RESEARCH ARTICLE

Temporal Discrimination, a Cervical Dystonia Endophenotype: Penetrance and Functional Correlates

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ABSTRACT: The pathogenesis of adult-onset primary dystonia remains poorly understood. There is variable age-related and gender-related expression of the phenotype, the commonest of which is cervical dystonia. Endophenotypes may provide insight into underlying genetic and pathophysiological mechanisms of dystonia. The temporal discrimination threshold (TDT)—the shortest time interval at which two separate stimuli can be detected as being asynchronous—is abnormal both in patients with cervical dystonia and in their unaffected first-degree relatives. Functional magnetic resonance imaging (fMRI) studies have shown that putaminal activation positively correlates with the ease of temporal discrimination between two stimuli in healthy individuals. We hypothesized that abnormal temporal discrimination would exhibit similar age-related and gender-related penetrance as cervical dystonia and that unaffected relatives with an abnormal TDT would have reduced putaminal activation during a temporal discrimination task. TDTs were examined in a group of 192 healthy controls and in 158 unaffected first-degree relatives of 84 patients with cervical dystonia. In 24 unaffected first-degree relatives, fMRI scanning was performed during a temporal discrimination task. The prevalence of abnormal TDTs in unaffected female relatives reached 50% after age 48 years; whereas, in male relatives, penetrance of the endophenotype was reduced. By fMRI, relatives who had abnormal TDTs, compared with relatives who had normal TDTs, had significantly less activation in the putamina and in the middle frontal and precentral gyri. Only the degree of reduction of putaminal activity correlated significantly with worsening of temporal discrimination. These findings further support abnormal temporal discrimination as an endophenotype of cervical dystonia involving disordered basal ganglia circuits. © 2014 International Parkinson and Movement Disorder Society

Key Words: cervical dystonia; temporal discrimination; functional magnetic resonance imaging; putamen; endophenotype

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Additional Supporting Information may be found in the online version of this article.

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Cervical dystonia is the commonest form of adult-onset primary torsion dystonia (AOPTD) with a female preponderance. It is believed that manifestation of the disease results from a combination of susceptibility genes with reduced penetrance,[1-4] individual genetic and environmental risk factors, and a likely effect of age of onset on the expression of the phenotype.[5] To date, apart from the protein-coding THAP domain containing, apoptosis associated protein 1 gene (*THAP1*),[6] no genes other than those affecting single families have been identified.[7,8]

Endophenotypes (state-independent subclinical markers of gene carriage) may provide clarity in the understanding of a poorly penetrant condition such as AOPTD. Several putative endophenotypes have been suggested over the past decade, along with the description of numerous sensory abnormalities in dystonia.[9] The temporal discrimination threshold (TDT) is the shortest time interval at which two separate stimuli are perceived as asynchronous and is abnormal in various dystonic[10-14] and other basal ganglia disorders.[15-18] We have examined the utility of an abnormal TDT as an endophenotype in both familial and sporadic AOPTD.[19-21]

Abnormal TDTs in unaffected first-degree relatives of patients with cervical dystonia are associated with putaminal enlargement,[19] a structural abnormality that also is found in patients with blepharospasm[22] and in musician's dystonia.[23] Functional magnetic resonance imaging (fMRI) studies of temporal discrimination in healthy participants have identified the putamen as a structure involved in the early encoding of time intervals of sensory signals.[24,25] Another study also found putaminal activation when participants, on presentation of sensory stimuli at varying intervals, were perceptually certain that these were either synchronous or separate.[26] We hypothesize that (1) the abnormal TDT in unaffected first-degree relatives of AOPTD patients is a mediational endophenotype, implying that endophenotype and disease are both caused by a genetic disorder and that the pathway from gene to disease passes through the endophenotype[27,28]; (2) temporal discrimination is a measure of the functioning of a subcortical-striatal re-entrant looped pathway; and (3) a genetically determined disorder in this pathway affects striatal processing of a temporal discrimination task.

The aims of this study were (1) to examine the penetrance of the endophenotype (an abnormal TDT) in relation to age and gender in unaffected first-degree relatives of patients with cervical dystonia and (2) to analyze putaminal activity by fMRI in unaffected relatives with and without abnormal TDTs during a temporal discrimination task. We postulated that the endophenotype in unaffected relatives would show a pattern of age-related and gender-related penetrance similar to that of the phenotype and that, as a functional correlate of the endophenotype (that is, disordered temporal discrimination), unaffected first-degree relatives with abnormal TDTs would show less putaminal activity by fMRI during a temporal discrimination task than those with normal TDTs.

Participants and Methods

Penetrance of an Abnormal TDT

Control participants

The control group of 192 healthy individuals included 91 men and 101 women between ages 21 years and 65 years (mean age, 42.7 years) who were recruited from hospital staff and visitors to the hospital. Exclusion criteria were a history of neurological disease, including neuropathy; severe visual or cognitive impairment; a history of cerebral, cervical, or brachial plexus injury; and a family history of dystonia.

Unaffected first-degree relatives

In *cross-sectional TDT testing*, 158 unaffected first-degree relatives, including 88 offspring and 70 siblings, of 84 cervical dystonia patients were examined for TDT (mean age, 40.9 years; age range, 18.1-65.7 years). None of the relatives had any symptoms or signs of a movement disorder. A full medical history was taken by the research registrars (O.K., A.M., D.B.), and an examination protocol was used to assess for any evidence of a neurological disorder, particularly focal dystonia. A video examination of the relatives was not performed. The data from a proportion of control participants and unaffected relatives in this study have been reported in previous publications.[19,21] In *longitudinal TDT testing* for 25 relatives of patients with cervical dystonia, TDTs were re-examined between 2 years and 4 years after their initial TDT examination.

Cervical dystonia patients

The notes on our clinic population of patients with cervical dystonia were examined for the age at onset of their initial cervical dystonia symptoms. We calculated the median age at onset of 117 women and 62 men who gave clinically reliable information in this regard.

Sensory Testing

TDT testing was carried out as described previously[19] in a single session for two sensory modalities: visual and tactile (for details, see Supporting Methods). Values in milliseconds (ms) for the visual, tactile, and combined visual and tactile TDTs were determined. Testing was carried out by the research registrars (O.K., A.M., D.B.) according to a standard protocol. Inter-rater reliability was determined by repeat randomized examination of 30 controls and relatives.

Statistical Analysis

All TDT results (in ms) were converted to standardized *Z*-scores to enable easy comparison of individual results using the formula:

$$\text{Z-score} = \frac{(\text{actual TDT} - \text{age \& gender related control mean TDT})}{\text{age \& gender related control SD}}$$

For each participant, the *Z*-score was calculated using the relevant age-related and gender-related control data set to determine each participant's visual,

TABLE 1. Mean visual, tactile, and combined temporal discrimination threshold results with standard deviations, mean Z-scores (and range), and the number and percentage of abnormal results for the 192 control participants by age group (ages 20-35 years and 36-65 years) divided into four groups according to age and gender

		TDT (ms)		Z-Score		
TDT Task	No.	Mean	SD	Mean	Range	Abnormal TDTs: No. (%)
Ages 20-35 y						
Control women						
Visual	35	27.50	12.53	0	−1.40 to 2.59	1 (3)
Tactile	35	27.46	10.68	0	−1.40 to 1.93	0 (0)
Combined	35	27.48	10.84	0	−1.32 to 2.25	0 (0)
Control men						
Visual	33	34.41	9.96	0	−1.95 to 1.57	0 (0)
Tactile	33	28.71	9.29	0	−2.28 to 2.16	0 (0)
Combined	33	31.56	8.65	0	−2.35 to 2.06	0 (0)
Ages 36-65 y						
Control women						
Visual	66	35.88	14.75	0	−1.84 to 2.40	0 (0)
Tactile	61	33.68	14.10	0	−2.39 to 2.58	1 (2)
Combined	66	35.07	13.37	0	−1.70 to 2.35	0 (0)
Control men						
Visual	58	40.45	12.95	0	−2.16 to 1.90	0 (0)
Tactile	57	39.02	15.09	0	−2.59 to 2.30	0 (0)
Combined	58	39.78	12.49	0	−1.98 to 2.17	0 (0)

Abbreviations: TDT, temporal discrimination threshold; ms, milliseconds; SD, standard deviation.

tactile, and combined visual and tactile TDT (three *Z*-scores). A combined visual and tactile *Z*-score ≥ 2.5 was considered an abnormal TDT. The Kruskal-Wallis test was used for group comparisons, and the Mann-Whitney and Fisher's Exact tests were used for analyses between groups (P values < 0.05 were considered statistically significant). No explicit adjustments for multiple comparisons have been made.

fMRI Study

Two groups of participants were analyzed in the fMRI study. All participants were right-handed and had normal or corrected-to-normal vision.

Unaffected first-degree relatives of cervical dystonia patients

Of *14 relatives with abnormal TDTs* (n = 7 women), the median age was 46.9 years (range, 27.2-70.9 years), and their mean combined TDT *Z*-score was 3.96. Of *10 relatives with normal TDTs* (n = 6 men), the median age was 40.8 years (range, 30.5-61.2 years), and their mean combined TDT *Z*-score was 0.83. None of the 24 unaffected relatives had any symptoms or signs of a movement disorder on assessment, as described above.

MRI data acquisition

During presentation of the paradigm, 200 contiguous blood oxygen level-dependent (BOLD)-sensitive, three-dimensional volume images were acquired in each of three runs (for details, see Supporting Methods) on a 3.0-Tesla scanner.

Materials

Tactile stimulation was delivered using MRI-compatible piezoelectric stimulators that were custom built by The Magstim Company Limited (Spring Gardens, Whitland, Carmarthenshire, UK; www.magstim.com). Visual stimuli were presented via a head-mounted mirror that displayed a reflection from a back-projection screen. Presentation of stimuli and recording of responses were controlled by software written in Presentation (Neurobehavioral Systems, Inc., Albany, CA, USA; www.neurobs.com).

fMRI protocol

For details on the fMRI protocol, see the Supporting Methods.

Statistical/fMRI analysis

Data preprocessing and analyses were performed with statistical parametric mapping software (SPM8; by members and collaborators of the Wellcome Trust Centre for Neuroimaging, University College London, London, UK) (for preprocessing details, see Supporting Materials). Age and gender both were entered as nuisance covariates in the SPM second-level model. Data were compared across the whole brain with a conservative family-wise error (FWE) rate of $P = 0.05$ using a minimum cluster size of

8 voxels. The SPM Anatomy toolbox was used to extract the percentage signal change.[29]

Ethical approval for this work was granted by the Ethics and Medical Research Committee, St. Vincent's University Hospital, Elm Park, Dublin, Ireland. All participants gave written informed consent in accordance with the Declaration of Helsinki.

Results

TDT Testing

Control participants

Because of an effect of age and gender on temporal discrimination, control participants were divided into four groups: (1) women ages 20 to 35 years, (2) men ages 20 to 35 years, (3) women ages 36 to 65 years, and (4) men ages 36 to 65 years. The mean TDT (in ms) differed significantly between these groups (Table 1, Supporting Fig. 1). Five women and one man in the control group ages 36 to 65 years, despite normal sensory examination, could not do the tactile task; therefore, only the visual results are reported. Using the definition of mean combined TDT ±2.5 standard deviations (SD) for each of the four control groups as the upper limit of normal, none of the 192 control participants had an abnormal combined TDT.

Repeat testing of the TDT in 30 control participants and relatives at 1-week to 2-week intervals showed evidence of a mild practice effect at repeat testing (mean TDT: 47.9 ms at Time 1, 43.6 ms at Time 2). There was no evidence of significant inter-rater variability (intraclass correlation coefficient = 0.86).

Unaffected first-degree relatives of cervical dystonia patients

The mean combined TDT in the 158 unaffected first-degree relatives (69 men, 89 women) was 50.30 ms (SD, 20.91 ms; 95% confidence interval [CI], 47.01-53.59 ms; mean Z-score = 1.42 [range, −1.70 to 7.32]). Six female relatives and one male relative, despite normal sensory examination, were not able to reliably do the tactile task; therefore, only the visual result was included. Using TDT Z-scores determined from the age-matched and gender-matched control participants, abnormal TDTs were found in 37 of 158 relatives(23%). They were found more commonly in women (25 of 89 women; 28%) than in men (12 of 69 men; 17%; $P = 0.13$; female-to-male [F:M] ratio, 1.65) and were more common in siblings (20 of 70 siblings; 29%) than in offspring (17 of 88 offspring; 18%; $P = 0.19$). Among siblings, 15 of 38 sisters (39%) and 5 of 32 brothers (15%) had an abnormal TDT ($P = 0.035$); whereas, among offspring, the proportion of abnormal TDTs was almost equal, with 10 of 51 daughters (20%) and 7 of 37 sons (19%).

Age-Related and Sex-Related Frequency of Abnormal TDTs

Comparing TDT Z-scores in unaffected first-degree relatives and healthy control participants from the different age groups, the Kruskal-Wallis test showed significant group differences for both women (K = 62.88; $P < 0.0001$) and men (K = 34.08; $P < 0.0001$). Using the Mann-Whitney test in every age group between ages 18 and 65 years, except for the group of men ages 35 to 44 years, there were significant differences in the median combined TDTs of unaffected first-degree relatives compared with healthy age-matched and gender-matched control participants (Table 2, Fig. 1). A regression model was fitted to investigate the relationship between TDT, gender, group (controls/relatives), and age group and demonstrated a statistically significant association between TDT response and age, independent of group. There was also a consistent and statistically significant difference between controls and relatives having adjusted for age and gender ($t = 9.7$; $P < 0.001$) (Supporting Fig. 3).

Women

An abnormal TDT was detected in 1 of 9 women between ages 18 and 24 years. After age 45 years, abnormal TDTs were detected in 14 of 31 women (45%) (Fig. 2a); and, after age 48 years, abnormal TDTs were detected in 14 of 25 women (56%). Thus, an abnormal TDT is fully penetrant in unaffected first-degree female relatives of patients with cervical dystonia after age 48 years.

Men

In men, however, there were no abnormal TDTs in the youngest age group (0 of 10 men), and the frequency of abnormal TDTs increased to a maximum of 29% from age 25 years and remained at a reduced frequency of 25% for the group ages 35 to 45 years and 15% for the group ages 45 to 65 years (Fig. 2b). Overall, the frequency of abnormal TDTs was reduced for 12 of 59 men (20%) in the group ages 25 to 65 years, indicating a penetrance of 40% with no evidence of increasing penetrance after age 25 years.

Longitudinal evaluation of TDTs in relatives

In 25 unaffected first-degree relatives, TDTs were repeated 2 to 4 years after their initial examination. The repeat TDT Z-score remained normal in 21 relatives and remained abnormal in two relatives. In these 23 relatives, the baseline mean TDT Z-score was 0.61, and the repeat mean TDT Z-score was 0.94. In two women, the TDT Z-score became abnormal on second testing (1) in a daughter of a patient with cervical dystonia who was tested at ages 35 years and 38 years, the TDT Z-score increased from 0.23 to 3.59; and (2)

TABLE 2. Temporal discrimination thresholds in women (101 controls and 89 unaffected sisters and daughters of patients with cervical dystonia) and men (91 controls and 69 unaffected brothers and sons of patients with cervical dystonia) by age group[a]

	Ages 18-34 Years				Ages 35-44 Years				Ages 45-54 Years				Ages 55-65 Years			
	Women		Men		Women		Men		Women		Men		Women		Men	
Variable	Controls	Relatives	Controls	Relatives	Controls	Relatives	Controls	Relatives	Controls	Relatives	Controls	Relatives	Controls	Relatives	Controls	Relatives
No. of participants	34	30	31	24	21	28	20	12	22	15	22	19	24	16	18	14
TDT, ms																
Median	24.1	39.7	31.9	35.6	35.9	48.1	39.1	38.8	33.4	55.6	35.6	50	36.3	76.9	36.3	58.8
Mean	27.2	42.1	30.8	40.8	33.1	50.2	41.3	45.3	36.5	57	36.9	48.8	35.6	71.9	42	63.1
SD	10.9	14.6	8.2	16.8	12.5	18.4	12.4	22.1	15.5	23.6	9.9	14	12	21	14.8	27.3
Maximum	51.9	72.5	42.8	89.4	58.8	83.1	65	77.5	66.3	97.5	55.6	74.4	58.8	96.9	66.9	131.3
Mean combined Z-score	−0.03	1.34	−0.09	1.07	−0.06	1.23	0.23	0.80	0.11	1.64	−0.23	0.74	0.04	2.76	0.17	1.95
Abnormal, %	0	17	0	17	0	21	0	25	0	27	0	5	0	63	0	29
P value[b]	< 0.0001		0.0305		0.0013		0.913		0.0075		0.0077		< 0.0001		0.0179	

[a]Results shown are the median, mean, standard deviation (SD), and maximum temporal discrimination thresholds (TDTs) (in milliseconds [ms]); the mean combined TDT Z-score; and the proportion of individuals with abnormal TDTs in each age group.
[b]*P* values refer to a Mann-Whitney comparison of medians.

in a sister who was tested at ages 52 years and 56 years, the TDT *Z*-score increased from 1.3 to 2.66.

Age of onset of cervical dystonia

The 50th centile age of onset of 117 women with cervical dystonia was 47 years (mean age, 46.8 years; 95% CI, 44.7-48.9 years); and, for the 62 men, the age of onset was 41 years (mean age, 42.3 years; 95% CI, 39.3-45.4 years). The F:M ratio was 1.89 (see Supporting Fig. 2).

fMRI Study

fMRI analysis

Accuracy data (the mean ± SD percentage correct) were as follows: relatives with abnormal TDTs, 94.65% ± 5.84%; relatives with normal TDTs, 96.39% ± 4.39%. A pairwise comparison of accuracy scores did not reveal any significant difference ($P > 0.05$). Data from several participants did not pass the fMRI quality-control procedure (one relative with an abnormal TDT and two with normal TDTs), and those data are not presented here.

Relatives With Abnormal TDTs Versus Relatives With Normal TDTs

The largest difference in activation between relatives with abnormal TDTs versus relatives with normal TDTs was hypoactivation in the putamen contralateral to the stimulation (Supporting Table 1, Fig. 3). Relatives with abnormal TDTs also had hypoactivation of the left middle frontal gyrus and the left precentral gyrus compared with relatives who had normal TDTs. The BOLD response at the peak voxel in each significant region was then correlated with the TDT Z-score (the Bonferroni correction for multiple comparisons cutoff was set at $P < 0.0125$), and only the BOLD response in the putamen had a significant inverse correlation with the TDT *Z*-score (Supporting Table 1).

Discussion

In our large group of 192 healthy control participants, we identified both an age effect and a gender effect on the normal TDT. None of the control participants had an abnormal combined TDT result, indicating high specificity of the test. Previous studies have used control groups of ≤70 individuals without taking into account this significant gender difference. The prevalence of an abnormal TDT in unaffected female first-degree relatives of cervical dystonia patients increases steadily after age 25 years, with full penetrance after age 48 years. In unaffected brothers and sons, an abnormal TDT was observed in all age groups after age 25 years, and a mean of 20% of male relatives had an abnormal TDT (40% penetrance) without any evidence of increasing penetrance in the 5th decade. The evidence that an abnormal TDT becomes fully penetrant at the same age in unaffected female relatives (48 years) as the phenotype in our 117 women with cervical dystonia (median age of onset, 47 years) is consonant with the characteristics of a mediational endophenotype.[28] In 358 patients with cervical dystonia reported by the European Epidemiological Study Group, men had a significantly earlier mean age of onset at 39.2 years than women (42.9 years), and the F:M ratio was 1.4.[30] The gender ratio of the overall prevalence of an abnormal TDT in our unaffected first-degree relatives (F:M ratio, 28:17 [1.65]) also is congruent with that observed in the phenotype (1.89 in our cervical dystonia series). The differential effect of age and gender on the prevalence of the

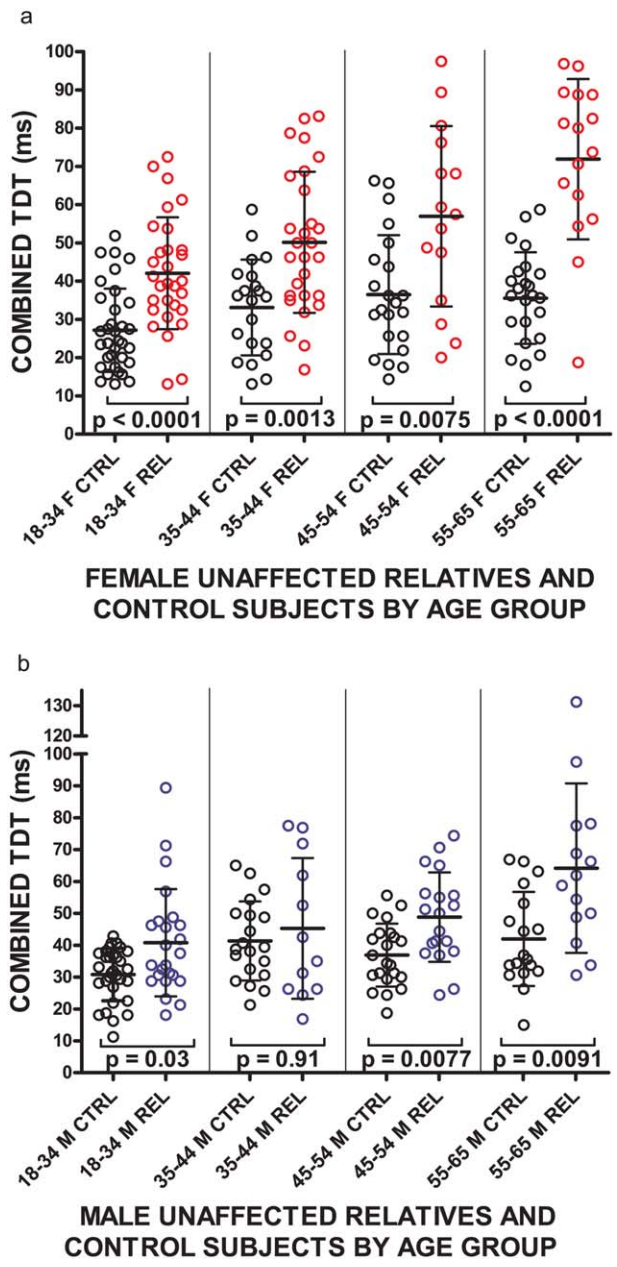

FIG. 1. (**a,b**) Combined temporal discrimination thresholds (TDTs) (in milliseconds) are illustrated for unaffected first-degree relatives of patients with cervical dystonia compared with the TDTs for healthy control participants according to age group and gender. Shown are the results for (**a**) female controls (F CTRL) (black circles) and relatives (F REL) (red circles) and for (**b**) male controls (M CTRL) (black circles) and relatives (M REL) (blue circles). The solid horizontal bars and error bars in the columns represent the mean TDT and standard deviation for each group, respectively. *P* values refer to a Mann-Whitney comparison of medians.

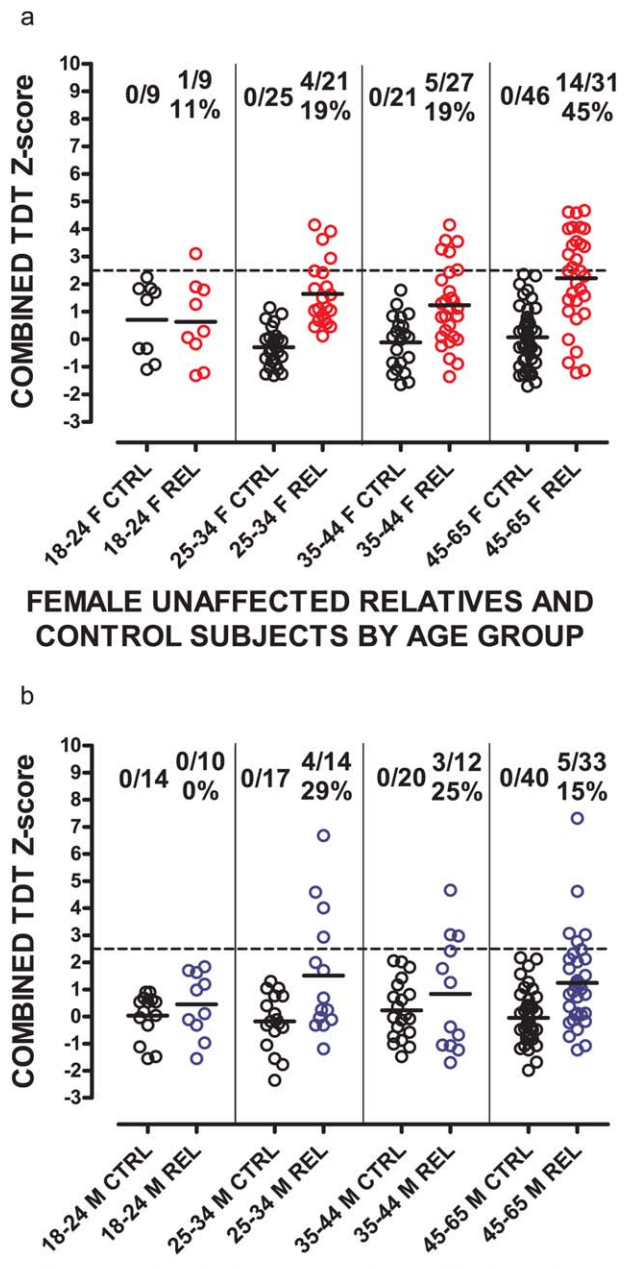

FIG. 2. (**a,b**) The frequency of combined abnormal temporal discrimination thresholds (TDTs) is illustrated in unaffected first-degree relatives of patients with cervical dystonia divided into subgroups according to age at testing and gender. The y-axis indicates the TDT *Z*-score (age and gender corrected). The horizontal dashed line indicates the upper limit of normal (TDT *Z*-score = 2.5). The number of abnormal TDTs out of the total number examined and the percentage of abnormal results for each age and gender group of unaffected first-degree relatives are indicated above each column. The solid bar in each column represents the mean TDT *Z*-score for each group. **(a)** TDT *Z*-scores of unaffected sisters and daughters (F REL) (red circles) are compared with the scores of female control participants (F CTRL) (black circles) for each age group. **(b)** TDT *Z*-scores of unaffected brothers and sons (M REL) (blue circles) are compared with the scores of control participants (M CTRL) (black circles) for each age group.

endophenotype, an abnormal TDT, is in keeping with the expression of an abnormal gene inherited in an autosomal dominant manner, which, however, is only fully penetrant in female carriers. The expression of the phenotype depends on other, as yet unknown factors, some of which may be environmental.[31-33] Except for writer's cramp, women are more frequently affected in all AOPTD phenotypes.[4,30,34] It has been suggested

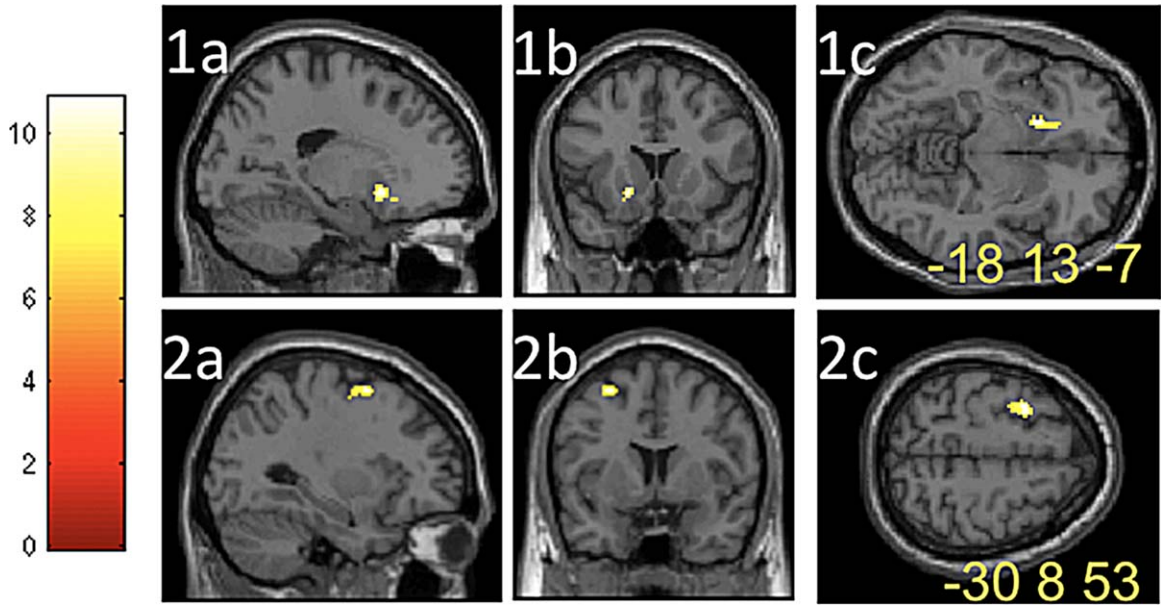

FIG. 3. This is a statistical parametric map of activation for unaffected first-degree relatives of patients with cervical dystonia who had abnormal temporal discrimination thresholds (TDTs) versus the activation for unaffected first-degree relatives with normal TDTs. The top row displays voxels in the putaminal region that were significantly hypoactive for relatives with abnormal TDTs versus relatives with normal TDTs in (**1a**) sagittal, (**1b**) coronal, and (**1c**) axial views. The bottom row displays voxels in the left frontal lobe that were significantly hypoactive for first-degree relatives with abnormal TDTs versus first-degree relatives with normal TDTs in (**2a**) sagittal, (**2b**) coronal, and (**2c**) axial views. The *F* value is depicted by the color scale. Voxels that indicated significance at $P < 0.001$ that were uncorrected for multiple comparisons are presented for display purposes; their coordinates (x/y/z) are given on the axial view images (1c and 2c) (see also Supporting Table 1).

that (1) higher awareness of symptoms among women, (2) genetic factors, and (3) increased exposure to environmental factors are possible factors leading to the higher prevalence of focal dystonia in women.[35] The evidence from this study suggests that epigenetic factors acting in men alone lead to reduced penetrance of the endophenotype and, thus, of the phenotype. While it remains speculative, epigenetic programming via nuclear hormone receptors may play a role.[36] Given full penetrance of the endophenotype in women, to increase power and specificity of an exploratory study of environmental factors in cervical dystonia, we would propose to compare affected women with their unaffected female siblings of similar or older age who have an abnormal TDT. The hypothesis is that there will be significant differences between the environmental experiences of women with cervical dystonia compared with their unaffected sisters who have abnormal TDTs.

We have also demonstrated that first-degree relatives of cervical dystonia patients with abnormal TDTs, in fMRI studies during a temporal discrimination task, have reduced activation in the putamen compared with relatives who have normal TDTs. The putamen was the only region that showed a significant negative correlation between TDT *Z*-scores and activation on fMRI: the greater the abnormality in temporal discrimination, the less the degree of putaminal activation. This is consistent with our previous finding of a structural abnormality by voxel-based morphometry in which relatives with abnormal TDTs had larger putamina than those with normal TDTs.[19] Accuracy rates did not differ between the two groups; therefore, the differences in brain activity cannot be attributed to differences in performance.

It has been proposed that temporal discrimination may be a cortical function[37]; however, in Parkinson's disease, dopamine replacement, but not subthalamic deep brain stimulation, improves temporal discrimination,[38] and fMRI studies in healthy individuals have shown that the putamen is involved in the early encoding of time intervals before the insula and dorsolateral prefrontal cortex are activated.[24,25] When two stimuli at varying short interstimulus intervals are recognized by participants as being distinctly asynchronous or synchronous, then putaminal activation occurs. The basal ganglia act as a default system for temporal discrimination unless there is perceptual uncertainty when prefrontal areas become engaged.[26] Abnormal temporal discrimination as a marker of putaminal dysfunction is highly relevant to the underlying concept of the pathogenesis of dystonia and is supported by our finding of a significant negative correlation between the degree of putaminal activation and performance on the TDT task. Impaired processing of time-dependent components of movement recently was reported in patients with writer's cramp during a temporal expectation task.[39] This adds to the evidence that perception and processing of time in relation to movement are affected in focal dystonia. Functional imaging studies would be necessary to define specific areas of activity during such a task.

Endophenotypes may highlight mechanisms of disease pathogenesis that are not obvious from the phenotype. ■

Conclusion

Our data add support to the hypothesis that an abnormal TDT is a mediational endophenotype in AOPTD. The assumed usefulness of endophenotypes rests upon the belief that the genetic basis of endophenotypes will be easier to analyze than that of the disease.[40] This study and the various studies of TDT in patients and relatives have demonstrated that the TDT is the most promising endophenotype in primary dystonia.

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