

Striatal dopaminergic dysfunction at rest and during task performance in writer's cramp

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Writer's cramp is a task-specific focal hand dystonia characterized by involuntary excessive muscle contractions during writing. Although abnormal striatal dopamine receptor binding has been implicated in the pathophysiology of writer's cramp and other primary dystonias, endogenous dopamine release during task performance has not been previously investigated in writer's cramp. Using positron emission tomography imaging with the D₂/D₃ antagonist ¹¹C-raclopride, we analysed striatal D₂/D₃ availability at rest and endogenous dopamine release during sequential finger tapping and speech production tasks in 15 patients with writer's cramp and 15 matched healthy control subjects. Compared with control subjects, patients had reduced ¹¹C-raclopride binding to D₂/D₃ receptors at rest in the bilateral striatum, consistent with findings in previous studies. During the tapping task, patients had decreased dopamine release in the left striatum as assessed by reduced change in ¹¹C-raclopride binding compared with control subjects. One cluster of reduced dopamine release in the left putamen during tapping overlapped with a region of reduced ¹¹C-raclopride binding to D₂/D₃ receptors at rest. During the sentence production task, patients showed increased dopamine release in the left striatum. No overlap between altered dopamine release during speech production and reduced ¹¹C-raclopride binding to D₂/D₃ receptors at rest was seen. Striatal regions where D₂/D₃ availability at rest positively correlated with disease duration were lateral and non-overlapping with striatal regions showing reduced D₂/D₃ receptor availability, except for a cluster in the left nucleus accumbens, which showed a negative correlation with disease duration and overlapped with striatal regions showing reduced D₂/D₃ availability. Our findings suggest that patients with writer's cramp may have divergent responses in striatal dopamine release during an asymptomatic motor task involving the dystonic hand and an unrelated asymptomatic task, sentence production. Our voxel-based results also suggest that writer's cramp may be associated with reduced striatal dopamine release occurring in the setting of reduced D₂/D₃ receptor availability and raise the possibility that basal ganglia circuits associated with premotor cortices and those associated with primary motor cortex are differentially affected in primary focal dystonias.

Keywords: dystonia; dopamine; PET; raclopride; striatum

Abbreviation: AFNI = analysis of functional neuroimages; BP = binding potential; FWE = family-wise error; PET = positron emission tomography; RAC = ¹¹C-raclopride; ROI = region of interest; SD = spasmodic dysphonia; WC = writer's cramp; WCRS = writer's cramp rating scale

Introduction

Primary dystonia is a neurological disorder characterized primarily by involuntary muscle spasms giving rise to patterned movements and abnormal postures occurring in the absence of a brain lesion, neurodegeneration or identifiable exogenous cause (Tarsy and Simon, 2006; Albanese *et al.*, 2011). Focal dystonias affect one body part or region and can be task-specific, affecting the fine motor control required for tasks such as writing (writer's cramp), speaking (spasmodic dysphonia), playing a musical instrument, or running (Torres-Russotto and Perlmutter, 2008). Evidence from a number of investigations suggests that primary focal dystonias might share a common aetiology and that abnormalities in the striatal dopamine system may contribute to dystonia pathophysiology (Hallett, 2006a, 2006b; Defazio *et al.*, 2007; Breakefield *et al.*, 2008).

Most dopaminergic imaging studies in primary focal dystonia have focused on detecting abnormalities in striatal D₂-like receptor binding. Striatal D₂/D₃ receptor availability has been reported to be reduced in writer's cramp (Horstink *et al.*, 1997; Berger *et al.*, 2007), cervical dystonia (Naumann *et al.*, 1998), blepharospasm (Horie *et al.*, 2009), and in a mixed group of patients with hand and cranial dystonia (Perlmutter *et al.*, 1997b). However, some conflicting findings on dopamine receptor binding have been reported. For example, no significant differences in striatal D₂/D₃ availability were detected in earlier studies in patients with cervical dystonia (Leenders *et al.*, 1993; Hierholzer *et al.*, 1994; Becker *et al.*, 1997). Similarly, a recent study of a mixed group of hand and cranial dystonia patients using the more selective D₂ receptor radioligand ¹⁸F-*N*-methyl-benperidol found no significant differences from control subjects (Karimi *et al.*, 2011). Importantly, binding by the radioligands used in dopamine receptor imaging studies can be affected by competition with synaptic concentration of dopamine (Laruelle, 2012). Thus, discrepancies in striatal D₂-like receptor availability among previous dopamine receptor imaging studies might be a consequence of abnormal tonic release of striatal dopamine when subjects were scanned at rest.

Although the number of pathological studies in primary focal dystonia is limited, most have not found evidence for abnormal cellular degeneration of nigro-striatal neurons in focal dystonia (Standaert, 2011). Nevertheless, abnormal striatal dopamine release may contribute to the disorder. In non-human primates, transient dystonia is seen following an acute reduction in striatal dopamine induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine—a neurotoxin that selectively destroys dopaminergic neurons (Perlmutter *et al.*, 1997a; Tabbal *et al.*, 2006). In addition, low levels of striatal dopamine have also been associated with the manifestation of dystonia in DYT5 or DOPA-responsive dystonia caused by genetic mutations interfering with dopamine production, typically without the loss of nigro-striatal neurons (Knappskog *et al.*, 1995; Clot *et al.*, 2009).

In post-mortem studies of generalized early-onset DYT1 dystonia caused by the *TOR1A* mutation, striatal dopamine has also been found to be reduced (Hornykiewicz *et al.*, 1986; Furukawa *et al.*, 2000; Augood *et al.*, 2002). The reduction in striatal dopamine in these cases was not accompanied by degeneration of

neurons within the substantia nigra except in one case where the individual tested positive for the *TOR1A* mutation, but during life was diagnosed with parkinsonism at age 53 and treated with dopamine replacement therapy (Augood *et al.*, 2002). Further support for reduced dopamine release in primary dystonia has been suggested in mouse models of DYT1 dystonia (Balcioglu *et al.*, 2007; Page *et al.*, 2010; Song *et al.*, 2012), which may be linked to altered dopamine transporter function (Torres *et al.*, 2004; Hewett *et al.*, 2010). Normal or increased levels of striatal dopamine, however, have also been reported in mouse models of DYT1 dystonia (Dang *et al.*, 2005, 2006; Grundmann *et al.*, 2007; Zhao *et al.*, 2008), and in a mouse model of DYT11 or myoclonus-dystonia caused by mutations in the epsilon sarcoglycan gene (Zhang *et al.*, 2012). Although these animal models of dystonia have showed some inconsistencies in how striatal dopamine is altered in dystonia, they do help support the notion that dystonia is associated with dysfunction of the striatal dopamine system.

To date, imaging investigations into presynaptic dopaminergic function in adult-onset primary focal dystonia have been restricted to assessments during a resting state. One group using ¹⁸F-fluorodopa reported increased presynaptic dopaminergic activity in the striatum of patients with idiopathic dystonia compared with control subjects (Otsuka *et al.*, 1992), but the study included patients with generalized dystonia in addition to focal hand and cervical dystonia and was further confounded by the inclusion of patients with dystonic symptoms at rest. In another study involving patients with cervical dystonia who had reduced D₂/D₃ availability at rest, the presynaptic dopamine transporter was found to be normal (Naumann *et al.*, 1998). Abnormal presynaptic dopamine release in these patients, however, could still account for the reduced D₂/D₃ availability despite normal levels of dopamine transporter being detected.

The aims of the present study were 2-fold: (i) examine striatal dopamine receptor availability using the PET D₂/D₃ antagonist radioligand ¹¹C-raclopride (¹¹C-RAC) during the resting state in patients with writer's cramp who have no dystonic symptoms at rest; and (ii) examine ¹¹C-RAC displacement induced by endogenous dopamine release during performance of a sequential finger-tapping task involving the dystonic hand and an asymptomatic sentence production task. ¹¹C-RAC was used because it is a reversible binder of D₂/D₃ receptors that has been well validated in providing indirect measures of task-induced synaptic dopamine release during behavioural or pharmacological challenges in the living human brain (Laruelle, 2012).

We hypothesized that reduced D₂/D₃ receptor availability in writer's cramp would be accompanied by abnormal ¹¹C-RAC displacement during the sequential finger-tapping task that involved recruitment of similar muscle groups as those affected by writer's cramp. Additionally, we hypothesized that compensatory mechanisms could lead to abnormal ¹¹C-RAC displacement during performance of an asymptomatic speech production task. A finger-tapping task rather than a writing task was used to assess hand motor performance in patients with writer's cramp to limit the potential confounding of excessive muscle spasms occurring during writing and motor and sensory feedback influences during writing on brain responses (Torres-Russotto and Perlmutter, 2008). A speech production task was examined as a

putative unaffected task in patients with writer's cramp that involved motor control pathways distinct from writing. We further hypothesized that D₂/D₃ receptor availability and changes in task-induced ¹¹C-RAC displacement in writer's cramp would relate to the clinical features of symptom severity and disease duration.

Materials and methods

Participants

We studied 15 patients with writer's cramp and 15 age-matched healthy control subjects (Table 1). All subjects were right-handed (Oldfield, 1971), and none had any history of neurological or psychiatric disorders with the exception of dystonia in patients with writer's cramp. Subjects were excluded if they were taking medication known to affect dopaminergic function. All patients with writer's cramp had adult-onset dystonia (>26 years old), had no dystonia in other body regions or at rest, and had normal laryngeal anatomy and function confirmed by nasolaryngoscopy. Nine of the patients with writer's cramp were receiving regular botulinum toxin injections, but none had received injections within the past 4 months and were fully symptomatic. Patients were excluded if they had dystonic symptoms at rest to avoid the potential confound of dystonic spasms occurring during the rest scan. A similar investigation into dopaminergic function in patients with spasmodic dysphonia was conducted at the same time as the present study, and some control subjects were shared in the two studies (Simonyan *et al.*, 2013a). Some control subjects were also reported in a previous study by Simonyan *et al.* (2013b). The Institutional Review Boards of the National Institutes of Health (NIH) and the Icahn School of Medicine at Mount Sinai, as well as the NIH Radiation Safety Committee approved this study, and all participants gave their written informed consent before participation.

Patient disease duration was estimated based on patients' report of earliest recalled symptoms of hand cramping while writing. Patient symptom severity was assessed using the Writer's Cramp Rating Scale (Wissel *et al.*, 1996; Kruidijk *et al.*, 2007). The Writer's Cramp Rating Scale scores the manifestation of dystonia during writing involving the first three fingers, wrist, and elbow (rated 0 to 2), as well as the latency to dystonia onset (rated 1 to 2) and presence of tremor (rated 0 to 2) during writing.

Magnetic resonance imaging scanning

All participants underwent MRI scanning on a 3 T GE Signa Excite system (General Electric Medical Systems) for PET image registration and to rule out presence of gross brain abnormalities. A high-resolution anatomical MRI of each participant's brain was obtained

using a T₁-weighted MPRAGE: echo time, 3 ms; inversion time, 450 ms; flip angle = 10°; matrix size = 256 × 256; field of view = 240 mm; slice thickness = 1.2 mm.

Positron emission tomography scanning

PET scanning with ¹¹C-RAC was used to investigate striatal D₂/D₃ receptor binding potential at rest and estimate changes in ¹¹C-RAC binding potential during task production as a measure of striatal dopamine release. ¹¹C-RAC binds to D₂/D₃ receptors with sufficiently low binding affinity to compete with endogenous dopamine and therefore a reduction in binding potential can be used to estimate an increase in extracellular concentration associated with dopamine release in response to a variety of interventions (Seeman *et al.*, 1989; Laruelle, 2000, 2012; Watabe *et al.*, 2000; Garraux *et al.*, 2007). Subjects were instructed not to drink any beverages containing caffeine or alcohol for 24 h and to fast for a minimum of 3 h before the PET scans. All PET scanning was started in the morning (before noon) to limit the effect of possible diurnal fluctuations in dopamine transmission on our findings. Head movements during PET scanning were minimized by the use of a thermoplastic mask moulded around the subject's head.

All PET data were acquired on a GE Advance tomograph (GE Medical Systems). An 8-min transmission scan using a ⁶⁸Ge source was obtained before tracer injection for attenuation correction. A target dose of 20 mCi of ¹¹C-RAC was delivered in a 20 ml syringe and administered as a 1-min bolus injection followed by a 99-min constant infusion using a computer-controlled pump (Harvard Instruments). Based on prior recommendations on how to maximize the signal-to-noise ratio (Watabe *et al.*, 2000), a bolus-plus-infusion method was used (Fig. 1). Two 100-min ¹¹C-RAC scans were

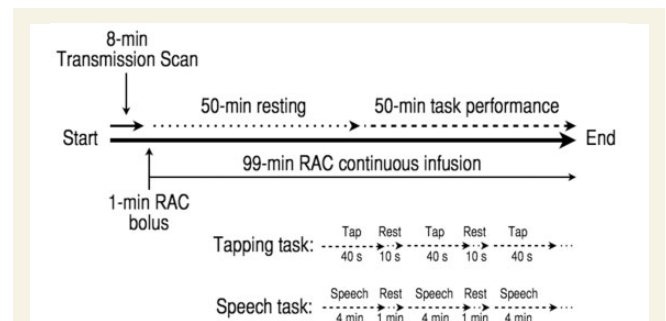


Figure 1 Experimental design for PET scans with ¹¹C-raclopride (RAC) using a bolus-plus-infusion design to assess D₂/D₃ receptor availability at rest and endogenous striatal dopamine release as measured by displacement of ¹¹C-RAC during sequential finger tapping and speech production tasks.

Table 1 Subject demographic data

	Patients with writer's cramp (n = 15)	Control subjects (n = 15)	P-value
Age (mean ± SD, years)	52.4 ± 9.0	55.1 ± 9.3	0.42
Gender	10M:5F	6M:9F	0.15
Handedness	Right	Right	NA
Disease duration (mean ± SD, years)	14.4 ± 6.5	—	NA
Disease severity (WCRS)	13.1 ± 4.7	—	NA

M = male; F = female; WCRS = Writer's Cramp Rating Scale; NA = not applicable.

acquired, during which subjects initially rested and then performed either sequential finger tapping or sentence production, respectively. During each 100-min dynamic ^{11}C -RAC PET scan, 27 frames of 30 s to 5 min epochs were generated (reconstructed resolution 6 mm in all directions) according to a PET scanning timeline for assessment of task-related dopamine release as previously reported by our group (Garraux *et al.*, 2007; Simonyan *et al.*, 2013a, 2013b). The mean actual administered ^{11}C -RAC doses [mean \pm standard deviation (SD)] did not significantly differ between patients with writer's cramp and control subjects for both the finger tapping (writer's cramp: 20.07 ± 1.11 mCi, control subjects: 20.45 ± 0.30 mCi; $P = 0.22$) and speech production scans (writer's cramp: 20.20 ± 0.42 mCi, control subjects: 19.63 ± 1.56 mCi; $P = 0.19$).

Tasks

All participants underwent two 100-min ^{11}C -RAC PET scans separated by a minimum of 1 day. Each PET scan consisted of two consecutive experimental conditions of 50-min duration each: (i) resting quietly with eyes closed without falling asleep (Baseline); and (ii) performance of a task (Task). The tasks included a five-finger sequential tapping sequence that subjects performed by alternating 40 s of continuous tapping with 10 s of rest, and a speech production that subjects performed by alternating 4 min of repeating sentences aloud (e.g. 'Tom is in the army') with 1 min of rest (Fig. 1). The order of the scans was pseudo-randomized by alternating the order of task acquisition with each subject enrolled.

Participants were instructed in the tapping sequence on the day of scanning and briefly practiced it at a pace of ~ 2 taps/s until comfortable with the sequence. Tapping was performed by the dominant right hand at an internally paced rate and consisted of a repeating sequence starting with the thumb (I) as follows: I \rightarrow II \rightarrow III \rightarrow IV \rightarrow V \rightarrow IV \rightarrow III \rightarrow II. Finger tapping presses were recorded using a five-finger fibre-optic button response unit (Psychology Software Tools) and PowerLab 8/30 amplifier with LabChart6 Pro software (ADInstruments). For the speech production task, subjects were instructed immediately before scanning to listen attentively to an acoustically presented sample sentence and repeat each sentence four times at the comfortable conversational speech level.

Volumetric magnetic resonance image processing

The high-resolution MPRAGE images of each participant's brain underwent processing using FreeSurfer (v4.5.0), an automated program for calculating volumetric segmentation and cortical thickness (<http://www.surfer.nmr.mgh.harvard.edu>). Subcortical segmented volumes were produced based on the geometric structures of the white/grey matter interface and regions of interest based on standardized caudate, putamen, and nucleus accumbens segmentation units in FreeSurfer. Following automated segmentation, all images were visually inspected to rule out segmentation processing errors. If any segmenting errors in striatal structures were found, the segmentation routine was repeated and the repeat results inspected. Despite several attempts, the anatomical MRI scan for one healthy control subject (62-year-old female) did not accurately segment the subcortical volumes and so her data were not included in the final analysis. Subcortical volumes were compared using two-sample *t*-tests with a significance threshold of $P < 0.05$.

Positron emission tomography imaging data processing

Preprocessing of ^{11}C -RAC PET images included correction for possible head motion-induced artefacts during task performance using the registered attenuation correction method as previously described (Garraux *et al.*, 2007; Simonyan *et al.*, 2013a, 2013b). Emission images were first reconstructed with filtered back-projection and without attenuation correction. All emission frames were then registered with mutual information to the prime emission image and smoothed with a 6-mm full-width at half-maximum Gaussian filter using FMRIB's Linear Image Registration Tool from the FMRIB Software library (Jenkinson *et al.*, 2002). The transmission images were registered to the same prime emission image, and the transmission frame reconstructed with filtered back-projection in order to perform attenuation correction.

PMOD (PMOD Technologies) and analysis of functional neuroimages (AFNI; Cox, 1996) software were used to perform registrations of each subject's ^{11}C -RAC scans to their individual anatomical brain MRI followed by normalization of all ^{11}C -RAC images to the Montreal Neurological Institute's Colin N27 brain in standard Talairach space (Talairach and Tournoux, 1988). Voxel-based analyses of PET data were performed with AFNI using volumes of interest (caudate nucleus, putamen, and cerebellum) derived from cytoarchitectonic probability maps distributed with AFNI for the Colin N27 brain (Eickhoff *et al.*, 2005). The caudate nucleus and putamen volumes were sampled across their entire rostro-caudal and dorso-ventral extents, while the cerebellar volume was restricted to grey matter defined over five consecutive slices of both hemispheres.

^{11}C -RAC binding potential was determined under equilibrium conditions from the radioactivity concentration in the D_2 receptor-rich target regions (C, putamen and caudate nucleus) and in a receptor-poor background region (C', cerebellum) using the equation: binding potential = $[(C - C') / C']$ (Carson, 2000). Parametric images of ^{11}C -RAC binding potential during baseline and task performance were created using frames 14–16 (40–50 min) and frames 20–27 (60–100 min), respectively. Task-induced dopamine release was estimated by calculating the percent change in ^{11}C -RAC binding potential (ΔBP) during task performance: $\Delta\text{BP} = [(\text{BP}_{\text{Baseline}} - \text{BP}_{\text{Task}}) / \text{BP}_{\text{Baseline}}] \times 100\%$ (Watabe *et al.*, 2000).

To examine outliers in data and remove noisy data that could contribute to signal variability, we calculated 'spikiness' of each voxel in all individual subject ^{11}C -RAC binding potential and ^{11}C -RAC ΔBP images. Outliers were identified using the AFNI program '3dToutcount', which was used to calculate voxelwise median absolute deviations for each individual data set. The data set was excluded as an outlier if their median lay outside $\pm 3.5 \times$ median absolute deviations. Applying these methods led to one patient with writer's cramp and one healthy control subject being removed from the resting ^{11}C -RAC binding potential analysis. No subjects were removed as outliers from either of the task-induced ^{11}C -RAC ΔBP analyses.

Assessment of between-group differences in ^{11}C -RAC binding potential at rest and ^{11}C -RAC ΔBP during task performance was performed using voxel-wise two-sample *t*-tests. The AFNI Monte Carlo simulation program '3dClustSim' was used to estimate the probability of false positive clusters within a volume restricted to the striatum. Based on the smoothness of noise in individual subject ^{11}C -RAC binding potential and ^{11}C -RAC ΔBP scans estimated using the AFNI program '3dFWHMx', a family-wise error (FWE)-corrected $P < 0.05$ was reached using a voxel-level threshold of $P = 0.025$ and cluster size

threshold of 212 voxels for the ^{11}C -RAC binding potential contrasts and 100 voxels for the ^{11}C -RAC ΔBP contrasts.

Relation of positron emission tomography findings to clinical features

AFNI software was used to perform voxel-wise Spearman's correlation analyses in order to investigate potential relationships between ^{11}C -RAC binding potential at rest and ^{11}C -RAC ΔBP during task performance in patients with writer's cramp with disease duration and symptom severity. Significance level for the correlations was set at a voxel-level threshold of $P < 0.025$, to account for the two clinical measures evaluated, with a correlation coefficient threshold of $|r| \geq 0.6$ and cluster size threshold of 100 voxels.

Region of interest analyses

Conventional region of interest analyses were performed to complement the voxel-based analyses, quantify changes in ^{11}C -RAC binding potential at rest and ^{11}C -RAC ΔBP during task performance in patients with writer's cramp, and examine scatter plots of relationships observed between PET findings and clinical features. Extractions of ^{11}C -RAC binding potential at rest and ^{11}C -RAC ΔBP during task performance from individual subject data were performed with AFNI using the caudate nucleus and putamen volumes of interest derived from probability maps distributed with AFNI as described above (Eickhoff *et al.*, 2005). Additionally, significant clusters identified in the voxel-based analyses at the group level were used to generate masks for extraction of ^{11}C -RAC binding potential at rest and ^{11}C -RAC ΔBP during task performance from individual subject data. Two-sample *t*-tests were used to assess significant differences between patients with writer's cramp and control subjects, and a statistical threshold of $P < 0.05$ applied.

Results

Volumetric magnetic resonance imaging

No significant differences in the volumes of the putamen, caudate nucleus, or nucleus accumbens between patients with writer's cramp and healthy control subjects were found (Table 2).

Participants and positron emission tomography scanning performance

Patients with writer's cramp and control subjects did not significantly differ in age ($P = 0.42$) or gender ($P = 0.15$) (Table 1). The total number of taps during the tapping task scans also did not significantly differ between patients and control subjects (writer's cramp: 4378 ± 1649 , control subjects: 4151 ± 929 ; two-tailed *t*-test: $P = 0.66$). Tapping count data from two control subjects, however, were lost because of technical issues. Following the tapping task scanning, four patients with writer's cramp reported experiencing a vague sense of 'tightness' in their hands, but all denied experiencing their typical dystonic symptoms or feeling hand muscle fatigue. None of the subjects reported experiencing dystonia-like laryngeal spasms during speech production during scanning. Furthermore, no dystonic hand posturing while tapping

Table 2 Striatal region volumes in patients with writer's cramp compared with healthy control subjects

Striatal region	Volume (mean \pm SD)		P-value
	Healthy controls (n = 14)	Patients with writer's cramp (n = 15)	
Putamen			
Left	5437 \pm 727	5500 \pm 790	0.82
Right	5281 \pm 638	5252 \pm 720	0.91
Caudate nucleus			
Left	3166 \pm 494	3488 \pm 577	0.12
Right	3255 \pm 480	3549 \pm 548	0.14
Nucleus accumbens			
Left	618 \pm 98	584 \pm 127	0.43
Right	637 \pm 104	618 \pm 148	0.70

was observed and no speech changes consistent with laryngeal dystonia were heard during continuous monitoring of patients with writer's cramp during task performance.

^{11}C -raclopride binding potential at rest

Voxel-wise analysis of ^{11}C -RAC binding potential at rest revealed significantly reduced striatal D_2/D_3 availability in the bilateral striatum in patients with writer's cramp (Fig. 2A–C and Table 3). There were no significant differences between the resting ^{11}C -RAC binding potential scans acquired before the finger-tapping task to those scans acquired before the speech production task.

Using whole striatal volumes, ^{11}C -RAC binding potential at rest in patients with writer's cramp was significantly reduced in the left putamen (writer's cramp: 2.07 ± 0.07 , control subjects: 2.25 ± 0.07 ; $P < 0.05$) and right caudate nucleus (writer's cramp: 1.33 ± 0.07 , control subjects: 1.51 ± 0.06 ; $P < 0.05$). Patients with writer's cramp also showed a trend toward reduced ^{11}C -RAC binding potential in the left caudate nucleus (writer's cramp: 1.32 ± 0.08 , control subjects: 1.51 ± 0.09 ; $P < 0.06$; Fig. 5A). Using regions of interest generated from significant clusters identified in the voxel-wise analysis, significantly reduced ^{11}C -RAC binding potential was observed in the left striatum (writer's cramp: 1.94 ± 0.55 , control subjects: 2.32 ± 0.44 ; $P < 0.05$) and right striatum (writer's cramp: 1.56 ± 0.48 , control subjects: 2.03 ± 0.35 ; $P < 0.05$) of patients with writer's cramp during rest (Fig. 5B). There were no significant differences between the resting ^{11}C -RAC binding potential scans acquired before the finger-tapping task to those scans acquired before the speech production task ($P > 0.05$).

^{11}C -raclopride Δ binding potential during task performance

Voxel-wise analysis of ^{11}C -RAC ΔBP revealed significant increases in the displacement of ^{11}C -RAC throughout the bilateral striatum during finger tapping in control subjects and patients with writer's cramp (Fig. 3A–B and Table 4). Contrasting patients with writer's cramp with control subjects, however, revealed reduced ^{11}C -RAC displacement (decreased ^{11}C -RAC ΔBP) in the left caudate nucleus

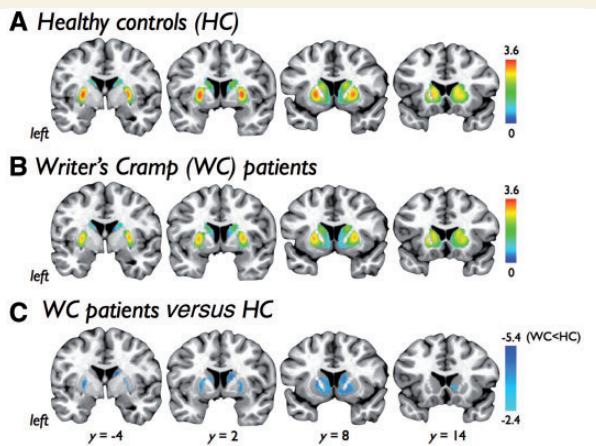


Figure 2 Statistical parametric maps showing ^{11}C -raclopride binding potential to striatal dopamine receptors (D_2/D_3) at rest in (A) healthy control subjects (HC) and (B) patients with writer's cramp (WC). A contrast analysis (C) showed patients with writer's cramp had a significant reduction in D_2/D_3 binding in the bilateral striatum. Colour bars show range of t -values displayed. Images are shown at $P < 0.05$, FWE corrected, on coronal slices of a standard brain in Talairach space.

Table 3 Clusters with significant decreases in ^{11}C -raclopride binding at rest in patients with writer's cramp compared with controls

Striatal Region	Cluster size (voxels)	Talairach coordinates			Peak t -value
		x	y	z	
Right caudate/putamen	2686	14	-8	18	-5.42
Left caudate/putamen	1958	-15	6	11	-4.31

and bilateral putamen in patients (Fig. 3C). *Post hoc* analysis revealed one cluster where decreased ^{11}C -RAC ΔBP during finger tapping overlapped with reduced ^{11}C -RAC binding potential at rest in the left putamen (Fig. 3D).

Significantly increased ^{11}C -RAC displacement during speech production was seen in the control subjects in the bilateral putamen and right caudate nucleus, and in the bilateral striatum in patients with writer's cramp (Fig. 4A–B and Table 3). During asymptomatic speech production, the patients with writer's cramp compared to control subjects showed greater ^{11}C -RAC displacement (increased ^{11}C -RAC ΔBP) in the left caudate nucleus and left putamen, as well as a cluster of reduced ^{11}C -RAC displacement (decreased ^{11}C -RAC ΔBP) in the posterior left putamen (Fig. 4C). *Post hoc* analysis showed there was no overlap between striatal regions of altered ^{11}C -RAC ΔBP during speech production and reduced ^{11}C -RAC binding potential at rest (Fig. 4D).

Region of interest analysis of ^{11}C -RAC ΔBP using the whole striatum volumes revealed no significant differences in ^{11}C -RAC displacement in either putamen or caudate nucleus during finger

tapping or speech production between patients with writer's cramp and control subjects. A trend toward increased ^{11}C -RAC displacement, however, was seen in the right caudate nucleus (writer's cramp: $11.3 \pm 20.8\%$, control subjects: $0.57 \pm 19.0\%$; $P = 0.06$) during speech production. Using regions of interest generated from significant clusters identified in the voxel-wise analysis, significant decreases in ^{11}C -RAC displacement were observed in the right putamen (writer's cramp: $6.5 \pm 6.4\%$, control subjects: $9.7 \pm 4.6\%$; $P < 0.05$) and left caudate nucleus (writer's cramp: $6.6 \pm 4.4\%$, control subjects: $9.3 \pm 6.4\%$; $P < 0.05$), with a trend toward decreased ^{11}C -RAC displacement observed in the left putamen (writer's cramp: $1.0 \pm 1.8\%$, control subjects: $6.1 \pm 5.1\%$; $P < 0.1$), during finger tapping (Fig. 5C). Significant increases in ^{11}C -RAC displacement were observed in the left putamen (writer's cramp: $14.9 \pm 4.1\%$, control subjects: $8.3 \pm 5.0\%$; $P < 0.005$) and left caudate nucleus (writer's cramp: $15.8 \pm 4.8\%$, control subjects: $1.3 \pm 4.8\%$; $P < 0.005$) during speech production (Fig. 5D).

Correlations between positron emission tomography findings and clinical measures

In patients with writer's cramp, ^{11}C -RAC binding potential at rest was positively correlated ($r \geq 0.60$, voxel $P < 0.025$, cluster size ≥ 100 voxels) with disease duration with a greater cluster size seen in the left striatum compared with the right striatum (Fig. 6A and Table 5). A region consisting of a negative correlation between ^{11}C -RAC binding potential at rest and disease duration ($r \leq -0.60$, voxel $P < 0.025$, cluster size ≥ 100 voxels) was also found in the left nucleus accumbens. The striatal regions showing increasing ^{11}C -RAC binding with writer's cramp disease duration were lateral to and non-overlapping with those regions identified as having reduced D_2/D_3 binding potential at rest with the exception of a cluster of an overlap in the left nucleus accumbens (Fig. 6B). Using individual patient writer's cramp PET data extracted with regions of interest generated from significant clusters identified in the voxel-wise correlation analysis, scatter plots supported the presence of positive correlations between ^{11}C -RAC binding potential at rest and disease duration in the left striatum ($r = 0.85$, $P < 0.001$) and right striatum ($r = 0.87$, $P < 0.001$), as well as the negative correlation between ^{11}C -RAC binding potential at rest and disease duration in the left nucleus accumbens ($r = -0.66$, $P < 0.01$; Fig. 6C).

No significant correlations were found between ^{11}C -RAC binding potential at rest and symptom severity as measured by the Writer's Cramp Rating Scale. Additionally, no significant correlations were found between ^{11}C -RAC ΔBP during the finger tapping and speech production tasks and disease duration or symptom severity.

Discussion

This study was designed to assess binding of the D_2/D_3 receptor antagonist ^{11}C -RAC at rest and displacement of ^{11}C -RAC during

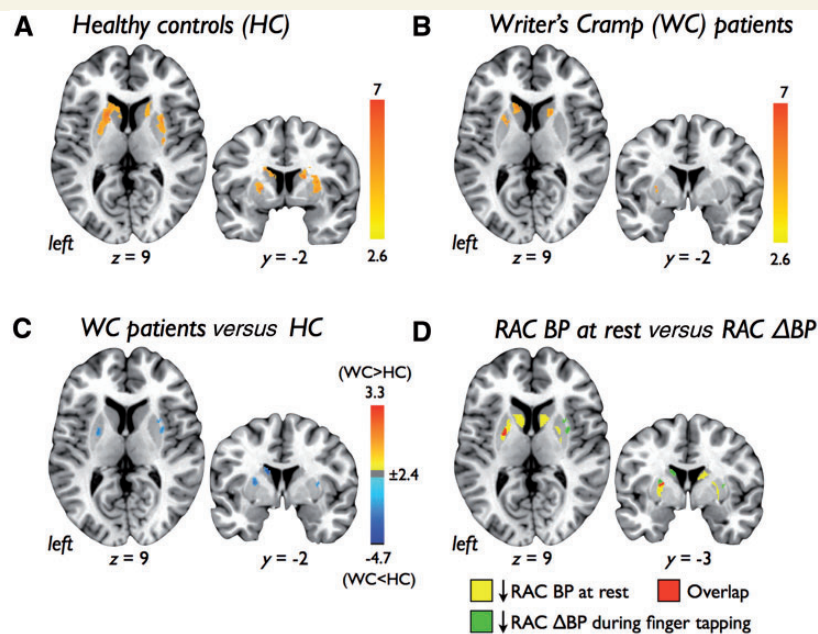


Figure 3 Statistical parametric maps showing endogenous dopamine release as measured by displacement of ^{11}C -raclopride (RAC Δ BP) during a right-hand finger tapping task in (A) healthy control subjects (HC), (B) patients with writer's cramp (WC), and (C) patients with writer's cramp compared with healthy control subjects. (D) Left striatal regions showing decreased ^{11}C -RAC Δ BP during the tapping task (green) and striatal regions found to have reduced D_2/D_3 receptor availability at rest (yellow) showed one cluster of overlap in the left putamen (red). Colour bars show range of t -values displayed. Images are shown at $P < 0.05$, FWE corrected, on axial and coronal slices of a standard brain in Talairach space.

Table 4 Significant clusters of task-induced ^{11}C -raclopride displacement (RAC Δ BP) in patients with writer's cramp compared with control subjects

Task	Striatal region	Cluster size (voxels)	Talairach coordinates			Peak t -value
			x	y	z	
Finger tapping	Healthy control subjects					
	Left putamen/caudate	3709	-19	11	5	9.64
	Right caudate/putamen	2773	19	-2	18	9.67
	Patients with writer's cramp					
	Left caudate	722	-11	14	12	6.38
	Left putamen	382	-16	10	-2	6.00
	Right caudate	149	16	11	9	4.43
	Left putamen	144	-26	-2	7	5.65
	Patients with writer's cramp versus control subjects					
Left caudate	232	-11	-2	19	-4.74	
Right putamen	209	31	9	5	-3.66	
Left putamen	121	-23	-2	10	-3.43	
Speech production	Healthy control subjects					
	Left putamen	239	-17	11	5	4.65
	Right caudate	128	12	12	2	3.96
	Left putamen	100	-25	-8	10	3.82
	Patients with writer's cramp					
	Right putamen/caudate	862	22	11	6	6.02
	Left putamen	763	-26	-8	-2	4.10
	Left caudate	490	-6	12	-3	4.41
	Patients with writer's cramp versus control subjects					
Left putamen	194	-11	15	-3	3.57	
Left caudate	100	-14	12	-3	3.14	

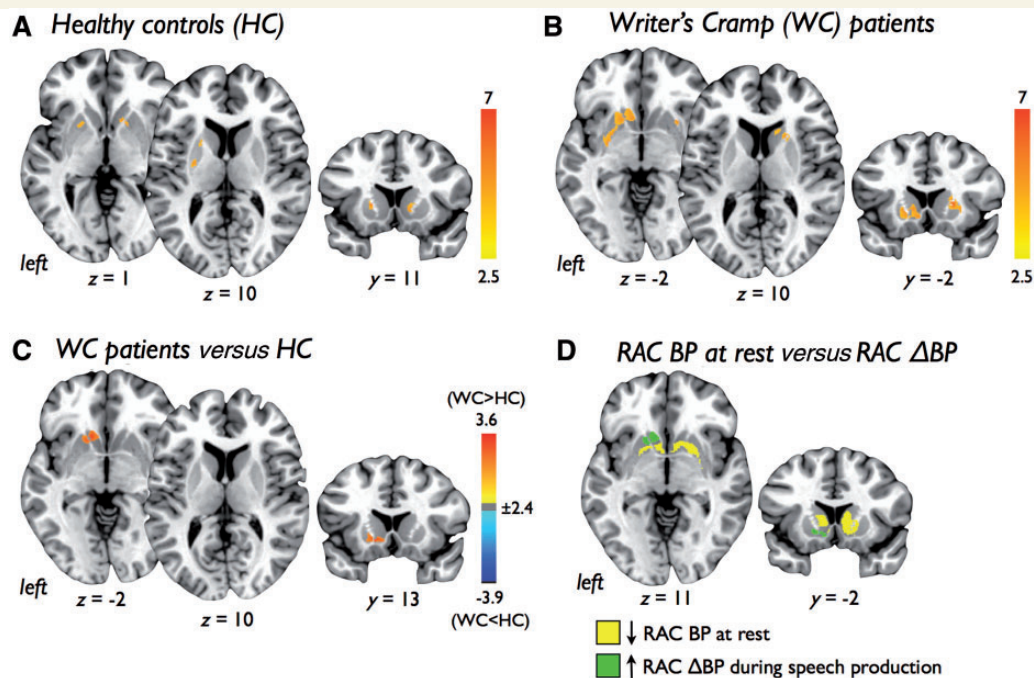


Figure 4 Statistical parametric maps showing endogenous dopamine release as measured by displacement of ^{11}C -raclopride (RAC ΔBP) during a speech production task in (A) healthy control subjects (HC) and (B) patients with writer's cramp (WC), and (C) patients with writer's cramp compared with healthy control subjects. Colour bars show range of t -values displayed. (D) Left striatal regions showing decreased ^{11}C -RAC ΔBP during the speech production task (green) were non-overlapping with striatal regions found to have reduced D_2/D_3 receptor availability at rest (yellow). Images are shown $P < 0.05$, FWE corrected, on axial and coronal slices of a standard brain in Talairach space.

performance of two tasks in patients with writer's cramp. Using a voxel-based image analysis approach, we found decreased ^{11}C -RAC displacement in the left striatum and right putamen in patients with writer's cramp during a right-handed finger-tapping task that was asymptomatic, but used the same effectors that are involved in dystonia. We also found increased ^{11}C -RAC displacement in the left striatum, as well as a region of decreased ^{11}C -RAC displacement in the left putamen, in the same patients with writer's cramp during an asymptomatic speech production task. Furthermore, ^{11}C -RAC binding at rest showed a significant relationship with disease duration. These novel findings provide direct evidence that suggests adult-onset primary focal dystonia is associated with abnormal dopaminergic neurotransmission.

Reduced ^{11}C -raclopride binding to striatal D_2/D_3 receptors during rest

During the resting state, ^{11}C -RAC binding to D_2/D_3 receptors in the striatum of patients with writer's cramp was reduced. This finding is consistent with the majority of prior D_2 -like dopamine receptor imaging studies in primary focal dystonias (Horstink *et al.*, 1997; Perlmutter *et al.*, 1997b; Naumann *et al.*, 1998; Berger *et al.*, 2007; Horie *et al.*, 2009). Localized changes in expression of D_2/D_3 receptors might help explain some of the inconsistency in previously reported D_2 -like receptor imaging studies that

applied region of interest methods and averaged across striatal structures.

As our patient cohort was a carefully selected group of patients with task-specific focal hand dystonia who did not experience any dystonic symptoms at rest, the finding of reduced ^{11}C -RAC binding is unlikely to have been confounded by dystonic movements occurring during rest. This finding, therefore, could potentially be explained by abnormal D_2 -like receptor expression in writer's cramp or possibly by a defect in receptor turnover or trafficking (Seeman *et al.*, 1989; Volkow *et al.*, 1994; Beaulieu and Gainetdinov, 2011). The presence of increased tonic striatal dopamine release, however, could also lead to the finding of reduced D_2/D_3 availability in the absence of any receptor deficit.

Altered ^{11}C -raclopride displacement during task performance

^{11}C -RAC displacement was significantly decreased in the left caudate nucleus and bilateral putamen during right-handed finger-tapping task in patients with writer's cramp compared to control subjects. As motor performance was not significantly different between patients and control subjects, and since patients did not experience dystonic spasms during tapping, motor performance cannot explain the difference found between the groups. One of the two significant clusters of decreased ^{11}C -RAC displacement within the left putamen identified during tapping overlapped with

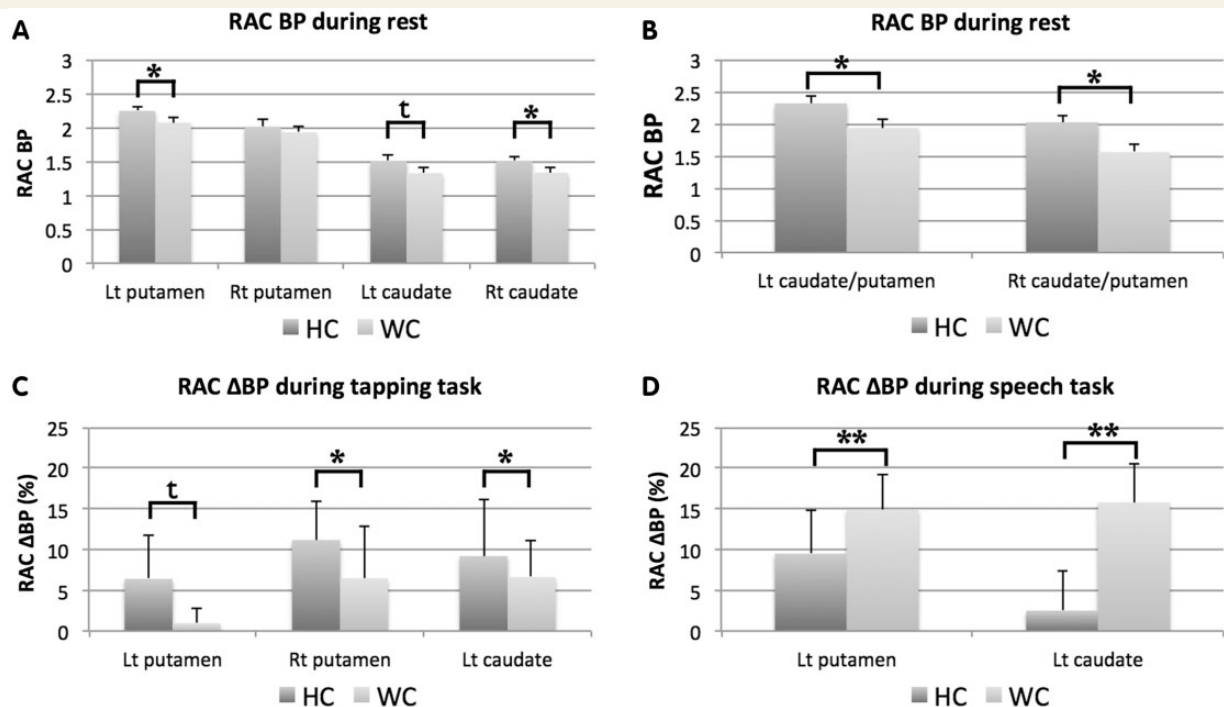


Figure 5 Differences in ^{11}C -raclopride binding potential (RAC BP) to striatal dopamine receptors (D_2/D_3) during rest in healthy control subjects (HC) and patients with writer's cramp (WC) generated using (A) atlas-defined whole putamen and caudate volumes of interest and (B) clusters defined by those striatal regions found to be significantly different between healthy control subjects and writer's cramp in the voxel-based analyses. Also shown are bar graphs showing dopamine release as measured by displacement of ^{11}C -raclopride (^{11}C -RAC ΔBP) during (C) right-hand finger tapping and (D) speech production tasks in healthy control subjects and patients with writer's cramp using clusters within the striatum found to be significantly different between healthy control subjects and writer's cramp in the voxel-based analyses. Significant differences were evaluated using t -test comparisons (* $P < 0.05$; ** $P < 0.005$; t : $P < 0.1$). Error bars reflect standard error of the mean. Lt = left; Rt = right.

a striatal region associated with reduced D_2/D_3 availability. As such, the focal manifestation of dystonia in these patients may be related to deficient task-induced dopamine release occurring in the setting of reduced D_2/D_3 receptor availability. In a similar investigation in patients with spasmodic dysphonia, we found decreased ^{11}C -RAC displacement during a symptomatic speech production task (Simonyan *et al.*, 2013a). Together these findings help support the presence of abnormal task-dependent (phasic) dopaminergic neurotransmission in adult-onset primary focal dystonia. These congruous findings are in line with previous animal and human studies where reduced striatal dopamine release has been associated with the manifestation of dystonia (Knappskog *et al.*, 1995; Perlmutter *et al.*, 1997a; Tabbal *et al.*, 2006; Balcioğlu *et al.*, 2007; Clot *et al.*, 2009; Hewett *et al.*, 2010; Page *et al.*, 2010; Song *et al.*, 2012).

During performance of the asymptomatic speech production task, ^{11}C -RAC displacement was significantly increased in patients with writer's cramp in the left striatum. In our comparable ^{11}C -RAC study of patients with spasmodic dysphonia (Simonyan *et al.*, 2013a), increased ^{11}C -RAC displacement was observed during asymptomatic sequential finger tapping. These findings suggest that an increase in phasic striatal dopamine release may occur during the performance of asymptomatic tasks in patients with focal dystonia. These increases might reflect a compensatory response to reduced striatal D_2/D_3 receptor availability; however,

we found no areas where reduced D_2/D_3 availability at rest overlapped with the significantly increased or decreased ^{11}C -RAC displacement during speech production arguing against this possible explanation. Another possibility is that patients with writer's cramp have subclinical alterations of the dopaminergic system involved in speech production. To test this hypothesis, future investigations focused on identifying speech initiation and production disturbances in patients with writer's cramp will be needed.

Correlations of ^{11}C -raclopride findings with clinical measures

Our voxel-based correlation analysis identified positive relations between D_2/D_3 availability at rest as measured by ^{11}C -RAC binding potential and disease duration in writer's cramp throughout the lateral aspects of the left striatum and to a lesser degree in the right striatum. Our analysis also revealed a small region of negative correlation between D_2/D_3 availability at rest and disease duration in writer's cramp within the left nucleus accumbens. This region of negative correlation overlapped with an area of reduced D_2/D_3 availability found in writer's cramp compared to control subjects. Interestingly, however, the lateral striatal regions showing increasing D_2/D_3 availability with disease duration were non-overlapping with the medial distribution of reduced D_2/D_3 availability found in writer's cramp compared with control subjects.

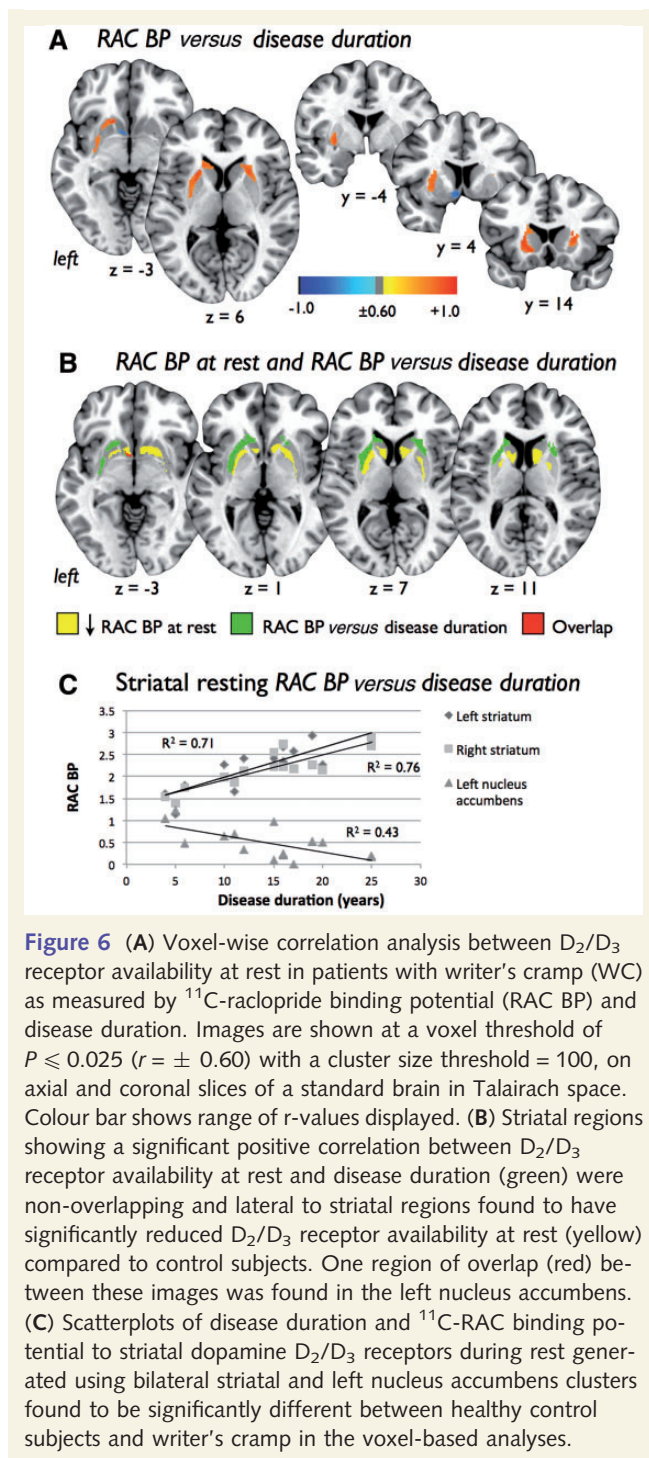


Figure 6 (A) Voxel-wise correlation analysis between D_2/D_3 receptor availability at rest in patients with writer's cramp (WC) as measured by ^{11}C -raclopride binding potential (RAC BP) and disease duration. Images are shown at a voxel threshold of $P \leq 0.025$ ($r = \pm 0.60$) with a cluster size threshold = 100, on axial and coronal slices of a standard brain in Talairach space. Colour bar shows range of r -values displayed. (B) Striatal regions showing a significant positive correlation between D_2/D_3 receptor availability at rest and disease duration (green) were non-overlapping and lateral to striatal regions found to have significantly reduced D_2/D_3 receptor availability at rest (yellow) compared to control subjects. One region of overlap (red) between these images was found in the left nucleus accumbens. (C) Scatterplots of disease duration and ^{11}C -RAC binding potential to striatal dopamine D_2/D_3 receptors during rest generated using bilateral striatal and left nucleus accumbens clusters found to be significantly different between healthy control subjects and writer's cramp in the voxel-based analyses.

Non-human primate neuroanatomical tracing studies (Takada *et al.*, 1998; Nambu *et al.*, 2002; Kelly and Strick, 2004; Miyachi *et al.*, 2006; Haber and Calzavara, 2009; Nambu, 2011) and human imaging studies (Maillard *et al.*, 2000; Gerardin *et al.*, 2003; Bingel *et al.*, 2004) have helped elucidate the organization of the striatum and other basal ganglia structures, which is thought to reflect somatotopically organized cortical inputs to the striatum and outputs back to the cortex. Disorganization of the striatal somatotopic organization has been reported both in

Table 5 Significant clusters from voxel-wise correlation analysis between ^{11}C -raclopride binding at rest and disease duration in patients with writer's cramp

Striatal region	Cluster size (voxels)	Talairach coordinates			Peak r -value
		x	y	z	
Left caudate/putamen	2770	-14	15	-2	0.95
Right caudate/putamen	814	24	13	8	0.89
Left nucleus accumbens	102	-3	3	-6	-0.75

mouse models of dystonia (Chicken *et al.*, 2008) as well as in humans (Vitek *et al.*, 1999; Delmaire *et al.*, 2005). A medio-lateral organization for the striatum has also been described with medial regions receiving somatotopic inputs from the supplementary motor area and lateral regions receiving inputs primarily from the primary motor cortex (Nambu, 2011). Thus, the reduced D_2/D_3 availability at rest in the medial striatum may indicate that basal ganglia circuits involving premotor cortices and those involving the primary motor cortex are differentially affected in writer's cramp. Although this hypothesis is supported by a voxel-based morphometry study that found patients with cervical dystonia had decreased grey matter density in the supplementary motor area accompanied by increased grey matter density in primary motor cortex (Draganski *et al.*, 2003), reported changes in premotor cortices in patients with focal hand dystonia have been more varied (Garraux *et al.*, 2004; Delmaire *et al.*, 2007; Egger *et al.*, 2007; Granert *et al.*, 2010). Still, premotor dysfunction in writer's cramp has been well supported in these morphometry studies and in a large number of electrophysiological (Yazawa *et al.*, 1999; Zeuner *et al.*, 2009) and functional imaging studies (Odergren *et al.*, 1998; Ibanez *et al.*, 1999; Oga *et al.*, 2002; Hu *et al.*, 2006; Castrop *et al.*, 2012). Abnormal dopaminergic function specifically affecting the medial striatal regions that are connected to premotor cortices, and thereby associated with the generation, planning and selection of movements (Chouinard and Paus, 2006; Cohen *et al.*, 2010; Da Cunha *et al.*, 2012), might underlie the task-specific nature of the focal dystonia in writer's cramp. Future multimodal imaging investigations, such as those combining functional MRI and PET techniques, however, will be needed to try and link the molecular changes and larger scale physiological changes identified in writer's cramp.

The one region where decreased striatal D_2/D_3 availability at rest in patients with writer's cramp overlapped with reducing D_2/D_3 availability over disease duration was the left nucleus accumbens. This finding suggests that the nigro-striatal and mesolimbic dopamine pathways could be affected differently in writer's cramp. Given the prevailing findings of previous investigations, along with the widespread striatal dopaminergic dysfunction we found in patients with writer's cramp and patients with spasmodic dysphonia (Simonyan *et al.*, 2013a), dysfunction within the nigro-striatal dopaminergic system in primary dystonia is well supported. The role that mesolimbic dopamine pathways stemming from the ventral tegmental area might play in primary dystonia is not known. In a hamster model of idiopathic primary generalized

dystonia, however, D_2 binding was decreased in the dorsomedial striatum and increased in nucleus accumbens (Nobrega *et al.*, 1996). In the same hamster model, significant decreases in dopamine transporter binding were also found in the nucleus accumbens and ventral tegmental area of those animals expressing severe dystonia (Nobrega *et al.*, 1999). In a post-mortem examination of two patients with early-onset generalized dystonia, reduced concentrations of dopamine were detected in the nucleus accumbens (Hornykiewicz *et al.*, 1986). In a more recent voxel-based morphometry study of a group of patients with focal hand dystonia and cervical dystonia, the volume of the nucleus accumbens was found to be increased (Egger *et al.*, 2007). Together these findings suggest that alterations within the mesolimbic dopamine pathway could be present in primary dystonia. While involvement of the mesolimbic pathway might help explain the increased prevalence of depression and anxiety in the disorder (Kuyper *et al.*, 2011; Stamelou *et al.*, 2012), its role and contribution to symptoms in primary dystonia remain to be determined.

Limitations

One potential limitation in our study is that patients with writer's cramp were not scanned during the dystonia-inducing task of writing. The use of the finger-tapping task, however, allowed for a more accurate matching of motor behaviour between patients and control subjects and helped avoid the confounding effect of excessive muscle spasms occurring during writing on our findings. Additionally, the fact that no patient with writer's cramp experienced dystonic spasms during the tapping task helped substantiate the isolated and task-specific nature of focal dystonia in these patients. Still, future studies on dopamine release during dystonic-inducing tasks could help better define the relationship between dopaminergic neurotransmission dysfunction and manifestation of symptoms in focal hand dystonia. Likewise, PET investigations using task-free pharmacologically-induced dopamine release or radioligands with presynaptic targets could help better characterize dopaminergic dysfunction in primary dystonia (Cummings *et al.*, 2011).

Given the limited spatial resolution of PET, it is possible partial volume effects may have affected some of our findings. As no volumetric differences were detected in the striatum of our patients with writer's cramp compared to healthy control subjects, however, morphometric alterations, such as those that have been previously reported in a variety forms primary dystonia (Neychev *et al.*, 2011; Zoons *et al.*, 2011), are unlikely to have contributed significantly to our findings. Another limitation is that PET, in contrast to microdialysis, provides indirect measures of dopamine release. ^{11}C -RAC, however, has been previously shown to have specific affinity for D_2/D_3 receptors and behave as predicted by the occupancy (competitive) model such that the magnitude of changes in ^{11}C -RAC displacement corresponds directly to the amount of change in synaptic dopamine concentration (Seeman *et al.*, 1989; Laruelle, 2000, 2012). Still, dopamine release is thought to likely exert a non-competitive action on ^{11}C -RAC binding through mechanisms such as dopamine-induced internalization of striatal D_2 receptors (Ginovart, 2005). Non-competitive actions of dopamine on ^{11}C -RAC binding, however, have largely been

described under amphetamine-induced dopamine release conditions in which a massive release is triggered. It is not known to what extent similar mechanisms occur under more physiological task-induced dopamine release conditions. Furthermore, non-competitive mechanisms like internalization of D_2 receptors are implicated in late stage responses to dopamine surges (Laruelle, 2012), and so likely play a limited role during the relatively brief 50 min of task performance used in our study. Regardless of the extent non-competitive mechanisms contribute to our ^{11}C -RAC displacement findings, endogenous dopamine release is the trigger that leads to changes in ^{11}C -RAC binding in both the competitive and non-competitive models proposed to date. Still, if writer's cramp is associated with dysregulation of D_2 receptor trafficking as has been described in some genetic forms of primary dystonia (Torres *et al.*, 2004; Esapa *et al.*, 2007), our results may be an underestimate or exaggeration of the amount of striatal dopamine release depending on whether there is reduced or increased internalization of D_2 receptors, respectively.

Although the order of the 100-min PET scans were counterbalanced in terms of which task was performed in the second half of the scan, and all scanning procedures and their timing kept consistent across patients and control subjects to limit factors that might alter ^{11}C -RAC binding, we did not include a separate control group that performed no task during the second half of the scan. If ^{11}C -RAC binding differences exist between patients with dystonia and control subjects during the second 50 min compared to the initial baseline 50 min (e.g. from differing levels of or altered competition with cold raclopride), it might affect measures of ^{11}C -RAC displacement during the performance of the tasks. As such, future investigations assessing differences in task-induced dopamine release could potentially benefit from adding a non-task performing control group to test whether ^{11}C -RAC binding differs at rest between the first and second half of the scan in patients with writer's cramp. Another limitation to our study is the lack of a counterbalanced design in terms of the order of the task and rest conditions within a scanning session. Unfortunately, counterbalanced task designs are not able to be implemented using ^{11}C -RAC and the bolus-plus-infusion method because pharmacological challenges and performance of tasks induce changes in dopamine receptor binding that persist for over an hour and would therefore lead to a contamination of the resting state if it followed the task (Laruelle *et al.*, 1997; Carson, 2000; Houston *et al.*, 2004). The bolus-plus-infusion method, however, does have a number of advantages over bolus-only studies including the ability to maintain ^{11}C -RAC in equilibrium while both control and task data are collected as well as allowing for ^{11}C -RAC displacement to be measured during a single scanning session thereby limiting the effects of changes in cerebral blood flow and other physiological processes on obtained measures during different scanning sessions (Watabe *et al.*, 2000; Slifstein and Laruelle, 2001).

Lastly, while the ^{11}C -RAC scanning procedures used here have been shown to maximize signal-to-noise ratio for detection of synaptic dopamine release (Watabe *et al.*, 2000), a limitation to the imaging method used is its inability to distinguish primary from secondary changes or between cause and effect (Zoons *et al.*, 2011). Thus, the striatal dopaminergic dysfunction detected

could stem from distinct yet linked pathophysiological processes such as inhibitory deficits, maladaptive neuroplasticity, and defective sensorimotor function (Hallett, 2006a, 2011; Breakefield *et al.*, 2008; Peterson *et al.*, 2010; Neychev *et al.*, 2011).

Conclusion

In conclusion, our findings suggest that reduced striatal D₂/D₃ receptor availability at rest as measured by decreased ¹¹C-RAC binding potential in writer's cramp is accompanied by disturbances in task-induced endogenous dopamine release as measured by a change in ¹¹C-RAC binding. During asymptomatic sequential finger tapping involving the affected right hand, dopamine release was reduced in the left striatum in patients with writer's cramp. In contrast, during asymptomatic speech production, dopamine release was increased in the left striatum. The manifestation of a task-specific primary focal dystonia in a susceptible individual may therefore stem from reduced task-induced dopaminergic neurotransmission occurring in the setting of reduced dopamine receptor availability. The positive correlation between disease duration and D₂/D₃ receptor availability in the lateral striatum raises the possibility that there may be a localized compensatory response or that the pathophysiological process in writer's cramp selectively involves circuits associated with the medial striatum.

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