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ORIGINAL COMMUNICATION

Sensory processing in the auditory and olfactory domains is normal in laryngeal dystonia

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Abstract

Abnormal sensory discriminatory processing has been implicated as an endophenotypic marker of isolated dystonia. However, the extent of alterations across the different sensory domains and their commonality in different forms of dystonia are unclear. Based on the previous findings of abnormal temporal but not spatial discrimination in patients with laryngeal dystonia, we investigated sensory processing in the auditory and olfactory domains as potentially additional contributors to the disorder pathophysiology. We tested auditory temporal discrimination and olfactory function, including odor identification, threshold, and discrimination, in 102 laryngeal dystonia patients and 44 healthy controls, using dichotically presented pure tones and the extended Sniffin' Sticks smell test protocol, respectively. Statistical significance was assessed using analysis of variance with non-parametric bootstrapping. Patients had a lower mean auditory temporal discrimination threshold, with abnormal values found in three patients. Hyposmia was found in 64 patients and anosmia in 2 patients. However, there were no statistically significant differences in either auditory temporal discrimination threshold or olfactory identification, threshold, and discrimination between the groups. A significant positive relationship was found between olfactory threshold and disorder severity based on the Burke–Fahn–Marsden dystonia rating scale. Our findings demonstrate that, contrary to altered visual temporal discrimination, auditory temporal discrimination and olfactory function are likely not candidate endophenotypic markers of laryngeal dystonia.

Keywords Sensory discrimination · Threshold · Endophenotype · Dystonia

Introduction

Laryngeal dystonia (LD) is an isolated focal dystonia characterized by involuntary contractions of the laryngeal muscles and concomitant strained-strangled or breathy voice quality, predominantly during speech production. Although the exact pathophysiology of this disorder is unclear, several lines of evidence point to abnormal sensory processing in addition to altered motor control [6, 15, 29]. Previous studies in LD patients have determined abnormally elevated temporal discrimination thresholds following visual and proprioceptive stimulation, which is in line with similar alterations found in the majority of other forms of isolated dystonia [2, 27, 30]. Altered visual temporal discrimination has been further associated with structural and functional changes in the primary somatosensory and middle frontal cortices, implicating their pathophysiological relevance [30]. However, spatial tactile discrimination has been found to be normal in LD, and temporal visual discrimination has been reported within the normal range in the subtype of LD, singer's dystonia [20, 22, 30]. While altered sensory discrimination is considered an endophenotypic marker of isolated dystonia [19], these diverging findings point to the presence of *sensory domain-specific* alterations that appear to be linked to *dystonia form-specific* characteristics.

In this study, we expanded our investigation of sensory processing in LD to determine the involvement and extent of alterations in other sensory domains as potential contributors to the disorder pathophysiology. We examined the auditory

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temporal discrimination thresholds (aTDT) because of the relevance of sound processing to speech production [13] and the olfactory function, including odor identification, threshold, and discrimination (ITD) because of possible deficits of odorant signaling associated with dystonia gene mutations [12, 25]. We hypothesized that auditory discrimination would be abnormally elevated, and the olfactory function diminished in LD patients compared to healthy individuals.

Methods

Study participants

A total of 102 patients with isolated focal LD (54.8 ± 12.4 years old, 82 females/20 males) and 44 healthy controls (50.4 ± 9.5 years old, 29 females/15 males) participated in this study (see detailed demographics in Table 1). None of the participants had any history of neurological (except focal LD and co-occurring dystonic tremor), psychiatric, or laryngeal disorders. All participants had normal cognitive function scoring ≥ 27 points on the Mini-Mental State Examination. Patients who received botulinum toxin injections participated in the study at least 3 months after the last injection and were fully symptomatic at the time of testing. All participants were negative for *TOR1A*/DYT1, *TUBB4A*/DYT4, *THAP1*/ DYT6, *GNAL*/DYT25 mutations. No participant was on any centrally acting medications. No participant reported a hearing loss that would have impacted auditory testing. One patient reported a history of sinus surgeries and was excluded from the analysis of olfactory function. Another patient was unable to complete olfactory testing and was excluded from the analysis of olfactory function. The final cohort of 100 patients (54.8 ± 12.5 years, 80 females/20 males) was included in the statistical analysis of olfactory function.

Experimental procedures

For the aTDT testing, pairs of pure tones (400 ms, 950 Hz) were presented dichotically to participants through the headphones at 2.4-s intervals. Tones were first presented simultaneously to both ears and then gradually separated by delaying the signal in 10-ms steps in either the left or right ear, randomized between subjects. Participants were instructed to verbally state after each pair of presented tones whether the tones were played at the same or different times by saying either "same" or "different". A trial was complete once the participant responded "different" three consecutive times, which was considered the individual aTDT for that trial. Each participant completed three trials. The median value across the three trials was computed as the individual aTDT score. The aTDT scores were then converted into the standardized *Z*-scores relative to the healthy control group according to the formula:

$$Z\ score = \frac{Patient\ aTDT - Control\ mean\ aTDT}{Control\ standard\ deviation\ aTDT}$$

. *Z*-scores ≥ 2.0 were considered abnormal.

Olfactory testing was carried out using the extended Sniffin' Sticks smell test protocol [18] with the separate tests for odor identification, threshold, and discrimination. All participants were blindfolded during testing. In all tests, the Sniffin' Sticks pens were presented at a 1–1.5-cm distance from the participant's nose for 3 s. The pens were presented one at a time, and 10 s were given between successive pen presentations.

The olfactory identification test included 16 pens with everyday smells, which the participants were asked to name using a card with 4 odorant choices. The maximum possible

Table 1 Demographic and clinical characteristics

	Laryngeal dystonia	No family history of dystonia		Family history of dystonia		Healthy controls
		ADLD	ABLD	ADLD	ABLD	
N of participants	102	40	32	23	7	44
Age (years)	54.8 ± 12.4	55.6 ± 10.6	52.5 ± 12.5	56.8 ± 14.5	53.7 ± 15.3	50.4 ± 9.5
Sex (female/male)	82/20	29/11	28/4	20/3	5/2	29/15
Cognitive status	Mini-mental state examination ≥ 27					
Genetic status	Negative for *TOR1A*/DYT1, *TUBB4A*/DYT4, *THAP1*/ DYT6, *GNAL*/DYT25 mutations					
Dystonia onset (years)	39.9 ± 13.4	43.3 ± 11.8	38.2 ± 12.6	36.5 ± 16.4	39.9 ± 12.9	NA
Dystonia duration (years)	14.9 ± 10.7	12.5 ± 9.1	14.4 ± 9.2	20.3 ± 13.9	13.9 ± 8.7	NA
BFMDRS score	4.3 ± 2.8[a]	3.5 ± 1.3	4.3 ± 2.6	5.2 ± 4.1[a]	5.4 ± 3.7	NA
Symptom self-evaluation score	7.3 ± 2.2[a]	7.0 ± 2.1	7.6 ± 2.0	7.1 ± 2.6[a]	7.6 ± 1.5	NA

s.d. standard deviation, *ADLD* adductor laryngeal dystonia, *ABLD* abductor laryngeal dystonia, *BFMDRS* Burke-Fahn-Marsden Dystonia Rating Scale

[a]Data missing in one patient. Demographic and clinical values are presented as mean ± s.d., as applicable

score for the olfactory identification test was 16 points, reflecting the correct identification of all odors.

The olfactory threshold test included 16 triplet pens (16 dilutions of *n*-butanol and 32 blanks), which were presented to the participants as a set of 1 with *n*-butanol odorant and 2 blanks. The participants were asked to verbally choose which pen contained the odorant. The first set presented to the participant contained the pen with the highest *n*-butanol concentration, followed by the next sets of pens with gradually decreasing *n*-butanol concentration after three consecutive correct answers. If the participants provided three consecutive incorrect answers, they were presented with the previous concentration level until three consecutive correct responses were received. The lowest detected *n*-butanol concentration at which the participant gave three consecutive correct answers was recorded as an individual olfactory threshold. The maximum possible score for the olfactory threshold test was 16 points, reflecting the highest sensitivity to odor.

The olfactory discrimination test included 48 pens (16 triplets of odorants, each with 1 pen of distinct odor and 2 pens of the same odor). The participants were asked to verbally differentiate between the same and different odors after each set of presented pens by saying either "same" or "different". The number of times the participant correctly identified the distinct odor was marked as a correct response. The maximum possible score for the olfactory discrimination test was 16 points, reflecting the best odor discriminatory ability.

The individual olfactory ITD score was calculated as a sum of each participant's odor identification, threshold, and discrimination values. The ITD score of 31–48 was considered normosmia, 30–16 hyposmia, and < 15 anosmia [18].

Statistical analysis

Contrary to the previous studies reporting age-dependent differences in temporal discrimination thresholds [2, 7], no within-group differences were found between participants who were younger vs. older than 50 years in either group (HC: $W = 271$, $p = 0.47$, LD: $W = 761$, $p = 0.11$). Therefore, the experimental groups were not divided based on age for statistical analysis. However, between-group age differences were found in healthy controls and LD patients ($t_{144} = -2.09$, $p = 0.04$). In addition, the duration of dystonia was different between LD patients with and without a family history of dystonia ($t_{100} = -2.41$, $p = 0.02$). Therefore, these variables were added as covariates of no interest in statistical analysis, as applicable.

Shapiro–Wilk tests found that standardized auditory threshold *Z*-scores were non-normally distributed in either healthy controls ($W = 0.86$, $p \leq 0.0001$) or LD patients ($W = 0.82$, $p \leq 0.0001$). Similarly, Shapiro–Wilk tests found that the olfactory identification scores were non-normally distributed in LD patients ($W = 0.78$, $p \leq 0.0001$); the olfactory threshold scores were non-normally distributed in healthy controls ($W = 0.90$, $p = 0.001$) and LD patients ($W = 0.96$, $p = 0.005$), and the olfactory discrimination scores were non-normally distributed in LD patients ($W = 0.94$, $p \leq 0.0001$). Because all statistical comparisons of interest included at least one group that did not satisfy the assumption of normality, group comparisons were carried out using the analysis of variance (ANOVA) testing framework with non-parametric bootstrapping, with age and dystonia duration as nuisance covariates. Null distributions for each comparison were generated by calculating the *F*-statistic for the group effect in 10,000 bootstrapped samples after centering each comparison group at the mean of the total sample [10]. Nonparametric bootstrapped *p*-values were derived by comparing the *F*-statistic from the sample with this distribution and corrected for multiple comparisons by controlling the false discovery rate (FDR). The frequency rates of abnormal aTDT and olfactory ITD between healthy controls and LD patients were compared using Chi-square association tests at $p \leq 0.05$.

Finally, the relationships between aTDT/olfactory ITD and LD clinical characteristics (dystonia duration, age of onset, symptom severity) were computed using Spearman's coefficients at $p \leq 0.05$. LD severity was assessed using the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) and patients' self-evaluation of their overall voice effort during speaking using a visual analog scale of severity from 0 (no effort) to 10 (constant struggle) [26].

Results

In healthy controls, the mean aTDT was 45.5 ± 30.3 ms, with a mean *Z*-score of 0 (Table 2) (Fig. 1A, Table 2). In LD patients, the mean aTDT was lower at 39.7 ± 28.9 ms, with a mean *Z*-score of − 0.19. Abnormal aTDT was found in 2 out of 44 healthy controls (all *Z*-score = 2.79) and 3 out of 102 LD patients (*Z*-score range = 2.46 to 3.78). There were significant differences in aTDT from the first to the third trial toward improved auditory discrimination (all $\chi^2 \geq 12.9$, $p \leq 0.008$). However, these differences were present in both healthy and patient groups, likely reflecting a learning adaptation to auditory stimuli not specific to the disorder. Statistical comparisons between the groups showed that there were no significant differences in either aTDT *Z*-scores ($F_{1,143} = 1.76$, $p = 0.19$) or the frequency of these abnormalities between the groups ($\chi^2 = 0.22$, $p = 0.64$) (Fig. 1A). Moreover, compared to healthy controls, no significant differences were found in either LD patients with different phenotypes ($F_{2,141} = 2.51$, $p = 0.10$) or LD patients with and without a familial history of dystonia ($F_{2,141} = 1.61$, $p = 0.23$). There were no significant correlations between

Table 2 Auditory and olfactory processing in patients with laryngeal dystonia and healthy controls

	Auditory processing			
	Threshold (ms)	Mean *Z*-score	*Z*-score range	Group abnormal frequency
Healthy controls	45.5 ± 30.3	0.0	− 1.17 to 2.79	2 (4.5%)
LD patients	39.7 ± 28.9	− 0.19	− 1.17 to 3.78	3 (2.9%)
ADLD	44.8 ± 33.0	− 0.02	− 1.17 to 3.78	3 (4.8%)
ABLD	31.5 ± 18.1	− 0.46	− 1.17 to 1.47	0 (0%)
Sporadic LD	42.6 ± 31.6	− 0.93	− 1.17 to 3.78	3 (4.2%)
Familial LD	32.7 ± 19.6	− 0.42	− 1.17 to 1.14	0 (0%)

	Olfactory processing				
	Identification	Threshold	Discrimination	Composite ITD score	Group abnormal frequency
Healthy controls	12.4 ± 2.0	5.5 ± 1.8	10.9 ± 2.1	28.9 ± 3.7	33 H (75%)
LD patients	12.4 ± 2.3	5.5 ± 2.2	10.2 ± 2.3	28.1 ± 4.9	63 H (63%)/2 A (2%)
ADLD	12.7 ± 1.8	5.6 ± 2.0	10.5 ± 1.9	28.7 ± 4.3	39 H (63.9%)
ABLD	12.0 ± 2.9	5.5 ± 2.5	9.7 ± 2.8	27.2 ± 5.7	24 H (61.5%)/2 A (5.1%)
Sporadic LD	12.5 ± 2.6	5.4 ± 2.1	10.2 ± 2.4	28.1 ± 5.2	2 A (2.9%)
Familial LD	12.2 ± 1.6	5.8 ± 2.5	10.0 ± 2.2	28.1 ± 4.1	22 H (73.3%)

s.d. standard deviation, *ADLD* adductor laryngeal dystonia, *ABLD* abductor laryngeal dystonia, *LD* laryngeal dystonia, *H* hyposmia, *A* anosmia. Auditory threshold and olfactory processing values are presented in mean ± s.d., as applicable. Sporadic—absence of a family history of dystonia, Familial—presence of a family history of dystonia

the aTDT *Z*-score and clinical features of LD (all $R_s \leq 0.17$, all $p \geq 0.09$).

Related to the olfactory function, 32 out of 44 healthy controls and 63 out of 100 LD patients were found to have hyposmia (ITD range 30–16), and 2 LD patients had anosmia (ITD range 13–11) (Fig. 1B, Table 2). However, there were no significant differences in olfactory identification ($F_{1,141} = 0.02$, $p = 0.89$), threshold ($F_{1,141} = 0.07$, $p = 0.77$), discrimination ($F_{1,141} = 1.92$, $p = 0.18$), or the frequency of total olfactory ITD score ($\chi^2 = 2.47$, $p = 0.29$) between LD patients and controls. Neither LD phenotypes nor the presence/absence of a familial history of dystonia showed significant differences from healthy controls in the olfactory ITD score (all $F_{2,141} \leq 2.71$, $p \geq 0.11$). A significant positive relationship was found between olfactory threshold and BFM-DRS score in LD patients ($R_s = 0.45$, $p = 3.4^{-6}$) (Fig. 1C).

Discussion

We demonstrate that in LD patients, sensory processing within the auditory and olfactory domains is within the normal ranges compared to healthy individuals. Although subtle sensory alterations have been implicated as potential endophenotypic markers of isolated dystonia [2, 16, 19, 27], our findings suggest that these abnormalities are likely dystonia form-specific. That is, abnormal sensory processing within the same domain (e.g., olfactory, auditory, visual) does not appear to represent an overarching pathophysiological feature across all forms of dystonia. For example, visual temporal discrimination processing has been reported to be abnormally delayed in all forms of dystonia, except musician's dystonia [2, 3, 7, 11, 20, 22, 31]. Conversely, patients with musician's dystonia, but not writer's cramp, have been found to exhibit generalized timing alterations in response to tactile and auditory sequential stimuli [21] without any deficits on a battery of sensory and sensorimotor synchronization tasks [32]. Spatial discrimination threshold abnormalities have been shown in patients with focal hand dystonia but not LD and DYT1/DYT6 dystonia mutation carriers [1, 9, 24, 30]. Spatial judgments in patients with cervical dystonia have been found to be more abnormal for auditory than visual stimuli [5]. However, auditory mismatch negativity in patients with cervical dystonia has been determined to be within the normal ranges in contrast to abnormal somatosensory mismatch negativity [4]. In LD patients, a recent study has shown that auditory feedback during symptomatic speaking is normal, concluding that it does not contribute to abnormal cortical activity [8]. In line with these findings, our data show that the processing of auditory discrimination is intact and does not represent a characteristic endophenotypic feature of LD pathophysiology.

Olfactory impairment is a well-described phenomenon in other movement disorders, e.g., Parkinson's disease [14], but only recently has evidence suggested that it might be a marker of isolated dystonia [16]. One family of five

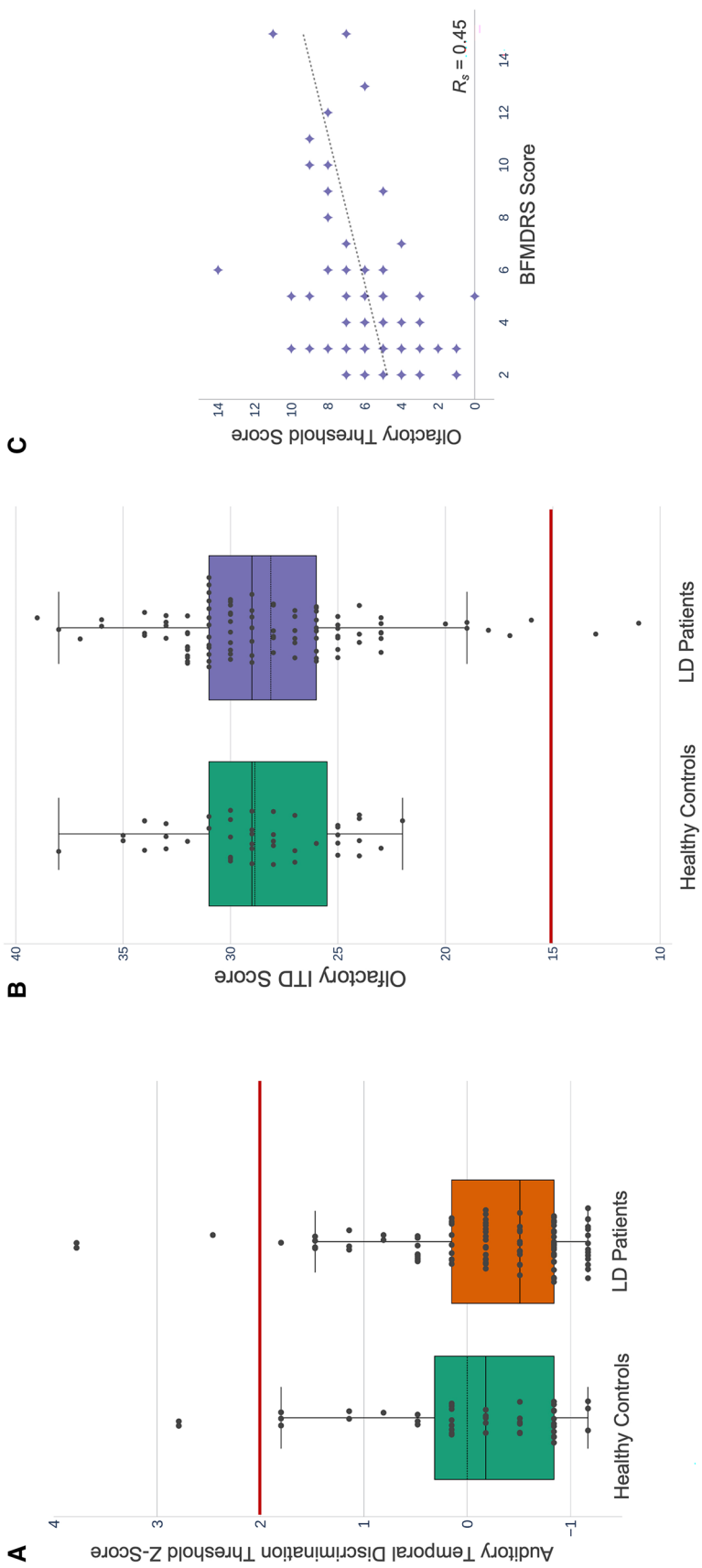

Fig. 1 **A** Auditory temporal discrimination threshold (*Z*-score) in healthy controls and patients with laryngeal dystonia (LD). The horizontal red line indicated the cut-off abnormal *Z*-scores ≥ 2.0. **B** Olfactory ITD (identification, threshold, discrimination) score in healthy controls and LD patients. The horizontal red line indicated the cut-off score ≤ 15 for anosmia. Boxplots show the distribution of individual *Z*-score **A** and ITD **B** values; each participant is represented as a dot; the bold line indicates the median of the group; the dotted line indicates the mean of the group. For the range of values, see Table 2. **C** The correlation plot between olfactory threshold and Burke–Fahn–Marsden dystonia rating scale (BFMDRS) scores in LD patients

patients with *GNAL* (DYT25) dystonia gene mutation has been described to have a significantly lower olfactory identification score [33], likely due to the association of *GNAL* gene mutation with deficient odorant signaling in olfactory epithelium [12]. Recent studies in patients with cervical dystonia without reported dystonia gene mutations have also shown impaired olfactory identification and threshold but not discrimination [17, 23]. Yet, another study has found no significant changes in olfaction in patients with different forms of dystonia [28]. We found that a large proportion of both LD patients and healthy controls had hyposmia, and two patients had anosmia. Such an overall reduction in olfactory processing in both groups may be age dependent, given that the average age of participants was over 50 years. Furthermore, our finding of a positive correlation between the olfactory threshold and BFMDRS scores suggests that altered olfactory function may be more prominent in patients with milder LD. However, with no between-group significant differences, our data suggest that the olfactory function is largely within the normal ranges in LD patients.

Taken together, altered visual [30] but not auditory temporal discrimination or olfactory function reflects a disorder-specific dissociation between different somatosensory processing streams and highlights the relevance of alterations within a specific sensory (visual) domain in LD pathophysiology. Abnormal aTDT and olfaction are likely not candidate mediational endophenotypes of LD.

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Author contributions Study concept and design—KS; acquisition of data—KS; analysis of data—SAF, LCO; statistical analysis—SAF, KS; drafting the manuscript—SAF; revising the manuscript—KS; study supervision—KS; obtaining funding—KS.

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Data availability statement The anonymized participant data presented here are available upon request from the correspondent author.

Declarations

Conflict of interest This study was funded by the grants R01DC011805 and R01NS088160 from the National Institutes of Health to KS. No conflict of interest relevant to this study for all authors.

Ethical approval statement All participants gave written informed consent, which was approved by the Institutional Review Boards of Mass General Brigham and the Icahn School of Medicine at Mount Sinai. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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