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Electrophysiological characteristics of CM-pf in diagnosis and outcome of patients with disorders of consciousness

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A R T I C L E I N F O

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A B S T R A C T

Background: Deep brain stimulation (DBS) in the centromedian-parafascicular complex (CM-pf) has been reported as a potential therapeutic option for disorders of consciousness (DoC). However, the lack of understanding of its electrophysiological characteristics limits the improvement of therapeutic effect.
Objective: To investigate the CM-pf electrophysiological characteristics underlying disorders of consciousness (DoC) and its recovery.
Methods: We collected the CM-pf electrophysiological signals from 23 DoC patients who underwent central thalamus DBS (CT-DBS) surgery. Five typical electrophysiological features were extracted, including neuronal firing properties, multiunit activity (MUA) properties, signal stability, spike-MUA synchronization strength (syncMUA), and the background noise level. Their correlations with the consciousness level, the outcome, and the primary clinical factors of DoC were analyzed.
Results: 11 out of 23 patients (0/2 chronic coma, 5/13 unresponsive wakefulness syndrome/vegetative state (UWS/VS), 6/8 minimally conscious state minus (MCS-)) exhibited an improvement in the level of consciousness after CT-DBS. In CM-pf, significantly stronger gamma band syncMUA strength and alpha band normalized MUA power were found in MCS- patients. In addition, higher firing rates, stronger high-gamma band MUA power and alpha band normalized power, and more stable theta oscillation were correlated with better outcomes. Besides, we also identified electrophysiological properties that are correlated with clinical factors, including etiologies, age, and duration of DoC.
Conclusion: We provide comprehensive analyses of the electrophysiological characteristics of CM-pf in DoC patients. Our results support the 'mesocircuit' hypothesis, one proposed mechanism of DoC recovery, and reveal CM-pf electrophysiological features that are crucial for understanding the pathogenesis of DoC, predicting its recovery, and explaining the effect of clinical factors on DoC.

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1. Introduction

Disorders of consciousness (DoC) are a group of disorders characterized by abnormalities in awareness and/or arousal that commonly result from critical brain damage caused by trauma, stroke, or anoxia. DoC encompasses coma, unresponsive wakefulness syndrome/vegetative state (UWS/VS) [1–3], and minimally conscious state (MCS) [4]. MCS can be further divided into MCS+ and MCS- based on the presence or absence of language-related responses (command-following behavior, etc.). Managing DoC poses a significant challenge for patients, families, and healthcare providers, as the chances of spontaneous recovery are generally low. Efforts have been made to investigate whether neuromodulation therapy can facilitate recovery [5]. Among these therapies, deep brain stimulation (DBS) has emerged as a promising option. DBS involves implanting electrodes into specific deep brain nuclei to modulate abnormal neurological functions. While DBS has shown efficacy in conditions like Parkinson's disease [6] and epilepsy [7], its potential for DoC treatment is still being explored. In 2007, Schiff et al. reported positive behavioral outcomes in a traumatic brain injury patient treated with DBS targeting the central thalamic nuclei [8]. Subsequent studies have also examined the effects of central thalamus DBS (CT-DBS) on DoC. However, the results have been inconsistent, possibly due to small sample sizes and the lack of control groups [8–12]. As a result, there is a scarcity of reliable evidence, and the electrophysiological mechanisms underlying the development and recovery of DoC remain poorly understood.

Abbreviations

DoC	Disorders of Consciousness
UWS	Unresponsive Wakefulness Syndrome
VS	Vegetative State
MCS	Minimally Conscious State
MCS	Minimally Conscious State minus
MCS+	Minimally Conscious State plus
eMCS	Emergence from MCS
DBS	Deep Brain Stimulation
CT-DBS	Central thalamus DBS
CM-pf	Centromedian/parafascicular
MSP	Multiple Spike
MUA	Multiunit Activity

The "mesocircuit" model has been proposed as a potential mechanism underlying the pathogenesis of DoC [13–19], focusing on disruptions in the circuits between the brainstem, thalamus, and cortex. Within this model, the central thalamus is considered as an important hub in the extensively interconnected functional network [20,21]. Therefore, understanding the relationship between central thalamic activity and consciousness is of great importance, both for assessing the level of consciousness and predicting the likelihood of recovery. In particular, the centromedian/parafascicular (CM-pf) complex, a significant component of the central thalamus, exhibits strong connections with various subcortical structures. Previous studies have consistently highlighted the pivotal role of the CM-pf complex in motor, associative-limbic and integrative circuits, situated at the crossroads of the basal ganglia [22–24]. Therefore, the CM-pf complex plays an important role at the intersection of motor function and arousal, making it an ideal target for brain stimulation [9–12]. Moreover, the "mesocircuit" model provides an explanation for the arousal effects of CT-DBS, where the central thalamic nuclei are involved in activating the forebrain [14,15,25–27]. Therefore, CT-DBS has the potential to restore the normal functioning of the cortico-striatal-thalamo-cortical pathway in patients with DoC, whose background synaptic activities are chronically reduced following brain injury.

In current clinical practice, microelectrode recording (MER) is commonly used to guide the precise implantation of DBS electrodes. By analyzing the electrophysiological characteristics of the targeted nuclei before implantation, MER confirms their suitability for DBS placement. Additionally, the recording of single-cell spikes or local field potentials (LFPs) during MER serves as a crucial basis for selecting appropriate stimulation parameters post-surgery. While extensive experience exists with other common nuclei, such as the subthalamic nucleus and globus pallidus internus in Parkinson's disease treatment, the electrophysiological characteristics of the CM-pf nucleus have only been briefly described by Schiff et al. [28]. The lack of detailed pathophysiological mechanisms in the central thalamus poses challenges in developing accurate localization and tailored therapeutic strategies during CT-DBS treatment.

Previous studies, including the work by Schiff [28] and our own experience, have highlighted the challenges in analyzing the limited spike discharge of the CM-pf nucleus. However, there are alternative perspectives to consider. The background neuronal activity of the nucleus consists of a large collection of spiking activity, which contains various potentially valuable indicators. The multiunit activity (MUA) has been identified as a reliable indicator of nucleus specificity [29] and the level of consciousness following global hypoxic-ischemic brain injury [30]. Similar to the LFP, MUA provides valuable information about the overall neural activity at the population level. MUA reflects the average spiking activity within a localized range of approximately 200–300 μm from the recording electrode, making it more specific to the CM-pf nucleus compared to LFPs, which have a larger spatial extent of up to 2.5 mm [31–35]. MUA offers stability in the information obtained, surpassing the variability of individual spiking activities and providing spatial-selectivity superior to LFPs [22]. Recent studies in Parkinson's disease have demonstrated that MUA can directly measure the oscillatory dynamics of neural activity in smaller areas, enabling more accurate assessment of time-frequency synchronization of local neurons [36,37]. In our current study, we focused on extracting mainly MUA-based features from the CM-pf nuclei. These features encompassed various aspects, including neuron firing properties, MUA properties, signal stability, synchronization between firing rates and MUA (syncMUA), and the level of background noise. By investigating these electrophysiological characteristics, we aimed to gain insights into the pathogenesis of DoC and its recovery.

Furthermore, over the past two decades, numerous studies have placed significant emphasis on clinical factors associated with DoC, including etiologies such as hypoxia, stroke, and trauma, as well as age and duration of the condition [3,38–46]. However, the underlying electrophysiological properties related to these clinical factors remain largely unknown. Given the central thalamus's pivotal role in the "mesocircuit" model, we sought to analyze the correlation between its electrophysiological activity and clinical factors to investigate how these clinical factors influence the level of consciousness in relation to central thalamic activities.

In summary, the main objective of this study is threefold: firstly, to uncover the shared pathophysiological mechanisms underlying DoC by examining the relationship between CM-pf electrophysiological indices and diagnosis; secondly, to investigate the neuronal firing patterns within the CM-pf that may contribute to the possibility of consciousness re-emergence by examining the electrophysiological properties in relation to clinical outcomes; and thirdly, to elucidate the relationship between electrophysiological characteristics and primary clinical factors of DoC. Collectively, these findings aim to provide valuable biological insights into the pathological mechanisms of DoC and enhance our understanding of the emergence from the DoC.

2. Material and methods

2.1. Patients, inclusion criteria, exclusion criteria, and ethics

39 DoC patients underwent CT-DBS treatment from June 2011 to June 2021 at the Seventh Medical Center of PLA General Hospital and Beijing Tiantan Hospital. The inclusion and exclusion criteria were consistent with our previous study [47]. In short, all patients were diagnosed with DoC and showed no significant improvement or deterioration in consciousness for a period longer than 4 weeks. Patients with severe brain deformation, untreated hydrocephalus, other chronic neurological diseases or life-threatening systemic diseases were excluded. Finally, 23 consecutive DoC patients (2 in chronic coma, 13 in UWS, and 8 in MCS-) met the criteria and were included in this study. Detailed clinical information of each patient is shown in Table S1. The CRS-R score of the patients was determined by experienced clinicians through repeated assessments. This study was performed in line with the principles of the Declaration of Helsinki. Written informed consents were obtained form the caregivers of all patients. The study was approved by the ethics committee of PLA Army General Hospital and the ethics committee of Beijing Tiantan Hospital, Capital Medical University.

2.2. Surgical and recording procedures

Magnetic resonance imaging (MRI) was scanned after fixation of the stereotactic Leksell Coordinate Frame (Elekta®, Stockholm, Sweden). These scans were then fused and registered with the MRI performed before surgery in the surgical planning system. Based on the indication provided by Schiff et al. [8], the bilateral CM-pf were targeted. Multi-channel microelectrodes (leadpoint, Medtronic, USA) were implanted, and the electrical signals were recorded from 10 mm above the target down to 2 mm below it and we used the signal within a 1mm range above and below the target as the data for subsequent analysis. All procedures were conducted under general anesthesia. The administration of propofol and sevoflurane, which could influence neuronal firing, were discontinued 20 min prior to the microelectrode recording (MER). Two quadripolar electrodes (PINS L302, Beijing PINS) were positioned at the target site based on the microelectrode trajectory on both sides. To assist more accurate localization, the LFP signals were filtered out to enhance the observation of firing activities. Postoperative CT OR 1.5T MRI were performed to verify the position of DBS electrodes (Fig. S1).

2.3. DBS treatment and outcome evaluation

The pulse generator was turned on for periodic electrical stimulation at least one week after the operation. The stimulation frequency was set at 100 Hz, with a pulse width of 120 us and a 1.0–4.0 V voltage. Clinical follow-up were performed for 12 months after the surgery in all patients. For the follow-up diagnosis, the patients were divided into chronic coma, UWS, MCS-, MCS+, and the emergence from MCS (eMCS, with functional object use or functional accurate communication) according to the best CRS-R score during the 12 months of follow-up.

2.4. Signal processing

Signal Preprocessing. The signal from each electrode was amplified (10 k), bandpass filtered (500–10,000 Hz), and sampled at 24 kHz (Alpha-Map 5.4; Alpha-Omega) online. Then the CM-pf recordings were further off-line preprocessed to remove residual low-frequency components and power-line interference. Specifically, a bandpass filter (third-order Butterworth) between 500 and 5 kHz was applied, followed by a set of notch filters (eight-order Butterworth) suppressing the 50 Hz power-line interference's harmonics. Besides, the signal segments with large artifacts were manually detected and excluded.

2.4.1. Signal extraction

Multiple spikes (MSPs). MSPs [48] were detected in the 24 kHz-sampling frequency traces using the shape template [49,50]. Specifically, spikes were only included in the analyses if the following criteria were met [1]: they were well isolated to ensure a clear refractory period [2], their peak or valley amplitude was greater than 5 times the background noise level [51]. This threshold ensured that the estimation was minimally affected by fluctuations in neuronal discharges or vibration artifacts, providing a high signal-to-noise ratio. A sample depicting the spike threshold and noise level can be found in Fig. S2A. Single unit was then identified in the offline-sorter (Plexon) when the shape of neuronal firing waveform had obvious clustering properties.

2.4.2. MUA

The computational process was based on the amplitude of population activity, eliminating the necessity for spike detection and isolation. MUA was estimated by clipping extreme values (larger or smaller than the mean $\pm$ 2 SDs), and computing the sample-by-sample root mean square (RMS) (Fig. S2B): 1) square it to give an instantaneous measure of spike-band power, raising to the second power; 2) mean, low-pass filtering (third-order Butterworth) at 100 Hz followed by down-sampling to 500 Hz; 3) root, taking the square root. Then MUA outliers were detected and removed using moving average RMS (20 ms long, a threshold of 2.58 SDs) [48,52].

2.5. Electrophysiological features

On the basis of MSPs and MUA, five types of electrophysiological features in CM-pf were then calculated, including neuron firing properties, MUA properties, signal stability, synchronization between firing rates and MUA (syncMUA) and the background noise level (see supplementary materials for details).

2.6. Statistical analysis

During the analysis, we pooled chronic coma and UWS patients together, as all patients in this category were in a chronic state showing no evidence of consciousness. The MCS+ and eMCS patients were also pooled together, as this group of patients all exhibit evidence of command following (language processing) and all have improvement after DBS treatment (recovery of reproducible response to command, functional object use or communication). Wilcoxon ranksum test and Kruskal–Wallis (KW) test were applied for group comparisons. Effect size were also calculated for both test. Conover's all-pairs rank comparison test were used as the posthoc analysis for KW test. Moreover, Spearman correlation analysis was adopted between clinical factors and electrophysiology indices. The BH method was used in the multiple comparisons (see supplementary materials for details). Uncorrected p values are reported in the results.

Significance differences are shown with asterisks (**$p < 0.01$, *$p < 0.05$, n.s. $p \geq 0.05$).

3. Results

3.1. Clinical outcomes

Clinical information is shown in Table S1. 47.8% of patients (11/23) had an improved consciousness level (0% chronic coma, 38.5% UWS (5/13), 75% MCS- (6/8) got improved diagnosis after treatment) (Table 1) (Fig. 2B). Among them, eight patients (2 UWS and 6 MCS-) who improved to MCS + or eMCS with reproducible response to command, functional object use or communication were considered as "recovered" (Table 1). Overall, patients with MCS tend to have better prognoses, which is consistent with previous reports [46,53]. Also, consistent with previous studies [3,13,38–45,54–58], patients with younger age have better outcomes after CT-DBS ($p = 0.008$, Table S2). However, in our

Table 1
Summary of patients' statistics.

Variables	Preoperative Diagnosis		Follow-up Diagnosis	
	chronic coma/UWS (N = 15)	MCS- (N = 8)	Unrecovered (N = 15)	Recovered (N = 8)
Age, year, average (± SD)	35.3 (±16.4)	50.6 (±11.5)	51.5 (± 11.0)	33.6 (± 15.0)
Age distribution, N (%)				
≤35	1 (6.7)	5 (62.5)	1 (6.7)	5 (62.5)
36–50	7 (46.7)	1 (12.5)	6 (40.0)	2 (25.0)
>50	7 (46.7)	2 (25.0)	8 (53.3)	1 (12.5)
Gender, N (%)				
Male	9 (60.0)	5 (62.5)	8 (53.3)	6 (75.0)
Female	6 (40.0)	3 (37.5)	7 (46.7)	2 (25.0)
Etiology, N (%)				
Anoxia	7 (46.7)	2 (25.0)	7 (46.7)	2 (25.0)
Stroke	5 (33.3)	3 (37.5)	6 (40.0)	2 (25.0)
Trauma	3 (20.0)	3 (37.5)	2 (13.3)	4 (50.0)
Duration, month, N (%)				
≤5	14 (93.3)	3 (37.5)	13 (86.7)	4 (50.0)
6–11	1 (6.7)	4 (50)	2 (13.3)	3 (37.5)
≥12	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)
Showing improvements after DBS, N (%)				
Unimproved	10 (66.7)	2 (25.0)		
Improved	5 (33.3)	6 (75.0)		

UWS: Unresponsive Wakefulness Syndrome; MCS-: Minimally Conscious State minus; MCS+: Minimally Conscious State plus; Unrecovered: chronic coma/UWS/MCS- patients, Recovered: MCS+/eMCS patients; SD: standard deviation.

study, we did not find a significant correlation between traumatic etiology (p = 0.071, Table S2) nor the duration (p = 0.102, Table S2) with the outcomes.

3.2. The DoC-related electrophysiological characteristics in CM-pf

After verifying the effectiveness of the long-term effects of DBS, we further investigated the electrophysiological properties of CM-pf in DoC. The framework is shown in Fig. 1.

Neuron Firing Properties. Disfacilitation occurs in the central thalamus of DoC [13]. Due to the sparse discharge in the CM-pF complex of DoC patients, it is difficult to obtain well-isolated single-unit from every patient. To evaluate the firing strength of the CM-pF complex as many patients as possible, we analyzed unsorted MSPs (Fig. 2A) [48,49] instead. The patient with higher firing rates was likely to have a better outcome ($p = 0.047$, effect size: $\eta^2 = 0.27$). In the posthoc test of outcome (Fig. 2C), there were significantly higher firing rates in the MCS+/eMCS group than in the chronic coma/UWS group ($p = 0.018$) and no significance between MCS+/eMCS and MCS- ($p = 0.079$).

Other discharging patterns were also analyzed, including burst index, burst ratio, pause index and pause ratio (see supplementary materials for details). However, none of these patterns were found to be statistically significant between different diagnoses or outcomes (Table S2).

MUA Properties. LFP and its power spectrum were utilized to investigate the electrophysiological features that could help understand the pathophysiology [59] and improve the treatment [60]. Since the LFP data was not recorded during the surgery, we have conducted MUA (visualized in Fig. 2A) analysis instead, which provides information regarding population activities similar to the LFP.

There was no significant difference in the mean MUA strength. However, we found several significant frequency-specific indicators for MUA raw power and MUA normalized power separately (Table S2 for details across frequency bands), which are elaborated as follows.

The differences in MUA power with the representative high-gamma band are shown in Fig. 3A, B, C. Clearly, high-gamma band MUA waves and their corresponding power spectral density (PSD) were much stronger in the patients with better outcome. MUA raw power was significant different for follow-up diagnosis ($p = 0.026$, effect size: $\eta^2 = 0.31$). In the posthoc test of outcome, there was a significantly stronger high-gamma power in the MCS+/eMCS group compared with both the chronic coma/UWS ($p = 0.035$) and the MCS- ($p = 0.013$) groups, while the power strength for chronic coma/UWS and MCS- groups were more similar to each other.

In addition, MUA normalized power was analyzed to eliminate the influence of overall signal intensity variability and investigate the frequency specificity. The representative alpha band normalized power was strongly higher in MCS- patients compared with chronic coma/UWS patients ($p = 0.033$, effect size: $r = 0.45$, Fig. 3D, F), meanwhile, their broad-band power exhibited smaller differences (Fig. 3E, light blue and dark blue lines have relatively close values; Table S2). The alpha band

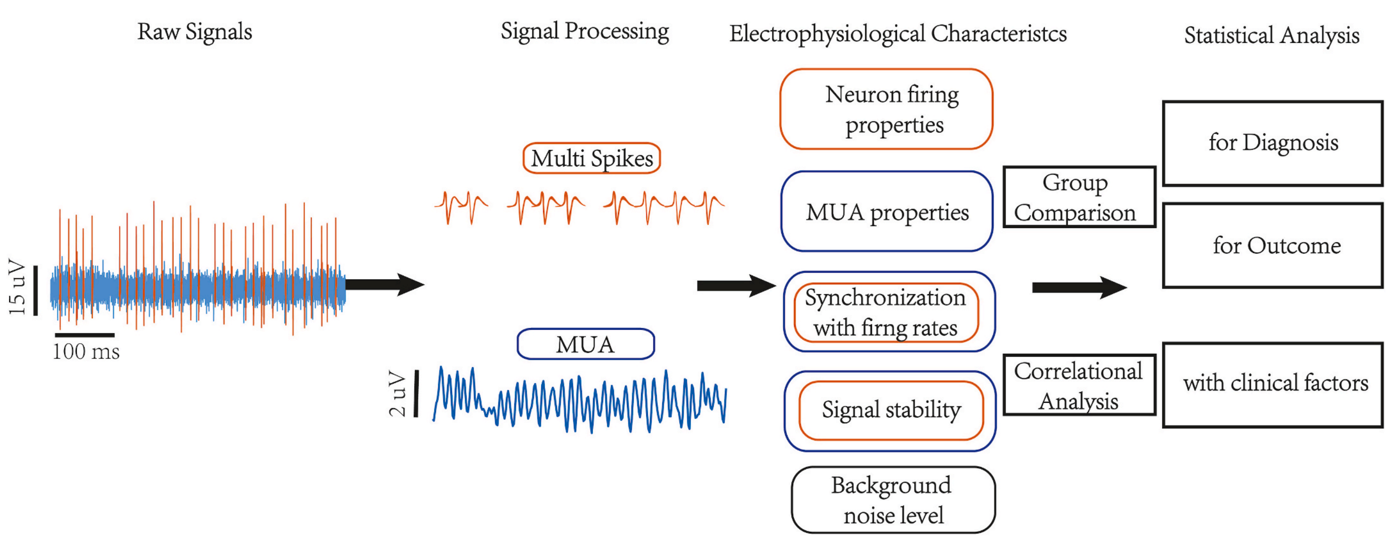

Fig. 1. The framework of Study. **(A)** Signal processing. After preprocessing, we extracted signals from the raw recordings in two modalities respectively, including unsorted multiple spikes and MUA. **(B)** Feature extraction. We generated five types of features for subsequent statistical analysis. **(C)** Mechanism investigation. To acquire statistically significant electrophysiological characteristics for the pathophysiological mechanisms underlying DoC and its recovey, each feature was compared between diagnoses and among outcomes.

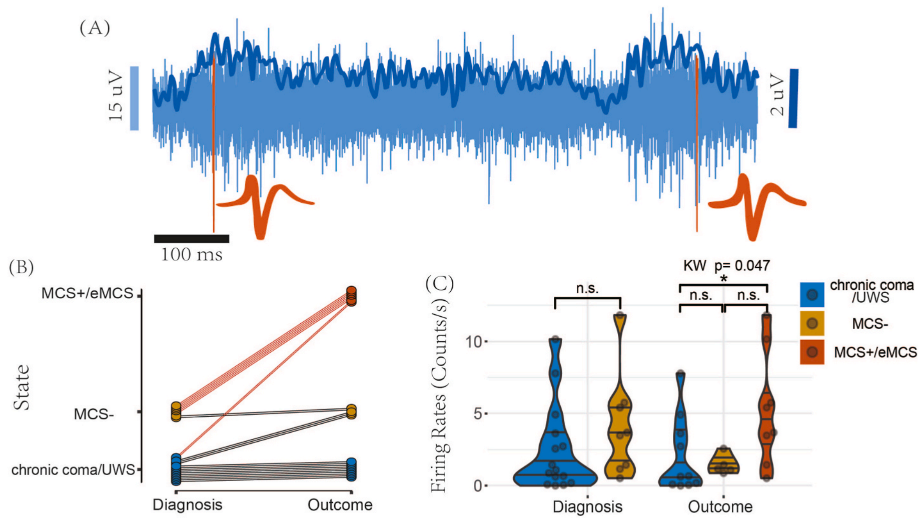

Fig. 2. Signal visualization, consciousness state changes, and MSP firing rate analysis. (A) Signal visualization. Two neuronal spikes (orange) and MUA signals (dark blue) were extracted from the raw recording (light blue). **(B)** Consciousness state changes. The line in red represents the patients with "recovered" outcomes. Note that the best state is 'MCS-' before the DBS therapy. **(C)** Group Comparison. MSP firing rate was not significantly different when we compared MCS- and chronic coma/UWS groups in the preoperative diagnosis, whereas, significance occurred in the outcome comparison (KW test: p = 0.047, effect size: η2 = 0.27). Significance differences are shown with asterisks (**p < 0.01, *p < 0.05, n.s. p ≥ 0.05) MCS+/eMCS: Minimally Conscious State plus or emergence from MCS, MCS-: Minimally Conscious State minus, chronic coma/UWS: Chronic coma or Unresponsive Wakefulness Syndrome. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

normalized power was also significantly higher for the DoC with better outcomes ($p = 0.038$, effect size: $\eta^2 = 0.28$). In the posthoc test of outcome, there was significantly higher normalized alpha band power in the MCS+/eMCS group compared with the chronic coma/UWS ($p = 0.014$), while no difference was found between MCS- and chronic coma/UWS or MCS+/eMCS groups.

Signal Stability. Previous studies found that there was an intermediate state between the fully silent and healthy states of central thalamus that was identified by the representative theta rhythm due to low threshold bursting behavior [13,19,61,62]. Therefore, we used the signal stability index to quantify the process from the lack of firing to the gradual generation of theta activity in the central thalamus. Specifically, we found that the MUA stability in the theta band was found to be informative (Table S2).

Fig. 4A shows theta band MUA waves and their envelopes for two patients with widely varying outcomes. Their theta oscillation intensities were close though, there was a visible difference in stability in terms of MUA envelopes. By obtaining the local standard deviation trend over time, stability differences are better visualized in Fig. 4B. Stronger theta band MUA stability was found in patiens with a better follow-up diagnosis ($p = 0.003$, effect size: $\eta^2 = 0.43$, Fig. 4C), rather with the preoperative diagnosis (Table S2). In the posthoc test of follow-up diagnosis, there was remarkably higher stability in the MCS+/eMCS group compared with both the chronic coma/UWS ($p = 0.001$) and the MCS- ($p = 0.044$) groups, while no difference was found between chronic coma/UWS and MCS-. The gap between chronic coma/UWS and MCS+/eMCS was more pronounced than that between chronic coma/UWS and MCS-.

Synchronization between Firing Rates and MUA (SyncMUA). A series of similar indicators were used to measure the synchrony of neuronal spiking activity with population rhythm, including the group coupling index [63–65], spike-triggered average [66,67] and the spike-filed coherence [68–71]. We investigated the synchrony of neuronal spiking activity and population fluctuation rhythm of MUA in CT, named syncMUA index, representing the local synchronization of CM-pF neurons.

In our results, Fig. 5A shows syncMUA in the representative gamma band for a chronic coma/UWS and an MCS- patient. Although gamma band-filtered MUA activities fluctuated similarly in both of them, there was a clear difference in their correlation strength with firing rates. Obtaining the correlation strength over frequency bands in Fig. 5B, the synchronization differences became clearer, that a higher consciousness level was correlated with stronger syncMUA strength in the gamma band ($p = 0.008$; effect size: $r = 0.55$, Fig. 5C). Unlike other CM-pf characteristics which are more informative in the follow-up diagnosis, syncMUA showed significant differences among groups regarding the preoperative diagnosis in gamma and alpha bands (Table S2).

The background Noise Level. The underlying noise, as shown in Fig. S2A, was often discarded from the detected spikes. Nonetheless, recent findings reported that the background noise amplitude could distinguish the CM-pf complex from its surrounding nuclei [72]. The specificity of CM-pf localization suggested its potential as an indicator related to consciousness. However, the background noise level was found unrelated to the level of consciousness in our study, both in the preoperative diagnosis and in the follow-up diagnosis (Table S2).

3.3. The electrophysiological properties underling clinical factors of DoC

To investigate electrophysiological properties underlying clinical factors, we analyzed the correlation relationship between the CM-pf features and primary clinical factors of DoC, including etiology (anoxia, stroke, trauma), injury duration and age. To be noticed, only electrophysiological features that were found to be significant with consciousness level in the above mentioned analysis were used here.

As for the etiology, we found that both anoxia and stroke showed a strong correltation with CM-pf features (Table S3). To be specific, anoxia was negatively correlated with firing rates strongly ($p < 0.001$, $r = -0.68$). Considering the effect of firing rates on predicting the outcome (Fig. 2B), lower firing rates found in patients with anoxia indicated their worse outcome. An intermediary role similar to firing rates was also found in the alpha band normalized power and gamma band syncMUA for anoxia (Table S3). On the contrary, electrophysiological features, including alpha band syncMUA and alpha band normalized power, showed positive correlation with stroke (Table S3). And traumatic patients were found a positive correlation with firing rates ($p = 0.047$, $r = 0.42$, Table S3).

Electrophysiological characteristics, including alpha band normalized power and syncMUA, showed positive correlation with the duration

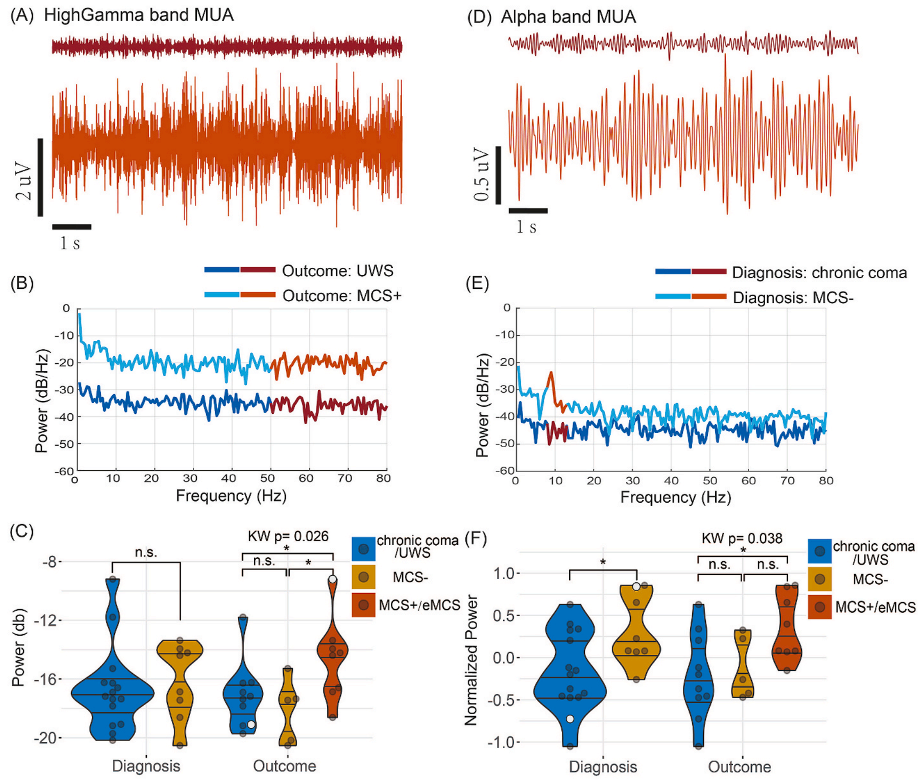

Fig. 3. MUA power. (A) MUA visualization in the high gamma band. The UWS patient (No. 6) recovering to MCS+ (bottom orange) has several times stronger oscillation amplitude than a UWS patient (No. 15) staying UWS after DBS treatment (top red). (B) Outcome: UWS. A visible difference is shown in the high gamma band power strength for these two patients. The high gamma band is marked in red and orange separately. (C) Group comparison. High gamma band MUA raw power was significant only in the follow-up stage (KW test: $p = 0.026$, effect size: $\eta 2 = 0.31$) but not in the preoperative diagnosis. The two sample patients in (A) and (B) are marked here with white-filled points in the bar of outcome. (D) MUA visualization in the alpha band. A MCS- case (No. 21, bottom orange) has stronger oscillation amplitude than the other chronic coma case (No. 16, top red). (E) MUA PSD. A visible frequency-specific difference is shown in the alpha band power strength for these two patients. The alpha band is marked in red and orange separately. (F) Group Comparison. There were statistical significances both in the preoperative diagnosis (Wilcoxon ranksum test: $p = 0.033$, effect size: $r = 0.45$) and in the follow-up diagnosis (KW test: $p = 0.038$, effect size: $\eta 2 = 0.28$). The two sample patients in (E) and (F) are marked here with white-filled points in the bar of diagnosis. Significance differences are shown with asterisks (**$p < 0.01$, *$p < 0.05$, n.s. $p \geq 0.05$) MCS+/eMCS: Minimally Conscious State plus or emergence from MCS, MCS-: Minimally Conscious State minus, chronic coma UWS/Coma: chronic coma or Unresponsive Wakefulness Syndrome. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

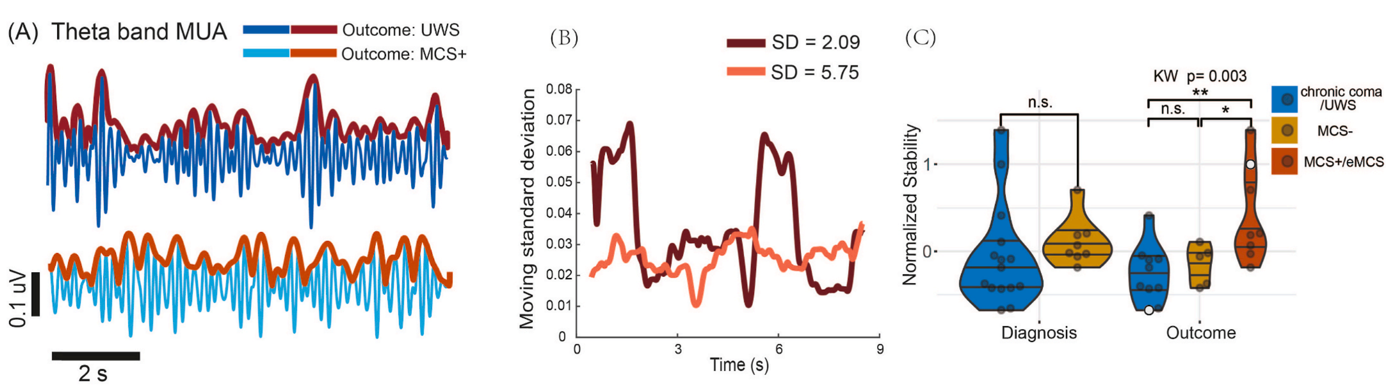

Fig. 4. MUA Stability. (A) Signal stability visualization in the theta band. The oscillation amplitude for the theta band filtered MUA (dark blue and light blue) and its envelope (red and orange) are presented for two patients separately. Compared with a UWS patient staying UWS (No.11, red and dark blue), the UWS patient recovering to MCS + after DBS treatment (No.17, orange and light blue) has a visibly stronger and more stable theta oscillation. **(B)** The variation trend for the envelope's local standard deviation over time. Compared with the patient in a severe condition (dark red. Stability Degree = 2.09), the one in a mild condition is with visible stronger theta band stability (light orange. Stability Degree = 5.75). **(C)** Group Comparison. The feature was on the brink of significance in the diagnosis (Wilcoxon ranksum test: $p = 0.081$) and was remarkably significant in the follow-up stage (KW test: $p = 0.003$; effect size: $\eta 2 = 0.43$). The two sample patients in (A) and (B) are marked here with white-filled points in the bar of outcome. Significance differences are shown with asterisks (**$p < 0.01$, *$p < 0.05$, n.s. $p \geq 0.05$) MCS+/eMCS: Minimally Conscious State plus or emergence from MCS, MCS-: Minimally Conscious State minus, chronic coma/UWS: chronic coma or Unresponsive Wakefulness Syndrome. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

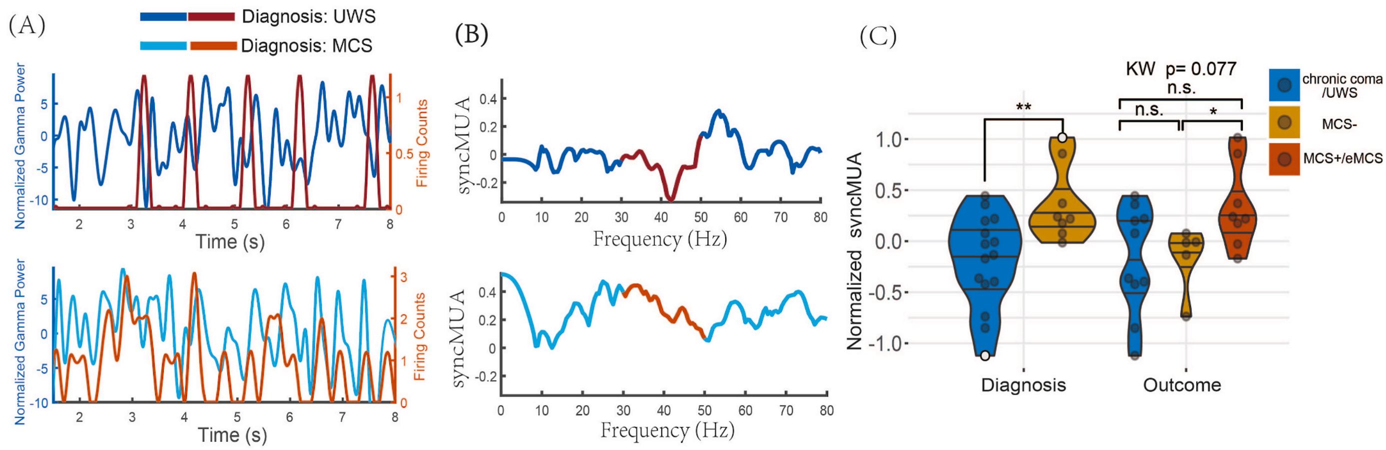

Fig. 5. SyncMUA. (A) SyncMUA visualization. In the time-frequency diagram, the gamma band MUA activity (red or orange) is compared with the synchronous MSP firing rate (dark blue or light blue) over time. Compared with a UWS case (No.23, red and dark blue in the top.), the other MCS- case (No.19, orange and light blue at the bottom.) has a visibly stronger syncMUA. **(B)** The correlation strength between firing rates and MUA is presented among all frequencies, where the gamma band is marked in red (top, one severe patient) and orange (bottom, one milder patient). **(C)** Group Comparison. The feature was quite significant (Wilcoxon ranksum test: $p = 0.008$, effect size: $r = 0.55$) in the diagnosis and nearly significant in the follow-up stage (KW test: $p = 0.077$). The two sample patients in (A) and (B) are marked here with white-filled points in the bar of diagnosis. Significance differences are shown with asterisks (**$p < 0.01$, *$p < 0.05$, n.s. $p \geq 0.05$) MCS+/eMCS: Minimally Conscious State plus or emergence from MCS, MCS-: Minimally Conscious State minus, chronic coma/UWS: chronic coma or Unresponsive Wakefulness Syndrome. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of DoC (Table S3). However, no significant correlation was found between age and CM-pf characteristics (stabilityMUATheta, $p = 0.076$, Table S3).

4. Discussion

Our study provides further evidence supporting the long-term therapeutic effects of CM-pf DBS in patients with DoC. Among the 23 patients included in our study, 11 individuals (47.8%) demonstrated an improvement in their level of consciousness following CM-pf DBS. Additionally, we investigated the electrophysiological characteristics of the CM-pf underlying DoC and its recovery.

Overall, our analysis revealed a consistent association between a higher level of consciousness and increased measures of MUA normalized power and syncMUA strength. Moreover, patients who regained consciousness exhibited elevated firing rates, MUA raw power, MUA normalized power, and MUA stability. These electrophysiological properties of CM-pf provided valuable complementary insights into the state of consciousness in DoC patients, particularly in cases where behavioral assessments may not adequately capture responses in patients with impaired afferent or efferent pathways. By providing an enriched understanding of the neuronal activity characteristics, our findings contribute to a broader understanding of CM-pf dynamics and its role in consciousness.

4.1. Electrophysiological characteristics of CM-pf related to consciousness recovery

Previous studies have reported a lack of firing activities in the central thalamus among patients with severe DoC [13,19,73]. Consistent with these findings, our results showed that better outcomes were correlated with more active central thalamus activities, including higher firing rates and higher MUA raw power strength (Figs. 2 and 3). Concretely, our results indicated that higher firing rates and stronger MUA raw power, specifically within the high-gamma band, were associated with a greater likelihood of regaining consciousness in patients with DoC. Notably, these activity strengths were not significantly stronger in patients with better diagnoses, but rather in patients with better outcomes.

Many previous studies have found a positive correlation between the level of consciousness and the alpha activity [74,75]. Although we didn't find any significant differences across DoC patients in the alpha band MUA raw power (Table S2), we found that patients with DoC, regardless of their higher preoperative consciousness levels or better outcomes, exhibited stronger normalized alpha waves within the CM-pf (Fig. 3). Unlike MUA raw power, the MUA normalized power provided a measure of the relative variation ratio of a specific frequency band in relation to the overall spectrum power strength. This normalized index allowed for highlighting the frequency-specific characteristics. However, given the generally better outcomes observed in patients with higher consciousness levels [46], we hypothesized that the predictive value of this normalized indicator for outcomes is mainly influenced by its diagnostic variations.

Previous studies have proposed the existence of an intermediate state in the central thalamus, characterized by the presence of a representative theta band rhythm that lies between the fully quiescent and healthy states [13,19,62,76]. This theta band activity arose from intrinsic membrane potential oscillations mediated by low threshold “T” type calcium channels in the thalamus [77]. Nevertheless, when we initially investigated theta band MUA power in the central thalamus, no significant differences were found between different conscious states (Table S2). This may be due to the fact that the DoC patients in our study, including those in chronic coma/UWS and MCS-, were all reported to have quiescent central thalamus activation [73].

Besides, previous studies found that this theta activity, as an intermediate state feature, is maintained through a stable excitatory-inhibitory interaction between the central thalamus and the inhibitory thalamic reticular nucleus (TRN) [78,79]. However, this theta rhythm is absent, when the resting membrane potential is highly hyperpolarized, as observed in severe DoC cases [73]. Therefore, we aimed to identify an earlier index that could provide insights into the transition process of the central thalamus from a quiet state to the intermediate state characterized by stable theta band synchronization. To achieve this, we calculated the stability of MUA and observed that a more stable theta activity strongly correlated with better outcomes (Fig. 4). This theta band stability of MUA served to differentiate the seemingly silent central thalamus and potentially reflected the process of the TRN-CT interaction transforming from unstable to stable [78,79], shedding light on the electrophysiological changes underlying the early-stage recovery of consciousness. In comparison with the classification based on the state of the central thalamus in the ‘ABCD’ model [13,19,76], the theta band stability index might quantitatively correspond to its transition from category A to B and then to the category C.

In summary, our findings revealed a positive correlation between higher firing rates, increased MUA raw power in the high-gamma band, enhanced normalized power in the alpha band, and greater MUA stability in the theta band with better outcomes in patients with DoC. Notably, the stability of theta activity emerged as a valuable indicator for predicting outcome differences, particularly in patients exhibiting seemingly silent thalamic activity. This finding might provide insight into the transition from quiescent to bursting activity within the central thalamus and hold potential as a predictive indicator for the outcome of patients with DoC.

4.2. Electrophysiological characteristics of CM-pf related to preoperative level of consciousness

Previous studies have consistently reported increased alpha band activity in the thalamus during wakefulness compared to anesthesia states [75]. The alpha band activity has also been found to be more prominent under light anesthesia compared to deep anesthesia [74]. Additionally, positive correlations have been observed between alpha activity and blood-oxygenation-level-dependent activity in the thalamus in earlier studies [80–84]. Consistent with these findings, our study revealed stronger normalized alpha-band oscillations in the CM-pf among patients with higher preoperative consciousness levels (Fig. 3). This further supports the role of alpha band activity as a potential marker for consciousness and underscores its relevance in understanding DoC.

Previous studies have demonstrated that enhanced synchronization of spiking output in neuronal populations can amplify their impact on postsynaptic target cells [68] and establish a robust communication structure among activated neuronal populations by imposing selective synchronization patterns [69]. In our study, we measured this synchronization using the syncMUA index, which was calculated similarly to spike-field coherence [68–71] or group coupling [63–65]. Specifically, we observed significantly stronger syncMUA in the gamma band among patients with higher consciousness levels during the preoperative stage (Fig. 5). This finding aligns with previous studies that have demonstrated a close relationship between spiking activities and gamma band fluctuations in the membrane potential, known as spike-gamma coupling [74,75,85]. The strength of this coupling has been shown to be influenced by the correlation among neighboring neurons, regardless of their firing intensity [81,82]. Our results indicate that patients with higher consciousness levels exhibit stronger gamma band synchronization in CM-pf neurons. A similar phenomenon was observed in the alpha frequency band but not in other frequency bands (Table S2). Moreover, among all the electrophysiological features analyzed, syncMUA specifically provided diagnostic information rather than predicting the outcome (Table S2). Overall, we found that syncMUA exhibited clinical-stage (only informative for preoperative diagnosis) and frequency specificity, reflecting the intrinsic discharging properties of neurons in the CM-pf. Previous studies have linked an increase in spike-field coherence to higher cognitive functions, such as increased gamma band activity during attentional tasks [70,86] and increased alpha band activity during the maintenance of working memory [71]. Therefore, the presence of syncMUA in DoC patients may indicate the ability to mobilize more cognitive resources in the brain.

In summary, our study reveals that the intrinsic characteristics, including syncMUA and alpha band normalized power, provide valuable insights into the level of consciousness during the preoperative stage. Following FDR correction, we found that only gamma band syncMUA remained statistically significant among all CM-pf features in association with the preoperative diagnosis (Table S2). This suggestes that in patients with DoC, stronger gamma band syncMUA may indicate a better preoperative diagnosis, regardless of the strength of outcome-specific features as found above. These findings underscore the importance of gamma band synchronization as a potential marker for assessing consciousness levels in patients with DoC.

4.3. Electrophysiological characteristics of CM-pf related to primary clinical factors of DoC

Previous studies have highlighted the importance of clinical factors in understanding DoC patients and predicting their recovery [3,13,38–45,54–58]. Factors such as age and injury duration have been identified as primary factors for DoC in numerous studies [38–40]. Our study also found that younger DoC patients had a higher probability of recovery after DBS ($p = 0.008$, Table S2). Additionally, the etiology of the condition has been recognized to play a crucial role, with anoxia being considered the most negative prognostic characteristic among various etiologies [38,40,87–91]. Conversely, patients with DoC caused by trauma had a relatively higher probability of recovery compared to other causes [3,38,40–42,92–94]. However, these findings have primarily relied on clinical experience or weight analysis in predictive models, and lack support from electrophysiological evidence. In our study, we observed negative correlations between anoxia and electrophysiological indices, while stroke and trauma showed positive correlations with CM-pf activities (Table S3). These findings provide potential electrophysiological evidence supporting the distinguishing ability of these clinical factors in assessing the level of consciousness. For example, we found a correlation between higher MSP firing rates in the central thalamus and better outcomes (Fig. 2C), indicating that anoxia patients might have a worse outcome due to their lower firing rates in the central thalamus (Table S3). However, we did not find any significant correlations between age and CM-pf indices, despite previous findings indicating that age provides prognostic information for DoC [13,38,54]. Moreover, the positive correlation found between injury duration and CM-pf features (Table S3) could be attributed, at least in part, to our strict control of surgical indications for DBS treatment in patients with a long duration of DoC.

By examining the electrophysiological characteristics associated with clinical factors, our study contributes to a comprehensive understanding of DoC and its recovery prediction. Moreover, the correlation analyses between the electrophysiological activity of the central thalamus and clinical factors provide valuable insights into the electrophysiological properties underlying the effects of these clinical factors on the recovery of consciousness. Thus, the activity of the central thalamus may serve as an intermediary in understanding the influence of certain clinical factors on the restoration of consciousness.

4.4. Limitations and prospects

While our study provides insights into the CM-pf characteristics associated with DoC, there are several limitations that should be acknowledged. Firstly, our study specifically examined the MUA-based characteristics of CM-pf. MUA-based MER has proven effective in rapidly and objectively labeling the subthalamic nucleus borders [29,95,96]. Thus, The MUA-based characteristics we determined hold promise for improving the precision of surgical localization. However, further exploration is needed to identify nuclei-specific indicators of CM-pf.

Furthermore, the sample size of DoC patients in our study was still small, which may introduce noise and limit the generalizability of our findings. Meanwhile, due to the limited sample size, we combined certain diagnoses (chronic coma and UWS, MCS+ and eMCS) for the statistical analysis. In future studies, it is important to increase the sample size for more detailed subgroup analysis and further validate the observed correlations.

Lastly, while our study provides group-level insights, individual-level analysis is necessary to understand the variability and complexity of DoC. Consciousness state and recovery potential are influenced by multiple factors, and a combination of CM-pf characteristics may be more informative in predicting outcomes and guiding personalized DBS treatment. Future studies should consider a comprehensive approach that incorporates multiple electrophysiological indicators at the individual level.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

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Ethics approval

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Written informed consents were obtained form the caregivers of all patients. The study was approved by the ethics committee of PLA Army General Hospital (2011–0415) and the ethics committee of Beijing Tiantan Hospital, Capital Medical University (2017– 361- 01).

CRediT authorship contribution statement

Jianghong He: Conceptualization, Investigation, Resources, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Haoran Zhang:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Yuanyuan Dang:** Investigation, Resources, Writing – review & editing. **Yutong Zhuang:** Investigation, Resources, Writing – review & editing. **Qianqian Ge:** Writing – original draft, Writing – review & editing. **Yi Yang:** Investigation, Resources, Writing – review & editing. **Long Xu:** Investigation, Resources. **Xiaoyu Xia:** Investigation, Resources. **Steven Laureys:** Writing – review & editing. **Shan Yu:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Wangming Zhang:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.09.021.

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