PROCEEDING

Neuroimaging in human dystonia

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Abstract : Functional neuroimaging, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), provides a valuable technique for detecting regional changes in brain metabolic activity associated with human disease. These techniques have been applied in different dystonic disorders including primary generalized dystonia and dopa-responsive dystonia (DRD), as well as focal dystonic syndromes such as torticollis, writer's cramp, and blepharospasm. A common finding is abnormality of the basal ganglia and associated outflow pathways to sensorimotor cortex and other regions involved with motor performance. Other recent imaging research has utilized diffusion-based MRI techniques to localize distinct microstructural abnormalities in dystonia patients and gene carriers. This presentation will focus on an integrated approach to understanding the pathophysiology of this genetic and biochemically diverse disorder. J. Med. Invest. 52 Suppl. : 272-279, November, 2005

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ABNORMAL RESTING STATE METABOLISM IN DYT1 CARRIERS

Patients with primary dystonia lack specific histopathological changes (1-3). Similarly, many functional imaging studies with dystonia patients have yielded conflicting results (4). Nonetheless, we have used a novel regional network analytical approach (5) to identify a reproducible pattern of abnormal regional glucose utilization in two independent cohorts of clinically non-manifesting DYT1 carriers (6, 7). We found that these subjects express a specific metabolic topography characterized by increases in the posterior putamen/globus pallidus, cerebellum, and supplementary motor area (SMA) (7) (Figure 1A). In an ancillary study, we demonstrated that this abnormal torsion dystonia-related pattern (TDRP) was also present in clinically affected patients, persisting even following the suppression of involuntary dystonic movements by sleep induction (6, 8). Moreover, TDRP expression is not specific for the DYT1 genotype. We have recently demonstrated abnormal network activity in both manifesting and non-manifesting carriers of the DYT6 dystonia mutation (North American Mennonites) (Figure 1B) (7) . In all likelihood, this resting pattern represents a metabolic trait of dystonia. The use of PET to quantify TDRP expression in individual family members may be valuable for gene identification in selected kindreds.

The identification of abnormal brain networks in dystonia has several practical implications. As mentioned above, the resting TDRP metabolic network can potentially be used as a marker in linkage studies to identify potential gene carriers among family members of dystonia patients. Additionally, disease-related networks can prove useful for assessing mechanisms of therapeutic interventions, as has been demonstrated in Parkinson's disease (9, 10).

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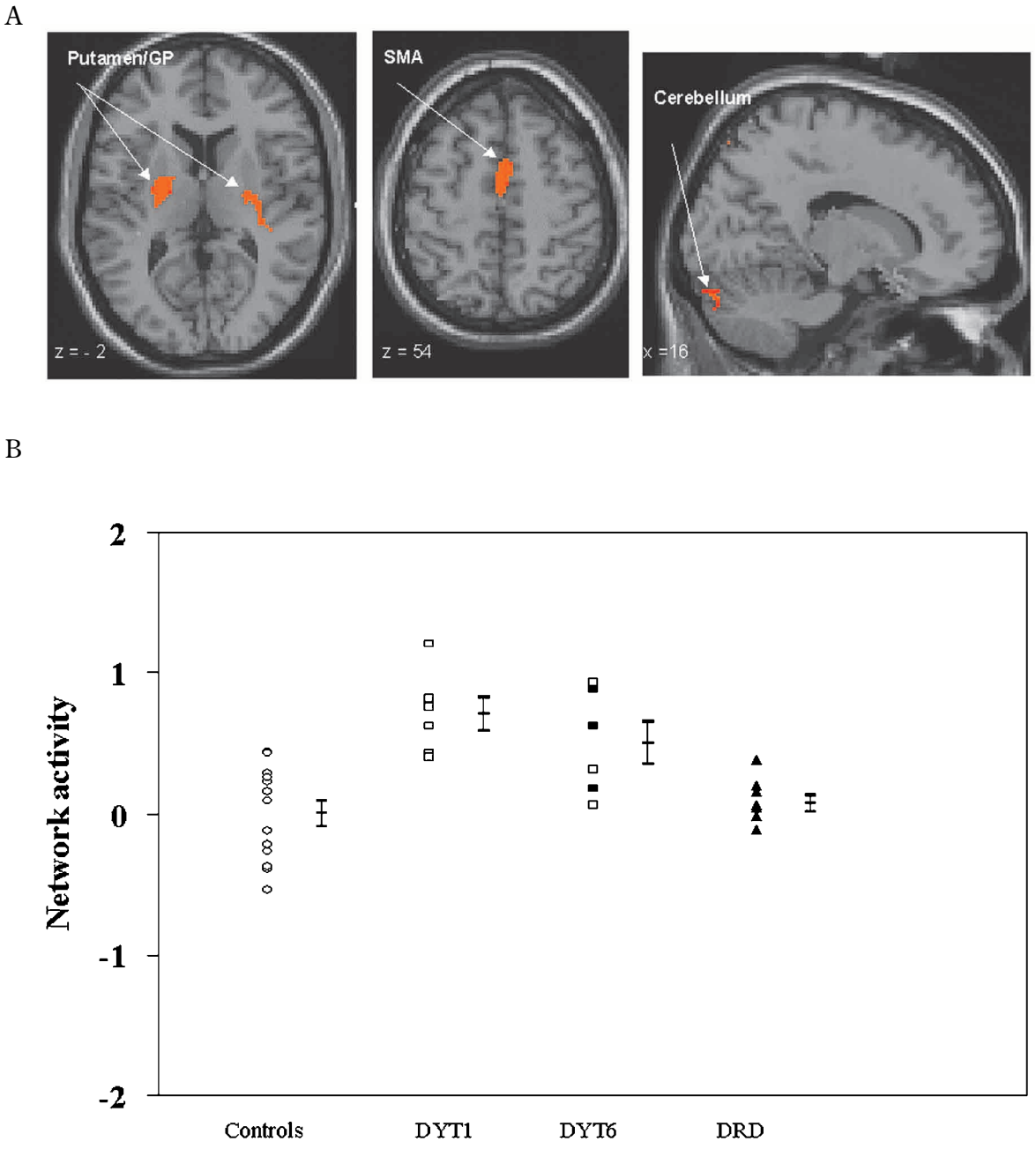

Figure 1.
A. Regional metabolic covariance pattern identified with FDG/PET and network analysis in non-manifesting DYT1 gene carriers and control subjects (see text). This torsion dystonia-related pattern (TDRP) was characterized by bilateral covarying metabolic increases in the putamen, extending into the globus pallidus (GP), the supplementary motor area (SMA), and the cerebellar hemisphere. Subject scores for this pattern discriminated the DYT1 carriers from controls ($p<0.002$). [The display represents voxels that contribute significantly to the network at $p = 0.001$. Voxels with positive region weights (metabolic increases) are color-coded red].
B. Scatter diagram of TDRP subject scores computed prospectively in six new non-affected DYT1 gene carriers, six DYT6 gene carriers, seven dopa-responsive dystonia (DRD) patients, and 13 control subjects. Subject scores were abnormally elevated in DYT1 ($p<0.001$) and DYT6 carriers ($p<0.007$), but not in DRD patients ($p = 0.4$). [The error bars indicate subgroup standard errors of the mean. Circles represent normal controls;squares represent subjects with genotypes associated with primary torsion dystonia;triangles represent DRD patients. Open symbols represent clinically non-manifesting subjects ; filled symbols represent affected dystonia patients].

ABNORMAL RESTING STATE METABOLISM IN DOPA-RESPONSIVE DYSTONIA (DRD)

Dopa-responsive dystonia (DRD) is typically an autosomal dominant postural dystonia associated with mutations in the GTP cyclohydrolase 1 (GCH1) gene (11-13). The onset of DRD is often early and characterized by diurnal fluctuation of symptoms ; parkinsonian symptoms may appear later in the clinical course. A defining feature of DRD is a marked and sustained response to low doses of levodopa, suggesting that the lesion may be functional rather

than anatomical. Indeed at postmortem, there is little morphologic change in nigra and striatum (14, 15), and positron emission tomography (PET) studies have revealed minimal abnormalities in pre- and postsynaptic functioning neurons (16, 17).

The TDRP network is not expressed in DRD patients (7) (Figure 1B). Given the well-described features of DRD, it is likely that a different metabolic network abnormality characterizes this specific form of dystonia. Using network analysis of FDG PET images, we found that DRD is associated with a distinct metabolic topography that is characterized by relative increases in the dorsal midbrain, cerebellar vermis, and SMA, associated with covarying decrements in the putamen, and in lateral premotor and motor cortical regions (Figure 2A) (18) . This DRD-related pattern (DRD-RP) is not expressed in manifesting and non-manifesting dystonia gene carriers harboring the DYT1 or DTY6 gene mutation (Figure 2 B) (18). These findings support the hypothesis that the pathophysiology of DRD differs from that of other forms of dystonia. We also found that Parkinson's disease-related pattern (PDRP) expression is not elevated in DRD, despite the presence of parkinsonian features in this disorder, and the dramatic response to dopaminergic therapy. This pattern is also not present in PTD where the relationship to dopaminergic dysfunction is less obvious (19, 20).

The DRD-RP topography is characterized by cortical changes reflecting metabolic features of both PD and torsion dystonia. The presence of relative metabolic decrements in the lateral premotor region in the DRD-RP is a consistent feature of the PD topography (21-23). By contrast, the DRD-RP includes metabolic increases in SMA as described previously in PTD (5-7). The presence of increases and decreases in motor cortical association regions raises the possibility that changes in the functioning of the direct and indirect pathways coexist in DRD.

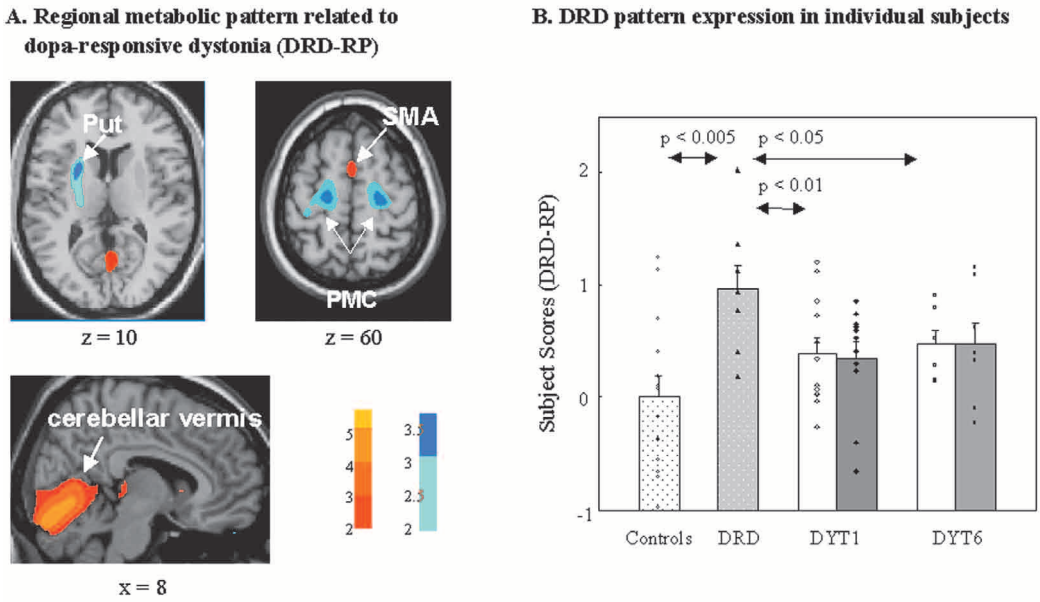

Figure 2.
A. Regional metabolic pattern associated with dopa-responsive dystonia (DRD)
The DRD-related pattern (DRD-RP) was characterized by reduced metabolism in the left putamen (PUT ; left) and in the motor and premotor cortical (PMC) regions (right). The pattern also included metabolic increases in the supplementary motor area (SMA) and in the cerebellar vermis (bottom). The display represents voxels that contributed significantly to the network at p<0.005 (see Table 1), and that were demonstrated to be reliable with bootstrap estimation procedures (see text). [Voxels with positive region weights (metabolic increases) are color coded from red to yellow ; those with negative region weights (metabolic decreases) are color coded blue.]
B. DRD pattern expression in individual subjects
Left : Network expression (subject scores) in DRD patients (filled triangles) and healthy volunteers (open circles) used to identify the disease-related pattern described in Figure 1A (see text). DRD-RP scores were significantly elevated (p<0.005) in the disease group relative to controls. [Open columns represent the normal control group and shaded columns represent the DRD cohort.]
Right : DRD-RP expression quantified prospectively in DYT1 and DYT6 dystonia mutation carriers. DRD-RP scores in these groups did not differ significantly from control values (p>0.1), but were lower than for the DRD cohort (p<0.01, and 0.05 for the DYT1 and the DYT6 groups, respectively). [Open columns represent non-manifesting (NM) gene carriers ; shaded columns represent clinically manifesting (MAN) dystonia patients.] Error bars indicate standard error of the mean for each cohort.

ABNORMAL BRAIN-BEHAVIOR RELATIONSHIPS IN DYT1 CARRIERS

We explored the possibility that subtle behavioral changes may exist as a metabolic correlate of TDRP activity in gene positive individuals. The basal ganglia have been shown to mediate specific aspects of motor learning. We therefore selected motor sequence learning as a behavioral paradigm to study brain-performance relationships in DYT1 carriers (24). We studied 12 non-manifesting DYT1 carriers and 12 healthy age-matched controls and measured psychophysical performance indices during the execution of simple movements in both timed-response and reaction time paradigms, as well as during a sequence learning task (25-27). To assess brain activation responses during task performance, we concurrently scanned seven members of each group with ^{15}O-water ($H_2{}^{15}O$) and PET.

DYT1 carriers performed the motor execution tasks in both the timed-response and reaction time mode without significant differences from controls. Specifically, movement initiation and movement time during motor execution was normal in DYT1 carriers, as were mean reaction times and floor reaction times. Thus, in contrast to clinically affected dystonia patients (28), motor preparation did not appear to be impaired in non-manifesting DYT 1 carriers. In contrast to the execution of simple movements, a significant defect in motor sequence learning was present in DYT1 carriers.

PET recordings during task performance demonstrated significant group differences in regional brain activation responses. Non-manifesting DYT 1 carriers displayed comparative increases in SMA activation during motor execution, despite normal movement characteristics. By contrast, motor activation responses were reduced in the posterior-medial cerebellum of non-manifesting DYT1 carriers, perhaps as a consequence of deposition of mutant torsin A protein in this region (29, 30). Given the comparatively normal motor performance of these subjects, it is possible that the changes in local activation responses represent an effective means of compensating for impaired resting metabolic dysfunction within key nodes of the major motor pathways.

While neural resources within the motor CSPTC loops may compensate for baseline metabolic dysfunction in DYT1 carriers performing simple movements, this may not be the case for sequences of movements. During sequence learning, DYT1 carriers showed significantly greater activation than controls in the right pre-SMA and posterior parietal cortex, as well as in the right anterior cerebellum and left prefrontal cortex. Nonetheless, this overactivation did not result in normal learning performance. These PET findings are limited to mean differences between the two groups and do not relate these changes to the behavioral abnormalities that were detected in the DYT1 carriers.

To examine the nature of these brain-behavior relationships, we first determined whether a previously validated learning network in normal subjects accurately predicted performance in DYT1 carriers. In earlier sequence learning studies (26), we found that a specific covariance pattern, characterized mainly by caudate, prefrontal, and posterior parietal activation, accurately correlated with the learning achieved during imaging in both healthy volunteers and in patients with Parkinson's disease. While reproducible in these populations (27), this learning network failed to predict performance in the DYT1 carrier group. To determine whether a different network mediated sequence learning in these subjects, we performed an exploratory analysis restricted only to the DYT1 carriers (31) and detected a novel pattern that correlated with learning in this cohort (Figure 3). Indeed, this candidate topography incorporated several regions not used by control subjects, such as the cerebellar cortex and dentate nucleus, as well as the ventral prefrontal cortex. Interestingly, the caudate nucleus contributed significantly to the learning network in normals (26, 27), but not to that identified in DYT1 carriers.

It is also suggested from network analyses that sequence learning in DYT1 carriers is not mediated by the activation network utilized by normal cohorts, but by a novel learning network that incorporates several regions not used by control subjects such as cerebellar cortex and dentate nucleus. Indeed, a shift from striatal to cerebellar processing may be a feature of the DYT1 carrier state. The status of network-performance relationships in clinically affected DYT1 patients and potential changes in these relationships with treatment (32) is a topic of ongoing investigation.

DIFFUSION TENSOR IMAGING (DTI)

Magnetic resonance diffusion tensor imaging (DTI) is a new technique that can be used to visualize and measure the anisotropic water diffusion in neural fibers such as nerve, white matter in spinal

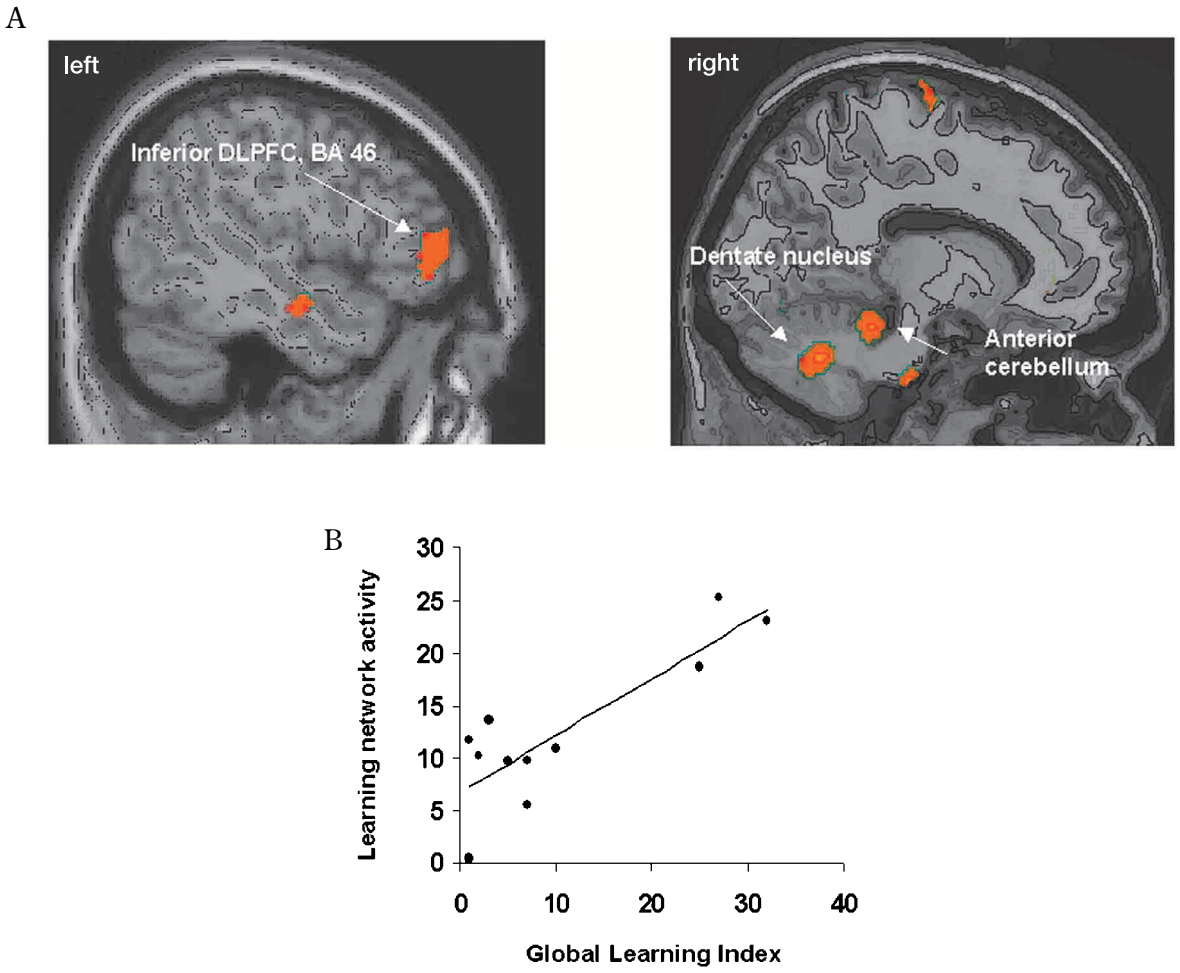

Figure 3.
Voxel-based network analysis of $H_2{}^{15}O$/PET data from seven non-manifesting DYT1 carriers scanned during motor sequence learning : retrieval pattern.
A. This network topography was characterized by covarying learning-related activations (*arrows*) in the cerebellum and dentate nucleus (*left*), and in the inferior dorsolateral prefrontal cortex (DLPFC) (*right*). [Positive region weights (red-yellow) were thresholded at Z = +2 to display clusters contributing significantly ($p<0.01$) to the network (see text)].
B. Subject scores for this topography, representing network activity in individual gene carriers, correlated with the learning that was achieved concurrently during the scanning epoch ($R^2 = 0.72$, $p<0.001$).

cord, or white matter to track fiber pathways (33).

To test the hypothesis that themicrostructural integrity of motor control pathway is locally disturbed in DYT1 carriers, we used DTI to assess the microstructure of white matter pathways in 12 mutation carriers and 17 age-matched control subjects. Fractional anisotropy (FA), a measure of axonal integrity and coherence, was reduced ($p<0.005$) in the subgyral white matter of the sensorimotor cortex of DYT1 carriers (34). Abnormal anatomical connectivity of the supplementary motor area may contribute to the susceptibility of DYT1 carriers to develop clinical manifestations of dystonia.

DOPAMINE RECEPTOR STUDIES

The neurochemical basis for primary dystonia is currently unknown. However, abnormal dopaminergic neurotransmission has been suggested to play a role in certain forms of this disorder (20, 35). A moderate reduction of dopamine content in the rostral putamen and caudate has been reported in a DYT1 patient studied at postmortem (36). Additionally, postmortem measurements in three DYT1 dystonia brains have revealed a significant increase of the 3, 4-dihydroxyphenylacetic acid (dopamine metabolite)/dopamine ratio in the striatum with a trend toward reduced D_1 and D_2 receptor binding (37). Several studies have reported decreased D_2 receptor binding in the striatum in idiopathic focal dystonia using PET or SPECT radioligands (38, 39). To determine whether this abnormality is a feature of the dystonia genotype, we used [^{11}C] raclopride and PET to compare D_2 receptor binding in non-manifesting DYT1 gene

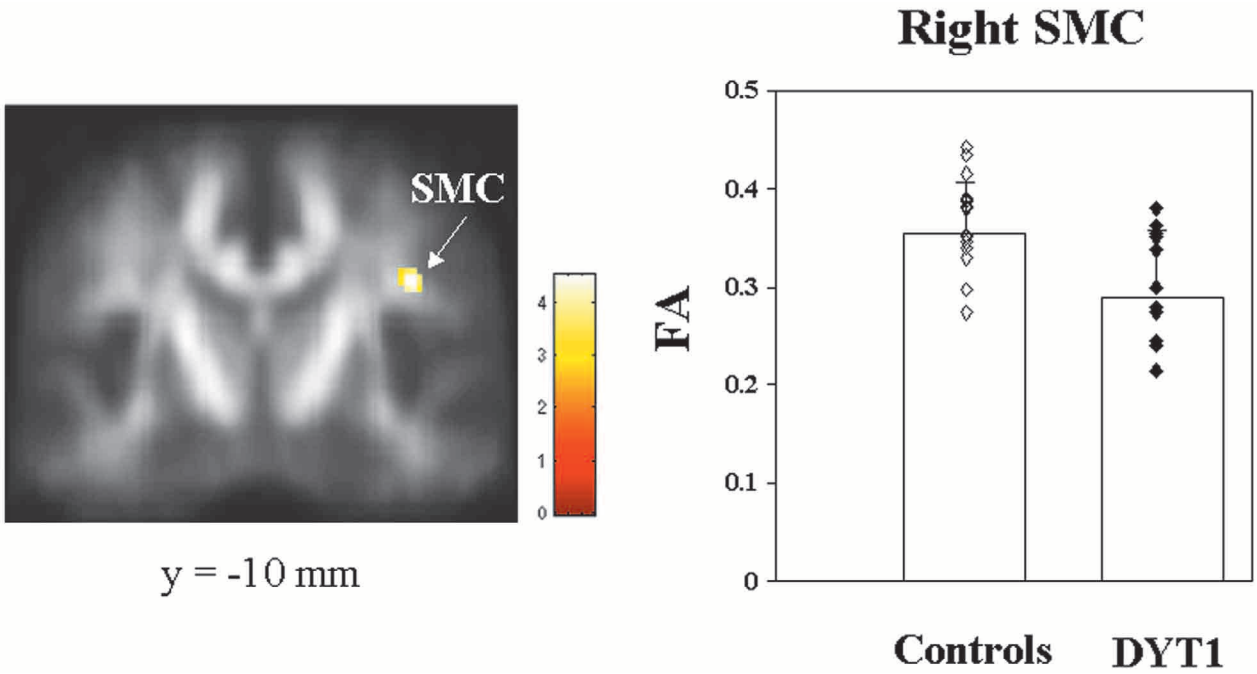

Figure 4.
A. Statistical parametric map comparing fractional anisotropy (FA) in DYT1 gene carriers and age-matched controls. The group differences (DYT1<controls) were superimposed on the mean group FA map.
B. The bar chart illustrates significant reduction in FA values in the subgyral white matter of the primary sensorimotor cortex (SMC) of DYT1 gene carriers (filled symbols) relative to controls (open symbols). The color scale represents T-scores at a threshold of 2.9, p less than 0.005 ; each voxel represents 8 mm 3. Bars indicate standard error.

carriers with control subjects (Figure 4). We found that raclopride binding in caudate and putamen was reduced (14%, $p<0.005$) in the gene carrier group (19). These reductions are somewhat lower than the 29% mean reduction in D_2 receptor binding measured in focal dystonia (38).

Although raclopride PET is useful in assessing the integrity of D_2-bearing striatal projection neurons (40), it has relatively lower receptor binding affinity than other D_2 binding ligands (38, 39). While our results in non-manifesting DYT1 carriers are similar to those from affected scanned with less displaceable tracers, we cannot exclude the possibility that the RAC PET findings stemmed at least in part from an increase in dopamine turnover (37). It is conceivable that both factors are involved to varying degrees, resulting in overactivation of both the D_1-mediated direct and D_2-mediated indirect pathways (5). Additional studies with more specific radioligands, including those for D_1 receptors and correlation with patho-physiological data will further shed light in the role of dopaminergic transmission in DYT1 and other forms of primary torsion dystonia.

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