Neuroscience 164 (2009) 220–229

ABNORMAL STRUCTURE-FUNCTION RELATIONSHIPS IN HEREDITARY DYSTONIA

M. CARBON[a,b] AND D. EIDELBERG[a,b]*

[a]*Center for Neurosciences, The Feinstein Institute for Medical Research, North Shore–Long Island Jewish Health System, 350 Community Drive, Manhasset, NY 11030, USA*

[b]*Departments of Neurology and Medicine, North Shore University Hospital, 300 Community Drive, Manhasset, NY 11030, USA 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 positron emission tomography (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 D_2 receptor availability. Likewise, we have identified a unique penetrance-related metabolic network characterized by increases in the pre–supplementary motor area (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.

*Corresponding author. Tel: +1-516-562-2498; fax: +1-516-562-1008.
E-mail address: david1@nshs.edu (D. Eidelberg).

Abbreviations: ANOVA, analysis of variance; DBS, deep brain stimulation; DTI, diffusion tensor MRI; DYT-RP, dystonia manifestation-related pattern; FDG, [^{18}F]-fluorodeoxyglucose; GPi, internal globus pallidus; MSEQ, motor sequence learning task; MT, movement time; OT, onset time; PET, positron emission tomography; PMC, premotor cortex; PTD, primary torsion dystonia; RAC, [^{11}C]-raclopride; SMA, supplementary motor area; TDRP, torsion dystonia-related pattern; VSEQ, visual sequence learning task.

Key words: primary torsion dystonia, positron emission tomography, motor sequence learning, brain activation, DYT1, DYT6.

Contents

Abnormal functional connectivity in PTD 221
Abnormal anatomical connectivity in PTD 223
Abnormal striatal D_2 receptor availability in PTD 224
Abnormal brain-behavior relationships in DYT1 carriers 224
Behavioral results 224
Imaging studies during motor performance 225
Imaging studies during sequence learning 226
Sequence learning studies in affecteds 226
The effect of deep brain stimulation (DBS) in primary cervical dystonia 226
Conclusion 227
Acknowledgments 227
References 227

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 (Breakefield et al., 2001; Nery et al., 2008). 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 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

0306-4522/09 $ - see front matter © 2009 IBRO. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuroscience.2008.12.041

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).

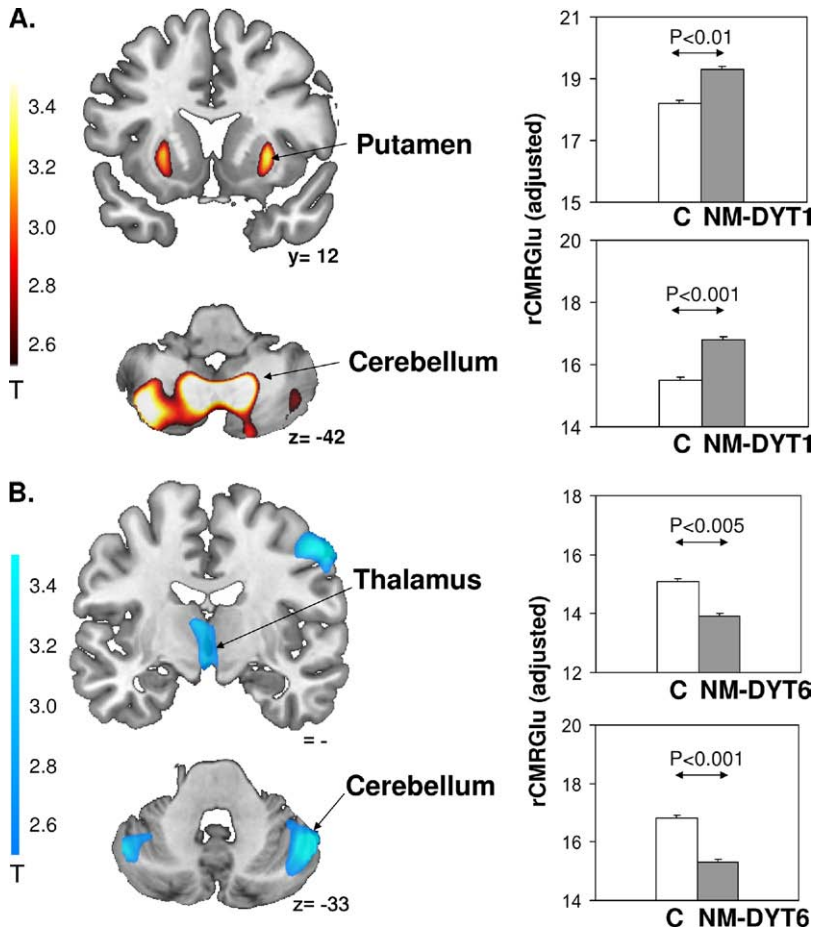

Fig. 1. (A) Increased resting state glucose metabolism in the putamen (top) and cerebellum (bottom) of non-manifesting (NM) DYT1 carriers and gene negative controls (C). (B) Reduced metabolism in the thalamus (top) and cerebellum (bottom) of NM-DYT6 carriers (see text). [Statistical parametric maps (SPMs) (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±SE) from each significant cluster (arrows)].