The Laryngoscope

A Separation of Innate and Learned Vocal Behaviors Defines the Symptomatology of Spasmodic Dysphonia

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Objective: Spasmodic dysphonia (SD) is a neurological disorder characterized by involuntary spasms in the laryngeal muscles. It is thought to selectively affect speaking; other vocal behaviors remain intact. However, the patients' own perspective on their symptoms is largely missing, leading to partial understanding of the full spectrum of voice alterations in SD.

Methods: A cohort of 178 SD patients rated their symptoms on the visual analog scale based on the level of effort required for speaking, singing, shouting, whispering, crying, laughing, and yawning. Statistical differences between the effort for speaking and the effort for other vocal behaviors were assessed using nonparametric Wilcoxon rank-sum tests within the overall SD cohort as well as within different subgroups of SD.

Results: Speech production was found to be the most impaired behavior, ranking as the most effortful type of voice production in all SD patients. In addition, singing required nearly similar effort as speaking, ranking as the second most altered vocal behavior. Shouting showed a range of variability in its alterations, being especially difficult to produce for patients with adductor form, co-occurring voice tremor, late onset of disorder, and familial history of dystonia. Other vocal behaviors, such as crying, laughing, whispering, and yawning, were within the normal ranges across all SD patients.

Conclusion: Our findings widen the symptomatology of SD, which has predominantly been focused on selective speech impairments. We suggest that a separation of SD symptoms is rooted in selective aberrations of the neural circuitry controlling learned but not innate vocal behaviors.

Key Words: Laryngeal dystonia, voice symptoms, learned vocal behaviors.

Level of Evidence: 4.

***Laryngoscope*, 9999:1–7, 2018**

INTRODUCTION

Spasmodic dysphonia (SD) is a form of isolated laryngeal dystonia that affects speech production. Spasmodic dysphonia is a rare disorder with a prevalence of up to 5.9 per 100 thousand in the general population,[1] with greater frequency among individuals of European descent and women. SD develops spontaneously in midlife and, similar to other forms of dystonia, progresses into a chronic, debilitating condition that severely impacts a patient's life, leading to stress, social embarrassment, and often loss of employment.

SD symptomatology includes strangled, strained quality of voice, with breaks on vowel production characteristic of the adductor form of the disorder (ADSD) or breathy quality of voice, with breaks on voiceless consonants that are typical for the abductor form (ABSD). In rare cases, patients exhibit both adductor and abductor symptoms in a mixed form of SD. About one-third of SD patients have co-occurring dystonic voice tremor (VT). Symptoms generally develop in midlife, with varying degrees of severity and progression over the course of approximately 1 year. A small population of patients develop symptoms in their adolescent or early adulthood, and about 16% to 20% of patients report an incidence of SD or other forms of dystonia in their families.[2,3]

The clinical management of SD is challenging due in part to the absence of objective diagnostic markers, which often leads to inaccuracies in SD diagnosis and differentiation from other voice problems such as VT and muscle tension dysphonia.[4] One study found that SD patients receive their final diagnosis on average 4.43 years after the first onset of symptoms and after being seen on average by 3.95 physicians.[5] The current diagnostic criteria of SD revolve around a combination of perceptual evaluation of voice and speech symptoms, nasolaryngoscopy, and neurological examination. Commonly, the negative outcome of voice and speech therapy on the one hand and the positive outcome of botulinum toxin treatment on the other hand are used as indirect measures of differential diagnosis of SD.

One of the important aspects in the development of accurate and objective criteria for SD diagnosis pertains to the detailed understanding of SD symptomatology. Based on physicians and speech-language pathologists' evaluations, it has generally been accepted that SD is a disorder selectively affecting speech production, whereas other types of voice production remain relatively intact.[6] However, the patients' own perspective on their

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Editor's Note: This Manuscript was accepted for publication on September 17, 2018.

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This study was supported by the National Institute on Deafness and Other Communication Disorders, the National Institutes of Health (grants R01DC011805 and R01NS088160 to K.S.). The authors have no other funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.27617

symptoms has been largely missing, leading only to partial understanding of the full spectrum of voice alterations in this disorder. Therefore, in this study, we sought to investigate the detailed self-reports of SD patients on the quality of their voice, which were obtained in the experimental setting. A large cohort of SD patients (N = 178) were asked to rate their symptoms on the visual analog scale (VAS) based on the level of effort required to produce everyday speech, as well as other laryngeal behaviors such as crying, laughing, yawning, shouting, whispering, and singing, which typically are not considered to be affected in SD.[7] Based on the available knowledge of SD symptomatology and our clinical observations, we hypothesized that SD patients will report the highest score for effort during voiced (overt speaking) but not voiceless (whisper) speech production. However, we also expected to find higher effort scores during singing and shouting as these are similarly complex learned voice behaviors that require volume projections. We expected to find the lowest scores for the effort during crying, laughing, and yawning due to the innate (involuntary) nature of these vocalizations.

MATERIALS AND METHODS

Study Participants

A total of 284 patients with SD participated in this study. Because the focus of the study was on isolated focal SD, 38 patients were excluded due to the presence of other dystonias as confirmed by neurological examination; 64 patients were excluded due to partial completion of the study questionnaire; and four patients were removed because they were not fully symptomatic at the time of study participation and thus their diagnosis could not have been confirmed. The final study cohort included 178 patients with isolated focal SD (142 females, mean age 39.3 $\pm$ 14.2 years; 46 males, mean age 40.3 $\pm$ 12.3 years) whose diagnosis was confirmed based on the conventional criteria including perceptual, laryngological, and neurological examinations. None had any other major neurological (other than SD), psychiatric, or laryngeal problems.

Among this cohort, 101 patients (56.7%) were diagnosed with ADSD and 77 patients (43.3%) presented with ABSD (see patient demographics in Table I). In 53 patients (29.8%), VT co-occurred with SD symptoms. The overall mean age of SD onset was 39.5 $\pm$ 13.8 years. Among these, 69 patients (38.8%) were classified as having an early onset of SD (i.e., symptom manifestation at or prior to 35 years of age), whereas 109 patients (61.2%) had a late onset of SD with symptom manifestation after 35 years of age.

Forty-five SD patients (25.3%) had a family history of dystonia, whereas 21 patients (11.8%) had a family history of other movement disorders such as Parkinson's disease and essential tremor of hand and head. Sporadic SD without any family history of dystonia was reported in 133 patients (74.7%).

Overall, 143 patients (80.3%) received botulinum toxin injections to manage their voice symptoms on a regular basis, whereas 35 patients (19.7%) were naïve to this treatment. Those who received injections were enrolled in the study at the end of their treatment cycle at least 3 months after their last injection; thus, all patients were fully symptomatic at the time of study participation.

Written informed consent was obtained from each patient prior to data collection, which was approved by the institutional review board of the Massachusetts Eye and Ear Infirmary.

TABLE I.
Patient Demographics.

		Number of Patients	Age of Onset (mean $\pm$ st. dev.)	*P* Value
Gender	Male	36 (20.2%)	40.3 $\pm$ 12.3	0.80
	Female	142 (79.8%)	39.3 $\pm$ 14.2	
Age		178	39.5 $\pm$ 13.8	NA
Phenotype	ABSD	77 (43.3%)	38.5 $\pm$ 12.3	0.36
	ADSD	101 (56.7%)	40.2 $\pm$ 14.9	
	With voice tremor	53 (29.8%)	43.3 $\pm$ 13.1	0.013
	Without voice tremor	125 (70.2%)	37.85 $\pm$ 13.8	
	Early onset	69 (38.8%)	25.1 $\pm$ 7.2	< 0.0001
	Late onset	109 (61.2%)	48.6 $\pm$ 8.0	
Genotype	Familial	45 (25.3%)	39.4 $\pm$ 14.7	0.97
	Sporadic	133 (74.7%)	39.5 $\pm$ 13.5	
Total SD		178	39.5 $\pm$ 13.8	NA

ABSD = abductor form of spasmodic dysphonia; ADSD = adductor form of spasmodic dysphonia; NA = not applicable; SD = spasmodic dysphonia; st. dev. = standard deviation.

Data Collection

In the experimental setting, an eight-point questionnaire was administered to 178 patients to capture the voice symptomatology of SD (Table II). This questionnaire was similar to a screening questionnaire proposed earlier to be used as a tool for the assessment of SD diagnosis.[7] Using a 10-point VAS, all patients were first asked to rate their symptoms during speech production by reporting the level of effort required for them to speak. On the VAS, the first gradation represented "no effort," and the last gradation marked a "constant struggle." Participants were then asked to rate the levels of effort required for them to elicit other types of voice production, including laughing, crying, shouting, whispering, singing, and yawning, relative to the level of effort required for speaking. A similar VAS was used, with the first gradation denoting "normal" (i.e., the absence of symptoms when producing the behavior) and the last gradation denoting "same as speaking" effort (i.e., symptom severity similar to that during speaking).

Statistical Analysis

As an initial step, we used the Shapiro–Wilk tests to assess normality of data distribution, which showed that data in neither the overall SD cohort nor the different SD subgroups (i.e., ADSD and ABSD; sporadic and familial cases; SD with and without VT; SD with early and late onset) were normally distributed (all $W \geq 0.721$, $P \leq 2.172e\text{-}07$). Therefore, we used nonparametric Wilcoxon rank-sum tests with continuity correction to examine statistical differences in the levels of effort between examined vocal behaviors within the overall SD cohort. The same nonparametric tests were further applied to examine different SD subgroups to assess whether there are any distinct trends in voice symptomatology based on SD phenotype or genotype. Because overt speech production is assumed to be a hallmark feature of SD symptomatology,[6–8] we compared each category of voice production (i.e., laughing, crying, yawning, whispering, shouting, and singing) to the patient's ratings of the effort to speak. The stringent Bonferroni correction was used to account for multiple comparisons within the examined groups, which set the threshold for statistical significance at $P \leq 0.002$ (0.05/6 comparisons/5 group categories).

TABLE II.
Voice Symptoms Questionnaire.

(I). Effort Speaking

1. Is it a lot of work for you to talk? _____Yes _____No

no effort constant struggle

2. How long has it been an effort for you to talk?
_____Months _____Years

(II). Can you laugh, cry, shout, whisper, sing, or yawn normally?

3. Laughing

normal same as speaking

4. Crying

normal same as speaking

5. Shouting

normal same as speaking

6. Whisper

normal same as speaking

7. Singing

normal same as speaking

8. Yawning

normal same as speaking

RESULTS

Overall Spasmodic Dysphonia Group

As hypothesized, the median effort for speaking was highest among all SD patients, ranking at 7.50 on VAS (interquartile range [IQR] = 2.69) (Table III) (Fig. 1), followed by the effort for singing (median = 7.50; IQR = 5.23). Differences in the effort ratings for speaking and singing did not reach a statistical significance ($P = 0.049$), indicating similar difficulties during production of both vocal behaviors.

However, there were statistically significant differences in the effort for speaking versus other vocal behaviors (all $P \leq 0.0002$), with a descending order in difficulty from shouting (median = 6.25; IQR = 6.25), laughing, crying, and whispering (all median = 1.25; IQR ≥ 2.50) to yawning (median = 0.625; IQR = 2.50) (Table III) (Fig. 1).

Spasmodic Dysphonia Phenotype

Abductor form of spasmodic dysphonia and adductor form of spasmodic dysphonia. When examining vocal effort based on clinical diagnosis, both ABSD and ADSD groups reported overall similar distributions of effort on different tasks (Table III) (Fig. 2A). The median effort ratings for speaking and singing were at 7.50 in both groups (speaking IQR = 2.50–3.75; singing IQR = 5.00–5.78), without showing any significant differences between the two behaviors in either group ($P \leq 0.04$). As a characteristic feature of distinct SD phenotypes, the effort for shouting in ABSD showed a trend toward significance compared to the effort for speaking (median = 7.50; IQR = 6.25; $P = 0.003$), whereas the effort for shouting in ADSD was similar to that for speaking (median = 6.25; IQR = 6.25; $P = 0.013$).

On the other hand, the effort for crying, laughing, whispering, and yawning was significantly different from speaking in both ADSD and ABSD groups (all median ≤ 1.25; all IQR = 1.95–3.75; all $P \leq 0.0001$), indicating that these patients had minimal, if any, symptoms during the production of these vocal behaviors.

Spasmodic Dysphonia With Voice Tremor and Spasmodic Dysphonia Without Voice Tremor

When examining the impact of co-occurring VT on SD symptomatology, we observed features that were both

TABLE III.
Summary Statistics of SD Symptomatology.

	Median Effort	IQR	*P* Value
Overall SD group			
Speak	7.50	2.69	NA
Sing	7.50	5.23	0.049
Shout	6.25	6.25	0.0002
Cry	1.25	2.82	< 0.0001
Laugh	1.25	2.50	< 0.0001
Whisper	1.25	2.50	< 0.0001
Yawn	0.63	2.50	< 0.0001
SD Phenotype			
ADSD/ABSD			*P* Value
Speak	7.50/7.50	2.50/3.75	NA
Sing	7.50/7.50	5.78/5.00	0.41/0.04
Shout	6.25/7.50	6.25/6.25	0.013/0.003
Cry	1.25/0.63	3.75/1.95	< 0.0001/< 0.0001
Laugh	1.25/0.63	3.13/2.50	< 0.0001/< 0.0001
Whisper	1.25/1.25	3.75/2.50	< 0.0001/< 0.0001
Yawn	0.63/0.63	2.50/2.03	< 0.0001/< 0.0001
SD with VT/SD without VT			
Speak	7.50/7.50	3.13/2.75	NA
Sing	8.75/6.25	2.97/5.75	0.33/0.004
Shout	7.50/5.00	5.31/6.25	0.69/< 0.0001
Cry	0.63/1.25	2.97/2.58	< 0.0001/< 0.0001
Laugh	0.63/1.25	2.50/2.50	< 0.0001 < 0.0001
Whisper	1.25/1.25	3.44/2.50	< 0.0001/< 0.0001
Yawn	0.63/0.78	2.50/2.50	< 0.0001/< 0.0001
SD early onset/late onset			
Speak	7.50/7.50	2.50/4.38	NA
Sing	7.81/6.25	5.63/5.63	0.83/0.01
Shout	6.25/7.50	6.25/6.25	0.0002/0.12
Cry	1.25/1.00	4.06/1.88	< 0.0001/< 0.0001
Laugh	1.25/0.63	2.73/2.50	< 0.0001/< 0.0001
Whisper	1.25/0.63	3.67/1.88	< 0.0001/< 0.0001
Yawn	0.62/0.47	2.50/2.03	< 0.0001/< 0.0001
SD Genotype			
Familial/sporadic			
Speak	7.50/7.50	2.50/2.50	NA
Sing	6.88/7.50	5.78/5.39	0.14/0.16
Shout	7.50/6.00	8.13/6.25	0.42/< 0.0001
Cry	0.16/1.25	2.50/2.91	< 0.0001/< 0.0001
Laugh	0.63/1.25	2.50/2.50	< 0.0001/< 0.0001
Whisper	1.25/1.25	3.75/2.50	< 0.0001/< 0.0001
Yawn	0.00/0.94	1.88/2.50	< 0.0001/< 0.0001

IQR = interquartile range; NA = not applicable; SD = spasmodic dysphonia; VT = voice tremor

similar to and distinct from the overall SD group. The median effort for speaking was consistently rated at 7.50 on VAS by both groups (with VT: IQR = 3.13; without VT: IQR = 2.75) (Table III) (Fig. 2B). Compared to speaking, the median effort for singing was somewhat higher at 8.75 in SD with VT (IQR = 2.97) and lower at 6.25 in SD without VT (IQR = 5.75), showing no statistical differences from speaking ($P \leq 0.004$). Furthermore, the effort for shouting was significantly different from speaking in SD patients without VT (median = 5.0, IQR = 6.25; $P \leq 0.0001$) but not in SD patients with VT (median = 7.5, IQR = 5.31; $P = 0.69$).

In both groups, the median effort ratings for crying, laughing, whispering, and yawning were significantly different compared to speaking in SD patients both with and without VT (with VT: median ≤ 1.25; IQR = 2.50–3.44; without VT: median ≤ 1.25; IQR = 2.50–2.58; $P \leq 0.0001$).

Spasmodic Dysphonia Early Onset and Spasmodic Dysphonia Late Onset

The effort ratings in SD patients with early (≤ 35 years of age) and late (> 35 years of age) symptom onset showed consistently similar levels during speaking (median = 7.50; IQR = 2.50–4.38) (Table III) (Fig. 2C). Singing effort ratings did not show statistical difference from speaking in either group (median ≤ 7.81; IQR = 5.63; $P \geq 0.01$). Shouting effort ratings differed between SD patients with early and late symptom onset, with late-onset SD reporting effort similar to that for speaking (median = 7.50; IQR = 6.25; $P = 0.12$).

The other vocal behaviors, including crying, laughing, whispering, and yawning in both groups, as well as shouting in the early-onset SD group, showed significant differences in effort compared to speaking (median ≤ 6.25; IQR = 1.88–6.25; $P \leq 0.0002$).

Spasmodic Dysphonia Genotype

Familial spasmodic dysphonia and sporadic spasmodic dysphonia. One-quarter (25.3%) of patients in the overall SD cohort had a family history of SD and/or other dystonias. Patients with both familial and sporadic forms of SD had their effort ratings for speaking at a median of 7.5 on VAS (IQR = 2.50) (Table III) (Fig. 2D). Singing was reported to require as much effort as speaking in both groups (median ≤ 7.50; IQR = 5.39–5.78; $P \geq 0.14$), whereas shouting was effortful in the familial group (median = 7.50; IQR = 8.13; $P = 0.42$) but not in the sporadic group (median = 6.00; IQR = 6.25; $P \leq 0.0001$). The effort for crying, laughing, whispering, and yawning followed features similar to the overall SD group, showing significant differences from the effort for speaking (median ≤ 1.25; IQR = 1.88–3.75; $P \leq 0.0001$).

DISCUSSION

There are four principal findings of this study: 1) We confirm that speech production is the most impaired behavior, ranking as the most effortful type of voice production across all examined phenotypes and genotypes of SD; 2) we demonstrate that singing requires nearly similar effort as speaking, ranking as the second most altered vocal behavior in SD; 3) shouting shows a range of variability in its alterations, being especially difficult to produce for patients with ADSD, SD with VT, late-onset SD, and a familial history; and 4) the production of other vocal behaviors, such as crying, laughing, whispering,

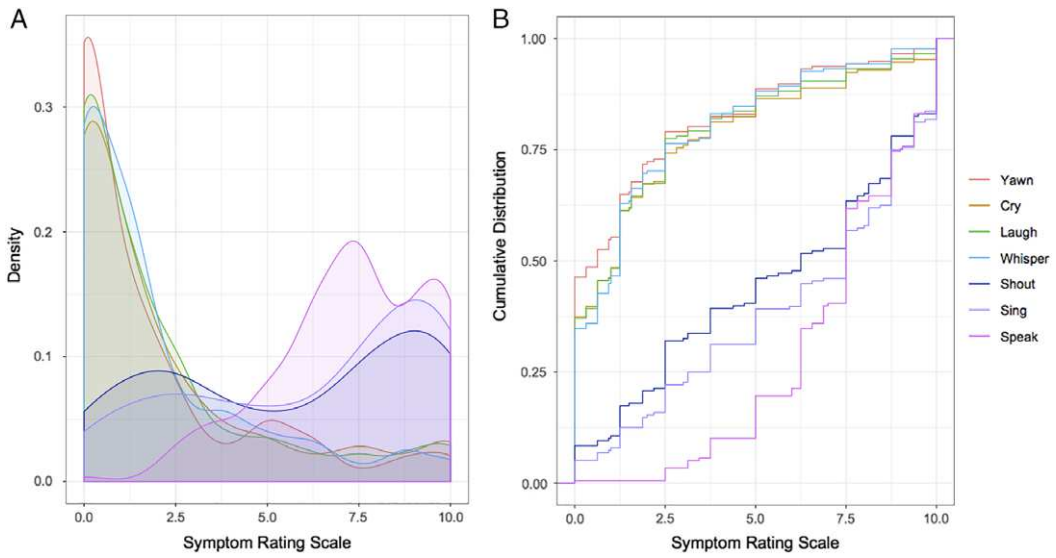

Fig. 1. (A) Density plot depicts the distribution of voice symptoms based on the ratings using a 10-point visual analog scale. Innate vocalizations are heavily skewed toward lower severity values, whereas voluntary vocalizations show the opposite trend. (B) The empirical cumulative distribution curves for each rating scale among all patients display differences in distribution between the voluntary and innate vocalization curves. Whispering, yawning, and crying show a convex, left skew, with higher probabilities at lower rankings. Shouting, singing, and speaking show the opposite, a concave, right skew, with higher probabilities at higher rankings.

and yawning, is within the normal ranges across all examined SD forms.

These findings are largely in line with our hypothesis that SD symptomatology is grounded in a separation of innate from learned types of voice production (Fig. 3). As a neurological disorder, SD symptoms appear to be related to selective aberrations within the neural circuitry associated with the voluntary control of learned voice production, such as speech and song. The final cortical output structure within this circuitry is the laryngeal motor cortex, which directly controls laryngeal motoneurons in nucleus ambiguus of the brainstem[9,10] and which has been shown to be functionally and structurally abnormal in SD patients.[11–15] Among different types of voluntary voice production, speech and song are the most highly learned and skilled vocal motor behaviors that require unique organization of large-scale brain networks.[16] It is therefore not surprising that speech is the most affected type of voice production in SD. On the other hand, the presence of voice symptoms during singing reported by all examined forms of SD is a novel finding because it has been long thought to remain unaffected in this disorder.[7] This discrepancy might be due, in part, to the fact that singing is not as essential for everyday communication as speaking, and not all patients are capable singers that would be particularly concerned by and report symptom occurrence during singing. Thus, it is plausible that symptomatology pertaining to singing remained covert and underreported while being erroneously perceived as a normal behavior in SD.

Within the range of learned voice production are also shouting and whispering, which showed varied degrees of difficulties in SD. While our SD cohort, including all examined phenotypes and genotypes, showed significantly normal whispering compared to symptomatic speaking, some groups of patients stated the presence of symptoms during shouting similar to those of speaking. These were patients with adductor form of SD, those who had co-occurring VT, SD patients with the late onset of disorder, and those who had a family history of dystonia. Symptoms during shouting may be associated with the difficulties to project voice due to the amount of straining and tremor in patients with ADSD and VT, respectively, whereas putative neurogenetic factors may underlie shouting abnormalities in SD patients with late onset and a familial history of disorder.

In contrast to shouting, whispering was nearly asymptomatic in SD patients. Although whispering is a voluntary, learned vocal behavior that engages the same neural circuitry as during speaking, this is a voiceless behavior that does not require a complete closure and opening of vocal folds necessary for speaking. Hence, SD-characteristic spasms leading to hyperadduction or hypoadduction of vocal folds during speaking have little impact during whispering, rendering it significantly less affected by dystonic symptoms than voiced speech.[7,8,17] While the neural circuitry controlling whispering is similar to that of speaking, it is known to exhibit a much lower connectivity profile for voiceless whispering compared to voiced speech.[18] Thus, a combination of particular laryngeal functional anatomy with associated adjustments in the central nervous system for the control of a voiceless behavior may underlie alleviated dystonic symptomatology during whispering in SD patients.

Finally, the least affected types of voice production across all examined forms of SD were innate voiced and voiceless vocalizations, including crying, laughing, and yawning. These are genetically preprogrammed vocal

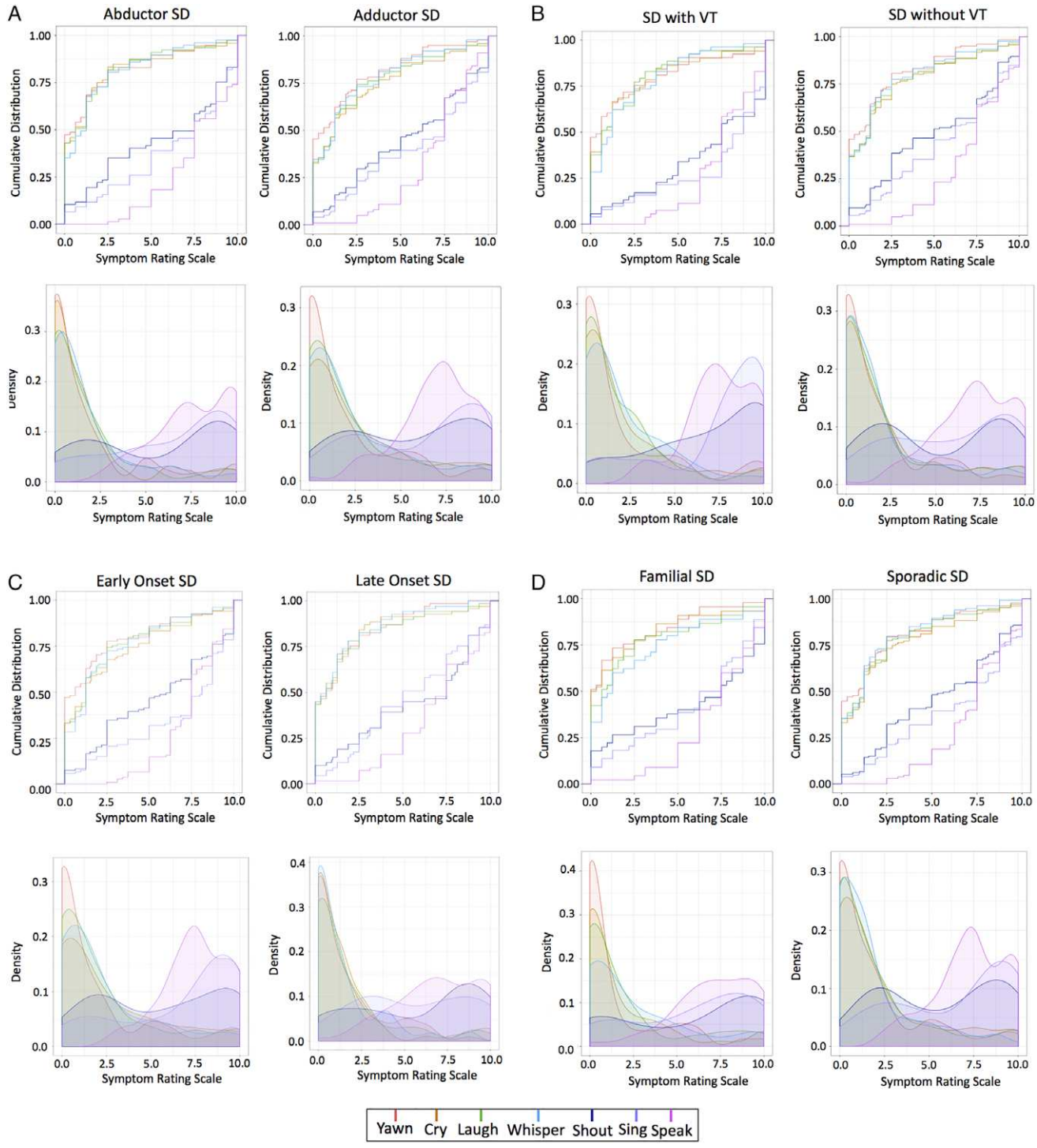

Fig. 2. Density plots and empirical cumulative distribution curves show symptom ranges in different phenotypes and genotypes of SD, including (A) abductor and adductor forms; (B) SD with and without VT; (C) SD with early and late onset of disorder; and (D) familial and sporadic cases. SD = spasmodic dysphonia; VT = voice tremor.

behaviors that do not require an auditory feedback and vocal motor learning in order to produce them.[19] These vocalizations rely on a different set of neural structures, including the brainstem and cingulate cortex, with the circuitry running parallel to the one controlling the production of learned vocal behaviors, such as speech and song.[20] There is, however, an interplay between these two parallel pathways for innate and learned vocalizations, which may provide an explanation why patients' speech may become less symptomatic when they speak while crying or laughing. It appears that the intact innate vocal circuitry "overrides" the abnormal voluntary

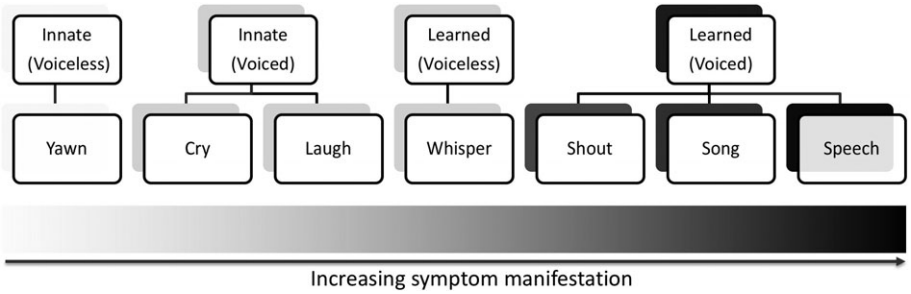

Fig. 3. Schematic distribution of spasmodic dysphonia symptomatology, with increasing symptom manifestation (left to right) from yawning (innate voiceless behavior) to speaking (learned, most complex voiced motor behavior). Gray shading (light to dark) indicates the severity of symptoms during the production of different vocal behaviors, which are grouped based on the organization of their neural control.

vocal motor circuitry, leading to temporary mitigation of SD symptoms. The fact that not only voiced innate behaviors (crying and laughing) but also voiceless innate behavior (yawning) was found to be within the normal ranges in SD patients suggests that there is no selective deficit within this neural circuitry as opposed to a range of alterations within the neural circuitry controlling learned vocal behaviors.

CONCLUSION

In summary, we examined different types of voice production across different forms of SD based on the patients' perspective of their own symptomatology. We demonstrate that SD selectively affects voiced types of learned vocal behaviors, including not only speech but also singing and shouting, albeit the latter at a various degree of abnormalities. These findings widen the symptomatology of SD, which has predominantly been focused on speech impairments. We suggest that a separation of SD symptomatology is rooted in selective alterations of the neural circuitry controlling learned but not innate vocal behaviors.

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