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Neural correlates of abnormal sensory discrimination in laryngeal dystonia

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ABSTRACT

Aberrant sensory processing plays a fundamental role in the pathophysiology of dystonia; however, its underpinning neural mechanisms in relation to dystonia phenotype and genotype remain unclear. We examined temporal and spatial discrimination thresholds in patients with isolated laryngeal form of dystonia (LD), who exhibited different clinical phenotypes (adductor vs. abductor forms) and potentially different genotypes (sporadic vs. familial forms). We correlated our behavioral findings with the brain gray matter volume and functional activity during resting and symptomatic speech production. We found that temporal but not spatial discrimination was significantly altered across all forms of LD, with higher frequency of abnormalities seen in familial than sporadic patients. Common neural correlates of abnormal temporal discrimination across all forms were found with structural and functional changes in the middle frontal and primary somatosensory cortices. In addition, patients with familial LD had greater cerebellar involvement in processing of altered temporal discrimination, whereas sporadic LD patients had greater recruitment of the putamen and sensorimotor cortex. Based on the clinical phenotype, adductor form-specific correlations between abnormal discrimination and brain changes were found in the frontal cortex, whereas abductor form-specific correlations were observed in the cerebellum and putamen. Our behavioral and neuroimaging findings outline the relationship of abnormal sensory discrimination with the phenotype and genotype of isolated LD, suggesting the presence of potentially divergent pathophysiological pathways underlying different manifestations of this disorder.

1. Introduction

Isolated focal dystonia is a multifactorial disorder with unclear causes and pathophysiology, which may affect various body regions, from eyelid to foot muscles. This phenotypical heterogeneity is further expanded by the task-specific forms of focal dystonia, which selectively affect similar muscle groups but lead to clinically distinct symptoms, such as writer's cramp vs. musician's hand dystonia or adductor vs. abductor laryngeal dystonia. Whether the different forms of dystonia have a common underlying pathophysiological mechanism and whether there are additional genetic or environmental factors that divert patients into different clinical phenotypes remain largely unknown. Contributing to this, gene discovery for isolated task-specific focal dystonias has been stagnant due, in part, to the small effect size of a risk allele on phenotypic variance, the lack of neural integrity markers of dystonia carriers, and poor understanding of their interplay with genes contributing to this disorder. However, several factors, including the family history of dystonia in up to 12% of patients with isolated focal dystonias (Chan et al., 1991; Friedman and Fahn, 1986; Grandas et al., 1988; Kirke et al., 2015; Maniak et al., 2003; Sheehy et al., 1988), suggest that genetic susceptibility or dominantly inherited genes with reduced penetrance may be involved in the etiopathophysiology of this disorder.

To this end, behavioral studies examining the underlying quantitative traits have recently hinted to the presence of the mediational endophenotypic markers of dystonia, which reflect gene expression and share common pathogenetic mechanisms with phenotype, thus linking genes with phenotype (Hutchinson et al., 2013). Specifically, the abnormal temporal discrimination threshold (TDT), a significantly extended

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time interval at which a subject perceives two stimuli as being asynchronous, has been proposed as a mediational endophenotype of dystonia (Hutchinson et al., 2013) based on the findings in writer's cramp, cervical dystonia, blepharospasm and generalized dystonia (Aglioti et al., 2003; Bradley et al., 2009, 2012; Fiorio et al., 2003, 2008) as well as in up to 52% of unaffected relatives of patients with DYT1 and adult-onset cervical dystonias (Bradley et al., 2009; Fiorio et al., 2007; Kimmich et al., 2014). However, despite its possible importance in the pathophysiology of dystonia, our understanding of the relationships between abnormal sensory processing as a dystonia endophenotype and brain abnormalities underlying the pathophysiology of dystonia remains scarce.

In this study, we examined the visual temporal discrimination thresholds (TDT) in a large cohort of 84 patients with isolated laryngeal form of dystonia (LD), including patients with different clinical phenotypes (adductor vs. abductor forms) and possibly different genotypes (sporadic vs. familial forms), in order to determine phenotype- and putative genotype-specific features of abnormal temporal discrimination. We further investigated the relationships between TDT abnormalities, LD clinical symptoms, and brain structural and functional changes using voxel-based morphometry (VBM) of gray matter volume and functional MRI (fMRI) during both symptomatic speech production and the resting state. In addition, because the tactile spatial discrimination thresholds (SDT) have been previously reported to be altered in writer's cramp, blepharospasm, cervical dystonia but not in generalized DYT1 dystonia (Molloy et al., 2003), we assessed the SDT in the same cohort of LD patients. To establish the baseline measures, the TDT and SDT were also examined in 30 age- and gender-matched healthy individuals.

We hypothesized that both TDT and SDT will be significantly abnormal across the different groups of LD patients compared to controls. Because abnormal discrimination may represent a mediational endophenotype closer to genes than to clinical phenotype of dystonia (Hutchinson et al., 2013), we hypothesized that these alterations would be greater in familial than sporadic patients. Based on the prior reports of TDT abnormalities in unaffected first-degree relatives of cervical dystonia patients and asymptomatic carriers of DYT1 mutation (Kimmich et al., 2011, 2014), we hypothesized that abnormalities in discrimination would not significantly correlate with LD symptom duration or severity. However, because genes have an immediate impact on brain organization (Meyer-Lindenberg, 2010), we expected that abnormal sensory discrimination would establish significant correlations with the structure and function of brain regions, which likely contribute to dystonia pathophysiology (Neychev et al., 2011; Ramdhani and Simonyan, 2013; Zoons et al., 2011) and are related to abnormal speech motor control in patients with laryngeal dystonia. Specifically, we hypothesized that distinct patterns of correlations between sensorimotor, basal ganglia and cerebellar abnormalities and abnormal sensory discrimination would differ between sporadic and familial LD as well as adductor (ADLD) and abductor (ABLD) forms.

2. Methods

2.1. Subjects

We recruited 102 LD patients and 53 healthy controls. Our exclusion criteria included the presence of other forms of dystonia, left-handedness, bilingual non-native English speakers, past or present history of neurological, psychiatric, laryngeal or cognitive problems, impaired visual or tactile acuity, and known dystonia gene mutation. Based on these stringent exclusion criteria as well as study dropouts, the final subject groups comprised:

(1) 60 sporadic LD patients without family history of any form of dystonia, including 30 ADLD and 30 ABLD forms;
(2) 24 familial LD patients with one or more family members affected with LD or other forms of primary dystonia, including 17 ADLD and 7 ABLD;
(3) 30 healthy controls.

All final study participants were right-handed and monolingual native English speakers. None had any history of neurological (other than isolated LD in patients), psychiatric, or laryngeal problems. All subjects scored ≥27 points at the Mini-Mental State Examination, which is indicative of normal cognition (Table 1). Genetic testing performed on blood samples from all final study participants found no *TOR1A* (DYT1), *THAP1* (DYT6), *TUBB4A* (DYT4) or *GNAL* (DYT25) mutations. None of the subjects had any conditions resulting in a loss of visual or tactile acuity, which may have interfered with the completion of experimental testing. The diagnosis of LD was confirmed by fiberoptic nasolaryngoscopy. The patients who received botulinum toxin injections participated in the study only when they were symptomatic, i.e., at the end of their treatment cycle at least 3–4 months after their last injection.

All subjects provided written informed consents, which was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai.

2.2. Sensory testing

The visual TDT exam was performed using a custom-made device with two LED flashing lights according to a previously reported protocol (Bradley et al., 2009). The subject was instructed to focus on a reference focal point in the middle of the subject's field of view at a constant distance of 70 cm, while the device with two LED-flashing lights was positioned within the subject's left or right peripheral vision at a constant distance of 10 cm from the reference focal point. The left/right setup was randomized between the subjects, and both sites were tested in all subjects. While focusing on a focal point, all subjects were instructed to assess the flashing of the two LED lights, which were presented at 5-s intervals and illuminated

Table 1
Demographic and clinical data.

	Sporadic		Familial		Controls
	ADLD	ABLD	ADLD	ABLD	
Number of subjects	30	30	17	7	30
Age (years; mean ± standard deviation)	57.4 ± 10.4	53.1 ± 12.5	55.9 ± 15.9	58.1 ± 13.0	49.7 ± 9.5
Gender (female/male)	23/7	26/4	16/1	5/2	18/12
Handedness (Edinburgh inventory)	Right				
Language	Monolingual native English				
Cognitive status	Mini-Mental State Examination ≥ 27 points				
Genetic status	Negative for DYT1, DYT4, DYT6 and DYT25				
Disease duration (years; mean ± standard deviation)	14.7 ± 9.6	12.2 ± 8.9	20.6 ± 13.9	24.7 ± 19.7	N/A
Symptom severity (visual analog scale; mean ± standard deviation)	7.2 ± 1.9	7.8 ± 1.9	7.0 ± 2.4	7.9 ± 1.5	N/A

TDT and SDT values did not show statistical differences between younger (<50 years old) and older (>50 years old) participants or between male and female participants (all $p \geq 0.05$, corrected for multiple comparisons). There were no statistically significant differences between the groups in age or gender; the patient groups did not differ statistically in their symptom severity or disorder duration (all corrected $p > 0.05$).