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Disruption of network for visual perception of natural motion in primary dystonia

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Abstract

In healthy subjects, brain activation in motor regions is greater during the visual perception of “natural” target motion, which complies with the two-thirds power law, than of “unnatural” motion, which does not. It is unknown whether motion perception is normally mediated by a specific network that can be altered in the setting of disease. We used block-design functional magnetic resonance imaging and covariance analysis to identify normal network topographies activated in response to “natural” vs. “unnatural” motion. A visual motion perception-related pattern (VPRP) was identified in 12 healthy subjects, characterized by covarying activation responses in the inferior parietal lobule, frontal operculum, lateral occipitotemporal cortex, amygdala, and cerebellum (Crus I). Selective VPRP activation during “natural” motion was confirmed in 12 testing scans from healthy subjects. Consistent network activation was not seen, however, in 29 patients with dystonia, a neurodevelopmental disorder in which motion perception pathways may be involved. Using diffusion tractography, we evaluated the integrity of anatomical connections between the major VPRP nodes. Indeed, fiber counts in these pathways were substantially reduced in the dystonia subjects. In aggregate, the findings associate normal motion perception with a discrete brain network which can be disrupted under pathological conditions.

Keywords

amygdala; diffusion tensor imaging; dystonia; fMRI; motion perception

INTRODUCTION

Dystonia is a movement disorder characterized by abnormal muscle contractions that may be sustained and associated with fixity of posture (Phukan et al., 2011). In recent years, a
variety of non-motor disease manifestations have been described, involving mainly sensory and perceptual abnormalities (e.g., Stamelou et al., 2012; Patel et al., 2014). Abnormalities of sensorimotor integration have been observed as a general feature of dystonia (Abbruzzese and Berardelli, 2003; Patel et al., 2014). Little is known, however, of the stereotyped changes in cerebral structure and function that mediate clinical manifestations in dystonia patients. Recent evidence points to the presence of consistent changes in cerebello-thalamo-cortical connectivity that regulates penetrance and phenotypic variation of motor signs and symptoms in dystonia patients (Argyelan et al., 2009; Vo et al., 2015). It has remained unclear, however, whether analogous pathway changes mediate non-motor manifestations in these individuals.

In a recent functional magnetic resonance imaging (fMRI) study, we identified a set of highly localized structure–function abnormalities in DYT1 dystonia patients scanned while perceiving target motion (Sako et al., 2015). In humans, curved hand movements obey the two-thirds power law, which relates the speed of the movements to the curvature of the path (Lacquaniti et al., 1983; Huh and Sejnowski, 2015). Importantly, the two-thirds power law is not limited to movement kinematics, but also applies to the visual perception of target motion (Levit-Binnun et al., 2006). Indeed, in healthy subjects, significant differences in regional activation were noted during the perception of trajectories with kinematic properties conforming to the two-thirds power law of motion (termed “natural” motion) and those that violated this rule (termed “unnatural” motion) (Dayan et al., 2007; Casile et al., 2010; Sako et al., 2015). Interestingly, we found that differences in activation in response to “natural” vs. “unnatural” motion perception were altogether lacking in the dystonia subjects (Sako et al., 2015). Region-level analysis of the fMRI activation data localized these changes to the pons and cerebellum, which comport with alterations in structural connectivity seen in the same individuals with magnetic resonance diffusion tensor imaging (DTI).

The identification of localized structure–function abnormalities in dystonia has helped create new mechanistic hypotheses concerning the origins of the clinical manifestations of the disorder (Argyelan et al., 2009; Vo et al., 2015). The regional changes such as those described above provide limited information concerning their impact at the circuit level. Indeed, in many neurological diseases, signs and symptoms are intimately linked to the activity of spatially distributed functional brain networks as opposed to localized changes in individual brain regions (see, e.g., Eidelberg, 2009; Niethammer and Eidelberg, 2012). In the current study, we utilized a multivariate network-based approach to identify a reproducible activation pattern in healthy subjects associated with visual motion perception. By measuring differences in pattern expression in individual subjects’ fMRI scans acquired during “natural” vs. “unnatural” motion perception, we determined whether network activation responses were intact in manifesting and non-manifesting carriers of the DYT1 and DYT6 dystonia mutations and in individuals with sporadic disease.

**MATERIALS AND METHODS**

**Participants**

We studied 27 dystonia gene carriers (10 men/17 women; age 41.0±17.8 (mean±SD) years) of whom 12 had the DYT1 mutation and 15 had the DYT6 mutation. Of these subjects, 16
manifested (MAN) clinical signs of dystonia and 11 were clinically non-manifesting (Non-MAN). The DYT1 group was comprised of 4 men and 8 women (10 MAN/2 Non-MAN), age 46.3±16.2 years. The DYT6 group was comprised of 6 men and 9 women (6 MAN/9 Non-MAN), age 36.7±18.5 years. We additionally studied a group of 13 sporadic dystonia subjects comprised of 7 men and 6 women, age 49.9±16.5 years. A group of 12 healthy subjects comprised of 6 men and 6 women, age 39.8±10.2 years served as controls. Because the prevalence of the DYT1 and DYT6 mutations are very low in the general population, it was unlikely (<0.1%) that any of these healthy individuals was a mutation carrier (Vo et al., 2015). All participants were right-handed; no significant difference between groups was noted for either age or gender (p>0.1). The dystonia subjects were rated according to the movement subscore on the Burke–Fahn–Marsden Dystonia Rating Scale (Burke et al., 1985) at the time of imaging. Demographic and clinical data from these subjects are provided in Supplementary Table SI. Informed consent was obtained from all participants under protocols approved by the institutional review boards of the participating institutions.

Procedures

Image Acquisition—Images were acquired in the Signa HDxt 3.0 T scanner (GE Healthcare) at North Shore University Hospital, with an 8-channel head coil. For fMRI scans, the field of view (FOV) was 240 mm, 40 slices were acquired with 3 mm thickness, the imaging matrix was 64 × 64, flip angle = 77°, repetition time (TR) = 2 s, echo time (TE) = 27.2 ms, with total scan acquisition time of 320 s. The healthy subjects were scanned in two trial blocks in a single imaging session. For high resolution T1-weighted structural scans, the FOV was 240 mm, 176 slices were acquired with 1 mm thickness, the imaging matrix was 256 × 256, flip angle = 8°, TR = 7.6 ms, TE = 2.9 ms, inversion time = 650 ms, with resolution of 0.9 × 0.9 × 1 mm³. For DTI, a single-shot spin-echo echo planar imaging sequence was used with 33 diffusion gradient directions and 5 b0 images. The b-value in the diffusion-weighted images was 800 s/mm². The FOV was 240 mm, 55 slices were acquired with 2.5 mm thickness, TE = 82.7 ms, TR = 15 s, flip angle = 90°, and scan time = 9.5 min. The images were zero filled to a matrix size 256 × 256, yielding an image resolution of 0.9 × 0.9 × 2.5 mm³.

fMRI Design—We used an fMRI block design to assess neural responses to visual perception of motion that obeys or violates the “two-thirds power law,” as detailed elsewhere (Sako et al., 2015). Briefly, the subjects were asked to fixate on a red cross at the center of the display while a white ball moved in elliptical trajectories on a black background. The ball was moving according to the law in the form:

\[ V = KR^{3/2} \]

where V is the tangential velocity, K is the fixed velocity gain factor, with which the average velocity was maintained across the conditions, and R is the radius of elliptical curvature. “Natural” motion was defined by \( \beta = 1/3 \), which corresponds to the “two-thirds power law” and gives larger velocity in the less curved path and smaller velocity in the more curved path. “Constant” motion was defined by \( \beta = 0 \), which gives a constant Euclidean velocity and served as control motion to detect activation differences associated with the velocity.
changes. An fMRI block comprised 12 s of visual perception of motion (β=1/3 or 0) and 8 s of rest, and each condition had a total of 4 blocks in 1 session. We have confirmed that the eye fixation was maintained in these conditions in healthy subjects and patients (Sako et al., 2015).

**fMRI Processing**—Preprocessing and first level analysis of fMRI data were performed using FEAT in FMRIB’s Software Library version 5.0 (FSL; fsl.fmrib.ox.ac.uk) (Smith et al., 2004). The first four volumes of each dataset were discarded to account for T1-saturation effects. The remaining volumes underwent motion correction using MCFLIRT (Jenkinson et al., 2002), slice timing correction, brain extraction using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of full width at half maximum (FWHM) 8 mm, and high-pass temporal filtering equivalent to 100 s. After preprocessing, first level statistical analysis was performed using the general linear model. The contrasts estimated included (β=1/3) – rest and (β=0) – rest. Statistical maps were thresholded using clusters determined by $Z>2.3$ and a corrected cluster significance threshold of $p=0.05$, according to Gaussian random field theory. The fMRI images were registered to the participants’ high resolution T1-weighted images (brain-extracted using BET) using FLIRT/BBR (Greve and Fischl, 2009), and the high resolution images were registered to Montreal Neurological Institute (MNI) 152 T1 brain template (1×1×1 mm$^3$) using FLIRT/12DOF (Jenkinson et al., 2002).

**Network Analysis**—To identify a specific activation pattern relating to the visual perception of “natural” (β=1/3) vs. “unnatural” constant velocity (β=0) motion, we applied Ordinal Trend Canonical Variates Analysis (OrT/CVA) (Habeck et al., 2005), a within-subject network mapping algorithm, to fMRI data acquired in the two behavioral conditions. This computational algorithm relies on supervised principal component analysis (PCA) to identify distinct spatial covariance patterns (functional brain networks) with consistent changes in expression (network activity) across task conditions (Mure et al., 2011; Mure et al., 2012; Ko et al., 2014a). This approach differs from voxel-wise mass univariate methods in that it requires an ordinal trend, i.e., a consistent change in expression across conditions at the individual subject level, in the scan data. Thus, in OrT/CVA, network activity is required to increase (or decrease) monotonically in all or most of the subjects. As in other forms of spatial covariance analysis, large-scale networks are described in terms of the voxel loadings (“region weights”) on each of the relevant principal component (PC) topographies (Spetsieris et al., 2013). Likewise, the expression of a given pattern in each scan is quantified by a specific network activity measure (“subject score”), the PC scalar multiplier for the subject at each experimental time point.

For inferential statistics, we used non-parametric tests as detailed elsewhere (Habeck et al., 2010). Permutation testing of the relevant subject scores was performed to confirm that the monotonic changes in pattern expression seen across conditions in individual subjects did not occur by chance. An ordinal trend was considered significant in the derivation set if a consistent increase (or decrease) in network activity across perceptual conditions was observed in the subjects, with few if any violations. The reliability of voxel weights on the network was similarly assessed using bootstrap resampling.
To assess the within-group reproducibility of candidate patterns, the first or second fMRI sessions of the 12 healthy subjects were randomly assigned to either a derivation (training) or validation (testing) sample. For pattern identification, $\beta=0$ (baseline) and $\beta=1/3$ (active) scan pairs from the 12 healthy volunteer subjects were analyzed within the MNI152 brain mask (Grabner et al., 2006). Using OrT/CVA, we explored the data for the presence (or absence) of a specific covariance pattern that exhibited a significant ordinal trend, i.e., for which expression values increased in the active relative to the baseline condition in all or nearly all of the subjects. The pattern was selected from among combinations of linearly independent (orthogonal) principal components (PCs) according to the following criteria: (a) the analysis was limited to the PC combinations with the smallest possible Akaike Information Criterion (AIC) values; (b) pattern expression values in the derivation sample showed a monotonically increasing trend from $\beta=0$ to $\beta=1/3$ conditions that differed from chance as determined by the permutation test ($p<0.05$; 1,000 iterations). The reliability of the voxel weights on the pattern was tested using a bootstrap resampling procedure with 1,000 iterations (Habeck et al., 2010). The significance level for voxel weight reliability was set at an inverse coefficient of variation (ICV) threshold of $|Z|=1.96$, corresponding to $p<0.05$. For validation, expression values were prospectively computed for each subject and condition in the testing set. An ordinal trend was confirmed in the testing data by the presence of consistent increases in pattern expression in the $\beta=1/3$ relative to $\beta=0$ conditions ($p<0.05$; binomial test).

In a recent report, biological motion perception was linked to the default mode network (DMN) (Dayan et al., 2016). We therefore used voxel-based correlation analysis (Ko et al., 2014b) to evaluate the topographic relationship between the VPRP and a probabilistic DMN template described previously using resting-state fMRI and independent component analysis (ICA) (Wang et al., 2014).

Following validation, we computed pattern expression values for the two conditions in the dystonia subjects. These calculations were performed using an automated algorithm that was blind to subject identity, group, and experimental condition. Differences in pattern expression between conditions were evaluated for each group according to the binomial test. Differences from normal were evaluated for the dystonia groups using one-way analysis of variance (ANOVA) with post-hoc Dunnett’s tests, which were considered significant for $p<0.05$.

**Diffusion Tensor Imaging**—We assessed the tractographic correlates of pattern expression using DTI. Fractional anisotropy (FA) maps were determined and registered, according to registration of b0 images, to MNI152 space using FSL (Smith et al., 2004), as previously described (Sako et al., 2015; Vo et al., 2015). We assessed correlation between network expression and FA values in a predetermined cluster in the right deep cerebellar white matter in which FA was reduced in inherited dystonia (10 DYT1 MAN and 3 DYT6 MAN) subjects in a previous study (Vo et al., 2015). We then prospectively searched whole brain white matter mask defined by the average FA map of the entire group (n=52), thresholded at FA=0.18. Using voxel-wise multiple regression analysis of smoothed images (Gaussian kernel of FWHM=8 mm), we interrogated the data for clusters in which FA correlated with pattern expression values. Regions were considered significant at a voxel-
level threshold of p<0.001 (uncorrected), with a cluster-level correction for multiple comparisons at p<0.05. To rule out the possibility of false positives due to smoothing, FA values for the significant regions were computed on the unsmoothed maps and correlated post-hoc with pattern expression. The resulting correlations were considered significant for p<0.05 (Pearson’s product-moment correlation coefficient).

For diffusion tensor tractography, data from each group were processed separately for eigenvector calculation and to visualize the group tracts. Diffusion-weighted images from the subjects in a particular group were registered to the template; the gradient vectors were reoriented for tensor calculation (Vo et al., 2013; Vo et al., 2015). TrackVis (Massachusetts General Hospital; www.trackvis.org) was used to map white matter tracts with the fMRI activation clusters obtained above (thresholded at Z=1.96) as tracking parameters. The reconstructed tracts were displayed for each group. Differences in tract number across groups were evaluated using jackknife resampling and one-way ANOVA. Differences from normal were evaluated post-hoc for each dystonia group using Dunnett’s tests, and were considered significant for p<0.05.

RESULTS

Network Characterization

A significant functional network was identified in fMRI scan pairs acquired during the visual perception of “natural” (β=1/3) vs. “unnatural” (β=0) motion. This visual motion perception-related covariance pattern (VPRP) (Table I) was characterized by increased activity (Fig. 1A, red-yellow) in the right inferior parietal lobule (IPL), pars opercularis of inferior frontal gyrus (IFG), amygdala, lateral occipitotemporal cortex (LOTC), and right cerebellum (Crus I). These changes were associated with relative reductions (Fig. 1A, blue) in the posterior cingulate and ventromedial prefrontal cortex (vmPFC). The VPRP covariance topography represented a linear combination of the first two PC patterns in the OrT/CVA analysis, accounting for 8.4% of the overall voxel × (subject • condition) variance. Voxel weights on the VPRP in these regions were found to be reliable on bootstrap resampling (|ICV|>1.96, p<0.05; 1,000 iterations). Expression values for the VPRP exhibited a significant ordinal trend in the derivation data (Fig. 1B, left), with increasing network activity in “natural” relative to “unnatural” motion perception (p<0.001; permutation test; 1,000 iterations).

Abnormal Network Activation in Dystonia

The finding of an ordinal trend in the derivation data was confirmed in the testing set. VPRP expression values computed prospectively in the testing scans behaved similarly to the training set (Fig. 1B, right) with consistent increases during “natural” vs. “unnatural” motion (p=0.039; binomial test).

In contrast to the consistent network activation seen in healthy subjects perceiving “natural” vs. “unnatural” target motion, VPRP expression on average was unchanged in dystonia subjects scanned under the same perceptual conditions (p=1.0; binomial test). For group comparison, we computed ΔVPRP, the change in pattern expression for β=1/3 relative to

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\( \beta = 0 \), for the subjects in each group. Comparison of ΔVPRP for dystonia patients with corresponding healthy control values (Fig. 2A) revealed a significant difference across groups (\( p = 0.016 \); one-way ANOVA). ΔVPRP was reduced relative to control subjects in affected DYT1 and DYT6 carriers (\( p = 0.010 \) and \( p = 0.041 \), respectively; post-hoc Dunnett’s tests); a marginal ΔVPRP reduction relative to normal was noted in the sporadic dystonia group (\( p = 0.117 \); post-hoc Dunnett’s test). When affected and non-manifesting mutation carriers were considered together (Fig. 2B), a significant group difference was also present (\( p = 0.004 \); one-way ANOVA), with reduced ΔVPRP relative to control values in both genotypes (DYT1: \( p = 0.003 \); DYT6: \( p = 0.022 \); post-hoc Dunnett’s tests). Lastly, when manifesting and non-manifesting mutation carriers were considered separately (Fig. 2C), the difference across groups was also significant (\( p = 0.005 \); one-way ANOVA), with reduced ΔVPRP in both mutation groups compared to control values (MAN: \( p = 0.003 \); Non-MAN: \( p = 0.041 \); post-hoc Dunnett’s tests).

### Microstructural Correlates of Network Activation

To determine the relationship between network activation and white matter microstructure, we performed voxel-wise regression of ΔVPRP values on the reconstructed FA maps. The results of this analysis (Table II) are presented in Fig. 3A. In the healthy subjects (Fig. 3B), significant structure–function relationships were noted in the left occipital and right posterior temporal white matter regions. In DYT1 manifesting carriers (Fig. 3C), significant correlations were present in left occipital white matter. No regions with significant correlations were identified in the DYT6 or sporadic dystonia groups. Nonetheless, when all affected dystonia subjects were grouped together (Fig. 3D), significant correlations were discerned in white matter of the left middle frontal gyrus and the left occipital lobe, whereas in the combined sample of manifesting and non-manifesting mutation carriers, a single significant region was present in the right occipital lobe. Correlations in all the reported regions were highly significant (\( r > 0.59 \), \( p < 0.003 \); Pearson’s correlations). A weaker, though still significant correlations with ΔVPRP (\( r = 0.605 \), \( p = 0.037 \)) was additionally noted in the DYT1 carriers in the area of abnormal FA in cerebellar white matter that was described in prior familial dystonia studies (Supplementary Fig. S1).

We employed group-wise tractography to examine the anatomical interconnections of the major VPRP nodes. The number of tracts connecting the right IPL (Brodmann area [BA] 40) and IFG (BA 44) clusters as part of the perisylvian pathway (Fig. 4A) was reduced relative to normal in both inherited dystonia groups (\( p < 0.001 \) for DYT1 and DYT6; post-hoc Dunnett’s tests); the corresponding abnormality in the sporadic dystonia group did not reach significance (\( p = 0.149 \); post-hoc Dunnett’s test). By contrast, tracts linking the right amygdala and the LOTC (BA 19) as part of the inferior longitudinal fasciculus (ILF) (Fig. 4B) were reduced relative to normal in inherited as well as sporadic dystonia (\( p < 0.001 \) for each dystonia group; post-hoc Dunnett’s tests). Finally, tracts connecting the pons and the right cerebellar Crus I cluster via the middle cerebellar peduncle (MCP) (Fig. 4C) were reduced relative to normal in the DYT1 and sporadic dystonia groups (\( p < 0.001 \); post-hoc Dunnett’s tests), but were comparatively increased in the DYT6 group (\( p = 0.002 \); post-hoc Dunnett’s test). Notably, these tract changes, particularly those in the amygdala–LOTC pathways, were seen in manifesting as well as non-manifesting dystonia gene carriers.
DISCUSSION

In this study, we identified and validated the VPRP, an fMRI activation network associated with the visual perception of motion in healthy subjects. In keeping with the region-level findings reported in our previous study, VPRP network activity increased consistently in healthy subjects visually perceiving two-thirds power law compliant (“natural”) motion, compared to its rule non-compliant (“unnatural”) behavioral counterpart. We additionally noted that in healthy subjects, perception-related regional activation was greater during “natural” motion. The “natural” condition was not dominant, however, in DYT1 dystonia patients (Sako et al., 2015). In the current study, we observed similar findings at the network level: dominant VPRP activity in the “natural” condition was present in healthy subjects but not in DYT1 dystonia. We additionally observed an analogous loss of VPRP responses in DYT6 dystonia patients perceiving “natural” vs. “unnatural” motion, as well as in non-manifesting carriers of either the DYT1 or DYT6 dystonia mutations. Thus, the attenuated network-level responses to the visual perception of natural vs. unnatural motion seen in familial dystonia is consistent with a disturbance in the neural circuitry that mediates this function in healthy individuals. The findings accord with the notion that genetically determined pathway maldevelopment can disrupt the normal functioning of non-motor as well as motor circuits in susceptible individuals (Sako et al., 2015). The notion of circuit maldevelopment in dystonia is additionally borne out by the DTI-based reconstructions of the fiber tracts connecting the major VPRP nodes in each of the disease groups. Network activation in response to the perception of “natural” vs. “unnatural” motion was reduced in the familial (DYT1 and DYT6) dystonia groups relative to normal, and fiber tracts linking the inferior frontal opercular region (BA 44) and the IPL were likewise reduced in these individuals. Interestingly, in sporadic dystonia, ΔVPRP responses were not significantly reduced and and fronto-parietal tract counts were accordingly unaltered. That said, consistent reductions in fiber tracts linking the amygdala to the LOTC were seen in both familial and sporadic dystonia, suggesting a role for this pathway in the non-motor manifestations of the disorder independent of genotype.

The normal VPRP network was characterized by salient contributions from anatomically interconnected nodes in the frontal operculum (IFG, BA 44) and the parietal association cortex (IPL, BA 40). Indeed, both these areas have been reported to be activated during “natural” (vs. “unnatural”) motion in healthy subjects (Dayan et al., 2007). Importantly, these regions are elements of the mirror neuron system, a set of reciprocal fronto-parietal projections that is specialized for action recognition (Iacoboni and Dapretto, 2006; Molenberghs et al., 2012). The data suggest that this neural system is involved in normal motion perception, serving as a physiologic link between this cognitive function and the execution of movement in human subjects (Levit-Binnun et al., 2006). In this vein, the reduction in VPRP activation in DYT1 and DYT6 dystonia patients and in non-manifesting carriers of these mutations may relate to maldevelopment of this pathway as suggested by...
the tractographic findings. Such cortico-cortical abnormalities may underlie the impairment of sensorimotor integration that has been proposed as the basis for dystonia (Abbruzzese and Berardelli, 2003; Patel et al., 2014). That being said, the integrity of this pathway was preserved in sporadic dystonia. Moreover, voxel-wise regression of ΔVPRP values against FA, conducted over the entire white matter, failed to reveal significant correlations between these variables in fronto-parietal white matter. It is therefore likely that VPRP modulation is also influenced by microstructural alterations in other anatomical pathways within this functional brain network.

The current findings additionally implicate anatomical–functional pathways linking the amygdala to the LOTC. This brain region overlaps with or is adjacent to brain areas involved in the perception of specific body parts (extrastriate body area) (Downing et al., 2007), target motion (V5/MT) (Kolster et al., 2010), human movement (biological motion) (Grossman et al., 2000; Grosbras et al., 2012), and action observation (Caspers et al., 2010; cf. Lingnau and Downing, 2015). Of note, resting-state fMRI studies (Yeo et al., 2011) have shown that anterior MT+ (which overlaps the present LOTC cluster) connects to the IFG and IPL regions noted above, and is also likely to be part of the human mirror neuron system (Oosterhof et al., 2013). LOTC is also shown to be functionally coupled with amygdala during biological motion perception (Bonda et al., 1996). From a more general viewpoint, with its role in facilitating attention to salient stimuli (Phelps and LeDoux, 2005), amygdala can modulate processing in the visual cortex during evaluation of biological significance of affective visual stimuli (Pessoa and Adolphs, 2010).

Based on the functional connectivity mentioned above, it is reasonable to assume that anatomical links exist between amygdala and visual cortex including LOTC. Indeed, studies of macaques have shown anatomical connectivity of these regions, comprising sparse projections from amygdala to V5/MT (Iwai and Yukie, 1987). A seminal study of humans using 1.5 Tesla DTI (Catani et al., 2003) revealed fiber tracts in the ILF, connecting anterior temporal regions including amygdala with extrastriate visual areas (roughly V4). However, that study did not detect connections with V5/MT, probably because of the small number of fibers and the low magnetic field strength that was employed (Catani et al., 2003). Although our current visualized tracts were few in number, they likely represent the first demonstration of this anatomical component of the ILF in living human subjects using DTI. Apart from the higher MRI field strength employed in this study, the use of functionally interconnected nodes for tract reconstruction may have been more effective than conventional anatomical seed-based approaches. Importantly, we found that tract numbers in this pathway were reduced in both genotypic forms of familial dystonia and sporadic dystonia patients. Moreover, VPRP activation responses correlated with microstructural changes (FA reductions) in the posterior visual pathways, which overlapped with the ILF in both healthy subjects and dystonia patients. The abnormalities of ILF integrity seen in inherited dystonia are probably neurodevelopmental in origin. Indeed, myelination of the posterior visual pathways continues during childhood and adolescence (Barnea-Goraly et al., 2005; Lebel et al., 2008), coinciding with the onset of clinical signs and symptoms in affected DYT1 and DYT6 subjects. In this vein, changes in the amygdala have also been reported in the Dyt1 ΔGAG knock-in mouse model (Yokoi et al., 2009). Thus, amygdala–
LOTC projections via the ILF are likely to influence VPRP activity in dystonia patients and healthy subjects.

The role of the cerebellum in modulating VPRP expression is less clear. Crus I of the cerebellum contributes to this network, consistent with the activation of this region in conjunction with the superior temporal sulcus that has been described during biological motion perception (Baumann et al., 2015). The finding of differential activation of Crus II, lobule VI, and vermis during motion perception in healthy vs. DYT1 dystonia subjects supports a role for the cerebellum in this behavioral function (Sako et al., 2015). Indeed, the reduction in ponto-cerebellar tract numbers seen in this form of dystonia suggests that maldevelopment of these pathways contributes to the loss of network activation responses in the same patient group. We note, however, that while significant reduction in these tracts was also present in sporadic dystonia, analogous changes were not seen with DYT6, despite loss of the VPRP response in this group. Thus, the relationship between cerebellar pathway microstructure, network activation, and behavior may differ according to genotype (Carbon et al., 2011; Niethammer et al., 2011).

We note that the VPRP was characterized mainly by network-related activation (Fig. 1A, red-yellow) in response to the perception of “natural” target motion. Nonetheless, this topography also included significant contributions from regions in which deactivation (Fig. 1A, blue) occurred under the same perceptual conditions. As shown in Fig. 1A (inset), the deactivated regions, which were localized to the vmPFC, posterior cingulate gyrus, and precuneus, corresponded closely to a published DMN pattern identified using resting-state fMRI scan data (Wang et al., 2014). The close covariance relationship of these regions to the subspace of activated VPRP nodes is consistent with recent findings implicating the DMN in the perception of biological motion (Dayan et al., 2016). The degree to which the deficits in VPRP modulation seen in dystonia are a consequence of inherent DMN pathology is not known. Nonetheless, using a recently characterized DMN-like metabolic brain network (Spetsieris et al., 2015), we found normal expression levels for this covariance pattern in DYT1 (n=6) and DYT6 (n=6) patients (Supplementary Fig. S3). This suggests that the reduced VPRP responses seen in this population is likely attributable more to abnormal connectivity among activated regions, rather than to a selective failure of deactivation in DMN regions.

CONCLUSION

In conclusion, the current data provide useful insights into the functional network basis for human visual motion perception in healthy subjects and its disruption in neurodevelopmental disorders such as dystonia. The number of fiber tracts linking key network regions was also reduced in the disease state, which likely explains the observed functional network abnormalities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.
Acknowledgments

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References


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Figure 1.

(A) The visual motion perception pattern (VPRP) was characterized by task-related activation (red-yellow) in the right inferior parietal lobule (IPL), pars opercularis of inferior frontal gyrus (IFG), lateral occipitotemporal cortex (LOTC), cerebellar cortex (Crus I), and bilaterally in the amygdala, orbitofrontal cortex (OFC), and ventral tegmental area (VTA). The VPRP was additionally associated with bilateral deactivation (blue) of the posterior cingulate, precuneus, lateral occipital, and ventromedial prefrontal (vmPFC) regions. Inset: The distribution of regional deactivation within the VPRP network exhibited a significant relationship ($r=-0.494$, $p<0.001$; Pearson’s correlation) with previously reported regional components of the default mode network (DMN); see text. The spatial covariance activation pattern for the visual perception of “natural” ($\beta=1/3$) vs. “unnatural” ($\beta=0$) motion was identified using Ordinal Trend Canonical Variates Analysis (OrT/CVA); see text. Voxel

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weights were thresholded at $Z=1.96$, $p<0.05$. The display represents regions that were demonstrated to be reliable ($p<0.05$) by bootstrap resampling.) (B) *Left:* A significant ordinal trend in VPRP expression was observed for “natural” vs. “unnatural” motion perception ($p<0.001$; permutation test with, 1,000 iterations) in the identification (training) sample of 12 healthy subjects. The ordinal trend towards increased network activity in the “natural” condition remained significant ($p<0.02$; permutation test) after excluding an outlier with very low VPRP expression in the “unnatural” condition. *Right:* Consistent increases in VPRP expression in the “natural” vs. “unnatural” conditions ($p=0.039$; binomial test) were additionally noted in the validation (testing) sample of the same 12 healthy subjects. [VPRP expression levels in individual subjects were standardized ($z$-scored) to baseline ($\beta=0$) values measured in the identification sample of the 12 healthy subjects.]
Figure 2.
Changes in VPRP expression (ΔVPRP) during the perception of natural vs. unnatural target motion computed prospectively in (A) healthy subjects (n=12) and clinically manifesting (MAN) individuals with familial dystonia due to the DYT1 (n=10) or DYT6 (n=6) mutations, and individuals with sporadic disease (n=13); (B) healthy subjects (n=12) and affected and non-manifesting carriers (non-MAN) of the DYT1 (n=12) and DYT6 (n=15) mutations; (C) healthy subjects (n=12), affecteds with familial dystonia of both genotypes (n=16), and non-manifesting carriers (non-MAN) of either genotype (n=11). Significant loss of the ΔVPRP response was evident for clinically manifesting and non-manifesting dystonia mutation carriers. A smaller, nonsignificant reduction in ΔVPRP was discerned in the sporadic dystonia group. |ΔVPRP| differences were significant across groups for the three
depicted comparisons (A: p=0.016, B: p=0.004, C: p=0.005; one-way ANOVA). Contrasts of the disease vs. healthy control groups (horizontal arrows) were evaluated according to the post-hoc Dunnett’s tests (see text).]
Figure 3.

(A) Regression analysis was performed on a voxel-wise basis over the whole brain white matter to identify areas in which fractional anisotropy (FA), a measure of local microstructural integrity, correlated significantly with ΔVPRP values (see text). Significant correlations between these measures were seen in healthy subjects in the left occipital region adjacent to lateral occipitotemporal cortex (cluster 1, green). Analogous correlations were seen in neighboring regions (clusters 2 and 3) in DYT1 mutation carriers (yellow) and in the combined group of familial and sporadic affected subjects (red). [FA values for each cluster were z-scored with respect to corresponding healthy control values. The significant clusters identified in each group were overlaid on a common FA mask.] (B–D) Plots of the correlations between ΔVPRP and local FA values are presented to confirm the significance of these relationships in each of the clusters. For the groups shown, loss of the network response (negative ΔVPRP values) was associated with reduced microstructural integrity (low local FA values) in each of the clusters.
Figure 4.
Reconstructions of fiber pathways linking the major nodes of the normal VPRP network (see text for details). (A) Relative to healthy control subjects (left), the number of tracts connecting the right inferior parietal lobule (IPL) and the pars opercularis of the inferior frontal gyrus (IFG) is reduced in inherited (DYT1: −81%; DYT6: −92%) dystonia (middle) but not in the sporadic dystonia group (right). (B) By contrast, tracts connecting the right amygdala and the lateral occipitotemporal cortex (LOTC) clusters are reduced relative to normal (−98~−100%) in the sporadic as well as inherited groups. (C) Tracts through the middle cerebellar peduncle (MCP) that connect the pons with Crus I of the right cerebellar hemisphere are reduced relative to normal in the DYT1 (−69%) and sporadic (−79%) dystonia groups but not in affected DYT6 subjects.
Table I

Regions Contributing to the Network in Healthy Subjects

<table>
<thead>
<tr>
<th>Region</th>
<th>Coordinates (MNI152)</th>
<th>Zmax</th>
<th>Cluster Size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Supramarginal gyrus (anterior)/Inferior parietal lobule (area PF)</td>
<td>66 −30 39</td>
<td>4.20</td>
<td>3132</td>
</tr>
<tr>
<td>R Pars opercularis of inferior frontal gyrus (BA44), Precentral gyrus</td>
<td>57 11 5</td>
<td>4.03</td>
<td>2735</td>
</tr>
<tr>
<td>R Amygdala, Orbitofrontal cortex</td>
<td>28 11 −19</td>
<td>2.96</td>
<td>2712</td>
</tr>
<tr>
<td>R Middle temporal gyrus</td>
<td>58 −59 −3</td>
<td>3.21</td>
<td>1638</td>
</tr>
<tr>
<td>L Lateral occipital cortex (superior)</td>
<td>37 −80 36</td>
<td>3.27</td>
<td>1196</td>
</tr>
<tr>
<td>L Orbitofrontal cortex, Amygdala</td>
<td>−25 11 −24</td>
<td>2.54</td>
<td>1088</td>
</tr>
<tr>
<td>LR Ventral tegmental area</td>
<td>−1 −15 −7</td>
<td>2.59</td>
<td>1014</td>
</tr>
<tr>
<td>L Pars opercularis of inferior frontal gyrus (BA44)</td>
<td>−55 11 0</td>
<td>2.75</td>
<td>501</td>
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<tr>
<td>R Cerebellum Crus I</td>
<td>44 −49 −43</td>
<td>2.70</td>
<td>366</td>
</tr>
<tr>
<td>L Precentral gyrus</td>
<td>−33 −7 67</td>
<td>2.52</td>
<td>260</td>
</tr>
<tr>
<td>L Frontal pole</td>
<td>−6 63 21</td>
<td>2.84</td>
<td>231</td>
</tr>
<tr>
<td>L Temporal pole</td>
<td>−41 11 −21</td>
<td>2.27</td>
<td>187</td>
</tr>
<tr>
<td><strong>Deactivation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR Precuneus, Posterior cingulate gyrus, Lateral occipital cortex (superior), Angular gyrus</td>
<td>−6 −48 73</td>
<td>−7.00</td>
<td>41186</td>
</tr>
<tr>
<td>LR Ventromedial prefrontal cortex</td>
<td>3 56 −18</td>
<td>−6.17</td>
<td>8645</td>
</tr>
<tr>
<td>R Middle temporal gyrus (posterior)</td>
<td>66 −18 −4</td>
<td>−3.63</td>
<td>3907</td>
</tr>
<tr>
<td>R Frontal pole (BA45)</td>
<td>48 40 18</td>
<td>−3.49</td>
<td>1601</td>
</tr>
<tr>
<td>R Middle frontal gyrus</td>
<td>44 9 49</td>
<td>−2.90</td>
<td>1319</td>
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<tr>
<td>L Superior temporal gyrus (posterior)</td>
<td>−62 −25 −1</td>
<td>−2.49</td>
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<tr>
<td>L Middle frontal gyrus</td>
<td>−29 16 51</td>
<td>−2.42</td>
<td>279</td>
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<tr>
<td>R Orbitofrontal cortex</td>
<td>50 31 −8</td>
<td>−2.85</td>
<td>250</td>
</tr>
<tr>
<td>R Frontal pole</td>
<td>12 70 12</td>
<td>−2.56</td>
<td>189</td>
</tr>
</tbody>
</table>

*a* Region labels were determined according to Harvard-Oxford cortical and subcortical structural, Jülich histological, or cerebellar probabilistic atlases in FSLView.

*b* The listed coordinates were found to be reliable (i.e., shared) by the inverse coefficient of variation (ICV) map (thresholded at |ICV|=1.96) according to the bootstrap estimation with 1,000 iterations.

*c* Thresholded at |Z|=1.96.
This cluster is in anterior part of lateral occipitotemporal cortex (LOTC) and covers a coordinate of extrastriate body area (Downing et al., 2007).

BA = Brodmann area; L = left; MNI = Montreal Neurological Institute; R = right.
### Table II

Fractional Anisotropy Regions Correlated with the Network Expression

<table>
<thead>
<tr>
<th>Region</th>
<th>Coordinates (MNI152)</th>
<th>$z_{\text{max}}^b$</th>
<th>Cluster Size$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x (mm)</td>
<td>y (mm)</td>
<td>z (mm)</td>
</tr>
<tr>
<td>A. Healthy subjects (n=12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Occipital area adjacent to Lateral occipital cortex (inferior)</td>
<td>−48</td>
<td>−63</td>
<td>−8</td>
</tr>
<tr>
<td>R Temporal area adjacent to Supramarginal gyrus (posterior)</td>
<td>56</td>
<td>−41</td>
<td>12</td>
</tr>
<tr>
<td>B. DYT1 (n=12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Occipital area adjacent to Occipital fusiform gyrus</td>
<td>−27</td>
<td>−70</td>
<td>−10</td>
</tr>
<tr>
<td>L Occipital area adjacent to Temporal occipital fusiform cortex</td>
<td>−31</td>
<td>−48</td>
<td>−11</td>
</tr>
<tr>
<td>C. Dystonia patients (n=29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Frontal area adjacent to Middle frontal gyrus (BA44)</td>
<td>−36</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>L Occipital area</td>
<td>−24</td>
<td>−83</td>
<td>5</td>
</tr>
<tr>
<td>D. Mutation carriers (n=27)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>R Occipital area adjacent to Occipital fusiform gyrus</td>
<td>26</td>
<td>−67</td>
<td>−8</td>
</tr>
</tbody>
</table>

$^a$Region labels were determined according to Harvard-Oxford cortical structural or Jülich histological probabilistic atlases in FSLView.

$^b$Thresholded at $p<0.001$, voxel-level, uncorrected; $p<0.05$, corrected at the cluster-level.

BA = Brodmann area; L = left; MNI = Montreal Neurological Institute; R = right.