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ORIGINAL COMMUNICATION

Zona incerta deep-brain stimulation in orthostatic tremor: efficacy and mechanism of improvement

Greydon Gilmore[1,2] · Aditya Murgai[2] · Abdulrahman Nazer[3] · Andrew Parrent[2,3] · Mandar Jog[1,2]

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Abstract

Background Orthostatic tremor is a rare hyperkinetic movement disorder that is characterized by a 13–18 Hz tremor in both legs while standing. Deep-brain stimulation of the caudal zona incerta has re-emerged as an alternate target for tremor control in various etiologies.

Object Explore the clinical efficacy and mechanism of action of caudal zona incerta deep-brain stimulation in orthostatic tremor.

Methods Four patients (63.1 ± 4.1 years, female = 50%) with orthostatic tremor were recruited for this open label study (63.1 ± 4.1 years, female = 50%). In two patients, the electrodes were externalized to determine the effectiveness of caudal zona incerta as a target. Surface EMG (leg muscles), EEG (leg motor cortex) and caudal zona incerta local field potential recordings were recorded. Data were recorded in sitting and standing positions with stimulation OFF and ON.

Results EMG frequency analysis showed tremor frequency at 13–17 Hz. EMG–EEG coherence was found in the tremor frequency band and double tremor frequency band. EMG–caudal zona incerta coherence was higher in the tremor frequency band, while EEG coherence was higher in the double tremor frequency band. Upon stimulation, there was a selective reduction in tremor frequency band EEG-EMG coherence in all patients. All the patients had reduction in feeling of unsteadiness and increase in the stance duration.

Conclusions Bilateral caudal zona incerta deep-brain stimulation is effective in refractory orthostatic tremor. Two independent central oscillations were found at tremor and double tremor frequency. Zona incerta DBS produces improvement in OT patients possibly by modifying the abnormal oscillatory proprioceptive input from leg muscles. Frequent changes in deep-brain stimulation settings were required for maintaining the clinical benefit.

Keywords Deep-brain stimulation · Motor control · Basal ganglia · Parkinson's disease · Neurophysiology

Introduction

Orthostatic tremor (OT) is a rare hyperkinetic movement disorder that is characterized by a 13–18 Hz tremor in both legs while standing with improvement on walking [1, 2]. The tremors can be alleviated by sitting or leaning on an object to displace body weight. Oral medications like clonazepam are the first-line therapy for OT. Bilateral deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of thalamus may alleviate symptoms in patients resistant to medical treatment [3–7].

Though the central network contributors of OT are not clear, the network is believed to involve primary leg sensory-motor cortex, the supplementary motor area, thalamus, and the cerebellum [8]. Many electrophysiological and functional neuroimaging studies have suggested the role of

Greydon Gilmore and Aditya Murgai have contributed equally to the manuscript.

✉ Aditya Murgai
murgai03@gmail.com

[1] School of Biomedical Engineering, Western University, London, Canada

[2] Department of Clinical Neurological Sciences, University Hospital, 339 Windermere Road, London, ON N655, Canada

[3] Department of Neurosurgery, University Hospital, London, Canada

cerebellum in OT pathogenesis. Voxel-based morphometry analysis in OT has shown reduced grey matter volume in cerebellar lobules VI and increased grey matter volume in superior cerebellar vermis [9].

DBS data currently available for patients with OT are mostly based on VIM-DBS. Bilateral VIM stimulation has shown to be safe, well tolerated and effective in medically refractory OT. (30) Zona incerta (Zi) is another target for tremor control and its efficacy in Parkinson's disease was first described in 1972 [10]. In recent years, caudal Zi (cZi) has re-emerged as an alternate target for tremor control not just in PD but tremors of many other etiologies [11]. Anatomically, the Zi is a strip of grey matter that lies dorsal and posterior to subthalamic nucleus. It receives afferents from basal ganglia nuclei, deep cerebellar nuclei, dorsal column nuclei and multiple cortical regions including motor and primary somatosensory cortex [12]. Efferents connections are with the basal ganglia output nuclei, multiple thalamic nuclei, and the cortex [13]. Caudal portion of Zi is believed to be associated with motor functions [14].

Stimulation of cZi has been shown to improve parkinsonian tremors better than stimulation of subthalamic nucleus [15]. Furthermore, bilateral cZi-DBS stimulation has shown to improve tremors in cerebellar disorders, essential tremors, dystonic tremors and tremors of multiple sclerosis [16]. Based upon the results of previously published studies showing efficacy of cZi-DBS in tremor of multiple etiologies, bilateral cZi-DBS electrodes were implanted in four OT patients. Postoperative EEG, surface EMG and cZi local field potential (LFP) recordings were performed, to further understand the mechanism for clinical improvement in these patients.

Material and methods

Patients

This open label study included four patients that were scheduled for bilateral cZi-DBS surgery at University Hospital, London Health Sciences Centre. The diagnosis of OT was made by clinical assessment using surface EMG according to the Consensus Statement of the Movement Disorder Society on Tremor [17]. Only patients with idiopathic orthostatic tremors were selected for the surgery. The local Human Subjects Research Ethics Board was notified of the study, formal approval was not required. All patient data collection was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Surgical procedure

The implantable pulse generator was implanted 2–5 days after DBS lead implantation. Axial T2-weighted (T2w) MRI images (echo time = 110 ms, repetition time = 2800 ms, receiver bandwidth = 20.83 kHz, field of view = 26 cm, matrix size = 256 × 224, slice thickness = 1.5 mm, resolution = 1.25 × 1.25 × 1.50 mm) and post gadolinium enhanced volumetric T1-weighted (T1w) images (echo time = 1.5 ms, inversion time = 300 ms, flip angle = 20°, receiver bandwidth = 22.73 kHz, field of view = 26 cm x 26 cm, matrix size = 256 × 256, slice thickness = 1.4 mm, resolution = 1.25 × 1.25 × 1.50 mm) were obtained 2 weeks prior to surgery (Signa, 1.5 T, General Electric, Milwaukee, Wisconsin, USA). As reported by Blomstedt et al., cZi was identified slightly posteromedial to the posterior tail of the subthalamic nucleus at the level of maximal diameter of the red nucleus [18]. All surgical planning was done using the StealthStation (StealthStation, Medtronic Corp, MN). All procedures were performed by the same surgeon (AP).

On the day of surgery, a stereotactic Leksell frame was mounted on the patients' head (Elekta instruments, Sweden) and a CT scan (Philips Medical System, Best, The Netherlands) was performed. The CT scan was fused with the preoperative 1.5 T MRI to bring the surgical plan into the reference frame of the patient. In the operating room, the Leksell frame was mounted to the operating room table to avoid head movement. All patients were operated under local anesthesia with slight sedation for comfort. Patients were placed in a supine position with the head elevated 20°–30° to minimize outflow of cerebrospinal fluid. Surgical entry points were chosen pre-coronal and 30.0–40.0 mm lateral from the midline on a suitable gyrus. The Leksell arc was attached to the Leksell head frame and set to the planned coordinates. Intraoperative stimulation was performed using a tungsten microelectrode placed in the central position of Ben's gun (Alpha Omega, Nazareth, Israel) in awake patients. Two patients received 3389 DBS leads (Medtronic, Minneapolis, Minnesota, USA) and the other two received Vercise directional DBS leads (Boston Scientific, Valencia, CA, USA).

Electrode localization

Postoperative CT scans were acquired for all patients. The MRI and CT images were converted to Nifti file format using dcm2niix [19]. The 1.5 T T1w volume was used as the reference image, the CT and T2w images were registered to the T1w image using NiftyReg [20]. Using the postoperative CT scan, the coordinates of the DBS

electrode tip were identified within 3D Slicer [21]. The individual DBS electrode contacts were visualized using in-house Python (v3.6.5) code and Visualization Toolkit (Kitware, Clifton Park, NY).

Electrophysiology and tasks

Since the DBS surgery stage I (electrode implantation) was performed on a separate day from stage II (implantable pulse generator implantation) the DBS electrodes were externalized, which allowed for cZi LFP recordings (sample frequency 1375 Hz). In house cables were manufactured that allowed connection to the DBS electrodes. All electrophysiology recordings were collected using a Neuro Omega system (Alpha Omega Engineering, Nazareth, Israel). Bipolar surface EMG (sample frequency 11,000 Hz) recordings were done with pre-gelled adhesive Ag/Agcl foam electrodes from bilateral vastus lateralis, lateral gastrocnemius and tibialis anterior muscles. Bipolar EEG recordings (sample frequency 1375 Hz) were done with silver cup electrodes with active electrode placed on Cz and reference electrode 3 cm behind Cz in midline.

Post-surgery cZi LFP recordings were performed in two patients through the externalized electrodes, the electrodes were externalized prior to the implantation of the IPG, as experience with cZi-DBS for OT is very limited. Zi recordings were made from four contacts in each hemisphere but only the recordings from the lower most contact was used for analysis. The subsequent two patients did not undergo electrode externalization as the lessons learnt from the first two were adequate to determine the effectiveness of cZi as target. All patients underwent EEG and EMG recordings during the ON and OFF stimulation state. The patients were asked to complete two sitting and two standing recording sessions. The tasks were performed with the DBS device OFF and then repeated with the DBS device turned ON. Zi LFP data were not collected when the DBS device was ON, as the electrodes needed to be connected to an external stimulator (model 3625 screener, Medtronic Inc., Minneapolis, MN, USA). During the standing task, patients sat if they could no longer tolerate standing. Contacts providing the maximum benefit in the stance duration with minimal side effects were chosen for stimulation.

Data processing

Data analysis was performed using custom scripts written in Matlab (vR2017a) and Python (v3.6.5). The Matlab toolbox NeuroSpec 2.0 (www.neurospec.org) was used to calculate power spectra, coherence, phase and cumulant density for each patient [22]. All data were down sampled to 1000 Hz. A 1 Hz highpass Butterworth filter (fourth order) and a 100 Hz lowpass Butterworth filter (fourth order) was applied to both the EEG and Zi LFP signal. A 5 Hz highpass Butterworth filter (fourth order) and a 250 Hz lowpass Butterworth filter (fourth order) were applied to the EMG signal. Notch filter was set at 60 Hz for all the recordings. Full-wave rectification was done for EMG signal after applying the filters to determine the envelope of the discharge rate. A Fourier transformation of 1024 data points was performed using a Matlab script and NeuroSpec tool box. Phase lag was calculated for the segment showing significant coherence using the formula ΔRadian/ΔFrequency $*2\pi$ [23]. The Phase information was calculated separately if there were more than one coherence bands.

Results

Patient characteristics

EMG and EEG recordings were obtained from four patients and bilateral Zi recordings from two patients. The cZi stimulation frequency varied from 130 to 180 Hz and pulse width from 50–90 microseconds. DBS produced immediate improvement in the feeling of unsteadiness and increased the duration of stance in all the patients (Table 1). All the patients required frequent changes in the DBS settings to maintain the beneficial effect. The average duration for which the patients were on a DBS setting was 4 months (range 3–6 months). Change in contacts, current amplitude, pulse-width and frequency were made to sustain clinical benefit. Mild ataxia was seen as a side effect of stimulation in all four patients. The clinical characteristics of the patients have been provided in Table 1.

Zona incerta electrode localization

For every patient, the DBS electrode was within the surgical target of cZi [24]. The position of the bottom contact on the DBS lead for each patient is shown in Fig. 1. The bottom contacts on the left were located -10.56 ± 2.05 mm lateral, -7.41 ± 0.30 mm posterior and -4.10 ± 1.59 mm below the midcommissural point. The bottom contacts on the right were located 10.99 ± 1.39 mm lateral, -7.45 ± 1.81 mm posterior and -4.87 ± 1.57 mm below the midcommissural point (Fig. 1).

Electrophysiology

EMG–EMG coherence analysis

In the present study, all four patients showed peak tremor activity between 13 and 17 Hz with multiple harmonics. The EMG tremor activity was alternating between tibialis

Table 1 Clinical and demographic data

Symptom onset latency/max stance duration (s)							
Patient	Age/sex	Disease duration (years)	DBS-OFF	DBS-ON	DBS settings	Stimulation SE	Medications
01	67/M	12	10/ 30	30/ 90	(L)Contact (2,3,4) +, contact (5,6,7) −, 1.5ma, 50msec, 149hz (R)Contact (10,11,12) +, contact (13,14,15) −, 2.5ma, 50msec, 149hz	Mild gait ataxia	Clonazepam Gabapentin Primidone
02	57/ F	8	10/ 40	60/ 300	(L)Case +, contact 1 −, 1.0ma, 60msec, 180hz (R)Case +, contact 9 −, 1.7ma, 60msec, 180hz	Mild gait ataxia	Clonazepam
03	68/M	8	05/ 30	30/ 120	(L)Contact 0 +, contact 1 −, 2.5ma, 60msec, 170hz (R)Contact 8 +, contact 9 −, 2.5ma, 60msec, 170hz	Mild gait ataxia	Clonazepam Levetiracetam Primidone
04	76/ F	25	05/ 15	90/ 180	(L)Case +, contact 1 −, 1.0ma, 90msec, 130hz (R)Case +, contact 9 −, 1.1ma, 90msec, 130hz	Mild gait ataxia	Clonazepam

anterior and gastrocnemius muscles on the same side and synchronous between identical muscles on the contralateral side (Fig. 2).

EMG–EEG coherence analysis

Highest EMG–EEG coherence was seen in the DTF (double tremor frequency) band with a smaller TF (tremor frequency) band peak. The phase information of EEG–EMG coherence in DTF band showed EEG activity preceding EMG by 25–46 ms in all patients. The phase information of EEG–EMG coherence in TF band was not clear (biphasic) but EMG activity preceding EEG was seen in one patient. No tremor activity or significant EMG–EEG coherence was seen in the sitting position (Fig. 3).

EMG-Zi LFP and Zi LFP-EEG coherence analysis

EMG-Zi LFP coherence analysis showed highest coherence in the TF band and a lower coherence peak in the DTF band. Zi-EEG coherence analysis showed highest coherence in the DTF band (Fig. 4).

Caudal zona incerta DBS effect

DBS produced a selective reduction in EMG–EEG coherence peak of TF band in all patients and in all the recorded muscles. This reduction was associated with clinical improvement in unsteadiness while standing. The tremor activity persisted during stimulation. (Fig. 5).

Discussion

Mechanism of improvement with cZi stimulation

Deep-brain stimulation of cZi reduced feeling of unsteadiness, even though there was persistence of tremor activity in the leg muscles. This result is in accordance with a previous study of thalamic DBS in OT. The authors concluded that improvement in unsteadiness was a result of stimulation-induced changes in the proprioceptive input to the sensory-motor cortex [8]. Similar conclusions have been made in studies showing improvement in OT with spinal cord stimulation (SCS) [25, 26]. The therapeutic effect of SCS on OT is believed to be due to modulation of sensory input to the central network generating orthostatic tremor, without improvement in the tremor activity [25].

Other studies of VIM-thalamic DBS in OT patients have shown reduction the leg tremor amplitude, delay onset of tremors and periods of quiescence in tremor activity, without change in the tremor frequency [3, 4, 27].

Individuals with OT show a disproportionate increase in unsteadiness with eye closure, implying increased dependence on the visual feedback for maintaining balance while standing. This also implies that the sensory input from legs may not be properly utilized. Finally, it has been suggested that the tremor activity in leg muscles entrains the proprioceptive information from muscle spindles and Golgi bodies at TF, resulting in disruption of normal postural afferent proprioceptive feedback [28]. Our results showed maximum EMG-cZi LFP coherence in

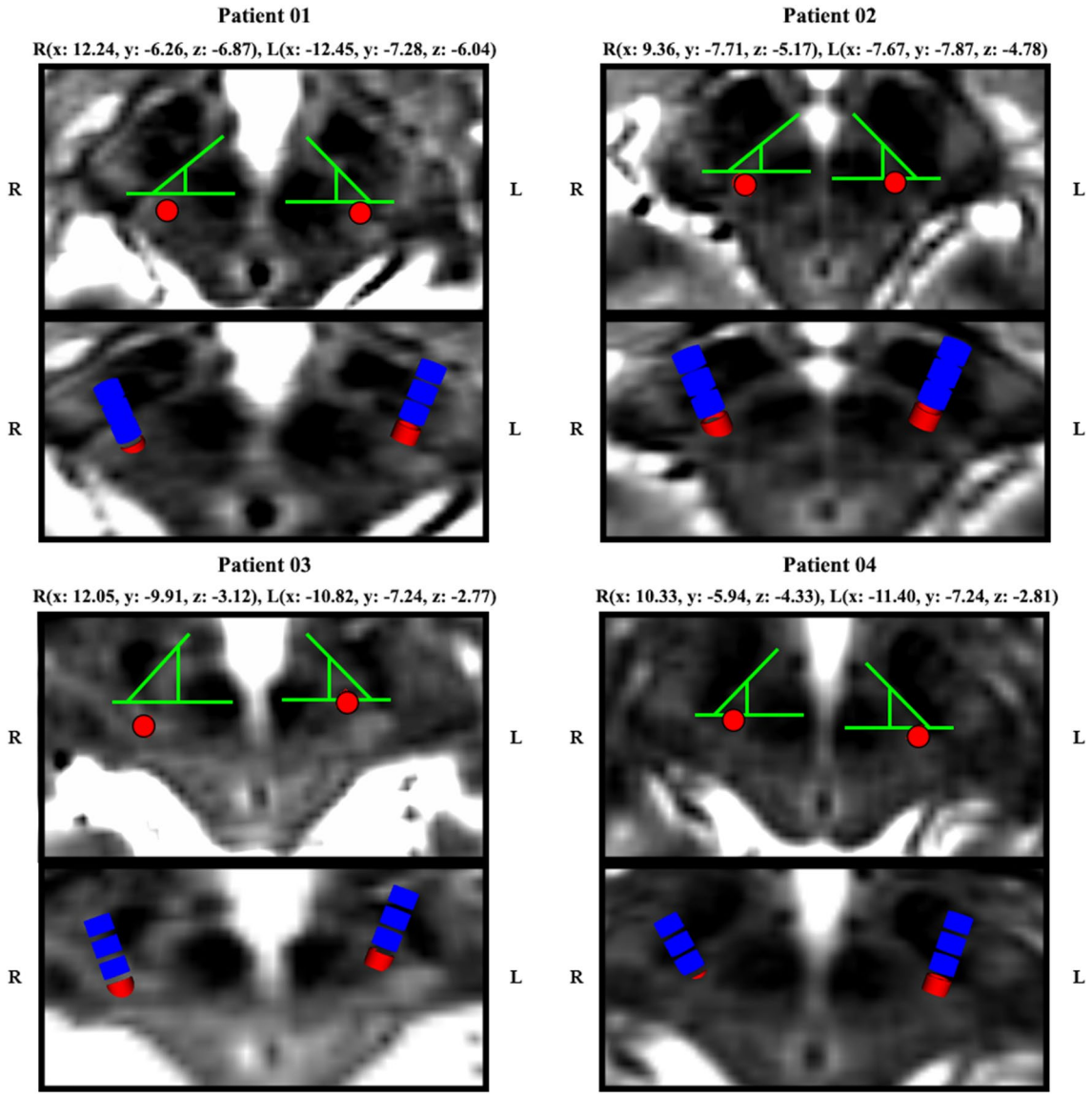

Fig. 1 cZI-DBS electrode reconstruction. The top panel, for each patient, depicts the bottom DBS electrode contact on the axial T2w image. The green lines indicate the cZi targeting technique described by Blomstedt et al. (2018), posteromedial to the posterior tail of STN at the maximal red nucleus diameter. The bottom panel, for each patient, provides a 3D rendering of the DBS electrode contacts on the T2w image (bottom contact in red). The coordinates for the bottom DBS contacts are provided above each panel group and are relative to the midcommissural point. Right (R) and left (L) sides are noted beside each panel

the TF band, suggesting the synchronization of cZi with the tremor activity. Zi receives afferents from dorsal column nuclei, explaining the high coherence seen at tremor frequency [12]. Stimulation of cZi resulted in selective reduction of TF band EEG–EMG coherence, which correlated with improvement in the feeling of unsteadiness. By disrupting the phase locking of cZi LFP activity with proprioceptive input at tremor frequency and hence modifying the abnormal oscillatory proprioceptive input from the muscles, cZi stimulation could have produced an improvement in unsteadiness.

Multiple central oscillations in OT

Frequency analysis of EMG from leg muscles showed multiple peaks at tremor frequency and its harmonics. Multiple harmonics are classically described in PD tremor and this feature has been used to differentiate PD tremor from tremors due to other etiologies [8]. Current evidence suggests different oscillators for the tremor frequency and its first harmonic in PD. EEG–EMG coherence analysis in PD patients showed different cortical origin for tremor frequency and its first harmonic. It has been suggested that the basic tremor frequency originates from the supplementary motor cortex

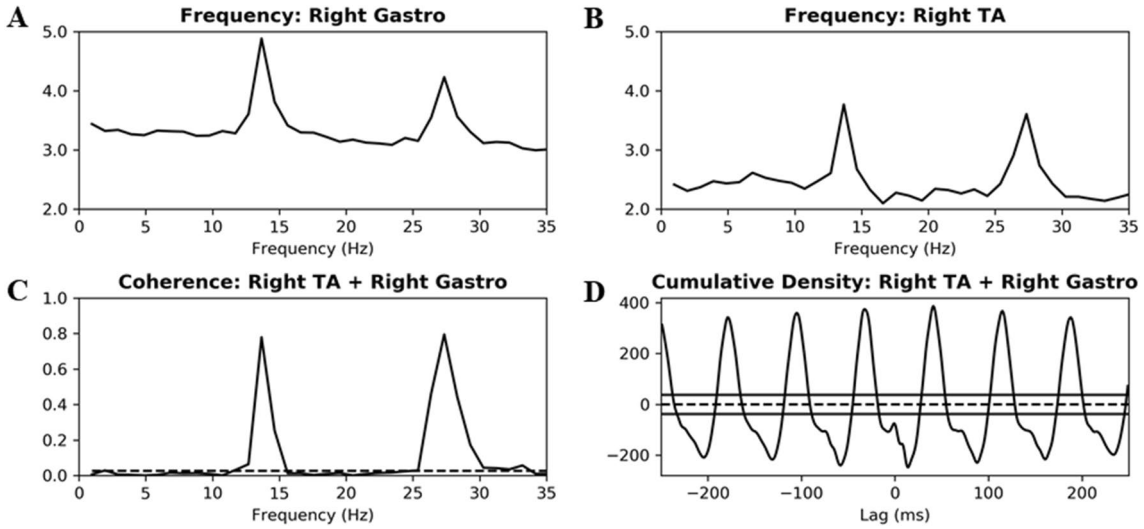

Fig. 2 EMG–EMG coherence. **a** Frequency plot of right gastrocnemius EMG showing tremor at 13.7 Hz with second peak at first harmonic. **b** Frequency plot of right tibialis anterior EMG showing tremor at 13.7 Hz with second peak at first harmonic. **c** Right gastrocnemius and tibialis anterior EMG–EMG coherence analysis showing high coherence in TF and DTF bands. **d** Cumulant density function showing negative peak at around 0 ms, suggestive of an alternate pattern of contraction between the muscles. *Gastro* Gastrocnemius, *TA* tibialis Anterior, *TF* tremor frequency, *DTF* double tremor frequency

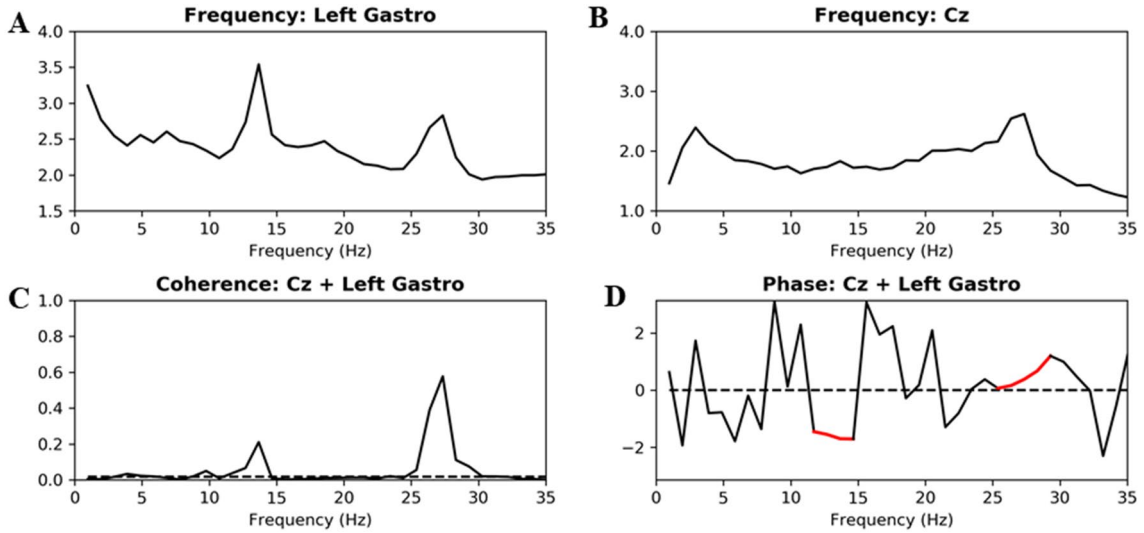

Fig. 3 EMG–EEG coherence analysis. **a** Frequency plot of left gastrocnemius EMG showing peak tremor frequency of 13.7 Hz. **b** Frequency plot of Cz EEG showing a peak at 27hz. **c** EMG–EEG coherence analysis showing high coherence in TF and DTF bands. **d** Slope of the corresponding phase lag showing Cz EEG preceding the left gastrocnemius EMG by 46 ms in DTF band, suggestive of a corticospinal drive at DT frequency. *Gastro* Gastrocnemius

and harmonic from the primary sensory-motor cortex in PD [29].

There are three key findings in this study that suggested the presence of two independent oscillations at TF and DTF. First, cZi stimulation produced a selective reduction in the TF band EEG–EMG coherence without reducing DTF band coherence. Second, EMG-cZi LFP coherence analysis showed peak coherence in the TF band, whereas EMG–EEG and EEG-cZi LFP coherence analysis showed peak coherence in the DTF band. Presence of different coherence peaks again suggests the presence of two separate oscillations. Finally, the phase information of EEG–EMG coherence in the DTF band showed EEG activity preceding EMG by a lag corresponding to the conduction time from the cortex to the leg muscles, suggesting an efferent corticospinal drive at DTF. The phase information of the TF band was not

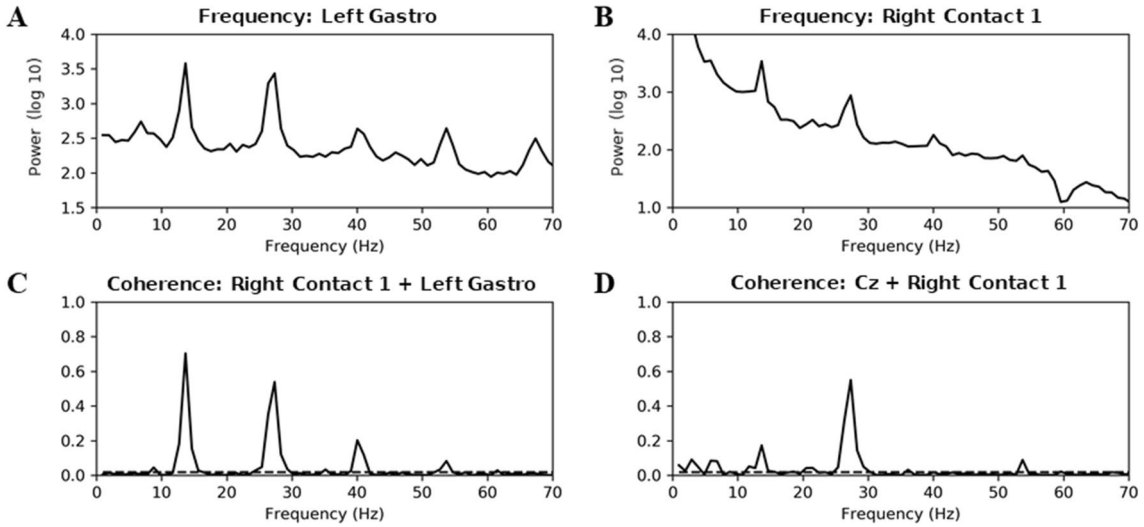

Fig. 4 EMG, EEG, and Zi LFP coherence analysis. **a** Frequency plot of left gastrocnemius EMG showing peak tremor frequency of 13.7 Hz with multiple harmonics. **b** Right **c**Zi LFP frequency plot showing well-formed peaks at 13.7 Hz and 27.4 Hz. **c** Left gastrocnemius EMG and right cZi LFP coherence analysis showing maximum coherence in the TF band. **d** Cz EEG and right cZi LFP coherence analysis showing maximum coherence in DTF band. *Gastro* Gastrocnemius

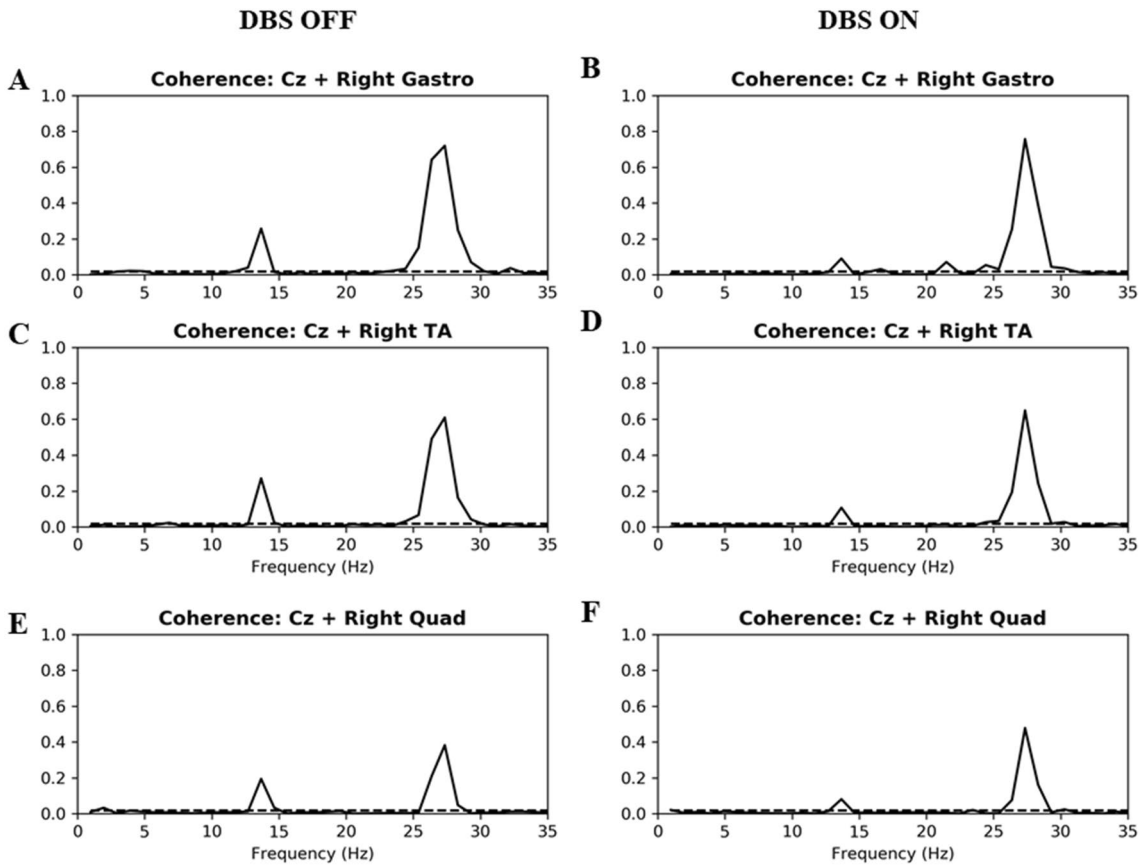

Fig. 5 Zi DBS effect. cZi stimulation producing a selective reduction in TF band EMG–EEG coherence in (**a, b**) right gastrocnemius (**c, d**) right tibialis anterior, and (**e, f**) right quadriceps (vastus lateralis). The left column is cZi-DBS OFF and the right column is cZi-DBS stimulation ON. *Gastro* Gastrocnemius, *TA* tibialis anterior, *Quad* quadriceps (vastus lateralis)

clear (biphasic slope) except in one patient in whom EEG preceded the EMG. Different phase information in the two frequency bands also suggests the presence of two separate oscillations.

Clinical implications

Ventral intermediate nucleus of thalamus is the most common site for stimulation in medically refractory OT. A recently published multicenter international registry showed the efficacy of thalamic VIM DBS in OT. The study showed 21.6% improvement in the composite activities of daily living/instrumental activities of daily living scores, which gradually attenuated (12.5%) in about half of the patients in long-term follow-up [30] DBS of cZi has been successfully used for many years for treating a variety of tremor disorders but its use in OT has not been described before. We performed bilateral cZi-DBS in four patients with medically refractory OT and all patients showed reduction in the orthostatic unsteadiness with stimulation. The effectiveness of a setting reduced after few months but all patients were still better compared to what they were before surgery and worse with stimulation turned off. Frequent changes in deep-brain stimulation settings were required for maintaining the clinical benefit. Mild gait ataxia was seen in all the patients as a side effect of the stimulation. This could be related to the stimulation of ascending cerebellothalamic fibers and traversing rubral fibers, located posteromedial to Zi within the Raprl fibers [31]. Reduction in current amplitude or the pulse-width improved ataxia in all patients. There are two major limitations of this study. Lack of blinding of patients and assessor could have affected the results. Another limitation was not using any clinical scale to quantify the improvement in functional disability.

Conclusions

Our study shows the efficacy of bilateral cZi-DBS in refractory OT, providing a new target for stimulation. This study further shows the presence of two different central oscillations at tremor frequency and double tremor frequency in the pathogenesis of OT. Modification of the abnormal oscillatory proprioceptive input from the leg muscles could be the possible mechanism for improvement of unsteadiness with cZi stimulation.

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Data availability The data and analysis scripts that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflicts of interests Greydon Gilmore has received graduate funding from the Canadian Institute of Health Research, AGE-WELL and Mitacs. Aditya Murgai: none. Abdulrahman Nazer: none. Andrew Parrent: has received an honorarium from Boston Scientific. Mandar Jog receives research grants from Allergan, Merz Pharmaceuticals, Abbvie, and Medtronic. Dr. Jog also receives speaker honoraria fees from the same companies and serves on advisory boards of these companies from time to time.

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