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Basal Ganglia and Related Disorders: From Cellular and Circuit Dysfunctions to Therapy.

Pallidal neuronal activity in Gilles de la Tourette syndrome and dystonic patients: A comparative study

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Abstract

Gilles de la Tourette syndrome (GTS) and dystonia (DYS) are both hyperkinetic movement disorders effectively treated by deep brain stimulation (DBS) of the internal part of the globus pallidus (GPi). In this study, we compared single-neuron activity in the GPi between 18 GTS patients (with an average of 41 cells per patient) and 17 DYS patients (with an average of 54 cells per patient), all of whom underwent bilateral pallidal stimulation surgery, under general anesthesia or while awake at rest. We found no significant differences in GPi neuronal activity characteristics between patients operated on under general anesthesia versus those who were awake, irrespective of their diagnosis (GTS or DYS). We found higher firing rates, firing rate in bursts, pause duration and interspike interval coefficient of variation in GTS patients compared to DYS patients. On the opposite, we found higher number of pauses and bursts frequency in DYS patients. Lastly, we found a higher proportion of GPi oscillatory activities in DYS compared to GTS patients, with predominant

Abbreviations: BG, basal ganglia; DBS, deep brain stimulation; DYS, dystonia; GPi, internal part of the globus pallidus; GTS, Gilles de la Tourette syndrome; ISIcv, coefficient of variation of the interspike interval; ISIsd, interspike interval standard deviation; LFP, local field potential; MAD, median absolute deviation; MN, Minnesota; PD, Parkinson's disease; USA, United States of America.

activity within the low-frequency band (theta/alpha) in both patient groups. These findings underscore the complex relationship between the different neuronal discharge characteristic such as oscillatory or bursting activity within the GPi in shaping the clinical phenotypes of hyperkinetic disorders. Further research is warranted to deepen our understanding of how neuronal patterns are transmitted within deep brain structures and to develop strategies aimed at normalizing these pathological activities, by refining DBS techniques to enhance treatment efficacy and individual outcomes.

KEYWORDS
dystonia, electrophysiology, Gilles de la Tourette syndrome, internal globus pallidus

1 | INTRODUCTION

The internal globus pallidus (GPi) is a key output structure within the basal ganglia (BG) networks (Nambu, 2007). Its activity is finely regulated by dopaminergic inputs from the substantia nigra pars compacta to the striatum, mediated through both the direct striato-pallidal and indirect striato-external globus pallidus-subthalamic pathways (Bonnavion et al., 2019; Onla-or & Winstein, 2001). These intricate pathways play pivotal roles in movement initiation, goal-directed motor behaviors and habits. Specifically, the direct pathway facilitates movement, while the indirect pathway contributes to movement inhibition (Schultz, 2016; Yanagisawa, 2018). Anatomical and physiological studies in non-human primates have revealed that the GPi comprises three distinct subareas. The sensorimotor component is predominantly located in the posterior region, whereas the cognitive and limbic components are situated anteriorly (Cacciola et al., 2018; Johnson et al., 2020; Saga et al., 2017).

Pathological conditions affecting the sensorimotor part of the BG networks result in movement disorders, such as abnormal postures or myoclonus in dystonic syndrome (DYS), or motor and vocal tics in Gilles de la Tourette's syndrome (GTS) (Baldermann et al., 2016; Tremblay et al., 2015; Tsuboi et al., 2020). In the latter, patients can also present comorbid psychiatric signs, such as obsessive-compulsive symptoms, attention-deficit-hyperactivity syndrome or self-injuries, which are thought to be related to an involvement of the more anterior limbic part of the BG (Faraone et al., 2015; Robertson et al., 2017; Stein et al., 2019).

Deep brain stimulation (DBS) of the GPi has emerged as an effective treatment for both DYS and GTS patients, leading to significant improvements in abnormal movements (Baldermann et al., 2016; Moro et al., 2017; Welter et al., 2017). In DYS patients, DBS electrodes are typically placed in the posterior-sensorimotor part of the GPi, while in GTS patients, they are positioned more anteriorly to alleviate associated behavioral disorders (Baldermann et al., 2016; Moro et al., 2017; Welter et al., 2017). Limited studies have explored the neuronal activity of the GPi in patients with DYS or GTS. Existing research suggests differences in single-neuron activity, with GTS patients exhibiting lower firing rates relative to DYS patients (Alam et al., 2015; Giorni et al., 2017), along with burst activities or pauses during tics (Vinner et al., 2017; Zhuang et al., 2009). Additionally, recordings of local-field potentials (LFP) have revealed theta and beta oscillations in both patient groups (Neumann et al., 2018), with increased high-frequency oscillations associated with tics in GTS patients (Jimenez-Shahed et al., 2016).

Here, we aim to investigate the GPi neuronal activity in larger cohorts of patients with DYS or GTS who have undergone DBS and by using a novel semi-automatic spike sorting method, namely SpykingCircus. By employing this technique, we seek to provide a comprehensive characterization of single-cell neuronal activity and compare it between these distinct neurological disorders.

2 | PATIENTS AND METHODS

2.1 | Patients

We analyzed data collected from 18 patients with GTS (13M/5F) and 17 patients (7M/10F) with DYS (Table 1). The DYS group included seven patients with primary generalized DYS, three of whom had the DYT1 mutation, six patients with myoclonus DYS, four of whom had the DYT11 mutation, three patients with idiopathic cervico-facial DYS and one patient with idiopathic multifocal DYS. These patients were included in three separate French national clinical research programs, aimed at evaluating the effectiveness of bilateral GPi-DBS in

TABLE 1 GPi neuronal activity characteristics of GTS and DYS patients.

Variable	GTS	DYS	Statistics
Anesthetized patients	50%	47%	$X^2 = 0$, $p = 1$
Age, years	31.11 (12.3)	36.5 (12.1)	$W = 59.5$, $p = 0.1$
Recording duration, s	151.2 (115.7)	46.3 (16.8)	$W = 9$, $p < 0.001$
Number of recordings/patient	67.90 (24.9)	58 (19.1)	$W = 118.5$, $p = 0.26$
Number of cells/patient	40.8 (20.9)	53.9 (15.6)	$W = 216.5$, $p = 0.04$
Firing rate, Hz	19.4 (7.2)	14.5 (2.8)	$W = 76$, $p = 0.01$
RPV value, %	0.7 (0.2)	0.7 (0.1)	$W = 156$, $p = 0.93$
Firing rate in bursts, Hz	58.9 (16.3)	45.4 (13.2)	$W = 74$, $p = 0.01$
Number of burst/min, *n*	1.2 (0.8)	2.3 (1)	$W = 256$, $p < 0.001$
Burst duration, ms	586 (217)	549 (196)	$W = 137$, $p = 0.61$
Percent of total spikes in burst, %	3 (1)	2.8 (1.2)	$W = 121$, $p = 0.30$
Burst index	0.46 (0.11)	0.51 (0.20)	$W = 169$, 0.61
Number of pause/min, *n*	7.3 (6.3)	19.1 (6.2)	$W = 275$, $p < 0.001$
Pause duration, ms	1611 (693)	1136 (309)	$W = 91$, $p = 0.04$
Pause index	0.070 (0.02)	0.077 (0.01)	$W = 183$, $p = 0.33$
ISIcv	0.09 (0.05)	0.04 (0.01)	$W = 38$, $p < 0.001$
Oscillatory activity (Hz), NA: number of subject without neuron with oscillatory activity in the given frequency band	Theta: 5.23 (1.22), NA = 5	Theta: 5.28 (0.97), NA = 1	
	Alpha: 8.95 (1.36), NA = 8	Alpha: 9.08 (1), NA = 3	
	Low beta: 14.45 (2.23), NA = 13	Low beta: 13.85 (1.61), NA = 8	
	High Beta: 22.46 (2.93), NA = 15	High beta: 23.79 (2.76), NA = 7	
	Low gamma: 40.61 (1.78), NA = 10	Low gamma: 37.11 (0.62), NA = 8	
	High gamma: 50.78, NA = 16	High gamma: 52.73, NA = 17	
Oscillatory activity (% of total neurons)	Theta: 10.7 (10.8)	Theta: 17.3 (11.4)	ANOVA Frequency band: $F = 27.9$, $p < 0.001$ Disorder: $F = 6.26$, $p < 0.01$ Interaction: $p = 0.17$
	Alpha: 5 (6.8)	Alpha: 6.6 (7.1)	
	Low beta: 0.7 (1.4)	Low beta: 1.7 (2)	
	High beta: 0.4 (1.1)	High beta: 3 (5.4)	
	Low gamma: 2.1 (3.4)	Low gamma: 2.1 (3)	
	High gamma: 0.1 (0.2)	High gamma: 0.1 (0.5)	
Neuron with at least one oscillatory activity (% of total neurons)	12.2 (11.4)	20.5 (11.2)	$W = 227$, $p = 0.02$

The values are the mean (SD). The ANOVA model was the following: % of total neurons ~ frequency band * disorder.

Abbreviations: DYS, dystonia; GTS, Gilles de la Tourette syndrome; ISIcv, interspike interval coefficient of variance; RPV, refractory period violation; W, Wilcoxon rank sum tests, $X^2 = \text{chi}^2$.

reducing the severity of movement disorders (STIC trial NCT00478842, and SPIDY trials, NCT00169403 and NCT00169338). Detailed inclusion and exclusion criteria for these trials can be found elsewhere (Vidailhet et al., 2005; Welter et al., 2017). All participants provided informed written consent, and the protocols were approved by a local ethics committee.

2.2 | Recordings

All patients underwent bilateral GPi-DBS surgery (Vidailhet et al., 2009; Welter et al., 2017). The stimulating electrodes (Medtronic, model 3389, Minneapolis, MN, USA) were implanted bilaterally on the same day. Surgical targeting involved preoperative anatomical and perioperative electrophysiological recordings to place the electrodes in the anterior part of the GPi for GTS patients (Welter et al., 2017) and the posterior part for DYS patients (Vidailhet et al., 2009). Extracellular single-neuron activity was recorded simultaneously from 3 to 5 microelectrodes (FHC, Medtronic), with awake patients at rest (nine DYS and nine GTS patients) or under general anesthesia (eight DYS and nine GTS patients), with increments of .2 to .5 mm. Sampling rate was 24,000 or 48,000 Hz (see supplementary methods).

2.3 | Off-line analysis

Analysis of GPi neuronal activity was conducted off-line using the semi-automatic SpykingCircus software (Yger et al., 2018). Initially, raw neuronal activity traces were visually inspected to detect and remove periods with artifacts. Spike sorting was performed using a detection threshold with a signal to noise ratio of four median absolute deviations (MADs). This threshold was chosen based on thresholds used in previous studies (Giorni et al., 2017; Sedov et al., 2020). Single-cell clusters obtained from spike sorting were visually inspected and merged if identical, based on shape, principal component analysis, and cross-correlograms results (Figure 1). Clusters corresponding to artifacts were deleted. The refractory period was set at 2 ms (Sukiban et al., 2019). Details about the sorting and the parameters are in supplementary methods.

Subsequently, firing rates, bursts and pauses of unit activities were calculated for each identified single-cell neuronal activity cluster. The rank surprise (RS) method was employed to identify bursts, with bursts defined as unexpected increases in spike frequency as defined by the following formula:: $RS = -\log(p)$, where p is the probability that the sum of ISI ranks in a given sequence of consecutive ISI is inferior or equal to the sum of uniformly distributed values between 1 and N, where N is the total number of ISI (Gourévitch & Eggermont, 2007). Pauses were defined as a lack of spikes for at least 500 ms (Elias et al., 2007). The burst and pause indexes were calculated. The coefficient of variation of the interspike interval (ISIcv) was also calculated as follows (Sedov et al., 2020; Semenova et al., 2021):

$$\mathrm{ISIcv} = \frac{\mathrm{ISIsd}}{\mathrm{ISImean}}$$

where sd is the standard deviation and ISI is the time in millisecond between two consecutive spikes.

Finally, we characterized the oscillatory activity of the units, following the method described by Mureşan et al. (2008). This was based on the shape of the autocorrelograms leading us to determine the oscillatory activity in the different frequency bands (4–8 Hz = theta band, 8–12 Hz = alpha band, 12–20 Hz = low beta band, 20–30 Hz = high beta band, 30–60 Hz = low gamma band, >60 = high gamma band). Only neurons with an oscillation score > 10 were considered in this latter analysis (Welter et al., 2011).

2.4 | Statistical analysis

Differences in GPi neuronal activity between patient groups and between patients operated on under generalized anesthesia and those operated awake at rest were compared using non-parametric Wilcoxon rank tests for quantitative data and chi2 tests for qualitative data. Statistical analysis was done using the R software version 4.2.2 (https://www.r-project.org/).

3 | RESULTS

We recorded 734 GPi neurons in GTS patients and 917 GPi neurons in DYS patients (Table 1). The mean duration of recordings was higher in GTS relative to DYS patients ($p < .001$, Table 1).

No significant differences were found in the GPi neuronal activity characteristics between patients operated on under general anesthesia or awake at rest for both patient groups (GTS and DYS; Table 2). Therefore, we combined the data for statistical comparison between the two patient groups.

We found significant higher firing rate, firing rate within the bursts, pause duration and ISIcv in GTS compared to DYS patients (Table 1; Figure 2). On the opposite, we found a significant higher number of bursts and pauses in DYS patients compared to GTS patients. We

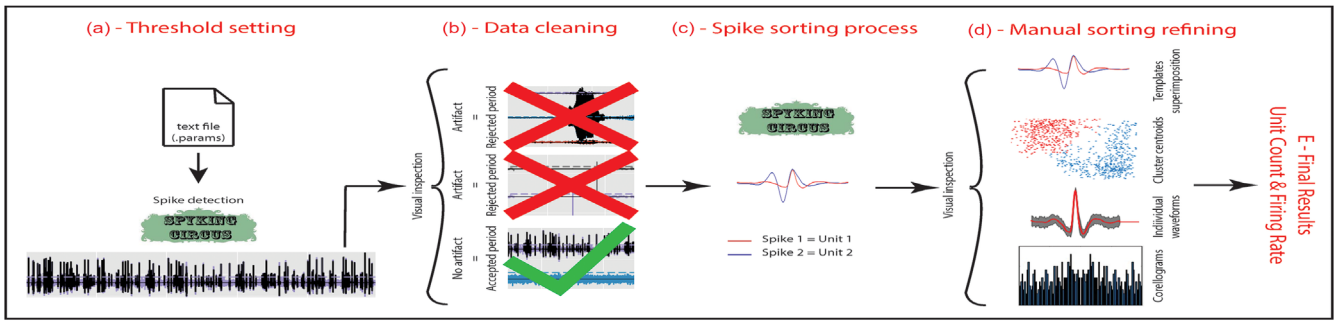

FIGURE 1 Schematic representation of the general analysis process of the GPi neuronal activity. (a) Extraction of the spikes using SpikingCircus. (b) Cleaning of data with artifact suppression. (c) Spike sorting through the SpikingCircus algorithm. (d) Sorting refining by superimposition of the different spikes, visual checking of the PCA results, global spike shape and cross correlograms: if spikes were perfectly superimposed, without distinguishable point clouds on the PCA and the cross correlogram showed a clear gap, the neurons were merged. GPi, internal part of the globus pallidus; PCA, principal component analysis.

TABLE 2 GPi neuronal activity recorded in GTS and DYS patients on under generalized anesthesia or awake at rest.

	GTS			DYS		
	Anesthesia ($n = 9$)	**Awake ($n = 9$)**	**Statistics**	**Anesthesia ($n = 8$)**	**Awake ($n = 9$)**	**Statistics**
Firing rate, Hz	18.5 (7.8)	20.3 (6.8)	$W = 50$, $p = 0.44$	15.4 (3.4)	13.7 (2)	$W = 24$, $p = 0.28$
Number of bursts, n/min	1.2 (0.6)	1.3 (0.9)	$W = 41$, $p = 1$	2.6 (1.2)	2 (0.8)	$W = 25$, $p = 0.32$
Burst duration, ms	599 (262)	574 (178)	$W = 43$, $p = 0.86$	518 (168)	576 (224)	$W = 41$, $p = 0.67$
Firing rate in bursts, Hz	55.1 (16.1)	62.7 (16.5)	$W = 50$, $p = 0.44$	45.6 (16)	45.2 (11)	$W = 39$, $p = 0.81$
Number of pauses, n/min	11.2 (4.8)	12.2 (7.5)	$W = 35$, $p = 0.67$	19.3 (7.5)	19 (5.3)	$W = 40$, $p = 0.74$
Pause duration, ms	1658 (533)	1564 (856)	$W = 33$, $p = 0.55$	1107 (339)	1162 (299)	$W = 45$, $p = 0.42$

Values are mean (SD).
Abbreviations: DYS, dystonia; GTS, Gilles de la Tourette syndrome; W, Wilcoxon test statistic.

found no significant differences in the percentage of total spikes in bursts, burst duration, burst index or pause index (Table 1; Figure 2).

We found oscillatory activities in both patient's groups, mainly in the low-frequency bands (theta/alpha; Figure 2). Comparing GTS and DYS patients, we found a significant higher proportion of oscillatory activity for GPi neurons in DYS compared to GTS patient in all frequency bands ($p < .001$; Table 1; Figure 2), and when pooling all frequency bands together ($p = .02$; Table 1).

4 | DISCUSSION

Our findings revealed that GPi neurons in GTS patients exhibited higher firing rate, firing rate in bursts, longer pause durations and greater ISIcv. Conversely, GPi neurons in DYS patients showed a higher number of pauses and bursts, with a larger proportion of neurons displaying oscillatory activity.

Both GTS and DYS patients manifest hyperkinetic disorders, albeit with distinct clinical characteristics. DYS patients typically exhibit a more tonic and continuous abnormal postures, whereas GTS patients display brief and more phasic abnormal movements known as tics (Robertson et al., 2017). Notably, we observed a lower firing rate in DYS patients, a physiological phenomenon previously reported in Parkinson's disease (PD) patients with levodopa induced-dyskinesia (Benazzouz et al., 1996; Galati et al., 2009; Zesiewicz et al., 2007). This lower firing rate aligns with the presumed functioning of the striato-pallidal pathway, resulting in increased

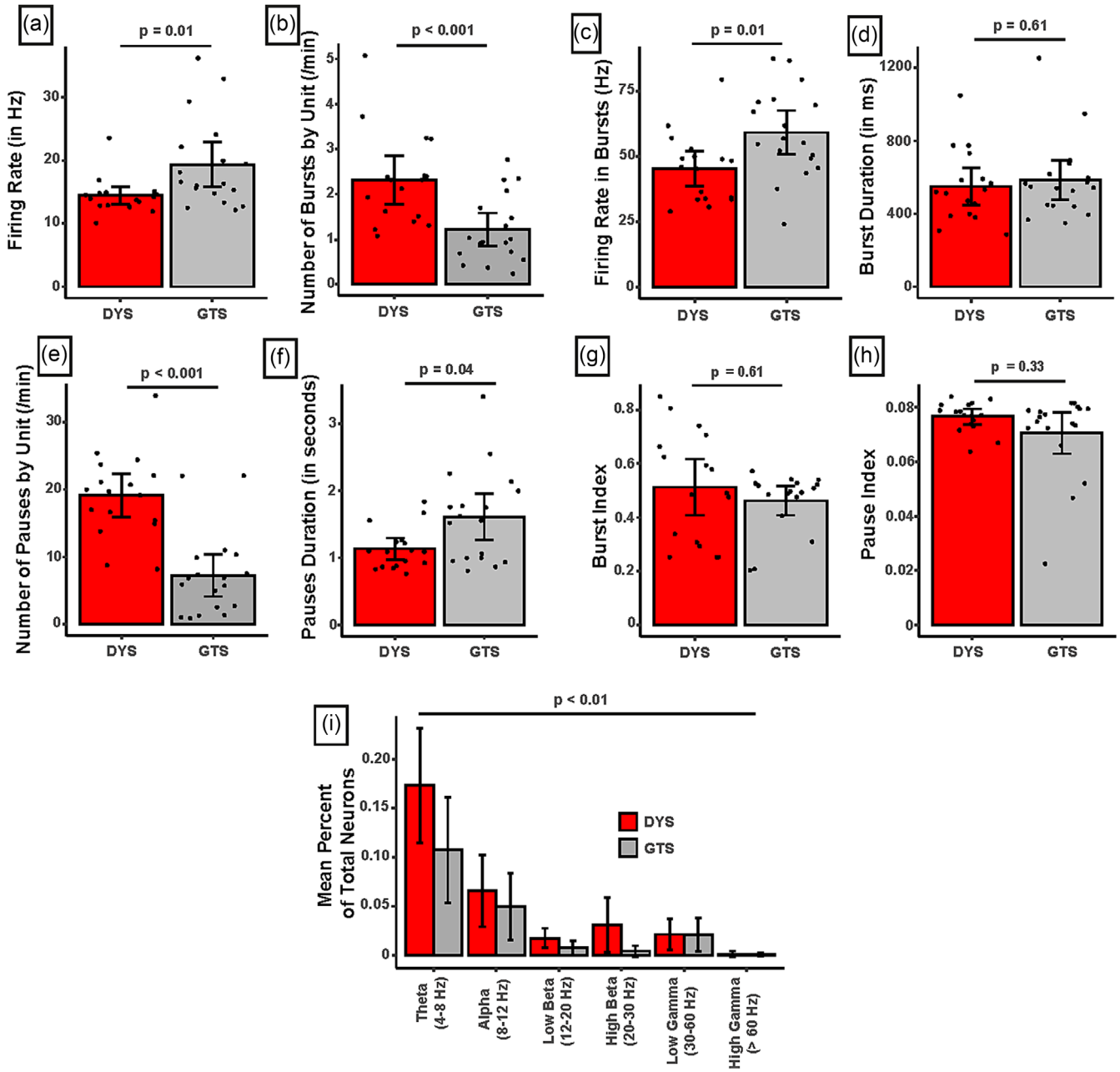

FIGURE 2 GPi neuronal activity characteristics in GTS and DYS patients. The graphs report the GPi neuronal activity of GTS (grey) and DYS (red) patients: (a) mean firing rate during the recordings, (b) mean burst rate, (c) firing rate in bursts, (d) mean duration of bursts, (e) mean pause rate, (f) mean pause duration, (g) burst index, (h) pause index and (i) % of neuron with oscillatory activities within the theta, alpha, beta and gamma band activities. DYS, dystonia; GPi, internal part of the globus pallidus; GTS, Gilles de la Tourette syndrome.

activity in thalamic nuclei and prolonged involuntary tonic muscle activation in DYS patients (Guehl et al., 2000; Macia et al., 2002). In GTS patients, the firing rate was consistent with previous reports (Zhuang et al., 2009) and higher than in DYS patients, but lower than in PD patients Off-dopa (Li et al., 2015). This indicates that firing rate alone cannot fully account for the differences in abnormal movements between the two patient groups.

The differences in pattern and oscillatory GPi activities observed in our study may also contribute to the clinical disparities in movement disorders between GTS and DYS patients (McCairn et al., 2009). We found that bursts were more frequent in DYS compared to GTS. This aligns with recent findings showing higher burst activity in DYS patients (Alam et al., 2015; Giorni et al., 2017). However, in GTS patients, we found a higher firing rate within burst. Interestingly, burst occurrence was previously

found to correlate with tic episodes in GTS patients (Zhuang et al., 2009), and in DYS patients, burst activity was more frequently reported in those with myoclonus compared to those with generalized DYS (Welter et al., 2015). We also observed a higher proportion of neurons with oscillatory activities in the low theta-alpha frequency bands for both groups, as previously reported (Alam et al., 2015; Levi et al., 2021; Lofredi et al., 2019; Starr et al., 2005), with a higher rate of oscillations in DYS patients compared to GTS. Altogether, these findings suggest that the balance between bursting/pause patterns and low-frequency oscillatory activity may contribute to the hyperkinetic phenomenology with high burst activity that could relate to brief abnormal movements (McCairn et al., 2009; Tinaz et al., 2014) and low-frequency activities to abnormal tonic postures (Alam et al., 2015; Giorni et al., 2017; Neumann et al., 2018; Welter et al., 2015; Zhuang et al., 2009). In GTS patients, this abnormal GPi neuronal activity could potentially be transmitted to the thalamus via pallido-thalamic coupling (Neumann et al., 2018; Zhuang et al., 2009), leading to aberrant supplementary motor area and sensorimotor cortices activity (Van Der Veen et al., 2022), which are implicated in tic occurrence (Wang et al., 2011). The differences observed between DYS and GTS patients may also be influenced by the distinct recording locations within the GPi. In DYS patients, recordings were made in the posterior-sensorimotor region of the GPi, whereas in GTS patients, recordings were obtained from a more anterior-associative/limbic region. Interestingly, our findings from the anterior GPi in GTS patients align with some previous data obtained in the posterior GPi of GTS patients (Alam et al., 2015; Neumann et al., 2018). This suggests that the pathological neuronal patterns in GTS patients may be widely distributed throughout the GPi. The distribution of these patterns may vary with the clinical spectrum of GTS, ranging from simple motor/vocal tics (posterior GPi) to more complex repetitive behaviors and psychiatric comorbidities (anterior GPi), as similarly reported within the cortico-basal ganglia networks through neuroimaging studies in GTS patients (Worbe et al., 2010).

Our study has several limitations. The sample size was relatively small. However, both disorders are rare. The chosen spike sorting method and parameters could also have influenced our results (Buccino et al., 2020; Magland et al., 2020), leading to quite low firing rate and ISIcv, as compared to some other reports (Giorni et al., 2017; Zhuang et al., 2009), with also no significant differences between patients operated on under anesthesia and awake conditions, in which we cannot fully excluded the impact of the surgical procedure on the neuronal recordings (Bos et al., 2019; Myrov et al., 2019). However, to our knowledge, no international standardization for spike sorting exists up to now (Febinger et al., 2018). In this study, we carefully selected one of the most efficient sorters (Buccino et al., 2020).

5 | CONCLUSION

Our study highlights distinct patterns of single-unit activity in the GPi between DYS and GTS patients, underscoring the different impairments of cortico-striatal loops between these two distinct movement disorders. Further research is essential to deepen our understanding of how neuronal patterns are transmitted within deep brain structures and to develop strategies aimed at normalizing these pathological activities. By refining DBS techniques, we could enhance treatment efficacy and improve outcomes for individuals with these disabling hyperkinetic movement disorders.

AUTHOR CONTRIBUTIONS

Conception and design of the study: M. L. W, C. K., L. M., M. V. Acquisition and analysis of the data: H. L., C. K., K. L., A. B., D. G., S. T., E. B., C. G., J. L. H, L. M., M. V., M. L. W. Drafting a significant portion of the manuscript or figures: H. L., C. K., K. L., M. L. W.

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CONFLICT OF INTEREST STATEMENT

H Lamothe, C Karachi, K Lehongre, A Buot, D Grabli, S Thobois, E Burguière, C Giordana, JL Houeto, L Mallet, M Vidailhet and ML Welter declare to have no competing financial interests directly linked to this study. ML Welter reports personal fees from BIAL for scientific consulting and travel grants from Pfizer. C Karachi reports personal

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16567.

DATA AVAILABILITY STATEMENT

All relevant data are within the article. Requests for anonymized data should be sent to M. L. Welter at the Brain Institute, 75013 Paris, France. The main code used to extract variables from raw data is freely available here: https://github.com/Hugues1273/LamotheWelter2024.

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