J Neurol (2009) 256:1307–1313
DOI 10.1007/s00415-009-5119-1

ORIGINAL COMMUNICATION

Striatal morphology correlates with sensory abnormalities in unaffected relatives of cervical dystonia patients

Richard A. Walsh · Robert Whelan · John O'Dwyer · Sean O'Riordan · Siobhan Hutchinson · Risteard O'Laoide · Kevin Malone · Richard Reilly · Michael Hutchinson

Received: 20 December 2008 / Revised: 17 March 2009 / Accepted: 20 March 2009 / Published online: 8 April 2009

Abstract Structural grey matter abnormalities have been described in adult-onset primary torsion dystonia (AOPTD). Altered spatial discrimination thresholds are found in familial and sporadic AOPTD and in some unaffected relatives who may be non-manifesting gene carriers. Our hypothesis was that a subset of unaffected relatives with abnormal spatial acuity would have associated structural abnormalities. Twenty-eight unaffected relatives of patients with familial cervical dystonia, 24 relatives of patients with sporadic cervical dystonia and 27 control subjects were recruited. Spatial discrimination thresholds (SDTs) were determined using a grating orientation task. High-resolution magnetic resonance imaging (MRI) images (1.5 T) were analysed using voxel-based morphometry. Unaffected familial relatives with abnormal SDTs had reduced caudate grey matter volume (GMV) bilaterally relative to those with normal SDTs (right $Z = 3.45$, left $Z = 3.81$), where there was a negative correlation between SDTs and GMV ($r = -0.76$, $r^2 = 0.58$, $p < 0.0001$). Familial relatives also had bilateral sensory cortical expansion relative to unrelated controls (right $Z = 4.02$, left $Z = 3.79$). Unaffected relatives of patients with sporadic cervical dystonia who had abnormal SDTs had reduced putaminal GMV bilaterally compared with those with normal SDTs (right $Z = 3.96$, left $Z = 3.45$). Sensory abnormalities in some unaffected relatives correlate with a striatal substrate and may be a marker of genetic susceptibility in these individuals. Further investigation of grey matter changes as a candidate endophenotype may assist future genetic studies of dystonia.

Keywords Dystonia · Voxel-based morphometry · Spatial discrimination · Basal ganglia

R. A. Walsh (✉) · R. Whelan · J. O'Dwyer · S. O'Riordan · S. Hutchinson · M. Hutchinson
Department of Neurology, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland
e-mail: richardawalsh@gmail.com

R. O'Laoide
Department of Radiology, St. Vincent's University Hospital, Dublin, Ireland

R. Whelan · K. Malone
Department of Psychiatry, St. Vincent's University Hospital, Dublin, Ireland

R. Whelan · R. Reilly
Department of Electronic Engineering, University College Dublin, Dublin, Ireland

Introduction

The genetic aetiology of adult-onset primary torsion dystonia (AOPTD) remains unknown. Some epidemiological studies suggest autosomal dominant inheritance with penetrance as low as 12% [1]. Success in the identification of responsible genetic loci has been modest, with progress hampered by poor penetrance and the absence of a marker of gene carrier status [2]. Up to 25% of apparently sporadic patients will have an affected relative and may therefore be manifesting a familial dystonia [1]. While the pathophysiology of AOPTD is unclear, a number of physiological abnormalities involving sensory processing have been described in affected subjects [3].

The difficulty involved in the genetic study of AOPTD, primarily due to its low penetrance, has led to interest in the identification of an endophenotype, or marker of gene carrier status [4]. Loss of sensory cortical somatotopy, possibly a

physiological correlate of a structural abnormality, has been proposed as a candidate endophenotype and is supported by the finding of abnormal spatial acuity both in AOPTD and in unaffected relatives [5–7]. Assessment of spatial acuity peripherally as a marker of structural and organisational changes in central structures relies on the integrity of the peripheral nervous system and subject attention during examination. Direct examination of cortical and subcortical structures may therefore be preferable.

Our objective was to look for a structural CNS correlate of abnormal spatial acuity previously identified in unaffected relatives of patients with sporadic and familial AOPTD. Our hypothesis was that relatives with abnormal acuity would have grey matter changes affecting the primary sensory cortex that have been previously described in affected subjects [8]. We also specifically looked for structural changes involving the caudate and putamen given their position as part of the striato-thalamo-cortical motor control loop and the prominence of the putamen in particular in previous imaging studies of AOPTD [9–11].

Methods

Unaffected relatives

Twenty-eight unaffected members of five multiplex AOPTD families (pedigrees 5, 6, 8, 10 and 26; Table 1) with mean age 38.1 ± 8.8 years were recruited. Fifteen were first-degree relatives of an affected family member and 13 were second-degree relatives. Of these familial relatives, 24 were right-handed and 4 were left-handed. Twenty-four unaffected first-degree relatives of patients with sporadic cervical dystonia (sporadic relatives) were also recruited with mean age of 38.6 ± 9.2 years; 22 were right-handed and 2 were left-handed.

Control subjects

Twenty-seven healthy control subjects were recruited from amongst hospital staff and members of the public. Mean age was 39.8 ± 11.8 years; 23 were right-handed and 4 were left-handed. Exclusion criteria included history of neurological illness, neuropathic symptoms or significant head trauma. Dystonia was excluded using a standardised examination [12].

Sensory testing

A grating orientation task was performed using Johnson–van Boven–Phillips domes applied to the index finger bilaterally as previously reported [6]. Spatial discrimination threshold (SDT) was defined as the grating width that would be expected to achieve a 75% level of accuracy for a given subject. Age-related control group means were established by the examination of 141 healthy control subjects during an earlier study [7]. Mean SDTs (±SD) for these healthy subjects were: for age group 20–29 years 1.172 ± 0.315 mm, for 30–39 years 1.051 ± 0.286 mm, for 40–49 years 1.465 ± 0.500 mm and for 50–64 years 1.851 ± 0.578 mm. The upper limit of normal for subjects in this study was set at a *Z*-score of 2.5 (control group mean +2.5 SD), which was 1.959 mm, 1.766 mm, 2.716 mm and 3.297 mm for each of the four age groups, respectively.

Of the 28 unaffected familial relatives, 12 were known to have abnormal SDTs (the familial abnormal SDT group) and 16 had normal SDTs (the familial normal SDT group). Of the 24 unaffected sporadic relatives, 13 were known to have abnormal SDTs (sporadic abnormal SDT group) and 11 had normal SDTs (sporadic normal SDT group). *Z*-scores of unaffected relatives and those of the 141 controls used to establish normative values for spatial acuity are shown in Fig. 1. All 27 control subjects participating in this imaging study had normal spatial acuity.

Table 1 Summary of affected family members in multiplex and singleton AOPTD families from which all unaffected relatives were recruited

	Number affected	Mean age at onset (years)[a]	AOPTD phenotypes
Multiplex families			
Pedigree 5	4	47.0	3 cervical dystonia, 1 blepharospasm
Pedigree 6	3	35.7	2 cervical dystonia, 1 spasmodic dysphonia
Pedigree 8	5	45.0	3 cervical dystonia, 1 FHD, 1 spasmodic dysphonia
Pedigree 10	4	47.5	All cervical dystonia
Pedigree 26	3	51.5	All cervical dystonia
All 5 pedigrees	19	45.3	–
Sporadic families	10	46.8	One family member with cervical dystonia

FHD focal hand dystonia

[a] Age at onset data unavailable for two patients with familial AOPTD and one patient with sporadic AOPTD

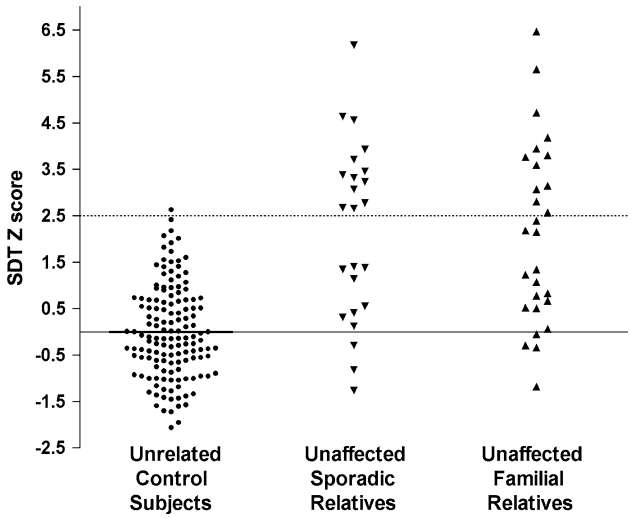

Fig. 1 SDT *Z*-scores in unrelated control subjects and unaffected relatives of patients with cervical dystonia. The *dashed line* represents the chosen cutoff value between normal and abnormal SDTs at a *Z*-score of 2.5

Voxel-based morphometry

Image acquisition

All MRI scans were obtained at 1.5 T on the same scanner (Siemens Avanto, Erlangen, Germany). A high-resolution three-dimensional T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence was acquired (TR = 1160 ms; TE = 4.21 ms, TI = 600 ms, flip angle = 15°) with a sagittal orientation, 256 × 256 matrix size and 0.9 mm isotropic voxels. A radiologist blinded to clinical status reviewed all images. Subjects were eliminated from further analysis if any macroscopic structural brain abnormality was identified or if there was movement artefact affecting image quality.

Pre-processing and statistical analysis of structural data

Statistical parametric mapping software (SPM5; Wellcome Centre for Neuroimaging, London, UK), running under Matlab 6.5 (Mathworks, Sherborn, MA, USA), was used to pre-process and analyse the MRI data obtained. Pre-processing incorporated image registration and classification into a single generative model [13]. Segmented grey matter data were modulated in order to preserve total grey matter volume. The spatially normalised and modulated grey matter partitions were smoothed using a 12 mm full-width at half-maximum Gaussian kernel allowing parametric statistical analysis to be performed in every analysis. Total grey matter volume, age, sex and handedness were entered as nuisance covariates in all analyses.

Each analysis was restricted to the predefined regions of interest using anatomically defined masks (Wake Forest University PickAtlas) [14]. This software employs SPM5's small volume correct feature, reducing the number of multiple comparisons. Type I errors were controlled using false discovery rate (FDR) of 0.05, controlling the expected proportion of false positives among supra-threshold voxels for each analysis performed [15]. For the purpose of this study we restricted our analysis to the primary sensory cortex, the caudate nucleus and the putamen bilaterally. We further restricted our findings to regions in which at least a conservative threshold of 100 contiguous voxels were found to be significant after FDR correction. The locations of significant voxels were summarised by their local maxima separated by at least 8 mm, and by converting the maxima coordinates from Montreal Neurological Institute (MNI) to Talairach coordinate space. These coordinates were assigned neuroanatomic labels using the Talairach Daemon brain atlas [16]. Correlations were calculated using individual voxel values at the local maxima of grey matter intensity in each predetermined region of interest to examine the relationship with spatial acuity. *Z*-scores are given in the "Results" section for each inter-group comparison of statistical significance. A summary of voxel-based morphometry (VBM) results and coordinates of voxels where peak GMV differences were found are given in Table 2.

Results

Unaffected relatives compared with unrelated healthy controls

Sensory cortical volume was increased bilaterally when comparing unaffected familial relatives with unrelated healthy control subjects (right $Z = 4.02$, left $Z = 3.79$; Fig. 2). No grey matter change in sub-cortical structures was noted in this comparison. This sensory cortical finding was not replicated in the sporadic relative group when analysed separately.

Unaffected relatives with abnormal SDTs compared with those with normal SDTs

In all 52 unaffected relatives of sporadic and familial dystonia subjects, putaminal volume was greater bilaterally in the normal SDT group (Fig. 3a). This, however, was significant at FDR < 0.06 rather than the predetermined FDR of 0.05. Amongst familial relatives alone, putaminal volume did not differ between normal SDT and abnormal SDT groups, but those with normal SDTs had significantly larger caudate volume bilaterally (right $Z = 3.45$, left $Z = 3.81$; Fig. 3b). Amongst the 24 sporadic relatives alone, normal SDT relatives had a bilateral increase in

Table 2 Summary of results including coordinates of peak GMV differences

Grey matter comparison	Region	Left				Right			
		Z	Coordinates (mm)			*Z*	Coordinates (mm)		
			x	*y*	*z*		*x*	*y*	*z*
Unaffected familial relatives > controls	Bilateral post-central gyrus	3.79	−38	−40	57	4.02	14	−31	70
Normal SDT (S + F) > abnormal SDT (S + F)[a]	Bilateral putamen	3.19	−24	14	7	3.27	24	18	1
Normal SDT (F) > abnormal SDT (F)	Bilateral caudate	3.81	−14	5	16	3.45	18	9	18
Normal SDT (S) > abnormal SDT (S)	Bilateral putamen	3.45	−22	16	7	3.96	24	19	−4
Grey matter correlating significantly with SDT *Z*-scores for all 52 relatives	Left caudate	3.8	−12	−7	19	–	–	–	–
Grey matter and SDT correlation for 28 unaffected familial relatives	Bilateral caudate	4.14	−14	−7	19	4.08	18	−11	19

F familial relatives, *S* sporadic relatives, *Z* *Z*-score

[a] FDR 0.06

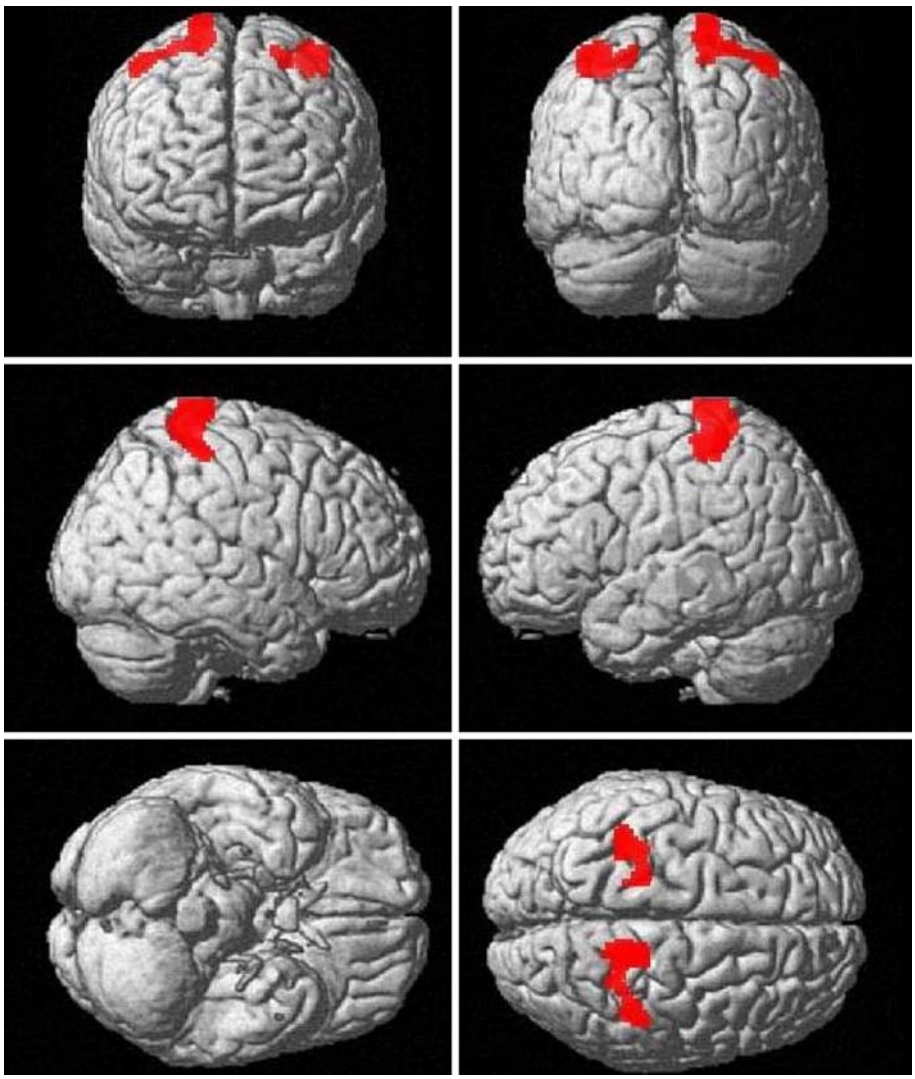

Fig. 2 Bilateral sensory cortical grey matter increase in all 28 unaffected familial relatives compared with 27 unrelated healthy controls shown on a three-dimensional (3D) surface render (peak difference $Z = 4.02$ at 14, −31, 70; cluster size threshold 100 voxels, FDR = 0.05)

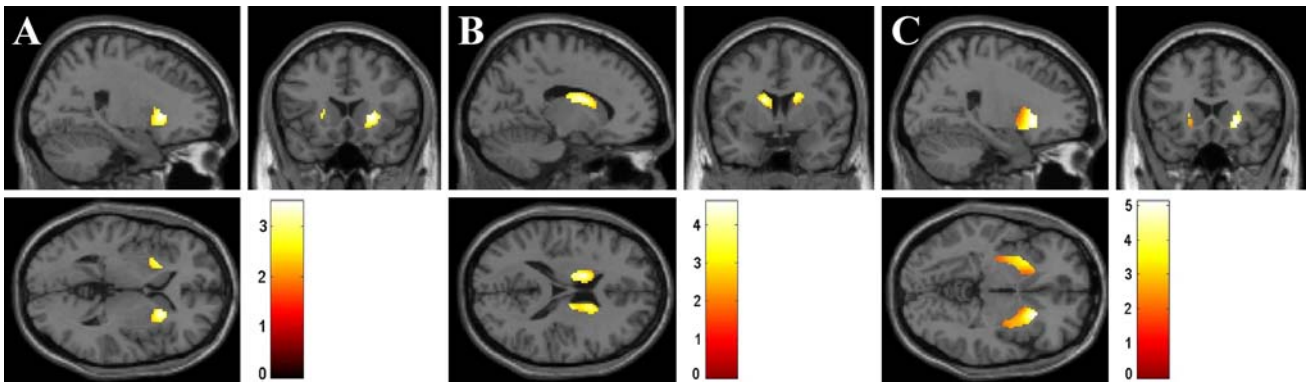

Fig. 3 Voxels in which grey matter volume in unaffected relatives with normal spatial acuity was greater than in those with abnormal spatial acuity. **a** All 52 sporadic and familial relatives combined ($Z = 3.27$ at 24, 18, 1), **b** All 28 unaffected familial relatives ($Z = 3.81$ at −14, 5, 16) and **c** All 24 sporadic relatives ($Z = 3.96$ at 24, 19, −4; cluster size threshold 100 voxels, FDR = 0.05)

putaminal volume in comparison with abnormal SDT relatives (right $Z = 3.96$, left $Z = 3.45$; Fig. 3c).

Correlation of spatial discrimination thresholds with grey matter intensity

The following correlations were estimated between the local maximum of intensity in the left caudate (Talairach *x*, *y*, *z* coordinates in parentheses) and SDT *Z*-scores, although significant correlations were identified for voxels in the caudate bilaterally. For all 52 unaffected relatives, greater SDT *Z*-scores (or greater impairment of spatial acuity) were associated with reduced grey matter intensities ($r = -0.53$, $r^2 = 0.28$, $p < 0.0001$; −12, −7, 19). The strongest correlation between grey matter intensity and SDT *Z*-scores was seen in the 28 unaffected familial relatives ($r = -0.76$, $r^2 = 0.58$, $p < 0.0001$; −14, −17, 19; Fig. 4a, b). In the 25 sporadic and familial relatives with abnormal SDTs, there was also a correlation between grey matter intensity and SDT *Z*-score ($r = -0.62$, $r^2 = 0.38$, $p = 0.001$; −14, −11, −19). This was observed in the 12 familial relatives with abnormal SDT *Z*-scores taken alone ($r = -0.75$, $r^2 = 0.56$, $p = 0.005$; −14, −7, 19) and in the 13 sporadic relatives alone there was a trend towards a correlation ($r = -0.47$, $r^2 = 0.22$, $p = 0.1$; −14, −11, 19). In the unrelated control group no voxels within the putamen or caudate correlated significantly with SDT *Z*-scores. There were therefore no supra-threshold voxels with which to similarly perform a correlation.

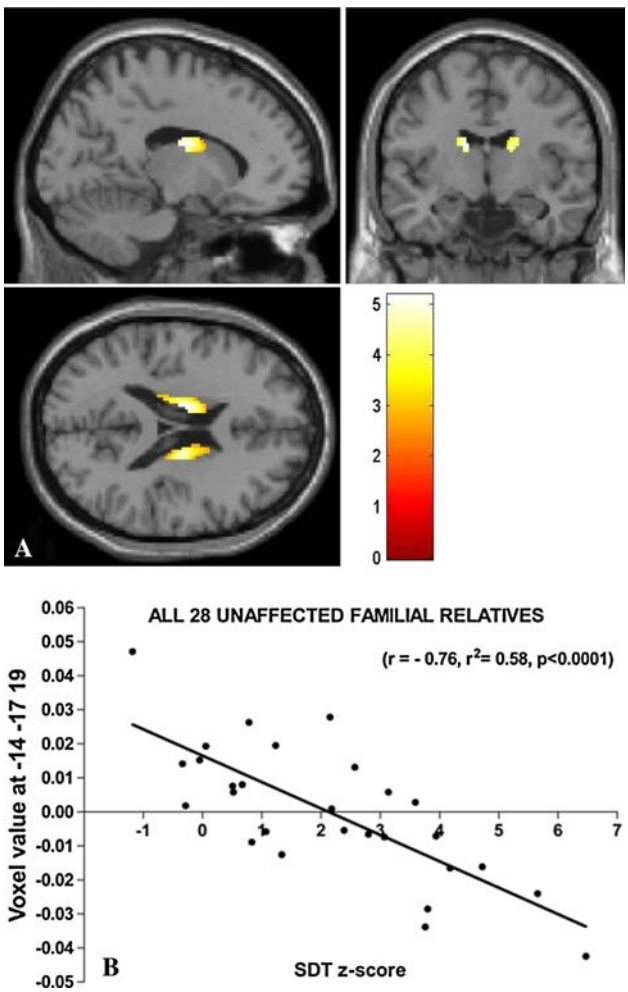

Fig. 4 **a** Grey matter voxels correlating significantly with spatial acuity in the 28 unaffected familial relatives ($Z = 4.14$ at −14, −7, 19; cluster size threshold 100 voxels, FDR = 0.05) and **b** correlation between SDT *Z*-scores and caudate grey matter intensity at the local maxima for the familial relative group

Discussion

Morphological grey matter changes involving sensorimotor circuits have been previously reported in patients with

AOPTD. Although the basal ganglia, in particular the putamen, have been frequently highlighted in anatomical and functional imaging studies, there have also been contradictory findings. In cervical dystonia, *reduced* grey matter volume has been described in the putamen bilaterally, with an increase in grey matter in the thalamus and caudate head bilaterally relative to control subjects [17]. An earlier volumetric study demonstrated an *increase* in putaminal volume bilaterally in cervical dystonia that was replicated in a VBM study of patients with blepharospasm [9, 11]. Other authors have not identified structural changes in the basal ganglia in AOPTD but have reported other potential structural substrates. In a study of 30 patients with writer's cramp, grey matter was reduced bilaterally in the thalamus and cerebellum as well as in the hand area of the contralateral sensorimotor cortex [18]. Heterogeneous patient populations, variations in group sizes studied and methodological differences in image acquisition and analysis may account for some discrepancies to date.

Our a priori hypothesis was that a structural sensory cortical abnormality would be found in a subset of unaffected relatives of patients with cervical dystonia, correlating with SDT abnormalities previously identified in this group. We were, however, unable to link altered cortical morphology with abnormalities of spatial acuity, although unaffected relatives from the multiplex pedigrees did have significantly greater sensory cortical grey matter volume bilaterally relative to unrelated controls. There may be no simple relationship between cortical organisation or morphology and spatial acuity [19]. Alternatively, the relationship may be a more complex one that volumetric analysis is insensitive to.

We had not anticipated the moderately strong and significant correlations between striatal grey matter volume and spatial acuity, although the basal ganglia do appear to serve both motor and sensory functions [20]. A functional MRI study revealed bilateral hyperactivity in the basal ganglia during a similar grating orientation task in patients with focal hand dystonia [21] and deficits of two-point discrimination can be found in Parkinson's disease [22]. The absence of a similar correlation between spatial acuity and striatal GMV in the unrelated control group suggests that this finding is reflective of true subclinical pathology. Maladaptive sensory processing of afferent inputs into basal ganglia structures may contribute to the pathogenesis of dystonia [23] and the finding of a link between abnormal sensory testing and striatal grey matter is therefore of interest.

Caudate GMV correlated bilaterally with abnormal SDTs in the familial group but putaminal GMV correlated bilaterally with SDTs in the sporadic group. As the sporadic group, or at least a subset of them, are possibly expressing the same inherited dystonia as the familial group, we postulate that morphological changes in both caudate and putamen may be found in both groups. The availability of greater numbers in each patient group may have allowed demonstration of such 'pan-striatal' grey matter changes in voxels that did not reach the significance threshold set in this study. Confounding by truly sporadic cases, phenocopies or genetic heterogeneity amongst sporadic cases may have further contributed to the differences between sporadic and familial relative groups.

We postulate that unaffected relatives with abnormal spatial acuity, and the correlated reduction in striatal volume, are non-penetrant gene carriers. Imaging asymptomatic relatives who are possible gene carriers has the potential to allow the observation of morphological changes reflecting the site of primary pathology of AOPTD. These asymptomatic family members will not manifest structural changes that are secondary to ongoing dystonic movements present in affected subjects. Also, imaging findings in manifesting gene carriers within families may evolve according to the AOPTD phenotype expressed, despite a common genetic aetiology. Bilateral basal ganglia changes in unaffected relatives in this study can be considered a candidate endophenotype in AOPTD and would fit with existing hypotheses implicating basal ganglia dysfunction in its pathophysiology.

Could putaminal changes in some unaffected relatives result from neural adaption to inherited putaminal pathology given the very low penetrance of the phenotype? Other studies of subclinical traits in idiopathic dystonia have revealed differences amongst manifesting and non-manifesting gene carriers, possibly reflective of protective or modifying genetic factors in unaffected subjects [24]. Frima and colleagues [4] investigated abnormal vibration-induced illusion of movement in patients with cervical dystonia and unaffected relatives. Both groups shared an abnormal interpretation of the vibratory stimulus but the unaffected group behaved more like an unrelated control group in their response to pre-testing muscle fatigue. The authors speculated that this might have been due to a more adaptive central handling of type Ia afferent fibres in the non-manifesting group. Manifesting and non-manifesting carriers of the *DYT1* mutation demonstrate similar degrees of abnormal intracortical inhibition, but manifesting carriers differ in their abnormally prolonged response to conditioning of the motor cortex using repetitive transcranial magnetic stimulation [25]. One weakness of this study is our inability to identify which unaffected relatives, if any, will go on to manifest dystonia and therefore we cannot be certain if the observed changes are a subclinical pre-symptomatic phase or a protective neuroplastic response. The low penetrance of the phenotype may make the latter more plausible but only prospective observation of unaffected relatives over time will clarify this.

Bilateral sensory cortical changes and altered striatal morphology correlating with established sensory deficits in these unaffected relatives offer an insight into the pathophysiology of AOPTD. The interpretation of structural changes observed in previous VBM studies has been restricted given the absence of a similar neurofunctional correlate. The relative contribution of the primary disease process and secondary neuroplastic phenomena to these grey matter changes is currently unknown and would be assisted by longitudinal studies. Further structural and functional imaging studies of both affected and unaffected individuals are needed. If identified, a shared striatal or cortical abnormality in manifesting and non-manifesting members of multiplex families would warrant further investigation as a potential endophenotype to assist genetic studies of AOPTD.

Acknowledgements This study was funded by Dystonia Ireland and a University College Dublin Seed Funding grant.

Conflict of interest statement The authors report no conflicts of interest.

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