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Atypical somatosensory-motor cortical response during vowel vocalization in spasmodic dysphonia

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HIGHLIGHTS

- Inhibition of slow motor cortical rhythms during vocalization is reduced in spasmodic dysphonia.
- Somatosensory-motor cortical synchrony during vocalization is excessive in spasmodic dysphonia.
- Abnormal cortical processing in spasmodic dysphonia is mainly lateralized in the left hemisphere.

ABSTRACT

Objective: Spasmodic dysphonia (SD) is a debilitating voice/speech disorder without an effective cure. To obtain a better understanding of the underlying cortical neural mechanism of the disease we analyzed electroencephalographic (EEG) signals of people with SD during voice production.
Method: Ten SD individuals and 10 healthy volunteers produced 50 vowel vocalization epochs of 2500 ms duration. Two EEG features were derived: (1) event-related change in spectral power during vocalization relative to rest, (2) inter-regional spectral coherence.
Results: During early vocalization (500–1000 ms) the SD group showed significantly larger alpha band spectral power over the left motor cortex. During late vocalization (1000–2500 ms) SD patients showed a significantly larger gamma band coherence between left somatosensory and premotor cortical areas.
Conclusions: Two atypical patterns of cortical activity characterize the pathophysiology of spasmodic dysphonia during voice production: (1) a reduced movement-related desynchronization of motor cortical networks, (2) an excessively large synchronization between left somatosensory and premotor cortical areas.
Significance: The pathophysiology of SD is characterized by an abnormally high synchronous activity within and across cortical neural networks involved in voice production that is mainly lateralized in the left hemisphere.
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1. Introduction

Spasmodic dysphonia (SD) is the third most prevalent type of dystonia (Castelon Konkiewitz et al., 2002) manifesting itself through speech-related involuntary contractions of the laryngeal musculature (Ludlow, 2009). Clinical manifestations of SD include difficulty in pronouncing words beginning with or containing vowels (adductor SD) or voiceless consonants (abductor SD) (Ludlow, 2011). A subgroup of patients also experiences the co-occurrence of voice tremor. Treatment options for SD are symptomatic in effect; mainly, the cyclical injection of Botulinum Toxin (BOTOX) to the laryngeal musculature, and selective laryngeal denervation surgeries (Ludlow, 2009).

The underlying pathophysiological mechanism of SD is largely unknown. Abnormal long-latency responses to peripheral nerve stimulation have been observed in SD (Ludlow et al., 1995) and

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other forms of focal dystonia such as blepharospasm and oromandibular dystonia (Berardelli et al., 1985). A shortened cortical silent period, indicative of reduced cortical inhibition, is another consistent feature of focal dystonia that has recently been confirmed in SD (Samargia et al., 2014). In the last decade, postmortem histological studies identified a range of structural abnormalities in SD, such as white matter changes (loss of axonal density and myelin content) in the genu of the internal capsule where head and neck muscles are represented (Simonyan et al., 2008). This was followed by the observation of subtle brainstem abnormalities in the reticular formation, and mild degeneration and depigmentation of the substantia nigra and the locus coeruleus (Simonyan et al., 2010). Furthermore, functional brain imaging assessments identified areas of abnormal activation that include the primary motor, premotor, and somatosensory cortex. However, the results are mixed; with one study showing reduced activation (Haslinger et al., 2005), while another reported increased activation of sensorimotor cortical areas in SD during voice production (Simonyan and Ludlow, 2010), compared to healthy adults. The discrepancy in outcomes might be attributable to differences in the vocalization task, i.e., testing symptomatic versus asymptomatic voice/speech production.

With respect to other forms of focal dystonia, analysis of EEG signals has confirmed signs of reduced cortical inhibition during movement execution. A movement-related reduction of beta band desynchronization has been shown in cervical and segmental dystonia (Crowell et al., 2012; Miocinovic et al., 2015) and in writer's cramp (Toro et al., 2000). For the SD, however, no equivalent movement-related EEG data exist, except for one report documenting a widespread abnormal bilateral resting-state activity in the delta and theta bands (Devous et al., 1990).

Previous work by our team had shown a generalized proprioceptive deficit in musician's dystonia (Konczak and Abbruzzese, 2013) and in SD (Konczak et al., 2015). This raises the question if one can identify atypical patterns of somatosensory activation and/or abnormal interaction between somatosensory and motor cortical areas that underlie the observed proprioceptive and motor dysfunction in spasmodic dysphonia. Previous studies using transcranial magnetic stimulation and functional brain imaging techniques have already provided evidence for abnormal patterns of functional connectivity between and within sensorimotor cortical areas in SD. For example, Giovannelli et al. (2015) reported abnormal excitability of the motor cortical area of the dominant hand during specific linguistic tasks in SD, which was interpreted as an atypical functional connectivity between the primary motor cortex and the cortical speech network. Battistella et al. (2016) showed significant decreases in the resting-state functional connectivity of the sensorimotor cortex and frontoparietal network in SD in relation to healthy controls. Putzel et al. (2018) showed that the polygenic risk of spasmodic dystonia was significantly correlated with a decline of functional connectivity in the left premotor/primary sensorimotor and inferior parietal cortices.

While functional neuroimaging assessments have advanced our understanding of the underlying neural mechanisms of SD, the inherent slow dynamics of these technologies necessitates the implication of higher temporal-resolution electrophysiological recordings that allow for the investigation of the transient brain processes that may contribute to the pathomechanism of the disease. Thus, this study recorded EEG signals to unveil the cortical activation dynamics associated with voice production in spasmodic dysphonia. Our specific aims were to (a) characterize the transient cortical processes underlying the voice/speech production, and (b) to extend previous work that had documented abnormal cortical activity during rest in SD (Devous et al., 1990). Characterizing the cortical activation patterns associated with voice production in patients with spasmodic dysphonia helps to elucidate further the underlying mechanisms of the disease. It may yield a more objective approach to differentiate SD from other voice disorders with overlapping symptoms such as muscle tension dysphonia.

2. Methods

2.1. Participants

Ten spasmodic dysphonia patients (6 females, 4 males) from the Fairview Clinic at the University of Minnesota (mean age ± standard deviation: 58.4 ± 13.3 years), and ten age and gender-matched control participants attended the study. The experimental protocol was approved by the University of Minnesota Institutional Review Board. All participants gave their informed consent prior to the experiment. Patients receiving botulinum toxin treatment were tested towards the end of their injection cycle (see Tables 1 and 2 for the clinical characteristics of SD participants).

A potential concern with regard to the recruitment of SD participants might be the issue of vocal fold immobility that is usually observed with higher dose, unilateral BOTOX injections. Patients in this study, however, had low dose injections given into both vocal folds (ranging between 0.2 and 2 units per vocal fold with the dose based on symptom response). With this technique, the vocal fold immobility is typically not present. Vocal fold bowing can occasionally be seen with laryngoscopy in the early (breathy) period after the first few days and can last for weeks following the injection. However, these laryngoscopic findings are absent during the period of improved vocal quality or the period of recurrence of vocal spasms (Brin et al., 1989). Since the timing of the subsequent BOTOX injection and, thus, inclusion in the study were symptom-based, vocal fold immobility was not expected to be present.

2.2. Description of the behavioral task

The experiment was held in an electrically and acoustically shielded chamber. Participants sat on a comfortable chair and were asked to restrict limb and body movements during recording. Upon receiving a 250 ms-long auditory cue (1000 Hz, 98 dB) they pronounced the vowel /a/ for 2500 ms. Cessation of vocalization was triggered by a second 250 ms-long auditory cue. Vocalization was repeated 50 times with 3000 ms resting intervals in between trials. Cortical EEG was recorded simultaneously. The task was performed in an eyes-open condition with participants focusing gaze at a fixation point on the front wall.

The following measures were used to examine the quality of voice in SD participants: (1) the number of voice breaks, (2) voice tremor, (3) the harmonics-to-noise ratio (HNR), and (4) a self-rated effort scale (range: 0 (easiest) to 10 (hardest)) for the vocalization of vowel /a/ and for reading a series of standard sentences devised for the assessment of voice quality in adductor/abductor spasmodic dysphonia (Woodson, 2010) (see the Appendix). The HNR, measured in dB, is an indication of the level of hoarseness of the voice, defined as the ratio of the periodic aspect of the voice to the random noise (Yumoto et al., 1982). It is reported that healthy adults have an HNR of around 10 dB (de Felippe et al., 2006). The PRAAT software was used for the analysis of the voice data (Boersma and van Heuven, 2001).

2.3. EEG recording

Electroencephalographic data were recorded using the ActiveTwo data acquisition system (Biosemi B.V. Ltd, Amsterdam, Netherlands) at the sampling rate of 512 Hz. Brain potentials were captured over 64 active electrodes embedded in the Biosemi EEG cap according to the Biosemi designed equiradial system.

Table 1
Clinical characteristics of the study participants.

Subject ID	Gender	Age	SD Type	Diagnosis Duration (mo.)	BOTOX Cycle (mo.)	Last BOTOX Injection (mo.)
SD 01	Male	60	Adductor	50	>3	3
SD 02	Male	73	Abductor	180	NA	36
SD 03	Female	57	Adductor	36	NA	NA
SD 04	Female	62	Adductor	411	5	2
SD 05	Male	26	Adductor	93	2–5	2.5
SD 06	Female	65	Adductor	204	2	2
SD 07	Female	56	Adductor	324	6	6
SD 08	Female	57	Adductor	15	3	3
SD 09	Male	74	Adductor	396	4	4
SD 10	Female	54	Adductor	288	3	3.5

Table 2
Clinical characteristics of the recorded voice data.

Subject ID	Number of Voice Breaks	Voice Tremor	HNR (dB)	Self-Rated Effort Scale (Abductor/Adductor Sentences)	Self-Rated Effort Scale (Vowel /a/)
SD 01	0	No	10.10	2	3
SD 02	12	No	15.20	3	2
SD 03	9	Moderate	8.80	5	7
SD 04	0	Mild to moderate	7.01	4	5
SD 05	2	No	13.02	7	6
SD 06	4	Mild to moderate	7.67	9	8
SD 07	2	Mild	17.09	2	2
SD 08	0	No	13.67	2	3
SD 09	0	No	17.75	2	2
SD 10	0	No	19.71	3	3

Participants were guided throughout the experiment by a series of auditory cues generated by the RPvdsEx software and the Tucker-Davis system (Tucker-Davis Technologies Ltd., Alachua, FL, USA). The event time-stamps were captured by the ActiveTwo system in a separate channel.

2.4. EEG signal processing

We used the MATLAB EEGLab toolbox version 13.6.5 (Delorme and Makeig, 2004) for the offline analysis of EEG data. EEG recordings were referenced to the average of two external electrodes attached to the left and right mastoid bones. Baseline drifts were removed by zero-phase 1 Hz high-pass filtering, and the power line noise (50 Hz) was excluded by zero-phase notch-filtering. Channels were then re-referenced to the common average of all electrodes to reduce the effect of non-cortical sources that may have been commonly captured. Segments of recording from 1000 ms before vocalization to 2500 ms afterward were derived as data epochs. Subsequently, we performed independent component analysis (ICA) on all 64 channels of data using the 'runica' algorithm and applied an automated multiple artifact rejection algorithm 'SASICA' (Chaumon et al., 2015) on the generated components to remove the contaminated ICs. The 'SASICA' algorithm uses spatiotemporal criteria to distinguish cortical components from artifactual ICs. This step was critical for removing muscle artifacts that may have interfered with the EEG data during vocalization. Finally, the remaining components were linearly added, and the resultant dataset was used for EEG feature extraction.

The following two measures were derived from the EEG data using the EEGLab functions: (1) event-related spectral perturbation (ERSP) at individual somatosensory and pre-motor/motor cortical electrodes (Makeig, 1993); and (2) event-related coherence (ERCOH) between somatosensory and premotor cortical electrodes (Pfurtscheller and Andrew, 1999).

ERSP reflects the logarithm of the event-related deviation in spectral power in relation to the baseline resting state (in dB). ERCOH (unit-less, ranging from 0 to 1) calculates the event-related coherence at different frequency bins between two electrodes and represents the level of synchronous activity between the two sites. EEG data epochs were pre-whitened prior to coherence computations to remove potential autocorrelations or trends that might have interfered with the results.

The conventional event-related averaging of epochs aims at capturing the synchronous neural activity that is both time- and phase-locked to a given stimulus. This, however, does not allow for probing the ongoing oscillatory activity that underlies individual components. Thus, it is possible that the latency jitter of single trials generated by background noise or delayed response latencies distort the overall averaged outcome. In order to control for jitter, we first applied the time-frequency analysis on individual trials, and then averaged the outcomes across all trials. Such induced activity is known to be dominantly generated by neuronal synchronizations which are reflective of coherent firing patterns that induce large fluctuations in the membrane potential of a cluster of neurons and contribute to the transfer of information between different brain regions (David et al., 2006; Koerner and Zhang, 2018).

Band-specific measures were computed for the physiologically-relevant frequency bands (i.e. < 50 Hz): theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and low gamma (30–49 Hz). Because the first 500 ms of the recording could also reflect cortical auditory evoked potentials or be affected by a participant's reaction time (Santee and Kohfeld, 1977), EEG assessments corresponding to vocalization focused on 500 ms post-stimulus to the end of the trial (2500 ms). In order not to miss early transient movement-related cortical phenomena (Riehle et al., 2013), this 2000 ms-long vocalization period was further divided into two windows: (1) early vocalization (500–1000 ms); and (2) late vocalization (1000–2500 ms).

EEG features were extracted for 12 electrode sites: CP3, CP4, CP5, CP6, C3, C4, C5, C6, FC3, FC4, FC5, and FC6. Centro-parietal electrodes (CP3, CP4, CP5, and CP6) were nearby somatosensory cortical areas. Central electrodes (C3, C4, C5, and C6) were nearby motor cortical areas. Fronto-central electrodes (FC3, FC4, FC5, and FC6) were nearby premotor areas. Locations '3' and '5' refer to the

cortical areas nearby the vocalization region on the left somatosensory and motor homunculi, while locations '4' and '6' refer to the corresponding positions in the right hemisphere (Caviness et al., 2006; Mor et al., 2017). ERSP measures were derived for each of the 12 electrodes at 4 distinct frequency bands (theta, alpha, beta, and gamma). ERCOH measures were derived for 4 electrode pairs: (CP3, FC3), (CP5, FC5), (CP4, FC4), and (CP6, FC6), for the same 4 frequency bands.

2.5. Statistical analysis

Statistical comparisons were applied for all electrodes/electrode-pairs, at each distinct frequency band between the two groups. The Kolmogorov-Smirnov test was used to assess the normality of the EEG data. Because the data were not normally distributed, the non-parametric Mann-Whitney U-test was applied for group comparisons. For each distinct frequency band, and for the cluster of electrodes within the left/right hemisphere, p-values were adjusted for multiple comparisons via false discovery rate (FDR) correction based on the Benjamini-Hochberg method (Benjamini and Hochberg, 1995). The significance level was set at 0.05. The effect size was computed using Cohen's d.

3. Results

3.1. Focal somatosensory/motor cortical synchronization based on ERSP

To illustrate the differences in cortical processing between healthy controls and people with SD during vocalization, Fig. 1 presents an exemplary time-frequency plot of the somatosensory (CP5) and premotor (FC5) cortical ERSP for one healthy and one SD participant. Expectedly, vocalization in the healthy participant was associated with the suppression of cortical oscillations below 30 Hz and the excitation of gamma band. In comparison, the SD patient showed higher levels of spectral power across most frequency bands.

The first step of the EEG analysis focused on markers of intra-regional cortical synchronization/desynchronization over those electrodes that encompass laryngeal somatosensory, premotor and motor cortical areas. We found that during the early stage of vocalization, the median of the alpha band ERSP in the SD group was significantly higher over the left motor cortex (C5: $p = 0.03$, *Cohen's* $d = 1.21$, and C3: $p = 0.03$, *Cohen's* $d = 1.28$). In contrast, assessment of the late vocalization period did not show any significant median ERSP differences between the two groups (see Fig. 2).

3.2. Inter-regional somatosensory-motor cortical synchronization based on ERCOH

A coherence analysis was performed to examine potential differences in the spectral characteristics of somatosensory-motor cortical interactions in each hemisphere. We found that during the early stage of vocalization median ERCOH in all frequency bands tended to be larger for SD patients for both hemispheres when compared to healthy volunteers. The relative median ERCOH surplus for SD patients in the left hemisphere (CP5, FC5) was computed as follows: theta band = +22%; alpha band = +28%; beta band = +27%; gamma band = +13%. For the right hemisphere (CP6, FC6) the same analysis yielded: theta band = +30%; alpha band = +37%; beta band = +6%; gamma band = +18%. However, no statistically significant difference was detected between the two groups.

Analysis of the gamma band ERCOH during late vocalization yielded a significantly higher median for the SD group in comparison to controls ((CP5, FC5): $p = 0.03$, *Cohen's* $d = 1.06$). Fig. 3B highlights that during late vocalization, the SD group tended to exhibit an enlarged somatosensory-premotor cortical coherence in both hemispheres and in the other three frequency bands as well. The relative median ERCOH change for SD patients in the left hemisphere (CP5, FC5) was: theta band = +34%; alpha band = +57%; beta band = +30%; gamma band = +28%. The respective relative median ERCOH change in the right hemisphere (CP6, FC6) was: theta band = +36%; alpha band = +11%; beta band = −4%; gamma band = +35%).

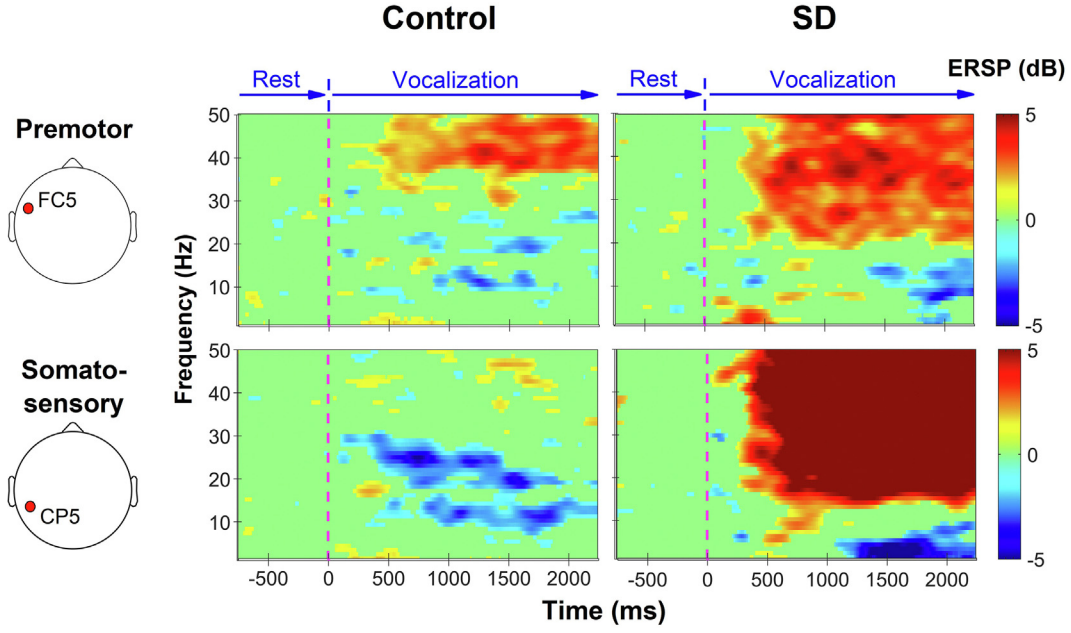

Fig. 1. Example spectrograms of somatosensory (CP5) and premotor (FC5) cortical electrodes in one healthy and one SD participant during vocalization. Green indicates no significant change in relation to baseline (rest). Blue color depicts the suppression of oscillatory activities in relation to the baseline, and the red color shows the excitation of oscillations in relation to the baseline level. Vocalization in the healthy participant is associated with the suppression of lower frequency oscillations and excitation of gamma band. The SD patient shows smaller suppression (or excitation) in the majority of time-frequency bins. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

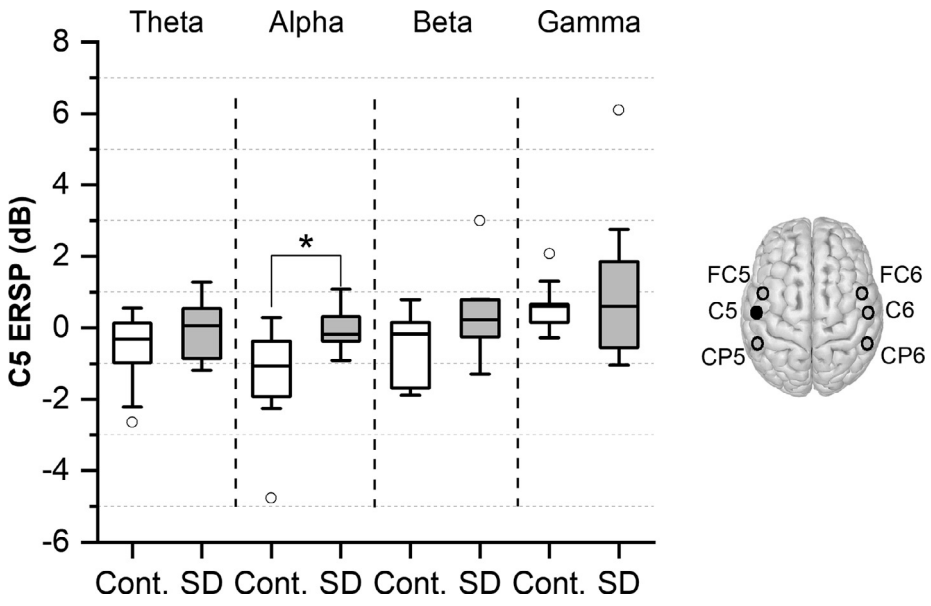

Fig. 2. Comparison of motor cortical ERSP at electrode 'C5' between the SD and control groups during early vocalization (500–1000 ms post-vocalization). The boxplots are generated based on individual ERSP values within each group and for four distinct frequency bands (theta, alpha, beta, and gamma). Lower and upper boundary of each box indicates the 25% and 75% quartiles, respectively. The horizontal line within the box depicts the median. The upper and lower whiskers extend to +1.5 and −1.5 inter-quartile range, respectively. Outliers are shown as white circles. *indicates a *p-value < 0.05*.

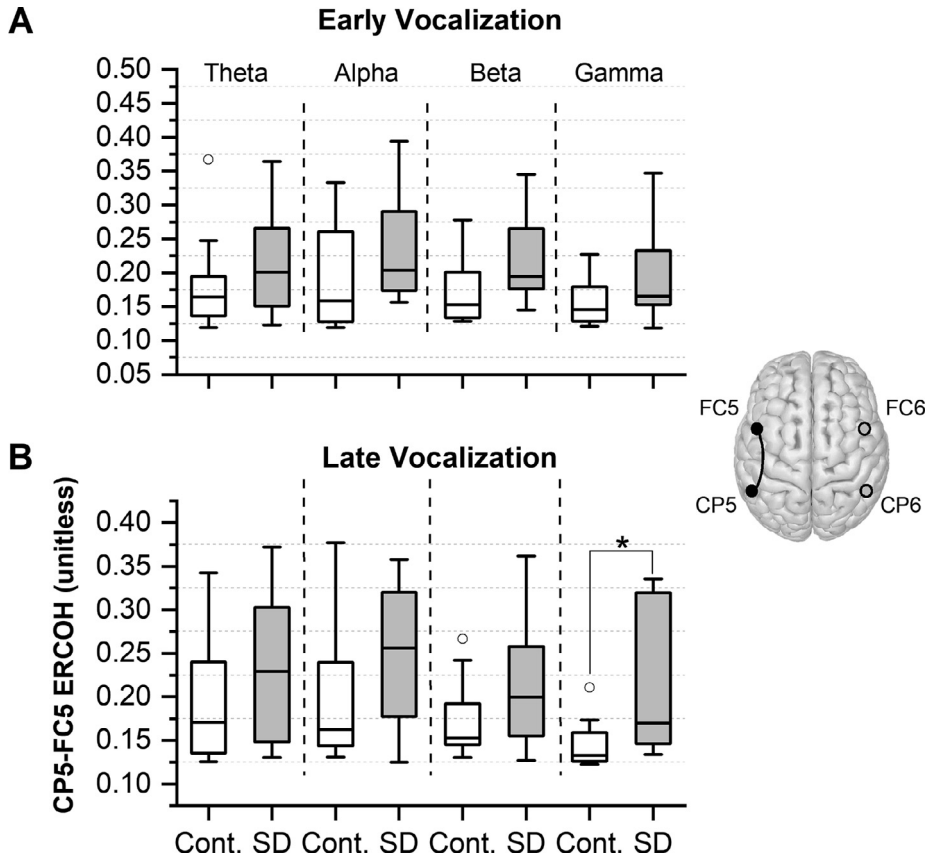

Fig. 3. Comparison of (CP5, FC5) ERCOH for four distinct frequency bands (theta, alpha, beta, and gamma) between SD participants and the control group (A) during early vocalization (500–1000 ms post-vocalization), and (B) during late vocalization (1000–2500 ms post-vocalization). The boxplots are generated based on individual coherence values within each group. The lower and upper boundaries of each box depict the 25% and 75% quartiles, respectively. The median is marked by the horizontal line within the box. The upper and lower whiskers extend to +1.5 and −1.5 inter-quartile range, respectively. Outliers are shown as white circles. *indicates a *p-value < 0.05*.

Although the SD and control participants in this study were gender- and age-matched, we sought to account for the effect of age on the outcome measures. To that effect, statistical group comparisons were evaluated via linear mixed effect modeling (Koerner and Zhang, 2018). ERSP or ERCOH constituted the dependent variable. GROUP (SD or Control) was set as the independent

variable, and AGE represented the random effect variable. Controlling for the effect of age, a significant group-difference was detected for the alpha band ERSP during early vocalization *(p = 0.04)*, not for gamma band ERCOH during late vocalization *(p = 0.06)*.

In addition, the relationship between disease duration and each of the significantly different neural measures (i.e., alpha band ERSP and gamma band ERCOH) was evaluated. The results revealed a significant positive relationship between the late-vocalization gamma band ERCOH and disease duration *(p = 0.008)*. This indicates that patients with longer disease duration tended to exhibit higher levels of left hemispheric parieto-motor cortical interactions.

4. Discussion

The purpose of this study was to provide a systematic assessment of the spectral characteristics of somatosensory-motor cortical activities and interactions during vowel vocalization in spasmodic dysphonia. Our findings revealed that an excessive intra- and inter-regional somatosensory-motor cortical synchronization during vowel vocalization is a characteristic feature of spasmodic dysphonia.

4.1. Abnormally large left motor cortical synchronization in SD

To the best of our knowledge, our work is one of the first studies that attempted to characterize the dynamics of transient somatosensory/motor cortical processes associated with spasmodic dysphonia. Previous research had applied functional brain imaging methods for this purpose, which due to the slower dynamics of these techniques, did not allow for capturing the fast cortical neuronal phenomena that correspond to abnormal speech phonatory functioning. Moreover, the only study which used EEG to identify cortical abnormalities in SD only captured the resting-state patterns (Devous et al., 1990).

It is well established that rhythmic neuronal activities over the sensorimotor cortex within the alpha and beta frequency bands are modulated during goal-directed movements (Brinkman et al., 2014). The rise of alpha band amplitude has been interpreted to reflect either the inhibition of task-irrelevant or the integration of task-relevant activity (Doesburg et al., 2009). Moreover, the increase of alpha band oscillatory amplitude is believed to indicate synchronized firing patterns in the underlying neuronal populations (Palva and Palva, 2011). In our assessments, both the healthy controls and SD participants exhibited the expected pattern of low-frequency cortical desynchronization during vocalization in relation to the resting state. However, in the SD group, this cortical inhibition tended to be lower over bilateral laryngeal somatosensory-motor cortical regions and was significantly lower over the left motor cortex in the alpha band. Our finding is compatible with previous reports of reduced cortical inhibition in SD as indicated by a reduced cortical silent period (Samargia et al., 2014) and reduced movement-related cortical desynchronization in other forms of focal dystonia (Toro et al., 2000, Crowell et al., 2012, Miocinovic et al., 2015) and may be reflective of overlapping underlying neural mechanisms in these dystonia subtypes.

4.2. Abnormally large left somatosensory-premotor cortical synchronization in SD

Our second aim in this study was to evaluate interregional interactions between somatosensory and motor cortical areas during active voice production in SD. Our analysis revealed that the synchronized activity between somatosensory and premotor cortices was abnormal for SD individuals. Within the patient group, the event-related coherence, a frequency-specific measure of functional connectivity, was significantly elevated in the left hemisphere in the gamma band during late vocalization. Synchronization of neuronal activities in the gamma band is known to correspond to task-specific functions such as somatosensory processing (Bauer et al., 2006) and motor preparation (Engel et al., 2001; Nowak et al., 2018). Cortical gamma oscillations have been detected during the speech (Palva et al., 2002) and are known to be related to the semantic retrieval of individual words and the integration between word pairs (Maguire and Abel, 2013). The gamma rhythm is also considered as a temporal code for performing complicated forms of information processing through neuronal coherence (Varela et al., 2001). Because the coordinated activity of neuronal networks across dispersed brain regions is implicated in neuronal communication (Arce-McShane et al., 2016), the excessive somatosensory-premotor coherence in SD suggests an abnormally large degree of interaction between these cortical regions in this disorder.

In addition, previous research documented defective sensorimotor integration mechanisms in other forms of dystonia (Breakefield et al., 2008; Butterworth et al., 2003; Quartarone et al., 2006). Accordingly, our observation of an excessive gamma band spectral coherence between somatosensory and motor cortical areas in SD might be a sign of atypical processes of sensorimotor integration in this disorder.

The observed pattern of excessive cortical synchronization can also be linked to the previously reported structural abnormalities in SD, e.g., the loss of axonal density and myelin content in the genu of the internal capsule (Simonyan et al., 2008) and the depigmentation of the substantia nigra (Simonyan et al., 2010). These structural changes can affect the regulation of brain's inhibitory processes, such as the reduction of the GABAergic outputs of the substantia nigra (Lee et al., 2011), which may consequently contribute to the disinhibition of the basal ganglia-thalamocortical circuitry and the atypical rise of task-specific cortical synchronizations in SD.

Moreover, abnormal patterns of cortical processing in SD were found to be largely lateralized over the left cortex, which likely reflects the functional lateralization of voice and speech production in the left hemisphere.

4.3. Limitations of the study

A main limitation of this study lies in the general weakness of EEG to localize the exact source of the detected cortical activity. While the EEG feature extraction was performed using electrodes that were nearby the vocalization region of the somatosensory and motor cortical homunculi (Mor et al., 2017), the precise localization of the detected abnormalities cannot be obtained. Another limitation of the study is that our analysis cannot establish a causal relationship between the excessive cortical synchronization observed in SD patients and the overt symptoms. That is to say, we cannot differentiate from our data, if the observed cortical patterns reflect a primary deficit or have to be understood as a compensatory response of the sensorimotor networks involved in voice production.

In addition, we cannot claim that the observed cortical abnormalities are specific to SD. On the contrary, similar movement-related reductions of cortical desynchronization were observed in cervical and segmental dystonia (Crowell et al., 2012; Miocinovic et al., 2015) as well as in writer's cramp (Toro et al., 2000). This elucidates a common underlying pathomechanism between SD and other focal dystonia subtypes.

Moreover, it needs to be considered that the recorded EEG signals reflect the activity of a somatosensory-motor cortical network.

That implies that the dystonic muscle contractions can alter the proprioceptive input to the somatosensory cortex, which then affects motor cortical activity. That is, the observed EEG output may be affected by abnormal muscle activity as well.

Finally, one needs to recognize that this study is exploratory in nature. To our knowledge, this is the first study that examined cortical activation patterns during vocalization in SD. We fully recognize that additional research is warranted to confirm our finding of excessive cortical activation during vocalization in SD. Although the statistical significance of our outcome measure provide support for the generalizability of our findings, follow up studies with a larger sample size could provide additional information about how consistent the observed abnormalities in cortical processing are across the SD population, and how these abnormalities relate to the severity of their voice symptoms.

5. Conclusions

In summary, this study revealed that two atypical patterns of cortical activity characterize the pathophysiology of spasmodic dysphonia. The first pattern is a reduced movement-related desynchronization of motor cortical neural networks during voice production. The second pattern is an excessively large synchronized activity between left somatosensory and premotor cortical areas during voice production. These neurophysiological findings could provide a basis for the development of more effective treatment opportunities for spasmodic dysphonia by examining ways to reduce this abnormal activity. For example, neuromodulation therapies such as the transcranial alternating current stimulation could use these insights in order to optimize stimulation waveform parameters with the goal to normalize the cortical oscillations in patients with SD.

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Conflict of interest

No conflicts of interest, financial, or otherwise, are declared by the authors. All authors have approved the final article.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.03.003.

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