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Single Unit “Pauser” Characteristics of the Globus Pallidus Pars Externa Distinguish Primary Dystonia from Secondary Dystonia and Parkinson's Disease

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Abstract

The presence of high frequency discharge neurons with long periods of silence or “pauses” in the globus pallidus pars externa (GPe) are a unique identifying feature of this nucleus. Prior studies have demonstrated that pause characteristics reflect synaptic inputs into GPe. We hypothesized that GPe pause characteristics should distinguish movement disorders whose basal ganglia network abnormalities are different. We examined pause characteristics in 224 GPe units in patients with primary generalized dystonia, Parkinson's disease (PD), and secondary dystonia, undergoing single unit microelectrode recording for DBS placement in the awake state. Pauses in neuronal discharge were identified using the Poisson surprise method. Mean pause length in primary dystonia (606.8 ± 373.3) was higher than in PD (557.4 ± 366.6) ($p < 0.05$). Interpause interval (IPI) was lower in primary dystonia (2331.6 ± 3874.1) than PD (3646.4 ± 5894.5) ($p < 0.01$), and mean pause frequency was higher in primary dystonia (0.14 ± 0.10) than PD (0.07 ± 0.12) ($p < 0.01$). Comparison of pause characteristics in primary versus secondary generalized dystonia revealed a significantly longer mean pause length in primary (606.8 ± 373.3) than in secondary dystonia (495.6 ± 236.5) ($p < 0.01$). IPI was shorter in primary (2331.6 ± 3874.1) than in secondary dystonia (3484.5 ± 3981.6) ($p < 0.01$). The results show that pause characteristics recorded in the awake human GPe distinguish primary dystonia from Parkinson's disease and secondary dystonia. The differences may reflect increased phasic input from striatal D2 receptor positive cells in primary dystonia, and are consistent with a recent model proposing that GPe provides capacity scaling for cortical input.

Keywords

Dystonia; Parkinson's disease; neuronal pauses; globus pallidus; microelectrode recording

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Introduction

Dystonia is a syndrome characterized by sustained muscle contractions leading to abnormal postures and twisting movements. It is believed to arise from abnormal function of the cortex-basal ganglia-thalamus-cortex loop circuitry (Marsden, et al., 1985, Vitek, et al., 1999). Dystonia has often been considered a “hyperkinetic” disorder, in contrast to the prototypic hypokinetic disorder, Parkinson's disease (Vitek, 2002). Dystonia can be classified as “primary” when there are no other neurological abnormalities, no structural brain abnormalities by MRI, and no obvious etiology; otherwise it is classified as “secondary” to a recognized brain lesion. Previous work on basal ganglia single unit discharge characteristics in human dystonia have focused on the major output nucleus, the internal segment of the globus pallidus (GPi) (Hutchison, et al., 2003, Lenz, et al., 1998, Merello, et al., 2004, Sanghera, et al., 2003, Starr, et al., 2005, Tang, et al., 2005, Vitek, 2002, Vitek, et al., 1999). Mean spontaneous GPi discharge rate distinguishes primary dystonia from PD. GPi spontaneous activity in dystonia shows bursting and oscillations which are similar to those seen in Parkinson's disease. Less attention has been paid to the external segment of the globus pallidus, (GPe) but several authors have shown that mean rate, oscillatory activity, and bursting activity in GPe do not distinguish dystonia from PD (Sanghera, et al., 2003, Starr, et al., 2005).

Several recent findings motivated us to perform a more detailed examination of GPe physiology in movement disorders. In both the normal nonhuman primate (NHP) (DeLong, 1971) and humans with PD (Vitek, et al., 1998), the majority of neurons in this nucleus have a high frequency discharge rate intervened by long periods of silence or pause, and are thus termed “pausers”. Elias *et al.* (Elias, et al., 2007), in an extensive analysis of pauser activity in normal NHPs, provided strong evidence indicating that the pauses arise from “network” properties of the basal ganglia, e.g. they are related to synaptic influences on GPe neurons, rather than to intrinsic GPe neuronal membrane properties. This finding predicts that evaluation of pause characteristics (pause length, frequency, and interpause interval) should be useful in distinguishing between movement disorders with differing network abnormalities. Further, recent models of basal ganglia function have redefined GPe in a more central role in basal ganglia processing compared to earlier models, that of “capacity scaling” of cortical inputs (Gurney, et al., 2001) rather than a simple relay on the indirect pathway. However, no prior work on GPe discharge in human movement disorders has focused on pause characteristics. Primary and secondary dystonias differ in their response to pallidal surgery (pallidal DBS and pallidotomy) (Eltahawy, et al., 2004). This dichotomy predicts differing network abnormalities in the two dystonia subtypes, which might potentially be illuminated by study of their GPe pause characteristics.

The purpose of the current study was to compare pause parameters in the GPe between primary generalized dystonia, secondary generalized dystonia, and PD, in patients undergoing physiological mapping for placement of deep brain stimulators. We analyzed the spontaneous activity of 175 GPe neurons sampled from 18 patients with dystonia, and 49 neurons from 7 patients with PD. Identical recording and analysis methods were used for all subjects. No systemic anesthetics or sedatives were used during recordings. We tested the following hypotheses: (1) GPe pauser characteristics distinguish primary dystonia from PD; and (2) GPe pauser characteristics distinguish primary dystonia from secondary dystonia.

Material and Methods

Patient population

Single-unit recording in GPe was performed in awake patients undergoing physiologic mapping for placement of GPi DBS electrodes. Patients in three disease groups were included: Primary generalized dystonia, secondary dystonia (generalized), and Parkinson's disease.

Patients with focal or segmental dystonias, and patients with tardive dystonia, were excluded. All subjects gave informed consent according to a protocol approved by the Institutional Review Board and all research related activities were performed in compliance with national legislation and the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association. Patients were excluded from this study if physiological mapping had to be performed with general anesthesia or intravenous sedation. A quantitative measure of dystonia severity was obtained in the month prior to surgery, using a standard clinical rating scale, the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) (Burke, et al., 1985), by a movement disorders neurologist (JLO). Division between primary versus secondary dystonia groups were made based on absence or presence of an identifiable etiology in the clinical history, and/or presence of an anatomic abnormality on magnetic resonance imaging (MRI) of the brain consistent with secondary dystonia. All juvenile-onset dystonia patients had genetic testing for the presence of a mutation at the DYT-1 locus (Ozelius LJ, 1997). For some analyses, primary dystonia patients were subdivided into three groups: Juvenile onset dystonia positive for the DYT1 mutation, juvenile onset dystonia negative for the DYT1 mutation, and adult onset dystonia. Patients undergoing pallidal DBS implantation for PD were rated preoperatively with the motor scale (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS), in the off medication state. Anti-dystonia or antiparkinsonian medications were not given during surgery or in the 12 hours prior to surgery.

Surgical procedures and data recording

Procedures for pallidal localization and electrophysiology were similar to those documented in recent publications (Lozano, et al., 1996, Starr, 2003, Starr, et al., 2006, Vitek, et al., 1998). Most patients required sedation with propofol for placement of the stereotactic headframe and stereotactic MRI, due to involuntary muscle spasms. All patients, including PD patients, received propofol for placement of a foley catheter immediately prior to surgery and for the surgical incision. In all cases, propofol was stopped 30 min prior to the start of pallidal recording, and the total dose of propofol given did not exceed 200 mg. All patients were alert and oriented at the start of microelectrode recording. Patients were instructed to keep their eyes open but make no voluntary movements during the recording. Some patients with dystonia at rest did experience spontaneous dystonic spasms during the recording.

Single-unit discharge was recorded with glass-coated platinum/iridium microelectrodes, impedance 0.4 –1.0 M Ω at 1000 Hz (Microprobe, Gaithersburg, MD, or FHC, Brunswick, ME). Recordings were filtered (300 Hz to 5 kHz), amplified, played on an audio monitor, and digitized (20-kHz sampling rate) using the Guideline System 3000 (Axon Instruments, Foster City, CA, now distributed by FHC). Microelectrodes were advanced into the brain using a motorized microdrive (Axon Instruments clinical micropositioner or FHC microdrive). In a typical surgical case, one to two parallel parasagittal microelectrode penetrations were made serially through GPe and GPi on each side, separated by 2–3 mm, in one to two parasagittal planes. The optic tract (OT) was detected by light-evoked action potential discharge at the pallidal base. Cells were recorded at approximately every 300–800 μ m along each trajectory. Neuronal activity was collected for a minimum of 20s. Prior to recording, subjects were asked to remain as still as possible during these periods of recording. The location and discharge characteristics of cells along each microelectrode track were plotted on scaled drawings, noting also the locations of white matter laminae and the OT. The tracks were superimposed on drawings of parasagittal sections from the Schaltenbrand and Warren human brain atlas, according to a visual judgment of “best fit” of the tracks to the atlas. Cells encountered between the striatum and the internal medullary lamina were considered external pallidal cells. Cells near the presumed GPe-GPi border, on a track where a definite white matter boundary was not identified, were excluded from analysis due to their uncertain localization.

Analysis of spontaneous activity

Digitized spike trains were imported into off-line spike sorting software (Plexon) for discrimination of single populations of action potentials by principal components analysis. This software generated a record of spike times (subsequently reduced to millisecond accuracy) for each action potential waveform detected. The interspike intervals (ISIs) between successive spike times were used to evaluate the data stream for occurrence of pauses and calculation of pause parameters (see following text). Analyses were performed in Matlab. Neuronal data were included in this study only if action potentials could be discriminated with a high degree of certainty (ISI histogram showed a clear refractory period), if the number of recorded action potentials were >800, and if the spontaneous activity of the neuron was recorded for >20 seconds.

Detection of pauses

We utilized the “Poisson surprise” method to detect periods with very low or zero spike activity based on the detailed description provided by Elias *et al.* (Elias, et al., 2007). The surprise algorithm detects how unlikely it is (surprise value) to find an ISI with a duration that is significantly higher than the mean ISI of that recording. The advantage of using the surprise method, however, is that adjacent very long duration ISIs separated by only one spike can be merged as a single pause, and additional ISIs can be added as long as the surprise value increases up to a set limit.

The algorithm consists of three steps. First, the program searches for an ISI that is longer than a “core interval” of 250ms. Second, it tests whether adding additional ISIs before or after the core interval increases the surprise (S) value which is calculated as:

$$S = -\log P(n)$$

$P(n)$ is the probability of finding n spikes or less in a time interval of T (ms) and is calculated as:

$$P(n) = e^{-rT} \sum_{i=0}^n (rT)^i / i!$$

The probability is based on a Poisson distribution. r is the probability of finding a spike in a 1ms bin and is calculated from the mean firing rate of the cell. The minimum surprise value is 5. If the value of P increases, the ISI is added and included in the pause. The process is repeated until a limit of 5 ISIs is reached before and after the core interval. If the final pause has a minimum length of 300ms it is considered a pause, otherwise it is rejected and the process is repeated at the next ISI. Lastly, if two pauses are separated by no more than three spikes (including the spike at the end of the first pause and beginning of the next one) they are merged as one pause. A neuron was categorized as a pauser if the Poisson analysis showed at least one pause, otherwise it was categorized as a non-pauser. The interpause interval (IPI) was calculated as the time (ms) between the end of a pause and start of the following pause. Pause frequency for an individual neuron was calculated by the total number of pauses divided by the recording time in seconds. In calculating grouped means of IPI, pause frequency, and pause length for each disease category, nonpauser neurons were excluded.

Statistical analysis

We tested the hypothesis that mean pause length, IPI, and pause frequency differed in patients with dystonia, dystonia subtypes, and PD, using the Wilcoxon Rank-sum test.

Results

Patients

Thirteen primary generalized dystonia patients, 5 secondary dystonia patients, and 7 PD patients were included in the study. Characteristics of dystonia patients are provided in Table 1. For the 7 PD patients, the mean ($\pm$ standard deviation) UPDRS-III off medication score was 45($\pm$ 4.8) and the mean duration of symptoms was 15.6 ($\pm$ 5.8) years.

Firing characteristics of a typical GPe pauser neuron (from a patient with primary generalized dystonia) are shown in Figure 1. Group statistics for neuronal firing rates, percentage of pauser neurons, and pause characteristics are presented in Table 2. There were 117, 58, and 49 GPe neurons recorded in primary dystonia, secondary dystonia, and PD patients, respectively. The mean recording time was 35.2 $\pm$ 15.3 (sec $\pm$ SD). The relatively short recording times (compared to GPe recordings in nonhuman primates (Elias, et al., 2007) reflects the intra-operative time limitations during awake human surgery. The percentage of GPe units categorized as pausers was 51.3, 36.21, and 61.22 for primary dystonia, secondary dystonia, and PD, respectively.

We first compared pause characteristics for all dystonia patients compared to PD. This showed a shorter interpause interval in all dystonia (2672.6 $\pm$ 4312.5) than in PD (3646.4 $\pm$ 5894.5) ($p<0.01$). Pause frequency was also higher in all dystonia (0.20 $\pm$ 0.21) than PD (0.07 $\pm$ 0.12) ($p<0.05$). Based on the hypothesis that primary dystonia and secondary dystonia differ in their pathophysiology, all subsequent analyses treated primary and secondary dystonia as separate groups. Mean pause length in primary dystonia (606.8 $\pm$ 373.3) was higher than in PD (557.4 $\pm$ 366.6) ($p<0.05$) (Table 2). IPI was lower in primary dystonia (2331.6 $\pm$ 3874.1) than PD (3646.4 $\pm$ 5894.5) ($p<0.01$) (Table 2)). Mean pause frequency was higher in primary dystonia (0.14 $\pm$ 0.10) than PD (0.07 $\pm$ 0.12) ($p<0.01$).

Comparison of pause characteristics in primary versus secondary generalized dystonia revealed a significantly longer mean pause length in primary (606.8 $\pm$ 373.3) than in secondary (495.6 $\pm$ 236.5) dystonia ($p<0.01$) (figure 2A). IPI was shorter in primary (2331.6 $\pm$ 3874.1) than in secondary (3484.5 $\pm$ 3981.6) dystonia ($p<0.01$) (figure 2B). We also examined pause characteristics of the DYT1+ subtype alone, as this represents the most homogeneous population of dystonia patients. This subtype reflected similar pause characteristics as the dystonia population as a whole, with pause length of 649.5 $\pm$ 416.6 ($p<0.01$ vs PD, $p<0.01$ vs secondary dystonia), IPI 2154.2 $\pm$ 2860.9 ($p<0.01$ vs PD, $p<0.01$ versus secondary dystonia), and mean pause frequency 0.17 $\pm$ 0.25 ($p<0.01$ vs PD, $p=0.07$ vs secondary dystonia).

Discussion

Here, we studied the characteristics of pauses in the spontaneous discharge of GPe neurons, in humans with three types of movement disorders. We found that in primary dystonia, pauses occur at a higher frequency, have longer lengths, and exhibit shorter interpause intervals when compared to secondary dystonia or PD. When primary and secondary dystonia patients are grouped together, differences between dystonia and PD become less significant than when comparing primary dystonia to PD. Prior studies have examined GPe neuronal discharge in dystonia and PD in terms mean firing rate, bursting, and oscillatory activity, but showed no differences in these parameters (Sanghera, et al., 2003, Starr, et al., 2005).

Pauses are highly characteristic of GPe discharge and were first described by DeLong *et al.* (DeLong, 1971) in the normal NHPs. Elias *et al.* (Elias, et al., 2007) defined objective statistical criteria for pause identification in normal NHPs. They showed that GPe pausing behavior is likely to reflect properties of the basal ganglia network (synaptic input into GPe), rather than membrane properties of the GPi cells. This view is supported by intracellular recordings of dissociated GPe neurons in culture, which do not show spontaneous pauses (Cooper and Stanford, 2000, Kita and Kitai, 1991, Nambu and Llinas, 1994). Based on this, movement disorders that reflect different basal ganglia network properties might be expected to show differences in pause characteristics.

The GPe receives its major input from D2 receptor positive (D2⁺) striatal medium spiny neurons (gabaergic) and from the subthalamic nucleus (glutamatergic) (Kita and Kita, 2001, Kita and Kitai, 1991, Parent and Hazrati, 1995). Pauses are thought to be generated at striato-GPe synapses from prolonged inhibitory post-synaptic potentials that are mediated by GABA_B metabotropic receptor activation (Chan, et al., 2004, Kaneda and Kita, 2005, Stefani, et al., 1999). Repetitive stimulation of the striatal GABA afferents in the rat have been shown to induce pauses of 200 to 500 msec duration (Kaneda and Kita, 2005). Thus, the increased pause duration and frequency in GPe in primary dystonia may reflect increased phasic input from striatal D2⁺ cells. This is consistent with functional imaging studies of primary generalized dystonia that have shown resting state striatal hypermetabolism (Eidelberg, et al., 1998) as well as decreased striatal binding of dopamine agonists at the inhibitory D2 receptor (Asanuma, et al., 2005).

Gurney *et al.* (Gurney, et al., 2001) have proposed an “action-selection” model of basal ganglia circuitry which envisions GPe in a new role compared to prior rate models (Albin, et al., 1989, DeLong, 1990) and “focused competition” models (Mink, 1996). In their model, the direct pathway selects motor programs according to the strength or “saliency” of cortical input into the striatum, while the “hyperdirect” pathway (monosynaptic cortical or thalamic input into STN) provides surround inhibition. The GPe serves the purpose of “capacity scaling”, that is adjusting the gain in the surround inhibition based on the number or strength of cortical inputs into the basal ganglia. In the resting state, primary dystonia and PD have opposite changes in the cortical metabolic activity in comparison with normals (Asanuma, et al., 2005, Huang, et al., 2007). Since this would require different degrees of capacity scaling by GPe, it is surprising that prior studies have found no difference in neuronal discharge parameters of GPe in the two disorders (Sanghera, et al., 2003, Starr, et al., 2005). This discrepancy may in part be resolved by our finding that pause characteristics distinguish generalized dystonia from PD. The increased frequency and duration of pauses in the dystonic GPe could reflect a “capacity scaling” compensation for cortical hypermetabolism, as the pauses would tend to disinhibit STN, increasing the degree of surround inhibition. Given the short duration of the pause, this capacity scaling adjustment would be brief. Although the action selection model described by Gurney *et al.* (Gurney, et al., 2001) does not distinguish “tonic” versus “phasic” demands for adjustment in capacity scaling, it is plausible that such brief changes in scaling of the surround inhibition could be important during transitions between different motor programs or between rest and activity. In support of this concept, in normal nonhuman primates, pause characteristics are indeed affected by the animal's motor behavior (Elias, et al., 2007).

Primary and secondary dystonia can be expected to have a different pathophysiology, based on their different responses to basal ganglia surgical interventions (Eltahawy, et al., 2004, Vercueil, et al., 2001). Some secondary dystonias may be associated with cortical hypometabolism, rather than the hypermetabolism seen in primary dystonias (Kerrigan, et al., 1991). Further, the syndromes are not clinically identical: fixed dystonic postures are more characteristic of secondary dystonia than primary dystonia. Our analysis of pause

characteristics does indicate differing network abnormalities in these dystonia subtypes. GPe pause characteristics in secondary dystonia resemble those in PD more than those in primary dystonia. Neuronal firing in other basal ganglia nuclei, however, clearly distinguish PD from secondary dystonia: spontaneous discharge rate in the internal pallidum is much greater in the former (Starr, et al., 2005).

The presented study bears some limitations. First, the neuronal recording times were relatively short, as is necessary in invasive studies of awake humans. Longer recordings might have allowed for study of a larger number of pauses, and allowed for characterization of larger percentage of recorded units as pausers. Second, our usual surgical approach to the posteroventral internal pallidum is 5 to 15 degrees from vertical in the coronal projection. This trajectory may have placed the microelectrode at the border of the GPe motor territory area, or not within the motor territory at all. If recordings had been confined to the GPe motor area (ventrolateral posterior region in the non-human primate) (Grabli, et al., 2004), the differences between our studied movement disorder groups may have been accentuated.

Conclusion

Pause characteristics recorded in the awake human GPe distinguish primary generalized dystonia from Parkinson's disease and secondary dystonia. This suggests differing basal ganglia network abnormalities in these conditions, likely related to GPe inputs from striatal medium spiny neurons.

References

1. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends in Neurosciences* 1989;12:366–375. [PubMed: 2479133]
2. Asanuma K, Carbon-Correll M, Eidelberg D. Neuroimaging in human dystonia. *J Med Invest* 2005;52 (Suppl):272–279. [PubMed: 16366514]
3. Asanuma K, Ma Y, Okulski J, Dhawan V, Chaly T, Carbon M, Bressman SB, Eidelberg D. Decreased striatal D2 receptor binding in non-manifesting carriers of the DYT1 dystonia mutation. *Neurology* 2005;64:347–349. [PubMed: 15668438]
4. Burke RE, Fahn S, Marsden D, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. *Neurology* 1985;35:73–77. [PubMed: 3966004]
5. Chan CS, Shigemoto R, Mercer JN, Surmeier DJ. HCN2 and HCN1 channels govern the regularity of autonomous pacemaking and synaptic resetting in globus pallidus neurons. *J Neurosci* 2004;24:9921–9932. [PubMed: 15525777]
6. Cooper AJ, Stanford IM. Electrophysiological and morphological characteristics of three subtypes of rat globus pallidus neurone in vitro. *J Physiol* 2000;527(Pt 2):291–304. [PubMed: 10970430]
7. DeLong MR. Activity of pallidal neurons during movement. *J Neurophys* 1971;34:414–427.
8. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends in Neurosci* 1990;13:281–285.
9. Eidelberg D, Moeller JR, Antonini A, Kazumata K, Nakamura T, Dhawan V, Spetsieris P, deLeon D, Bressman SB, Fahn S. Functional brain networks in DYT1 dystonia. *Ann Neurol* 1998;44:303–312. [PubMed: 9749595]
10. Elias S, Joshua M, Goldberg JA, Heimer G, Arkadir D, Morris G, Bergman H. Statistical properties of pauses of the high-frequency discharge neurons in the external segment of the globus pallidus. *J Neurosci* 2007;27:2525–2538. [PubMed: 17344390]
11. Eltahawy HA, Saint-Cyr J, Giladi N, Lang AE, Lozano AM. Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation. *Neurosurgery* 2004;54:613–619. [PubMed: 15028135]discussion 619–621
12. Grabli D, McCairn K, Hirsch EC, Agid Y, Feger J, Francois C, Tremblay L. Behavioural disorders induced by external globus pallidus dysfunction in primates: I. Behavioural study. *Brain* 2004;127:2039–2054. [PubMed: 15292053]

13. Gurney K, Prescott TJ, Redgrave P. A computational model of action selection in the basal ganglia. I. A new functional anatomy. *Biol Cybern* 2001;84:401–410. [PubMed: 11417052]
14. Huang C, Tang C, Feigin A, Lesser M, Ma Y, Pourfar M, Dhawan V, Eidelberg D. Changes in network activity with the progression of Parkinson's disease. *Brain* 2007;130:1834–1846. [PubMed: 17470495]
15. Hutchison WD, Lang AE, Dostrovsky JO, Lozano AM. Pallidal neuronal activity: Implications for models of dystonia. *Ann Neurology* 2003;53:480–488.
16. Kaneda K, Kita H. Synaptically released GABA activates both pre- and postsynaptic GABA(B) receptors in the rat globus pallidus. *J Neurophysiol* 2005;94:1104–1114. [PubMed: 16061489]
17. Kerrigan JF, Chugani HT, Phelps ME. Regional cerebral glucose metabolism in clinical subtypes of cerebral palsy. *Pediatr Neurol* 1991;7:415–425. [PubMed: 1797007]
18. Kita H, Kita T. Number, origins, and chemical types of rat pallidostriatal projection neurons. *J Comp Neurol* 2001;437:438–448. [PubMed: 11503145]
19. Kita H, Kitai ST. Intracellular study of rat globus pallidus neurons: membrane properties and responses to neostriatal, subthalamic and nigral stimulation. *Brain Res* 1991;564:296–305. [PubMed: 1810628]
20. Lenz FA, Suarez JI, Metman LV, Reich SG, Karp BI, Hallett M, Rowland LH, Dougherty PM. Pallidal activity during dystonia: somatosensory reorganisation and changes with severity. *J Neurol Neurosurg Psychiatry* 1998;65:767–770. [PubMed: 9810954]
21. Lozano A, Hutchison W, Kiss Z, Tasker R, Davis K, Dostrovsky J. Methods for microelectrode-guided posteroventral pallidotomy. *J Neurosurg* 1996;84:194–202. [PubMed: 8592221]
22. Marsden CD, Obeso JA, Zarranz JJ, Lang AE. The anatomic basis of symptomatic dystonia. *Brain* 1985;108:463–483. [PubMed: 4005532]
23. Merello M, Cerquetti D, Cammarota A, Tenca E, Artes C, Antico J, Leiguarda R. Neuronal globus pallidus activity in patients with generalized dystonia. *Mov Disord* 2004;19:548–554. [PubMed: 15133819]
24. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol* 1996;50:381–425. [PubMed: 9004351]
25. Nambu A, Llinas R. Electrophysiology of globus pallidus neurons in vitro. *J Neurophysiol* 1994;72:1127–1139. [PubMed: 7807199]
26. Ozelius LJ, H J, Page CE, Bressman SB, Kramer PL, Shalish C, de Leon D, Brin MF, Raymond D, Corey DP, Fahn S, Risch NJ, Buckler AJ, Gusella JF, Breakefield XO. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. *Nat Genet* 1997;17:40–48. [PubMed: 9288096]
27. Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. *Brain Res Brain Res Rev* 1995;20:128–154. [PubMed: 7711765]
28. Sanghera MK, Grossman RG, Kalhorn CG, Hamilton WJ, Ondo WG, Jankovic J. Basal ganglia neuronal discharge in primary and secondary dystonia in patients undergoing pallidotomy. *Neurosurgery* 2003;52:1358–1370. [PubMed: 12762881]discussion 1370-1353
29. Sanghera MK, Grossman RG, Kalhorn CG, Hamilton WJ, Ondo WG, Jankovic J. Basal ganglia neuronal discharge in primary and secondary dystonia in patients undergoing pallidotomy. *Neurosurgery* 2003;52:1358–1373. [PubMed: 12762881]
30. Starr PA. Placement of deep brain stimulators into the subthalamic nucleus or globus pallidus internus: technical approach. *Stereotact Funct Neurosurg* 2003;79:118–145. [PubMed: 12890973]
31. Starr PA, Rau GM, Davis V, Marks WJ Jr, Ostrem JL, Simmons D, Lindsey N, Turner RS. Spontaneous pallidal neuronal activity in human dystonia: comparison with Parkinson's disease and normal macaque. *J Neurophysiol* 2005;93:3165–3176. [PubMed: 15703229]
32. Starr PA, Turner RS, Rau G, Lindsey N, Heath S, Volz M, Ostrem JL, Marks WJ Jr. Microelectrode-guided implantation of deep brain stimulators into the globus pallidus internus for dystonia: techniques, electrode locations, and outcomes. *J Neurosurg* 2006;104:488–501. [PubMed: 16619651]

33. Stefani A, Spadoni F, Giacomini P, Lavaroni F, Bernardi G. The modulation of calcium current by GABA metabotropic receptors in a sub-population of pallidal neurons. *Eur J Neurosci* 1999;11:3995–4005. [PubMed: 10583488]
34. Tang JK, Moro E, Lozano AM, Lang AE, Hutchison WD, Mahant N, Dostrovsky JO. Firing rates of pallidal neurons are similar in Huntington's and Parkinson's disease patients. *Exp Brain Res* 2005;166:230–236. [PubMed: 16082534]
35. Vercueil L, Pollak P, Fraix V, Caputo E, Moro E, Benazzouz A, Xie J, Koudsie A, Benabid AL. Deep brain stimulation in the treatment of severe dystonia. *J Neurol* 2001;248:695–700. [PubMed: 11569899]
36. Vitek JL. Pathophysiology of dystonia: a neuronal model. *Mov Disord* 2002;17:S69–72. [PubMed: 11948757]
37. Vitek JL, Bakay RAE, Hashimoto T, Kaneoke Y, Mewes K, Zhang J, Rye D, Starr P, Baron M, Turner R, DeLong MR. Microelectrode-guided pallidotomy: Technical approach and application for medically intractable Parkinson's disease. *J Neurosurg* 1998;88:1027–1043. [PubMed: 9609298]
38. Vitek JL, Chockkan V, Zhang JY, Kaneoke Y, Evatt M, DeLong MR, Triche S, Mewes K, Hashimoto T, Bakay RAE. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. *Ann Neurol* 1999;46:22–35. [PubMed: 10401777]

Figure 1.

Single unit activity from a GPe pauser neuron in a patient with primary generalized dystonia. A, Sample recording length of 2 seconds. B, Raster diagram for the same neuron. Consecutive rows (5 seconds of data per row) from bottom to top represent a continuous 50 second recording. C, Interspike interval histogram of the same neuron, bin size of 1 msec. Inset shows the expanded timescale demonstrating no interspike intervals of less than 2 msec duration. Abbreviations used: ISI = interspike interval;

Table 1
Clinical characteristics of primary and secondary generalized dystonia patients.

Dystonia Subtype	Case #	Disease subtype	Body parts affected	Duration of symptoms (years)	Baseline BFMDRS-m	Preoperative medication (total per day in mg)
Primary	1	Juv DYT1 ⁺	M, N, A, T, L	9	51.5	trihexyphenidyl (80), clonazepam (1)
	2	Juv DYT1 ⁺	M, N, A, T, L	9	48.5	baclofen (60), baclofen pump (148)
	3	Juv DYT1 ⁺	S, A, T, L	22	74	trihexyphenidyl (70), diazepam (100), baclofen (80)
	4	Juv DYT1 ⁺	N, A, T	33	17	gabapentin (2400)
	5	Juv DYT1 ⁺	M, S, N, A, T, L	15	62.5	trihexyphenidyl (16), clonazepam (8)
	6	Adult Idio	E, M, N, A	3	28	lorazepam (8), hydrocortone (30)
	7	Adult Idio	S, N, A, T	13	41	baclofen (60), gabapentin (900), propranolol (240)
	8	Adult Idio	N, A, T	11	22	clonazepam (1.5), diazepam (5)
	9	Adult Idio	M, S, N, A, T	2	35.5	baclofen (30), amitriptyline (25), clonazepam (0.5)
	10	Adult Idio	M, N, A, T, L	14	29	venlafaxine (187.5), trazodone (150), clonazepam (2.5)
Secondary	11	Adult Idio	N, T, L	58	31	lorazepam (1), oxycodone (5)
	12	Adult Idio	E, M, N, T	4	22.5	clonazepam (3.75), venlafaxine (150)
	13	Adult Idio	N, A, T	17	20	none
	1	Post traumatic	M, S, N, A, T, L	3	54	trihexyphenidyl (16), pergolide (8), levodopa (800)
	2	Post stroke	A, T, L	6	32	diazepam (5)
	3	PKAN	S, A, L	13	30	levodopa (300), amantadine (200), gabapentin (900)
	4	CP	S, A, T	13	30	trihexyphenidyl (4), diazepam (10), pramipexole (0.75)
	5	CP	M, S, N, A, T, L	27	81	diazepam (10)

Abbreviations: A=arm; BFMDRS-m= Burke-Fahn-Marsden Dystonia Rating Scale motor subscale; CP=cerebral palsy; E=eye; Idio=idiopathic; Juv=juvenile; L=leg; M=mouth; N=neck; PKAN=Pantothenate kinase-associated neurodegeneration; T=trunk; S=speech/swallow;

Table 2
GPe single unit characteristics in dystonia and PD.

	Dystonia			PD
	All dystonia	Primary	Secondary	
Total No Patients / Animals	18	13	5	7
Total No Cells	175	117	58	49
No Pauser Cells	94	73	21	30
% Pausers	53.7	62.3	36.2	61.2
Firing Rate (HZ) (mean $\pm$ SD)	53.9 $\pm$ 23.5	54.0 $\pm$ 24.0	53.7 $\pm$ 21.2	57.46 $\pm$ 21.7
Recording Time (sec) (mean $\pm$ SD)	34.0 $\pm$ 14.9	34.5 $\pm$ 14.9	32.4 $\pm$ 14.3	39.5 $\pm$ 23.2
Pause Length (msec) (mean $\pm$ SD)	578.8 $\pm$ 343.4	606.8 $\pm$ 373.3 *	495.6 $\pm$ 236.5	557.4 $\pm$ 366.6
Interpause Interval (msec) (mean $\pm$ SD)	2672.6 $\pm$ 4312.5 **	2331.6 $\pm$ 3874.1 **	3484.5 $\pm$ 3981.6	3646.4 $\pm$ 5894.5
Pause Frequency (Hz) (mean $\pm$ SD)	0.20 $\pm$ 0.21 *	0.26 $\pm$ 0.24 **	0.14 $\pm$ 0.10	0.12 $\pm$ 0.13

* statistically significant difference between the value in dystonia, compared with PD, at $p < 0.05$

** significant difference between the value in dystonia, compared with PD, at $p < 0.01$