Published in final edited form as:

Neuroscience. 2009 November 24; 164(1): 220–229. doi:10.1016/j.neuroscience.2008.12.041.

ABNORMAL STRUCTURE-FUNCTION RELATIONSHIPS IN HEREDITARY DYSTONIA

MAREN CARBON, MD and **DAVID EIDELBERG, MD***

Center for Neurosciences, The Feinstein Institute for Medical Research, North Shore – Long Island Jewish Health System, 350 Community Drive, Manhasset, NY 11030, USA and Departments of Neurology and Medicine, North Shore University Hospital, 300 Community Drive, Manhasset, New York, and New York University School of Medicine, 550 First Avenue New York, NY 10016, USA

Abstract

Primary torsion dystonia (PTD) is a chronic movement disorder manifested clinically by focal or generalized sustained muscle contractions, postures, and/or involuntary movements. The most common inherited form of PTD is associated with the *DYT1* mutation on chromosome 9q34. A less frequent form is linked to the *DYT6* locus on chromosome 8q21–22. Both forms are autosomal dominant with incomplete (~30%) clinical penetrance. Extensive functional and microstructural imaging with PET and diffusion tensor MRI (DTI) has been performed on manifesting and non-manifesting carriers of these mutations. The results are consistent with the view of PTD as a neurodevelopmental circuit disorder involving cortico-striatal-pallido-thalamocortical (CSPTC) and related cerebellar-thalamo-cortical pathways. Studies of resting regional metabolism have revealed consistent abnormalities in PTD involving multiple interconnected elements of these circuits. In gene carriers, changes in specific subsets of these regions have been found to relate to genotype, phenotype, or both. For instance, genotypic abnormalities in striatal metabolic activity parallel previously reported reductions in local D₂ receptor availability. Likewise, we have identified a unique penetrance-related metabolic network characterized by increases in the pre-SMA and parietal association areas, associated with relative reductions in the cerebellum, brainstem, and ventral thalamus. Interestingly, metabolic activity in the hypermetabolic areas has recently been found to be modified by the penetrance regulating D216H polymorphism. The DTI data raise the possibility that metabolic abnormalities in mutation carriers reflect adaptive responses to developmental abnormalities in the intrinsic connectivity of the motor pathways. Moreover, findings of increased motor activation responses in these subjects are compatible with the reductions in cortical inhibition that have been observed in this disorder. Future research will focus on clarifying the relationship of these changes to clinical penetrance in dystonia mutation carriers, and the reversibility of disease-related functional abnormalities by treatment.

Keywords

primary torsion dystonia; positron emission tomography; motor sequence learning; brain activation; DYT1; DYT6

*Corresponding Author: David Eidelberg, MD, Center for Neurosciences, The Feinstein Institute for Medical Research, North Shore – Long Island Jewish Health System, 350 Community Drive, Manhasset, NY 11030, Phone: 516-562-2498; Fax: 516-562-1008; Email: david1@nshs.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Dystonia is a syndrome characterized by excessive involuntary movement leading to intermittent or constant abnormal postures, or distorted voluntary movements (Oppenheim, 1911). The dystonias can be divided into primary (unknown etiology) and secondary (known etiology) forms (Bressman, 2004). The manifestations of dystonia can be restricted to isolated muscle groups (e.g., blepharospasm, torticollis) or, as in generalized dystonia, may involve a variety of muscle groups. Primary torsion dystonia (PTD) is associated with a number of genotypes, the most common of which is a GAG deletion within the coding area for torsinA on chromosome 9q34 (Ozelius et al., 1997). This mutation, termed DYT1, is inherited as autosomal dominant, but clinical manifestations of dystonia are present in only 30% of mutation carriers (Bressman et al., 1994). TorsinA is a chaperone protein of the superfamily of AAA+ ATPases; its precise function is currently unknown. Multiple cellular functions have been associated with torsinA, including vesicle fusion, membrane trafficking, protein folding and cytoskeletal dynamics (Nery et al., 2008; Breakefield et al., 2001). Another less frequent autosomal dominant form of PTD has been described in North American Mennonites. This mutation, termed DYT6, is linked to chromosome 8q21–22 (Saunders-Pullman et al., 2007). To date, the precise DYT6 locus and its gene product have not been precisely identified. In contrast to the more common adult onset primary dystonias (Defazio et al., 2007), symptoms in the DYT1 and DYT6 genotype begin earlier in life. As a consequence, studies of gene-positive individuals past the age of clinical onset offer a unique means of identifying genotype-related trait characteristics without the confound of differences relating to clinical manifestations (Eidelberg, 2003). Nevertheless, in both these PTD genotypes, the pathophysiological link between gene carrier status and clinical penetrance is unknown.

In this review we will summarize the results of our neuroimaging studies in manifesting and non-manifesting carriers of these PTD mutations. We will focus on abnormalities in: (i) resting brain function at both the regional and network levels, (ii) pathway microstructure and anatomical connectivity, and (iii) dopamine neurotransmission. We will then outline the impact of these rest-state changes on neural activation during task performance and the modulation of these responses by treatment. Lastly, we will address the overall relevance of these findings to the pathophysiology of the primary dystonias.

Abnormal functional connectivity in PTD

In our original [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) studies, we employed a spatial covariance approach based on principal components analysis (PCA) to identify disease-specific patterns of regional metabolic activity in patients with sporadic PTD (Eidelberg et al., 1995). A similar pattern was subsequently detected in two independent cohorts of clinically non-manifesting DYT1 carriers (Eidelberg et al., 1998; Trošt et al., 2002). These subjects expressed an abnormal metabolic brain network characterized by relative increases in the posterior putamen/globus pallidus, cerebellum, and supplementary motor area (SMA). Interestingly, this abnormal torsion dystonia-related pattern (TDRP) was also present in clinically affected DYT1 carriers, who were found to express this network even when involuntary dystonic movements were suppressed by sleep induction (Eidelberg et al., 1998; Hutchinson et al., 2000). The distinctive TDRP metabolic topography has since been confirmed in a larger cohort of non-manifesting DYT1 carriers and controls using routine voxel-based univariate comparisons. Abnormal striatal and cerebellar metabolic increases were found in these subjects (Fig. 1A). By contrast, in non-manifesting carriers of the DYT6 mutation, the regional abnormalities involved metabolic reductions in the putamen and cerebellum (Carbon et al., 2004b), and in the upper brainstem extending into the thalamus (Fig. 1B).

Although trait-related metabolic abnormalities differed across genotypes, all affected subjects showed relative metabolic increases in the pre-SMA and parietal association regions (Carbon et al., 2004b). Notably, these cortical abnormalities were not related to specific clinical

characteristics of dystonia. By contrast, they were found as a shared characteristic of individuals with clinically heterogeneous manifestations. While multifocal or generalized signs of dystonia are evident in the majority of manifesting subjects in the DYT1 genotype (Bressman, 2004), this is the case in only a third of DYT6 haplotype carriers (Saunders-Pullman et al., 2007). In DYT1, the cranial musculature is involved in less than 15% of carriers, while in DYT6 cervico-cranial dystonia is present in 60% and represents the major source of disability in this genotype.

The phenotype specific metabolic effects were mainly segregated from the genotype-specific changes. That said, the reductions in putamen metabolic activity that characterize non-manifesting DYT6 carriers (Carbon et al., 2004b) were found to be of greater magnitude in affecteds of the same genotype. Thus, in certain regions, metabolic “trait” features can also contribute to clinical penetrance.

We have recently used spatial covariance analysis to identify a distinct metabolic pattern related to penetrance. This pattern (Fig. 2A) was characterized by relative metabolic increases in the pre-SMA and parietal association cortices, associated with decreases in the inferior cerebellum, brainstem and ventral thalamus. The expression of this dystonia manifestation-related pattern (DYT-RP) distinguished manifesting from non-manifesting mutation carriers across genotypes (Fig. 2B). DYT-RP scores were computed in the individual scans of manifesting and non-manifesting DYT1 and DYT6 mutation carriers as well as normal controls. The data revealed a significant effect of phenotype ($F[1;79]=23.8$; $p<0.001$; two-way ANOVA), with increased pattern expression in manifesting carriers of either genotype, compared to their non-manifesting counterparts ($p<0.005$ respectively). By contrast DYT-RP expression was reduced (Fig. 2B) in the non-manifesting carriers ($p<0.01$). These findings are consistent with the notion that in dystonia, clinical penetrance is associated with abnormal sensorimotor integration as indicated by metabolic abnormalities in the cortical regions involved in this process.

These results expand upon our earlier studies on penetrance showing that non-manifesting subjects express changes in brain regions that mediate symptom manifestations in addition to the genotype-related trait features (Carbon et al., 2004b). The network abnormalities that characterize the manifesting subjects actually fall below normal in non-manifesting carriers (Fig. 2B), raising the possibility of specific adaptive responses in these clinically normal subjects. In line with our earlier results, these findings indicate that penetrance-related cortical metabolic increases are distinct from the genotype-related trait effects. Nonetheless, these effects are less separable in brain areas with penetrance-related metabolic reductions. In particular, metabolic abnormalities in the cerebellum may reflect an interaction of trait and state effects, with changes in non-manifesting DYT1 carriers that are less evident in clinically penetrant subjects.

Of note, network-related metabolic reductions in the DYT-RP are evident in the rostral pons and midbrain, and in the ventral thalamus. These clusters include targets of pallidal inhibitory output to the pedunculopontine nucleus (PPN), and the ventrolateral (VL) and centromedian (CM) thalamus. As regional metabolism correlates with afferent synaptic activity (Eidelberg et al., 1997; Lin et al., 2008), the relative reductions in these areas (i.e., positive DYT-RP subject scores) seen in clinically affected mutation carriers are compatible with the loss of GPI functional output (Starr et al., 2005). The cause of this reduction in PTD is unknown although overactivation of striato-pallidal projections was originally proposed as a potential cause (Eidelberg et al., 1995).

A recently identified allelic polymorphism at residue 216 of the torsinA codon has been related to the penetrance of the DYT1 mutation (Kock et al., 2006; Risch et al., 2007), an association supported by the increased frequency of the 216H allele in non-manifesting relative to

manifesting DYT1 carriers (Risch et al., 2007). We have noted elevations in metabolic activity in parietal association cortex, pre-SMA, and dorsal premotor cortex (PMC) in “unprotected” D216 non-manifesting DYT1 carriers. In these subjects, regional metabolism fell between values for controls and affecteds in the first two regions, and was in the range of affecteds in the latter region (Fig. 3). By contrast, regional metabolism in the “protected” 216H non-manifesting carriers fell in the normal range for the pre-SMA and were below normal for parietal association cortex and PMC (Carbon et al., 2008d). These findings lend further credence to the notion of a stepwise breakdown of cortical sensorimotor integration in dystonia.

Abnormal anatomical connectivity in PTD

The frequent onset of PTD in childhood or adolescence and the likely role of torsinA in cytoskeletal dynamics (Nery et al., 2008; Hewett et al., 2006) together suggest a neurodevelopmental basis for this disorder. Indeed, diffusion tensor MRI (DTI) as an *in vivo* probe of pathway microstructure has provided valuable evidence to support this contention. In our original study (Carbon et al., 2004a) we reported that fractional anisotropy (FA), a DTI measure of axonal coherence and integrity, is reduced in the subgyral white matter of the sensorimotor area in both manifesting and non-manifesting DYT1 carriers. This finding was confirmed in a subsequent DTI study, in which additional microstructural abnormalities were described in the vicinity of the superior cerebellar peduncle as a feature of clinical penetrance (Carbon et al., 2008c). These observations implicate abnormalities in the cerebello-thalamo-cortical pathways in the pathogenesis of dystonia. In this light, the resting state metabolic abnormalities in the cerebellum may represent a response to partial outflow pathway disconnection in non-manifesting gene carriers (Carbon et al., 2008c). Indeed, this functional response may not be effective in the setting of increased microstructural disconnection as occurs in clinically affected subjects.

Abnormal striatal D₂ receptor availability in PTD

Abnormalities of dopaminergic neurotransmission have also been linked to dystonia, although experimental animal models have yielded conflicting results in this regard (Augood et al., 2004). *In vivo* imaging studies have shown a moderate reduction in striatal D₂ receptor binding in idiopathic dystonia (Perlmutter et al., 1997; Naumann et al., 1998). In line with these findings in patients with sporadic disease, we have reported reductions in caudate and putamen D₂ receptor binding in non-manifesting DYT1 carriers scanned with [¹¹C]-raclopride (RAC) and PET (Asanuma et al., 2005). Preliminary RAC PET results from an expanded cohort including affected DYT1 and DYT6 mutation carriers have revealed significant reductions ($p < 0.001$, ANOVA) in striatal D₂ receptor availability in mutation carriers relative to healthy controls. These reductions were significantly more pronounced in DYT6 ($-38.0 \pm 3.0\%$) as compared to DYT1 carriers ($-15.0 \pm 3.0\%$, $p < 0.001$), with no effect of clinical penetrance on radioligand binding.

Overall, these findings indicate that impaired dopaminergic neurotransmission can be regarded mainly as a trait characteristic of mutation carrier status. That said, decreases in striatal D₂ receptor availability have been found to correlate with increasing DYT-RP expression in a combined group of 28 manifesting and non-manifesting DYT1 and DYT6 mutation carriers ($R^2 = 0.36$, $p < 0.001$). Thus, although direct comparison of manifesting and non-manifesting carriers did not reveal a robust effect of penetrance on striatal D₂ receptor availability, the significant correlation between this measure and the expression of the penetrance-related metabolic pattern suggests that abnormalities in dopaminergic transmission do contribute, to some degree, to the expression of clinical signs and symptoms.

Abnormal brain-behavior relationships in DYT1 carriers

Both the basal ganglia and cerebellum have been shown to mediate specific aspects of motor learning, especially the process of combining individual movements into sequences (Doyon, 2008). Given the likely presence of resting abnormalities of both structures in PTD, motor sequence learning was chosen as a behavioral paradigm for the study of brain-performance relationships in dystonia mutation carriers (Ghilardi et al., 2003; Carbon et al., 2008b). In these studies, conducted with $H_2^{15}O$ PET, gene carriers and controls performed paced reaching movements from a central starting point to one of eight radial targets with their dominant right hand. In the simple motor execution task, the eight targets appeared in a predictable counterclockwise order. In the motor sequence learning task (MSEQ), the eight targets appeared in an unknown repeating order. Subjects were instructed to learn the sequence order while reaching for the targets and to anticipate successive targets. Affected subjects also performed a visual sequence learning task (VSEQ) to control for potential confounds of abnormal movement during the learning epoch. Additionally, each subject performed a reaction time task outside the scanner to determine the reaction time floor as a criterion for target anticipation in the sequence learning task (Nakamura et al., 2001; Fukuda et al., 2002).

Behavioral Results

Movement characteristics, including spatial error, directional errors, movement time, and onset time were quantified in the motor tasks (Ghilardi et al., 2000; Fukuda et al., 2001). For MSEQ, we additionally computed the number of correct movements initiated before the floor onset time in the reaction time task. These movements reflect anticipation and successful retrieval of previously acquired targets, and represented the major descriptor of learning performance in our studies (Nakamura et al., 2001; Fukuda et al., 2002). We found that non-manifesting DYT1 carriers performed the motor execution tasks in a manner similar to controls (Ghilardi et al., 2003). Specifically, movement initiation (onset time, OT) and speed of movement (movement time, MT) were normal in non-manifesting DYT1 carriers, as was the mean reaction time (Ghilardi et al., 2003). By contrast, preliminary data in manifesting DYT1 carriers revealed impaired general task performance. While controls correctly hit 80% ($\pm 5\%$) of the targets, the affecteds correctly hit 58% ($\pm 5\%$) of the targets ($p < 0.05$). In the correct movements, OT and spatial errors (reflecting movement accuracy) did not differ from control values. However, there was a significant group difference in movement time variability, defined as the standard deviation (SD) of the movement time over each 90s trial. This measure reflects the homogeneity of the repetitive movements in each subject. Indeed, MT SD was higher in manifesting DYT1 mutation carriers relative to age-matched controls and non-manifesting gene carriers ($p < 0.002$, ANOVA), indicating greater movement irregularity in the affecteds. In these patients, this measure correlated with Burke-Fahn-Marsden (BFM) Dystonia Rating Scale scores ($R^2 = 0.59$, $p < 0.003$) for the dominant right upper limb (that performed the motor task). Thus, the MT SD measure of movement variability may have use as an objective descriptor of dystonia severity for correlation with concurrent recordings of brain activation responses during task performance.

In non-manifesting DYT1 carriers the overall normal execution of simple movement contrasted with the significant defect in motor sequence learning performance (Ghilardi et al., 2003; Carbon et al., 2008b). By the end of the learning task, most gene carriers correctly anticipated the appearance of 3 targets, compared to an average of 6 targets in controls ($p < 0.007$). By contrast, adaptation to visuo-spatial rotation, an implicit form of motor learning, was normal in the DYT1 carriers. These findings demonstrate that non-manifesting DYT1 carriers exhibit specific defects in the explicit learning of sequential information but not in movement preparation or in the learning of visuo-spatial transformations.

Imaging studies during motor performance

PET recordings during task performance demonstrated significant group differences in regional brain activation responses. Non-manifesting DYT1 carriers displayed abnormal increases in SMA and PMC activation during simple motor execution, despite exhibiting normal movement characteristics during this task. By contrast, motor activation responses were reduced in the posterior-medial cerebellum of non-manifesting DYT1 carriers, perhaps reflecting the deposition of mutant torsinA protein in this region (Augood et al., 2000; Konakova et al., 2001). Given that motor performance in these subjects was normal, it is possible that the observed increases in cortical activation represent an effective means of compensating for these baseline abnormalities.

As expected, motor activation responses in manifesting DYT1 carriers differed substantially from their non-manifesting counterparts and from controls ($p < 0.05$, corrected) (Carbon et al., 2008a). Relative to healthy controls, both manifesting and non-manifesting DYT1 carriers exhibited similar increases in motor activation in PMC. Additionally, MAN-DYT1 showed increased motor activation in the sensorimotor cortex (SMC), SMA and in the parietal region (Fig. 4), as well as in the right anterior cerebellum. In non-manifesting DYT1 carriers, the other activated regions assumed an intermediate position between controls and affecteds. Thus, in parietal association cortex, SMA, and anterior cerebellum, overactivation was genotype-related and graded in degree with respect to clinical penetrance (Fig. 4A). Lastly, abnormal increases in SMC activation occurred in affecteds, but not in non-manifesting DYT1 carriers or gene-negative controls (Fig. 4B). These findings are consistent with previous activation studies of patients with generalized and focal primary dystonia (e.g., Ceballos-Baumann and Brooks, 1997; Detante et al., 2004; Lerner et al., 2004; Blood et al., 2004). Nonetheless, by parsing the effects of phenotype and genotype, the current observations point to the existence of an intermediate phenotype in non-manifesting DYT1 carriers involving subclinical deficits in motor planning and sensorimotor integration.

The notion of increased activity of primary and secondary motor cortices as a correlate of cortical disinhibition is consistent with the results from electrophysiological studies in DYT1 mutation carriers. Edwards and colleagues (2003) noted reduced intracortical inhibition and a shortened silent period as electrophysiological correlates of impaired cortical inhibition in both manifesting and non-manifesting DYT1 mutation carriers. By contrast, the late phase of spinal reciprocal inhibition of the H-reflex was abnormal only in DYT1 affecteds. Likewise, an isolated change in this late phase following a normal early disynaptic phase has also been reported in non-hereditary forms of primary dystonia and in secondary dystonia (Nakashima et al., 1989; Panizza et al., 1989; Boesch et al., 2007). Nonetheless, this apparent penetrance-related feature has also been reported in the unaffected limbs of patients with focal dystonia (Chen et al., 1995; Deuschl et al., 1992). The specificity of this finding is subject to further query by the presence of changes in the early and late phases of reciprocal inhibition in individuals with hemiplegia secondary to stroke as well as in psychogenic dystonia (Nakashima et al., 1989; Espay et al., 2006).

Imaging studies during sequence learning

The results described above indicate that during simple involvement, neural resources within cortico-striato-pallido-thalamic (CSPTC) pathways can be mobilized to compensate for resting structure/function abnormalities in non-manifesting DYT1 carriers. This may however not be the case for cognitively more challenging tasks like sequence learning. Indeed, during this task, non-manifesting DYT1 carriers showed significantly greater activation than controls in the right pre-SMA, posterior parietal cortex, and right anterior cerebellum, and in the left prefrontal cortex (Ghilardi et al., 2003). Nonetheless, these overactive responses did not result in normal learning performance. Because the subjects differed greatly in the learning that they achieved

during the imaging session, we conducted a follow-up study designed to evaluate compensatory brain changes without the potential confound of individual performance differences. Using trial-and-error guided learning of sequences of different lengths, we were able to compare mutation carriers and controls at equiperformance (Carbon et al., 2008b). Indeed, to achieve a normal level of learning performance, non-manifesting DYT1 carriers overactivated the lateral cerebellum. Nonetheless, they also exhibited impairment of learning-related activation in the DLPFC bilaterally, and in the left anterior cingulate cortex and dorsal PMC. By contrast, age-matched control subjects exhibited bilateral cerebellar and prefrontal activation only when confronted with substantially greater levels of task difficulty (load) (Mentis et al., 2003). These findings suggest that the dystonia mutation carriers did not recruit the DLPFC, cingulate, and PMC regions because of inherent abnormalities in fronto-striatal connectivity (Carbon et al., 2004a). In this regard, the cerebellum may play a compensatory role, although a direct contribution of this structure to the disease process is also possible (2008b; Carbon et al., 2004c).

Sequence learning studies in affecteds

In a subsequent study, we observed the effect of penetrance on sequence learning performance in DYT1 carriers. To determine the genotypic specificity of this behavioral abnormality, we also assessed learning performance in manifesting and non-manifesting DYT6 carriers. Comparison of performance measures in manifesting and non-manifesting gene carriers and controls revealed highly significant group differences ($F=11.3$, $p=0.001$; 2×3 ANOVA, controlling for age). In DYT1 carriers, learning performance was reduced relative to controls, irrespective of the presence or absence of clinical manifestations ($p<0.0001$). By contrast, in DYT6 haplotype carriers performance was normal irrespective of phenotype ($p=0.4$). Because of the possibility that these findings were confounded by motor dysfunction in affecteds, we also measured performance while the subjects learned the sequence visually, without limb movement. We found that during visual learning, performance was reduced in DYT1 ($p<0.05$), but not in their DYT6 counterparts. Thus, the sequence learning deficit represents a trait feature specific for DYT1 that is present in both manifesting and non-manifesting carriers of this mutation. This behavioral abnormality is, however, not present in DYT6 carriers with or without clinical manifestations.

To assess the neural substrates of impaired sequence learning in manifesting DYT1 carriers without the potential confound of abnormal movement, the affecteds were scanned while performing the motor sequence learning task (MSEQ) as well as its visual counterpart (VSEQ). In manifesting DYT1 carriers, both MSEQ and VSEQ were associated with task-specific increases in ACC, superior parietal cortex, as well as the posterior cerebellum. In these subjects, the dorsal PMC was activated in MSEQ but not VSEQ. In the cerebellum, a significant stepwise increase in learning-related activation was found across the three groups (i.e., controls < non-manifesting < manifesting) for both the visual and motor tasks ($p<0.01$, ANOVA for both MSEQ and VSEQ). These results extend our original observation that DYT1 carriers exhibit impaired sequence learning and abnormal task-related cerebellar activation. These abnormalities are compatible with a shift from striatal to cerebellar processing in DYT1 carriers, perhaps occurring in response to resting state metabolic changes in the putamen/globus pallidus of these subjects (Carbon et al., 2004b; Trošt et al., 2002; Blood et al., 2004). We note that increased cerebellar activation failed to correct the observed learning deficits. Indeed, in DYT1 carriers, microstructural abnormalities in cerebellar outflow pathways may also involve projections to the prefrontal cortex (Middleton and Strick, 2001), thereby affecting performance on sequence learning tasks (Carbon et al., 2004c; 2008b). By contrast, these cerebello-thalamo-prefrontal projections may be relatively spared in DYT6, accounting for the normal performance observed in carriers of this genotype.

The effect of deep brain stimulation in primary cervical dystonia

Bilateral internal globus pallidus (GPi) deep brain stimulation (DBS) represents an important treatment option for medically refractory primary dystonia (Ostrem and Starr, 2008). However, the mechanism by which this intervention alleviates the symptoms of dystonia is not known. Earlier imaging studies have revealed a specific effect of DBS on abnormal motor activation in the primary and secondary motor cortices (Kumar et al., 1999), and in the prefrontal region (Detante et al., 2004). We assessed brain activation responses on and off GPi stimulation in idiopathic cervical dystonia patients performing the activation tasks described above. Across tasks, stimulation was associated with significant decreases ($p < 0.001$) in the SMC, pre-SMA, ACC, inferior prefrontal cortex, and DLPFC. The specific effect of stimulation on simple motor activation was similar, with significant stimulation-mediated reductions in the left SMC, SMA, ACC, and anterior-superior cerebellar cortex. Of note, network analysis of stimulation-induced differences in regional activation disclosed relative increases in the *right* parietal association cortex and SMC. The increase in sensorimotor activation *ipsilateral* to the moving hand suggests improvement in transcallosal inhibition during stimulation. Overall, these data suggest that the major functional effect of GPi stimulation for dystonia is to normalize pathologically overactive motor activation responses in these patients (Kumar et al., 1999; Detante et al., 2004).

Conclusion

In summary, the studies summarized in this review point to a prominent role of the cerebellum in hereditary dystonia. The microstructural deficits in white matter integrity detected by DTI are consistent with a fundamental neurodevelopmental disturbance leading to anatomical/functional disconnection at the cerebellar and fronto-striatal levels (Carbon et al., 2004a; 2008c). Indeed, maldevelopment of cerebellar output pathways is a likely cause for the localized metabolic abnormalities seen in the resting state. The cerebellum has been suggested to have a prominent role in modulating cortical plasticity (Molinari et al., 2002; Luft et al., 2005; Manto et al., 2006). Thus, basal abnormalities in the cerebellum and its outflow pathways may give rise to alterations in cortical activation responses during movement and learning. These changes appear to be incremental. Full maladaptive plasticity is evident in the abnormal movements displayed by manifesting gene carriers. In non-manifesting DYT1 carriers, this abnormality is limited to an impairment of complex motor integrative functions like sequence learning.

We have also identified reductions in D₂ receptor availability in gene carriers as an additional susceptibility factor. It has been suggested that dystonia occurs in a multiple hit setting (Schicatano et al., 1997). Recently, Jinnah and colleagues (Neychev et al., 2008) have emphasized abnormal cerebellar and striatal interactions as a mechanism of dystonia in experimental animal models. TorsinA, as a AAA⁺⁺⁺ chaperone protein, is involved in multiple cellular functions (Nery et al., 2008). Regions with high levels of torsinA are most likely to be affected by the mutation. During periods of synaptogenesis, high levels of torsinA have been noted in dopaminergic neurons of the substantia nigra as well as in the deep cerebellar nuclei (Shashidharan et al., 2000; Siegert et al., 2005), creating the molecular basis for such regional interactions in DYT1 carriers. The findings further indicate the potential utility of the abnormal functional brain networks identified in PTD. Such networks have already proved useful in the objective assessment of novel therapeutic interventions for brain disease (Asanuma et al., 2006; Feigin et al., 2007). These patterns may also have use as endophenotypic markers in gene-finding population studies.

Acknowledgments

This work was supported by the National Institutes of Health (NIH R01 NS 047668 [D.E.]), the Bachmann-Strauss Dystonia and Parkinson Foundation (M.C.) and the General Clinical Research Center of The Feinstein Institute for Medical Research (M01 RR018535). The authors wish to thank Drs. Thomas Chaly and Vijay Dhawan for their technical expertise, and Ms. Toni Flanagan for editorial assistance. We are also grateful to our clinical collaborators Dr. S. Bressman, Dr. E. Moro and Dr. L. Verhagen.

Comprehensive List of Abbreviations

PTD	primary torsion dystonia
DTI	diffusion tensor imaging
CSPTC	corticostriatal-pallido-thalamocortical
FDG	[¹⁸ F]-fluorodeoxyglucose
PET	positron emission tomography
PCA	principal components analysis
SMA	supplementary motor area
TDRP	torsion dystonia-related pattern
DYT-RP	dystonia manifestation-related pattern
PPN	pedunculopontine nucleus
VL	ventrolateral
CM	centromedian
PMC	premotor cortex
FA	fractional anisotropy
RAC	[¹¹ C]-raclopride
MSEQ	motor sequence learning task
VSEQ	

visual sequence learning task

MT SD

standard deviation of movement time

BFM

Burke-Fahn-Marsden dystonia rating scale

Gpi

internal globus pallidus

DBS

deep brain stimulation

References

- Asanuma K, Ma Y, Okulski J, Dhawan V, Chaly T, Carbon M, Bressman SB, Eidelberg D. Decreased striatal D2 receptor binding in non-manifesting carriers of the DYT1 dystonia mutation. *Neurology* 2005;64:347–349. [PubMed: 15668438]
- Asanuma K, Tang C, Ma Y, Dhawan V, Mattis P, Edwards C, Kaplitt MG, Feigin A, Eidelberg D. Network modulation in the treatment of Parkinson's disease. *Brain* 2006;129:2667–2678. [PubMed: 16844713]
- Augood SJ, Hollingsworth Z, Albers DS, Yang L, Leung J, Breakefield XO, Standaert DG. Dopamine transmission in DYT1 dystonia. *Adv Neurol* 2004;94:53–60. [PubMed: 14509654]
- Augood SJ, Martin DM, Ozelius LJ, Breakefield XO, Penney JBJ, Standaert DG. Distribution of the mRNAs encoding torsinA and torsinB in the normal adult human brain. *Ann Neurol* 2000;46:761–769. [PubMed: 10553994]
- Blood AJ, Flaherty AW, Choi JK, Hochberg FH, Greve DN, Bonmassar G, Rosen BR, Jenkins BG. Basal ganglia activity remains elevated after movement in focal hand dystonia. *Ann Neurol* 2004;55:744–748. [PubMed: 15122718]
- Boesch SM, Muller J, Wenning GK, Poewe W. Cervical dystonia in spinocerebellar ataxia type 2: clinical and polymyographic findings. *J Neurol Neurosurg Psychiatry* 2007;78:520–522. [PubMed: 17220291]
- Breakefield XO, Kamm C, Hanson PI. TorsinA: movement at many levels. *Neuron* 2001;31:9–12. [PubMed: 11498045]
- Bressman SB. Dystonia genotypes, phenotypes, and classification. *Adv Neurol* 2004;94:101–107. [PubMed: 14509661]
- Bressman SB, deLeon D, Kramer PL, Ozelius LJ, Brin MF, Greene PE, Fahn S, Breakefield XO, Risch NJ. Dystonia in Ashkenazic Jews: clinical characterization of a founder mutation. *Ann Neurol* 1994;36:771–777. [PubMed: 7979224]
- Carbon M, Argyelan M, Flanagan T, Dhawan V, Bressman S, Eidelberg D. Abnormal brain activation during sequential movements in DYT1 dystonia. *Neurology* 2008a;70:A432.
- Carbon M, Ghilardi MF, Argyelan M, Dhawan V, Bressman SB, Eidelberg D. Increased cerebellar activation during sequence learning in DYT1 carriers: an equiperformance study. *Brain* 2008b;131:146–154. [PubMed: 17947338]
- Carbon M, Kingsley PB, Su S, Smith GS, Spetsieris P, Bressman S, Eidelberg D. Microstructural white matter changes in carriers of the DYT1 gene mutation. *Ann Neurol* 2004a;56:283–286. [PubMed: 15293281]
- Carbon M, Kingsley PB, Tang C, Bressman S, Eidelberg D. Microstructural white matter changes in primary torsion dystonia. *Mov Disord* 2008c;23:234–239. [PubMed: 17999428]
- Carbon M, Ozelius LJ, Raymond D, Bressman S, Eidelberg D. Metabolic correlates of genetic susceptibility in DYT1 torsion dystonia. *Neurology* 2008d;70:A432.
- Carbon M, Su S, Dhawan V, Raymond D, Bressman S, Eidelberg D. Regional metabolism in primary torsion dystonia: effects of penetrance and genotype. *Neurology* 2004b;62:1384–1390. [PubMed: 15111678]
- Carbon M, Trost M, Ghilardi MF, Eidelberg D. Abnormal brain networks in primary torsion dystonia. *Adv Neurol* 2004c;94:155–161. [PubMed: 14509669]

- Ceballos-Baumann AO, Brooks DJ. Basal ganglia function and dysfunction revealed by PET activation studies. *Adv Neurol* 1997;74:127–139. [PubMed: 9348408]
- Chen RS, Tsai CH, Lu CS. Reciprocal inhibition in writer's cramp. *Mov Disord* 1995;10:556–561. [PubMed: 8552105]
- Defazio G, Berardelli A, Hallett M. Do primary adult-onset focal dystonias share aetiological factors? *Brain* 2007;130:1183–1193. [PubMed: 17242025]
- Detante O, Vercueil L, Thobois S, Broussolle E, Costes N, Lavenne F, Chabardes S, Lebars D, Vidailhet M, Benabid AL, Pollak P. Globus pallidus internus stimulation in primary generalized dystonia: a H215O PET study. *Brain* 2004;127:1899–1908. [PubMed: 15231585]
- Deuschl G, Seifert C, Heinen F, Illert M, Lucking CH. Reciprocal inhibition of forearm flexor muscles in spasmodic torticollis. *J Neurol Sci* 1992;113:85–90. [PubMed: 1469459]
- Doyon J. Motor sequence learning and movement disorders. *Curr Opin Neurol* 2008;21:478–483. [PubMed: 18607210]
- Edwards MJ, Huang YZ, Wood NW, Rothwell JC, Bhatia KP. Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the DYT1 gene mutation. *Brain* 2003;126:2074–2080. [PubMed: 12821514]
- Eidelberg D. Brain networks and clinical penetrance: lessons from hyperkinetic movement disorders. *Curr Opin Neurol* 2003;16:471–474. [PubMed: 12869805]
- Eidelberg D, Moeller JR, Antonini A, Kazumata K, Nakamura T, Dhawan V, Spetsieris P, deLeon D, Bressman SB, Fahn S. Functional brain networks in DYT1 dystonia. *Ann Neurol* 1998;44:303–312. [PubMed: 9749595]
- Eidelberg D, Moeller JR, Ishikawa T, Dhawan V, Spetsieris P, Przedborski S, Fahn S. The metabolic topography of idiopathic torsion dystonia. *Brain* 1995;118:1473–1484. [PubMed: 8595478]
- Eidelberg D, Moeller JR, Kazumata K, Antonini A, Sterio D, Dhawan V, Spetsieris P, Alterman R, Kelly PJ, Dogali M, Fazzini E, Beric A. Metabolic correlates of pallidal neuronal activity in Parkinson's disease. *Brain* 1997;120:1315–1324. [PubMed: 9278625]
- Espay AJ, Morgante F, Purzner J, Gunraj CA, Lang AE, Chen R. Cortical and spinal abnormalities in psychogenic dystonia. *Ann Neurol* 2006;59:825–834. [PubMed: 16634038]
- Feigin A, Kaplitt MG, Tang C, Lin T, Mattis P, Dhawan V, Durr MJ, Eidelberg D. Modulation of metabolic brain networks after subthalamic gene therapy for Parkinson's disease. *Proc Natl Acad Sci U S A* 2007;104:19559–19564. [PubMed: 18042721]
- Fukuda M, Ghilardi MF, Carbon M, Feigin A, Dhawan V, Ma Y, Mentis M, Moeller JR, Ghez C, Eidelberg D. Pallidal stimulation for parkinsonism: improved brain activation during sequence learning. *Ann Neurol* 2002;52:144–152. [PubMed: 12210783]
- Fukuda M, Ghilardi MF, Mentis MJ, Nakamura T, Dhawan V, Antonini A, Hammerstad J, Koller WC, Ghez CP, Eidelberg D. Functional correlates of pallidal stimulation for Parkinson's disease. *Ann Neurol* 2001;124:1601–1609.
- Ghilardi MF, Carbon M, Silvestri G, Dhawan V, Tagliati M, Bressman S, Ghez C, Eidelberg D. Impaired sequence learning in carriers of the DYT1 dystonia mutation. *Ann Neurol* 2003;54:102–109. [PubMed: 12838525]
- Ghilardi MF, Ghez CP, Moeller JR, Dhawan V, Eidelberg D. Patterns of regional brain activation associated with different aspects of motor learning. *Brain Res* 2000;871:127–145. [PubMed: 10882792]
- Hewett JW, Zeng J, Niland BP, Bragg DC, Breakefield XO. Dystonia-causing mutant torsinA inhibits cell adhesion and neurite extension through interference with cytoskeletal dynamics. *Neurobiol Dis* 2006;22:98–111. [PubMed: 16361107]
- Hutchinson M, Nakamura T, Moeller JR, Antonini A, Belakhlef A, Dhawan V, Eidelberg D. The metabolic topography of essential blepharospasm: a focal dystonia with general implications. *Neurology* 2000;55:673–677. [PubMed: 10980732]
- Kock N, Naismith TV, Boston HE, Ozelius LJ, Corey DP, Breakefield XO, Hanson PI. Effects of genetic variations in the dystonia protein torsinA: identification of polymorphism at residue 216 as protein modifier. *Hum Mol Genet* 2006;15:1355–1364. [PubMed: 16537570]
- Konakova M, Huynh DP, Yong W, Pulst SM. Cellular distribution of torsin A and torsin B in normal human brain. *Arch Neurol* 2001;58:921–927. [PubMed: 11405807]

- Kumar R, Dagher A, Hutchison WD, Lang AE, Lozano AM. Globus pallidus deep brain stimulation for generalized dystonia: clinical and PET investigation. *Neurology* 1999;53:871–874. [PubMed: 10489059]
- Lerner A, Shill H, Hanakawa T, Bushara K, Goldfine A, Hallett M. Regional cerebral blood flow correlates of the severity of writer's cramp symptoms. *Neuroimage* 2004;21:904–913. [PubMed: 15006657]
- Lin TP, Carbon M, Tang C, Mogilner AY, Sterio D, Beric A, Dhawan V, Eidelberg D. Metabolic correlates of subthalamic nucleus activity in Parkinson's disease. *Brain* 2008;131:1373–1380. [PubMed: 18400841]
- Luft AR, Manto MU, Ben Taib NO. Modulation of motor cortex excitability by sustained peripheral stimulation: the interaction between the motor cortex and the cerebellum. *Cerebellum* 2005;4:90–96. [PubMed: 16035190]
- Manto M, Oulad ben Taib N, Luft AR. Modulation of excitability as an early change leading to structural adaptation in the motor cortex. *J Neurosci Res* 2006;83:177–180. [PubMed: 16385580]
- Mentis MJ, Dhawan V, Feigin A, Delalot D, Zgaljardic D, Edwards C, Eidelberg D. Early stage Parkinson's disease patients and normal volunteers: comparative mechanisms of sequence learning. *Hum Brain Mapp* 2003;20:246–258. [PubMed: 14673808]
- Middleton FA, Strick PL. Cerebellar projections to the prefrontal cortex of the primate. *J Neurosci* 2001;21:700–712. [PubMed: 11160449]
- Molinari M, Filippini V, Leggio MG. Neuronal plasticity of interrelated cerebellar and cortical networks. *Neuroscience* 2002;111:863–870. [PubMed: 12031409]
- Nakamura T, Ghilardi MF, Mentis M, Dhawan V, Fukuda M, Hacking A, Moeller JR, Ghez C, Eidelberg D. Functional networks in motor sequence learning: abnormal topographies in Parkinson's disease. *Hum Brain Mapp* 2001;12:42–60. [PubMed: 11198104]
- Nakashima K, Rothwell JC, Day BL, Thompson PD, Shannon K, Marsden CD. Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke. *Brain* 1989;112(Pt 3):681–697. [PubMed: 2731027]
- Naumann M, Pirker W, Reiners K, Lange KW, Becker G, Brucke T. Imaging the pre- and postsynaptic side of striatal dopaminergic synapses in idiopathic cervical dystonia: a SPECT study using [123I] epidepride and [123I] beta-CIT. *Mov Disord* 1998;13:319–323. [PubMed: 9539347]
- Nery FC, Zeng J, Niland BP, Hewett J, Farley J, Irimia D, Li Y, Wiche G, Sonnenberg A, Breakefield XO. TorsinA binds the KASH domain of nesprins and participates in linkage between nuclear envelope and cytoskeleton. *J Cell Sci* 2008;121:3476–3486. [PubMed: 18827015]
- Neychev VK, Fan X, Mitev VI, Hess EJ, Jinnah HA. The basal ganglia and cerebellum interact in the expression of dystonic movement. *Brain* 2008;131:2499–2509. [PubMed: 18669484]
- Oppenheim H. Über eine eigenartige Krampfkrankheit des kindlichen und jugendlichen Alters (Dysbasia lordotica progressiva, Dystonia musculorum deformans). *Neurol Centralblatt* 1911;30:1090–1107.
- Ostrem JL, Starr PA. Treatment of dystonia with deep brain stimulation. *Neurotherapeutics* 2008;5:320–330. [PubMed: 18394573]
- Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, Shalish C, deLeon D, Brin MF, Raymond D, Corey DP, Fahn S, Risch NJ, Buckler AJ, Gusella JF, Breakefield XO. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. *Nat Genet* 1997;17:40–48. [PubMed: 9288096]
- Panizza ME, Hallett M, Nilsson J. Reciprocal inhibition in patients with hand cramps. *Neurology* 1989;39:85–89. [PubMed: 2909917]
- Perlmuter JS, Stambuk MK, Markham J, Black KJLM-M, Jankovic JSMM. Decreased [18F] spiperone Binding in Putamen in Idiopathic Focal Dystonia. *J Neurosci* 1997;17:843–850. [PubMed: 8987805]
- Risch NJ, Bressman SB, Senthil G, Ozelius LJ. Intragenic Cis and Trans modification of genetic susceptibility in DYT1 torsion dystonia. *Am J Hum Genet* 2007;80:1188–1193. [PubMed: 17503336]
- Saunders-Pullman R, Raymond D, Senthil G, Kramer P, Ohmann E, Deligtisch A, Shanker V, Greene P, Tabamo R, Huang N, Tagliati M, Kavanagh P, Soto-Valencia J, Aguiar Pde C, Risch N, Ozelius L, Bressman S. Narrowing the DYT6 dystonia region and evidence for locus heterogeneity in the Amish-Mennonites. *Am J Med Genet A* 2007;143A:2098–2105. [PubMed: 17702011]

- Schicatanio EJ, Basso MA, Evinger C. Animal model explains the origins of the cranial dystonia benign essential blepharospasm. *J Neurophysiol* 1997;77:2842–2846. [PubMed: 9163399]
- Shashidharan P, Kramer BC, Walker RH, Olanow CW, Brin MF. Immunohistochemical localization and distribution of torsinA in normal human and rat brain. *Brain Res* 2000;853:197–206. [PubMed: 10640617]
- Siebert S, Bahn E, Kramer ML, Schulz-Schaeffer WJ, Hewett JW, Breakefield XO, Hedreen JC, Rostasy KM. TorsinA expression is detectable in human infants as young as 4 weeks old. *Brain Res Dev Brain Res* 2005;157:19–26.
- Starr PA, Rau GM, Davis V, Marks WJ Jr, Ostrem JL, Simmons D, Lindsey N, Turner RS. Spontaneous pallidal neuronal activity in human dystonia: comparison with Parkinson's disease and normal macaque. *J Neurophysiol* 2005;93:3165–3176. [PubMed: 15703229]
- Trošć M, Carbon M, Edwards C, Raymond D, Mentis M, Moeller JR, Bressman SB, Eidelberg D. Primary dystonia: is abnormal functional brain architecture linked to genotype? *Ann Neurol* 2002;52:853–856. [PubMed: 12447944]

Fig. 1.
(A) Increased resting state glucose metabolism in the putamen (*top*) and cerebellum (*bottom*) of non-manifesting (nm) DYT1 carriers and gene negative controls (C). **(B)** Reduced metabolism in the thalamus (*top*) and cerebellum (*bottom*) of nm DYT6 carriers (see text).

[Statistical parametric maps (SPMs) (*left*) comparing normalized regional glucose metabolism (adjusted rCMRGlc) in non-manifesting mutation carriers with controls. The maps were superimposed on a single-subject T1-weighted MRI template. The color stripe represents T values thresholded at 2.6, $p < 0.005$. Bar graphs (*right*) illustrate regional metabolic values (mean $\pm$ SE) from each significant cluster (*arrows*)]

Fig. 2.

(A) Spatial covariance analysis of 42 FDG PET scans from manifesting and non-manifesting DYT1 and DYT6 mutation carriers (see text). The analysis disclosed a significant covariance pattern (PC1, accounting for 18.7% of the subject×voxel variance in the derivation sample) that correlated with clinical penetrance. This dystonia-related pattern (DYT-RP) was characterized by increased metabolic activity in the pre-SMA and parietal regions, associated with decreases in the inferior cerebellum, brainstem and ventral thalamic nuclei. Voxel weights on this pattern were demonstrated to be stable by bootstrap estimation ($p < 0.01$). [The voxel weights were thresholded at $Z < 2$ for positive weights (yellow-red) and $Z < -2$ for negative weights (blue), reflecting significant ($p < 0.01$) metabolic contributions of these regions to network activity]

(B) Bar graph of DYT-RP expression in manifesting (MAN; black) and non-manifesting (NM; gray) dystonia mutation carriers and gene-negative controls (C; open). Network computations were performed on FDG PET scans from 18 MAN-DYT1, 17 NM-DYT1, 11 MAN-DYT6, 11 NM-DYT6, and 22 control subjects. Analysis of variance (ANOVA) revealed a significant effect of phenotype ($F[1;79] = 23.8$; $p < 0.001$), but not genotype.

Fig. 3.

(A) Abnormal metabolic increases in the left pre-supplementary motor area (preSMA, *left*), dorsal premotor cortex (*middle*), and parietal association cortex (*right*) in “unprotected” D216-DYT1 non-manifesting carriers (see text). [The color stripe represents T values thresholded at 2.0, $p < 0.01$].

(B) Bar graphs illustrating regional metabolic activity (adjusted rCMRGlu) in each of the significant clusters (*arrows*) for healthy controls (C, open), “protected” 216H-DYT1 non-manifesting carriers (NM-P, light gray), “unprotected” D216-DYT1 non-manifesting carriers (NM-U, dark gray), and manifesting DYT1 carriers (MAN, black). [Bars indicate mean $\pm$ SE]

Fig. 4.

Left: Regions in which motor activation in manifesting and non-manifesting DYT1 carriers differed with respect to controls (see text). [The color stripe represents T-values thresholded at 3.5, $p < 0.001$] *Right:* Bar graphs of adjusted regional cerebral blood flow (rCBF) during motor activation (mean $\pm$ SE) measured in each of the significant regions (*arrows*) for manifesting (MAN, black) and non-manifesting (gray) carriers, and gene-negative controls (C, open).

(A) Abnormally increased motor activation ($p < 0.05$) was present in the left supplementary motor area (SMA) in DYT1 carriers, regardless of phenotype.

(B) Abnormally increased activation in the left sensorimotor cortex (SMC) was present in manifesting but not non-manifesting DYT1 carriers.