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The visual perception of natural motion: abnormal task-related neural activity in DYT1 dystonia

Wataru Sako, Koji Fujita, An Vo, Janet C. Rucker, John-Ross Rizzo, Martin Niethammer, Maren Carbon, Susan B. Bressman, Aziz M. Uluğ and David Eidelberg

Although primary dystonia is defined by its characteristic motor manifestations, non-motor signs and symptoms have increasingly been recognized in this disorder. Recent neuroimaging studies have related the motor features of primary dystonia to connectivity changes in cerebello-thalamo-cortical pathways. It is not known, however, whether the non-motor manifestations of the disorder are associated with similar circuit abnormalities. To explore this possibility, we used functional magnetic resonance imaging to study primary dystonia and healthy volunteer subjects while they performed a motion perception task in which elliptical target trajectories were visually tracked on a computer screen. Prior functional magnetic resonance imaging studies of healthy subjects performing this task have revealed selective activation of motor regions during the perception of ‘natural’ versus ‘unnatural’ motion (defined respectively as trajectories with kinematic properties that either comply with or violate the two-thirds power law of motion). Several regions with significant connectivity changes in primary dystonia were situated in proximity to normal motion perception pathways, suggesting that abnormalities of these circuits may also be present in this disorder. To determine whether activation responses to natural versus unnatural motion in primary dystonia differ from normal, we used functional magnetic resonance imaging to study 10 DYT1 dystonia and 10 healthy control subjects at rest and during the perception of ‘natural’ and ‘unnatural’ motion. Both groups exhibited significant activation changes across perceptual conditions in the cerebellum, pons, and subthalamic nucleus. The two groups differed, however, in their responses to ‘natural’ versus ‘unnatural’ motion in these regions. In healthy subjects, regional activation was greater during the perception of natural (versus unnatural) motion (P < 0.05). By contrast, in DYT1 dystonia subjects, activation was relatively greater during the perception of unnatural (versus natural) motion (P < 0.01). To explore the microstructural basis for these functional changes, the regions with significant interaction effects (i.e. those with group differences in activation across perceptual conditions) were used as seeds for tractographic analysis of diffusion tensor imaging scans acquired in the same subjects. Fibre pathways specifically connecting each of the significant functional magnetic resonance imaging clusters to the cerebellum were reconstructed. Of the various reconstructed pathways that were analysed, the ponto-cerebellar projection alone differed between groups, with reduced fibre integrity in dystonia (P < 0.001). In aggregate, the findings suggest that the normal pattern of brain activation in response to motion perception is disrupted in DYT1 dystonia. Thus, it is unlikely that the circuit changes that underlie this disorder are limited to primary sensorimotor pathways.
Introduction

Primary dystonia is characterized by involuntary co-contraction of agonist and antagonist muscles resulting in abnormal movements and postures (Bressman, 2004). The DYT1 mutation, a GAG deletion at the TOR1A locus on chromosome 9q, is the most common inherited form of the disorder (Breakefield et al., 2008). Imaging studies of resting state cerebral metabolism and pathway microstructure (Carbon et al., 2008; Niethammer et al., 2011; Lerner et al., 2013) have revealed consistent changes in the structure and function of sensorimotor networks in human and mouse carriers of this mutant gene. Indeed, recent studies have shown that in carriers of the DYT1 gene [and of the phenotypically similar DYT6 (THAP1) mutation] (Saunders-Pullman et al., 2007; Fuchs et al., 2009), gene penetrance and the somatic distribution and severity of signs and symptoms relate to a set of stereotyped microstructural changes in cerebello-thalamo-cortical motor pathways (Argyelan et al., 2009; Ulug et al., 2011; Vo et al., 2014).

A growing body of evidence suggests, however, that the clinical manifestations of dystonia are not restricted to the motor system. Indeed, a variety of non-motor abnormalities have been described in patients with dystonia of familial or sporadic origin (Stamelou et al., 2012). In addition to the deficits in motor sequence learning that have been observed in manifesting and non-manifesting DYT1 carriers (Ghilardi et al., 2003; Carbon et al., 2011), abnormalities in sensory processing (Walsh et al., 2007; Bradley et al., 2012) and finger-hand perception (Tinazzi et al., 2009, 2013) have also been described in subjects with primary dystonia. Indeed, in addition to movement, the cerebellum likely supports a variety of cognitive and affective functions in healthy individuals (Stoodley and Schmahmann, 2010). Whether the cerebellum plays a role in mediating the non-motor manifestations of dystonia is not currently known.

Based on prior findings, we have suggested that the cognitive/perceptual manifestations of dystonia develop through disordered connectivity affecting higher order ‘non-motor’ projection pathways (Carbon et al., 2011). In the current study, we explored this notion by determining whether dystonia subjects exhibited changes in the structure and function of neural pathways associated with the visual perception of motion. To this end, we used functional MRI to record regional activation responses in DYT1 dystonia and healthy control subjects who were visually exposed to different types of target motion. This non-movement motion perception paradigm (Dayan et al., 2007) relied on the fact that generally human movements are constrained by the ‘two-thirds power law’ that relates instantaneous velocity along a path to the radius of curvature (Hicheur et al., 2005; Beets et al., 2010). Many forms of biological movement obey this law, including free hand movements (Viviani and Schneider, 1991) and the visual perception of motion (Flach et al., 2004; Dayan et al., 2007). Previous functional MRI experiments in healthy human subjects have revealed system-specific increases in activation in response to the perception of motion that obeys the two-thirds power law (termed ‘natural’ motion) as compared to motion that violates this law (termed ‘unnatural’ motion) (Dayan et al., 2007; Casile et al., 2010). Indeed, the perception of ‘natural’ motion was associated with motor cortical activation responses not seen with ‘unnatural’ motion. Based on the underlying motor network changes that characterize DYT1 dystonia, we predicted that the neural responses that normally distinguish the visual perception of ‘natural’ versus ‘unnatural’ motion are not present in individuals with this disorder.

Materials and methods

Subjects

We studied 10 right-handed clinically manifesting carriers of the DYT1 dystonia mutation [four males and six females, age 43.5 ± 17.7 (mean ± SD) years] who were recruited through the Dystonia Research Center of the Mirken Department of Neurology at Beth Israel Medical Center in New York; demographic and clinical data from these subjects are provided in Supplementary Table 1. None of these subjects had evidence of blepharospasm or evidence of eye movement abnormalities on detailed neuro-ophthalmological examination (J.C.R.). The subjects additionally underwent eye movement recordings with infrared video-oculography during task performance (J-R.R.). The data from the dystonia subjects are presented as online Supplementary material. Overall, standard saccadic analysis was normal in the dystonia subjects. Main sequence relationships were also normal, without evidence of slowing.

Ten right-handed healthy volunteers (five males and five females, age 42.4 ± 9.1 years) served as control subjects in this study. Informed consent was obtained from all participants.

Abbreviation: DTI = diffusion tensor imaging

Keywords: DYT1 dystonia; motion perception; functional MRI; diffusion tensor imaging; two-thirds power law

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from varying the exponent \( \beta \) across experimental conditions (see below), motion parameters were held constant at mean speed of 9.4 cm/s, with a fixed gain multiplier \( K \). 'Natural motion' was defined by \( \beta = 1/3 \), which corresponds to the two-thirds power law (Beets et al., 2010). For 'unnatural motion,' we studied two different experimental conditions that violated the two-thirds power law. The first was \( \beta = 0 \) in which there was no change in speed over the elliptical target path. This perceptual condition served to control for potential activation differences relating specifically to target acceleration. The second was \( \beta = -1/3 \) in which the target slowed along the flat portion of the ellipse and accelerated as it approached the edge of the major axis. Each block was interleaved with an 8-s interval of rest. The conditions (\( \beta = 1/3, 0, -1/3 \) and rest) were presented in random order for a total of four blocks per condition. Each block consisted of 12 s of stimulation and 8 s of rest; irrespective of condition, one elliptical cycle was completed every 1.5 s. To control for potential confounds referable to eye movements during task performance, the subjects were instructed to fix on a cursor positioned at the centre of the visual field (Dayan et al., 2007). Habituation to the stimulus was avoided by varying the orientation of the trajectory in each block. This was done by rotating the major axis of the ellipse by 0°, 45°, and −45° across.

**Image acquisition**

For MRI, images were acquired in the General Electric 3.0 T Signa HDxt scanner at North Shore University Hospital, with an eight-channel head coil. For functional MRI, the field of view was 240 × 240 mm²; 40 slices were acquired with 3 mm thickness, the imaging matrix was 64 × 64, flip angle = 77°, repetition time = 2 s, echo time = 27.2 ms, with total scan acquisition time 320 s (see above). A high resolution structural image (resolution = 0.9 × 0.9 × 1 mm³) was also acquired for each subject. For these \( T_1 \)-weighted structural scans, the field of view was 240 mm, 176 slices were acquired with 1 mm thickness, the imaging matrix was 256 × 256, flip angle = 8°, repetition time = 7.6 ms, echo time = 2.9 ms, inversion time = 650 ms.

For diffusion tensor imaging (DTI), a single-shot spin-echo echo planar imaging sequence was used with 33 diffusion gradient directions and five \( b_0 \) images. The b-value in the diffusion-weighted images was 800 s/mm². For DTI, the field of view was 240 × 240 mm²; 55 slices were acquired with 2.5 mm thickness, echo time = 82.7 ms, repetition time = 15 s, flip angle = 90° and scan time 9.5 min. The images were zero filled to a matrix size of 256 × 256, yielding an image resolution of 0.9 × 0.9 × 2.5 mm³.

**Image analysis**

**Functional MRI**

Image preprocessing and first level analysis were performed using FEAT in FMRIB's Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/). All volumes underwent motion correction, slice-timing correction, high-pass temporal filtering, spatial smoothing and normalization to the MNI-152 image template \( (1 \times 1 \times 1 \text{ mm}^3) \). Average functional data were registered to \( T_1 \)-weighted images in native space, and then \( T_1 \)-weighted images were registered to the MNI-152 template through 12-parameter affine transformation (using FMRIB's Linear Image Registration Tool) (Jenkinson et al., 2002). In first level analysis, activation maps were constructed for each subject according to the general linear model. Motion perception-related activation responses in each condition (\( \beta = 1/3, 0, -1/3 \)) were considered significant for \( P < 0.05 \), corrected.

![Figure 1 The visual motion perception task. Target motion (dots) based on the relationship between instantaneous velocity and the radius of curvature of the elliptical trajectory (see text). In this display, \( R \) and \( r \) represent the radii of minimum (red) and maximum (blue) curvature for the trajectory, and \( V_1 \) and \( V_2 \) represent target velocity at the two points, where \( V_1 = KR^\beta \) and \( V_2 = Kr^\beta \). The 'natural' movement profile (\( \beta = 1/3 \), for which \( V_1 > V_2 \)) defined by increasing target velocity as the path straightens and slowing of velocity as the path becomes more curved. The 'unnatural' profiles are defined by either fixed target velocity (\( \beta = 0 \), for which \( V_1 = V_2 \)) or by a reversal (\( \beta = -1/3 \), for which \( V_1 < V_2 \)) of the 'natural' profile, such that target velocity increases rather than declines as the point of maximal curvature is reached.](Image)

\[
\begin{align*}
\beta &= 1/3, \quad V_1 > V_2, \quad \text{natural condition} \\
\beta &= -1/3, \quad V_1 < V_2, \quad \text{unnatural condition} \\
\beta &= 0, \quad V_1 = V_2 = K, \quad \text{unnatural condition}
\end{align*}
\]
In a second level analysis, we evaluated activation maps at the group level for each of the perceptual conditions, as well as differences between groups (DYT1 versus healthy subjects) within and between conditions. These analyses were performed using Statistical Parametric Mapping 5 (SPM5) software (http://www.fil.ion.ucl.ac.uk/spm/). Group differences in the overall activation response collapsed across perceptual conditions (i.e. the main effect of group, which was defined as $[(\beta = 1/3) - \text{REST}] + [(\beta = 0) - \text{REST}] + [(\beta = -1/3) - \text{REST}]$, and in each of the perceptual conditions separately [i.e. $[(\beta = 1/3) - \text{REST}]; [(\beta = 0) - \text{REST}];$ and $[(\beta = -1/3) - \text{REST}]]$ were considered significant at a voxel level threshold of $P < 0.001$ (uncorrected), with a correction for cluster extent at $P < 0.05$.

Lastly, we determined whether changes in activation response across perceptual conditions differed significantly for the two groups. Thus, group (DYT1, healthy subjects) × condition ($\beta = 1/3, 0, -1/3$) interaction effects were examined to determine whether the pattern of regional activation seen in healthy subjects in response to natural versus unnatural motion (i.e. $\beta = 1/3 > \beta = 0, -1/3$) was also present in DYT1 dystonia patients. To this end, general linear model coefficients of +2, −1, −1 were chosen for the ‘natural’ ($\beta = 1/3$) and ‘unnatural’ ($\beta = 0, -1/3$) conditions, respectively. Interaction effects were considered significant at the same threshold as was used for main effects: $P < 0.001$ at the voxel level (uncorrected), with a correction for cluster extent at $P < 0.05$.

**Diffusion tensor imaging**

The structural relevance of the significant activation clusters was explored using the corresponding volumes of interest as seeds in the tractographic data from each group. Before analysis, diffusion-weighted images were corrected for eddy current-induced distortions and head motion in FSL. Non-brain tissue was removed from the images with the brain extraction tool in FSL (Smith, 2002). Diffusion tensor components for each brain pixel were then calculated; fractional anisotropy maps were determined for each subject using the DTIFIT routine in FSL to fit the diffusion tensor model. $b_0$ images were registered to the MNI-152 ($1 \times 1 \times 1 \text{ mm}^3$) template using a 12-parameter affine transformation (Jenkinson et al., 2002) and the resulting transformation was then applied to the fractional anisotropy maps to register them to MNI space.

Data from each group were processed separately for eigenvalue calculation and to visualize the group tracts (Uluğ et al., 2009; Vo et al., 2013). DWIs from the subjects in a particular group were registered to the template; the gradient vectors were reoriented for tensor calculation. TrackVis software (www.trackvis.org) was used to map white matter tracts with tracking parameters that were identical for the two groups. The cerebellar target mask was used to reconstruct fibre tracts connecting this structure to each of the volumes of interest with significant group × condition interaction effects on motion perception-related neural activity. Pathways associated with cerebellar output were identified using a thalamic mask to distinguish the superior from the inferior and middle cerebellar tracts. Fibre tracts were also reconstructed connecting regions with significant main effects of motion perception (i.e. motion perception-related activation responses independent of the specific condition) to the cerebellar cortex. Thus, a significant parieto-occipital cluster was identified as a main effect of the task ($\beta = 1/3, 0$, and $-1/3$ relative to rest). This cluster was extracted and used as a seed mask to assess the integrity of cerebellar efferent pathways projecting via the thalamus to this motion perception area. Group differences in visualized tract count were determined as described elsewhere (Vo et al., 2014).

**Results**

We first evaluated activation responses during visual motion perception performance independent of variation in $\beta$, the exponent in the velocity-curvature relationship that defines the motion as being ‘natural’ or ‘unnatural.’ To assess these main effects, activation maps were averaged across the three experimental conditions and analysed separately for each group. We found that in both healthy subjects and DYT1 dystonia (Fig. 2A and B) significant activation responses (Supplementary Tables 2A and 3A) were present mainly in parietal and occipital association regions as main effects of the motion perception. We next examined activation responses in the healthy subjects for each of the perceptual conditions (Fig. 2A and Supplementary Table 2B). In normal subjects, activation in the pons was greater in response to natural motion perception (Supplementary Table 4). In this group, no region was found with significantly greater activation in response to unnatural relative to natural motion perception.

The pattern of activation across perceptual conditions was different, however, in the DYT1 group (Fig. 2B and Supplementary Table 3B). The abnormal dominance of responses to unnatural relative to natural motion in DYT1 dystonia was highlighted by direct comparison with the control group. To assess group differences independently from variation in target trajectory, we collapsed the activation maps across conditions, and compared the two cohorts. During the three perceptual conditions (Fig. 3 and Table 1), increased activation was observed in the left occipital pole and in the right frontal regions of dystonia relative to healthy control subjects. Separate group comparisons (Fig. 3 and Table 1) were performed using scans acquired in each of the perceptual conditions. In the unnatural $\beta = 0$ condition in which subjects in both groups perceived target motion at constant velocity, activation responses were increased in the left temporal cortex and frontal operculum. During the unnatural $\beta = -1/3$ condition in which the velocity of perceived target motion increased with declining radius of curvature, relatively greater activation was seen bilaterally in the occipital pole, and in the right pons. We note, however, that most of the increases in regional activation seen in dystonia subjects in response to the latter form of unnatural motion failed to reach significance when the data were averaged across the three task conditions. These observations suggest that activation responses to natural motion dominate in healthy subjects, whereas in DYT1 dystonia, responses to unnatural motion dominate the same regions.

The difference in neural responses was highlighted by the presence of significant group × condition interaction effects...
(Fig. 4A and Table 2) in the right pons and left pontomesencephalic and subthalamic nucleus regions, and in the right lateral cerebellum. Analysis of the individual clusters (Fig. 4B) revealed significant interaction effects in each of the regions \( F(1,38) > 19.26, P < 0.001; \) repeated measures ANOVA. Indeed, in healthy subjects, neural activation in response to natural motion was greater than for unnatural motion in each of these regions \( (P < 0.05; \) post hoc pairwise Bonferroni tests). Dystonia subjects, by contrast, exhibited the opposite effect, with relatively lower activation responses in these regions during natural compared to unnatural motion perception \( (P < 0.01) \). Further analysis revealed that in these regions, activation responses to natural motion were similar for patients and control subjects. Nonetheless, responses to unnatural motion measured in the same regions were significantly greater \( (P < 0.05; \) post hoc Bonferroni test) in the disease group. Post hoc analysis revealed no correlation between activation response and subject age or gender in any of the regions.

**Figure 2 Brain activation during motion perception.** (A) Healthy subjects: Left, Main effect of activation across the three perceptual conditions (‘All’ > Rest). Right, Motion perception-related activation in the individual experimental conditions. In healthy subjects, frontal, parietal, and occipital association activation responses were similar for the three conditions (1/3 > Rest; 0 > Rest; −1/3 > Rest). Cerebellar activation was not evident in the various experimental conditions. The colour bar represents voxels thresholded at \( T = 4.3 \) \( (P < 0.001, \) uncorrected). (B) DYT1 dystonia: Left, Main effect of activation across the three perceptual conditions (‘All’ > Rest). Right, Motion perception-related activation in the individual experimental conditions. In DYT1 dystonia, cortical activation response to motion perception was observed in similar regions to those activated by healthy subjects; qualitative increases in local activation responses were seen in the disease group. Motion perception-related cerebellar activation was evident only in DYT1 dystonia subjects scanned during unnatural motion perception \( (\beta = 0 > \text{Rest}; \beta = -1/3 > \text{Rest}) \). The colour bar represents voxels thresholded at \( T = 4.3 \) \( (P < 0.001, \) uncorrected).
Diffusion tensor imaging tractography

DTI tractography was used to map changes in anatomical connectivity associated with the functional abnormalities seen in the dystonia subjects. Seeds were positioned on the DTI scans in the areas that exhibited significant group x condition interaction effects on functional MRI. These were used with DTI to reconstruct bidirectional pathways (‘fibre tracts’) to and from the cerebellar target mask in each of the groups (see ‘Materials and methods’ section). Ponto-cerebellar pathways in healthy subjects (Fig. 5A) and DYT1 dystonia patients (Fig. 5B) were defined by projections linking the significant pontine region on the right (and the contralateral ‘mirror’ region on the left) to the homolateral cerebellum via the middle cerebral peduncles. The number of visualized fibre tracts in these pathways was significantly reduced in dystonia relative to healthy control subjects on both sides [Right: healthy 1640 ± 55.66 (mean ± standard error), dystonia 1399 ± 38.27; Left: healthy 1690 ± 59.77, dystonia 1268 ± 43.64; Mean: healthy 1665 ± 51.23, dystonia 1333.5 ± 23.72, P < 0.001 for all comparisons; Student’s t-tests]. By contrast, no group difference was detected in the number of visualized fibre tracts connecting the major task-related activation region in parieto-occipital cortex (Supplementary Fig. 1), in which there was a significant main effect of task across groups (Fig. 2A and B) but no group x condition interaction effect, to the pontine seed region (Right: healthy 439 ± 12.33, dystonia 358 ± 45.54; Left: healthy 394 ± 10.75, dystonia 392 ± 26.25; Mean: healthy 416.5 ± 8.54, dystonia 375 ± 29.09, P > 0.3). By contrast, significant group differences were not observed for measurements of fractional anisotropy, a DTI index of axonal integrity and coherence, computed in the corresponding pontine seed regions. That said, pontine fractional anisotropy values in the DYT1 dystonia subjects correlated with corresponding measurements obtained in the major genotype-associated area of altered microstructure in the superior cerebellar white matter (Fig. 5C) that has been observed consistently in DYT1 carriers. In the DYT1 dystonia group, a significant correlation was observed (Fig. 5D) between...
fractional anisotropy measurements in the two regions ($r = 0.72$, $P = 0.02$; Pearson’s correlation of right/left averaged fractional anisotropy values from each subject measured in the pontine and cerebellar white matter regions). This correlation did not reach significance ($P = 0.13$) in the healthy control sample.

**Discussion**

The results of this study suggest that the distinctive pattern of neural activation that normally characterizes the perception of ‘natural’ versus ‘unnatural’ motion is not present in DYT1 dystonia. An unbiased voxel-wise interrogation of the entire brain volume in dystonia subjects revealed regions in the brainstem and cerebellum in which the pattern of activation across perceptual conditions differed significantly from normal. Complementary DTI scan data from the same subjects suggested the presence of a significant relationship between the changes in motion perception-related activation seen in DYT1 dystonia and underlying reductions in the integrity of ponto-cerebellar fibre tracts. Moreover, a significant correlation was observed in the DYT1 dystonia subjects between measurements of local microstructural integrity in the pons and corresponding values from a discrete cerebellar white matter region found previously to be abnormal carriers of this mutation (Argyelan et al., 2009; Uluğ et al., 2011; Vo et al., 2014).

| Table 1 Regions with abnormal activation responses in DYT1 dystonia subjects |
|---------------------------------|----------------|----------------|----------------|----------------|
| Contrast                        | Brain region                                           | $Z_{max}$ | Coordinates (MNI-152) | Cluster size |
|                                |                                                           |           | $x$ | $y$ | $z$ |            |
| A. 'All' > Rest                 | L white matter adjacent to lateral occipital cortex, inferior division | 3.94     | -36 | -52 | 1  | 338       |
|                                | L occipital pole                                      | 3.71     | -20 | -100| -18| 615       |
|                                | L occipital pole                                      | 3.64     | -5  | -97 | -9 | 396       |
|                                | R frontal pole                                       | 3.49     | 7   | 64  | -4 | 268       |
| Healthy Subjects > DYT1        |                                                          |           |     |     |    |           |
|                                | No regions                                            |           |     |     |    |           |
| B. '1/3' > Rest                 | R cerebellum (Crus II)                                | 3.59     | 16  | -79 | -35| 149       |
|                                | L occipital pole                                      | 3.47     | -36 | -95 | -10| 193       |
| Healthy Subjects > DYT1        |                                                          |           |     |     |    |           |
|                                | No regions                                            |           |     |     |    |           |
| '0' > Rest                     | Midbrain                                              | 3.79     | -3  | -31 | -10| 420       |
| Healthy Subjects > DYT1        |                                                          |           |     |     |    |           |
|                                | No regions                                            |           |     |     |    |           |
| '-1/3' > Rest                  | R white matter adjacent to occipital fusiform gyrus    | 3.92     | 36  | -56 | -4 | 233       |
|                                | LR occipital pole                                     | 3.76     | 1   | -100| -7 | 474       |
|                                | L white matter adjacent to temporal fusiform cortex    | 3.69     | -36 | -52 | 0  | 287       |
|                                | R white matter adjacent to temporal fusiform cortex    | 3.59     | 43  | -37 | -12| 179       |
|                                | R pons                                                | 3.52     | 16  | -30 | -30| 170       |
|                                | L occipital pole                                      | 3.48     | -29 | -97 | -16| 144       |
|                                | L lingual gyrus                                       | 3.38     | -4  | -87 | -22| 132       |
|                                | R occipital pole                                      | 3.33     | 18  | -102| -1 | 109       |
| Healthy Subjects > DYT1        |                                                          |           |     |     |    |           |
|                                | No regions                                            |           |     |     |    |           |

$L =$ left; $R =$ right.
In aggregate, the data suggest that the underlying circuit abnormality in DYT1 dystonia is not limited to motor cerebello-thalamo-cortical projection pathways.

The current findings accord well with previous functional MRI studies in which this experimental paradigm was used in healthy subjects (Dayan et al., 2007; Casile et al., 2010). As previously reported, task-related activation in visual and motor association regions predominated for natural versus unnatural motion perception. The DYT1 dystonia patients notably exhibited motion perception-related activation responses in many of the same regions deployed by healthy subjects (Fig. 2A and B). Nonetheless, the spatial extent of these clusters, which were located mainly in posterior parietal and occipital association areas, was relatively greater in the patients; the cerebellum was activated during visual motion perception in dystonia but not in healthy subjects. Importantly, motion perception-related cerebellar activation in the patient group was seen mainly during the perception of unnatural, rather than natural motion trajectories. This accords well with the notion of cerebellar functional overactivity in dystonia (Carbon et al., 2010; Hallett, 2011), with consequent suppression of activity in the downstream pathways that normally facilitate intracortical inhibition (Argyelan et al., 2009; Lerner et al., 2013).

This hypothesis was further borne out when the data were interrogated for the presence of regions in which changes in activation across conditions differed for the patient and control groups. In keeping with the within-group

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**Figure 4 Group differences in activation profiles across task conditions.** (A) Group differences in activation responses across perceptual conditions were assessed on a voxel by voxel basis. Significant group × condition interaction effects (Table 2) were found in the cerebellum, and in the ponto-mesencephalic region extending into the region of the thalamus, subthalamic nucleus (STN), and globus pallidus (GP). The colour bar represents voxels thresholded at T = 3.2 (P < 0.001, uncorrected). (B) Analysis of the data from each of the significant clusters revealed consistent within-subject activation increases during the perception of natural versus unnatural motion in normal individuals (blue lines) and concomitant reductions in DYT1 dystonia subjects (red lines). Brackets on the left side of each graph indicate group differences between DYT1 and normal for the unnatural [\( \beta = 0 \) + (-1/3)] condition. Brackets above each graph indicate the difference between natural and unnatural conditions in the DYT1 dystonia group; those below each graph represent the corresponding difference in healthy subjects (\( ^* P < 0.05; ^{**} P < 0.01; ^{***} P < 0.001; \) post hoc Bonferroni tests).
Table 2 Regions with abnormal changes in neural activation across perceptual conditions in the DYT1 dystonia subjects

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Z_{max}</th>
<th>Coordinates (MNI152)</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midbrain – pons / cerebellum (vermis) / R GP – thalamus / L STN</td>
<td>5.00</td>
<td>x: -6  y: -28  z: -10</td>
<td>23613</td>
</tr>
<tr>
<td>R cerebellum (lobule VI)</td>
<td>4.66</td>
<td>x: 37  y: -51  z: -28</td>
<td>3805</td>
</tr>
</tbody>
</table>

GP = globus pallidus; L = left; R = right; STN = subthalamic nucleus.

data, significant group x condition interaction effects (Fig. 4A and B) were noted in the somatosensory zone of the superior cerebellum, an area with prominent anatomical and functional connections to motor and somatosensory cortical regions, and to the middle temporal visual motion area (Kelly and Strick, 2003; O’Reilly et al., 2010). Because of the specificity of its cortical connections, this cerebellar region is thought to play a key role in visuomotor integration processes such as those involved in motion perception. The notion that the changes seen in dystonia involve a broadly distributed functional-anatomical circuit is supported by the presence of two additional regions in which significant interaction effects were noted: the dorsolateral pons in the vicinity of the middle pontine pathways that support normal motion perception (Kelly and Strick, 2003; O’Reilly et al., 2010). These data suggest that in healthy subjects, ponto-cerebellar projections to target regions in the sensorimotor zone of cerebellar hemisphere operate singly—or in combination with other regions—to optimize network activity in response to the perception of ‘biological’ motion. In DYT1 dystonia, however, this ‘perceptual tuning’ mechanism may be defective as a result of inadequate calibration of visuomotor afferent signals to the cerebellum (Glickstein et al., 1994; O’Reilly et al., 2010).

The data further suggest that the abnormal motion perception-related activation responses seen in the brainstem and cerebellum of the DYT1 dystonia subjects were accompanied by microstructural changes in the fibre pathways that connect these structures. While fewer ponto-cerebellar tracts were evident in the dystonia group (Fig. 5A and B), the number of visualized fibre tracts connecting activation regions in the parieto-occipital cortex with the pontine functional MRI cluster (Supplementary Fig. 1) was not significantly different from normal. That is, the cortico-pontine pathways that support normal motion perception are intact in DYT1 dystonia. Thus, it is likely that the corresponding circuit abnormality in this disorder reflects changes in the structural and functional integrity of pontocerebellar input channels. Indeed, the data further suggest that DYT1 dystonia is associated with more widespread maldevelopment of cerebellar pathways than assumed based on previous DTI studies (Argyelan et al., 2009; Vo et al., 2014).

Of note, fractional anisotropy values in the pontine region did not differ significantly from normal, perhaps because of the mixed grey–white matter tissue composition of this region. Indeed, compared to control values, the reduction in ponto-cerebellar fibre tracts seen in DYT1 dystonia was smaller (~20%) than analogous genetic changes described previously in relation to the cerebellorhinalic (~60%) and thalamocortical (between ~60% and ~80%) pathway segments (Vo et al., 2014). Despite the modest size of the ponto-cerebellar fibre tract abnormality seen in these patients, other lines of evidence point to the relevance of this finding with regard to the pathophysiology of the disorder. First, fractional anisotropy values measured in the functionally defined pontine region (specified as it was by the presence of a significant group x condition interaction effect in the functional MRI data) exhibited a strong positive correlation with values measured in the same subjects in the previously identified area of microstructural abnormality that was localized to the deep cerebellar white matter of gene carriers (Argyelan et al., 2009; Vo et al., 2014). These findings raise the possibility that the ponto-cerebellar tract changes seen in DYT1 dystonia subjects develop in parallel with the cerebellar outflow tract abnormality as likely trait features (Ulugu et al., 2011; Vo et al., 2014). Second, highly significant fractional anisotropy reductions and corresponding fibre tract changes have been identified in homologous ponto-cerebellar regions of DYT1 knock-in mice containing the endogenous torsin A (TOR1A) mutation, as well as in other genetic animal models of the disorder (Ulugu et al., 2011; Zhao et al., 2011).

Although the subjects in each group exhibited consistent patterns of motion perception-related activation across conditions, the behavioural relevance of these changes cannot be appreciated without concurrent psychophysical indices of perceptual performance. The measurement of anticipation errors after abrupt cessation of target motion in mid-trajectory may be useful in this regard (Flach et al., 2004), given the increased accuracy of predictions made immediately following exposure to natural (rather than unnatural) elliptical paths (Flach et al., 2004). It will be interesting to know whether patients with primary dystonia are capable of this form of anticipation. Of note, we did not record extraocular movements at the time of imaging. Thus, potential confounds stemming from group differences in the maintenance of central
fixation (an essential requirement of the perceptual task), or in the amplitude of eye movements (if visual tracking of target motion takes place during the task) are a possible concern. While biases of this sort cannot be excluded with certainty, the results of oculographic recordings conducted in the subjects (Supplementary material) suggest that such confounds are unlikely in the current data. Indeed, the recordings demonstrated that in the motion perception task, fixation on the central cursor was nearly perfect for both patients and control subjects in the three perceptual conditions ($\beta = 1/3$, 0, and $-1/3$). Moreover, no differences in the magnitude of eye movements were
observed between the groups when the subjects were instructed to pursue the moving target in a non-imaging tracking task. In any event, systematic oculographic recordings will need to be performed during imaging to exclude fully the possibility of these confounds.

The findings overall raise a number of questions for future investigation. We have previously described replicable motor sequence learning deficits in manifesting and non-manifesting DYT1 carriers (Ghilardi et al., 2003; Carbon et al., 2011). Changes in learning performance were not seen, however, in DYT6 carriers, suggesting that this particular manifestation is likely to be genotype-specific (Carbon et al., 2011; Niethammer et al., 2011). In this vein, it is not known whether the abnormal pattern of activation seen during motion perception in DYT1 dystonia patients is also present in motorically non-manifesting DYT1 carriers, in manifesting and/or non-manifesting carriers of other dystonia mutations, or in individuals with non-familial forms of the disorder. Indeed, in a preliminary study [Fujita et al., 2015 (abstract)], we have reported abnormal ‘unnatural’ > ‘natural’ activation response in sporadic dystonia subjects scanned in conjunction with this paradigm. Moreover, analogous activation changes have recently been noted in non-manifesting carriers of dystonia mutations (W. Sako, personal communication). Given the generalizability of the functional MRI findings, the approach described in this paper may have utility in the clinical domain. For example, as a disease (‘state’) marker, loss of normal ‘natural’ > ‘unnatural’ activation may help distinguish dystonia from a clinically similar functional ‘look-alike’ disorder. The abnormal ‘reversal’ response on functional MRI may also have utility as an endophenotypic (‘trait’) marker to identify clinically unaffected members of familial clusters who are genetically at risk. Prospective studies will be needed to determine the sensitivity and specificity of this imaging change at the individual subject level.

Intriguingly, it will be important to determine whether other behaviours are affected as a consequence of the observed connectivity changes. For example, recent work (Pavlova, 2012; Sokolov et al., 2012) has associated the visual processing of human motion with a neural pathway linking the superior lateral cerebellar hemisphere to middle temporal and occipital association regions. It is perhaps not surprising that brain networks that support this aspect of visuomotor perception overlap with those involved more generally in designating elemental motion as being either ‘natural’ or ‘unnatural’ in origin. Given the relevance of this form of motion processing to social cognition, it may also be useful to know whether this particular behaviour, as well as its neural correlates recorded during task performance, is altered in dystonia subjects.

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**Conflict of interest**

Dr Eidelberg has served as a scientific advisory board member and has received honoraria from The Bachmann-Strauss Dystonia and Parkinson Foundation and is listed as co-inventor of patents re: Markers for use in screening patients for nervous system dysfunction and a method and apparatus for using same, without financial gain. He has received research support from the NIH (NINDS) and The Bachmann-Strauss Dystonia and Parkinson Foundation. All other authors declare no conflict of interest.

**Supplementary material**

Supplementary material is available at Brain online.

**References**


