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Functional Imaging in Hereditary Dystonia

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Abstract

Background—Impaired cortical inhibition and maladaptive cortical plasticity are functional hallmarks of sporadic focal dystonias. Whether or not these mechanisms translate to generalized dystonias and whether these features reflect state or trait characteristics is a topic of research in hereditary dystonias.

Methods—We present a series of studies using a multitracers approach with positron emission tomography (PET) and diffusion tensor MRI (DTI) in the DYT1 and the DYT6 genotype.

Results—In these hereditary dystonias maladaptive motor cortical plasticity was present as a state characteristic. As a trait characteristic neuroplastic changes were also found in secondary motor cortices and in multimodal association regions. Consistent abnormalities of resting regional brain metabolism were additionally found in interconnected elements of cortico-striatal-pallido-thalamocortical (CSPTC) and related cerebellar-thalamo-cortical circuits. Changes in specific subsets of these regions have been found to relate to genotype, phenotype, or both. Thus, a penetrance-related metabolic network was characterized by increases in the pre-supplementary motor area (pre-SMA) and parietal association areas, associated with relative reductions in the cerebellum, brainstem, and ventral thalamus. By contrast, genotype-specific abnormalities were localized to the basal ganglia, SMA and cerebellum. In both genotypes, the striatal metabolic abnormalities were paralleled by genotype-specific reductions in D₂ receptor availability. Moreover, DTI studies disclosed microstructural changes within CSPTC and related cerebellar pathways. These disruptions may represent the main intrinsic abnormality underlying cortical downstream effects, such as increased sensorimotor responsiveness.

Conclusions—These studies are consistent with the view of primary torsion dystonia as a neurodevelopmental circuit disorder involving CSPTC and related cerebellar pathways.

Keywords

primary torsion dystonia; positron emission tomography; dopamine; motor activation; DYT1; DYT6

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Introduction

To date, postmortem studies of histopathological changes in primary dystonia have yielded inconsistent results with brainstem pathology in some, but not all affected subjects [1-3]. Thus, in vivo studies of brain function are of particular importance for the understanding of mechanisms of disease in dystonia. Complementary to electrophysiological studies, which probe brain function during rest and simple movements only, neuroimaging adds the opportunity to assess neurotransmitter functions and structure-function relationships during complex tasks. However, neuroimaging studies in dystonias have yielded highly controversial results, partly due to methodological differences, but also due to the heterogeneity of the dystonias. Therefore, we have focused in a series of studies on DYT1 and DYT6 dystonia. In these prototype disorders the fundamental cause of the disease (the mutation) has been identified, but the link between mutation and disease manifestation is only partly understood. The most common mutation in primary torsion dystonia (PTD), termed DYT1, is a GAG deletion within the coding area for torsinA on chromosome 9q34 [2]. 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 [4,5]. Another less frequent form of PTD has been found in North American Mennonites. This mutation, termed DYT6, is associated with two mutations in the coding region of THAP1 on chromosome 8 [6]. THAP domains as parts of C-terminal binding proteins are suggested to control cellular processes by serving as transcriptional activators and transcriptional corepressors [7]. Importantly, they also act as regulators of the cytoskeleton, highlighting their potential role in neurodevelopment [7,8]. Both mutations are inherited as autosomal dominant traits, but clinical manifestations of dystonia are present in only 30% (DYT1) to 60 % (DYT6) of mutation carriers. Studies in these genotypes thus offer the unique opportunity to separate the effects of genotype and phenotype.

The aims of the studies, summarized in this manuscript were (1) to evaluate the effect of these mutations on brain metabolism using [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET); (2) to assess microstructural white matter integrity in mutation carriers using diffusion tensor MRI (DTI-MRI); (3) to re-visit the role of dopaminergic neurotransmission in PTD and (4) to explore structure-function relationships using learning and motor tasks during PET. Throughout our studies, we combined the use of univariate and multivariate image analysis. Brain regions identified by significant t-tests and/or behavior correlations are not necessarily functionally connected within a spatial covariance network. Nonetheless, these regions may still contribute to the network and aid in the understanding of disease mechanisms [9].

Metabolic trait and state characteristics

A series of FDG-PET studies, in conjunction with spatial covariance analyses disclosed an abnormal DYT1 specific metabolic brain network characterized by relative increases in the posterior putamen/globus pallidus, cerebellum, and supplementary motor area (SMA) patterns of regional metabolic activity in patients with sporadic PTD [10-12]. Interestingly,

this abnormal torsion dystonia-related pattern (TDRP) was also present in symptomatic DYT1 carriers, who showed elevated network activity even when involuntary dystonic movements were suppressed during sleep [11]. This distinctive topography was thus interpreted as trait feature of the DYT1 carrier status. We have subsequently confirmed the presence of this trait feature in our expanded cohort of non-manifesting DYT1 carriers and controls using routine voxel-based univariate comparisons instead of the spatial covariance approach. Genotype specific changes were identified in direct comparisons of non-manifesting mutation carriers to controls [13]. Surprisingly, non-manifesting carriers of the DYT6 mutation showed a quite contrasting pattern of genotypic abnormalities, involving metabolic reductions in the putamen and cerebellum [14], and in the upper brainstem extending into the thalamus [13].

Despite the presence of these genotype-related metabolic features, all clinically affected subjects showed relative metabolic increases in the pre-SMA and parietal association regions [14]. These state-specific effects were mainly segregated from the genotype-specific changes, however the reductions in putamen metabolism that characterize non-manifesting DYT6 carriers [14] 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.

In the next analytical step, we used spatial covariance analysis to identify a distinct metabolic pattern related to penetrance. This pattern 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. Network expression of this dystonia manifestation-related pattern (DYT-RP) separated manifesting from non-manifesting mutation carriers across genotypes [13]. Prospective network calculation including controls in addition to mutation carriers showed 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 ($p<0.005$). DYT-RP expression was reduced in the non-manifesting carriers ($p<0.01$). These results are in line with the suggestion that clinical penetrance in dystonia is related to abnormal sensorimotor integration as indicated by metabolic abnormalities in the cortical regions involved in this process. Furthermore, these findings highlight the segregation of penetrance-related cortical metabolic *increases* and genotype-related trait effects. By contrast, the segregation is less clear in brain areas with penetrance-related metabolic *reductions*. In particular, metabolic abnormalities in the cerebellum may thus reflect an interaction of trait and state effects, with changes in non-manifesting DYT1 carriers that are less evident in clinically penetrant subjects.

It is noteworthy that low metabolic activity as part of the DYT-RP included the rostral pons, midbrain and ventral thalamus. These clusters consist of targets of pallidal inhibitory output to the pedunclopontine nucleus (PPN), and the ventrolateral (VL) and centromedian (CM) thalamus. Since regional metabolism is closely associated with afferent synaptic activity [15, 16], the relative reductions in these areas (i.e., positive DYT-RP subject scores) seen in dystonics are compatible with the loss of GPi functional output [17]. The cause of this

reduction in PTD remains currently elusive, although overactivation of striato-pallidal projections was originally proposed as a potential cause [10].

Impaired cerebellar connectivity in PTD

PTD is likely to represent a neurodevelopmental disorder, as suggested by disease onset in childhood or adolescence, as well as the putative role of torsinA in cytoskeletal dynamics [4,18]. We have thus used diffusion tensor MRI (DTI) as an *in vivo* technique to assess the integrity of white microstructure [19]. We found 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. The notion of reduced sensorimotor connectivity was subsequently confirmed and additional FA reductions were found in the dorsal brainstem in the vicinity of the pedunculopontine nucleus and cerebellar outflow pathways as a characteristic of manifesting subjects [20].

Thus, our most recent DTI study tested the hypothesis of reduced cerebellar connectivity in DYT1 and DYT6 dystonia. We used probabilistic tractography to define the precise neuroanatomical pathways that are involved [21]. This method was used to reconstruct the cerebello-thalamo-cortical projection system for each subject (see Figure 1A). We then assessed the integrity of these fiber tracts in mutation carriers relative to controls using voxel-wise comparisons at the group level. Two discrete areas of reduced pathway connectivity were identified in the cerebello-thalamo-cortical projection system of PTD mutation carriers, irrespective of genotype. A highly localized abnormality was present in all mutation carriers involving the proximal segment of the cerebello-thalamic pathway near the dentate nucleus (see Figure 1B). Post-hoc analysis of connectivity in this cluster revealed abnormally reduced values in both affected and asymptomatic carriers, with the latter occupying an intermediate position between the affecteds and controls. Notably, clinical penetrance was determined by an additional region of reduced connectivity situated distally, involving thalamo-cortical projections in sub-rolandic white matter. Connectivity in this region was almost intact in manifesting mutation carriers, but clearly reduced in non-manifesting subjects. Our data suggest that the specific combination of lesions in the cerebello-thalamo-cortical pathway determines penetrance in the DYT1 genotype [21]

In light of these results, resting state metabolic abnormalities in the cerebellum may represent a response to partial outflow pathway disconnection in gene carriers [20,21]. Indeed, this functional response may not be effective in the setting of increased microstructural disconnection as occurs in clinically affected subjects.

Reduced D₂ receptor availability represents a trait characteristic in PTD

As dystonia has traditionally been conceptualized as a basal ganglia disorder, abnormalities of dopaminergic neurotransmission are often thought to play a key role in the manifestation of dystonic symptoms. Nevertheless, experimental animal models have yielded conflicting results in this regard [22]. *In vivo* imaging studies have shown an only moderate reduction in striatal D₂ receptor binding in idiopathic dystonia [23,24]. 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 [25]. These results have been confirmed and expanded in a cohort including affected DYT1 and DYT6 mutation carriers using a region of interest analysis targeting the striatum as well as a voxel-based whole brain analysis [26] (Fig. 2). We found significant reductions ($p<0.001$, ANOVA) in putamen and caudate D₂ receptor availability in mutation carriers regardless of clinical penetrance. These reductions were significantly more pronounced in DYT6 ($-38.0 \pm 3.0\%$) as compared to DYT1 carriers ($-15.0 \pm 3.0\%$, $p<0.001$). By contrast, there was no effect of clinical penetrance on radioligand binding. Interestingly, the voxel-based analysis disclosed highly significant reductions of D₂ receptor availability in the ventrolateral (VL) thalamus in DYT1 and DYT6 mutation carriers. As with the striatal binding reductions, these thalamic binding reductions were independent of the presence of symptoms, and were more pronounced in the DYT6 genotype.

The role of dopaminergic modulation of thalamic activity has yet to be defined. Notably however, dopaminergic input to the thalamus is almost lacking in rodents, and it is possible that the paucity of this system contributes to the shortcomings of transgenic animal models of dystonia.

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 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.

Since the D₂ receptor binding reductions are not profound, it can be suggested that dysfunction of D₂-bearing striatal projection neurons to the external globus pallidus (i.e., the classic indirect pathway) represents “a permissive factor” for the development of primary dystonia. It remains elusive though, whether or not this dysfunction results from functional changes or from structural changes, as suggested by MRI based morphometry [27].

Learning and motor activation studies in DYT1 mutation carriers

Healthy neuronal plasticity during learning is associated with a long-term, experience-dependent reorganization of cortical networks [28,29]. While this adaptive process is beneficial in health, it likely is dysfunctional, i.e. maladaptive, in dystonia, particularly in task specific dystonias [30]. Structural and physiological correlates of maladaptive cortical plasticity have been demonstrated in task specific dystonias [30-32]. Little is known however about the role of these mechanisms in hereditary dystonias.

Given the presence of resting abnormalities in basal ganglia and cerebellum in DYT1 mutation carriers, motor sequence learning and simple motor execution were chosen as behavioral paradigms for the study of brain-performance relationships in DYT1 mutation carriers [33,34]. These studies demonstrated abnormal increases in SMA, PMC and inferior

parietal activation during simple motor execution, despite normal movement characteristics during this task. Possibly this shift of activation reflects compensatory mobilization of neural resources within cortico-striato-pallido-thalamic (CSPTC) pathways to compensate for resting structure/function abnormalities in non-manifesting DYT1 carriers. However, during the cognitively more challenging task of sequence learning, this reorganization failed to provide sufficient compensation, as a significant defect in motor sequence learning was present in these subjects [33,34]. During the learning task, non-manifesting DYT1 carriers showed abnormal activation increases in the right pre-SMA, posterior parietal cortex, and right anterior cerebellum, and in the left prefrontal cortex [33]. In order to control for potential confounds related to the lower performance in mutation carriers, we conducted a follow-up study designed to evaluate compensatory brain changes using an equiperformance study design [34]. Indeed, to achieve a normal level of learning performance, non-manifesting DYT1 carriers overactivated the lateral cerebellum. In addition they exhibited impairment of learning-related activation in the DLPFC bilaterally, and in the left anterior cingulate cortex and dorsal PMC. These observations suggest that microstructural abnormalities in cerebellar outflow pathways may also involve projections to the prefrontal cortex, thereby affecting performance on sequence learning tasks [34,35]. Moreover, these results may reflect downstream effect of abnormalities in fronto-striatal connectivity as a trait characteristic of dystonia [19].

As expected, motor activation responses in manifesting DYT1 carriers differed substantially from their non-manifesting counterparts and from controls. $H_2^{15}O$ PET in manifesting DYT1 mutation carriers during repetitive reaching showed salient overactivation in the contralateral sensorimotor and supplementary motor cortex as well as in the dorsal premotor and inferior parietal association cortex bilaterally [36]. These findings are consistent with some previous activation studies of patients with generalized and focal primary dystonia [e.g. 37-40], whereas other studies, showed decreased sensorimotor activation in dystonia [37]. Surprisingly, significant rCBF elevations were also present in major motor regions, namely in the anterior cerebellum and in the sensorimotor cortex in the absence of any motor challenge during the audiovisual control task.

Since the overactive cortical areas represent key regions of the sensorimotor network, we hypothesized that the expression of a normal movement-related spatial covariance pattern would be elevated in dystonia mutation carriers. To identify a normal motor activation pattern (NMRP), we analyzed 39 pairs of motor and audio-visual reference condition scans acquired in an independent cohort of 18 healthy subjects who underwent $H_2^{15}O$ PET imaging. The scan data were analyzed using Ordinal Trends Canonical Variate Analysis (OrT/CVA) [41]. This is a supervised principal component analysis technique designed to identify spatial covariance patterns that change in expression within-subject across experimental conditions. The property of consistent change in pattern expression across tasks/conditions is called an “ordinal trend”. This attribute differs from routine assessments of task-related changes at the group mean level, employing mass univariate procedures such as SPM. In addition to detecting one or more significant activation patterns, OrT/CVA quantifies the expression of the resulting pattern(s) in each subject and condition.

We demonstrated significantly elevated network activity in the affecteds relative to controls during both, the motor task and the audiovisual reference task [36]. These increases related closely to reduced measures of cerebellar connectivity [21]. Moreover, increased expression of the normal motor related pattern was associated with clinical measures of disease severity ($r=0.70$, $p=0.04$).

In non-manifesting DYT1 mutation carriers, normal motor network activity was in the normal range during the motor condition, but abnormally increased in the “non-motor” audiovisual reference condition. The notion of increases in sensorimotor activity during audio-visual processing is consistent with the idea of impaired sensorimotor integration as well as with notion of decreased inhibition within the sensorimotor cortex in dystonia.

Conclusion

In summary, our studies expand the traditional view of dystonia as a basal ganglia disorder to highlight the role of the cerebellum in hereditary dystonia. The microstructural deficits in white matter integrity detected by DTI are suggestive of a neurodevelopmental disturbance leading to anatomical/functional disconnection at the cerebellar and fronto-striatal levels [19,20]. Possibly maldevelopment of cerebellar output pathways relates to the localized metabolic abnormalities seen in the resting state. Interestingly, the cerebellum has been suggested to have a prominent role in modulating cortical plasticity [42,43]. 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.

In addition to microstructural and metabolic trait features, we have identified reductions in D₂ receptor availability in dystonia mutation carriers as a susceptibility factor. This notion is well in line with the suggestion of dystonia as a consequence of a multiple hit setting [44]. Importantly, this idea has also been supported by recent animal studies [45]. TorsinA, is involved in multiple cellular functions [4] and 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 [46,47], creating the molecular basis for such regional interactions in DYT1 carriers.

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Fig. 1. Reduced cerebello-thalamo-cortical connectivity in dystonia gene carriers

(A) DTI based tractography starting in the dorsal brainstem (seed volume, *left*) showed strong cerebello-thalamo-cortical connectivity in controls (*middle*) but only scarce cerebello-thalamo-cortical pathways in manifesting DYT1 mutation carriers (*right*).

(B) Decreased measures of connectivity were found in DYT1 and DYT6 mutation carriers in the white matter surrounding the deep cerebellar nuclei. [A statistical parametric map (SPM) of significant differences in the probabilistic tracts between mutation carriers and controls was superimposed on a single-subject T1-weighted MRI template (*left*: axial slice; *right*: coronal slice). The color scale represents a T-threshold at 3.0, $p < 0.001$].

Fig. 2. Reduced striatal and thalamic D₂ receptor binding in dystonia gene carriers
 Voxel-based comparison of D₂ receptor availability in dystonia mutation carriers and healthy volunteers. Significant regional differences were present in the putamen (*top left*) and thalamus (*bottom left*). Bar diagrams (*right*) illustrate binding values from each significant cluster (arrows) in non-manifesting (NM) and manifesting (MAN) DYT1 and DYT6 carriers and healthy controls (C). [Overlay as in Fig. 1B. The color scale represents a T-threshold of 4.2, $p < 0.05$ (FWE-corrected)].