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**Anesthesia reduces discharge rates in the human pallidum
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**Short Communication: Anesthesia reduces discharge rates
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Abstract

Classical rate models of basal ganglia circuitry only associate the discharge rate of the globus pallidus external and internal segments (GPe, GPi respectively) with the dopaminergic state and predict an inverse ratio between the discharge rates of the two pallidal segments. The effects of other rate modulators, such as general anesthesia (GA), on this ratio have been ignored. Here, we recorded the neuronal activity in the GPe and GPi in awake and anesthetized human patients with dystonia (57 and 53 trajectories respectively) and in awake patients with Parkinson's disease (PD, 16 trajectories) undergoing deep brain stimulation procedures. This enabled us to dissociate the pallidal discharge ratio from the general discharge modulation. An automatic offline spike detection and isolation quality system was used to select 1560 highly-isolated units for analysis. The mean discharge rate in the GPi of awake PD patients was dramatically higher than in awake dystonia patients although the firing rate in the GPe was similar. Firing rates in dystonic patients under anesthesia were lower in both nuclei. Surprisingly, in all three groups, GPe firing rates were correlated with firing rates in the ipsilateral GPi. Thus, the firing rate ratio of ipsilateral GPi/GPe pairs was similar in awake and anesthetized patients with dystonia and significantly higher in PD. We suggest that pallidal activity is modulated by at least two independent processes: the dopaminergic state that changes the GPi/GPe firing rate ratio, and anesthesia that modulates firing rates in both pallidal nuclei without changing the ratio between their firing rates.

Introduction

The classical rate model of the basal ganglia was consolidated in the late 1980's (Albin

et al., 1989; Alexander et al., 1990; Bergman et al., 1990). Today, more than 25 years later, it is still the most widely accepted model linking dopamine imbalance in the striatum, rate of discharge in the different nuclei of the basal ganglia, and motor expression of hypo- and hyper-kinetic movement disorders. Deep brain stimulation (DBS), an established treatment for both dystonia and Parkinson's disease, enables researchers to test some of the predictions of this model in humans (Deffains et al., 2014a; Starr et al., 2005; Tang et al., 2007).

In this work we tested the classical basal ganglia model prediction that increased discharge rates in the external segment of the globus pallidus (GPe) lead to reduction of discharge rates in its internal segment (GPi) and vice versa. We analyzed data from three different groups of human patients who were undergoing DBS surgery: awake patients with dystonia, awake patients with Parkinson's disease (PD) and dystonic patients under general anesthesia (GA). This enabled us to dissociate the striatal dopaminergic state and the general changes in neuronal discharge rates induced by anesthesia. We used an automatic offline spike detection and sorting method to objectively select only well isolated single neurons to test the rate model with greater accuracy.

Materials and Methods

Patients, surgical procedure and recording of neuronal activity

Neuronal activity was collected intra-operatively from 45 patients (39 with dystonia and 6 patients with PD) during surgical implantation of a DBS lead in the ventro-posterior-lateral GPi. Surgeries were performed between 2003 and 2014 at the

Hadassah Medical Center in Jerusalem. Written informed consent was obtained from all patients and the study was approved by the local Institutional Review Board (reference code: 0168-10-HMO).

Surgery was performed using a CRW stereotactic frame (Radionics, Burlington, MA) and planning software (Framelink 4 or 5, Medtronic, Minneapolis, Minnesota). Target coordinates were calculated by direct targeting with either 1.5 or 3 Tesla T2 magnetic resonance imaging (MRI). Trajectory angles varied from 50 to 80 degrees from the axial AC-PC plane and 0-10 degrees from the mid-sagittal plane, adjusted for the cortical, ventricular, and blood vessel anatomy (based on gadolinium-enhanced T1 MRI images) of individual patients. On the day of the surgery the stereotactic frame was attached to the patient and a high resolution computerized tomography (CT) was performed. In patients operated under general anesthesia this procedure was also performed under general anesthesia (see below). The T1, T2 and other MRI images were fused and registered with the CT images (Framelink 4 or 5, Medtronic, Minneapolis, Minnesota) and the target coordinates and trajectory angles were calculated. The final location of the permanent electrode was based on the results of intraoperative micro-recordings and (in PD patients) the results of macro-stimulation.

General anesthesia was induced with intravenous propofol (1.5-2mg/kg) and alfentanil (10 μ g/kg). Neuromuscular blockade was achieved with vecuronium (0.1 mg/kg) to facilitate endotracheal intubation. Anesthesia was then maintained with nitrous oxide in oxygen (70%:30%) and isoflurane (0.4- 0.5% end-tidal concentration). Before the skin incision, a local anesthetic (0.5% bupivacaine) was applied. At least ten minutes prior to the micro-electrode recording, the isoflurane dose was reduced to the point where single neuronal units could be observed. In the surgeries that were performed

without general anesthesia, the patients' state of full arousal was continuously monitored and confirmed by a team member.

Electro-physiological recording was performed using polyamide-coated tungsten microelectrodes (Impedance at 1000Hz – 0.3-0.9Mohm). The position of the electrode was controlled through the MicroGuide system (AlphaOmega Engineering, Nazareth, Israel). The signal was amplified by 10000, filtered with a four-pole Butterworth filter (250-6000 Hz) and sampled at 24-48 kHz by a 15+1-bit A/D converter (using $\pm 5V$ input range).

Recording involved two parallel microelectrodes 2 mm apart that were simultaneously moved toward the estimated target (ventral border of the lateral-posterior portion of the GPi). Recording started 15 mm above the estimated target (as per imaging). A third microelectrode penetration was only necessary in a few cases. Microelectrodes were advanced simultaneously in steps of 50-400 μm (the shorter steps while inside the pallidum).

Spiking activity was classified on-line by an expert neurophysiologist as belonging to the striatum, GPe, GPi, or border cells on the basis of the signal characteristics and the spatial display of the normalized root mean square value of the microelectrode recordings (Zaidel et al., 2009). For the purpose of our analysis, recordings that could not be classified were discarded.

Offline data analysis

Recording stability was assessed (Deffains et al., 2014b) and only stable recording segments exceeding 10 seconds were used for further analyses. An automatic spike

detection and sorting method was then implemented to isolate single units (Deffains 2014) from the stable recording segments. An isolation score was calculated for each unit that was identified by the spike sorter software (Joshua et al., 2007). This score ranges from 0 (i.e. highly noisy spiking activity) to 1 (perfect isolation). Only units with an isolation score equal or greater to 0.7 were further analyzed. For each unit the peak-to-peak duration of the spike waveform was calculated as the difference between the maximal and the minimal amplitude on the time axis. The coefficient of variation of the inter spike intervals (ISI CV, standard deviation/mean), and the power spectrum as a measure of the discharge pattern (regularity, Poisson like, bursting and periodic oscillations) of spiking activity were also computed. The raster plots of units with an ISI CV larger than 2.5 were inspected visually to remove possible unstable segments.

Data are expressed as the mean \pm standard error of the mean (S.E.M.). All analyses were conducted with Matlab 7.5 2007 (Mathworks, Natick MA).

Results

Patients and neuronal database:

During DBS surgery we recorded the neuronal extracellular activity from 39 patients with dystonia and 6 patients with PD. In 19 patients with dystonia (14 with isolated generalized dystonia and 5 with segmental dystonia) recordings were performed in the awake state, without any sedation or anesthesia. In the other 20 dystonic patients (16 with isolated generalized dystonia, 4 with secondary generalized dystonia and 2 with focal cervical dystonia) recordings were performed under generalized anesthesia. Recordings in all PD patients were performed in the awake state, at least 12 hours

following withdrawal of dopaminergic medication. The demographic characteristics of the patients are reported in Supplementary Table 1.

Recordings were made in 8430 sites. These included 3806 sites in awake dystonic patients, 3536 sites in anesthetized dystonia patients and 1088 sites in patients with PD. We then used an offline automatic sorting system to isolate single units. 1560 pallidal (GPe and GPi) cells fulfilled our stringent criteria (isolation score, $IS \geq 0.7$, stable recording time $>10s$) and were used for further analysis. This relatively small fraction ($<20\%$) of units reflected our strategy to use only highly-isolated neurons (recorded in the noisy environment of an operating theater). Details regarding our database are presented in Supplementary Table 2. An example of 2 seconds of raw recording and the aligned spike waveforms in the different structures and conditions can be seen in Supplementary Fig. 1. This short report focuses on mean firing rates. We carried out further analyses of the discharge patterns and oscillations, but failed to find robust results (see supplementary text).

Mean firing rates of pallidal neurons:

Awake dystonia vs. awake PD - Our analysis database was composed of 222 GPe neurons from awake patients with dystonia and 79 units from awake patients with PD. There were no significant differences in the frequency of the GPe discharge rate of these two groups of patients (mean \pm S.E.M, dystonia: 58.60 ± 1.77 Hz, PD: 53.79 ± 3.2 Hz, t-test $p = 0.17$, $t = 1.37$, $df = 299$).

GPi analysis covered 415 units from awake patients with dystonia and 63 units from awake patients with PD. The frequency of discharge was significantly lower in dystonia (dystonia: 56.89 ± 1.20 Hz, PD: 81.24 ± 3.43 Hz, t-test $p < 0.001$, $t = 7.26$, $df = 476$). The

frequency of discharge was significantly higher in GPi than in GPe in PD (t-test $p < 0.001$, $t=5.83$, $df=140$), but did not differ in dystonia (t-test $p = 0.41$, $t=0.82$, $df=635$). These results are consistent with non-human primate studies (Bergman et al. 1994; Heimer et al. 2002).

Awake dystonia vs. dystonia under general anesthesia - We analyzed the activity of 244 GPe and 415 GPi neurons in dystonic patients under general anesthesia. These were compared to the GPe and GPi neurons ($n=222$ and 415, respectively) characterized above that were recorded in awake dystonic patients. The analysis revealed that the discharge rates were significantly lower in the GPe (dystonia anesthetized: 40.1 ± 1.9 Hz, t-test $p < 0.001$, $t=6.97$, $df=464$) and the GPi (dystonia anesthetized: 40.7 ± 1.0 Hz, t-test $p < 0.001$, $t=10.43$, $df=950$) under general anesthesia and that in this population, as was the case in awake dystonic patients, mean firing rates in the GPe and the GPi did not differ significantly.

Relationships between GPe and GPi firing rates:

The classical rate model of the basal ganglia predicts that increased firing rates in the GPe should lead to a decrement in the firing rates in the GPi (and vice versa) through the GPe-STN-GPi indirect path. The recently discovered GPe to GPi GABAergic projections (Hazrati et al., 1990; Sato et al., 2000) suggests there may be a complementary mechanism for the reciprocal relationships between the GPe and the GPi discharge rates. We showed above that in awake patients with PD the firing rates in the GPi were significantly higher than in awake dystonic patients, although the firing rates in the GPe were similar in both conditions (Fig. 1). This finding is in line with

previous observations (Starr et al., 2005; Tang et al., 2007), but contrasts with the prediction of the classical model of the basal ganglia network.

To further test these findings, we calculated the mean firing rate in the two pallidal segments for each individual patient and for each hemisphere separately. We then plotted these mean firing rates in each of the GPi against the mean values of the ipsilateral GPe (Fig. 2A-C). Since we used stringent criteria to filter our database (see above), this analysis yielded only 63 ipsilateral GPe-GPi pairs (dystonia awake 30, PD awake 8 and dystonia anesthetized 25). Surprisingly, and in contrast to the predictions of the classical model, in all 3 states increased GPe firing rates were associated with increased GPi firing rates. The slope of fitted linear least squares line was positive in all 3 states (dystonia awake: 0.96, 95% interval 0.85-1.07, PD awake: 1.40, 1.12-1.67, dystonia anesthetized 1.01, 0.90-1.12).

The seemingly steeper slope for GPe-GPi firing rates in awake PD patients led us to calculate the ratio of the GPi mean firing rate to the GPe mean firing rate for each of these GPe-GPi pairs (Fig. 3). This ratio was similar in both awake and anesthetized patients with dystonia (dystonia awake: 1.13 ± 0.11 , dystonia anesthetized 1.12 ± 0.05 , $p=0.92$, $df=53$, $t=0.1$) but significantly higher in awake PD patients (1.49 ± 0.11 , significantly different from dystonia in the awake [t-test $p < 0.05$, $t=2.08$, $df=36$] and anesthetized state [t-test $p=0.006$, $t=2.92$, $df=31$]).

Discussion

In this work we used an automatic offline sorting system to analyze only highly isolated human pallidal units (<20% of our recorded units). The analysis revealed major differences in firing rates in the GPi between awake dystonic and PD patients although

the firing rates in the GPe was similar in these two populations. Firing rates in dystonic patients under general anesthesia were lower in both nuclei. In contrast to the prediction of the classical basal ganglia model, in each population, increased GPe firing rates were associated with increased firing rates in the ipsilateral GPi. The firing rate ratio of ipsilateral GPi/GPe pairs was similar in awake and anesthetized patients with dystonia but significantly higher in PD.

By using an automatic offline spike detection and a sorting system and analyzing only well-isolated neurons, our analysis confirmed that the firing rate of GPi neurons was significantly lower in the awake patients with dystonia than in the awake PD patients. This finding is in line with the classical model of the basal ganglia (Albin et al., 1989; Alexander et al., 1990; Bergman et al., 1990), physiological studies in the MPTP primate models of PD (Heimer et al., 2002) and with previous work in awake patients (Starr et al., 2005; Tang et al., 2007; Alam et al., 2015). Unlike the difference observed in the GPi, the discharge rates in the GPe were similar in the PD and dystonia patients (Starr et al., 2005; Tang et al., 2007). Thus small changes in discharge rates in the GPe may lead to pronounced changes in discharge rates in the GPi. This may stem from the converging nature of the basal ganglia; i.e., the gradual reduction of the neuron population between the striatum, GPe and the output structures of the basal ganglia (Goldberg and Bergman, 2011).

General anesthesia with isoflurane depresses firing in both pallidal segments in dystonia. This is congruent with previous work reporting a depressed firing rate in the GPi or STN under anesthesia (Hutchison et al., 2003; Moll et al., 2014; Raz et al., 2010) and contrasts with the unchanged firing rates in the STN found by others (Kim et al., 2014; Lettieri et al., 2012). This difference might be related to the anesthesia protocol, the site of recordings or the strict selection of the units included in the analysis. In any

case this state enabled us to test the relationship between GPe and GPi firing rates while dissociating dopaminergic state and discharge rates.

We found that for each of the conditions, increased firing rates in the GPe were associated with increased firing rates in the GPi, and vice versa for decreased discharge rates. This finding conflicts with the prediction of the classical model and is even more striking given recent discoveries regarding the direct GPe to GPi strong inhibitory GABAergic input (Hazrati et al., 1990; Sato et al., 2000). Since we did not use electroencephalograms to monitor the level of arousal of the patients, we can only speculate that this finding may reflect the effect of different arousal states during recording. This speculation is based on our finding of decreased firing rates in both pallidal nuclei under general anesthesia, and on previously demonstrated decreased firing rates in both segments of the pallidum in non-human primates with decreased arousal levels (Adler et al., 2010).

The main finding is that the firing rate ratio GPi/GPe was not affected by the discharge rates in the GPe but rather was determined by the type of disease. Importantly, this ratio was not affected by differences in the discharge pattern (burstiness and oscillations) between the awake and anesthetized states (see supplementary analysis). Based on these results we suggest that the firing rates in the GPe and in the GPi are modulated by two apparently independent processes (Fig. 4). The first is dopamine deficiency that changes the ratio between the GPi and GPe firing rates (probably by increasing the GPi discharge rate with no major change in GPe), and the second is anesthesia (possibly the arousal state) that modulates the firing rates in both of these nuclei without changing the ratio between their discharge rates. Testing this hypothesis in PD patients under general anesthesia is crucial to proving this hypothesis. However, we did not have access to such data.

Our findings may suggest a more complex view of the basal ganglia network, where the striatum and the STN constitute the input stage of the basal ganglia, and the activity of the GPi (output stage) is affected by the projections from the GPe, STN and striatum (Goldberg and Bergman, 2011). Arousal level, as well as dopamine level, affects the different components of this network, leading to the complementary effects of arousal and dopamine on the discharge rate of pallidal neurons.

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Figures

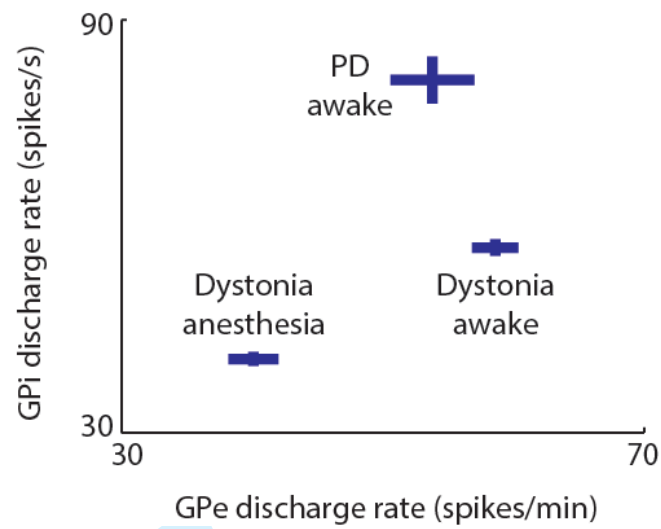


Fig. 1. Summary of mean GPe and GPi firing rates. Mean firing rates over the entire recorded data (center of cross) and S.E.M for each of the three states.

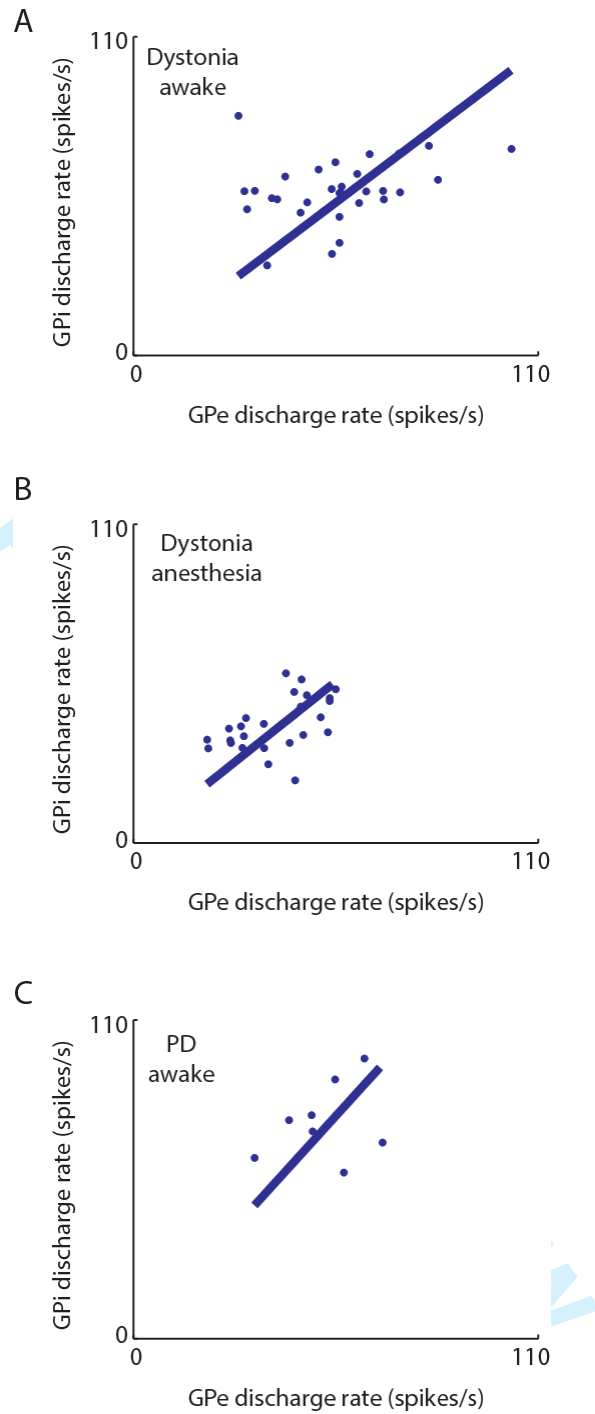


Fig. 2. Relationships between ipsi-lateral GPe and GPi firing rates. (A-C) For each state the mean firing rate in the GPi is plotted against the mean firing rate of the ipsi-lateral GPe in the same individual. Fitted least-squares line is plotted for each of the conditions.

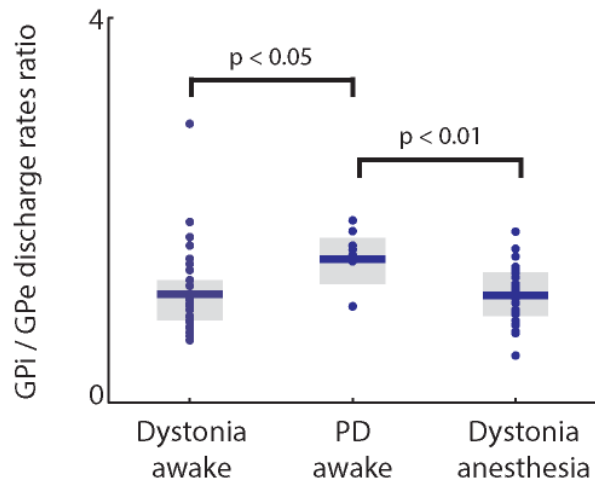


Fig. 3. GPe-GPi firing ratio. Ratio of mean firing rates of ipsilateral GPe-GPi pairs. For each condition the horizontal line represents the mean and the gray box delineates the 25th to 75th percentiles.

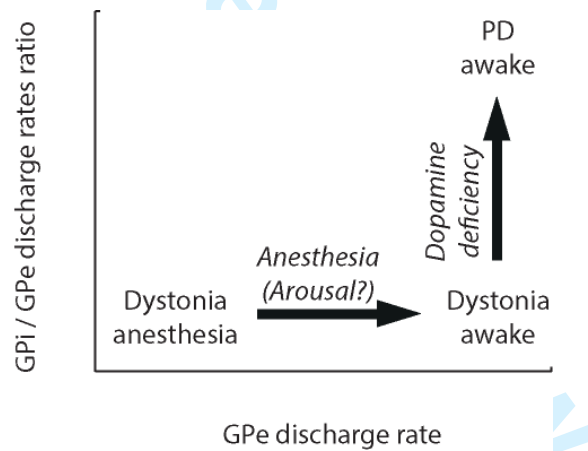
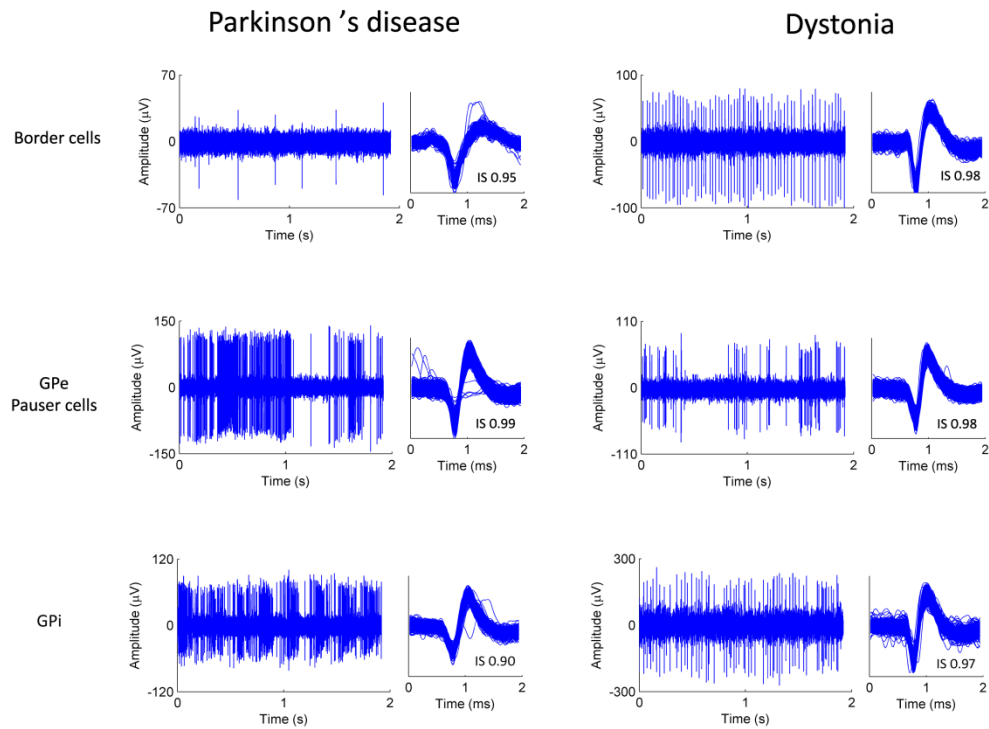


Fig. 4. Effects of dopamine depletion and anesthesia on the GPe and GPi discharge rate. A schematic representation of the two independent processes that shape the firing rates of the GPe and the GPi - dopamine state and arousal.



Supplementary Fig. 1. Spike trains and waveforms. An example of 2 seconds of raw recording and the aligned spike wave forms of different neuron types in Parkinson's disease and dystonia. The isolation score (IS) of each neuron is shown.

Supplementary Tables

Supplementary Table 1. Patients' demographic data in the three recording states

	Dystonia- awake	Dystonia - anesthesia	PD - awake
Gender (M / F)	6 / 13	8 / 12	2 / 4
Age at onset	23.3 ± 3.5	12.8 ± 2.8	50.0 ± 1.9
Age at surgery	37.7 ± 3.6	26.1 ± 3.5	62.5 ± 3.7
Disease duration	14.4 ± 2.7	13.5 ± 2.3	18.0 ± 1.9

Note that age of onset, age at surgery and disease duration are given in years (mean ± SEM).

Supplementary Table 2 - Neuronal database.

	Dystonia - awake	Dystonia - anesthesia	PD - awake
<i>GPe</i>			
Trajectories	49	48	16
Sites	1269	1242	426
Neurons with $IS \geq 0.7$	222	244	79
<i>GPi</i>			
Trajectories	57	53	16
Sites	2537	2294	662
Neurons with $IS \geq 0.7$	415	537	63

Number of trajectories, recording sites, and neurons with an isolation score (IS) > 0.7 sorted by neuron type and recording state.

Supplementary Analysis

ISI CV: The discharge rate and coefficient of variation of the inter-spike intervals (ISI CV, standard deviation/mean) is a measure of the discharge pattern (regularity, Poisson like, bursting) of spiking activity. There were no significant differences in the ISI CV between awake patients with dystonia and PD in the GPe (1.44 ± 0.05 and 1.25 ± 0.05 respectively) or the GPi (1.08 ± 0.02 and 1.06 ± 0.07 respectively). Under general anesthesia the ISI CV was significantly higher both in the GPe (1.7 ± 0.1 , $p < 0.001$) and the GPi (1.2 ± 0.02 , $p < 0.001$), indicating more bursty spiking activity under general anesthesia in both segments. In all conditions, the ISI CV was significantly higher in the GPe than in GPi ($p < 0.001$) and probably reflected the presence of pauses in the GPe.

Power spectral density (PSD): To calculate the power spectral density (PSD) of the population spiking activity, a Z-score normalization was performed on the stable selected sections. The z-normalized signal was rectified by an absolute 'operator' to enable detection of periodic oscillations with an oscillation frequency below the operating room high-passed filter (250 Hz) (Zaidel et al., 2010). The PSD was calculated using the Welch method with a Hamming window of 1.5 seconds (50% overlap) and a spectral resolution of 1/3 Hz (Deffains et al., 2014). All DC components were removed by subtracting the mean of every windowed segment of the rectified signal.

PSD was performed on 1269, 2537 and 426, 662 multiunit activity traces in GPe and GPi of awake dystonic and awake PD patients respectively. PSD in awake dystonia patients showed a peak in the low frequency (5-10 Hz) in both GPe and GPi. In awake PD patients, PSD showed a peak in the low beta frequency (around 15 Hz) in both GPe and GPi. A 5Hz peak was also found in 5 trajectories in patients with PD and resting tremor. In contrast to the awake state, PSD analysis on 1242 and 2294 GPe and GPi multiunit traces in dystonic patients under general anesthesia did not show any peaks, either in the GPe or in the GPi. The PSD of single unit activity (with an isolation score > 0.7) was also calculated and was similar to that of the multiunit activity.

Coherence analysis: We calculated the coherence between the stable segments of the background multi-unit spiking activity and the activity of single units. To clean the trace of multi-unit activity from the dominant spikes, we removed the spikes detected by the offline sorter and replaced them with a 2 ms trace taken from the middle of the closest spike free segment exceeding 10 ms (Moran et al., 2008). The background clean multi-unit activity was rectified by an absolute operator and the single unit activity was low-passed filtered (cut-off frequency 40 Hz) to obtain a rate-like function of the single unit. The coherence was calculated using a 1.5 second Hamming window (50% overlap) and a spectral resolution of 1/3 Hz. Frequencies below 3 Hz were removed to avoid possible physiological artefacts (i.e. cardiac activity or respiration). The coherence of each pairs was smoothed and z-transformed, averaged and then back-transformed to calculate the mean coherence in each target.

A coherence analysis of the background activity and single unit activity was conducted for 218 and 73 GPe pairs in awake dystonic and awake PD patients, respectively. No coherence peaks were found in dystonia whereas in PD there was a possible indication of a peak around 15Hz. The same analysis was also conducted for 413 and 62 pairs in the GPi of dystonia and PD patients, respectively. This analysis suggested there may have been two peaks at low frequency (5-10Hz) in the GPi but only in PD.