ABSTRACT: Although dystonia represents a major source of motor disability in Huntington’s disease (HD), its pathophysiology remains unknown. Because recent animal studies indicate that loss of parvalbuminergic (PARV+) striatal interneurons can cause dystonia, we investigated if loss of PARV+ striatal interneurons occurs during human HD progression, and thus might contribute to dystonia in HD. We used immunolabeling to detect PARV+ interneurons in fixed sections, and corrected for disease-related striatal atrophy by expressing PARV+ interneuron counts in ratio to interneurons co-containing somatostatin and neuropeptide Y (whose numbers are unaffected in HD). At all symptomatic HD grades, PARV+ interneurons were reduced to less than 26% of normal abundance in rostral caudate. In putamen rostral to the level of globus pallidus, loss of PARV+ interneurons was more gradual, not dropping off to less than 20% of control until grade 2. Loss of PARV+ interneurons was even more gradual in motor putamen at globus pallidus levels, with no loss at grade 1, and steady grade-wise decline thereafter. A large decrease in striatal PARV+ interneurons, thus, occurs in HD with advancing disease grade, with regional variation in the loss per grade. Given the findings of animal studies and the grade-wise loss of PARV+ striatal interneurons in motor striatum in parallel with the grade-wise appearance and worsening of dystonia, our results raise the possibility that loss of PARV+ striatal interneurons is a contributor to dystonia in HD.

Key Words: Huntington’s disease; dystonia; striatum; parvalbuminergic interneurons

Motor disturbances represent a disabling and defining feature of Huntington’s disease (HD). Two disturbances receive the greatest attention—the early occurring chorea/hyperkinesia and the late occurring bradykinesia/akinesia. The chorea has been attributed to the early preferential loss of enkephalinergic (ENK+) indirect pathway striatal projection neurons projecting to the external pallidal segment (GPe), while the bradykinesia/akinesia has been attributed to the more slowly occurring loss of substance P-containing (SP+) direct pathway striatal projection neurons projecting to the internal pallidal segment (GPI). The dystonia that invariably develops by HD grade 2 is, however, also a significant contributor to HD-related disability and functional decline. In juvenile HD and young adult-onset HD, dystonia is, in fact, the presenting and predominant symptom.

The standard direct-indirect pathway model of basal ganglia function leaves uncertain the basis of the...
TABLE 1. Tabular grade-wise listing of information about the human cases examined here, including gender, age at death, PMD between death and brain fixation, CAG repeat, and the overall number of cases and the case per striatal region

| Grade | Males (n) | Females (n) | Gender not known (n) | Total cases (n) | Age (years) | PMD (hours) | WT allele CAG | HD allele CAG | Cases with rostral caudate (n) | Cases with rostral putamen (n) | Cases with mid-putamen (n) |
|-------|-----------|-------------|---------------------|-----------------|-------------|-------------|--------------|--------------|-----------------------------|-----------------------------|--------------------------|
| Control | 15 | 6 | 4 | 25 | 60.3 | 13.8 | 17.0 | 20.6 | 19 | 19 | 14 |
| 1 | 5 | 2 | 2 | 9 | 64.6 | 9.8 | 17.8 | 41.2 | 5 | 6 | 4 |
| 2 | 5 | 5 | 0 | 10 | 63.5 | 12.6 | 20.3 | 42.9 | 9 | 8 | 3 |
| 3 | 6 | 7 | 0 | 13 | 55.0 | 14.0 | 18.6 | 45.3 | 8 | 8 | 8 |
| 4 | 2 | 3 | 0 | 5 | 58.4 | 17.2 | 18.0 | 50.0 | 3 | 3 | 3 |

PMD, postmortem delay; WT, wild-type; HD, Huntington's disease.

dystonia in HD.\(^{3,11,12}\) Considerable recent attention has been devoted to the feed-forward inhibitory influence of parvalbuminergic (PARV+) interneurons on striatal projection neurons,\(^{13-19}\) and evidence from rodent models suggests that their loss or hypofunction can cause dystonia.\(^{20-26}\) Thus, the effect of HD on PARV+ striatal interneurons is of interest for understanding dystonia in HD. Existing published data are, however, equivocal as to whether PARV+ interneurons are lost from striatum as HD progresses.\(^{27-29}\) In the present study, we report that PARV+ striatal interneurons are rapidly lost in HD, and that the progression of loss from motor striatum coincides with dystonia emergence.

Materials and Methods

Approach

To quantify PARV+ neuron loss in HD, we determined PARV+ interneuron abundance in caudate and putamen of normal brains, and in HD victims spanning all 4 symptomatic grades. We also counted interneurons co-containing neuropeptide Y-containing (NPY) and somatostatin (SS), and expressed PARV+ interneuron abundance as the ratio of PARV+ interneurons to interneurons co-containing NPY and SS. Since NPY/SS+ interneurons are not lost in HD,\(^{3,30}\) a decline in the ratio of PARV+ neurons to NPY/SS neurons linearly reflects PARV+ interneuron loss, by controlling for the impact of striatal shrinkage due to advancing HD grade on neuronal spatial density.

Subjects and Tissues

Coronal tissue blocks or slide-mounted sections containing caudate and putamen at a level rostral to globus pallidus, and/or at a level posterior to the anterior commissure at which GPe and GPi are well formed (and henceforth called mid-putamen or motor putamen) were obtained for 37 HD cases (male = 18; female = 15; unknown = 3) verified by pathology, symptoms, family history, and/or CAG repeat, with age at death ranging from 35 to 87 years (mean age = 60.7 ± 2.2) (Table 1). Three were obtained from the University of Michigan Medical Center (Ann Arbor, MI, USA), 3 from the National Neurological Resource Bank (NNRB, Los Angeles, CA, USA), 2 from the Harvard Brain Tissue Resource Center (HBTRC, Belmont, MA, USA), 2 from the Douglas Hospital Research Center (DHRC, Montreal, Quebec, Canada), 2 from the University of Rochester (UR, Rochester, NY, USA), and 25 from the Neurological Foundation of New Zealand Human Brain Bank (Auckland, New Zealand).

The mean death age for the HD cases was generally less with advancing grade (Table 1), which reflects the tendency of disease severity to be associated with earlier death.\(^{31}\) Mean CAG repeat for the HD allele also increased with HD grade, ranging from 41.2 for grade 1 cases to 50.0 for grade 4 cases. This is consistent with prior findings that higher CAG repeats are associated with greater disease severity.\(^{31}\)

Coronal tissue blocks or slide-mounted sections containing caudate and putamen at a rostral basal ganglia and/or a mid-basal ganglia level were also obtained for 25 control specimens from the University of Michigan Medical Center (1), the HBTRC (2), the University of Tennessee Health Science Center (UTHSC) Department of Pathology (2), and the Neurological Foundation of New Zealand Human Brain Bank (19). The control cases included 15 males, 6 females, and 4 cases of unknown gender, with age at death ranging from 15 to 81 (mean = 60.3 ± 3.5) years (Table 1). All control specimens were neurologically normal, except for 1 Parkinson’s disease case. Control specimens were from individuals whose autopsies were performed within the same range of dates as HD cases.

Brains from all sources other than University of Auckland were obtained at autopsy and immersion-fixed in formalin. Brains from the New Zealand Human Brain Bank were perfused as described previously through the basilar and internal carotid arteries with 15% of formalin in 0.1 M phosphate buffer (pH 7.4) for 1 hour.\(^{32}\) Postmortem delay for control brains ranged from 4.5 to 39 (mean = 13.8 ± 1.6) hours, and for HD brains from 4 to 31 (mean = 12.5 ± 1.1) hours (Table 1). Differences in age at death and postmortem delay between HD cases and controls were not statistically significant, and HD and control cases were well...
matched for agonal status. HD cases were staged according to Vonsattel et al., and the HD specimens included 9 grade 1, 10 grade 2, 13 grade 3, and 5 grade 4 cases (Table 1).

As our goal was to determine if loss of PARV+ striatal interneurons helped explain the pathophysiology of dystonia in HD, information on motor symptoms in our HD cases was pertinent. Clinical information was, however, only available for 2 of our 9 grade 1 cases, 4 of our 10 grade 2 cases, 9 of our 13 grade 3 cases, and 2 of our 5 grade 4 cases, and in many cases was not current with date of death. The limited clinical information indicated, as expected, that the prevalence of dystonia increased with advancing grade, being absent in our grade 1 cases, present in half of the grade 2 cases, and present in all of the grade 3 and 4 cases. However, due to the facts that the clinical information was in many cases not current with date of death and was rarely a quantified dystonia score, we were unable to statistically correlate degree of dystonia with magnitude of PARV+ interneuron loss.

**Immunohistochemical Methods**

Since our tissue was of diverse types in terms of section thickness and disease grade, we chose to express the abundance of PARV+ neurons in striatum as a ratio of PARV+ neurons counted to interneurons co-containing NPY and/or SS counted, adjusted by the Abercrombie correction for perikarya size. Tissue blocks for HD and/or control cases from DHRC, UR, UM, NNRB, and UTHSC were immunostained for parvalbumin (PARV), NPY, and/or SS at UTSHC using methods described in Deng et al., using antisera whose specificity has been previously shown. Tissue from the New Zealand Human Brain Bank was processed by immunolabeling for PARV, NPY, and/or SS at the Centre for Brain Research of the University of Auckland using described procedures.

Further details are provided in the Supporting Information.

**Quantification of Neuronal Abundance**

We counted PARV+ interneurons, NPY+ interneurons, and SS+ interneurons in rostral caudate, rostral putamen, and mid-putamen. After an Abercrombie double-counting correction, the abundance of the PARV+ interneurons, NPY+ interneurons, and SS+ interneurons were expressed per mm² for each region in each case. The abundance of NPY/SS neurons was considered to be the average of the NPY and SS counts in those instances in which both were available. The final NPY/SS neuron count for each case and each striatal region was used to express PARV+ interneuron abundance as a ratio to NPY/SS interneuron abundance. For simplicity, we will refer to the PARV+ interneuron to NPY/SS interneuron ratio as the PARV/NPY ratio in the Results, as in most instances only NPY immunolabeling was available. One-way analysis of variance (ANOVA) with post hoc analysis (Fischer LSD) was used to evaluate results. Further details on our neuron counting methods are provided in the Supporting Information.

**Results**

Examination of our control and HD cases suggested that a large decrease in PARV+ interneurons occurs in striatum with increasing pathological disease grade. In these same cases, the NPY+/SS+ striatal interneurons were preserved, as expected based on prior reports. PARV+ interneurons were progressively fewer with advancing HD grade, and they also appeared to be diminished in size, perikaryal labeling intensity, and dendritic labeling. The abundance of PARV+ interneurons in grade 1 HD mid-putamen was not notably different from that in control putamen, although the labeling intensity of neurons appeared reduced. By contrast, PARV+ interneuron abundance in caudate at all grades and in putamen at grades 2 to 4 was clearly reduced. Examples of immunolabeling for PARV+ and NPY/SS+ interneurons in control, grade 1 HD, and grade 3 HD are shown in Figure 1.

Quantitative analysis confirmed and extended these observations. As shown in Figure 2A, NPY/SS+ neuron abundance showed a trend toward an increase in spatial density across advancing HD grades, although the differences were only significant between control and grade 4 for rostral striatum. Note that because of the relatively few grade 4 cases for each region, the grade 4 NPY/SS+ neuron counts tended to be variable, but still significantly more than in control in the case of the rostral caudate and putamen.

The PARV/NPY ratios revealed a profound and highly statistically significant loss (P < 0.0077) of PARV+ neurons in the rostral caudate nucleus at all grades, with an approximately 75% loss evident already at grade 1 (Fig. 2B). The grade 1 loss of PARV+ interneurons was less prominent for the rostral putamen than for the rostral caudate, but significant nonetheless (P < 0.0120). The losses at HD grades 2 to 4 for rostral putamen were substantial (>80%), and the difference between control and HD grades 2 to 4 was highly significant (P < 0.0001). In the case of mid-putamen, PARV+ neuron abundance was indistinguishable from control at grade 1, but then significantly and progressively less than control over grades 2 to 4 (Fig. 2B). Table 2 shows the loss of PARV+ interneurons per grade and per region expressed as a percent of control for that region. Note also that NPY/SS+ interneuron abundance in control cases was similar for all 3 striatal regions examined (Fig. 2A), while PARV+ interneuron abundance was
FIG. 1. Series of images showing NPY+ striatal interneurons (A-C) and PARV+ striatal interneurons (D-F) in putamen of a control case (A, D), grade 1 HD case (B, E), and grade 3 HD case (C, F). Note that NPY neurons show no alteration in size, abundance, or labeling intensity with HD progression, while PARV+ interneurons show progressive decline in all 3 parameters. Magnification is the same in all images. NPY, neuropeptide Y; PARV, parvalbumin; PARV+, parvalbuminergic; HD, Huntington’s disease.

FIG. 2. Graphs showing the mean abundance (± SEM) of NPY/SS interneurons across control and HD symptomatic grades in rostral caudate, rostral putamen, and mid-putamen (A), and the mean abundance (± SEM) of PARV+ interneurons across control and HD symptomatic grades for rostral caudate, rostral putamen, and mid-putamen (B). No decline occurs for NPY/SS interneurons, but PARV+ interneurons show prominent loss in HD that is greatest for rostral caudate, and more gradual for mid-putamen. NPY, neuropeptide Y; SS, somatostatin; HD, Huntington’s disease; SEM, standard error of the mean; PARV, parvalbumin; PARV+, parvalbuminergic.
interneurons can yield dystonia. For interneurons to 1 mutant Syrian hamsters, GPi neuronal firing is reduced in the medial ganglionic eminence into striatum during development. Finally, recording studies in humans show that, like in dt<sup>sz</sup> hamsters, GPI neuronal firing is reduced in dystonic individuals. The anatomy and physiology of PARV<sup>+</sup> striatal interneurons is consistent with the idea that their loss can lead to dystonia. PARV<sup>+</sup> interneurons fire repetitively when depolarized by cortical stimulation, with a shorter latency and lower threshold than striatal projection neurons. As a consequence, cortical activation of PARV<sup>+</sup> neurons prevents or reduces the response to this same cortical activation of the striatal projection neurons to which the PARV<sup>+</sup> interneurons project. PARV<sup>+</sup> interneurons have much of their axonal arborization beyond their own dendritic field, and PARV<sup>+</sup> interneurons preferentially inhibit SP<sup>+</sup> striato-GPi neurons. Given the reported small size of the cortical terminals ending on PARV<sup>+</sup> interneurons, it seems likely that they receive their cortical input from the intratelencephalic projection type (IT-type) corticostriatal neurons, which also preferentially innervate SP<sup>+</sup> striatal neurons. Thus, SP<sup>+</sup> neurons lying within the dendritic field of a given PARV<sup>+</sup> neuron would be activated by convergent input from diverse cortical areas, as would be the given PARV<sup>+</sup> interneuron itself. The SP<sup>+</sup> neurons outside the PARV<sup>+</sup> interneuron domain, however, also receive input from some of the same IT-type neurons due to the diffuse nature of the IT-type axonal arborization (Fig. 3). As a result, both sets of SP<sup>+</sup> neurons can be activated, though to differing degrees, by the same IT-type input, potentially leading to facilitation of conflicting movements. If the cortical activation within the domain of a particular PARV<sup>+</sup> interneuron exceeds that to other nearby domains, rapid feed-forward inhibition of the SP<sup>+</sup> neurons in neighboring domains from this activated PARV<sup>+</sup> interneuron may serve to suppress their responses, ensuring that only a narrow set of SP<sup>+</sup> neurons is sufficiently activated to trigger a particular movement. Consistent with this interpretation, Gage et al. found that PARV<sup>+</sup> striatal interneurons in behaving rat were active at choice points, suggesting PARV<sup>+</sup> interneurons suppress nonpreferred behaviors.

Thus, PARV<sup>+</sup> interneurons may act locally to regulate nearby SP<sup>+</sup> striatal neuron activity in response to cortical input. Studies in monkeys have shown that the putamen contains somatotopically organized microexcitable zones from which body movement can be elicited, supporting the view that cortical activation of GluA2-lacking 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid [AMPA] receptors) into mouse sensorimotor striatum, which preferentially blocks excitation of PARV<sup>+</sup> interneurons, elicits dystonia. Moreover, haploinsufficiency of the Nkx2.1 gene in humans causes dystonia, which may stem from deficient migration of PARV<sup>+</sup> neurons from the medial ganglionic eminence into striatum during development.
Striatal projection neuron sets can trigger movement. Moreover, fMRI studies show participation of motor putamen in humans in movement sequencing during task execution.\textsuperscript{58} Given the apparent role of PARV+ interneurons, therefore, it would be predicted that their loss with preservation of SP+ neurons (as occurs in mid-HD) should yield a basal ganglia that simultaneously initiates conflicting motor routines, exhibiting as dystonia. With the extensive loss of enkephalinergic striatal projection neurons by mid-grade HD, it may be that loss of PARV+ interneurons mainly affects SP+ neuron activity during HD progression.\textsuperscript{2,33} The vulnerability of PARV+ striatal interneurons in HD stands in contrast to the resistance of 2 other striatal interneuron types to loss, namely cholinergic interneurons and interneurons co-containing SS, NPY, and/or neuronal nitric oxide synthase.\textsuperscript{4,30,59} A vulnerability of PARV+ interneurons, and a resistance of cholinergic interneurons and somatostatinergic interneurons, however, also is evidenced following transient global ischemic insult to striatum,\textsuperscript{36,60,61} and intrastratal injection of the NMDA-receptor excitotoxin quinolinic acid.\textsuperscript{26,35} The basis of the vulnerability of PARV+ striatal interneurons in HD is uncertain, but given their prominent excitatory input, their enrichment in Ca\textsuperscript{2+}-permeable AMPA receptors and their BDNF dependence, excitotoxicity, Ca\textsuperscript{2+}-mediated injury, or BDNF deprivation could be candidate pathogenic mechanisms.\textsuperscript{13,35,62}

FIG. 3. Schematic illustrating hypothesized role of PARV+ striatal interneurons in controlling the responses of nearby SP-containing direct pathway striatal neurons to their driving input from IT-type corticostriatal neurons. Rapid feed-forward inhibition of SP+ neurons by cortically activated PARV+ neurons is hypothesized to suppress the responses of SP+ striatal neurons in nearby domains but not within the domain of the PARV+ interneuron itself. In the illustration, by suppressing cortical activation of SP+ neurons controlling behavior B, the PARV+ interneuron ensures that IT-type cortical input activates SP+ neurons controlling behavior A. In the absence of the PARV+ interneuron, the conflicting behaviors A and B would both be initiated, leading potentially to dystonia if A and B involve opposing muscle groups. PARV, parvalbumin; PARV+, parvalbuminergic; SP, substance P; IT, intratelencephalically projecting.
Nonetheless, it is not established that PARV+ striatal interneuron loss explains HD dystonia. Another possible explanation could be that GPI output is diminished, not because of increased striato-GPI neuron activity due to PARV+ interneuron loss, but due to GPI neuron loss, leading to disinhibition of motor thalamus domains controlling antagonistic muscle groups. The observation that GPI hypoactivity occurs in human generalized and segmental dystonia, as well as in mouse models of DYT1 human familial dystonia, is consistent with this possibility. Additionally, 35% deficiency in PARV+ putamen interneurons has been reported in Tourette syndrome, without evidence of dystonia. These studies, however, also found a 2.5-fold elevation in PARV+ neurons in the Gpi, and they attributed the GPI excess and putamen shortfall in PARV+ neurons to a possible migration defect during development. Thus, the absence of dystonia despite the deficiency in striatal PARV+ interneurons and the occurrence of Tourette symptoms may stem from an alteration in Gpi function stemming from its PARV+ neuron excess. Finally, it is also possible that the extensive loss of SP+ neurons by grade 3 HD plays a role in the observed dystonia, since mutant mice with prenatal or postnatal ablation of D1 dopamine receptor-bearing neurons (mainly SP+ neurons) typically have dystonia as a symptom.

These results must be viewed with caution, however, since ablation of neurons possessing D1 receptors also eliminates D1 receptor-bearing cortical neurons. Thus, it is uncertain if the dystonic phenotype in these mice is attributable to loss of SP+ striatal neurons, or whether loss of cortical D1 neurons accounts for the phenotype. In any event, the present findings show that PARV+ striatal interneuron loss is prominent in HD, and available animal data on basal ganglia function are consistent with the view that this loss in motor striatum might contribute to dystonic symptoms. Further studies are, however, needed to evaluate the possible contributions of GPI neuron loss or striatal SP+ neuron loss to the pathophysiology of dystonia in HD. Similarly, characterization of PARV+ striatal interneuron loss in HD cases with quantitative assessment of dystonia near the time of death, such as possible for HD patients enrolled in the COHORT and Enroll-HD observational studies, would aid evaluation of the role of PARV+ striatal interneuron loss in HD, since it would enable correlation between such neuron loss and the degree of dystonia.

Acknowledgments: We acknowledge the generosity of the HD families in New Zealand, the New Zealand Neurological Foundation Human Brain Bank. We also thank the University of Michigan Medical Center (Ann Arbor, MI, USA), National Neurological Resource Bank (NINDB, Los Angeles, CA, USA), the Harvard Brain Tissue Resource Center (HBTRC, Belmont, MA, USA), the Douglas Hospital Research Center (DHRC, Montreal, Quebec, Canada), the University of Rochester (UK), and the University of Tennessee Health Science Center (UTHSC) for providing tissues used in this study.

References
1. Albin RL, Tagle DA. Genetics and molecular biology of HD. Trends Neurosci 1995;18:11–14.
2. Guo Z, Rudow G, Pletnikova O, et al. Striatal neuronal loss correlates with clinical motor impairment in Huntington’s disease. Mov Disord 2012;27:1379–1386.
3. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989;12:366–375.
4. Albin RL, Reiner A, Anderson KD, Penney JB, Young AB. Striatal and nigral neuron subpopulations in rigid HD: implications for the functional anatomy of chorea and rigidity-akinesia. Ann Neurol 1990;27:347–365.
5. Deng YP, Albin RL, Penney JB, Young AB, Anderson KD, Reiner A. Differential loss of striatal projection systems in HD: a quantitative immunohistochemical study. J Chem Neuroanat 2004;27:143–164.
6. Reiner A, Albin RL, Anderson KD, D’Amato CJ Penney JB, Young AB. Differential loss of striatal projection neurons in HD. Proc Natl Acad Sci U S A 1998;85:5733–5737.
7. Sapp E, Ge P, Aizawa H, et al. Evidence for a preferential loss of enkephalin immunoreactivity in the external globus pallidus in low grade HD using high resolution image analysis. Neuroscience 1995;64:397–404.
8. Feigin A, Kieburz K, Bordwell K, et al. Functional decline in HD. Mov Disord 1995;10:211–214.
9. Kirkwood SC, Su JL, Conneally PM, Foroud T. Progression of symptoms in the early and middle stages of HD. Arch Neurol 2001;58:273–278.
10. Louis ED, Lee P, Quinn L, Murray K. Dystonia in HD: prevalence and clinical characteristics. Mov Disord 1999;14:95–101.
11. DeLong M. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990;13:281–285.
12. Kravitz AV, Freeze BS, Parker PR, et al. Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature 2010;466:622–626.
13. Deng YP, Shelby E, Reiner A. Immunohistochemical localization of AMPA type glutamate receptor subunits in the striatum of Rhesus monkey. Brain Res 2010;1344:104–123.
14. Kawaguchi Y, Wilson CJ, Augood SJ, Emson PC. Striatal interneurons: chemical, physiological and morphological characterization. Trends Neurosci 1995;18:527–535.
15. Kita H. GABAergic circuits of the striatum. Prog Brain Res 2001;99:51–72.
16. Koos T, Tepper JM. Inhibitory control of neostriatal projection neurons by GABAergic interneurons. Nat Neurosci 1999;2:467–472.
17. Lapper SR, Smith Y, Sadikot AF, Parent A, Bolam JP. Cortical input to parvalbumin-immunoreactive neurons in the putamen of the squirrel monkey. Brain Res 1992;580:215–224.
18. Rudkin TM, Sadikot AF. Thalamic input to parvalbumin-immunoreactive GABAergic interneurons: organization in normal striatum and effect of neonatal decortication. Neurosci 1999;8:1165–1175.
19. Tepper JM, Koos T, Wilson CJ. GABAergic microcircuits in the neostriatum. Trends Neurosci 2004;27:662–669.
20. Bennay M, Gernert M, Richter A. Spontaneous remission of paroxysmal dystonia coincides with normalization of entopeduncular activity in d6 mutants. J Neurosci 2001;21:RC153.
21. Gernert M, Richter A, Löscher W. Alterations in spontaneous single unit activity of striatal subdivisions during ontogenesis in mutant dystonic hamsters. Brain Res 1999;821:277–285.
22. Gernert M, Richter A, Löscher W. Subconvulsive dose of pentyletereazol increases the firing rate of substantia nigra pars reticulata neurons in dystonic but not in nondystonic hamsters. Synapse 1999;33:259–267.
23. Gernert M, Richter A, Löscher W. In vivo extracellular electrophysiology of pallidal neurons in dystonic and nondystonic hamsters. J Neurosci Res 1999;57:984–905.
24. Gernert M, Hamann M, Bennay M, Löscher W, Richter A. Deficit of striatal parvalbumin-reactive GABAergic interneurons and decreased basal ganglia output in a genetic rodent model of idopathic paroxysmal dystonia. J Neurosci 2000;20:7052–7058.
25. Gernert M, Bennay M, Fedrowitz M, Rheders JH, Richter A. Altered discharge pattern of basal ganglia output neurons in an animal model of idiopathic dystonia. J Neurosci 2002;22:7244–7253.

26. Gittis AH, Leventhal DK, Fensterheim BA, Pettibone JR, Berke JD, Kreitzer AC. Selective inhibition of striatal fast-spiking interneurons causes dyskinesias. J Neurosci 2011;31:15727–15731.

27. Dom R, Baro F, Brucher JM. A cytometric study of the putamen in different types of Huntington’s chorea. In: Barbeau A, Chase TN, Paulson GW, eds. Huntington’s Chorea. Advances in Neurology. Vol. 1. New York: Raven Press; 1973:369–385.

28. Ferrer I, Kulisevsky J, Gonzalez A, Escartín A, Chivite A, Casas R. Parvalbumin-immunoreactive neurons in the cerebral cortex and striatum in HD. Neurodegeneration 1994;3:169–173.

29. Harrington KM, Kowall NW. Parvalbumin immunoreactive neurons resist degeneration in HD striatum. J Neuropathol Exp Neurol 1991;50:309.

30. Ferrante RJ, Kowall NW, Beal MF, Martin JB, Bird ED, Richardson EP Jr. Morphological and histochemical characteristics of spared striatal neurons in HD. J Neuropathol Exp Neurol 1987;46:12–27.

31. Penney JB Jr, Vonsattel JP, MacDonald ME, Gusella JF, Myers RH. CA8 repeat number governs the development rate of pathology in Huntington’s disease. Ann Neurol 1997;41:689–692.

32. Waldvogel HJ, Curtis MA, Baer K, Rees MI, Faull RLM. Immunohistochemical staining of post-mortem adult human brain sections. Nat Protoc 2006;1:2719–2732.

33. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP. Neuropathological classification of HD. J Neuropathol Exp Neurol 1985;44:559–577.

34. Celio MR. Calbindin D28k and parvalbumin in the rat nervous system. Neuroscience 1990;35:375–475.

35. Figueredo-Cardenas G, Harris CL, Anderson KD, Reiner A. Relative resistance of striatal neurons containing calbindin or parvalbumin to quinolinic acid-mediated excitotoxicity compared to other striatal neuron types. Exp Neurol 1998;149:336–372.

36. Meade CA, Figueredo-Cardenas G, Fusco FR, Nowak TS, Pulsenelli W, Reiner A. Transient global ischemia in rats yields striatal projection neuron and interneuron loss resembling that in Huntington’s disease. Exp Neurol 2000;166:307–323.

37. Thu DC, Oorschot DE, Tippett LJ, et al. Cell loss in the motor and cingulostriatal cortex correlates with symptomatology in Huntington’s disease. Brains 2010;133:1094–1110.

38. Richter A, Löscher W. Pathophysiology of idiopathic dystonia: findings from genetic animal models. Prog Neurobiol 1998;54:633–677.

39. Kreil A, Hamann M, Sander SE, Reiner A. Changes in dynorphin immunoreactivity but unaltered density of enkephalin immunoreactive neurons in basal ganglia nuclei of genetically dystonic hamsters. Synapse 2011;65:1196–1203.

40. Muramatsu S, Yoshida M, Nakamura S. Electrophysiological study of dyskinesia produced by microinjection of picROTOX into the striatum of the rat. Neurosci Res 1990;7:369–380.

41. Yoshida M, Nagatsu Y, Muramatsu S, Ninjima K. Differential roles of the caudate nucleus and putamen in motor behavior of the rat as investigated by local injection of GABA antagonists. Neurosci Res 1991;10:34–51.

42. Breedveld GJ, Dongen JWF, Danesino C, et al. Mutations in TITF-1 are associated with benign hereditary chorea. Hum Mol Genet 2002;11:971–979.

43. Hashimoto T. Neuronal activity in the globus pallidus in primary dystonia and off-period dystonia. J Neurol 2000;247(Suppl 5):V49–V52.

44. Hutchison WD, Lang AE, Dostrovsky JO, Lozano AM. Pallidal neuronal activity: implications for models of dystonia. Ann Neurol 2003;53:480–488.

45. 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;52:1338–1373.

46. Vitek JL, Chockkan V, Zhang JY, et al. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. Ann Neurol 1999;46:222–35.

47. Zhuang P, Li Y, Hallett M. Neuronal activity in the basal ganglia and thalamus in patients with dystonia. Clin Neurophysiol 2004;115:2542–2557.

48. Mallet N, Le Moine C, Charpier S, Gonon F. Feedforward inhibition of projection neurons by fast-spiking GABA interneurons in the rat striatum in vivo. J Neurosci 2005;25:3857–3869.

49. Gittis AH, Nelson AB, Thwin MT, Palop JJ, Kreitzer AC. Distinct roles of GABAergic interneurons in the regulation of striatal output pathways. J Neurosci 2010;30:2223–2234.

50. Planet H, Szydlowski SN, Hjorth JJ, Grillner S, Silberberg G. Dynamics of synaptic transmission between fast-spiking interneurons and striatal projection neurons of the direct and indirect pathways. J Neurosci 2010;30:3599–3607.

51. Lei WL, Jiao Y, Del Mar N, Reiner A. Evidence for differential cortical input to direct pathway neurons, and spiny interneurons, of the striatum in dystonia patients. J Neurosci 2004;24:8289–8299.

52. Reiner A, Hart NM, Lei W, Deng Y. Corticostriatal projection neurons—dichotomous types and dichotomous functions. Front Neuroanat 2010;4:142.

53. Ramanathan S, Hanley JJ, Deniau JM, Bolam JP. Synaptic convergence of motor and somatosensory cortical afferents onto GABAergic interneurons in the rat striatum. J Neurosci 2002;22:8138–8169.

54. Wilson CJ. The contribution of cortical neurons to the firing pattern of striatal spiny neurons. In: Houk JC, Davis JL, Beise DG, eds. Models of Information Processing in the Basal Ganglia. Cambridge, MA: MIT Press; 1995:29–50.

55. Gage GJ, Stoettner CR, Wiltchko AB, Berke JD. Selective activation of striatal fast-spiking interneurons during choice execution. Neuron 2010;67:466–479.

56. Berke JD. Uncoordinated firing rate changes of striatal fast-spiking interneurons during behavioral task performance. J Neurosci 2008;28:10075–10080.

57. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex, Annu Rev Neurosci 1986;9:377–381.

58. Wymbs NF, Bassett DS, Mucha PJ, Porter MA, Grafton ST. Differential recruitment of the sensorimotor putamen and frontoparietal cortex during motor chunking in humans. Neuron 2012;74:936–946.

59. Ferrante RJ, Beal MF, Kowall NW, Richardson EP, Martin JB Jr. Sparing of acetylcholinesterase-containing striatal neurons in HD. Brain Res 1987;411:161–166.

60. Gonzales C, Lin RC, Chesselet MF. Relative sparing of GABAergic interneurons in the striatum of gerbils with ischemia-induced lesions. Neurosci Lett 1992;135:3–58.

61. Mallard EC, Waldvogel HJ, Williams CE, Faull RL, Gluckman PD. Repeated asphyxia causes loss of striatal projection neurons in the fetal sheep brain. Neuroscience 1995;65:827–836.

62. Agerman K, Erofs P. Differential influence of BDNF and NT3 on the expression of calcium binding proteins and neuropeptide Y in vivo. Neuroreport 2003;14:2183–2187.

63. Starr PA, Rau GM, Davis V, et al. Spontaneous pallidal neuronal activity in human dystonia: comparison with Parkinson’s Disease and normal macaque. J Neurophysiol 2005;93:3165–3176.

64. Tang JKH, Moro E, Mahant N, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO. Neuronal firing rates and patterns in the globus pallidus internus of patients with cervical dystonia differ from those with Parkinson’s disease. J Neurophysiol 2007;98:720–729.

65. Nambu A, Chikun S, Shashidharan P, et al. Reduced pallidal output causes dystonia. Front Syst Neurosci 2011;5:89.

66. Kalanithi PSA, Zheng W, Kataoka Y, et al. Altered parvalbumin-positive neuron distribution in basal ganglia of individuals with Tourette syndrome. Proc Natl Acad Sci U S A 2005;102:13307–13312.

67. Kataoka Y, Kalanithi PS, Grantz H, Schwartz ML, Saper C, Leckman JF, Vaccarino FM. Decreased number of parvalbumin and cholinergic interneurons in the striatum of individuals with Tourette Syndrome. J Comp Neurol 2010;518:277–291.

68. Drago J, Padungchaichot W, Wong JY, et al. Targeted expression of a toxin gene to D1 dopamine receptor neurons by cre-mediated site-specific recombination. J Neurosci 1998;18:9845–9857.

69. Gantois I, Fang K, Jiang L, et al. Ablation of D1 dopamine receptor-expressing cells generates mice with seizures, dystonia,
hyperactivity, and impaired oral behavior. Proc Natl Acad Sci U S A. 2007;104:4182–4187.

70. Wong JY, Padungchaichot P, Massalas JS, Drago Late direct and transneuronal effects in mice with targeted expression of a toxin gene to D1 dopamine receptor neurons. Neuroscience 2000;95:1035–1041.

71. Tomiyama K, Kim HA, Kinsella A, et al. Phenotypic disruption to orofacial movement topography in conditional mutants with generalized CamKIIa-Cre D1Tox versus striatal-specific DARPP-32-Cre D1Tox ablation of D1 dopamine receptor-expressing cells. Synapse 2011;65:835–842.

72. Ha AD, Beck CA, Jankovic J. Intermediate CAG repeats in Huntington’s disease: analysis of COHORT. Tremor Other Hyperkinet Mov (N Y) 2012;2:tre-02-64-287-4.

73. Seay M, Giuliano J, Handley O; Enroll HD Steering Committee. Enroll-HD: a prospective observational study in a global Huntington’s disease cohort. J Neurol Neurosurg Psychiatry 2012;83:A46–A47.

74. Waldvogel HJ, Faull RL, Williams MN, Dragoon M. Differential sensitivity of calbindin and PARV immunoreactive cells in the striatum to excitotoxins. Brain Res 1991;546:329–335.