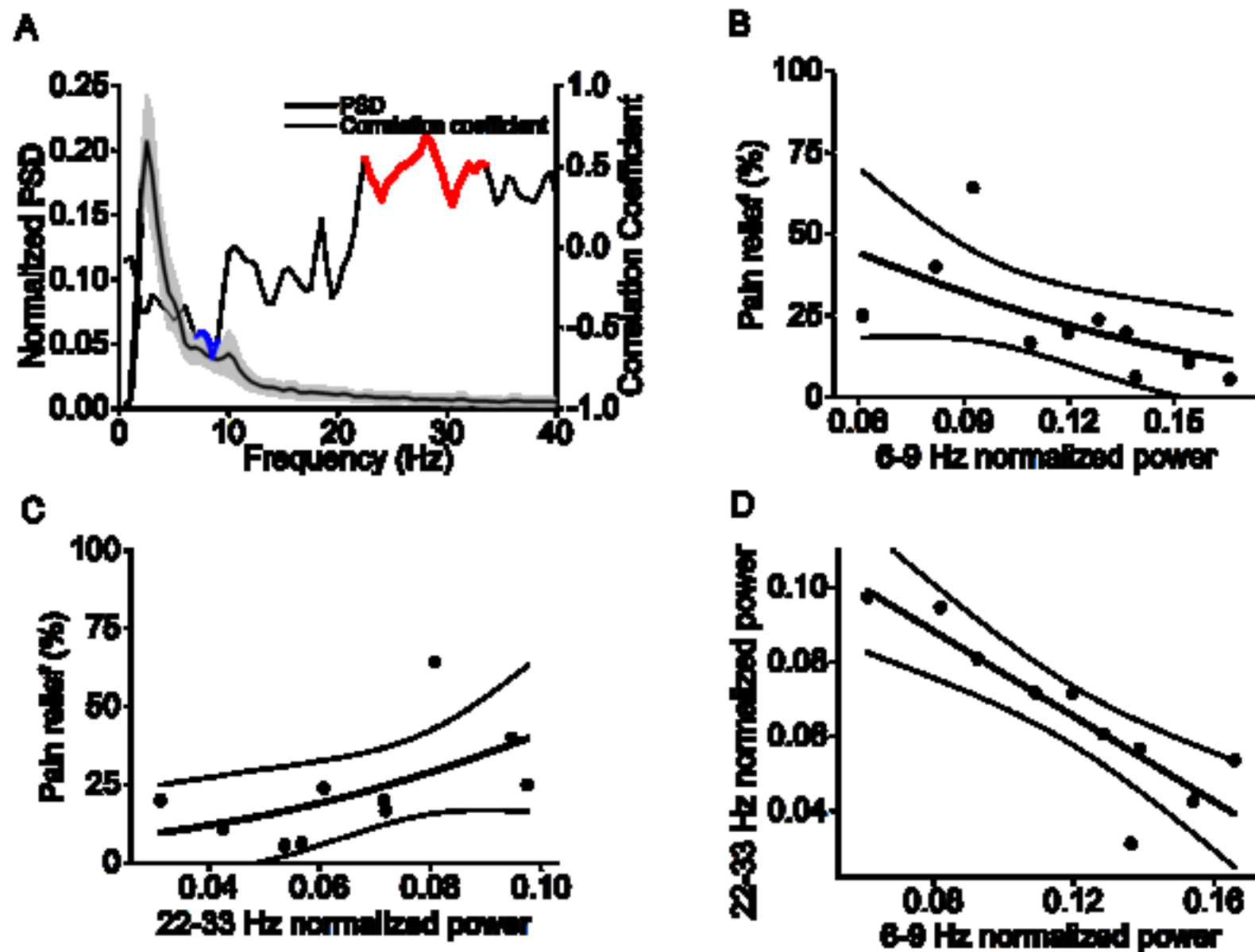


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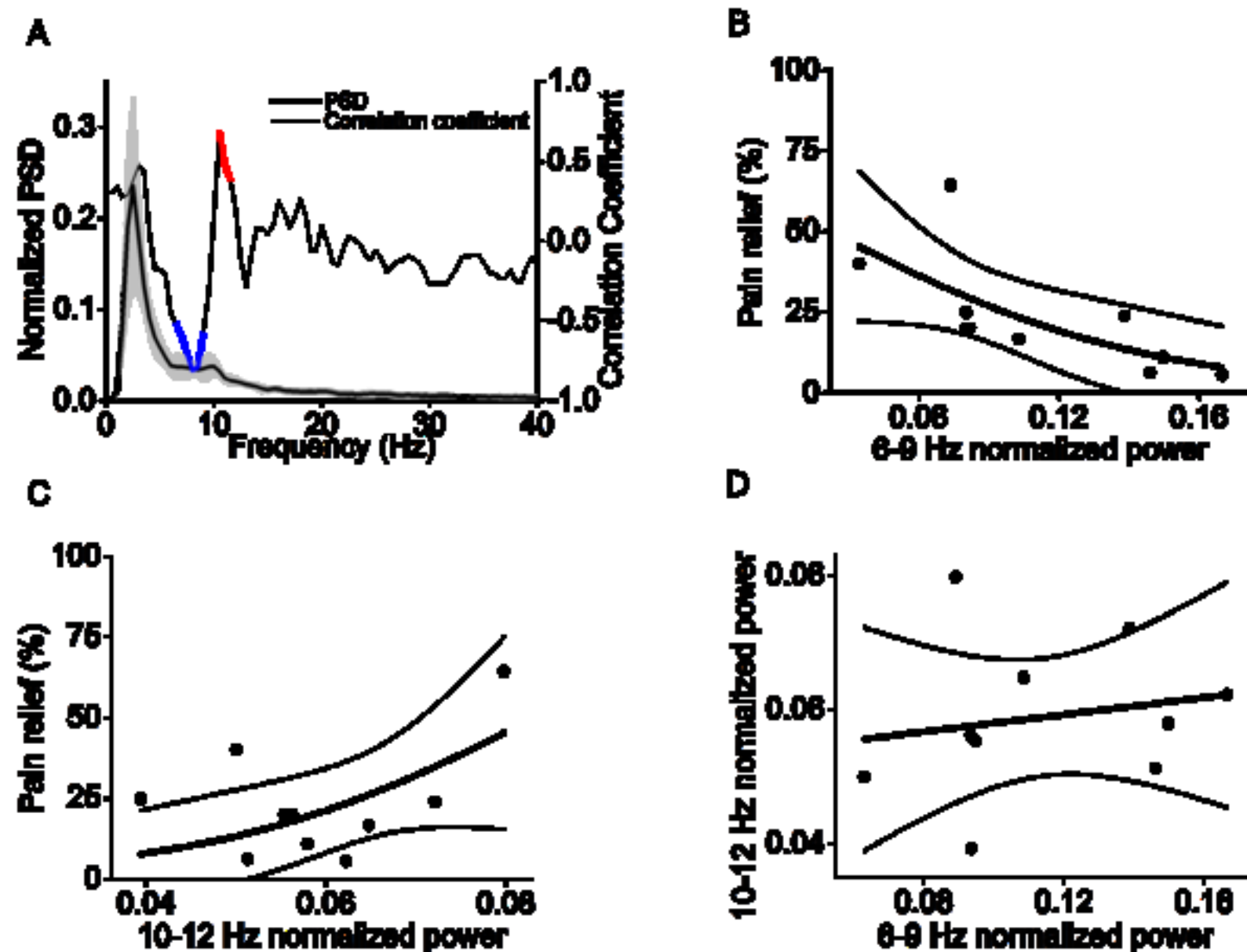


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