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The direct basal ganglia pathway is hyperfunctional in focal dystonia

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Focal dystonias are the most common type of isolated dystonia. Although their causative pathophysiology remains unclear, it is thought to involve abnormal functioning of the basal ganglia-thalamo-cortical circuitry. We used high-resolution research tomography with the radioligand ^{11}C-NNC-112 to examine striatal dopamine D_1 receptor function in two independent groups of patients, writer's cramp and laryngeal dystonia, compared to healthy controls. We found that availability of dopamine D_1 receptors was significantly increased in bilateral putamen by 19.6–22.5% in writer's cramp and in right putamen and caudate nucleus by 24.6–26.8% in laryngeal dystonia (all $P \leqslant 0.009$). This suggests hyperactivity of the direct basal ganglia pathway in focal dystonia. Our findings paralleled abnormally decreased dopaminergic function via the indirect basal ganglia pathway and decreased symptom-induced phasic striatal dopamine release in writer's cramp and laryngeal dystonia. When examining topological distribution of dopamine D_1 and D_2 receptor abnormalities in these forms of dystonia, we found abnormal separation of direct and indirect pathways within the striatum, with negligible, if any, overlap between the two pathways and with the regions of phasic dopamine release. However, despite topological disorganization of dopaminergic function, alterations of dopamine D_1 and D_2 receptors were somatotopically localized within the striatal hand and larynx representations in writer's cramp and laryngeal dystonia, respectively. This finding points to their direct relevance to disorder-characteristic clinical features. Increased D_1 receptor availability showed significant negative correlations with dystonia duration but not its severity, likely representing a developmental endophenotype of this disorder. In conclusion, a comprehensive pathophysiological mechanism of abnormal basal ganglia function in focal dystonia is built upon upregulated dopamine D_1 receptors that abnormally increase excitation of the direct pathway, downregulated dopamine D_2 receptors that abnormally decrease inhibition within the indirect pathway, and weakened nigrostriatal phasic dopamine release during symptomatic task performance. Collectively, these aberrations of striatal dopaminergic function underlie imbalance between direct and indirect basal ganglia pathways and lead to abnormal thalamo-motor-cortical hyperexcitability in dystonia.

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Abbreviations: BP = binding potential; HRRT = high resolution research tomography

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Introduction

Focal dystonias are the most frequent forms of isolated dystonia and are characterized by sustained and intermittent muscle contractions that cause abnormal and often repetitive movements, postures, or both (Albanese *et al.*, 2013). Although the exact pathophysiology of dystonia is unclear, the link between dystonia and basal ganglia dysfunction has been apparent (Marsden, 1984; Hallett, 1998). The basal ganglia set the pattern for facilitation of voluntary movements and simultaneous inhibition of competing/interfering movements by balancing excitation and inhibition within the thalamo-cortical circuitry. This is achieved by a synergistic action of the net excitatory direct basal ganglia pathway, which predominantly expresses dopamine D_1 family receptors, and the net inhibitory indirect basal ganglia pathway, which expresses dopamine D_2 family receptors (Gerfen, 1992, 2000; Surmeier *et al.*, 1998; Redgrave *et al.*, 2010). Endogenously released striatal dopamine influences direct and indirect pathways both separately and via bridging collaterals between the two pathways, allowing dynamic modulation of thalamo-cortical neurons for physiologically normal facilitation of movements initiated in the motor cortex (Alexander and Crutcher, 1990; Wichmann and DeLong, 1996; Calabresi *et al.*, 2014; Cazorla *et al.*, 2014).

This balance between excitation and inhibition within the basal ganglia pathways is thought to be altered in dystonia (Hallett, 1998, 2004, 2006), leading to abnormal decreases of intracortical inhibition and subsequently abnormal increases of motor cortical excitability (Ridding *et al.*, 1995*a*, *b*; Chen *et al.*, 1997; Filipovic *et al.*, 1997). As a potential pathophysiological mechanism, reduced function of the indirect pathway with decreased pallidal inhibition of the thalamo-cortical circuitry has been suggested based on evidence of decreased availability of dopamine D_2 receptors and striatal dopaminergic dysfunction (Horstink *et al.*, 1997; Perlmutter *et al.*, 1997; Bressman, 1998; Lenz *et al.*, 1998; Naumann *et al.*, 1998; Hallett, 2004; Berger *et al.*, 2006; Berman *et al.*, 2013; Simonyan *et al.*, 2013*a*). On the other hand, hyperfunctional activity of the direct basal ganglia pathway has also been proposed to contribute to abnormal motor cortical excitability in dystonia (Hallett, 1993; Eidelberg *et al.*, 1995). To that end, studies in patients with cervical dystonia (Placzek *et al.*, 2001) and blepharospasm (Misbahuddin *et al.*, 2002) have identified a polymorphism in the gene coding for the dopamine D_5 receptor (part of the D_1 family of dopamine receptors), whereas the *GNAL* (DYT25) mutation found in cervical, laryngeal and segmental dystonias has been directly linked to dopamine D_1 receptor signalling (Fuchs *et al.*, 2013; Vemula *et al.*, 2013; Putzel *et al.*, 2016). However, by and large, detailed studies on the contribution of direct pathway to the pathophysiology of dystonia remain lacking, which hinders complete characterization of basal ganglia involvement in this disorder.

To address this critical question, we used a high resolution research tomograph (HRRT) with the radioligand ^{11}C-NNC-112 [in full: (+)-8-chloro-5-(7-benzofuranyl)-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine] as a potent and selective marker of postsynaptic D_1 receptors (Halldin *et al.*, 1998) to (i) examine striatal dopamine D_1 receptors in two independent groups of patients with focal dystonia, writer's cramp and laryngeal dystonia, and compare them to healthy controls; and (ii) assess the relationships between abnormal function within the direct pathway and clinical characteristics of dystonia. Based on our recently reported findings of dopaminergic function within the indirect pathway (Berman *et al.*, 2013; Simonyan *et al.*, 2013*a*), we further sought to outline the cumulative topology of abnormal dopaminergic neurotransmission in dystonia as a contributing factor to its pathophysiology. Our overarching hypothesis on the role of basal ganglia circuitry in the pathophysiology of dystonia is that deficient function of dopamine D_2 receptors abnormally reduces inhibition within the indirect pathway while concurrently excessive function of dopamine D_1 receptors abnormally increases excitation within the direct pathway. This leads to imbalance between the indirect and direct pathways and consequently instigates hyperexcitability of thalamo-cortical outputs.

Materials and methods

Subjects

A total of 35 subjects participated in this study. Among these, 11 patients had writer's cramp (five males/six females, 56.3 ± 14.3 years old), 12 patients had laryngeal dystonia (three males/nine females, 58.8 ± 13.7 years old), and 12 subjects were healthy volunteers (three males/nine females, 63.6 ± 8.5 years old) without any history of neurological (except for focal dystonia in patients) or psychiatric problems (Table 1). There were no statistical differences between the groups based on their age or sex (all $P \geqslant 0.15$). All subjects were right-handed and monolingual, native English speakers. History and physical, neurological and laryngological (when appropriate) examinations confirmed the presence of isolated focal dystonia in all patients and ruled it out in healthy subjects. Writer's cramp and laryngeal dystonia were focal to right hand and larynx only, respectively, without any additional body part involvement. All patients with laryngeal dystonia had the most common adductor type only to ensure symptom homogeneity. All patients were fully symptomatic at the time of study participation, which was determined during neurological examination; those who received botulinum toxin injections participated in the study at the end of their treatment cycle, i.e. they had their last injection at least 3 months prior to the scanning and were fully symptomatic as established by neurological and/or laryngological examination. No subject received any medication affecting the CNS, including those affecting dopaminergic, GABAergic, acetylcholinergic or serotoninergic neurotransmission.

Table 1 Demographic and clinical characteristics of participants

	WC patients	LD patients	Healthy subjects	*P*-value
Demographic characteristics				
n of final subjects[a]	11	11	12	N/A
Age (years)	56.3 ± 14.3	59.3 ± 14.2	63.6 ± 8.5	⩾0.15
Gender	5M / 6F	3M / 9F	3M / 9F	⩾0.57
Handedness	Right			N/A
Spoken language	Monolingual native English			N/A
Other language experience	None			N/A
Clinical characteristics				
Other forms of dystonia	None			
Symptomatic patients, *n*	11	11	N/A	N/A
Dystonia duration (years)	20.5 ± 12.5	18.4 ± 9.7	N/A	0.67
Dystonia severity[b]	11.3 ± 3.8	7.3 ± 1.9	N/A	N/A

[a]One patient with laryngeal dystonia was removed from final analysis (see 'Materials and methods' section).
[b]Dystonia severity was assessed using the Writer's Cramp Rating Scale (Wissel *et al.*, 1996; Kruisdijk *et al.*, 2007) and perceptual evaluation of the severity of laryngeal dystonia symptoms using a visual analogue scale from 0 to 10 (Simonyan and Ludlow, 2010; Rumbach *et al.*, 2017).
F = female; LD = laryngeal dystonia; M = male; N/A = not applicable; WC = writer's cramp.

All patients and healthy subjects provided written informed consent before participation in the study, which was approved by the Institutional Review Boards of the National Institute of Neurological Disorders and Stroke and the National Institutes of Health (NIH) Radiation Safety Committee. The majority of subjects in the current study have also participated in our previous studies, which defined abnormalities of dopamine D_2 receptors and striatal dopamine release in dystonia (Berman *et al.*, 2013; Simonyan *et al.*, 2013*a*). While this allowed us to examine the dopaminergic function in a relatively homogeneous group of subjects, it might have limited the generalizability of the results.

Data acquisition

All subjects were instructed not to drink any beverages containing caffeine or alcohol within 24 h of scanning and fast for 3 h before the PET scan. All scans were performed on a HRRT scanner (Siemens Medical Solutions) between 8:10 a.m. and 2:30 p.m. to control for possible diurnal variations in dopaminergic neurotransmission. The HRRT scanner has high sensitivity, a spatial resolution of 2.5 mm, and an axial field of view of 25 cm, which makes it particularly suitable for obtaining high resolution images of small and deep brain structures. All subjects were scanned in the resting state in a relaxed and comfortable position with eyes closed in an environment with dimmed lights and reduced ambient noise. An individually shaped thermoplastic mask was comfortably moulded around the subject's head and fixed to the scanner table to minimize head motions during scanning. In addition, all subjects wore a swimming cap with small light reflectors to capture and monitor the head position and movements during the scan. This information was used to reduce any blurring of PET images and to correct for potential head motion during individual image reconstruction.

Prior to radiotracer administration, a transmission scan was obtained with a rotating ^{137}Cs source for attenuation correction of emission data. The radioligand ^{11}C-NNC-112 displays high affinity for dopamine D_1 receptors (dissociation constant K_D = 0.18 nmol/l), has higher specific-to-non-specific binding ratios compared to another commonly used ligand ^{11}C- SCH-23390, is highly reliable for PET quantifications, and has a relatively modest radiation burden in humans (Halldin *et al.*, 1998; Abi-Dargham *et al.*, 2000; Cropley *et al.*, 2006). ^{11}C-NNC-112 also shows affinity to cortical serotonin 5-HT_{2A} receptors, albeit with at least 5–10-fold reduced selectivity than to D_1 receptors. However, the ligand's binding to striatal 5-HT_{2A} receptors is not detectable, as D_1 receptor density is high and 5-HT_{2A} receptor density is negligible (Ekelund *et al.*, 2007; Slifstein *et al.*, 2007; Catafau *et al.*, 2010; Abi-Dargham *et al.*, 2012). Because our study was focused on examination of striatal neurotransmission, the contribution of 5-HT_{2A} receptor binding played an insignificant, if any, role in quantification of striatal dopamine D_1 receptor availability to NNC-112. ^{11}C-NNC-112 was synthesized as previously reported (Halldin *et al.*, 1998) and administered intravenously as a bolus over 1 min using a computer-controlled pump (Harvard Apparatus). A 90-min dynamic emission scan with a total of 27 time frames of increasing length (6 × 30 s; 3 × 1 min; 2 × 2 min; 16 × 5 min) was acquired in each subject. A mean injected dose of ^{11}C-NNC-112 was 19.4 ± 1.2 mCi with mean specific activity of 3059.2 ± 1374.2 mCi/μmol. There were no statistically significant differences in the tracer condition between patient and control groups (all $P \geqslant 0.38$).

A high resolution T_1-weighted image was acquired in each subject on a 3 T GE scanner as an individual anatomical reference (3D magnetization prepared rapid acquisition gradient echo sequence with inversion time = 450 ms; echo time = 3.0 ms; flip angle 10°; bandwidth = 31.25 mm; field of view = 240 mm; matrix = 256 × 256 mm; 128 contiguous axial slices; slice thickness = 1.2 mm).

Data analysis

As a first step in data analysis, head motion was corrected using the registered attenuation correction method. After reconstruction of emission images with filtered back-projection with no attenuation correction, all emission frames were registered with mutual information to the prime emission image

using FSL software (FLIRT toolbox). Transmission images were then registered to the same prime emission image, and the emission frame was reconstructed with filtered back-projection to be used for attenuation correction. The emission image was resliced back to the transmission position, thus correcting for motion. Additionally, individual quality indices were calculated for all preprocessed data using AFNI software to ensure that there were no residual head motions, which may have introduced artefacts in the acquired images.

Final motion- and decay-corrected images were averaged over 2–27 frames (Karimi *et al.*, 2013), aligned to individual high-resolution T_1-weighted images using Hellinger distance and the two-pass alignment method, smoothed with an isotropic 6 mm Gaussian kernel, and normalized to a standard Talairach-Tournoux space using PMOD Technologies and AFNI software packages, as described previously (Berman *et al.*, 2013; Simonyan *et al.*, 2013*a*). To minimize white matter influence on grey matter signal, partial volume correction was performed using the segmented grey matter, white matter, and CSF masks of individual T_1-weighted images that were coregistered to PET, as described earlier (Giovacchini *et al.*, 2004; Cropley *et al.*, 2008). Parametric voxelwise maps of ^{11}C-NNC-112 binding were calculated using the equilibrium ratio of bound ligand to free and non-specifically bound ligand under the assumption that non-specific binding is uniform throughout the brain (Innis *et al.*, 2007). The equation $BP_{ND} = (C - C') / C'$ (where BP = binding potential; and ND = free and non-specific concentrations) was based on the radioactivity concentrations in the striatum (C) as a region of the highest density of dopamine D_1 receptors and the cerebellar grey matter (C') as a reference region of low dopamine D_1 receptor density. A segmented and PET-coregistered mask of the entire striatum was used; the cerebellar mask was defined on five consecutive slices in both hemispheres and placed ventral to the occipital and temporal cortices and lateral to the cerebellar vermis. To account for the influences of potential outliers on ^{11}C-NNC-112 BP signal variance, voxelwise median absolute deviations (MADs) were calculated for each dataset; the subjects were considered as outliers if their values were outside the median $\pm$ 3.5 $\times$ MADs range (Berman *et al.*, 2013; Simonyan *et al.*, 2013*a*). One patient with laryngeal dystonia was an outlier and was, therefore, removed from final statistical analysis. While the presence of this outlier may be viewed as normal fluctuation within a population, it may also be a confound related to scanner instabilities, experimental issues, or acquisition artefacts during scanning. Statistical difference between each patient and control groups was assessed using a voxelwise two-sample independent *t*-test at family-wise error (FWE)-corrected $P \leqslant 0.05$.

Correlations between ^{11}C-NNC-112 binding potential measures and dystonia characteristics

The duration of dystonia was established from the time of symptom onset during the patients' history and neurological examination. Writer's cramp symptom severity was assessed using the Writer's Cramp Rating Scale (Wissel *et al.*, 1996; Kruisdijk *et al.*, 2007); laryngeal dystonia symptom severity was evaluated perceptually using a visual analogue scale from 0 (normal) to 100 (most severe) (Simonyan and Ludlow, 2010; Rumbach *et al.*, 2017). We expected that a subregion of the striatum would show correlations with clinical measures of dystonia. Because averaging all voxels in the whole-striatal region for a correlation analysis with clinical measures can often miss significant correlations due to averaged out signal in a significant subregion, we instead carried out voxelwise Spearman's rank order correlations between the clinical measures of dystonia and striatal BP_{ND} values. We applied a voxelwise FWE correction and set our *P*-level at $\leqslant 0.025$ accounting for patients' age to additionally correct for two examined measures (dystonia duration and severity).

Striatal topology of dopaminergic abnormalities

With the rationale to determine the overall striatal topology of abnormal dopaminergic neurotransmission in dystonia, we combined the findings from the current study with those from our previous reports (Berman *et al.*, 2013; Simonyan *et al.*, 2013*a*). The latter have identified decreased dopamine D_2 receptor availability at rest and decreased striatal dopamine release during symptomatic task production in writer's cramp and laryngeal dystonia patients. A combination of these datasets with current findings allowed us to map the spatial distribution of abnormal D_1 and D_2 receptor binding and phasic dopamine release in focal dystonia.

For this, in each patient and healthy control group, separately, we performed a conjunction analysis between the three binary masks of statistical parametric maps that were measures of distribution of ^{11}C-NNC-112 BP_{ND} (for dopamine D_1 receptor availability), ^{11}C-raclopride BP_{ND} (for dopamine D_2 receptor availability), and ^{11}C-raclopride ΔBP_{ND} (for phasic striatal dopamine release). An *a priori* threshold for generation of each statistical parametric map was set at FWE-corrected $P \leqslant 0.05$. The three types of output of conjunction analysis included statistical maps that showed the overlapping voxels between all three measures; the overlapping voxels between the two measures, and the non-overlapping, distinct voxels for each measure. Thus, the significant clusters of both overlapping and distinct distributions of D_1, D_2 receptors and dopamine release were identified within each patient and control group, separately.

Finally, we conducted a comparative qualitative analysis between the current findings and previously reported maps of somatotopic body representation within the striatum (Kunzle, 1975; Simonyan and Jurgens, 2003).

Results

Striatal dopamine D_1 receptor availability and its correlations with clinical measures

Compared to healthy controls, both patient groups were characterized by increased availability of dopamine D_1 receptors in the striatum. Specifically, patients with writer's cramp showed increased ^{11}C-NNC-112 binding in the bilateral putamen (mean difference: right = 22.5%, $P = 0.004$; left = 19.6%, $P = 0.009$). Patients with laryngeal dystonia had increased radioligand binding in the right putamen and caudate nucleus (mean difference: putamen = 24.6%,

$P = 0.006$; caudate nucleus = 26.8%, $P = 0.003$) (Fig. 1A, C and Table 2). These changes in dopamine D_1 receptor availability were observed along the anterior-posterior axis of the striatum, involving its associative (anterior) and sensorimotor (posterior) subdivisions in both patient groups.

Accounting for patients' age, the duration of dystonia showed a significant relationship with abnormally increased dopamine D_1 receptor availability. Duration of writer's cramp was negatively correlated with ^{11}C-NNC-112 binding in the right posterior putamen ($R_s = -0.87$, $P = 0.0005$) and left anterior caudate nucleus ($R_s = -0.71$, $P = 0.01$) (Fig. 1B). Duration of laryngeal dystonia was negatively correlated with increased radioligand binding in the bilateral anterior and right posterior putamen (all $R_s \geqslant -0.85$, $P \leqslant 0.001$) (Fig. 1D). No significant relationships were found between dopamine D_1 receptor availability and the severity of dystonia in either writer's cramp or laryngeal dystonia patients at $P \leqslant 0.025$.

Topological organization of striatal dopaminergic function

We found that healthy subjects had a great degree of overlap between the measures of dopamine D_1 and D_2 receptor availability and task-induced dopamine release, as well as smaller regions of distinct receptor distribution. This picture was reversed in patients with focal dystonia, where the overlap was largely diminished. Specifically, a conjunction analysis in healthy subjects showed common regions of D_1 receptor × D_2 receptor × dopamine release in the bilateral putamen as well as additional regions of D_1 receptor × D_2 receptor, D_1 receptor × dopamine release and D_2 receptor × dopamine release in the bilateral putamen (Fig. 2A and C). The latter overlap was also found in the right caudate nucleus. In addition, healthy subjects had non-overlapping clusters of dopamine D_1 and D_2 receptor availability (Fig. 2A and C).

This normal topology of striatal dopaminergic neurotransmission was profoundly disorganized in focal dystonia (Fig. 2B and D). Patients with writer's cramp showed a separation of topological distribution of D_1 and D_2 receptor availability, characterized by regions of bilateral increases of dopamine D_1 receptors, decreased D_2 receptors, and decreased dopamine release during production of a symptomatic task (Fig. 2B). Except for a small region of an overlap of D_1 × D_2 receptors in the right anterior putamen, there were no other common regions between direct and indirect pathways as well as dopamine receptor distribution and phasic dopamine release.

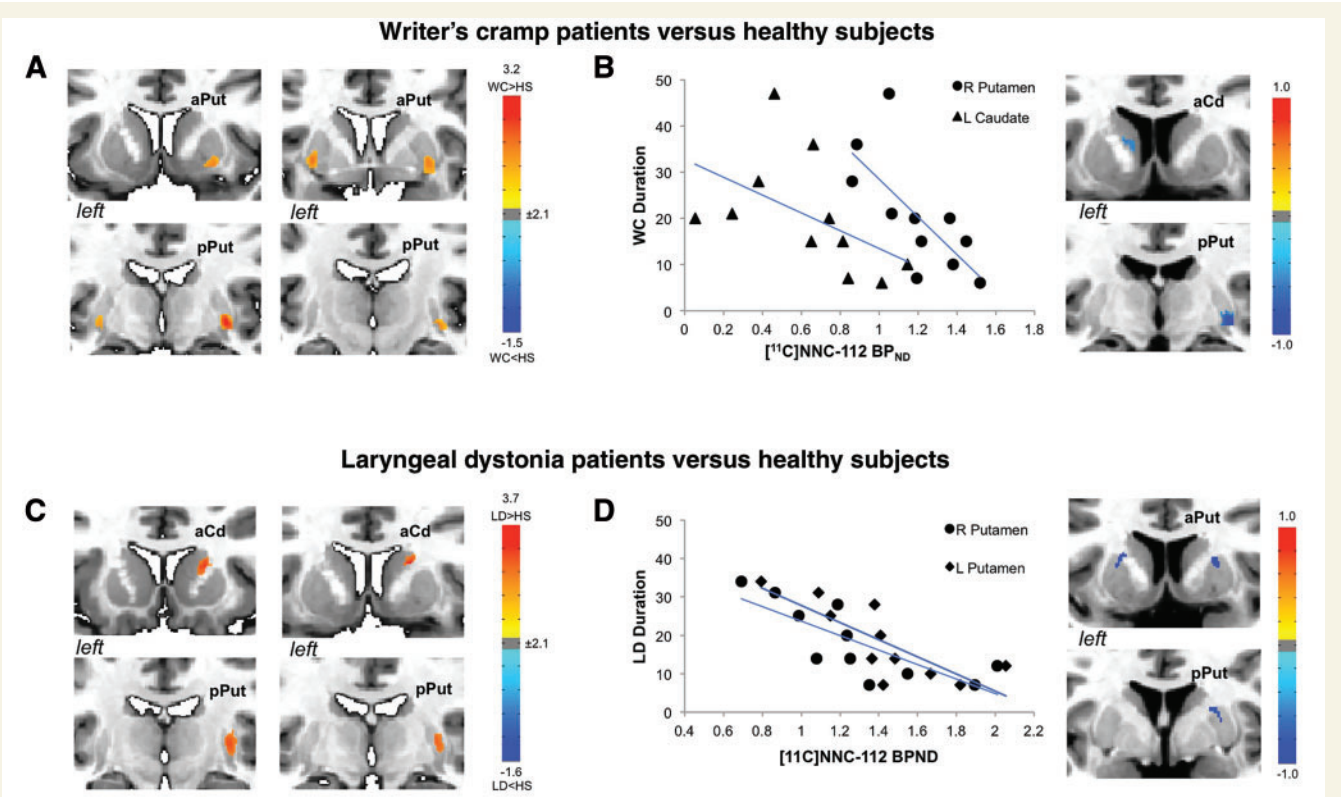

Figure 1 Striatal dopamine D_1 receptor availability and its correlations with clinical measures in focal dystonia. Group differences in ^{11}C-NNC-112 binding between writer's cramp (WC) patients and healthy subjects (HS) (**A**) and between laryngeal dystonia (LD) patients and healthy subjects (**C**). The colour bars represent the *t*-values and reflect the significance of changes in striatal ^{11}C-NNC-112 BP_{ND} measures in patients (yellow to red) compared to healthy subjects (dark blue to light blue). **B** and **D** depict relationships (Spearman's correlation coefficients) between dystonia duration and ^{11}C-NNC-112 BP_{ND} in writer's cramp and laryngeal dystonia, respectively. All statistical maps are shown in the series of coronal brain images in a Talairach-Tournoux standard space. aCd = anterior caudate nucleus; aPut = anterior putamen; pPut = posterior putamen.

Table 2 Significant differences in ^{11}C-NNC-112 binding between patient and control groups

Regional clusters of group differences in ^{11}C-NNC-112 BP_{ND} (Peak *x*, *y*, *z* coordinates)	^{11}C-NNC-112 BP_{ND} (patients / controls)	Mean group difference in ^{11}C-NNC-112 BP_{ND}	Cluster *P*-value
Writer's cramp versus healthy subjects			
Right putamen	1.29 ± 0.22 / 1.00 ± 0.29	WC > HS by 22.5%	0.004
30, −10, 0			
Left putamen	1.56 ± 0.24 / 1.25 ± 0.37	WC > HS by 19.6%	0.009
−28, −4, 1			
Laryngeal dystonia versus healthy subjects			
Right putamen	1.11 ± 0.14 / 0.84 ± 0.30	LD > HS by 24.6%	0.006
29, −12, 6			
Right caudate nucleus	1.27 ± 0.21 / 0.93 ± 0.30	LD > HS by 26.8%	0.003
18, 7, 14			

^{11}C-NNC-112 values are shown as group mean ± standard deviation for the significant clusters of striatal differences between patients and controls, as depicted in Fig. 1A and C. The same control subjects were used for the comparisons with both writer's cramp (WC) and laryngeal dystonia (LD) patients. The difference in the control ^{11}C-NNC-112 BP_{ND} values in the right putamen is due to the difference in the location of the significant cluster in writer's cramp versus healthy subjects (HS) and laryngeal dystonia versus healthy subjects comparisons.

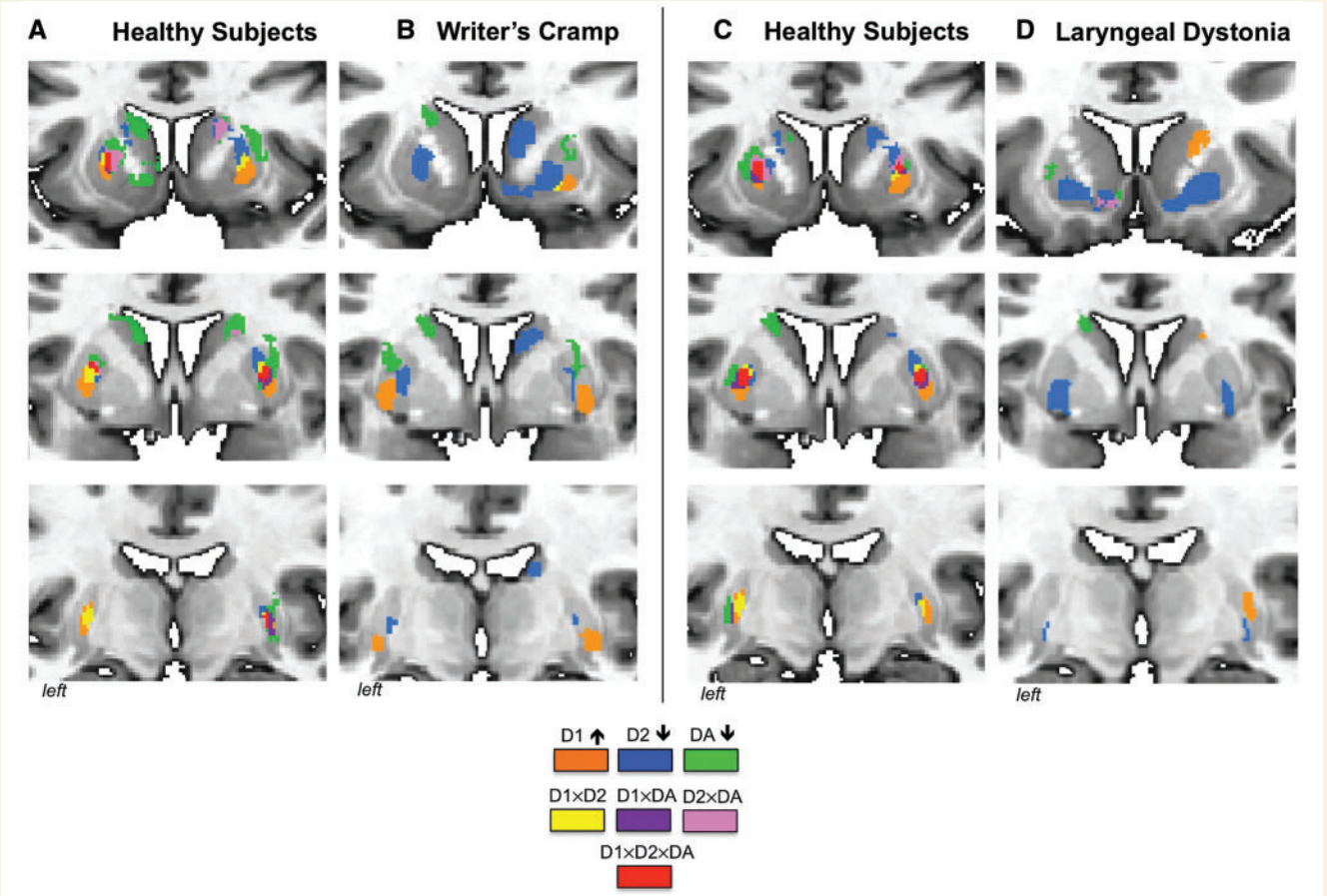

Figure 2 Topological distribution of striatal dopaminergic function in healthy subjects (A and C) and patients with writer's cramp (B) and laryngeal dystonia (D). Within each patient and control group, a conjunction analysis was used to examine the overlap and distinct distribution between the significant clusters derived from three measures of dopaminergic function: D_1 receptor binding; D_2 receptor binding, and striatal phasic dopamine release during finger tapping (for the comparison with writer's cramp) and sentence production (for the comparison with laryngeal dystonia). Our data show that healthy subjects have a great degree of overlap between all three measures as well as smaller regions of distinct receptor distribution (**A** and **C**). This topology is reversed in patients with dystonia, where the overlap is largely diminished (**B** and **D**). The legend provides the colour scheme for overlapping as well as the distinct regions of receptor activation and dopamine release. The results of conjunction analysis are shown in the series of coronal brain images in Talairach-Tournoux standard space. DA = dopamine.

Similarly, abnormal topology of striatal dopaminergic neurotransmission in laryngeal dystonia patients was characterized by a right-striatal increase in D_1 receptor availability, bilateral decreases in D_2 receptor availability, and a left-striatal decrease in dopamine release during symptomatic task production (Fig. 2D). Only a small cluster of an overlap of D_2 receptors × dopamine release was found in the left anterior caudate nucleus.

Despite topological disorganization of dopaminergic neurotransmission in dystonia, observed abnormalities largely followed a known somatotopic distribution of body representation within the striatum (Fig. 3A) (Kunzle, 1975; Simonyan and Jurgens, 2003). In patients with writer's cramp, dopaminergic function within both direct and indirect pathways was mainly altered within the hand representation in the mid-portion of the putamen (Fig. 3B), whereas patients with laryngeal dystonia had their abnormalities localized within the larynx representation in the ventral portion of the putamen (Fig. 3C).

Discussion

The concept that dystonia pathophysiology involves imbalance between direct and indirect basal ganglia pathways has been proposed more than two decades ago (Hallett, 1993, 1998). However, in the following years, the vast majority of research has focused on mapping and investigation of the potential role of indirect pathway, while studies on direct pathway remained scarce. Our current study provides critically missing experimental evidence for global dopaminergic dysfunction within the basal ganglia circuitry, affecting not only its indirect but also direct pathway.

Striatal dopamine D_1 receptor availability in focal dystonia

In two independent groups of patients with isolated focal dystonia of hand and larynx, we identified abnormally increased availability of dopamine D_1 receptors, as well as abnormally decreased D_2 receptor distribution (Berman *et al.*, 2013; Simonyan *et al.*, 2013*a*). These findings suggest that the direct basal ganglia pathway is hyperfunctional, and the indirect basal ganglia pathway is hypofunctional in focal dystonia. For understanding of a possible mechanism of such receptor abnormalities in dystonia, it is important to consider that high D_1 receptor availability might be due to the development of denervation

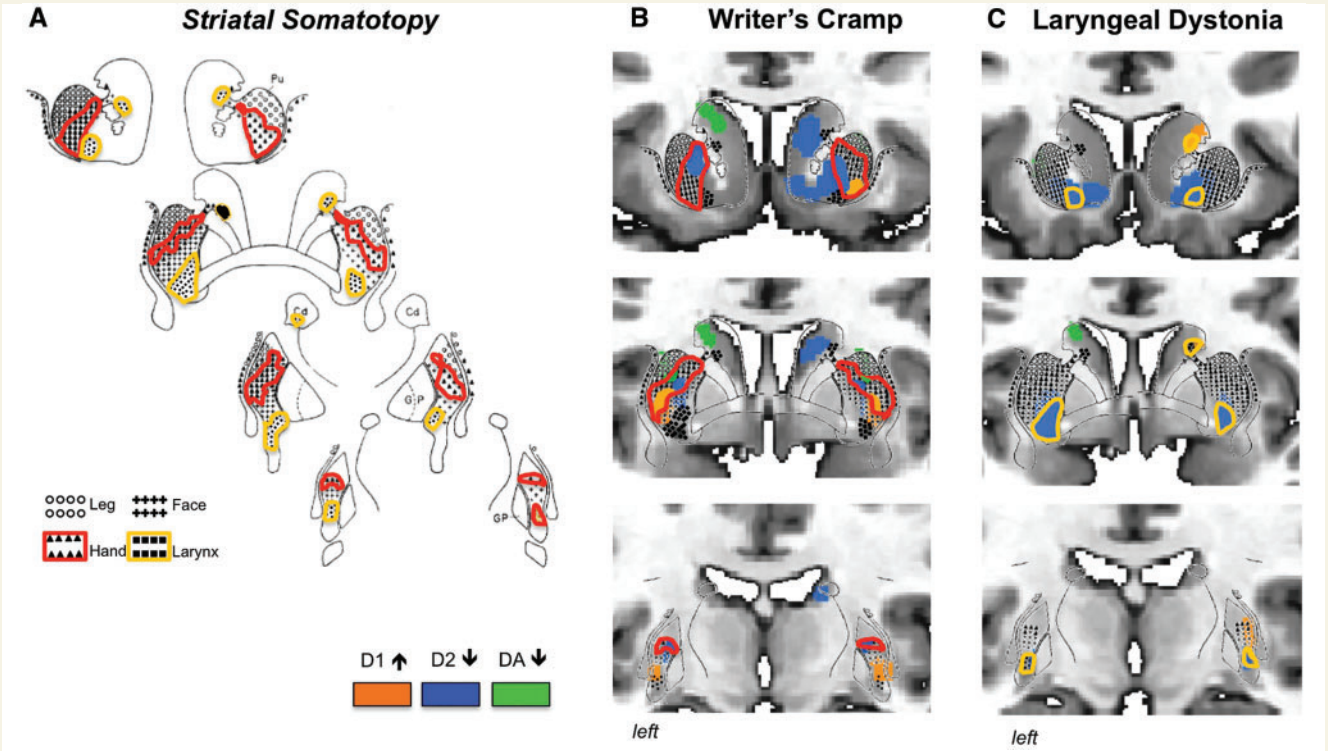

Figure 3 Somatotopic distribution of striatal dopaminergic function in patients with writer's cramp and laryngeal dystonia. (**A**) Somatotopy of body region representation within the striatum based on neuroanatomical tract tracing studies in the macaque monkey (modified from Kunzle, 1975; Simonyan and Jurgens, 2003). Red and yellow outlines show hand and larynx representations, respectively. (**B** and **C**) Corresponding group maps of distribution of dopaminergic abnormalities in writer's cramp and laryngeal dystonia with superimposed map of outlined somatotopic hand or larynx representations in the striatum. All statistical maps are shown in the series of coronal brain images in a Talairach-Tournoux standard space. DA = dopamine.

hypersensitivity. In review of the literature, PET studies in Parkinson's disease have reported an increase in striatal D_2 receptor binding, but no significant changes in D_1 receptor binding in the presence of certainly decreased dopamine release (reviewed in Niccolini *et al.*, 2014). A study of the lesioning effects of 6-hydroxydopamine (6-OHDA, used in modelling Parkinson's disease in animals) on D_1 and D_2 receptor availability in the rat showed increased D_2 receptors (consistent with human PET studies) and decreased D_1 receptors (Wedekind *et al.*, 2017). It has been suggested that, while an upregulation of D_2 receptors in early Parkinson's disease may be compensatory due to depletion of synaptic dopamine levels, it could be short-lived as D_2 receptor availability decreases either back to normal levels or less over the course of disease progression that is characterized by increased degeneration of nigrostriatal dopamine neurons (Brooks *et al.*, 1992; Schwarting and Huston, 1996; Antonini *et al.*, 1997; Dentresangle *et al.*, 1999). Taken together, these data indicate that dopamine decreases in Parkinson's disease would lead to changes opposite to our findings in focal dystonia that are an upregulation of D_1 and a downregulation of D_2 receptors. Furthermore, in contrast to Parkinson's disease, dystonia is not characterized by either a progression of the disorder, which typically plateaus within the first year of onset, or progressive neurodegeneration of nigrostriatal dopaminergic neurons. While D_1 receptor availability is negatively correlated with duration of focal dystonia, it does not become normal or lower than normal over the course of disorder, as it occurs in Parkinson's disease. Finally, in focal dystonia, there is not obvious net decrease of dopamine release as it fluctuates from lower than normal during symptomatic task to higher than normal during asymptomatic task. Thus, based on our knowledge to date, decreased dopamine release in dystonia and Parkinson's disease appears to have distinctly different pathophysiological influences on the basal ganglia circuitry in each disorder. It is likely that striatal receptor abnormalities in dystonia reflect primary pathophysiology rather than are reactive to dopamine depletion, as it may be a case in Parkinson's disease.

Topology and somatotopy of striatal dopaminergic abnormalities

Dopaminergic dysfunctions in writer's cramp and laryngeal dystonia involved both associative (anterior) and sensorimotor (posterior) striatal subdivisions. As different striatal subdivisions establish parallel cortical loops (Alexander *et al.*, 1986), alterations of dopaminergic function at the entire anterior-posterior striatal extent may have direct impact not only on hyperexcitability of motor cortex but also of parietal and prefrontal cortices, which are responsible for the normal control of sensorimotor integration and preparation to motor execution during writing and speaking (Horovitz *et al.*, 2013; Fuertinger *et al.*, 2015). This is in line with recent evidence suggesting that the pathophysiology of focal dystonia is not limited to the basal ganglia and rather involves large-scale functional network alterations (Jin *et al.*, 2011; Battistella *et al.*, 2017; Fuertinger and Simonyan, 2017), with multiple cortical regions showing abnormal activity and functional connectivity (Ibanez *et al.*, 1999; Simonyan and Ludlow, 2010; Battistella *et al.*, 2016; Gallea *et al.*, 2016). These cortical alterations may, in part, be due to propagation of abnormal dopaminergic function via different striato-cortical loops. One possible underlying mechanism may involve the dopaminergic influences on basal ganglia beta activity, which is important for movement initiation and termination as well as long-range synchronizations between neural populations relevant to movement execution (Kopell *et al.*, 2000; Schnitzler and Gross, 2005; Jenkinson and Brown, 2011). It has been shown that beta activity in the cortico-basal ganglia circuitry is abnormal in patients with dystonia (Toro *et al.*, 2000; Jin *et al.*, 2011; Brittain and Brown, 2014; Neumann *et al.*, 2015), and drugs that modulate dopamine release and the activity of D_1 and D_2 receptors can alter beta activity in the basal ganglia (Hammond *et al.*, 2007; Kuhn *et al.*, 2008; Puig and Miller, 2012). Although the functional significance of these oscillations remains unclear, it is plausible that abnormal striatal dopaminergic neurotransmission influences basal ganglia beta oscillations, which further propagate to cortical regions, contributing to large-scale functional network aberrations. This assumption warrants further verification in a future series of studies.

Another characteristic feature of altered striatal dopaminergic neurotransmission in dystonia was abnormal separation of clusters of D_1 and D_2 receptor availability and dopamine release. In contrast to healthy subjects, patients with dystonia showed negligible, if any, overlap between the regions of dopamine D_1 and D_2 receptor distribution, pointing to the loss of interface between the hyperfunctional direct and hypofunctional indirect pathways. Furthermore, the loss of a conjoint overlap between the regions of dopamine D_1 and D_2 receptor availability and phasic dopamine release suggests disorganization of a nigro-striatal input and may represent an important attribute of dopaminergic abnormalities contributing to the pathophysiology of dystonia.

Interestingly, despite this functional disorganization, dopaminergic abnormalities in both writer's cramp and laryngeal dystonia were largely confined within the representations of the affected body regions, i.e. hand and larynx. Similar to the motor cortex, the striatum is somatotopically organized with leg–hand/arm–face–larynx representations distributed along its dorsal–ventral axis, respectively (Kunzle, 1975; Simonyan and Jurgens, 2003). Abnormal dopamine D_1 and D_2 receptor function in writer's cramp patients was largely localized in the mid-portion of striatum, which receives direct output from the hand motor-cortical region (Kunzle, 1975), whereas D_1 and D_2 receptor alterations in laryngeal dystonia patients were found in the ventral portion of striatum, which receives direct terminals

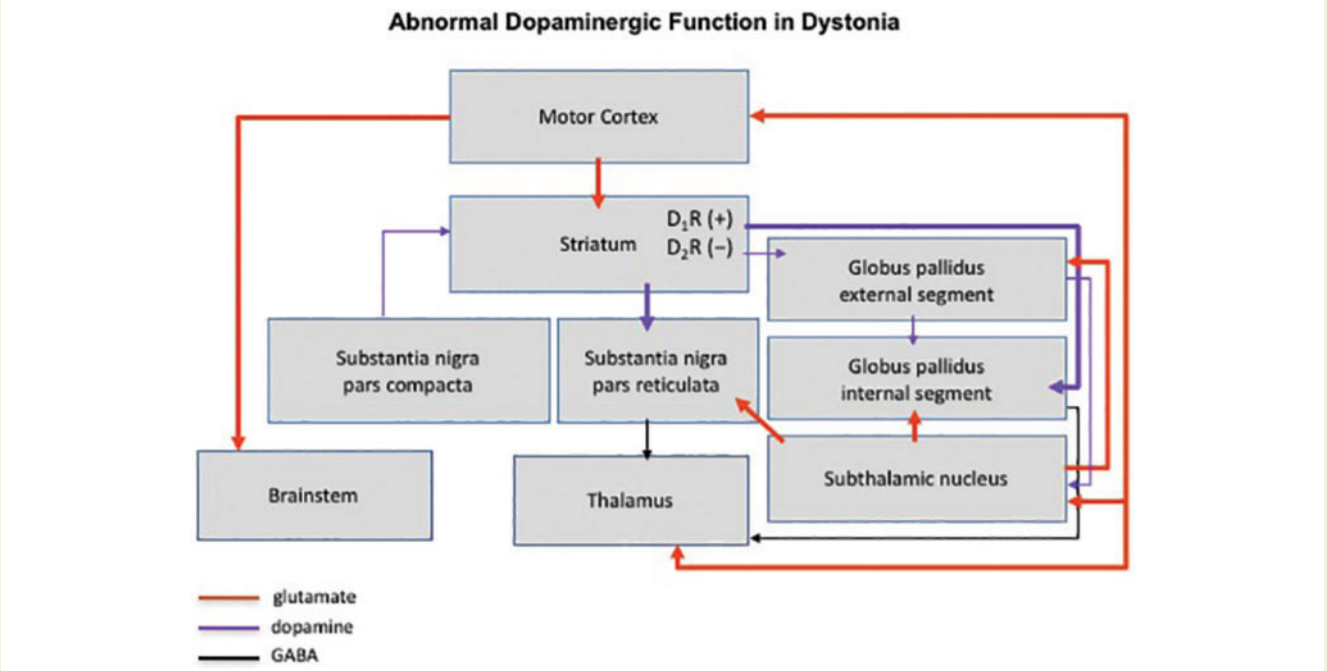

Figure 4 Simplified schematic representation of global dopaminergic abnormalities within the basal ganglia-thalamo-cortical circuitry in dystonia. Striatal dopaminergic input from the substantia nigra, pars compacta, is weakened; dopaminergic neurotransmission is enhanced via the direct pathway and diminished via the indirect pathway.

from the laryngeal motor cortex (Simonyan and Jurgens, 2003). Such spatial localization of dopaminergic abnormalities within affected body region representations along the anterior-posterior striatal axis is highly relevant to the control of writing and speaking in writer's cramp and laryngeal dystonia. It also characterizes a unique, disorder-specific pattern of otherwise commonly abnormal striatal function in each form of focal dystonia. This distinctive feature of dopaminergic alterations is potentially a reason why the only other attempt to map dopamine D_1 receptor alterations in dystonia has failed (Karimi *et al.*, 2013). That study found no significant differences in striatal dopamine D_1 receptor availability between healthy subjects and a mixed group of patients with cranial, cervical and hand dystonia, which may have lacked necessary sensitivity to striatal neuroanatomy and dystonia form-specific pathophysiology. Conversely, our study was successful in identifying dopamine D_1 receptor abnormalities by separating patients with focal hand and laryngeal dystonias into the independent cohorts and by using the highest possible resolution of the HRRT scanner to capture even subtle alterations of dopaminergic neurotransmission via the direct basal ganglia pathway.

Clinical correlates of abnormal striatal dopaminergic function

It is important to note that D_1 receptor increases were found in the bilateral putamen in writer's cramp and right striatum in laryngeal dystonia, whereas the duration but not severity of dystonia was significantly and negatively correlated with dopamine D_1 receptor availability in bilateral striatum, including its associative and sensorimotor subdivisions, in both groups of patients. Although somewhat counterintuitive, such distribution of receptor abnormalities in writer's cramp and laryngeal dystonia, which are task-specific dystonias affecting left-hemisphere lateralized behaviours in right-handed individuals, fit well their overall neuroimaging signature, including bilateral functional alterations in writer's cramp as well as right-sided abnormalities in laryngeal dystonia (Peller *et al.*, 2006; Simonyan *et al.*, 2008; Ramdhani *et al.*, 2014; Zeuner *et al.*, 2015; Kostic *et al.*, 2016). On the other hand, bilateral correlations of D_1 receptor availability with the duration of dystonia suggest that the highest levels of D_1 receptor upregulation may be present at the very early stages of symptom manifestation and appear to be variable over patients. Notably, the relationship between the duration of dystonia and abnormally increased dopamine D_1 receptor availability was independent of patients' age and, thus, may not be attributed to normal age-related changes in dopaminergic function. In addition to correlations between dystonia duration and high dopamine D_1 receptor availability, we previously reported that low dopamine D_2 receptor availability and decreased levels of symptom-induced striatal dopamine release increase over the duration of writer's cramp and laryngeal dystonia, respectively (Berman *et al.*, 2013; Simonyan *et al.*, 2013*a*). Thus, an upregulation of D_1 receptors, a downregulation of D_2 receptors and decreases of dopamine release at the early stages of clinical symptom manifestation with inverse relationships in the course of

dystonia duration but not its severity may represent a developmental endophenotype of this disorder.

Updated basal ganglia circuitry in focal dystonia

Taken together, striatal imbalance of dopaminergic neurotransmission is likely a major pathophysiological factor contributing to bottom-up alterations of the entire basal ganglia-thalamo-cortical circuitry: attenuated and topologically 'misplaced' dopamine release from the substantia nigra, pars compacta, into the dorsal striatum acts upon upregulated direct pathway (due to amplified dopamine D_1 receptors) and weakened indirect pathway (due to diminished dopamine D_2 receptors) (Fig. 4). This leads to overly excessive excitatory striatal output via the direct pathway in the presence of decreased inhibitory striatal output via the indirect pathway, which, collectively, disinhibit the thalamus and propagate further to the motor cortex and other cortical areas relevant to motor control. As phasic dopamine release is coupled with striatal neural activity and functional networks in healthy subjects (Simonyan *et al.*, 2013*b*), abnormal dopaminergic neurotransmission via both direct and indirect pathways potentially may underlie dissociations between increased activity in the striatum and sensorimotor cortex, establishing a dystonia-characteristic pathophysiological cortico-striatal loop.

Conclusion

Complex disorganization of striatal dopaminergic neurotransmission via both direct and indirect basal ganglia pathways is a common pathophysiological trait in focal dystonias. Somatotopically distinct and topologically disorganized distribution of striatal abnormalities in different forms of focal dystonia points to unique alterations of specific basal ganglia-thalamo-cortical circuits that support the motor control of an affected body region and/or task production. Finally, the associations between dopaminergic abnormalities and the duration but not severity of dystonia provide evidence that these alterations represent a developmental endophenotype of this disorder.

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