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Tremor and Other Hyperkinetic Movements

Brief Report

Spatial Discrimination Threshold Abnormalities are not Detected in a Pilot Study of *DYT6* Dystonia Mutation Carriers

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Abstract

Background: Spatial discrimination thresholds (SDTs) assess somatosensory integration, and provide a window into better understanding the pathophysiology of dystonia. They are abnormal in some focal dystonias, but normal in *DYT1* dystonia. It is unknown whether SDTs are altered in *DYT6* gene mutation carriers (C).

Methods: SDTs were assessed in 17 *DYT6* C (including eight manifesting carriers), 15 *DYT1* C (including seven manifesting carriers) and 34 controls, using a standardized grating orientation task. Subjects were asked to recognize the orientation of Johnson–Van Boven–Philips (JVP) dome gratings on either index fingertip until 40% or more answers were incorrect. SDTs between indexes were calculated and averaged, with a final SDT assigned to each subject, and tertiles for control SDTs were constructed.

Results: SDTs of *DYT6* C or *DYT1* C were comparable to those of controls, and not more likely to be in the worst tertile ($p=0.8$ for *DYT6* C vs. controls and $p=1.0$ for *DYT1* C vs. controls). This was independent of gene expression.

Discussion: *DYT6* carriers do not have impaired SDTs with the JVP dome paradigm. The normal SDT pattern thus suggests shared sensory physiologic patterns with *DYT1* dystonia.

Keywords: *DYT6*, *DYT1*, dystonia, sensory discrimination threshold

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Introduction

Dystonia is characterized by involuntary, sustained muscle contractions that result in twisting and repetitive movements and abnormal postures.[1] Both neurophysiologic and clinical observations suggest that dystonia is associated with a disturbance of sensory integration. Clinically, there is often improvement of dystonic postures using sensory tricks (*gestes antagonistes*).[2] Although basal ganglia dysfunction likely contributes to the pathogenesis of genetic dystonia, expanded neuronal circuits have been implicated. Positron emission tomography (PET) studies in carriers of the *DYT1* dystonia mutation suggest overexcitability of the sensorimotor system,[3] whereas reductions in cerebello-thalamic connectivity are thought to correlate with disease expression in both *DYT1* and *DYT6* gene mutation carriers.[4] Several models of sensory processing dysfunction in dystonia have been proposed,[2,5,6] and the role of somatosensory abnormalities in disease pathogenesis warrants further study.

Mapping with somatosensory evoked potentials demonstrates abnormal homuncular organization of finger representations in the primary somatosensory cortex in a primate genesis model of focal dystonia and repetitive strain injury.[7] A disorganized pattern, which

correlates with dystonia severity, is also seen in humans with brachial dystonia.[6] Although some functional neuroimaging studies have demonstrated decreased sensorimotor activation in dystonia (due perhaps to the heterogeneity of the cohorts of the patients examined),[8] the majority of studies suggests overactivation of contralateral sensorimotor and supplemental motor cortex. Motor tasks, such as repetitive learning show activation in bilateral dorsal pre-motor and inferior parietal association cortex,[3,9–11] and contralateral dorsolateral prefrontal cortex (gyrus frontalis medialis, superior frontal gyrus, fronto-orbital cortex) as well. Functional imaging also supports cortical sensory abnormalities in response to vibratory stimuli, albeit decreased, as measured by PET and $H_2(15)O$ blood flow scanning where the peaks were reduced in the primary sensorimotor area and supplementary motor area in writer's cramp.[12] Although the etiology of dystonia is often unknown, two genes for primary dystonia have been elucidated, *TOR1A* (*DYT1)* and *THAP1 (DYT6)*. Based on PET and magnetic resonance imaging (MRI) abnormalities, as well as their characteristic early age of disease onset, both disorders have been hypothesized as neurodevelopmental circuit disorders of cortico-striatal-pallido-thalamocortical and cerebellar-thalamo-cortical pathways.[13]

Spatial discrimination thresholds (SDTs) have been proposed as a method for understanding the role of sensory processing in different forms of dystonia through assessing the integrity of sensory integration. The SDT describes the shortest distance interval at which two stimuli applied to the same part of the body can be recognized as spatially separated and can be readily tested at the bedside.[14] SDTs have been found to be normal in patients with *DYT1* dystonia, but impaired in subjects with focal dystonias, notably, writer's cramp, blepharospasm, and cervical dystonia.[15] Although SDT testing is less sensitive in patients with adult-onset focal dystonias than another task of sensory discrimination, the temporal discrimination threshold (TDT),[16] SDT is highly portable and readily assessed.

SDT has not been evaluated in *DYT6* gene (*THAP1*) mutation carriers. As *DYT6* may present with focal or segmental dystonia, including writer's cramp and craniocervical dystonia,[17–21] this study was performed to establish whether SDTs are abnormal in *DYT6* mutation carriers, and may be an endophenotype of *DYT6* dystonia. Further, penetrance of the *DYT6* and *DYT1* genes is reduced, and symptoms of dystonia are present in approximately 60% of cases[22] with *DYT6* mutations and 30–40% of those with *DYT1* mutations.[23] As both *DYT1* and *DYT6* gene carriers who do not express symptoms may have abnormal brain circuitry, a function endophenotype of carrying the mutated *THAP* gene has been proposed.[13] In order to determine whether SDTs could detect a sensory endophenotype of *DYT6* dystonia, we also performed SDTs in *THAP1* non-manifesting mutation carriers.

Methods

Subjects

Subjects who participated in ongoing genetic studies of dystonia and movement disorders were recruited for SDT assessment and gave informed consent. This study was approved by the Internal Review Board at Beth Israel Medical Center. For dystonia family members, mutations in *THAP1* and *DYT1* were assessed as previously reported.[17,24] Controls were recruited from married-in or non-mutation carrying family members of probands and laboratory members. We evaluated *DYT6* mutation carriers (C), both with dystonia (manifesting carriers, MC) and without (non-manifesting carriers, NMC), and compared these with unaffected controls.

Sensory testing

SDTs were tested using a standardized grating orientation task, which employs plastic Johnson–Van Boven–Philips (JVP) domes (Stoelting Co, IL, http://www.stoeltingco.com/stoelting/3129/1465/1480/Physio/JVP-Domes), as has been previously reported.[15,25] The subjects were seated facing the examiner and blindfolded, with the right index finger resting extended against a table and the distal finger fat pad facing up. Each dome was applied on the fingertips a total of 20 times for about 1–2 seconds each time, starting with the largest width grating (4.5 mm for subjects aged 46 or more and 2.5 mm for subjects aged less than 46 years) and proceeding through gradually narrower ones (the dome with the smallest width grating was 0.75 mm). The purpose of using the widest grating for the older subgroup of subjects was to account for the expected age-related decline in sensory discrimination.[25,26] Domes were applied randomly with the gratings aligned either parallel ("down") or perpendicular ("across") to the axis of the finger, and with enough pressure to indent the skin by 1 mm. Prior to asking subjects to recognize the grating orientation in a blinded fashion, subjects were trained on the different orientations for each different grating size. The process continued until eight (40%) or more answers for a given grating width were incorrect. Sensory testing was then repeated on the contralateral index finger following the same paradigm. Subjects who attained 40% or more incorrect responses for the largest (4.5 mm or 2.5 mm, depending on the subject's age at the time of testing) groove widths were assigned the threshold of the largest width tested within their age group. The SDT for each hand was calculated by linear interpolation of the 75% level of accuracy and the final SDT was calculated as the mean of both index fingers.

Data analysis

SDTs from controls were divided by age into two groups (46 years or older and less than 46 years). Tertiles for each group were constructed, with the third (or highest) tertile containing SDTs from those individuals with the poorest performance. Non-control subjects were then categorized based on the control tertiles. Individuals scoring in the first two tertiles were considered to have normal SDTs, and those within the third tertile were considered abnormal. The distribution of abnormal SDTs was first compared between all *DYT6* mutation carriers and controls (STATA10, StataCorp LP, TX). To determine whether the presence of abnormal SDTs was a disease effect rather than a gene effect, we then divided the gene mutation carrier groups into MC and NMC, and compared each of these subgroups with

controls using Fisher's exact test. These analyses were repeated comparing *DYT1* groups with controls.

As botulinum toxin type A (BntxA) has been shown to transiently improve the SDT in patients with cervical dystonia, presumably by modulating afferent cortical inputs from muscle spindles,[26] we performed *post hoc* analyses on the subgroups of MC who had not received BntxA injections in the previous 3 months. We also compared SDT means stratified by age (subjects 45 years and younger or subjects older than 45 years) with controls.

Results

Seventy-five subjects were studied: 20 *DYT6* C (including 10 *DYT6* MC), 19 *DYT1* C (of which 10 were *DYT1* MC), and 36 healthy controls. To be eligible for the domes paradigm, subjects could not have evidence of central or peripheral neurologic abnormalities accounting for deficiencies in distal hand sensation (mainly, but not limited to, a known history or symptoms suggestive of carpal tunnel syndrome or sensory polyneuropathy), or other potential conditions that may falsely elevate their SDTs, such as the presence of heavy palmar callouses or a history of prolonged exposure to vibrating tools. After applying these exclusion criteria, a total of 66 subjects (eight *DYT6* MC, nine *DYT6* NMC, seven *DYT1* MC, eight *DYT1* NMC and 34 controls) completed the study. General characteristics of all groups are summarized in Table 1. Clinical characteristics of *DYT1* MC and *DYT6* MC are described in Table 2.

SDTs were not more likely to be in the worst tertile in *DYT6* C compared with controls (p=0.8), and this was independent of gene expression. That is, there was no difference between SDTs of the subgroups of *DYT6* C (*DYT6* MC and *DYT6* NMC) when compared with controls (p=0.2 and 1.0, respectively). Tertile distribution of SDTs for controls and *DYT6* C, MC and NMC is summarized in Table 3. As expected, *DYT1* C (p=1.0), MC (p=1.0) and NMC (p=1.0) were not more likely to have abnormal discrimination as defined as in the upper tertile compared with controls. Sensitivity subanalysis of the smaller group of *DYT6* C who did not receive BntxA injections 3 months prior to sensory testing also did not show a difference from controls (p=0.8).

Similar to the tertile approach, examination of raw data comparing age-stratified SDT means with those of controls showed no significant differences between the groups. *DYT6* C ages 45 years and younger were not different from controls (p=0.3); *DYT6* MC, NMC and control values were also not different (p=0.7). *DYT1* C younger than 46 years were not different from controls (p=0.9), nor was the comparison of *DYT1* MC, NMC and controls (p=0.7). For individuals aged 46 years and older, comparing *DYT6* C vs. controls and MC, NMC, and controls, (p=0.9 and 0.5, respectively), and *DYT1* C vs. controls (p=0.8) was also not significant.

Discussion

Our results suggest that *DYT6* mutation carriers, both manifesting and non-manifesting, do not have impaired SDTs. In agreement with a prior report,[15] we further demonstrate that *DYT1* MC also do not have abnormal SDTs. As similar results were noted in *DYT6* and *DYT1* mutation carriers, we postulate that the integrity of higher sensory circuitry assessed in the SDT paradigm is not compromised, or is compensated for, in both genetic forms of dystonia.

Neural circuit similarities have been noted in functional and MRI of both *DYT1* and *DYT6* dystonia carriers manifesting with dystonia. Fluorodeoxyglucose PET studies demonstrate that both *DYT1* C and *DYT6* C show relative metabolic increases in the pre-supplementary motor area and parietal association regions.[27,28] Further, both *DYT1* C and *DYT6* C scanned with [^{11}C]-raclopride PET were found to have

Table 1. Subject Demographics

Group	n	Median Age (years)	Gender (F/M)	Handedness (R/L)	Genotype	Median Onset Age (years)	Median Disease Duration (years)
DYT1 C	**15**	**43.2**	**(10/5)**	**(14/1)**			
DYT1 MC	7	39.2	(4/3)	(6/1)	c.904_906delGAG	8.5	23.2
DYT1 NMC	8	48.6	(6/2)	(8/0)	c.904_906delGAG		
DYT6 C	**17**	**41.8**	**(11/6)**	**(13/4)**			
DYT6 MC	8	21.7	(5/3)	(6/2)	indel[1] (n=6) c.65T→C (n=1) c.61T>A (n=1)	11.5	14.2
DYT6 NMC	9	47.4	(6/3)	(7/2)	indel (n=7) c.65T→C (n=2)		
Controls	**34**	**33.1**	**(16/18)**	**(34/0)**			

Abbreviations: C, carriers; MC, manifesting carriers; NMC, non-manifesting carriers.
[1]Amish-Mennonite Founder Insertion deletion (indel) mutation c.134_135insGGGTT; 137_139delAAC

Table 2. Clinical Characteristics of *DYT1* and *DYT6* Manifesting Carriers

Subject[1]	Age at Domes (years)	Age at Onset (years)	Symptom Duration	Distribution of Dystonia[2]	Genotype	BntxA
DYT1						
1	43.2	8.0	35.2	TAMRG	*	Yes
2	39.2	10.0	29.2	AMRG	*	No
3	39.6	9.0	30.6	AMKRG	*	No
4	23.1	7.0	16.1	AMG	*	Yes
5	23.3	6.0	17.3	UFLNAMKRG	*	Yes
6	19.0	13.0	6.0	ARG	*	Yes
7	53.5	12.0	41.5	A	*	No
DYT6						
8	19.0	8.0	11.0	TNAMR	indel[3]	Yes
9	19.4	16.0	3.4	L	indel	No
10	50.5	21.0	29.5	FJTNA	indel	No
11	24.0	3.0	21.0	LNAMRG	indel	No
12	17.7	2.0	15.7	FJTAMKRG	indel	No
13	45.7	12.0	33.7	FJTNAMKRG	c.65T→C	No
14	41.7	29.0	12.7	NA	c.61T>A	No
15	18.8	11.0	7.8	FTAMKR	indel	No

Abbreviations: A, right arm; BntxA, botulinum toxin type A; F, lower face; G, left leg; J, jaw; K, trunk; L, larynx; M, left arm; N, neck; R, right leg; T, tongue; U, upper face.
[1]All were right-hand dominant except subjects 7, 11, and 15.
[2]Sites affected at time of Johnson–Van Boven–Philips testing.
[3]Amish-Mennonite Founder Insertion deletion (indel) mutation c.134_135insGGGTT; 137_139delAAC
*All DYT1 mutation carriers harbored c.904_906delGAG.

Table 3. Tertile Distribution of Sensory Discrimination Thresholds (SDTs) for Controls and *DYT6* C Manifesting carriers (MC) and non-manifesting carriers (NMC)

Tertile	Tertile Limits for Subjects 45 and Younger	Tertile Limits for Subjects 46 and Older[1]	Controls in Tertile (n, %)	*DYT1* C in Tertile (n, %)	*DYT1* MC in Tertile (n, %)	*DYT1* NMC in Tertile (n, %)	*DYT6* C in Tertile (n, %)	*DYT6* MC in Tertile (n,%)	*DYT6* NMC in Tertile (n, %)
1st	1.09–1.64	1.95–2.44	12 (35.3)	7 (46.7)	2 (28.6)	5 (62.5)	8 (47.1)	4 (50)	4 (44.4)
2nd	1.73–2.33	3.39–3.48	9 (26.5)	3 (20)	3 (42.9)	0 (0)	4 (23.5)	3 (37.5)	1 (11.1)
3rd	2.38–2.87	3.82–3.84	13 (38.2)	5 (33.3)	2 (28.6)	3 (37.5)	5 (29.4)	1 (12.5)	4 (44.4)
Totals			34 (100)	15 (100)	7 (100)	8 (100)	17 (100)	8 (100)	9 (100)

Abbreviations: MC, manifesting carriers; NMC, non-manifesting carriers.

reductions in putamen and caudate D2 receptor availability, and recent work with diffusion tensor imaging MRI also suggests that both *DYT1* C and *DYT6* C share two discrete areas of reduced pathway connectivity in the cerebello-thalamo-cortical projection system.[13] However, there are also differences noted on functional imaging: raclopride PET demonstrates significantly more pronounced reductions in *DYT6* than in *DYT1* in striatal D2 availability.[13] The absence of an abnormality suggests that the SDT is not mediated through the cortico-striatal-pallido-thalamocortical and cerebellar-thalamo-cortical circuits abnormal in *DYT1* and *DYT6* dystonia, or that there is compensation in the circuitry, which facilitates normal sensory discrimination with this task.

Although studies in non-*DYT1* families suggest that SDT may identify an endophenotype of gene carriers in unaffected family members of dystonia subjects,[25] we did not detect SDT abnormalities in either the *DYT6* NMC or the *DYT1* NMC. This differs from functional imaging studies, which suggest that *DYT1* NMC and *DYT6* NMC have striatal metabolic abnormalities accompanied by changes in D2 receptor availability.[13]

There are several potential limitations to this study including age differences between the groups, treatment with botulinum toxin A in some subjects, paradigm sensitivity, and a relatively small sample size. The dystonia groups differed in age, with the *DYT6* MC group younger than the other groups. We therefore corrected for the age-related decline in sensory discrimination by using domes with a larger width grating, and, as expected, this caused a pronounced increase in the calculated threshold of subjects with impaired sensory discrimination. Nonetheless, despite the correction, we were unable to find a significant difference in SDTs in *DYT1* and *DYT6* subjects compared with controls.

Additionally, one (12.5%) of our *DYT6* MC and four (57%) of the *DYT1* MC had received BntxA within the last 3 months prior to sensory testing. The role of BntxA in affecting sensory discrimination is still not well understood. However, it has been suggested that BntxA may modulate afferent cortical inputs from muscle spindles and cause a sensory cortical reorganization in adult-onset primary torsion dystonia patients receiving this treatment.[26] Therefore we cannot be certain that the absence of an abnormality in SDT could be a medication-related effect. Although in their original study of *DYT1* subjects, the 2 out of the 13 *DYT1* MC who were on BntxA therapy did not receive injections in at least 3 months prior to testing,[15] which argues in favor of normal SDTs in *DYT1* regardless of treatment, the small sample size in their and our study precludes proper assessment of a BntxA effect.

Although we did not detect an abnormality with the JVP domes, we cannot exclude that there is a sensory endophenotype associated with a *DYT6* mutation that is not captured with this paradigm. We may not have had sufficient power to detect smaller changes in sensory discrimination abnormalities. Our sample size was limited by the availability of subjects with genetic forms of dystonia; therefore, there was only adequate power to detect differences greater than 0.35 between proportions. The rarity of *DYT6* renders obtaining greater sample sizes impractical.

The limitations may extend beyond sample size; SDT testing may not be a sufficiently sensitive test. Potential reasons include the already mentioned age-related loss of sensory discrimination and operator-dependent variations such as inconsistent pressure applied to the fingertips, a variable and inconsistent time during which the dome is applied, or inadvertent feedback to the study subject regarding the orientation of the domes. Sensory disturbances may be mild enough in *DYT1* (and perhaps also in *DYT6*) that SDT testing simply fails to detect them. Employment of more sensitive techniques to measure sensory integration in *DYT6* carriers may prove useful. TDT is defined as the shortest time interval at which two stimuli are discerned as separate. Studies indicate that such thresholds are higher in patients with *DYT1* dystonia,[29] and cervical and focal-hand dystonia[30] than in healthy controls. Abnormalities in the TDT may represent a reliable endophenotype in those predisposed family members who have not manifested with adult-onset focal dystonia.[30,31] As TDT testing is more sensitive than SDT in adult-onset focal dystonia,[16] it may demonstrate changes in sensory integration abnormalities in *DYT6* dystonia, and should be tested in this population.

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