

Case Reports

Clinical Outcome and Characterization of Local Field Potentials in Holmes Tremor Treated with Pallidal Deep Brain Stimulation

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Abstract

Background: Holmes tremor (HT) is an irregular, low-frequency rest tremor associated with prominent action and postural tremors. Currently, the most effective stereotactic target and neurophysiologic characterization of HT, specifically local field potentials (LFPs) are uncertain. We present the outcome, intraoperative neurophysiologic analysis with characterization of LFPs in a patient managed with left globus pallidus interna deep brain stimulation (Gpi DBS).

Case Report: A 24-year-old male underwent left Gpi DBS for medically refractory HT. LFPs demonstrated highest powers in the delta range in Gpi. At the 6-month follow-up, a 90% reduction in tremor was observed.

Discussion: Pallidal DBS should be considered as an alternative target for management of refractory HT. LFP demonstrated neuronal activity associated with higher power in the delta region, similarly seen in patients with generalized dystonia.

Keywords: Holmes Tremor (HT), Deep Brain Stimulation (DBS), Globus pallidus, Internal Arterio-Venous Fistula, Local Field Potentials (LFP), Power Spectral Densities (PSD)

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Ethics Statement: This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki. The authors' institutional ethics committee has approved this study and all patients have provided written informed consent.

Introduction

Holmes tremor (HT) is characterized by irregular, low-frequency (<4.5 Hz) rest and prominent action and postural tremors, often affecting proximal muscles. Also referred to as Benedick syndrome, and rubral or midbrain tremor, HT is commonly refractory to medical treatment with limited management options. Typically, HT is secondary to central nervous system lesions including stroke, traumatic brain injury, vascular malformations, multiple sclerosis, or tumors.¹ It manifests as an unusual combination of low-frequency rest and action tremor, with an associated postural component.^{2,3} Concurrent dystonia, chorea, or ataxias are common.^{2,3}

The management of HT is particularly challenging because of limited treatment options, rarity of the disease, and the lack of large prospective clinical studies. In single cases, responses to levodopa, pramipexole, zonisamide, trihexyphenidyl, clonazepam, clozapine, and levetiracetam have been reported.^{3,4} Nevertheless, medical treatment is unsatisfactory in most patients and the heterogeneity of this disorder precludes prospective treatment evaluations. Several reports have highlighted the efficacy of thalamic ventralis intermedius nucleus (VIM) deep brain stimulation (DBS) in HT.^{5–8} However, there is no consensus regarding the best stereotactic target for HT treatment. We identified 17 patients in the literature with HT treated with

Table 1. Case Reports and Series of Thalamic and Subthalamic Deep Brain Stimulation in Patients with Holmes Tremor

Study	Number of Patients and Etiology	Target	Outcome	Follow-up
Studies reporting VIM DBS for HT				
Pahwa et al. ⁷	Midbrain cavernous hemangioma (symptoms for 3 years)	Right VIM	Significant improvement in postural and resting tremor; kinetic component persisted	10 months
Samadani et al. 2003 ¹²	Left midbrain cavernous malformation (symptoms for 4 years)	Right VIM	57% increase in dexterity and four-point decrease in functional disability in TRS	N/A
Nikkhah et al. 2004 ¹³	1. Right infarct midbrain (tremor symptoms 6 months); 2. Left thalamic AVM	2 patients with Contralateral VIM	Almost complete tremor resolution (80% improvement). Dystonia and rigidity benefit reported	7 months and 6 months respectively
Piette et al. 2004 ¹⁴	Pontine tegmental hemorrhage	Right VIM	Major functional improvement	16 months
Diederich et al. ³³	1. Left venous pontine angioma (symptoms for 7 years) 2. Right midbrain hemiatrophy (symptoms for 32 years)	2 patients with contralateral VIM	Substantially ameliorated postural>rest>intention component	7 years and 5 years respectively
Peker et al. 2008 ¹⁵	Left thalamic abscess (symptoms 18 months)	Right VIM	90% overall improvement	2.5 years
Acar et al. 2010 ¹⁶	Subarachnoid hemorrhage (symptoms less than 1 month)	Bilateral VIM	No tremor and reduction in disability due to tremor.	3 months
Castrop et al. 2013 ¹⁷	1. Hypertensive mesencephalic hemorrhage (symptoms for 1 year) 2. Pontomesencephalic AVM hemorrhage (symptoms for 2 years)	2 patients with contralateral VIM	Good tremor suppression, whereas the other symptoms remained unchanged	7 years and 6 years respectively
Issar et al. 2013 ¹⁸	1 patient with post-traumatic tremor (symptoms for 6 months) with associated dystonia, cerebellar and cognitive difficulties.	Bilateral VIM	Moderate partial benefit (CGI scale 3). No TRS available	N/A
Follett et al. ⁹	Post-traumatic HT (symptoms for 15 years)	Bilateral VIM	Reduction of tremor from a score of 3 to a score of 1 in the right arm and from 3.5 to 0 in the left arm (TETRAS scale)	12 months
Espinoza-Martinez et al. ⁵	1 patient with ICH due to cavernous malformations, 1 patient with cerebral infarction, 1 patient with MS	1 patient with bilateral VIM (MS case) and 2 patients with unilateral VIM	83.3% mean improvement in TRS	Mean length of follow-up 7.3 years

Table 1. Continued

Study	Number of Patients and Etiology	Target	Outcome	Follow-up
Studies reporting other DBS targets for HT				
Bandt et al. 2008 ¹⁹	Left midbrain cerebral infarction (symptoms for 7 months)	Left lenticular fasciculus	Almost complete resolution of postural and intention tremors; scored 1/4 on the WHIGET	16 months
Plaha et al. 2008 ²⁰	No obvious MRI abnormality (symptoms for 6 years)	Caudal Zi	70.2% improvement in total TRS	N/A
Kilbane et al. ⁸	1. Multicystic brainstem tegmentum lesions 2. Right thalamic/subthalamic infarction	2 Patient received unilateral Gpi.	81% improvement in TRS	Mean length of follow-up 27 months
Espinoza-Martinez et al. ⁵	3. patients with cerebral infarction, 3 patients with ICH and 1 patient with MS.	6 patients with unilateral Gpi, 1 patient with bilateral Gpi (MS case).	78% mean modified TRS improvement	Mean length of follow-up 5.1 years
Studies reporting dual or multiple DBS leads for HT				
Romanelli et al. 2003 ²¹	Unknown, severe symptoms 6 years	Left VIM and left STN	Tremor component improved 66%	2 years
Foote et al. ¹¹	Post-traumatic tremors 3 patients with symptoms for 16 years, 3 years, 4 years	2 patients with VIM (border VIM/Vop and 1 with border Voa/Vop)	Total TRS improvement of 38.46%, 48.33% and 66.67% respectively	12 months, 6 months and 8 months respectively
Grabska et al. ¹⁰	Ischemic left thalamic stroke (symptoms 30 years)	Contralateral Voa and Zi	TRS 73% reduction in tremor	4 years
Kobayashi et al. ²²	1. Brainstem thalamus hemorrhage (symptoms for 6 years) 2. Cerebral infarction (symptoms for 3 years) 3. Intracerebral midbrain hemorrhage (symptoms 8 months) 4. Posttraumatic (symptoms for 2 years)	4 patients with dual-lead stimulation of ventralis oralis/ventralis intermedius nuclei (VO/VIM) and PSA	87% mean improvement in tremor	25 months
Kilbane et al. ⁸	1. Right Brainstem hemorrhage due to cavernous malformation 2. Left thalamic midbrain bullet fragment	Patient 1 had VIM/Voa and Gpi leads. Patient 2 had VIM/Gpi leads	77.5% improvement in TRS. VIM or combined stimulation was not superior to Gpi lead (only lead active)	Mean length of follow-up 40 months

Abbreviations: Gpi, Globus Pallidus Interna; ICH, Intracranial Hemorrhage; MS, Multiple Sclerosis; MRI, Magnetic Resonance Imaging; PSA, Posterior Subthalamic Area; STN, Subthalamic Nucleus; TETRAS, The Essential Tremor Rating Assessment Scale; TRS, Tremor Rating Scale; VIM, Ventral Intermedius Nucleus; Voa, Ventralis Oralis Anterior Nucleus; Vop, Ventralis Oralis Posterior Nucleus; VO, ventralis oralis; WHIGET, Washington HeightsInwood Genetic Study of Essential Tremor; Zi, Zona Incerta; AVM, arteriovenous malformation

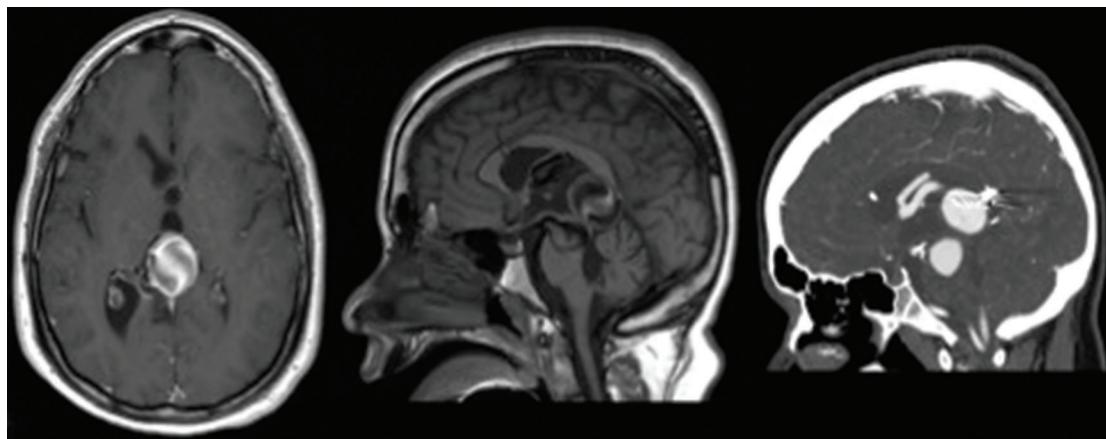


Figure 1. Axial (left) and sagittal (middle) T1 weighted MRI with gadolinium, and sagittal CT scan (right) of unsecured AV fistula.

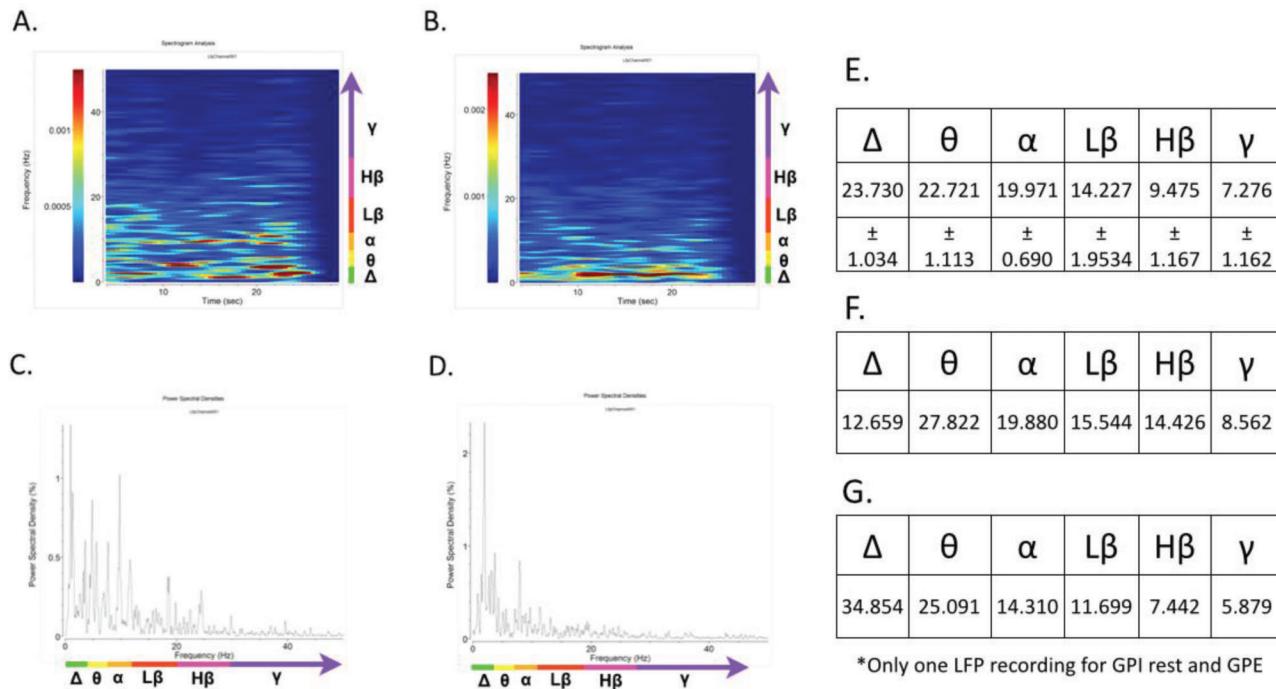


Figure 2. Sample LFP spectrograms in GPI (action) (A) and GPE (B). Corresponding GPI (C) and GPE (D) power spectral densities are included. Brackets (A-D): Δ, delta (0–3Hz); θ, theta (4–7 Hz); α, alpha (8–12Hz); Lβ, low beta (13–20Hz); Hβ, high beta (21–29Hz); γ, gamma (30–200Hz). Mean PSD values (\pm SEM) for each spectral band for GPI (action) (E), GPI (rest) (F) and GPE (G) are shown.

contralateral VIM DBS, 11 patients treated with globus pallidus interna (GPi) DBS, four patients treated with dual-lead stimulation in the VIM and posterior subthalamic area (PSA), and three patients treated with dual leads located at the border of VIM/ventralis oralis posterior nucleus (Vop) and ventralis oralis anterior nucleus (Voa)/Vop, three patients treated with VIM DBS with the deepest contact

located in the PSA, and individual cases of stimulation of the VoA and zona incerta (Zi), VIM and subthalamic nucleus (STN), lenticular fasciculus, and caudal Zi^{5–11} (Table 1). Although the outcome scales and follow-up varied among studies, the average overall improvement in tremor was 76% with an average age of 41 years (range 11–84 years), HT duration of 6 years (range 6 months to 32 years),

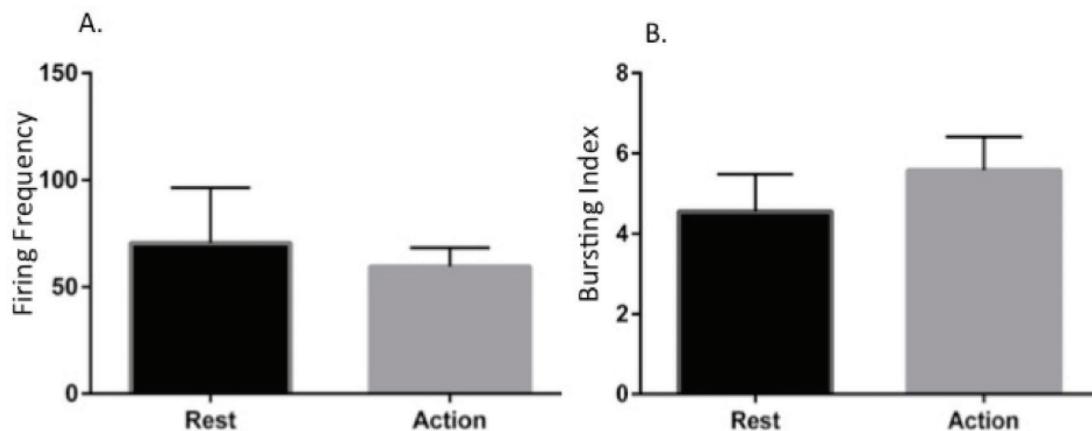


Figure 3. Paired t-test of GPI firing frequency at rest vs. action (A) and GPI bursting index at rest vs. action (B).

and an average follow-up of 3 years (range 6 months to 12 years). Dual thalamic stimulation, such as VIM with Voa/Vop or with PSA, was shown to offer significant improvements as it was proposed to override a hypothesized abnormality in both the pallido-thalamic and the cerebello-thalamic circuits.^{11,22} More recently, GPi DBS has been proposed as a potential target in small case series. An overall improvement of 64% and 78% in tremor scales was observed, and in a few exceptional cases there was complete tremor resolution.⁸

Owing to the diverse and variable injuries causing HT disrupting the basal ganglia or thalamic anatomy, careful selection of stimulation target for each patient is required. Kilbane et al.⁸ reported four patients managed with unilateral Gpi DBS with adequate and persistent tremor control long term, with a mean follow-up of 3 years. Similarly, Espinoza-Martinez et al.⁵ reported encouraging results with an average follow-up of 5 years in seven patients treated with Gpi DBS for HT. The pathophysiology of HT is complex with only scarce data regarding the neurophysiological characteristics of the disease. Kilbane et al.⁸ reported their analysis of single unit neuronal activity (SUA) in HT. They found mean firing rates in HT patients at rest (56.2 ± 28.5 Hz) and action (53.5 ± 19.4 Hz) to be much lower than Gpi recordings in Parkinson's disease (PD) patients.⁸ In this report, we present the clinical outcome of a patient treated with left Gpi DBS for HT due to midbrain injury secondary to ruptured arteriovenous (AV) fistula along with intraoperative neurophysiologic data. To the best of our knowledge, we are the first to report LFP data from a patient with HT adding to the understanding of neurophysiology in this rare condition.

Case report

The patient is a 24-year-old male who suffered a pontine and midbrain hemorrhage secondary to rupture of AV fistula at age 17. In addition, a large varix was found in the vein of the Galen and brainstem in the setting of a complex AV fistula. An embolization of the fistula was attempted, partially reducing the size of the fistula. The

anatomy of the vascular malformation precluded further treatment. After discharge from rehabilitation, he had mild cognitive deficits, severe ataxia, oculomotor difficulties, spastic dysarthria, and right arm clumsiness. Associated hand dystonia with finger and wrist flexion was present as well. Over the following 6 months, the patient noted insidious onset of progressive right arm low-frequency resting, postural, and action tremor diagnostic of HT. The symptoms initially worsened, with the development of right leg and palatal tremor. Multiple medical treatments were attempted including botulinum toxin injections (250 units), levetiracetam (3000 mg/day), carbidopa/levodopa (900 mg/day), trihexyphenidyl (6 mg/day), baclofen (40 mg/day), and propranolol (120 mg/day) with no benefit in tremor and intolerable side effects, namely sedation or cognitive difficulties. Tremor affected proximal muscles and rendered his right hand non-functional. After careful consideration of the surgical risks, DBS was considered. A pre-surgical computed tomography angiogram and brain magnetic resonance imaging (Figure 1) demonstrated a complex brain AV malformation with preserved pallidal anatomy. There was no evidence of parenchymal injury but a large varicose vein in the posterior circulation, thalamocapsular arteries territory, and mesencephalon was noted. The risks and benefits of the procedure were discussed at length and at multiple settings with both the patient, who was fully competent, and his mother. The treating neurosurgeon for the AV fistula provided preoperative clearance.

We opted to perform a single procedure with lead and battery placement the same day to minimize anesthetic risk. Blood pressure was closely regulated during the procedure, and was monitored using an arterial line until the next morning. He was discharged home on postoperative day 1 with no complications. The tremor severity was evaluated using the lateralized (right) Fahn-Tolosa-Marin Tremor Rating Scale (TRS). His preoperative score was 40. One month after the operation during monopolar review of the DBS electrodes, acute improvement in the tremor was noted. The tremor and limb dystonia improved with sustained benefit over the following 6 months. The

amplitude and pulse width were adjusted to maximize benefit. Interestingly, the patient also noted improvement in tongue and palatal tremor with unilateral stimulation. Programming settings were unipolar mode, case positive, contact 1 negative, pulse width 90 ms, and frequency 180 Hz. During programming, reversible corticospinal side effects at high amplitudes leading to dysarthria and facial tonic contractions were the most commonly reported side effect. At the 6-month follow-up, he was able to draw, color books, dress, and drink from a cup using one hand. Elements of cerebellar ataxia remained unchanged with otherwise normal muscle tone, strength, and resolution of dystonic postures. His TRS right hand score improved to a total score of 8, which represents an 80% overall improvement.

LFP and single unit (SU) recordings were obtained using microelectrodes during surgery in the Gpi and globus pallidus externa (Gpe) based on characteristic firing patterns.²³ LFPs were monitored using the Guideline 4000 LP Neuromodulation System (Frederick C. Haer, Bowdoin, ME), and recorded using glass-coated platinum/iridium microelectrode electrodes (0.4–1.0 mΩ). SUA signals were filtered (high pass 500 Hz and low pass 5 kHz), amplified, and digitized (48,000 Hz sampling frequency). SUAs were obtained at rest and during active movement (elbow flexion/extension). LFPs were filtered at 1000 Hz.

LFP analyses and spectrograms were generated from 0 to 50 Hz using a fast Fourier transform in NeuroExplorer (Nex Technologies, Madison, AL). The spectrogram was normalized so that the sum of all the spectrum values equaled the mean squared value of the signal and no overlap was used. Power spectral density (PSD) analyses were done on 10 seconds of trace with a 50 Hz cut-off. Bands were separated into delta (<4 Hz), theta (4–7 Hz), alpha (8–12 Hz), low beta (13–20 Hz), and high beta (21–29 Hz) bins for separate PSD analyses. Data were processed in Matlab to generate values for each band. Graphpad Prism was used to generate average band values among all microelectrode recordings. SU activity with a 2:1 signal-to-noise ratio was analyzed using principal component analysis using the Plexon offline sorter and quantified using NeuroExplorer. An analysis of interspike intervals in Neuroexplorer used to evaluate the stationarity of discharge and then exported into Matlab for processing was used to obtain the bursting index.

LFP recordings revealed highest powers in delta and theta followed by a decrease in power with each subsequent frequency after (alpha, beta, and gamma) with action (Figure 2). Beta frequencies had significantly more power than gamma in the Gpi ($p=0.0067$) (Figure 2). At rest, the LFP recording showed delta to be much lower than subsequent bands (theta, alpha, beta). The resting state Gpi LFP alpha-beta spectral peak was found to be at 12 Hz. In the Gpe, high delta and higher low beta frequencies were appreciated.

Microelectrode recording (MER) were obtained in the Gpi and Gpe to study neuronal firing rates and bursting indices (BIs) (Figure 3). The mean firing rate in the Gpi at rest was 70.57 ± 25.87 Hz ($n=7$ cells); with action it was 59.52 ± 8.84 Hz ($n=7$ cells), and 31.33 Hz ($n=1$ cell) in the Gpe at rest. There was no significant difference in firing frequency in the Gpi during rest and action ($p=0.69$). Furthermore, no

changes were found in the Gpi BI rest (4.55 ± 0.93) action (5.58 ± 0.84) ($p=0.28$, Figure 3). In the Gpe at rest, the BI was 7.46 ($n=1$).

Discussion

We present the outcome and neurophysiological findings in a HT patient treated with Gpi DBS. Our patient is unique as it is the first reported DBS surgery performed on a patient with HT having a partially treated significant vascular lesion and because of the assessment of electrophysiological data and analysis of Gpi LFP. Patients facing such challenges require specialized care and treatment.²⁴ Collaborating with other specialties is critical, as exemplified in this case with the need of collaboration between a vascular neurosurgeon and an experienced anesthesia team.

The optimal target for treating HT remains a subject of debate, although most case series and case reports have shown positive short-term results with a variety of stimulation targets. Although thalamic VIM has been traditionally considered the main target for refractory tremors, our case adds to the increasing body of literature demonstrating marked tremor benefit with pallidal stimulation in patients with HT. At the present time, stereotactic target selection in HT cases should be based on associated clinical features and surgical neuroanatomy. Gpi DBS should be particularly considered in cases where the VIM nucleus anatomy is grossly disrupted by intracranial pathology (affecting stereotactic planning and theoretically affecting cerebello-thalamic-cortical loop effects of DBS), when intraoperative tremor control is unsatisfactory despite VIM high-intensity stimulation and in patients with associated movement disorders such as chorea, parkinsonism, and dystonia.

The pathophysiological mechanisms underlying HT remain incompletely understood; however, abnormal synchronization of basal ganglia activity is suggested to underlie many movement disorders. We are the first to report LFP data from a patient with HT, adding to the understanding of this syndrome. We observed high power at low frequencies in the delta and theta regions with action (<3.5 Hz) in LFPs, a range consistently associated with hyperkinesias.²⁵ For example, PD patients on high dosages of levodopa with dyskinesias show increased delta activity, whereas PD patients experiencing bradykinesia or rigidity have low delta activity.²⁶ Higher power in the delta region of our patient is thus likely associated with hyperkinetic movements and tremor observed in our patient. There was higher beta activity relative to lower gamma power, similar to findings in PD.^{27,28} In a non-human primate model of PD, high power was seen in the late alpha and low-beta regions (7.8–15.5 Hz), and low power was seen in the late high-beta and early gamma regions (23.4–35.1 Hz).²⁹ These changes in power were significantly correlated with PD motor scores.²⁹ However, unlike in PD, our HT case presented an overall decrease in oscillatory activity upon approaching higher frequency values, producing a downward slope, with the greatest activity at delta and the lowest at gamma. Because PD patients exhibit low delta activity, recordings show a wave with the greatest activity peaking in the beta regions.²⁶ This difference showing the delta region as most active for HT, versus the beta region as most active in PD, can explain the

differences associated with motor pathophysiology, with greater hyperkinetic movements and less rigidity seen in HT than in PD. Spectral analysis of HT therefore more resembles dystonia than PD. Dystonia has been shown to have very low power in the beta range, associated with diminished bradykinesia and Parkinson's rigidity.²⁸ In addition, similar to our findings, it has been shown to have higher power in the delta and alpha regions than in PD and is similarly associated with hyperkinesia and dyskinesia.^{30,31} Although there was some beta activity present in our case, it was not prominent relative to the high delta and theta activity. Also, beta activity can vary substantially over small distances relative to electrode placement and therefore can decrease the correlation between motor movements and beta activity.³²

SUA in our patient showed firing rates similar to other cases of HT in the literature.³³ Kilbane et al.⁸ reported their mean firing rate for HT to be 56.2 ± 28.5 Hz at rest, and 63.5 ± 28.5 Hz with action. Our mean firing rate at rest was slightly higher, but as both had large standard errors of the mean (SEMs), they fell in the range of one another. In addition, our case reported a similar firing rate with action, suggesting our patient exhibited far lower firing during voluntary movement than the PD cohort, as concluded in Kilbane et al.⁸ Increased firing rates are associated with PD but lower firing rates occur during hyperkinetic disorders, such as generalized dystonia and Tourette syndrome.^{23,34,35} The mean BI at rest in this study was found to be higher than in a study comparing both dystonia and PD.²³ In a previous report, 22 dystonia patients, and 11 PD patients were found to have on average a higher BI (3.7 ± 0.1) in dystonia than in PD (2.2 ± 0.1).²³ Although the BI was higher in our patient, the dystonia BI fell in the range of the SEM of our patient's BI, suggesting our BI resembles that more closely associated with dystonia. In addition, the higher BI average may be due to differences in the methodology and limitations of our study. Starr et al.²³ reported a cohort of 22 patients providing a large sample of Gpi cells; however, due to high neuronal density and challenge in isolating single units, our BI at rest involved only seven cells from one patient. Additionally, HT patients in the Kilbane et al. report also exhibited higher BIs than that of the PD cohort, suggesting our SUA findings to be similar to the literature. Overall, these outcomes further support the pathophysiology of HT as a non-parkinsonian disorder. Elevated firing rates seen in PD are expected with high basal ganglia outputs associated with nigrostriatal denervation.⁸ Instead, the lower firing rate seen in our HT case is in agreement with the current literature that HT is involved with thalamostriate connections between basal ganglia and cerebellar pathways.^{8,36}

In conclusion, pallidal DBS should be considered as an alternative target for management of refractory HT as available data support remarkable tremor control regardless of the HT etiology. LFPs demonstrated neuronal activity associated with higher power in the delta region, similar to changes observed in patients with generalized dystonia. SUAs from our patient showed firing rates lower than that in PD but with a bursting index higher than both PD and dystonia.

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