RESEARCH ARTICLE

Normal Temporal Discrimination in Musician's Dystonia Is Linked to Aberrant Sensorimotor Processing

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ABSTRACT: Objectives: Alterations in sensory discrimination are a prominent nonmotor feature of dystonia. Abnormal temporal discrimination in focal dystonia is considered to represent its mediational endophenotype, albeit unclear pathophysiological correlates. We examined the associations between the visual temporal discrimination threshold (TDT) and brain activity in patients with musician's dystonia, nonmusician's dystonia, and healthy controls.

Methods: A total of 42 patients and 41 healthy controls participated in the study. Between-group differences in TDT *z* scores were computed using inferential statistics. Statistical associations of TDT *z* scores with clinical characteristics of dystonia and resting-state functional brain activity were examined using nonparametric rank correlations.

Results: The TDT *z* scores of healthy controls were significantly different from those of patients with nonmusician's dystonia, but not of patients with musician's dystonia. Healthy controls showed a significant relationship between normal TDT levels and activity in the inferior parietal cortex. This relationship was lost in all patients. Instead, TDT *z* scores in musician's dystonia established additional correlations with activity in premotor, primary somatosensory, ventral extrastriate cortices, inferior occipital gyrus, precuneus, and cerebellum, whereas nonmusician's dystonia showed a trending correlation in the lingual gyrus extending to the cerebellar vermis. There were no significant relationships between TDT *z* scores and dystonia onset, duration, or severity.

Conclusions: TDT assessment as an endophenotypic marker may only be relevant to nonmusician forms of dystonia because of the lack of apparent alterations in musician's dystonia. Compensatory adaptation of neural circuitry responsible for TDT processing likely adjusted the TDT performance to the behaviorally normal levels in patients with musician's dystonia, but not nonmusician's dystonia. © 2020 International Parkinson and Movement Disorder Society

Key Words: laryngeal dystonia; mediational endophenotype; musician's focal hand dystonia; resting-state functional activity; singer's dystonia; writer's cramp

Task-specific focal dystonia (TSFD) is characterized by isolated dystonic movements that are associated with the performance of a precisely learned motor task. These motor behaviors require high levels of dexterity and development, which are accumulated throughout the years of practice of an instrument, singing, speaking, or writing. TSFD may manifest as an isolated symptom, yet it presents a significant lifelong burden of disability for the patient. The detailed understanding of TSFD multifactorial pathophysiological mechanisms is necessary for the development of enhanced approaches to its clinical management.

To that end, recent studies have consistently demonstrated common neuroimaging and subclinical alterations in different forms of TSFD. The latter has been characterized by an abnormally elevated temporal discrimination threshold (TDT) across different forms of dystonia.[1-3] Increased TDT levels have been associated with functional and structural changes in the middle frontal and primary somatosensory cortices in patients

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with laryngeal dystonia[1] as well as with the putaminal enlargement in the first-degree unaffected relatives of patients with familial adult-onset torsion dystonia.[4] Based on these findings, TDT alterations in focal dystonia have been considered to represent its mediational endophenotype, reflecting gene expression and sharing common pathogenetic mechanisms with the clinical phenotype of disorder.[5]

However, the paradoxical finding across different forms of dystonia was an observation of relatively normal TDT in musician's dystonia.[6] Healthy musicians have previously been found to exhibit improved performance on visual timing,[7] which may have in part supported conferral of this advantage during TDT performance in patients with musician's dystonia. Nonetheless, given the fact that the symptoms of musician's dystonia are posited to be driven by maladaptive brain plasticity,[8,9] the minimal TDT deficits in these patients remained counterintuitive. We hypothesized that the superior TDT performance in musician's dystonia correlates with the distinct pattern of disorganized brain activity, especially in regions controlling sensorimotor planning and preparation. In this study, we examined the associations between TDT performance, clinical characteristics, and functional brain activity using resting-state functional magnetic resonance imaging (fMRI) in patients with musician's dystonia (musician's focal hand dystonia and singer's dystonia) and nonmusician's dystonia (writer's cramp and laryngeal dystonia) compared with healthy individuals (both professional musicians and those without any prior musical training).

Methods

Participants

A total of 83 participants were recruited to the study, including 19 patients with focal musician's dystonia of hand or larynx, 23 patients with focal nonmusician's dystonia of hand or larynx, and 41 healthy controls, including both professional musicians and those without any musical training (see demographics in Table 1). The exclusion criteria included any neurological disorders (except for isolated focal dystonia in patients), any past or present history of psychiatric illness, or any history of brain, larynx, or hand surgery or trauma. Of 42 patients, 26 have been treated with at least 1 botulinum toxin injection in the course of their dystonia, with the average time from the last injection to study participation 45.9 ± 70.82 months (mean $\pm$ standard deviation). Given this timing, the effect of residual treatment on TDT performance or resting-state functional activity is highly unlikely. Clinically, all patients were fully symptomatic at the time of study participation and did not have any residual effects of botulinum toxin treatment, which was determined by neurological and laryngological examinations, as appropriate. In addition to botulinum toxin injections, all patients and healthy controls were screened for any other medications with the central effect, and those who received any of such medications were excluded from the study. All participants were tested for *DYT1*, *DYT4*, *DYT6*, and *DYT25* gene mutations, and none were carriers of any of these mutations. There were no statistical differences in age between the groups ($F_{2,80} = 1.69$, $P = 0.19$); however, the groups differed in sex ($F_{2,80} = 4.38$, $P = 0.02$) in part as a result of the disorder-characteristic sex prevalence in different forms of focal dystonia. However, this did not impact the final results because bivariate linear regression found a non-significant effect of sex on overall TDT z scores ($F_{1,81} = 2.52$, $P = 0.12$ with $R^2 = 0.03$).

All 83 participants completed visual TDT testing. Among these, 51 participants underwent a resting-state fMRI scan. All of the participants provided written informed consent, which was approved by the institutional

TABLE 1. Descriptive characteristics of all groups in the study sample

	Groups		TSFD Subgroups	
Demographics	Controls (n = 41)	TSFD (n = 42)	Musician's Dystonia (n = 19)	Nonmusician's Dystonia (n = 23)
Age	47.59 ± 12.34	53.02 ± 14.09	50.83 ± 13.53	54.47 ± 14.44
Sex, % female	43.9	43.3	16.6	61.1
Handedness	Right		Right	
Language	English		English	
Musical debut	9.88 ± 3.98	12.95 ± 10.94	12.95 ± 10.94	–
Dystonia duration	–	13.81 ± 10.08	10.89 ± 8.39	16.22 ± 10.88
Dystonia onset	–	37.93 ± 11.38	38.53 ± 11.56	37.43 ± 11.46
Dystonia severity				
BFM movement scale	–	3.17 ± 2.27	1.43 ± 1.07	3.03 ± 2.19
BFM disability scale		1.47 ± 1.02	0.73 ± 0.80	2.05 ± 0.78
Genetic status	No known dystonia mutations		No known dystonia mutations	

Age, musical debut, disease duration, and disease onset are shown in years ± standard deviations. All participants were tested for *DYT1*, *DYT4*, *DYT6*, and *DYT25* gene mutations.
TSFD, task-specific focal dystonia; BFM, Burke-Fahn-Marsden dystonia rating scale.

review board of Partners HealthCare Research Program. Data from some participants were reported in our previous studies.[6,10,11]

Temporal Discrimination Testing

Visual TDT was assessed using a custom-built device[12] that incorporated 2 light-emitting diode (LED) lights flashing at varying intervals. The participants were required to focus on a reference focal point at a distance of 70 cm, which was positioned along the center of their field of view. The device with the LED flashing lights was randomly placed to the right or left side of the participants' field of view at a constant distance of 10 cm from the reference focal point, as described previously.[1,4,6] For each trial, the participants were requested to assess the synchronicity of 2 LED illuminations. Within each trial, the 2 lights illuminated simultaneously and then proceeded in a stepwise fashion to be illuminated with the increasing 5-ms delay increments. The participants verbally reported their assessment as the "same" or "different" to indicate whether the illuminations were synchronous or asynchronous, respectively. To reduce the training and learning bias, each participants completed 18 trials, which were randomized for the left-side/right-side stimulus delivery configuration and the bottom/top start of the first LED illumination between trials within each subject as well as between subjects. The first of 3 consecutive correct assessments in each trial were considered as the interstimulus interval, representing the trial-specific TDT for each participant. The median TDT score of each trial from the left and right sides was computed to adjust for the practice effect, skewed data distribution, and potential outliers. These median scores were then averaged to derive the TDT score for each participant. Standardized z scores of the raw TDT scores were computed for a comparison between patients and controls as follows:

$$\text{TDT } z\,\text{Score} = \frac{\text{Patient-specific score} - \text{Control group mean}}{\text{Control group standard deviation}}$$

As reported previously,[13] age tends to have a significant effect on TDT scores. Therefore, to account for this potential effect, TDT z scores were computed separately for participants aged older than 50 years (n = 43) and younger than 50 years (n = 40).[4] An individual TDT z score ≥2.5 was considered abnormal.

TDT z scores in each group were found to be normally distributed (Kolmogorov-Smirnov/Lillierfor test, all $P \geq 0.15$). As shown in Table 2, there was a 7.23 ± 4.15-ms difference in raw TDT scores between healthy musicians and healthy nonmusicians. This difference, however, did not reach the statistical threshold to be considered significant between these 2 groups at $P = 0.10$, based on a 2-tailed independent t test. We therefore conducted between-group comparisons using a combined group of all healthy participants.

TABLE 2. Performance on temporal discrimination threshold score for all participants groups and subgroups

		Temporal Discrimination Threshold	
Groups	N	Raw Score, Mean ± SD	Mean z Score, Median (IQR)
Healthy controls	41	38.56 ± 13.27	0.22 (0.17, 1.82)
Professional musicians	9	32.92 ± 9.68	−0.22 (−0.27, 0.91)
Nonmusicians	32	40.15 ± 13.83	0.35 (0.21, 1.45)
Task-specific focal dystonia	42	48.36 ± 19.63	1.08 (0.41, 2.21)
Musician's dystonia	19	42.83 ± 14.10	0.56 (−0.07, 2.01)
Nonmusician's dystonia	23	52.93 ± 22.53	1.51 (1.35, 3.18)

SD, standard deviation; IQR, interquartile range.

One-way analysis of variance examined the overall group difference between healthy controls, patients with musician's dystonia, and patients with nonmusician's dystonia at an a priori significance level of $P \leq 0.05$. The follow-up Scheffé post hoc tests examined group differences in TDT z scores between healthy controls and patients with musician's dystonia and between healthy controls and patients with nonmusician's dystonia at a corrected $P \leq 0.025$ to account for multiple comparisons. As a secondary, exploratory analysis, the independent t test assessed the difference in TDT z scores between patients with musician's and nonmusician's dystonia.

In addition, information about dystonia onset and duration was collected during neurological evaluation. Dystonia severity was assessed using the Burke-Fahn-Marsden dystonia rating scale, which comprises a movement scale of dystonia provoking and severity factors (scored 0–4 based on the neurological examination) and a disability scale (scored 0–4 based on the patient's opinion of his/her disability in daily activities).[14] Correlations between TDT z score and dystonia age of onset, duration, and severity were examined using a Kendall's τ rank correlation coefficient test, which is applied using a Bayesian framework to provide evidence for the hypothesis that these measures are significantly related. The significance level was set at $P \leq 0.017$ to correct for multiple comparisons.

MRI

To determine the neural correlates of normal and abnormal TDT in the healthy and patient groups, respectively, an MRI scan was acquired on a 3 Tesla Siemens Skyra (Erlangen, Germany) scanner equipped with a 32-channel head coil. During resting-state fMRI, all participants were instructed to rest in the scanner with their eyes closed without falling asleep and to avoid thinking of anything in particular. Functional data were obtained using a single-shot echo-planar imaging gradient-echo sequence (repetition time (TR) = 1000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FOV) = 240 mm, voxel

size = 2.2 mm^3, 70 slices covering the whole brain, 300 volumes, acquisition time 5.11 minutes). A whole-brain T1-weighted image was acquired using the MP2RAGE sequence (TR = 4000 ms, TE = 1.9 ms, inversion time TI_1/TI_2 = 633/1860 ms, FOV = 186 × 162 mm, voxel size = 1.0 mm isotropic, 2 averages) as an anatomical reference. Each participants' head was tightly cushioned within the coil to avoid movements during scanning.

Resting-state fMRI in all participants was processed using FSL and AFNI software. Briefly, the first 4 volumes were removed because of potential T1 stabilization effects. The images were motion corrected, slice-time corrected, high-pass filtered using a cut-off frequency of 0.01 Hz, smoothed using a Gaussian kernel full-width at half-maximum of 5 mm, registered to the participants' anatomical scan, and normalized to the AFNI standard Talairach-Tournoux space (TT_N27 template) using a nonlinear algorithm. Control for motion artifacts included regression of motion parameters, censoring of TR, and additional censoring of outlier TRs. Motion regression was based on 6 motion parameter estimates calculated during realignment of the echo-planar imaging volumes that were included as covariates of no interest and 3 quadratic polynomials that were used to model baseline drifts for the imaging run. TR censoring included exclusion of TR pairs where the Euclidean norm of the motion derivative exceeded 0.3. Outlier censoring included exclusion of a TR when more than 10% of the automasked brain were marked as outliers. Because outliers may capture residual motion in some cases where the motion parameters do not, this combined approach ensured the stringent exclusion of TRs containing motion artifacts. The final images across all participants were concatenated and decomposed to extract the sensorimotor network components. The group-averaged sensorimotor components were concatenated and used in a dual regression to generate subject-specific spatial maps and associated time series. Finally, the subject-specific spatial maps were concatenated across participants within each group to create a 3-dimensional +subject dataset and resampled to match the same grid spacing and orientation. Whole-brain voxelwise Spearman's rank correlation coefficients were computed between these functional datasets and individual TDT z scores within each group to assess their significant associations at a family-wise error (FWE)-corrected $P \leq 0.05$, with the voxelwise threshold at $P \leq 0.005$, 7 corresponding to $R_s \geq 0.6643$, and a minimum cluster size of 48 voxels (384 mm^3) as determined by the 3dClustSim program of the AFNI software.

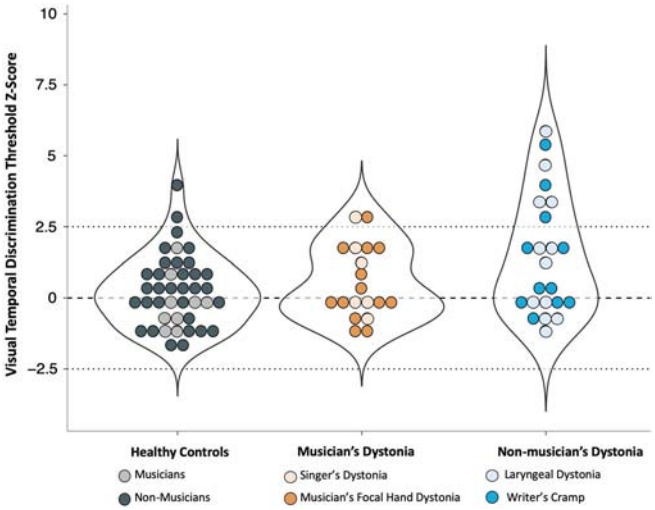

FIG. 1. Visual temporal discrimination threshold z score in healthy controls, patients with musician's dystonia, and patients with nonmusician's dystonia. A z score equal or greater than ±2.5 was considered abnormal as indicated by a horizontal dotted line. For the range of values, see Table 2.

Results

Sensory Processing

Consistent with the previous findings,[1,2,15] the raw TDT score of the control group was 38.56 ± 13.27 ms, although 2 of the 41 healthy participants (4.9%) had slightly elevated z scores (Fig. 1, Table 2). The TSFD patients had an overall increased raw TDT score at 48.36 ± 19.63 ms, with 9 of 42 patients (21.4%) showing abnormal TDT levels. Among these were 2 of 19 patients with musician's dystonia (10.5% of the group, mean score ± standard deviation: 42.83 ± 14.10 ms) and 7 of 23 patients with nonmusician's dystonia (30.4% of the group, mean score ± standard deviation: 52.93 ± 22.53; Fig. 1, Table 2). This represented a 3-fold increase in the number of patients with nonmusician's dystonia who had TDT abnormalities when compared with patients with musician's dystonia and a 6-fold increase when compared with healthy participants.

An initial 1-way analysis of variance comparing the TDT z scores between all groups found a significant group effect ($F_{2,80}$ = 5.22, P = 0.007). Using the Scheffé post hoc criterion for significance, the follow-up analysis showed that the TDT z score was significantly increased in patients with nonmusician's dystonia when compared with healthy controls (95% confidence interval, −1.29 to −2.29; P = 0.008), but not in patients with musician's dystonia when compared with healthy controls (95% confidence interval, −1.40 to 0.73; P = 0.74). The exploratory independent t test determined a significantly increased TDT z score in patients with nonmusician's dystonia when compared with patients with musician's dystonia (t_{37} = 1.82, P = 0.04).

Correlation of Temporal Discrimination with Clinical Measures

There were no significant correlations of TDT z scores with dystonia onset (r_τ = −0.07 to 0.16, $P \geq 0.30$) or

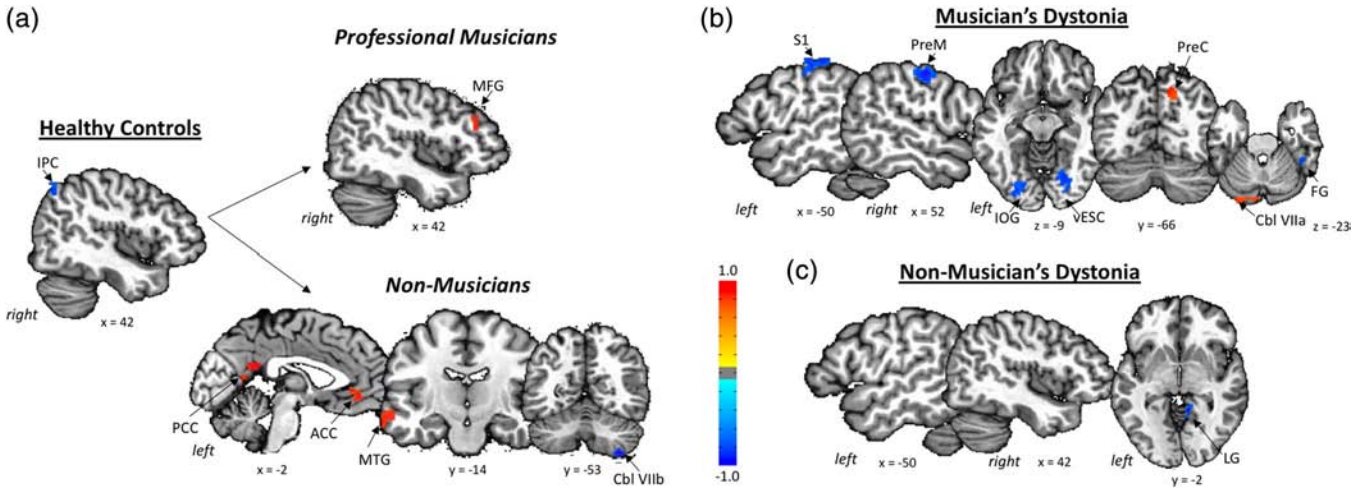

FIG. 2. Associations between visual temporal discrimination threshold *z* score with resting-state functional activity in (a) healthy controls, (b) musician's dystonia, and (c) nonmusician's dystonia. The color bar indicates the R_s values. For the cluster peak coordinates, cluster volume, and R_s score, see Table 3. ACC/PCC, anterior/posterior cingulate cortex; Cbl, cerebellum; FG, fusiform gyrus; IOG, inferior occipital gyrus; IPC, inferior parietal cortex; LG, lingual gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; PreM, premotor cortex; PreC, precuneus; S1, primary somatosensory cortex; vESC, ventral extrastriate cortex; VIIa, cerebellum, lobule VIIa.

duration of disorder (r_τ = −0.25 to 0.02, $P \geq 0.17$) in either musician's dystonia or nonmusician's dystonia. Similarly, the assessment of the relationship between TDT *z* score and dystonia severity on the Burke-Fahn-Marsden dystonia rating scale did not find a statistical significance in either patient group (all r_τ = −0.23 to 0.24, $P \geq 0.12$).

Correlation of Temporal Discrimination with Resting-State Brain Activity

Abnormalities in resting-state function activity and connectivity in patients with musician's and nonmusician's dystonia were reported in our previous articles.[10,11] In this study, voxelwise correlations between TDT *z* scores and resting-state brain activity were examined within each group. A negative correlation signified a shorter (normal) TDT *z* score.

Healthy controls, including both professional musicians and nonmusicians, showed a significant negative correlation between resting-state brain activity and TDT performance in the right inferior parietal cortex (angular gyrus, area PGa/PGp; cluster peak R_s = − 0.83, corrected $P \leq 0.05$) (Fig. 2a, Table 3). In addition, healthy professional musicians had a significant positive correlation between neural activity and TDT performance in the right middle frontal gyrus (cluster peak R_s = 0.98, corrected $P \leq 0.05$), whereas healthy nonmusicians showed a negative correlation in the right cerebellum (lobule VIIb, cluster peak R_s = −0.97) and positive correlations in bilateral anterior cingulate cortex (cluster peak R_s = 0.88), posterior cingulate cortex

TABLE 3. Neural correlates of temporal discrimination threshold in healthy controls and patients with task-specific focal dystonia

Group	Cluster Anatomical Location	Cluster Peak Coordinates *x y z*			Cluster Volume, mm^3	Cluster Peak R_s Score
Healthy controls	R inferior parietal cortex (area PGa/PGp)	44	−64	43	384	−0.83
Professional musicians	R middle frontal gyrus	46	30	31	488	0.98
Nonmusicians	L/R anterior cingulate cortex	−2	36	−7	800	0.88
	L/R posterior cingulate cortex	−3	−51	20	920	0.95
	L middle temporal gyrus	−58	−14	−7	792	0.97
	R cerebellum (lobule VIIb)	34	−56	−53	392	−0.97
Patients with musician's dystonia	R premotor cortex (area 6)	52	−12	43	1888	−0.90
	R ventral extrastriate cortex (area hOC3v)	20	−72	−7	1368	−0.83
	R precuneus	12	−66	43	480	0.84
	L inferior occipital gyrus (area hOC4v)	−24	−80	−9	760	−0.85
	L cerebellum (lobule VIIa Crus I)	−14	−82	−25	672	0.80
	L primary somatosensory cortex (area 1)	−50	−24	49	584	−0.86
Patients with nonmusician's dystonia	R lingual gyrus/cerebellar vermis	8	−46	−1	616	−0.86

R, right; L, left.

(cluster peak R_s = 0.95), and left middle temporal gyrus (cluster peak R_s = 0.97), all at a corrected $P \leq 0.05$ (Fig. 2a, Table 3).

Patients with musician's dystonia had no significant relationships between their TDT z score and resting-state activity in either the inferior parietal cortex or middle frontal gyrus (Fig. 2b,c, Table 3). However, they showed significant negative correlations in the right premotor cortex (area 6; cluster peak R_s = −0.90), ventral extrastriate cortex (area hOC3v; cluster peak R_s = − 0.83), left inferior occipital gyrus (area hOC4v; cluster peak R_s = −0.85), and left primary somatosensory cortex (area 1; cluster peak R_s = −0.86) as well as significant positive correlations in the right precuneus (cluster peak R_s = 0.84) and left cerebellum (lobule VIIa, Crus I; cluster peak R_s = 0.80), all at a corrected $P \leq 0.05$ (Fig. 2b, Table 3).

There were no significant correlations between TDT performance and resting-state brain activity in patients with nonmusician's dystonia at the a priori set significance voxelwise threshold of $P \leq 0.005$ and overall FWE–corrected $P \leq 0.05$. When the voxelwise significance was lowered to $P \leq 0.01$, a negative correlation emerged between TDT z score and activity in the right lingual gyrus, extending to the cerebellar vermis (cluster peak R_s = −0.86) in patients with nonmusician's dystonia (Fig. 2c, Table 3).

Discussion

Alterations in sensory discrimination have been consistently reported as one of the prominent nonmotor features of dystonia (eg, refs. 1,4,16-18). Among these, abnormally elevated visual TDT is considered as the mediational endophenotype of dystonia based on evidence of its presence across different forms of dystonia, penetrance in unaffected relatives of dystonia patients, and independence from symptom severity and clinical expression.[5,19] In line with this, we found that there are no significant associations between TDT performance and the severity of symptoms, disorder duration, or age of onset across different focal dystonias. However, we established the presence of variable abnormalities in temporal discrimination that are linked to the clinical diversity of dystonia manifestation. Specifically, stratification of patients based on their clinical phenotype allowed us to confirm [2,6] that the nonmusician's dystonia cohort has characteristically and abnormally increased levels of temporal discrimination, whereas patients with musician's dystonia exhibit overall normal TDT. We therefore suggest that clinical assessment of TDT as a dystonia-relevant endophenotypic marker might be relevant only to nonmusician forms of dystonia because of the lack of apparent alterations of TDT levels in musician's dystonia.

The normal range of temporal discrimination in patients with musician's dystonia may be grounded in their long-term musical skill acquisition. Musical training has been shown to have a positive impact on timing-based visual and auditory discriminatory behaviors.[7,8] It is plausible that, while performing temporal discrimination of the visual timing task, patients with musician's dystonia harnessed their inherently improved timing abilities for achieving behaviorally normal TDT levels. Alternatively, given the fact that both healthy professional musicians and nonmusicians had similar TDT levels, the discriminatory ability, as tested with this visual TDT paradigm, may not be influenced by musical history, and alterations in discriminative ability are not the substrate for maladaptive plasticity to occur in patients who develop musician's dystonia.

Notably, the neural correlates of behaviorally normal TDT in patients with musician's dystonia appear to be dissociated from those contributing to normal temporal discrimination in healthy individuals. In particular, we found that TDT in healthy participants, including both healthy professional musicians and nonmusicians, was correlated with brain activity in the right angular gyrus within the inferior parietal cortex. It has been shown that the learning of new skills, which require higher level motor-effector integration and the coordination of complex visual motion, leads to training-induced structural plasticity of the angular gyrus,[20] and the stimulation of the right parietal cortex enhances the accuracy of temporal discrimination.[21] Being central to processing and integration of multimodal sensorimotor information, this region contributed to the control of high spatial cognition, prospective memory retrieval, and spatiovisual attention,[22] all of which are relevant to the performance of a visual discrimination task and were found to be impaired in focal dystonia.[1,23-26]

In addition to the inferior parietal cortex, healthy musicians and healthy nonmusicians showed correlations between TDT and distinct sets of brain regions that are known to be functionally or structurally connected with the inferior parietal cortex.[27] In musicians, these included the middle frontal gyrus as a higher order cognitive center of spatial processing and short-term memory storage,[28] and in nonmusicians, the cingulate cortex for relevant conflict monitoring,[29] the middle temporal cortex for perceptual memory and gaze direction,[30,31] and the cerebellum for selective and divided attention, anticipation, and working memory.[32,33] Thus, the TDT neural associations in healthy professional musicians maybe linked to the distinct pattern of intrinsic brain reorganization that is necessary for enhanced plasticity and advanced processing of sensorimotor integration underlying fine control of highly skilled musical proficiency.[7,8,34-36] Conversely, long-term buildups of diverse memory reservoirs and error

feedback appear to be part of the neural TDT association pattern in healthy nonmusicians.

Taking into account these findings in healthy individuals, the correlations between temporal discrimination and inferior parietal activity as well as any other brain regions present in healthy individuals were lost in nonmusician's dystonia, likely leading to abnormally increased TDT in these patients. Abnormal structural organization, functional activity, and connectivity of the inferior parietal cortex, including the angular gyrus, have been increasingly implicated in the pathophysiology of focal hand dystonia and laryngeal dystonia.[10,37-39] Vulnerable parietal–premotor functional connectivity has been associated with the polygenic risk of dystonia,[40] whereas maladaptive plasticity of the inferior parietal cortex has been related to the loss of inhibition as a result of reduced gamma-aminobutyric acid (GABA)-ergic function.[41] A failure to integrate the inferior parietal cortex into the processing of temporal discriminatory information provides yet another clue about the importance of this region in the multifactorial pathophysiology of focal dystonia. Furthermore, patients with nonmusician's dystonia did not show additional compensatory adaptation for neural processing of discriminatory information, for example, by capitalizing additional working memory resources for temporal discrimination, as present in healthy individuals.

On the contrary, in musician's dystonia, the loss of associations between temporal discrimination and neural activity of the inferior parietal cortex and middle frontal gyrus was counterbalanced by the gain of such associations in other brain regions that are responsible for the control of somatosensory stimuli (primary somatosensory and visual cortex), visuospatioal attention (precuneus), and motor preparation (premotor cortex). As the angular gyrus is directly connected with visual, dorsal premotor, and superior parietal cortices,[27,42-44] the compensatory pathological activation of these regions within the same neuroanatomical network in musician's dystonia may be the result of an inability of the key region (the angular gyrus) to process temporal discrimination. Another interesting observation in patients with musician's dystonia was the additional involvement of the cerebellum, which, contrary to other regions, showed a positive relationship between increased cerebellar activity and increased TDT threshold. The cerebellum sends a disynaptic output to the inferior parietal cortex, potentially directly influencing its activity that pertains to sensory recalibration during multimodal information processing.[45]

Taken together, these 2 forms of TSFD may involve divergent neural correlates underlying the ability to process and discriminate temporal information. Abnormal TDT levels in patients with nonmusician's dystonia may be related to more susceptible neural network that was unable to adaptively compensate for the loss of normal regional TDT associations. Conversely, a distinct pattern of abnormal losses and gains of regional associations with TDT processing may have contributed to the behaviorally normal levels of temporal discrimination in patients with musician's dystonia. ■

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