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# Clinical outcome and intraoperative neurophysiology for focal limb dystonic tremor without generalized dystonia treated with deep brain stimulation

Adolfo Ramirez-Zamora (MD)[a,*], Brian Kaszuba[b], Lucy Gee (BS)[b], Julia Prusik (BS)[c], Eric Molho (MD)[a], Meghan Wilock (PA-C)[c], Damian Shin (PhD)[b], Julie G. Pilitsis (MD, PhD)[b,c]

[a] Department of Neurology, Albany Medical College, Albany, NY, United States
[b] Center for Neuroscience and Neuropharmacology, Albany, NY, United States
[c] Department of Neurosurgery, Albany Medical Center, Albany, NY, United States

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ABSTRACT

*Objectives:* Dystonic tremor (DT) is defined as a postural/kinetic tremor occurring in the body region affected by dystonia. DT is typically characterized by focal tremors with irregular amplitudes and variable frequencies typically below 7 Hz. Pharmacological treatment is generally unsuccessful and guidelines for deep brain stimulation (DBS) targeting and indications are scarce. In this article, we present the outcome and neurophysiologic data of two patients with refractory, focal limb DT treated with Globus Pallidus interna (Gpi) DBS and critically review the current literature regarding surgical treatment of DT discussing stereotactic targets and treatment considerations.
*Patients and methods:* A search of literature concerning treatment of DT was conducted. Additionally, Gpi DBS was performed in two patients with DT and microelectrode recordings for multi unit analysis (MUAs) and local field potentials (LFPs) were obtained.
*Results:* The mean percentage improvement in tremor severity was 80.5% at 3 years follow up. MUAs and LFPs did not show significant differences in DT patients compared with other forms of dystonia or PD except for higher interspikes bursting indices. LFP recordings in DT demonstrated high power at low frequencies with action (<3.5 Hz).
*Conclusions:* Gpi DBS is an effective treatment in patients with focal limb DT without associated generalized dystonia. Intraoperative neurophysiologic findings suggest that DT is part of phenotypic motor manifestations in dystonia.



## 1. Introduction

Dystonic tremor (DT) is a relatively new nosologic entity initially defined as a tremor occurring in a patient with dystonia [1]. The diagnosis of DT is challenging partially due to subtle and overlapping features with other clinical tremor syndromes. The current consensus statement from the Movement Disorder Society lists dystonic tremor as commonly being characterized by three features: (1) an associated dystonic posture, (2) irregular amplitudes and frequency (usually <7 Hz), and (3) postural/intentional tremor rather than resting tremor [1].

In more recent reports, several additional features have been proposed to assist with DT diagnosis, including the presence of a 'null point' (i.e., specific posture which when held by the patient alleviates the tremor), sensory tricks, tremor directionality, unilateral arm tremor, hand "spooning" and atypical features for Essential Tremor (ET) (e.g., lack of tremor when the finger touches the nose but severe tremor when attempting an arm movement toward an extended target such as an examiner's finger) [2,3]. Tremor associated with dystonia (TAD) is another type of similar tremor observed in the setting of segmental or generalized dystonia. TAD is present in a body region not affected by dystonia, but dystonia is present elsewhere (e.g. bilateral hand tremor in a patient with cervical dys-

* Corresponding author at: Albany Medical College, 47 New Scotland Ave., Albany, NY, 12208, United States.
*E-mail addresses:* RamireA@mail.amc.edu (A. Ramirez-Zamora), RamireA@mail.amc.edu (J.G. Pilitsis).

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tonia). This is a relatively symmetric, postural and kinetic tremor usually showing higher frequencies than typical DT [4].

Prevalence rates for tremor in dystonia varied greatly among different studies ranging from 11% to 87% [5]. Interestingly, tremor may be more frequent in patients with late-onset dystonia and in patients in whom dystonia spreads that in those with early-onset dystonia. Tremor oscillations usually have a low frequency (below 7 Hz) [5]. Traditionally, tremor in patients with dystonia has been characterized as postural or kinetic. This assumption, chiefly based on the rare reports describing rest tremor, has now apparently been revised as a large clinical series identified rest tremor in a considerable percentage of patients with dystonia [6]. DT diagnosis is challenging and probably under recognized and commonly mistaken as ET or tremor predominant-Parkinson's disease (PD) depending on the location and tremor characteristics [7]. There are very few studies specifically addressing the treatment of the DT and almost all of them are retrospective in nature and not randomized. Treatment outcome is highly variable, depending on the specific type of intervention and tremor distribution [8].

Traditionally, the ventral intermediate nucleus (VIM) of the thalamus has been considered the target for deep brain stimulation (DBS) for most tremor syndromes. However, based on the increasing evidence demonstrating the effectiveness of Globus pallidus interna (Gpi) in treatment of generalized and segmental dystonia, there is an increasing interest in the potential benefits of pallidal DBS in cases of focal, limb, task-specific DT without segmental or generalized dystonia. When reviewing the evidence of DBS for treatment in focal, limb tremor in patients with dystonia, the specific effects of Gpi DBS on tremor control are difficult to obtain as there are commonly not reported and cases are retrospective reviews in patients with generalized, multifocal, segmental and even secondary dystonia. Furthermore, there are reports of Gpi DBS occasionally causing worsening dystonia [9–13]. Moreover, intraoperative neurophysiological data in focal, limb DT without generalized or segmental dystonia is lacking and it remains unclear if tremor is a feature of dystonia with comparable neurophysiology or not.

In this report, we present the prospective outcome and intraoperative neurophysiology of two patients treated with medication-refractory focal, limb-DT treated with Gpi DBS, and critically review the literature regarding DBS for treatment of DT.

## 2. Material and methods

We performed a PubMed search using different combinations between the terms "Dystonic tremor", "tremor and dystonia" "atypical tremor" "tremor-associated with dystonia" and "deep brain stimulation/DBS". The respective medical subheading in the search strategy was included when available. Relevant case reports, case series and studies that were published in peer-reviewed journals and available in full text and written in English were included in our review (Table 1). Additionally, the clinical outcome and characterization of multi unit analysis (MUAs) and Local Field Potentials (LFPs) of two patients diagnosed with DT according to the criteria of the consensus statement of the Movement Disorder Society Group and treated with Pallidal DBS were prospectively analyzed [1]. Albany Medical College Institutional Review Board and approved this study. Tremor was evaluated pre-operatively and at each follow up using the Fahn-Tolosa-Marin tremor rating scale (FTM-TRS). Patients were evaluated monthly for the first 6 months and then every 3–6 months as clinically indicated. Post-operative tremor evaluation was conducted in the "ON" DBS state at each visit.

Neurosurgical procedures were performed as previously reported [14]. Briefly, the DBS procedure was conducted utilizing the Leksell stereotactic frame. Targeting was performed using a combination of AC-PC coordinates and adjustments based on direct imaging relative to MRI visible structures. Prior to recording, patients were sedated with propofol for placement of the stereotactic frame as well as the surgical incision. Propofol is cleared rapidly, and prior studies in PD and dystonia suggest no neuronal effect of propofol following 30–60 min of washout time [15]. Propofol was thus stopped 30 or more minutes prior to neuronal recordings. Low-dose infusion of dexmedetomidine (0.2 mcg/kg/h) was used during the rest of the procedure. Microelectrode recordings starting 10 mm above target to the bottom of the physiologically defined target were conducted. Macro stimulation was conducted to determine the efficacy and side effects after final lead position was selected. Patients returned one week later for placement of an internal pulse generator. Clinical, demographic and neurophysiologic data was collected prospectively and final postoperative electrode locations were confirmed utilizing volumetric CT scanning registered to the preoperative Brain MRI using BrainLab (https://www.brainlab.com/).

### 2.1. Intraoperative neurophysiological data

MUAs and LFPs recordings were obtained using microelectrodes during surgery in the Gpi and Globus Pallidus Externa (Gpe) based on characteristic firing patterns [15]. We suspected that neuronal firing would likely mirror the pattern seen in dystonia [15]. In patients with dystonia, the mean discharge rates in Gpi and Gpe are nearly identical in contrasts with those recorded in patients with PD in whom the mean Gpi discharge rate is significantly higher [14]. Different types of discharge patterns in the two nuclei were recognized allowing differentiation between them intraoperatively. In the Gpe, we identified the ubiquitous pauser neurons (cells with higher-frequency, tonic discharges interrupted by characteristic 100–300-ms pauses in neuronal activity) and the less common burster neurons (cells with lower frequency, irregularly spaced bursts superimposed on a very low background discharge rate). In the Gpi, we identified high-frequency bursting neurons (cells that discharged in irregularly spaced bursts superimposed on a relatively high background discharge rate). The identification of the internal medullary lamina between Gpe and Gpi and surrounding border cells helped to separate the two structures. Additionally, Gpi neurons were recognizably different from Gpe cells in that they fired more continuously [14,16]. Within the sensorimotor (postero-ventro-lateral) region of Gpi driving of the unit discharges was elicited by passive and/or active limb movements, often by multiple joints as previously reported [17].

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). MUA signals were filtered (high pass 500 Hz and low pass 5 kHz respectively), amplified, and digitized (48,000 Hz sampling frequency). MUAs 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 s 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 was processed in Matlab to generate values for each band. Graphpad Prism was used to generate average band values among all microelectrode recordings. MU activity with a 2:1 signal-to-noise ratio was analyzed using principal component analysis in Plexon offline sorter and quantified in NeuroExplorer. An analysis of interspike intervals (ISIs) in Neuroexplorer used to evaluate sta-