Parkinsonism and Related Disorders 65 (2019) 117–123

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

The extrinsic risk and its association with neural alterations in spasmodic dysphonia

Laura de Lima Xavier[a,b,c], Kristina Simonyan[a,b,c,*]

[a] Department of Otolaryngology, Massachusetts Eye and Ear, Boston, MA, USA
[b] Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
[c] Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Keywords:
Laryngeal dystonia
Extrinsic risk
Case-control study
fMRI

ABSTRACT

Introduction: Spasmodic dysphonia (SD) is an isolated focal dystonia characterized by laryngeal spasms during voluntary voice production. Environmental factors have been assumed to play a role in SD pathophysiology; however, the exact extrinsic risk factors and their association with neural alterations remain unknown.
Methods: A total of 186 SD patients and 85 healthy controls completed a structured 177-question survey, consisting of questions on general biographical information, medical history, symptomatology of dystonia. Data were imputed in a stepwise regression model to identify extrinsic risk factors for SD. In addition, functional MRI data from a subset of this cohort were analyzed to determine brain activation abnormalities associated with the SD extrinsic risk.
Results: We found that (1) recurrent upper respiratory infections, gastroesophageal reflux, and neck trauma, all of which influence sensory feedback from the larynx, represent extrinsic risk factors, likely triggering the manifestation of SD symptoms, and (2) neural alterations in the regions necessary for sensorimotor preparation and integration are influenced by an extrinsic risk in susceptible individuals.
Conclusions: These findings provide evidence for the extrinsic risk in SD development and demonstrate the link with alterations in the sensorimotor preparatory network that collectively contribute to the multifactorial pathophysiology of SD.

1. Introduction

Spasmodic dysphonia (SD), or laryngeal dystonia, is an isolated focal dystonia that selectively manifests during speaking. Laryngeal muscles may be distinctly affected, leading to adductor (ADSD) or abductor (ABSD) phenotypes that are characterized by a strained voice quality with breaks on vowel production or breathy voice quality with breaks on voiceless consonants, respectively. SD is known to predominantly affect Caucasians and females in their fourth decade, causing chronic and debilitating voice and speech impairment [1].

Although the exact etiology and pathophysiology of SD are unclear, the presence of a family history of dystonia in 16–20% of SD patients [2,3] suggests a genetic predisposition, while evidence of frequent upper respiratory infections, childhood viral infections, psychological stress, and professional voice use [4–6] points to a possible contribution of environmental triggers. Furthermore, neuroimaging studies of SD have consistently identified abnormal activity in sensorimotor cortex, basal ganglia, thalamus, and cerebellum [7–11]. It is thus plausible to suggest that the pathophysiology of SD involves the interplay between intrinsic genetic factors and extrinsic environmental triggers that influence abnormal functional brain organization [12]. In support of this assumption, a recent study demonstrated that the polygenic risk of dystonia is linked to vulnerable functional connectivity of sensorimotor cortex in SD [13]. However, the contribution of extrinsic risk factors to SD development and their influences on brain alterations have not yet been examined, leaving the understanding of the impact of *external* stressors on the pathophysiology of this disorder largely unaddressed. Because the current diagnosis of SD lacks objective biomarkers and is solely based on examination of its clinical features [14], detailed understanding of both intrinsic and extrinsic triggers underlying its causative pathophysiology is critical for the future development of better diagnostic and therapeutic approaches. Thus, the goal of this study was to examine the missing link between the external risk factors and functional brain alterations in SD. We hypothesized that, compared to

* Corresponding author. Department of Otolaryngology Head & Neck Surgery, Massachusetts Eye and Ear Infirmary, Harvard Medical School, 243 Charles Street, Suite 421, Boston, MA, 02493, USA.
E-mail address: Kristina_Simonyan@meei.harvard.edu (K. Simonyan).

https://doi.org/10.1016/j.parkreldis.2019.05.034
Received 30 December 2018; Received in revised form 24 April 2019; Accepted 23 May 2019

healthy individuals, SD patients with and without an exposure to extrinsic risk factors will show distinct patterns of altered sensorimotor brain activity, providing a signature characteristic marker of these influences on brain organization in dystonia.

2. Material and methods

2.1. Case-control study

We recruited a total of 186 SD patients (mean age 55.2 ± 12.3 years, 145 females/41 males) and 85 healthy controls (mean age 50.0 ± 10.6 years, 50 females/35 males). SD diagnosis was confirmed using voice and speech perceptual analysis and laryngological/neurological examinations. Exclusion criteria included any other neurological, laryngeal and/or major psychiatric diseases, other than mild anxiety and mild depression, which are frequent comorbidities in this disorder [6]. Subjects with a history of a structural damage to the brain and/or larynx were excluded. All subjects had a normal cognitive function as evident by their MMSE median score of ≥27, adjusted for age and education [15]. All subjects were screened for verified dystonia genes, including DYT1, DYT6, DYT4, and DYT25. None were positive for any of these genes, except for one SD patient who was DYT25 positive, as reported earlier [16]; this patient was not included in the imaging portion of this study.

All subjects completed a structured 177-question survey, consisting of wide-ranging questions on general biographical information, past and present medical history, life events and a family history, as well as questions specific to the development of SD symptomatology, other dystonias and other movement disorders (Supplementary Table 1). All subjects gave written informed consent prior to study participation, which was approved by the Institutional Review Board of Massachusetts Eye and Ear.

The survey responses were grouped into 27 categories based on their relevance, coded as factors, and analyzed using frequency and proportion tables, as applicable. Differences between all SD patients and healthy control were examined using chi-square tests within cross-tabulation multivariate analysis for categorical variables and two-tailed *t*-tests for continuous variables. The odds ratio (OR) was obtained using logistic regression for each variable, adjusted for potential confounding factors, including age, gender, race, ethnicity, and the education level. The overall significance was set at the confidence interval (CI) with a 95% coverage probability level, corresponding to Bonferroni-corrected $p \leq 0.002$ (0.05/27 categories). In addition, similar multivariate analyses were performed between familial/sporadic SD cohorts and healthy controls, respectively.

Next, a multivariate logistic regression was used to identify significant extrinsic risk factors contributing to the best predictive model associated with SD, controlled for age, gender, race, ethnicity, and education. A total of seven factors were eliminated due to high collinearity, resulting in a final model of 20 factors (Table 1). A stepwise factor selection was performed using backward elimination with Akaike information criterion as a means for model selection, which avoided determining a critical *p*-value as criterion for factor elimination [17].

As in any case-control study, the present investigation is susceptible to limitations inherent to its design. Importantly, while case-control studies may demonstrate associations, they cannot prove a causation, in this case, between an extrinsic risk factor and SD symptom manifestation. Furthermore, the case-control study design is vulnerable to a recall bias, which results from the fact that, commonly, patients are more likely to scrutinize the past, remembering the details of exposures more clearly than healthy controls [18]. To minimize such recall bias, we collected the data in an experimental setting during each subject's study visit, and the subjects were given enough time to clarify their recollection of past life events.

Table 1
Social and medical background frequency distribution for subjects with spasmodic dysphonia and healthy controls controlled for age, gender, race, ethnicity, and education.

	SD N (%)	HC N (%)	Chi-square *p*-value	OR	CI 95%
Neck injury or surgery					
Yes/No	31(17)/155(83)	2(2)/83(98)	< 0.001	6.9[a]	1.7–46.8
Family history of movement disorder					
Yes/No	99(53)/87(47)	10(12)/75(88)	< 0.001	4.9[a]	2.3–11.1
Frequent upper respiratory infections					
Yes/No	129(70)/57(30)	30(35)/55(65)	< 0.001	3.1[a]	1.7–5.7
Gastroesophageal reflux					
Yes/No	77(41)/109(59)	15(18)/70(82)	< 0.001	2.7[a]	1.3–5.7
Anxiety and/or depression before SD					
Yes/No	29(15)/157(85)	4(5)/81(95)	0.006	2.6[#]	0.8–10.2
Exposure to airway irritants					
Yes/No	41(22)/145(78)	8(9)/77(91)	0.009	1.6[#]	0.7–4.2
Mumps					
Yes/No	76(41)/110(59)	22(26)/63(74)	0.02	1.8[#]	0.8–3.7
Mononucleosis					
Yes/No	31(17)/155(83)	7(8)/78(92)	0.05	1.7[#]	0.6–4.9
Education ≥ College					
Yes/No	161(67)/25(13)	66(78)/19(22)	0.06	2.2	0.9–4.8
Exercise					
Yes/No	131(71)/55(29)	50(59)/35(41)	0.06	1.2	0.7–2.3
Traumatic loss of loved one					
Yes/No	108(58)/78(42)	40(47)/45(53)	0.08	1.1	0.6–2.1
Childhood speech difficulties					
Yes/No	22(12)/164(88)	5(6)/80(94)	0.1	2.1	0.7–7.1
Rubella					
Yes/No	44(24)/142(76)	13(15)/72(85)	0.1	0.8	0.4–2
Physical abuse victim					
Yes/No	18(10)/168(90)	5(5)/95(80)	0.2	1.8	0.7–9.2
Prenatal and/or birth complications					
Yes/No	32(17)/154(83)	11(13)/74(87)	0.4	1.1	0.4–2.7
Pertussis					
Yes/No	14(7)/172 (93)	4(5)/81(95)	0.4	1	0.3–4.7
Cigarette smoke exposure					
Yes/No	94(51)/92(49)	38(45)/47(55)	0.4	0.9	0.5–1.6
Measles					
Yes/No	89(48)/97(52)	26(31)/59(69)	0.4	1.4	0.7–2.8
Chicken pox					
Yes/No	152(82)/34(18)	71(84)/14(16)	0.7	0.9	0.4–2
Loss consciousness					
Yes/No	51(27)/135(73)	21(25)/64(75)	0.7	0.9	0.5–1.9

OR: Odds Ratio; CI: Confidence Interval.
[a] Odds Ratio showing statistically significant differences between patients with spasmodic dysphonia (SD) and healthy controls (HC) at $p < 0.002$; [#] Odds Ratio showing trend towards higher incidence in SD compared to HC.

2.2. Brain imaging study

Whole-brain MRI was acquired in 62 SD patients (mean age 53.5 ± 13 years, 49 females/13 males) and 35 healthy controls (mean age 51 ± 10 years, 23 females/12 males) on a 3.0 Tesla Philips scanner equipped with an 8-channel head coil. All subjects were right-handed as determined by the Edinburgh Handedness Inventory and native English speakers. SD patients were fully symptomatic at the time of study participation; those who received botulinum toxin injections participated at least 3 months after their last injection when fully symptomatic. Exclusion criteria were same as described above.

Images were obtained using a gradient-weighted echo planar imaging (EPI) pulse sequence and blood oxygen level dependent (BOLD) contrast with sparse-sampling event-related design (TR 2 s per volume and 8.6 s between volumes, effective TR 10.6 s; TE 30 ms; FA 90°; FOV 240 mm; voxel size 3.75 × 3.75 mm; 36 slices; 4-mm slice thickness), which minimized artifacts due to possible orofacial movements and neutralized the scanner noise interference with acoustic stimulus presentation. Experimental design included the production of English sentences, which elicited SD symptoms, and a resting condition as a baseline. Each subject completed four functional runs, consisting of 24

task and 16 resting conditions. A high-resolution T1-weighted image was acquired in each subject using 3D magnetization prepared rapid acquisition gradient echo sequence (3D-MPRAGE: TR 7.5 ms, TE 2 ms, TI 1000 ms, FA 8°, FOV 259 mm, 176 slices; 1 mm slice thickness) for an anatomical reference of fMRI and to rule out structural abnormalities.

Image analysis was performed using AFNI software. Briefly, the first two volumes of time series were discarded to account for the magnetization equilibrium. The pre-processing pipeline of the EPI datasets included removal of spikes; registration to the EPI volume collected closest in time to the anatomical scan using heptic polynomial interpolation; alignment of the EPI to the anatomical scan along with the motion alignment; spatial normalization of the anatomical scan to the AFNI standard Talairach-Tournoux space; application of the same transformation to the EPI along with the motion alignment using the volume with the minimum outlier fraction as the alignment base; spatial smoothing of EPI data with a 4-mm Gaussian filter, and normalization to the percent signal change. A regressor for the task was convolved with a canonical hemodynamic response function and entered into a multiple regression model to predict the observed BOLD response. Control for motion artifacts in each individual run included regression of motion parameters, censoring of TR, and additional censoring of outlier TRs. Motion regression was based on six motion parameter estimates calculated during realignment of the EPI volumes that were included as covariates of no interest and three quadratic polynomials that were used to model baseline drifts for each imaging run. TR censoring included exclusion of TR pairs where the Euclidean Norm of the motion derivative exceeded 1.0; this optimal cut-off value was set based on simulations of motion artifacts at the presence of slow effective TR of 10.6 s. 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. Using these parameters, 9 patients and 7 healthy controls were excluded from the final analysis. The final cohort consisted of 53 SD patients and 28 healthy controls.

To examine the neural correlates of identified extrinsic risk factors in SD, we used two-tailed independent *t*-tests to contrast: (1) 28 patients with at least two risk factors (age 53 ± 11.3 years, 20 female/8 male, 19 sporadic/9 familial) vs. 28 age- and gender-matched healthy controls (age 49.0 ± 9.7 year, 19 females/9 males), and (2) 25 patients without any risk factors (age 54.0 ± 14.7 years, 17 female/8 male, 17 sporadic/8 familial) vs. same 28 healthy controls (age 49.0 ± 9.7 year, 19 females/9 males). There were no statistically significant differences between the examined groups based on their age, gender, duration of SD, or a family history of dystonia, as applicable (all $p \geq 0.17$). Statistical significance was set at a corrected $p \leq 0.05$ using a minimum voxel-wise threshold $p \leq 0.001$, minimum cluster-wise threshold $p \leq 0.01$ and cluster size $\geq 250\,mm^3$.

In the exploratory analysis, using two-tailed independent *t*-tests at a corrected $p \leq 0.05$, we examined the interplay between the extrinsic risk factors and a putative genetic risk on brain activity in a smaller group of familial SD patients (with risk: 6 female/3 male, age 55 ± 13 years; without risk: 7 female/1 male, age 60 ± 16 years) compared to sporadic SD patients (with risk: 14 female/5 male, age 52 ± 10 years; without risk: 10 female/7 male, age 51 ± 13 years) and healthy controls (6 female/3 male, age 54 ± 6.7 years).

3. Results

3.1. Case-control study

3.1.1. Overall characteristics of spasmodic dysphonia cohort

Among 186 patients, 106 had ADSD, 79 ABSD, and 1 mixed SD. The mean age of SD symptom onset was 39.1 ± 13.2 years; however, the age at the first diagnosis of SD was 44.6 ± 12.6 years, suggesting on average a 5.5-year delay between the symptom onset and accurate diagnosis. This is consistent with the previous report that identified on average a 4.43-year delay in accurately diagnosing SD [19].

SD symptoms were reported to have a gradual onset in 74% of patients and a sudden onset in 26% of patients. Severe emotional stress and/or a traumatic event, such as the loss of a job or a loved one, were equally reported in patients with gradual (43%) and abrupt (46%) symptom onset ($p = 0.71$). Other factors reported by patients immediately prior to symptom onset included severe upper respiratory infection (URI, 20%), head trauma without apparent structural damage (5%), and general anesthesia (2%). Two patients experienced the symptom onset during pregnancy, a possible factor previously reported in the literature [4].

Within the first year of disorder manifestation, symptoms appeared to wax and wane in 62% of SD patients, with 13% experiencing a period of complete symptom resolution without a treatment. With respect to the disorder progression within the first year of onset, 66% of patients felt their symptoms have plateaued, 21% of patients reported ongoing worsening, and 13% of patients perceived symptom improvement. Pain associated with voice symptoms was stated by 20% of patients and throat irritation by 41% of patients; the latter was perceived either constantly (10%) or intermittently (88%) while speaking for a long period of time.

The majority of SD patients (78%) received at least one botulinum toxin treatment. Among these, 12% reported a complete symptom resolution, 61% stated significant symptom improvement, 5% had benefited from the first injection only, and 22% never received any benefits. ADSD patients (90%) were significantly more likely to benefit from injections then ABSD patients (58%) ($p = 0.00002$). Speech therapy was tried by 61% of patients, with 32% reporting mild benefits. Other frequently stated symptom management included physical exercise in 35% of patients, with one half of patients reporting improvement and the other half reporting worsening of symptoms. When questioned about symptom responsiveness to alcohol intake, 55% answered that drinking an alcoholic beverage improved their speech, matching previous reports of alcohol responsiveness in this disorder [2]. No differences in self-reported alcohol responsiveness were observed between different SD phenotypes (42% ABSD, 58% ADSD, $p = 0.76$).

3.1.2. Extrinsic risk factors of spasmodic dysphonia

When comparing all SD patients to healthy controls accounted by age, gender, race, ethnicity, and the education level, statistically significant differences were found in the prevalence of a history of recurrent URIs (≥4 episodes year) (OR: 3.1, CI: 1.7–5.7, $p < 0.001$), gastroesophageal reflux (GERD, OR: 2.7, CI: 1.3–5.7, $p < 0.001$), neck injury (e.g., thyroid surgery without laryngeal structural damage) (OR: 6.9, CI: 1.7–46.8, $p < 0.001$), and a family history of movement disorders, including SD, other forms of dystonia, Parkinson's disease, and tremor (OR: 4.9, CI: 2.3–11.1, $p < 0.001$) (Table 1). In addition, a past history of anxiety and depression prior to SD symptom onset (OR: 2.6, CI: 0.8–10.2, $p = 0.006$), exposure to airway irritants (coal dust, pesticide, airborne particles and chemicals; OR: 1.5, CI: 0.7–4.2, $p = 0.009$), mumps (OR: 1.8, CI: 0.8–3.7, $p = 0.02$) and mononucleosis (OR: 1.7, CI: 0.6–4.9, $p = 0.05$) showed a trend to the higher incidence in SD patients compared to healthy controls. Similar results were found when comparing sporadic and familial SD cohorts to healthy controls, respectively, with the exception of GERD that reduced its significance to a trend in familial SD patients (OR: 2.2, CI: 0.8–5.9, $p < 0.006$) (Supplementary Tables 2 and 3).

Using these factors, the follow-up stepwise selection within multivariable analysis identified the high incidence of frequent URIs, neck injury and GERD as the best independent predictors of an overall SD extrinsic risk (all $p \leq 0.01$). All three factors showed a similar significance as a risk for sporadic SD (all $p \leq 0.05$), whereas frequent URIs and neck injury were significant predictors of a risk in familial SD (all $p \leq 0.05$).

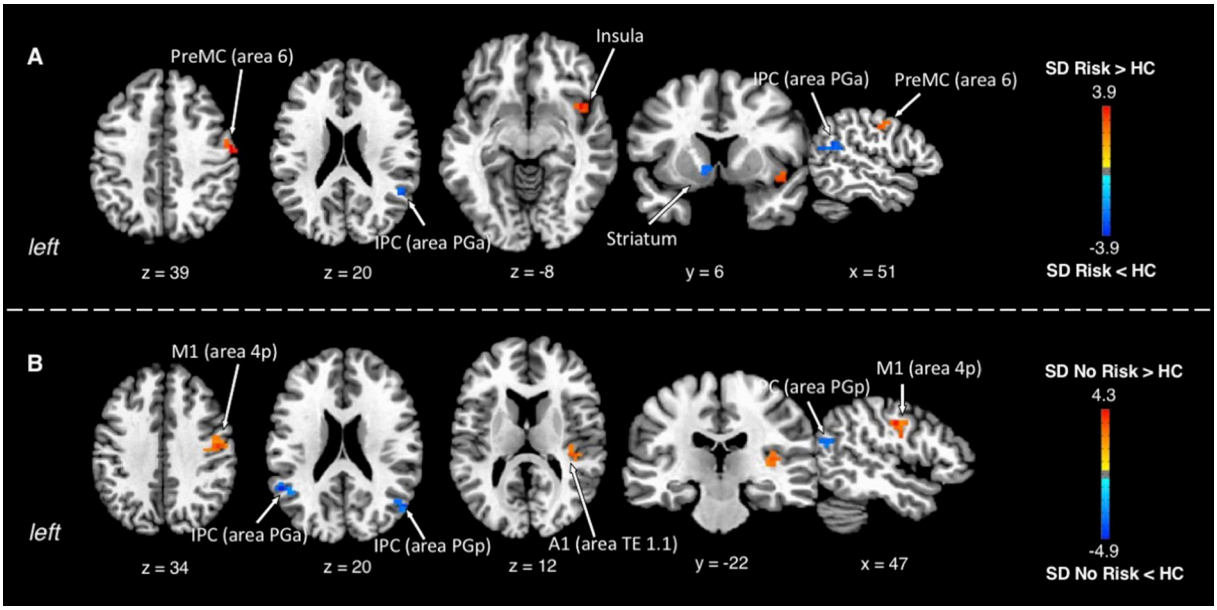

Fig. 1. Statistically significant differences in brain activity during symptomatic speech production in (A) SD patients with extrinsic risk factors compared to healthy controls (HC) and (B) SD patients without risk factors compared to healthy controls. Axial and sagittal brain slices are shown in the AFNI standard Talairach-Tournoux space. Color bar represents the *t*-score at a corrected $p \leq 0.05$. PreMC – premotor cortex; M1 – primary motor cortex; IPC – inferior parietal cortex; A1 – primary auditory cortex.

3.1.3. Brain imaging study

When comparing the two SD patient groups with and without identified extrinsic risk factors (i.e., GERD, URI, and neck injury) to age- and gender-matched healthy controls, we found distinct patterns of abnormal brain activity during symptomatic speech production. Specifically, SD patients exposed to the extrinsic risk showed activity increases in right premotor cortex (area 6) and anterior insula and decreases in right inferior parietal cortex (IPC; area PGa) and left striatum (Fig. 1A, Table 2). Conversely, SD patients not exposed to the extrinsic risk exhibited increased activity in right primary motor cortex (area 4p) and primary auditory cortex (area TE1.1) and decreased activity in bilateral IPC (left area PGa; right area PGp) (Fig. 1B, Table 2).

When further stratifying SD patients based on the presence of a family history of dystonia and comparing them to age- and gender-matched healthy controls, we found additional genotype-related features of abnormal brain activity, dependent on the extrinsic risk exposure. Notably, decreased brain activity was found in right IPC (area PGa) and premotor cortex (area 6) in familial SD patients exposed to the extrinsic risk and in bilateral IPC (left area PGa; right area PGp/PGa) and right primary motor cortex (area 4p) in familial SD patients not

Table 2
Differences in functional activity during symptomatic speech production in SD patients with and without extrinsic risk and stratified by genetic risk compared to healthy.

Anatomical Regions	**Cluster peak coordinates (x, y, z)**	Cluster size (mm^3)	Cluster peak *t*-level
Overall SD			
SD with Risk > Healthy Controls			
R. Premotor cortex (area 6)	54, −11, 38	515	3.9
R. Anterior insula	40, 10, −8	300	3.6
SD with Risk < Healthy Controls			
R. Inferior parietal cortex (area PGa)	51, −50, 20	600	−3.4
L. Striatum	−12, 10, −4	257	−3.9
SD no Risk > Healthy Controls			
R. Primary motor cortex (area 4p)	47, −11, 34	1158	4.3
R. Primary auditory cortex (area TE 1.1)	37, −22, 10	686	3.7
SD no Risk < Healthy Controls			
L. Inferior parietal cortex (area PGa)	−51, −50, 20	643	−4.9
R. Inferior parietal cortex (area PGp)	51, −64, 20	343	−4.0
Familial			
SD with Risk < Healthy Controls			
R. Premotor cortex (area 6)	37, −15, 45	686	−3.8
R. Inferior parietal cortex (area PGa)	44, −25, 31	539	−3.9
SD no Risk < Healthy Controls			
R. Inferior parietal cortex (area PGa)	54, −53, 34	1862	−7.4
L. Inferior parietal cortex (area PGa)	−51, −46, 17	735	−4.2
R. Inferior parietal cortex (area PGp)	33, −67, 48	882	−3.9
Sporadic			
SD with Risk > Healthy Controls			
R. Superior frontal gyrus	23, 20, 52	343	3.6
R. Premotor cortex (area 6)	54, −11, 38	294	3.8
SD no Risk > Healthy Controls			
R. Primary motor cortex (area 4p)	47, −11, 34	1421	4.3

R – right; L - left.

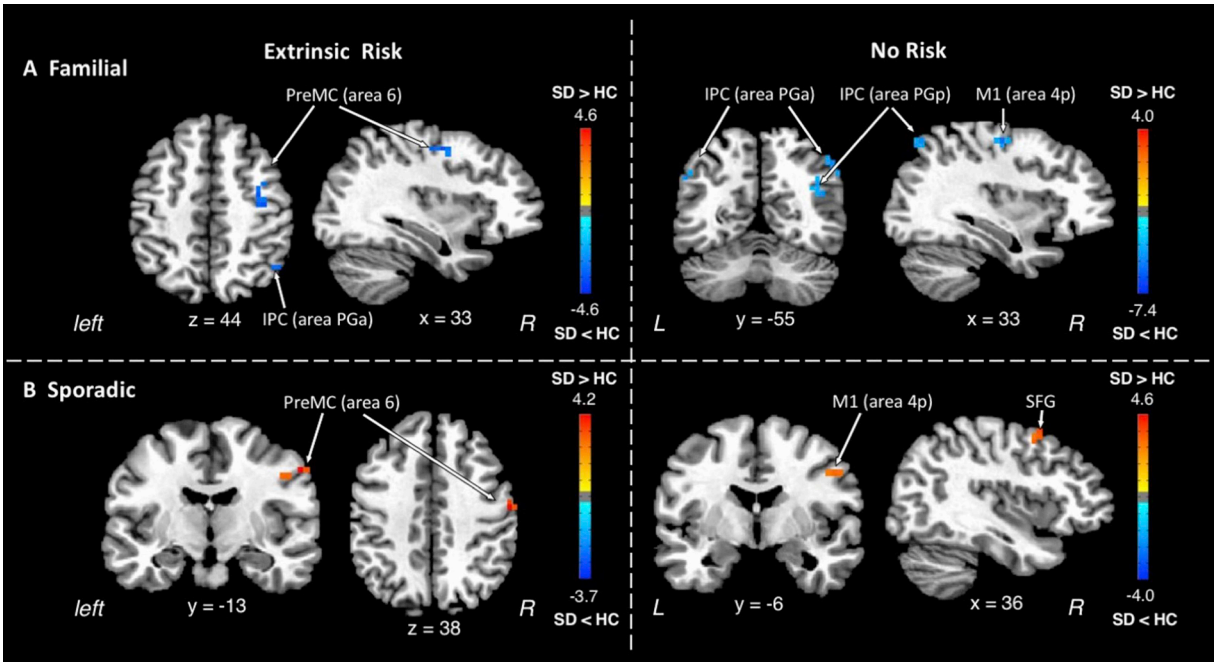

Fig. 2. A map of significant differences in brain activity during symptomatic speech production in (A) familial SD patients compared to healthy controls, and (B) sporadic SD patients compared to healthy controls stratified by the presence of the extrinsic risk. Axial and sagittal brain slices are shown in the AFNI standard Talairach-Tournoux space. PreMC – premotor cortex; M1 – primary motor cortex; IPC – inferior parietal cortex; SFG – superior frontal gyrus.

exposed to the extrinsic risk (Fig. 2A, Table 2). Conversely, increased brain activity was found in right premotor cortex (area 6) in sporadic SD patients exposed to the extrinsic risk and in right primary motor cortex (area 4p) and superior frontal gyrus in sporadic SD patients not exposed to the extrinsic risk (Fig. 2B, Table 2).

4. Discussion

The principal findings of this study include the identification of (1) recurrent URIs, GERD and neck trauma as the best independent predictors of the extrinsic risk for SD development, and (2) the associated specific pattern of neural alterations that is influenced by the extrinsic risk in susceptible individuals. Combined, these findings suggest the presence of multifactorial pathophysiology of SD and provide a finer grained understanding of possibly divergent mechanisms underlying symptom development in this disorder.

Among the identified risk factors contributing to the onset of SD, URIs have been commonly reported in previous observational studies [4–6]. Substantiating these reports and adding GERD and neck trauma as other significant extrinsic risk factors for SD manifestation, we suggest that repeated insults directed specifically to the peripheral (laryngeal) sensory feedback may play an important role in triggering dystonic symptoms. As sensory feedback is essential for providing information to fine tune and improve the motor output during production of highly complex motor behaviors, these extrinsic risk factors likely act upon higher individual susceptibility to laryngeal sensory alterations, as well as might be coupled with the intrinsic predisposition to aberrant central sensory processing. In line with this, it was reported that SD patients have a subclinically longer reaction time to initiate a motor sequence [20], an extended temporal discrimination threshold to process visual stimuli [21], and abnormal activity of primary somatosensory cortex that is correlated with their symptom severity while being decoupled from activity of motor cortex [8]. Abnormal processing of peripheral sensory information was also found in the other forms of focal task-specific dystonias, such as writer's cramp and musician's focal hand dystonia [22,23], pointing to a unifying trait across dystonias.

The pathophysiological relevance of the identified extrinsic risk factors is further extended by their association with unique neural alterations. Following the concept that aberrant sensory processing plays a fundamental role in the pathophysiology of dystonia [24], our data suggest that abnormal hypoactivity of IPC is a distinctive pathophysiological feature. It is notable that IPC alterations were commonly present across all SD patients, both with and without the exposure to the risk factors, albeit being more prominent in patients with familial SD. The latter finding is consistent with a previous report of a strong association between vulnerable functional connectivity of IPC and polygenic dystonia risk in SD patients [13], suggesting that IPC might be a focal point of influence by both genetic and environmental factors in susceptible individuals. The IPC is known to be involved in sensorimotor processing and integration prior to execution of voluntary movements [25–27], including semantic and phonological processing [28], as well as in a formation of action-oriented mental representations that allow for the conception of a motor act [29,30]. The IPC establishes strong connectivity with laryngeal motor cortex [31], with its PGa subdivision linked additionally to inferior frontal gyrus, ventral premotor cortex and basal ganglia and the PGp subdivision connected with ventromedial prefrontal cortex [32]. Independent of SD genotype, alterations in PGa area of IPC, premotor cortex, insula and striatum unified patients exposed to the extrinsic risk factors, whereas abnormalities in PGa/PGp areas of IPC, primary motor cortex and auditory cortex were common in patients not exposed to the extrinsic risk. Hence, brain alterations in regions necessary for sensorimotor preparation and integration characterized patients exposed to the risk factors vs. abnormalities in regions responsible for primary sensory processing and motor output in patients not exposed to these factors. Based on these findings, we propose a pathophysiological model where repeated peripheral somatosensory stressors (i.e., recurrent URI, GERD and neck injury) influence the internal representations and sensorimotor integration of speech-related movements via the premotor-inferior parietal-insular-striatal loop, ultimately triggering SD symptom manifestation in susceptible individuals (Fig. 3). Alternatively, the pathophysiological loop devoid of extrinsic influences involves direct alterations of primary sensory and motor regions that are responsible for the initial cortical auditory input and final cortical motor output necessary for speech production.

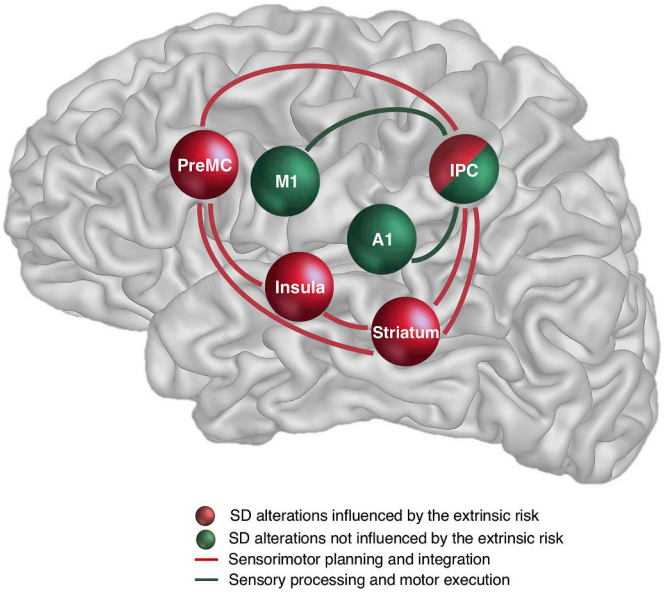

Fig. 3. Schematic presentation of distinct regional brain alterations dependent on the influence of extrinsic risk factors in spasmodic dysphonia. PreMC - premotor cortex; M1 - primary motor cortex; A1 - primary somatosensory cortex; IPC - inferior parietal cortex.

In summary, the integration of our findings from the case-control and neuroimaging studies identified recurrent URIs, GERD, and neck injury as extrinsic risk factors for SD development and determined differentially distributed patterns of sensorimotor abnormalities in these patients dependent on the contributing influence of the extrinsic risk. Based on these findings, a novel consideration of SD pathophysiology as a multifactorial sensorimotor network disorder, which is influenced by the presence of both extrinsic environmental (i.e., recurrent URIs, neck trauma, GERD) and intrinsic genetic (e.g., familial history of dystonia, polygenic risk [13]) factors can be formulated. As such, preventive and rehabilitative strategies could be developed to modulate abnormal peripheral sensory feedback and central processing, offering new possibilities for personalized interventions in carefully stratified patient populations that may be geared towards somatosensory stimulation, re-wiring of auditory or visual feedback, or sensory deprivation by means of immobilization.

Study funding

This study was funded by the grant R01DC011805 from the National Institute on Deafness and Other Communication Disorders, National Institutes of Health to KS.

Relevant conflicts of interest/financial disclosures

None.

Acknowledgments

This study was funded by the National Institute on Deafness and Other Communication Disorders, National Institutes of Health (R01DC011805) to K.S. ClinicalTrials.gov Identifier: NCT03042975. Statistical analysis was conducted with support from the Harvard Catalyst, the Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL1TR002541).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.05.034.

References

[1] A. Blitzer, Spasmodic dysphonia: focal laryngeal dystonia, in: K. Kompoliti, L.V. Metman (Eds.), Encyclopedia of Movement Disorders, Academic Press, Oxford, 2010, pp. 130–132.
[2] D.N. Kirke, S.J. Frucht, K. Simonyan, Alcohol responsiveness in laryngeal dystonia: a survey study, J. Neurol. 262 (6) (2015) 1548–1556.
[3] A. Blitzer, M.F. Brin, K. Simonyan, L.J. Ozelius, S.J. Frucht, Phenomenology, genetics, and CNS network abnormalities in laryngeal dystonia: a 30-year experience, Laryngoscope 128 (Suppl 1) (2018) S1–S9.
[4] L. Childs, S. Rickert, T. Murry, A. Blitzer, L. Sulica, Patient perceptions of factors leading to spasmodic dysphonia: a combined clinical experience of 350 patients, Laryngoscope 121 (10) (2011) 2195–2198.
[5] K. Tanner, N. Roy, R.M. Merrill, K. Kimber, C. Sauder, D.R. Houtz, D. Doman, M.E. Smith, Risk and protective factors for spasmodic dysphonia: a case-control investigation, J. Voice 25 (1) (2011) e35–46.
[6] T. Murry, Spasmodic dysphonia: let's look at that again, J. Voice 28 (6) (2014) 694–699.
[7] B. Haslinger, P. Erhard, C. Dresel, F. Castrop, M. Roettinger, A.O. Ceballos-Baumann, Silent event-related" fMRI reveals reduced sensorimotor activation in laryngeal dystonia, Neurology 65 (10) (2005) 1562–1569.
[8] K. Simonyan, C.L. Ludlow, Abnormal activation of the primary somatosensory cortex in spasmodic dysphonia: an fMRI study, Cereb. Cortex 20 (11) (2010) 2749–2759.
[9] K. Simonyan, C.L. Ludlow, Abnormal structure-function relationship in spasmodic dysphonia, Cereb. Cortex 22 (2) (2012) 417–425.
[10] F. Giovannelli, L. Marsili, A. Suppa, F. Di Stasio, L. Rocchi, N. Upadhyay, M. Cincotta, G. Ruoppolo, A. Berardelli, 116. Functional connectivity between cortical speech network and primary motor cortex is abnormal in spasmodic dysphonia, Clin. Neurophysiol. 126 (1) (2015) e27.
[11] G. Battistella, S. Fuertinger, L. Fleysher, L.J. Ozelius, K. Simonyan, Cortical sensorimotor alterations classify clinical phenotype and putative genotype of spasmodic dysphonia, Eur. J. Neurol. 23 (10) (2016) 1517–1527.
[12] K. Simonyan, Neuroimaging applications in dystonia, Int. Rev. Neurobiol. 143 (2018) 1–30.
[13] G.G. Putzel, G. Battistella, A.F. Rumbach, L.J. Ozelius, M.R. Sabuncu, K. Simonyan, Polygenic risk of spasmodic dysphonia is associated with vulnerable sensorimotor connectivity, Cereb. Cortex 28 (1) (2018) 158–166.
[14] C.L. Ludlow, R. Domangue, D. Sharma, H.A. Jinnah, J.S. Perlmutter, G. Berke, C. Sapienza, M.E. Smith, J.H. Blumin, C.E. Kalata, K. Blindauer, M. Johns, E. Hapner, A. Harmon, R. Paniello, C.H. Adler, L. Crujido, D.G. Lott, S.F. Bansberg, N. Barone, T. Drulia, G. Stebbins, Consensus-based attributes for identifying patients with spasmodic dysphonia and other voice disorders, JAMA Otolaryngol. Head Neck Surg. 144 (8) (2018) 657–665.
[15] R.M. Crum, J.C. Anthony, S.S. Bassett, M.F. Folstein, Population-based norms for the Mini-Mental State Examination by age and educational level, JAMA 269 (18) (1993) 2386–2391.
[16] G.G. Putzel, T. Fuchs, G. Battistella, E. Rubien-Thomas, S.J. Frucht, A. Blitzer, L.J. Ozelius, K. Simonyan, GNAL mutation in isolated laryngeal dystonia, Mov. Disord. 31 (5) (2016) 750–755.
[17] T.J. Cole, D.W. Hosmer, S. Lemeshow, Applied Logistic Regression, Wiley, New York, 1989, pp. 1162–1163 No. of pages: xiii 307. Price: £36.00, Stat. Med. 10(7) (1991).
[18] S. Lewallen, P. Courtright, Epidemiology in practice: case-control studies, Community Eye Health 11 (28) (1998) 57–58.
[19] F.X. Creighton, E. Hapner, A. Klein, A. Rosen, H.A. Jinnah, M.M. Johns, Diagnostic delays in spasmodic dysphonia: a call for clinician education, J. Voice 29 (5) (2015) 592–594.
[20] K. Simonyan, B.D. Berman, P. Herscovitch, M. Hallett, Abnormal striatal dopaminergic neurotransmission during rest and task production in spasmodic dysphonia, J. Neurosci. 33 (37) (2013) 14705–14714.
[21] P. Termsarasab, R.A. Ramdhani, G. Battistella, E. Rubien-Thomas, M. Choy, I.M. Farwell, M. Velickovic, A. Blitzer, S.J. Frucht, R.B. Reilly, M. Hutchinson, L.J. Ozelius, K. Simonyan, Neural correlates of abnormal sensory discrimination in laryngeal dystonia, Neuroimage Clin. 10 (2016) 18–26.
[22] J. Konczak, G. Abbruzzese, Focal dystonia in musicians: linking motor symptoms to somatosensory dysfunction, Front. Hum. Neurosci. 7 (2013) 297.
[23] L. Avanzino, M. Fiorio, Proprioceptive dysfunction in focal dystonia: from experimental evidence to rehabilitation strategies, Front. Hum. Neurosci. 8 (2014) 1000.
[24] M. Hallett, Is dystonia a sensory disorder? Ann. Neurol. 38 (2) (1995) 139–140.
[25] B.T.T. Yeo, F.M. Krienen, J. Sepulcre, M.R. Sabuncu, D. Lashkari, M. Hollinshead, J.L. Roffman, J.W. Smoller, L. Zöllei, J.R. Polimeni, B. Fischl, H. Liu, R.L. Buckner, The organization of the human cerebral cortex estimated by intrinsic functional connectivity, J. Neurophysiol. 106 (3) (2011) 1125–1165.
[26] M.I. Sereno, R.-S. Huang, Multisensory maps in parietal cortex, Curr. Opin. Neurobiol. 24 (1) (2014) 39–46.
[27] S. Fuertinger, B. Horwitz, K. Simonyan, The functional connectome of speech control, PLoS Biol. 13 (7) (2015) e1002209.
[28] C.J. Price, The anatomy of language: contributions from functional neuroimaging,

J. Anat. 197 Pt 3 (2000) 335–359.
[29] L. Jäncke, A. Kleinschmidt, S. Mirzazade, N.J. Shah, H.J. Freund, The role of the inferior parietal cortex in linking the tactile perception and manual construction of object shapes, Cereb. Cortex 11 (2) (2001) 114–121.
[30] S. Caspers, A. Schleicher, M. Bacha-Trams, N. Palomero-Gallagher, K. Amunts, K. Zilles, Organization of the human inferior parietal lobule based on receptor architectonics, Cereb. Cortex 23 (3) (2013) 615–628.
[31] V. Kumar, P.L. Croxson, K. Simonyan, Structural organization of the laryngeal motor cortical network and its implication for evolution of speech production, J. Neurosci. 36 (15) (2016) 4170–4181.
[32] L.Q. Uddin, K. Supekar, H. Amin, E. Rykhlevskaia, D.A. Nguyen, M.D. Greicius, V. Menon, Dissociable connectivity within human angular gyrus and intraparietal sulcus: evidence from functional and structural connectivity, Cerebr. Cortex 20 (11) (2010) 2636–2646.