




Pallidal Activity in Cervical Dystonia with and Without Head Tremor

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Abstract

The relationship between two common movement disorders, dystonia and tremor, is controversial. Both deficits have correlates in the network that includes connections between the cerebellum and the basal ganglia. In order to assess the physiological relationship between tremor and dystonia, we measured the activity of 727 pallidal single-neurons during deep brain stimulation surgery in patients with cervical dystonia without head oscillations, cervical dystonia plus jerky oscillations, and cervical dystonia with sinusoidal oscillations. Cluster analyses of spike-train recordings allowed classification of the pallidal activity into burst, pause, and tonic. Burst neurons were more common, and number of spikes within spike and inter-burst intervals was shorter in pure dystonia and jerky oscillation groups compared to the sinusoidal oscillation group. Pause neurons were more common and irregular in pure tremor group compared to pure dystonia and jerky oscillation groups. There was bihemispheric asymmetry in spontaneous firing discharge in pure dystonia and jerky oscillation groups, but not in sinusoidal oscillation group. These results demonstrate that the physiology of pallidal neurons in patients with pure cervical dystonia is similar to those who have cervical dystonia combined with jerky oscillations, but different from those who have cervical dystonia combined with sinusoidal oscillations. These results imply distinct mechanistic underpinnings for different types of head oscillations in cervical dystonia.

Keywords Dystonic tremor · Essential tremor · Dystonia · Globus pallidus

Introduction

The dystonias are a group of disorders characterized by excessive muscle contractions leading to involuntary postures or movements that have a repetitive or twisting quality [1, 2]. Tremors are defined by regular oscillations of a body region, typically with a sinusoidal pattern [3, 4]. Although dystonia and tremor are viewed as distinct disorders, they share many relationships. For example, both dystonia and tremor are considered disorders of network involving the cerebellum, thalamus, basal ganglia, midbrain, and the cerebral cortex; but

there are substantial differences in the network connectivity patterns between these two phenomenologies [5–30].

Cervical dystonia (CD) is the most common form of focal dystonia, and it is typically characterized by abnormal postures of the head. Sometimes CD can be associated with jerky head oscillations [31]. On some occasions, the head oscillations in CD can be sinusoidal [32–41]. The coexistence of two forms of oscillations (jerky versus sinusoidal) often results in disagreements regarding fundamental diagnostic process, leading to variability in therapeutic interventions and efficacy [4, 42, 43]. The physiological relationship between pure CD without

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any forms of head oscillations, CD with jerky oscillations, and CD with sinusoidal oscillations remains unclear. Contemporary literature utilizing the experimental strategies spanning across diverse disciplines such as neurophysiology, imaging, pathology, and clinical neuroscience highlighted the role of cerebellum. Patients with essential tremor who had presented with the involvement of the head also had reduced cerebellar gray matter density, while Purkinje cell loss is a known finding in patients with dystonia [13, 24]. Resting-state functional MRI revealed correlation of head tremor with cerebello-cortical areas [30]. The patients with head tremor had specific phenotype that highlights cerebellar involvement [9]. A phenotype of cervical dystonia that presents with early onset of head tremor had prominent ataxia compared to dystonia [20].

We set out to examine the physiological association between pure CD, CD with jerky head oscillations, and sinusoidal head oscillations. We analyzed the differences in the neuronal discharge patterns of the globus pallidus in three groups of patients – those with neck dystonia without any head oscillations (CD group), those with neck dystonia combined with jerky head oscillations (CD-J group), and those with neck dystonia combined with sinusoidal oscillations (CD-S group). We selected globus pallidus because it is accessible to measure single-unit physiology during standard-of-care deep brain stimulation surgery; and it is also a critical part of the network that is connected with the cerebellum. We *predict*: (1) If the two types of head oscillations in CD were both merely reflections of the underlying biology of dystonia, then we expect no differences among these three patient groups. (2) If the two types of head oscillations in CD reflected different biological processes, then we expect differences among all three patient groups. (3) If pure CD and CD-J groups were biologically related, then we expect to see their comparable physiological patterns that would be different compared to the CD-S group. (4) If pure CD and CD-S groups were biologically related, then we expect to see their comparable physiological patterns that would be different compared to CD-J group. (5) If pure CD-J and CD-S groups were biologically related, then we expect to see their comparable physiological patterns that would be different compared to pure CD group.

Methods

Subject Recruitment

Institutional ethics committee at N.N.Burdenko Neurosurgical Institute approved the study protocol. The subjects provided written consent prior to deep brain stimulation surgery. Thirteen idiopathic CD patients (7 men, age range of 31–60 years and 6 women age range 22–68 years), refractory to medical therapy, opted for the deep brain stimulation surgery of the bilateral globus pallidus. The average duration of

symptoms was 6.86 ± 4.9 years (range 2–17 years). None of the patients had the diagnosis of Parkinsonism, Parkinson's disease, history of stroke or other structural abnormalities affecting the basal ganglia or the cerebellum, exposure to dopamine receptor blocking agents, active psychiatric illness or dementia, and generalized dystonia. Table 1 depicts the clinical summary recorded immediately prior to the surgery.

Subject Classification

On clinical examination, five patients had pure dystonia of the neck without any clinically visible head oscillations (CD), five patients had jerky head oscillations in addition to neck dystonia (CD-J), and three patients had sinusoidal head oscillations in addition to neck dystonia (CD-S). In order to account for substantial inter-rater variability in calling oscillations sinusoidal versus jerky, we *quantitatively verified* the subjective classification by measuring the head position trajectory with a video-based face tracking algorithm. An example of sinusoidal head oscillations is depicted in Fig. 1a, while Fig. 1b depicts jerky oscillations. The trace depicted in Fig. 1c, an example of pure dystonia (i.e., CD group), has no oscillations. In all three traces in Fig. 1, the offset of head position is removed in order to facilitate better visualization of oscillations. The oscillation shape (in CD-J and CD-S groups, Fig. 1a, b) was further quantified by measuring total harmonic distortion – a measure of the ratio of the sum of the powers of all harmonic components to the power of the fundamental frequency of the time series. A smaller value of total harmonic distortion corresponds to a more sinusoidal nature, while any form of irregularity in the time series (in this case jerky oscillation) leads to higher values of total harmonic distortion. The value of total harmonic distortion of the sinusoidal oscillation group was 2.4 ± 0.3 , while it was 5.9 ± 2.2 in those who had jerky oscillations; the difference was statistically significant ($p < 0.01$). The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) revealed an average severity score of 20.3 ± 3.8 (range 15–30).

Surgical Procedure and Physiological Data Collection

As part of clinical standard-of-care, the microelectrodes were advanced in an obliquely directed trajectory toward globus pallidum internus (GPi) through intervening cerebral cortex. The typical electrode track passed through the putamen and the globus pallidum externus (GPe). Characteristic electrophysiological signatures were utilized to identify the pallidal nuclei. For example, the GPe neurons were characterized by their typical discharge pattern that was associated with an increase in the background noise and numerous cells with high discharge rate. Further advancement of the electrode through internal lamina between GPe and GPi found fewer units with much lower but regular firing rate. Finally, the entrance of the track in GPi was evident by numerous neurons with high firing rate [44, 45].

Table 1 Demographic information of recruited subjects

| N | Gender | Age | Duration | Dystonia phenomenology | Oscillations | Cells |
|----|--------|-----|----------|---|-------------------|-------|
| 1 | m | 42 | 3 | Right torticollis | Pure dystonia | 46 |
| 2 | f | 53 | 6 | Left laterocollis | Dystonic tremor | 49 |
| 3 | m | 44 | 2 | Left torticollis | Sinusoidal tremor | 51 |
| 4 | f | 22 | 17 | Right laterocollis Right torticollis | Pure dystonia | 22 |
| 5 | m | 42 | 2 | Right laterocollis Left torticollis | Dystonic tremor | 76 |
| 6 | m | 60 | 7 | Right laterocollis Right torticollis | Pure dystonia | 51 |
| 7 | m | 41 | 2 | Right torticollis | Pure dystonia | 109 |
| 8 | f | 54 | 12 | Right laterocollis Right torticollis | Dystonic tremor | 64 |
| 9 | m | 31 | 5 | Left laterocollis Left torticollis | Pure dystonia | 41 |
| 10 | f | 68 | 6 | Right torticollis | Sinusoidal tremor | 66 |
| 11 | f | 63 | 6 | Left laterocollis Right torticollis | Sinusoidal tremor | 61 |
| 12 | f | 40 | 15 | Left laterocollis Right torticollis | Dystonic tremor | 46 |
| 13 | m | 52 | 6 | Right torticollis | Dystonic tremor | 45 |

Spike Sorting and Classification

Spontaneous single-unit activity (in the absence of voluntary muscle activation) was recorded as the electrode advanced through GPe and GPi. Isolated single-unit responses were

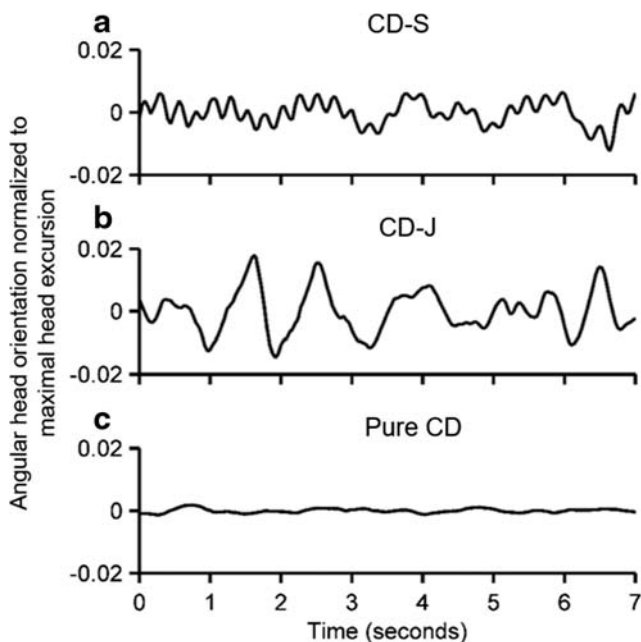


Fig. 1 Examples of three patients, one with (A) CD-S (B) CD-J and (C) pure CD. Angular head orientation normalized to maximal excursion are plotted on y-axis while corresponding timestamp is plotted on x-axis

saved on computer hard disk for post hoc analyses. Each cell was recorded for at least 20 s. Recording that contained more than 200 spikes was included in the analysis. The signals were preprocessed and analyzed with Spike 2 (CED, Cambridge, UK). The signal was band-pass filtered (300–5000 Hz) and then aligned for subsequent spike sorting. Amplitude threshold, at the value of 4 times standard deviation, was used to isolate the spikes. The threshold was unique for each recorded neuron. Once identified, the single units were separated by manual cluster selection in principal component analysis (PCA) feature space based on several waveform parameters. The cell that was recorded for at least 20 s with > 200 spikes was considered for further analyses. The spike-trains were clustered based on the histograms for neural activity recordings (spike density histograms SDHs); the analysis revealed parameters unique to the neuronal firing pattern [46]. For grouping spike-trains into the patterns, we used hierarchical clustering approach using the Ward’s method for merging the branches. Jensen-Shannon Divergence (JSD) was used as a distance metrics. The elbow method was used to determine the optimal number of clusters.

We used the Poisson Surprise (PS) algorithm for burst detection [47]. The PS algorithm assumes that baseline neural discharge follows a Poisson process. Therefore the PS statistic, defined as $S = -\log(p)$ where “ p ” is the probability of more or equal as “ N ” spikes occurring in interval, could be used to maximize the PS statistic with a surprise maximization algorithm [48]. We disregarded the bursts with PS lower than chosen threshold. Reliably detected bursts for each isolated

neuron were further used to determine parameters for the burst activity such as burst percent (ratio of spikes in burst to the total number of spikes) and inter-burst intervals. For burst, pause, and tonic neurons, we also analyzed instantaneous firing rate, coefficient of variance of interspike interval (ISI), and asymmetry index (median ISI/mean ISI) quantifying the skewness of irregularity in firing discharge.

Statistical analysis was performed in Matlab Statistics Toolbox (Mathworks, Natick, MA, USA); in some instances, we utilized available Matlab tools to prepare custom statistical software for the analysis. For variables that conformed to a normal distribution (Shapiro–Wilk’s W test, $p > 0.05$), we used one-way analysis of variance (ANOVA) for group comparisons. Post hoc analysis was performed with Tukey HSD test.

Results

Physiological Differences in Neuronal Discharge Patterns in Three Subgroups of CD

Our study addresses the controversial relationship between two common movement disorders, dystonia and tremor. Our overarching goal was to delineate whether there are biological differences in the pallidal activity in CD patients who have pure dystonia with or without phenomenologically distinct (i.e., jerky versus sinusoidal) forms of head oscillations. We studied 13 CD patients who opted for deep brain stimulation surgery, a clinical standard-of-care for refractory neck dystonia. In this population, five patients had CD with objectively confirmed (see methods and Fig. 1 for details) jerky head oscillations (CD-J group), five had objectively confirmed pure CD without clinically overt head oscillations (pure CD group),

and three patients had CD with objectively confirmed sinusoidal head oscillations (CD-S group).

We analyzed responses of 727 pallidal neurons (398 GPi and 329 GPe) recorded from 13 CD patients (26 hemispheres). Further classification of the neurons using unsupervised clustering revealed specific characteristic that further allowed their labeling as burst, pause, and tonic neurons (Fig. 2a). The tonic neurons were classified when the cell had continuous firing activity without intervals of silence (Fig. 2b). The burst neurons had the periods of regular burst and pause activity (Fig. 2c). The pause neurons had recurrent periods of high frequency discharges separated by relatively long interval of silence sometimes lasting for up to several seconds (Fig. 2d).

The survey of different types of neuronal patterns in GPi revealed that the patients in the CD group and the CD-J group had a smaller proportion of pause neurons as compared to those in the CD-S group. The burst neurons were highest in prevalence in the pure CD or CD-J groups. The results contrasted with the patients in the CD-S group, who had about the equal proportion of burst and pause neurons. The proportion of tonic neurons was much smaller in patients with pure CD or CD-J as compared to those with CD-S. This disparity in distribution of various cell types was significant in both GPi (X^2 test, Fig. 3a, $p < 0.001$) and GPe (Fig. 3b, X^2 test GPe, $p = 0.04$). In all three patient groups, the GPe had the least proportion of the pause neurons, followed by burst and tonic neurons.

In subsequent analyses, we measured whether the presence of head oscillations and its classification as jerky or sinusoidal is correlated with the firing rate of GPi and GPe neurons. Figure 4a provides the overview. The firing rate of GPi pause neurons was significantly higher in the pure CD group (median:38 (range:29–55) spikes/s) or CD-J group (median:33

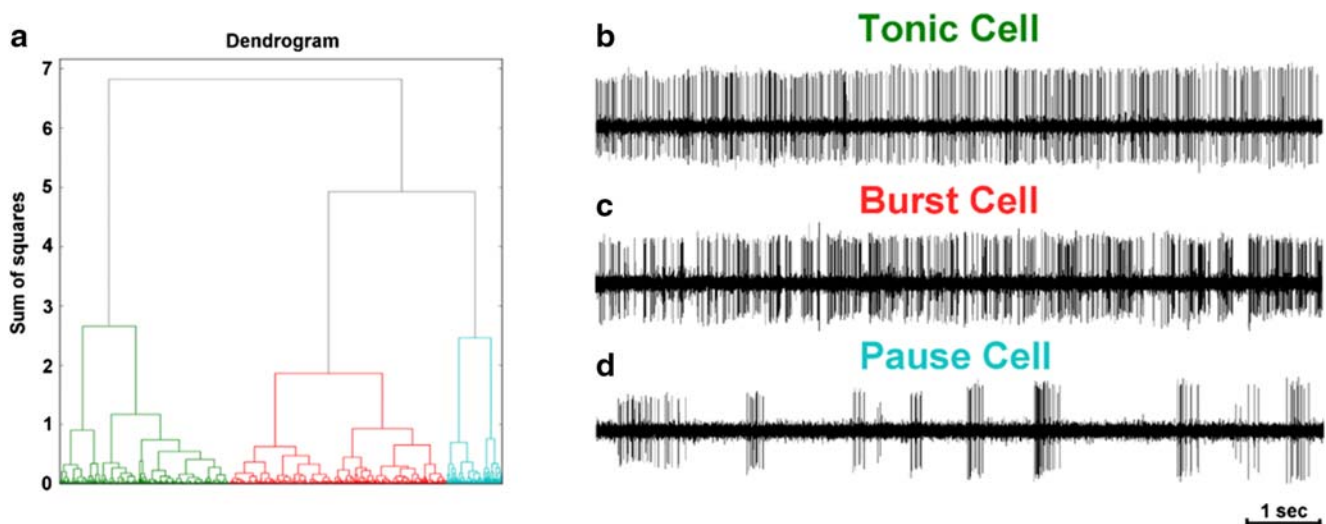


Fig. 2 (A) Dendrogram depicting clustering of spike train in three subtypes each with distinct firing characteristics – such as tonic neuron (B), burst neuron (C), and pause neuron (D)

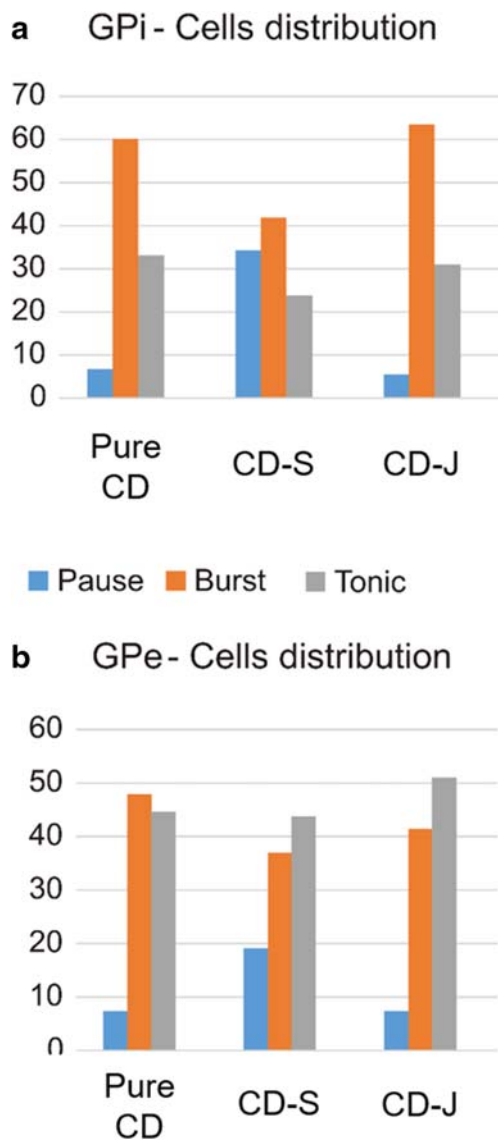


Fig. 3 Distribution of pause, burst and tonic neurons in globus pallidum interna (GPi) and externa (GPe). Number of cells in each category is plotted on y-axis, the x-axis depicts the patient category, color of bar plot depicts cell type

(range:31–43) spikes/s) compared to the CD-S (median:13 (range:8–21) spikes/s) (ANOVA: $p < 0.001$; Tukey: $p = 0.0001$ and $p = 0.0002$). The firing rate of GPi burst neuron in the CD-J group (median:61 (range:51–78) spikes/s) was also higher compared to the CD-S group (median:46 (range:32–67) spikes/s) (ANOVA, $p = 0.007$; Tukey: $p = 0.006$). The tonic cells had the highest firing rate among all three classes of GPi neurons. The CD-J group had the highest firing rate among tonic neurons (median:102 (range:72–135) spikes/s). The median firing rate of tonic neurons in the pure CD group was 78 spikes/s (range:43–111 spikes/s) and in CD-S group it was 54 spikes/s (range:24–82 spikes/s) (ANOVA: $p = 0.0006$; Tukey: $p = 0.0005$). Such differences were also seen in GPe, but they were not statistically significant

(ANOVA, $p > 0.05$). In summary, the group that had CD combined with sinusoidal head oscillations featured lowest firing rate among all three subtypes of GPi neurons when compared with the corresponding neuronal subtype in pure CD or CD plus jerky oscillations groups. There were no significant differences in the firing rates for pure CD compared with CD plus jerky oscillations.

Then we measured whether the presence of different types of head oscillations were associated with the firing regularity of pallidal neurons. Figure 4 b provides the overview by comparing the firing rate coefficient of variance (CV). The CV of the GPi pause neurons was significantly lower in the pure CD (median:1.46 (range:1.37–1.54), Tukey: $p = 0.0004$) (Fig. 4b) or CD-J (median:1.55 (range:1.27–1.84), Tukey: $p = 0.007$) groups compared to the CD-S group (median:2.32 (range:1.86–2.80)). On the contrary, we did not find a significant difference in the CV of burst or tonic neurons in the three groups of patients (burst: CD-J median:1.09 (range:1.01–1.19), pure CD group median:1.10 (range:1.02–1.19), CD-S median:1.12 (range:1.07–1.25), ANOVA $p = 0.42$; tonic: CD-J group median:0.87 (range:0.77–0.93), pure CD group median:0.85 (range:0.76–0.91), CD-S group median:0.86 (range:0.74–0.95), ANOVA, $p = 0.87$) (Fig. 4b). The CV of GPe pause neurons was significantly lower (ANOVA, $p = 0.03$; Tukey: $p = 0.03$) in patients from pure CD group (median:1.56 (range:1.39–1.68)) compared to those from the CD-S group (median:2.20 (range:1.87–2.69)) (Fig. 4b). However, we did not find significant difference in the CV of GPe burst or tonic neurons among three groups of patients (burst: CD-J group median:1.16 (range:1.04–1.34), pure CD group median:1.18 (range:1.09–1.31), CD-S group median:1.27 (range:1.06–1.64), ANOVA $p = 0.21$; tonic: CD-J group median:0.90 (range:0.76–0.98), pure CD group median:0.86 (range:0.72–0.98), CD-S group median:0.85 (range:0.72–0.90), ANOVA, $p = 0.73$) (Fig. 4b).

In subsequent analysis, we asked whether the presence of different types of head oscillations lead to the skewness in the irregularity of the neuronal discharge. Asymmetry index, the ratio of median interspike interval to mean interspike interval, was measured for each neuron to quantify the skewness of irregularity. Higher asymmetry index suggests more regular firing, as expected in tonic neurons compared to burst and pause neurons (Fig. 4c). The GPi pause neurons in patients with CD-J or pure CD had significantly higher asymmetry index compared to CD-S (CD-J median:0.48 (range:0.41–0.51), pure CD median:0.49 (range:0.43–0.51), CD-S median:0.34 (range:0.25–0.46), ANOVA $p < 0.005$; Tukey: $p = 0.04$ and $p = 0.003$). No significant differences in asymmetry index in patient subtypes were noticeable in GPi burst or tonic neurons, or any GPe neurons (Fig. 4c). These results confirmed that irregularity in the firing rate is higher in pause neurons. We also found that pause neurons in the CD-S group are more irregular and skewed compared to those in CD-J or

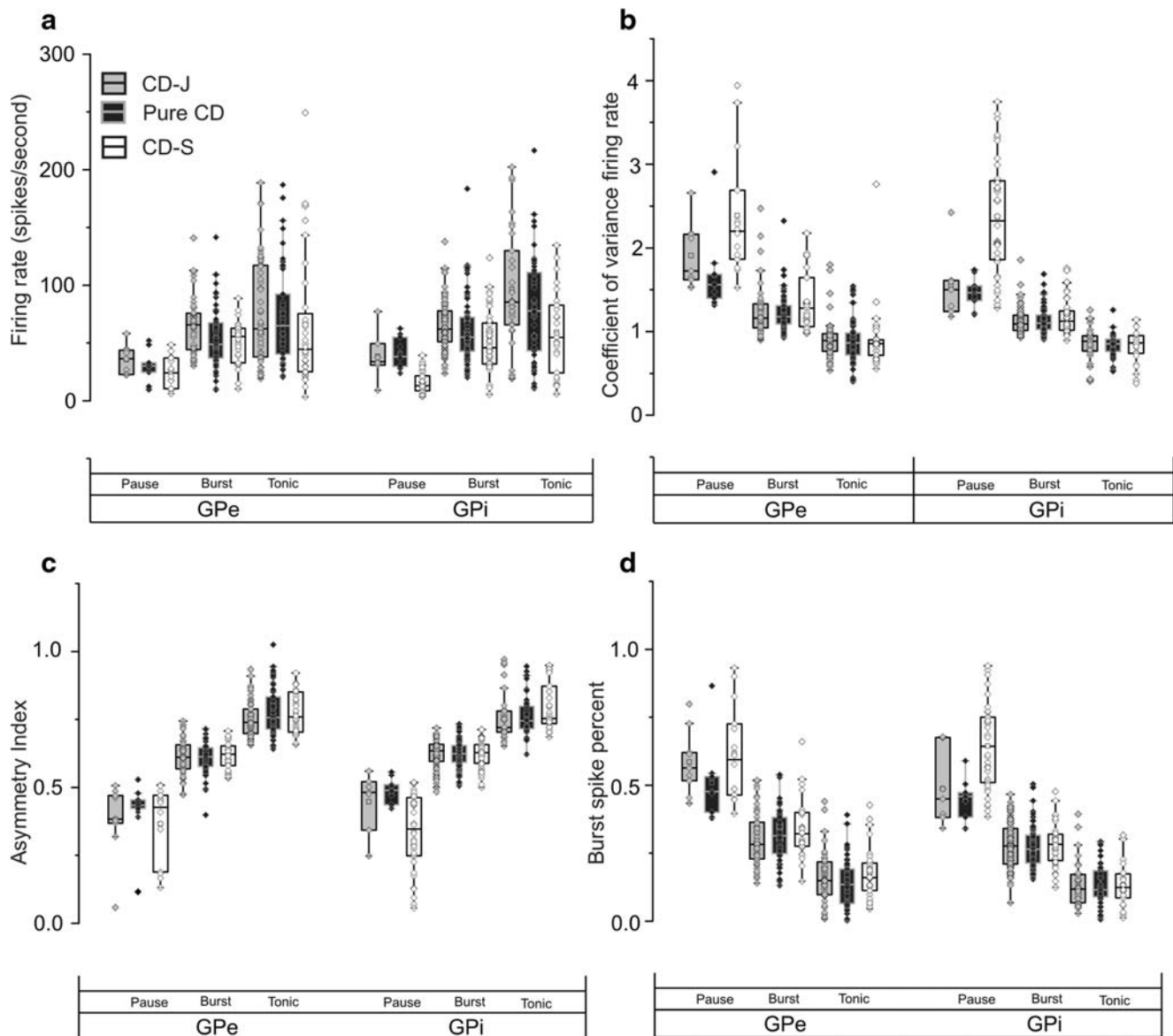


Fig. 4 Summary of firing rate (A), coefficient of variance of the firing rate (B), asymmetry index (C), and burst spike percent (D) in pause, burst and tonic neurons recorded from GPi and GPe. The values of corresponding

parameter are plotted on y-axis, while axis is category. Box length is interquartile interval, the dashed line in the center of the box is median value, while whisker is the range, symbols depict each single-unit

pure CD groups. There were no differences in the pause neuron irregularities or skewness among CD-J and pure CD groups.

Additional analysis, looking at bursting behavior, focused on burst and pause neurons. We computed burst spike percent – a measure of portion of total spikes that are part of the burst (Fig. 4d). GPi pause neurons had significantly lower burst spike percent in CD-J or pure CD groups (CD-J group (median:0.47 (range:0.38–0.60); pure CD group (median:0.45 (range:0.38–0.47)) compared to CD-S (median:0.64 (range:0.51–0.75), ANOVA: $p < 0.001$; Tukey: $p = 0.003$ and $p = 0.0001$). In GPe pause neurons, there was significantly lower burst spike percent in pure CD group (median:0.47

(range:0.40–0.53)) compared to the CD-S group (median:0.59 (range:0.46–0.72), Tukey: $p = 0.0008$, ANOVA $p < 0.001$) or CD-J group (median:0.58 (range:0.51–0.73), Tukey $p = 0.02$, ANOVA $p < 0.001$). Then we measured inter-burst interval – the time duration between two adjacent bursts. The inter-burst interval in GP pause neurons in CD-J (GPi: median:0.52 (range:0.34–0.66); GPe: median:0.64 (range:0.53–0.83)) and pure CD (GPi: median:0.42 (range:0.35–0.58); GPe: median:0.56 (range:0.47–0.73)) was significantly shorter compared to CD-S (GPi: median:1.05 (range:0.76–1.33); GPe: median:1.01 (range:0.75–1.59), ANOVA: $p < 0.001$; Tukey: $p < 0.005$). The inter-burst interval of the burst neurons measured in CD-J (GPi: median:0.48 (range:0.39–0.57); GPe:

median:0.53 (range:0.45–0.67)) or pure CD groups (GPi: median:0.52 (range:0.39–0.67); GPe: median:0.57 (range:0.46–0.87) was significantly shorter compared to CD-S group (GPi: median:0.65 (range:0.47–0.93); GPe:median:0.78 (range:0.73–0.97), ANOVA: $p < 0.01$; Tukey: $p < 0.005$).

Lateralized Asymmetry in Different Subtypes of Cervical Dystonia

Asymmetric pallidal activity is a feature of CD [27, 49, 50]. Such asymmetry is evident in GPi, but lateralized differences in GPe are insignificant; the asymmetry is much more robust in GPi tonic neurons [27]. Here we asked whether pallidal asymmetry is influenced by the presence of jerky or sinusoidal oscillations. We compared interhemispheric differences in the pallidal burst, pause, and tonic neurons in all three patient groups. The GPi tonic neurons had robust firing rate asymmetry in pure CD group; the neurons recorded from the GPi ipsilateral to the direction of torticollis (i.e., contralateral to the dystonic sternocleidomastoid) had significantly higher firing rate (ipsilateral: median:103 (range:73–119); contralateral: median:56 (range:31–93); ANOVA, $p < 0.01$). Such asymmetry of tonic neuron activity was not statistically significant in GPe tonic neurons (ipsilateral: median:58 (range:40–115); contralateral: median:70 (range:41–93); ANOVA, $p > 0.05$). In the CD-J group, there was interhemispheric disparity in tonic GPi neuron activity, but the difference was not statistically significant (ipsilateral: median:86 (range:65–124); contralateral: median:113 (range:75–152); ANOVA, $p = 0.26$). The summary of these differences is graphically described in Fig. 5. In the CD-S group, there was no interhemispheric disparity in instantaneous firing

rate in any type (burst, pause, or tonic) of GPi or GPe neurons (Fig. 5). Likewise, burst and pause neuron firing rates were not significantly different between two hemispheres in patients who had pure CD or CD-J (Fig. 5). Coefficient of variance, asymmetry index, burst percent, and inter-burst interval was also not significantly different between two hemispheres in all three groups of patients (Table 2).

Discussion

Two common movement disorders dystonia and tremor have correlates in abnormal neural network that comprises of the cerebellum, basal ganglia, thalamus, midbrain, and the cerebral cortex. We utilized our ability to measure single-unit activity from the basal ganglia (GPi and GPe) to distinguish physiological differences between CD patients who had pure neck dystonia, with or without jerky or sinusoidal head oscillations. We examined the physiological association between different types of head oscillations in CD. We expect if the two different types of head oscillations in CD are both merely reflections of the underlying biology of dystonia, then there will be no differences among these three groups of patients. If the two different types of head oscillations in CD reflect different biological processes, then we expect differences among all three groups of patients. We found that CD and CD-J groups have comparable physiological patterns that are different compared to CD-S group supporting biological relationship between pure CD and CD-J. Contemporary literature over the last one decade has increasingly supported the role of mesencephalic neural integrator in CD [26, 28, 51].

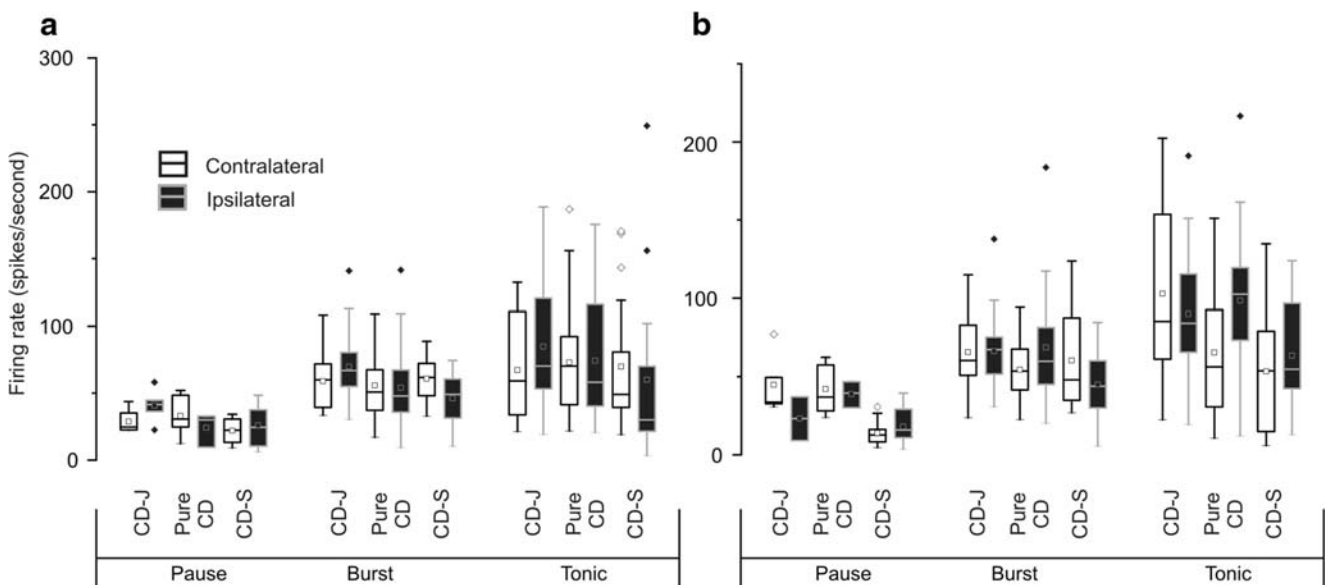


Fig. 5 Summary of comparison of ipsilateral versus contralateral firing rate of GPe(A) and GPi (B) neurons. Laterality is determined by the direction of the dystonia

Table 2 Bihemispheric (ipsilateral (ipsi) versus contralateral (contra)) comparison of burst parameters

| | No tremor | | | Tremor | | | Jerky | | |
|-------------------------|-----------|--------|----------|--------|--------|----------|-------|--------|----------|
| | Ipsi | Contra | <i>p</i> | Ipsi | Contra | <i>p</i> | Ipsi | Contra | <i>p</i> |
| GPi | | | | | | | | | |
| Firing rate | 58.64 | 53.14 | 0.06 | 30.70 | 31.05 | 0.87 | 65.52 | 59.47 | 0.61 |
| Coefficient of Variance | 1.13 | 1.10 | 0.65 | 1.44 | 1.40 | 0.93 | 1.12 | 1.10 | 0.54 |
| Asymmetry Index | 0.60 | 0.62 | 0.91 | 0.55 | 0.52 | 0.5 | 0.62 | 0.63 | 0.86 |
| Burst spike percent | 0.27 | 0.28 | 0.91 | 0.38 | 0.39 | 0.78 | 0.31 | 0.27 | 0.14 |
| Inter-burst interval | 0.46 | 0.56 | 0.01 | 0.75 | 0.98 | 0.68 | 0.48 | 0.48 | 0.62 |
| GPe | | | | | | | | | |
| Firing rate | 46.77 | 48.30 | 0.66 | 40.10 | 48.07 | 0.28 | 65.66 | 48.55 | 0.05 |
| Coefficient of variance | 1.19 | 1.25 | 0.32 | 1.36 | 1.70 | 0.74 | 1.20 | 1.29 | 0.48 |
| Asymmetry index | 0.61 | 0.59 | 0.39 | 0.59 | 0.56 | 0.54 | 0.60 | 0.59 | 0.86 |
| Burst spike percent | 0.33 | 0.34 | 0.59 | 0.39 | 0.40 | 0.90 | 0.31 | 0.32 | 0.73 |
| Inter-burst interval | 0.54 | 0.63 | 0.63 | 0.81 | 0.85 | 0.66 | 0.55 | 0.54 | 0.79 |

According to the network model in CD, the impairment anywhere in the network, even outside of the integrator, can lead to deficits in neural integration that is feedback dependent. There is increasing evidence for involvement of cerebellum in the network model for dystonia [5–30]. The cerebellar role in dystonia would be even more supported when the oscillations coexisting with dystonia have sinusoidal features as seen in the essential tremor that is also thought to be related to cerebellar deficits [25, 41]. Our results depicting distinct physiological characteristics of CD-J and pure CD, especially when compared with CD-S, suggest that the latter may have independent physiological correlate.

Consistent with previous studies of other types of dystonia, we found abnormal burst neurons in the GPi of CD patients [44, 45, 52–54]. There was a higher prevalence of burst neurons and lower prevalence of pause neurons in patients with CD or CD combined with jerky oscillations, compared with CD plus sinusoidal oscillations. Pause neurons were more irregular in the group with CD combined with sinusoidal oscillations. The number of spikes were higher (i.e., the bursts were denser) in the pause neurons in the group with sinusoidal oscillations compared to the other groups. Inter-burst interval measured in burst and pause neurons from the group with sinusoidal oscillations was significantly longer. These results suggest that physiology and classification of neuronal subtypes in the pallidum in patients with jerky oscillations were comparable to the patients with pure dystonia. However, those who had neck dystonia with sinusoidal oscillations were significantly different from the patients with pure dystonia or dystonia plus jerky oscillations. In other words, jerky oscillations appear to be a *forme fruste* of dystonia with no significant differences in the pallidal physiology; but a distinct biological dysfunction leads to dystonia with sinusoidal oscillations.

Previous studies quantifying the single-unit properties of GPi neurons in dystonia reported mean instantaneous firing

rate of 55.3 ± 1.3 spikes/s [53]. Our study, had a large variability in the instantaneous firing rate ranging between the median (confidence interval) value of 13 (range: 8–21) spikes/s in pause neurons in the CD-S group and median of 102 (range: 72–135) spikes/s in tonic cells of CD-J group. The disparity could be due to the fact that previous studies combined findings from different types of dystonia (idiopathic CD, generalized dystonia, tardive dystonia, and secondary dystonia). We also emphasize that we found comparable firing rate of burst neurons as reported in the previous studies that also found burst neurons as predominant subtype in their dystonic patients [53]. Another study reported GPe pause cell firing rate of 54 ± 24 spikes/s in isolated dystonia [52], while we found GPe pause cell firing rate of 24–38 spikes/s. The differences should be interpreted with the caveat that we only studied isolated CD, while dystonia in the other study included patients who had DYT1 or multifocal/segmental dystonia [52].

Previous studies discovered pallidal asymmetry in CD, and further predicted that such asymmetry is due to the imbalance in the extrinsic feedback to the GPi [27, 49, 50]. However, these studies utilized CD as an entire (unclassified) cohort to examine the asymmetry and its correlation with lateralized severity of dystonia. These results further classified previously published cohort [27] into CD-S, CD-J, and pure CD discovering asymmetric firing rate of tonic neurons in the CD-J and pure CD groups, but lack of such asymmetry in CD-S group. The GPi firing rate ipsilateral to the direction of head turning was higher in pure CD group with statistically significant difference, CD-J group had asymmetry that did not reach statistical significant. We speculate that asymmetry in the feedback to the pallidum may explain such disparity. For example, in patients with pure dystonia (i.e., no head oscillations), the pallidal feedback driven by asymmetric static pull in the direction of head turning leads to asymmetric increase in ipsilateral GPi firing rate. In contrast, in patients with jerky or

sinusoidal oscillations, the dynamic feedback due to rapid head oscillations may override the influence of slower head movements.

The interhemispheric differences in the firing rates that were seen in tonic neurons of pure CD or CD-J groups as opposed to the CD-S group is unlikely to explain overall differences in the firing rates that were noted in CD-S group. For example, the firing rates of tonic GPe neurons were also significantly different among patients with CD-S in comparison to pure CD or CD-J; however, there were no interhemispheric differences in the firing rates of GPe tonic neurons. Although the pause neurons in patients with CD-S were more irregular and skewed compared to those in CD-J or pure CD groups, there were no interhemispheric disparities in the asymmetry index and irregularity of these cells. Likewise, GPi pause neurons in CD-S patients had significantly higher burst-spike percent compared to pure CD and CD-J groups; however, the interhemispheric disparity was not present. In all subjects, the data collection was performed under identical protocol, i.e., at the time of single-unit recordings, the subjects were alert (non-anesthetized). Hence, the observed differences in single-unit physiology among different subgroups of neurons could not be attributed to pharmacological effects of the anesthetic agent.

Conclusion

Our results suggest biological differences in the basal ganglia network behavior in pure cervical dystonia or cervical dystonia combined with irregular head oscillations compared with cervical dystonia with sinusoidal oscillations. From the conceptual perspective, if we focus on the pure dystonia group as “benchmark,” then jerky head oscillations are physiologically comparable phenomenon, perhaps *forme fruste* of pure dystonia; however, a distinct biological process is present when dystonia is associated with sinusoidal head oscillations.

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