CHAPTER

# 20

# Implications of asymmetric neural activity patterns in the basal ganglia outflow in the integrative neural network model for cervical dystonia

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## Abstract

Cervical dystonia (CD) is characterized by abnormal twisting and turning of the head with associated head oscillations. It is the most common form of dystonia, which is a third most common movement disorder. Despite frequent occurrence there is paucity in adequate therapy, much of which is attributed to its uncertain pathophysiology. Recently we proposed a unifying network model highlighting the role of head neural integrator (hNI) for the pathophysiology of CD. According to our hypothesis the CD is due to abnormal output of hNI; the latter itself is not affected but its dysfunction is secondary to abnormal feedback. We hypothesized that asymmetry in the feedback to hNI is associated with severity in CD; the feedback asymmetry is greater in CD with lateralized head postures, such as turning of head in yaw plane (torticollis) or roll plane (laterocollis). The hypothesis also specifies that feedback to hNI—cerebellum, proprioception, and basal ganglia outflow (pallidus) are connected in a network; thus asymmetry is distributed through the feedback network. In 15 CD patients undergoing deep brain stimulation (DBS) surgery, with their informed consent, we used the opportunity to collect single unit neural responses and local field potential from the globus pallidus to measure whether feedback to hNI is asymmetric. Using machine learning algorithms developed to analyze single unit data, we found: (1) globus pallidus interna (GPi) firing rate, discharge

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pattern and gamma oscillation were asymmetric in patients with robust torticollis; (2) there was no asymmetry in these parameters in retrocollis; and (3) in those patients with oppositely directed laterocollis and torticollis. Firing rate was higher in GPi cells ipsilateral to the direction of head rotation; the asymmetry was more pronounced in tonic cells compared to burst neurons. In addition to confirming that CD is associated with an asymmetric pallidal activity, our data showed that neuronal asymmetry correlated with the degree of involuntary head turning. We propose that asymmetric pallidal activity results in asymmetric feedback to hNI causing its dysfunction.

## Keywords

Cervical dystonia, Human neural integrator, Globus pallidus, Microelectrode recording (MER), Local field potentials (LFP), Asymmetry

## 1 Introduction

Cervical dystonia (CD), the most common form of focal dystonia, is characterized by abnormal head posture often combined with neck pain and jerky head oscillations. Information regarding the brain regions that may cause CD is surprisingly limited, and views on the pathophysiological mechanisms of the disease are controversial. In 2002 a pretectal neural integrator, analogous to that in the ocular motor system, was proposed for the control of head movements (Klier et al., 2002). Our recent studies proposed that the head movement abnormalities in CD are due to the malfunctioning of the head neural integrator (hNI) putatively due to impaired feedback from the cerebellum, basal ganglia, or peripheral proprioceptors (Sedov et al., 2017, 2019; Shaikh et al., 2016). According to this model asymmetric feedback to the hNI results in abnormal head postures with or without jerky head oscillations. Support for this hypothesis comes from macaque experiments, where unilateral injection of muscimol into the mesencephalic interstitial nucleus of Cajal (INC) resulted immediately in position-dependent head drifts with intermittent rapid corrective movements, i.e., jerky head oscillation, whereas further progression of the effect led to tonic deviated head postures (Farshadmanesh et al., 2008; Klier et al., 2002). This was interpreted as an immediate bihemispheric imbalance in the hNI, followed by loss in the ability to correct the resulting head drift due to spread of the muscimol through the INC and adjacent midbrain structures. We predict that impaired or asymmetric hNI activity can be due to imbalance in the input to the integrator. The feedback sources to the neural integrator, which include the cerebellum, basal ganglia, and proprioceptors are mutually connected. Therefore the asymmetry in feedback from any of the sources could be reflected in any of the nodes of the network contributing to the hNI. We used the opportunity to measure single unit activity and local field potential (LFP) from the basal ganglia outflow, globus pallidus, during deep brain stimulation (DBS) surgery, asking a key question whether feedback to the hNI in CD is asymmetric. In particular we hypothesize that robust asymmetry in the feedback to hNI is associated with severe lateralized head postures in CD patients.

## 2 Materials and methods

We measured single unit physiology and LFP from 15 CD subjects undergoing globus pallidus DBS surgery. Surgeries were performed under local anesthesia in Burdenko National Scientific and Practical Center for Neurosurgery. We separated patients into three groups. Group 1 was represented by six patients with robust torticollis. Group 2 included six patients with mild latero-torticollis. Group 3 was presented by control group of three patients with retrocollis. The participants gave written informed consent for the surgery and the involvement in research. Studies were approved by the ethical committee and was performed according to the Declaration of Helsinki.

We recorded and analyzed 865 cells in internal (GPi) and external (GPe) segment of the globus pallidus. Cell localization was controlled by Lead-DBS (http://www.lead-dbs.org/). The signals acquired during recordings were pre-processed and analyzed using Spike2 software (CED, Cambridge, UK). The steps for data preprocessing included bandpass filtering (300–5000 Hz for MER) and spike sorting. Spikes were detected using an amplitude threshold and then sorted by means of principal component analysis (PCA). We used method of hierarchical spike train clustering to separate neurons to burst and tonic types (Myrov et al., 2019). We measured 22 objective spike train parameters and oscillations scores in each cell types. We used analysis of variance (ANOVA) and random forest algorithm to determine which parameter is dependent upon the laterality of CD. Oscillation scores (OS) for each frequency band were computed with the spectral analysis of LFP. To estimate the degree of head rotation we used facial feature tracking techniques from video frames with CLM-framework.package (https://github.com/TadasBaltrusaitis/CLM-framework).

## 3 Results

We analyzed 22 spike-train parameters in firing rates of GPi and GPe single neurons that were ipsilateral and contralateral to the direction of head rotation. These parameters are outlined in Table 1. Among 22 spike-train parameters only 3 parameters differed in ipsilateral versus contralateral GPi activity in patients who had prominent lateralized head posturing—firing rate (or mean interspike interval), burst index quantifying the pattern of burst firing, and pause index quantifying patterns of episodic burst in the firing rate. In these patients the firing rate was higher in GPi ipsilateral to the direction of dystonia (ANOVA, $P < 0.01$) (Fig. 1). There was no such laterality dependence of firing rate in GPe neurons (Fig. 1). The ipsilateral GPi activity had more bursting response and there were less pauses. Separation of neurons into burst and tonic types showed that the asymmetry was more pronounced in tonic cells compared to burst neurons; the difference was more robust in GPi (Wilks lambda = 0.97, $F(3,191) = 2.22$; $P = 0.08$) compared to GPe (Wilks lambda = 0.98, $F(3,110) = 0.77$; $P = 0.5$) (Fig. 2).

**Table 1** Parameters of single unit activity in contra- and ipsilateral globus pallidus.

| | | GPi | | | GPe | | |
|---|---|---|---|---|---|---|---|
| **N** | **Parameters** | **Contra** | **Ipsi** | ***P* value** | **Contra** | **Ipsi** | ***P* value** |
| 1 | **Firing rate—instantaneous firing rate** | **57.527** | **72.486** | **0.007** | 50.637 | 58.961 | 0.350 |
| 2 | Coefficient of variation | 1.043 | 0.973 | 0.260 | 1.052 | 1.073 | 0.946 |
| 3 | Asymmetry index—ratio of median to mean ISI | 0.654 | 0.682 | 0.142 | 0.693 | 0.688 | 0.830 |
| 4 | **Frequency variance—ratio of difference in maximum and minimum to maximum FR** | 43.704 | 39.258 | 0.452 | **39.415** | **51.453** | **0.024** |
| 5 | Local variance—measure of local spike randomness | 0.667 | 0.645 | 0.668 | 0.549 | 0.537 | 0.418 |
| 6 | Differential entropy (Nu)—the measure of spiking randomness | 0.761 | 0.786 | 0.160 | 0.707 | 0.716 | 0.963 |
| 7 | ISI larger mean—percent of ISI larger than mean ISI | 0.326 | 0.340 | 0.101 | 0.312 | 0.316 | 0.772 |
| 8 | **Burst index—ratio of number of 10–16 ms ISI to number of ISI > 16 ms** | **0.653** | **1.025** | **0.034** | 0.445 | 0.838 | 0.218 |
| 9 | Burst spike percent—ratio of spikes in bursts to the total number of spikes | 0.223 | 0.213 | 0.433 | 0.224 | 0.209 | 0.903 |
| 10 | Ratio burst time—ratio of burst spikes time to total time | 0.072 | 0.071 | 0.535 | 0.087 | 0.082 | 0.764 |
| 11 | Burst rate | 1.521 | 1.703 | 0.361 | 1.192 | 1.070 | 0.470 |
| 12 | Interburst interval | 0.528 | 0.523 | 0.687 | 0.707 | 0.695 | 0.677 |
| 13 | Mean burst length | 0.048 | 0.041 | 0.352 | 0.078 | 0.077 | 0.934 |
| 14 | **Mean ISI in burst** | **0.006** | **0.005** | **0.035** | 0.007 | 0.007 | 0.126 |
| 15 | Mean spikes in burst | 8.778 | 8.720 | 0.469 | 9.765 | 11.000 | 0.298 |
| 16 | **Pause index—ratio of the number of ISIs > 50 ms to the number of ISIs below** | **0.056** | **0.029** | **0.007** | 0.054 | 0.045 | 0.254 |
| 17 | O-score 3–8 Hz | 4.990 | 4.642 | 0.608 | 4.488 | 4.113 | 0.302 |
| 18 | O-score 8–12 Hz | 2.082 | 2.271 | 0.423 | 2.143 | 2.221 | 0.912 |
| 19 | O-score 12–20 Hz | 0.894 | 0.824 | 0.317 | 1.190 | 1.247 | 0.304 |
| 20 | O-score 20–30 Hz | 0.732 | 0.559 | 0.164 | 0.596 | 0.534 | 0.924 |
| 21 | O-score 30–60 Hz | 1.008 | 0.872 | 0.096 | 0.973 | 0.714 | 0.560 |
| 22 | O-score 60–90 Hz | 0.980 | 0.862 | 0.105 | 1.192 | 0.861 | 0.265 |

*Bold emphasis marks parameters with* $P < 0.05$.

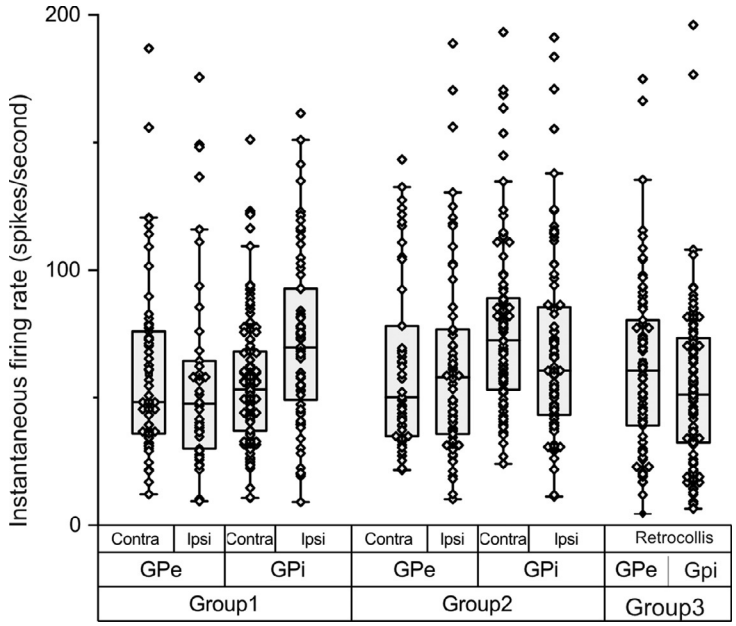


**FIG. 1**

The summary of instantaneous firing rate in individual neurons (each symbol). Box and whisker plot depicts the summary. The length of each box depicts interquartile interval. The horizontal line in the center depicts the median value, boxes depict interquartile interval, while whiskers represent the range. The instantaneous firing rate is plotted on the *y*-axis while each category is on the *x*-axis.

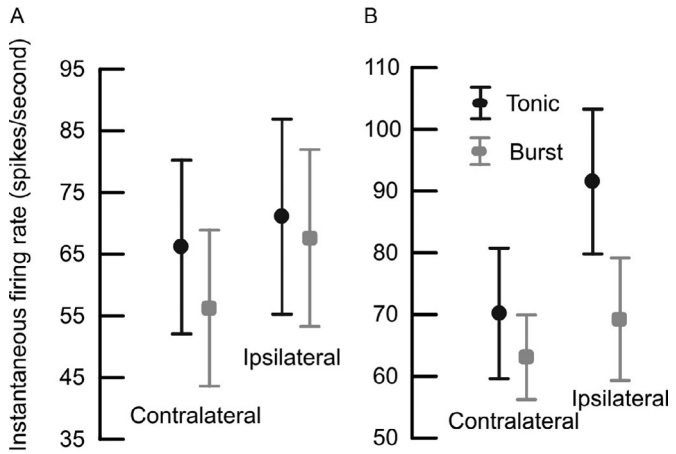


**FIG. 2**

The figure depicts the summary of mean and 95% confidence interval of instantaneous firing rate in (A) GPe and (B) GPi neurons. Symbol in the center depicts median while whiskers are 95% confidence interval. Gray line and symbols are burst neurons while black line and symbols are tonic cells.

There was no laterality dependence of the neuronal firing irregularity as quantified by frequency variance, local variance, differential entropy. There was no difference in percent of spikes distributed during the bursts, featuring the prominence of bursts in firing pattern between two hemispheres. Other burst parameters, such as mean burst interval, duration between adjacent bursts or number of spikes within a given burst were not different between hemispheres. The differences noted in those with lateralized posturing in torticollis were not evident in those who had lateraocollis (posturing in roll plane) in one direction while torticollis (posturing in yaw plane) in the other; or those who had retrocollis (posturing in pitch plane). None of the spike train parameters in any groups was asymmetric in GPe neurons, with an exception of small asymmetry in spike frequency irregularity in those who had robust torticollis.

In subsequent analysis we measured the synchronized neuronal activity in form of LFP in each group. We found significant ($P < 0.01$) differences in GPi gamma oscillations in those who had prominent torticollis. There were no significant differences in GPi oscillations in other frequency bands, in those who had prominent retrocollis or torticollis and laterocollis in opposite direction. There was no interhemispheric asymmetry in LFP measured from GPe in any patients.

We measured the strength of coupling between the GPi asymmetry and severity of head turning in nine patients who had robust torticollis. We found significant dependence between the angle of head turning and three asymmetric parameters (Fig. 3A–C).

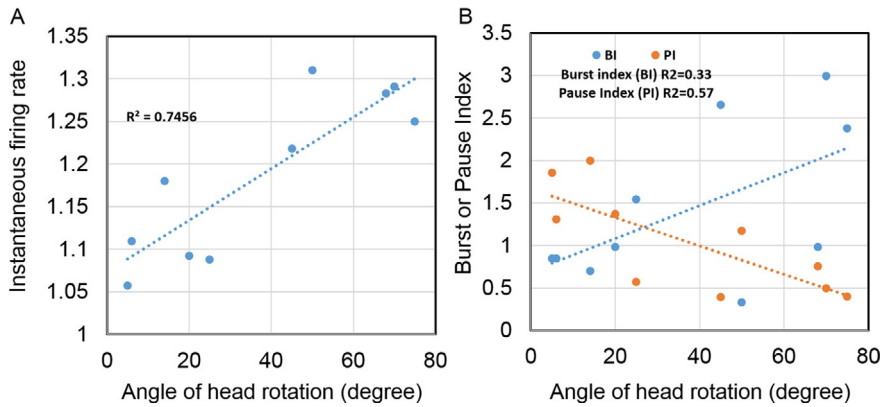


**FIG. 3**

Example of correlation of (A) asymmetry in instantaneous firing rate and (B) Burst Index or Pause Index and the angle of head rotation. Each data point depicts individual patient, dashed line is a linear fit.

## 4 Discussion

We measured single unit activity and synchronized discharges, i.e., LFP, in the globus pallidus the main output nuclei of the basal ganglia. In our unifying network model for CD the pallidus is part of interconnected source of feedback to the hNI, the dysfunction of which may lead to CD (Sedov et al., 2017, 2019; Shaikh et al., 2016). We found asymmetry in LFP and single unit activity measured from GPi, similar to previous studies (Lee and Kiss, 2014; Moll et al., 2014). We found differences in LFP and single unit activity in the same group of patients and nuclei; and it further related the asymmetry in firing rate discharge to the robustness in the severity of neck posturing in affected subjects. Another aspect of our study was that in addition to firing rate we found differences in discharge patterns. Specifically, we found that asymmetry were pronounced mainly in tonic cells. In contrast patients who had retrocollis or combinations of oppositely directed laterocollis and torticollis did not have such physiological asymmetry in the pallidus. These results suggest that higher asymmetry in the pallidal activity is correlated with the larger asymmetry in the neck tone. In support of neck muscle tone dependent neck asymmetry, we also found that amount of head rotation correlated with the level of asymmetry in pallidal activity. Due to the anatomically strategic location, the rotation of the head in torticollis is controlled mainly by the ipsilateral neck muscles. The "rate" theory of dystonia predicts that muscle hypertonus in dystonia is correlated with pallidal inhibition (i.e., reduction in firing rate) and thalamic hyperactivity. In contrast we found increased firing rate of GPi ipsilateral to affected neck muscles. It is therefore suggested that GPi hyperactivity is not primary cause of CD but rather reflects imbalanced feedback. Hence the deficits noted in the pallidum in CD patients is consequential, not causal. It is further suggested that asymmetric feedback via the pallidum to the hNI leads to leaky neural integration.

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