RESEARCH ARTICLE

Brain–Computer Interface Improves Symptoms of Isolated Focal Laryngeal Dystonia: A Single-Blind Study

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ABSTRACT: Background and objective: Laryngeal dystonia (LD) is a focal task-specific dystonia, affecting speaking but not whispering or emotional vocalizations. Therapeutic options for LD are limited. We developed and tested a non-invasive, closed-loop, neurofeedback, brain–computer interface (BCI) intervention for LD treatment.

Methods: Ten patients with isolated focal LD participated in the study. The personalized BCI system included visual neurofeedback of individual real-time electroencephalographic (EEG) activity during symptomatic speaking compared to asymptomatic whispering, presented in the virtual reality (VR) environment of real-life scenarios. During five consecutive days of intervention, patients used the BCI to learn to modulate their abnormally increased brain activity during speaking and match it to near-normal activity of asymptomatic whispering. Changes in voice symptoms and EEG activity were quantified for the evaluation of BCI effects.

Results: Compared to baseline, LD patients had a statistically significant reduction of their voice symptoms on Days 1–5 of BCI intervention. Thi was paralleled by improved controllability of the visual neurofeedback and a significant reduction of left frontal delta power, including superior and middle frontal gyri, on Day 1 and left central gamma power, including premotor, primary sensorimotor, and inferior parietal areas, on Days 3 and 5. The majority of patients (70%) reported sustained positive effects of the BCI intervention on their voice quality 1 week after the study participation.

Conclusion: The closed-loop BCI neurofeedback intervention specifically targeting disorder pathophysiology shows significant potential as a novel treatment option for patients with LD and likely other forms of task-specific focal dystonia. © 2025 International Parkinson and Movement Disorder Society.

Key Words: dystonia; sensorimotor rehabilitation; brain–computer interfaces; neurofeedback

Laryngeal dystonia (LD) is a common form of isolated focal dystonia characterized by involuntary laryngeal muscle contractions that interfere with daily communication, often leading to chronic stress, psychiatric comorbidities, societal withdrawal, and suicidal behaviors.[1,2] Despite its negative impact on the affected individual, the treatment of LD remains primarily limited to temporary symptom relief with botulinum toxin injections into the laryngeal muscles.[3-6] However, recent advances in understanding the neural network pathophysiology of LD have opened new directions for the development of targeted therapies, including sodium oxybate as an efficacious oral drug for the treatment of alcohol-responsive LD[7] and brain–computer interfaces (BCIs) for the rehabilitation of dystonic voice symptoms.[8]

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BCIs are typically designed to record brain activity, interpret neural signals, and employ this information to manipulate an effector, thereby augmenting or supplementing the standard means of communication.[9] While initial BCIs primarily aimed at delivering communication tools to patients with severe motor impairments,[10-13] more recent systems have focused on restoring motor function in patients with stroke,[14,15] Parkinson's disease,[16,17] and essential tremor.[18] A case report of a patient with focal hand dystonia has previously explored the electroencephalography (EEG)-based BCI for suppressing abnormal cortical sensorimotor activity in the beta frequency band during repetitive hand extensions.[19] Following 10 BCI sessions, this patient had a significant symptom reduction, demonstrating the initial feasibility of BCIs for dystonia treatment.

In this study, we leveraged the current knowledge of LD symptomatology and pathophysiology and rapid methodological and technological advances of the BCI field to develop a non-invasive, closed-loop, EEG-neurofeedback BCI for LD treatment. Our BCI paradigm was built to specifically target the pathophysiological feature of task-specificity of LD, which has been associated with abnormal brain activity in sensorimotor cortical regions as well as abnormally increased gamma synchronization within the prefrontal-parietal circuitry during speaking but not whispering.[20,21] Using real-time EEG neurofeedback, patients were trained to learn to self-modulate their abnormal neural activity (ie, disorder signature) during speaking and normalize it to the level of their near-normal neural activity during whispering (ie, target signature). We hypothesized that the closed-loop, neurofeedback-based, BCI intervention will show a significant reduction of LD symptoms due to active modulation of pathophysiologically abnormal brain activity specific to the dystonic behavior.

Methods

Study Participants

Ten patients diagnosed with isolated focal LD participated in the study (age 57.1 ± 12.3 years; five females/five males) (see demographics in Table 1). All patients were right-handed and native English speakers. No patient had any past or present history of other neurological (except for co-occurring voice tremor in one patient), psychiatric, or laryngeal problems as determined by the review of case history, laryngeal/neurological evaluations, and perceptual analysis of voice and speech recordings. All patients had normal cognitive function as assessed using the Montreal Cognitive Assessment (MoCA). None were on any centrally acting medications prior to or during study participation. Patients who received botulinum toxin injections to manage LD symptoms participated in the study at least 3 months after their last injection when fully symptomatic.

All patients gave written informed consent before study participation, approved by the Institutional Review Board of Mass General Brigham. The study was registered on ClinicalTrials.gov (NCT04421365).

Experimental Baseline and BCI Model

Patients underwent five consecutive days of a single-blind BCI experimental protocol (Fig. 1A). All patients and investigators who analyzed data were masked to study procedures.

Prior to the start of the study, patients were asked to choose one of six virtual avatars (three females/three males) created specifically for this intervention. The avatars were designed to speak or whisper the experimental tasks with realistic mouth and lip synchronization and gestures using audio recordings from native English healthy speakers.

Each experimental day started with baseline recordings of EEG activity and voice symptoms. Patients were seated in a comfortable chair and wore a 256-channel cap (EGI GTEN 200, Magstim, Inc.), which acquired high-density EEG at a sampling rate of 500 Hz. All leads were referenced to channel Cz, and impedances were kept below 50 kΩ following the manufacturer's recommendations, providing a satisfactory signal-to-noise ratio.[22] Speech was recorded using a ZOOM H6 Handy recorder equipped with a ZOOM SSH-6 stereo shotgun microphone, which was placed at a constant distance of 50 cm in front of the patient and directed at the patient's mouth.

Baseline on Day 1 included 100 trials per condition (speech and whisper) used for the calibration of the BCI model, while baseline on Days 2–5 included 40 trials per condition. Each patient completed a total of 260 baseline trials per condition. Each trial included the production of either 40 sentences in the spoken voice or 40 sentences in the whispered voice, which were presented one at a time by the avatar on the monitor screen for 3–4 s, depending on the length of the sentence. This was followed by a 4-s period, during which the patient repeated the presented sentence either in spoken or whispered voice, as instructed. The sentences comprised a high load of vowels and voiceless consonants to elicit symptoms of adductor and abductor LD, respectively (eg, "Sam has a rabbit in his hat", "Are the olives large?", "My father has a new car", "He is hiding behind the house").

The baseline EEG recording of Day 1 collected prior to any BCI intervention was used to create a personalized BCI model for each patient to be used in the subsequent BCI sessions. Our previous study, showing that the temporal–spatial signature of aberrant cortical oscillations is linked to an altered prefrontal-parietal circuitry

TABLE 1 *Patient demographics*

Patient	Sex	Age (years)	Cognitive status (MoCA)	LD form	Family history of dystonia	LD duration (years)	LD onset (years)	LD baseline severity	Last BoNT treatment (months)
1	M	70	30	ADLD	Yes	15	58	3.06	8
2	M	57	27	ADLD	No	42	15	3.76	25
3	F	58	26	ADLD	No	24	34	1.84	NA
4	M	63	26	ADLD	Yes	16	47	2.59	3
5	F	32	26	ADLD/VT	No	14	18	2.06	NA
6	F	41	30	ABLD	No	2	39	3.13	8
7	F	54	29	ADLD	No	10	44	3.03	5
8	F	70	27	ADLD	No	11	59	3.14	5
9	M	60	29	ADLD	Yes	22	38	3.07	226
10	M	66	28	ADLD/VT	No	20	46	1.95	8

Note: All patients were right-handed (Edinburgh Handedness Inventory) and monolingual native English speakers. Baseline severity of laryngeal dystonia is based on a normalized composite clinician-objective and patient-subjects visual analog scale score.
Abbreviations: ABLD, abductor form of laryngeal dystonia; ADLD, adductor form of laryngeal dystonia; BoNT, botulinum neurotoxin; F, female; LD, laryngeal dystonia; M, male; MoCA, Montreal Cognitive Assessment; NA, not applicable; VT, voice tremor.

in LD patients,[21] set the foundation. for the design of the BCI model in the present study. Specifically, we used individual pathophysiological alterations in the gamma band, as well as oscillations in the theta band that are generally implicated in speech motor control,[23,24] to model differences between the disorder signature and target signature in each patient. The BCI model was implemented as a regularized linear discriminant analysis (rLDA) classifier with a sigmoid function to scale the classifier output (ie, distance from the decision boundary) that interpolates between 0 (target signature) and 1 (disorder signature). The BCI model was validated in three steps, including (i) the offline calibration based on a train-split of the speech and whisper baseline data from Day 1, (ii) a pseudo-online validation based on a test-split of the same data and assessment of the model by the lead experimenter, and (iii) the embedding of the model in the online application and assessment of the model's functionality by the lead experimenter during the BCI session (Fig. 1C). The performance of the BCI model was robust and consistent across all patients, with a balanced classification accuracy $F1 = 0.87 \pm 0.1$ (mean ± standard deviation [SD]) and a coefficient of determination $R^2 = 0.66 \pm 0.2$.

BCI Intervention

The BCI intervention used the same experimental setup as described above. Additionally, patients wore a Vive Pro high-performance virtual reality (VR) head-mounted display (HTC Inc.), which immersed them into one of four realistic environments (scenes), including the settings in a restaurant, outdoors, office, or shopping mall[25] (Fig. 1B). Because LD symptoms are known to be impacted by the audiovisual complexity of social situations,[25] each VR scene featured four levels with gradually increasing audiovisual background noise, such as honking cars, people chattering and passing by, rain and thunderstorm, or sudden fire alarms (Level 1 the quietest to Level 4 the noisiest and most visually distracting).[25] The VR scenes were pseudorandomized between patients, and each patient interacted with the same, pre-chosen virtual avatar that spoke 40 sentences. The leveling-up from Level 1 to Level 4 of virtual scenes was performed gradually over the course of the 5-day intervention based on the patient's performance, which helped maintain patients' engagement, increase the challenge of the task, and have the patient experience various real-life scenarios.[25]

Each patient completed two BCI sessions per day, one in the morning and one in the afternoon, with about a 1-hr break in between sessions (Fig. 1A). Each session included two VR scenes of the same level; each VR scene included 200 trials. Each patient completed 4000 trials over 5 days of BCI intervention, except for one patient who underwent 4 days of BCI intervention due to technical problems during data acquisition on Day 1 and thus completed 3600 trials. Each BCI trial included the production of 40 sentences in the spoken voice, presented one at a time by the avatar in the VR environment for 3–4 s, depending on the length of the

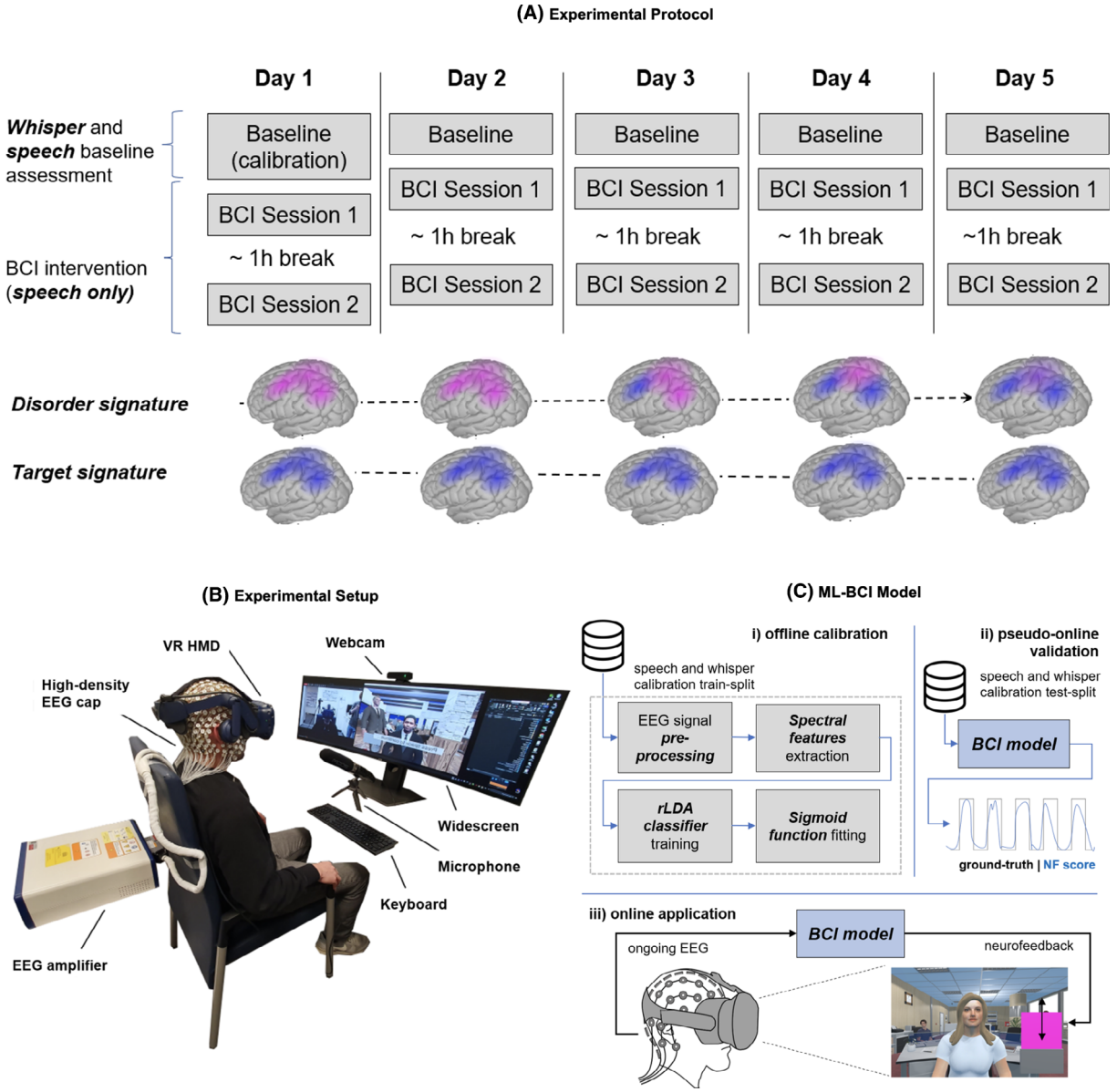

FIG. 1. (A) Experimental protocol. Schematic of the 5-day brain–computer interface (BCI) intervention protocol, including daily baseline recording followed by two sessions of BCI training. (B) Experimental setup. The patient is seated in a comfortable chair, wearing the high-density electroencephalography (EEG) cap and the virtual reality (VR) head-mounted display. A computer keyboard is in reach of the patient's left hand, a microphone is directed toward the patient's mouth to record the patient's voice with high fidelity, and a webcam video records the patient's face during the study. The widescreen monitor allows the experimenter to monitor the patient's VR scenes. (C) Machine-learning BCI model. The pipeline used for creating individual BCI models, illustrating (i) offline calibration based on a train-split of the speech and whisper calibration data from Day 1, (ii) pseudo-online validation based on a test-split of the same data, and (iii) embedding of the model in the online application. [Color figure can be viewed at wileyonlinelibrary.com]

sentence. This was followed by a 5-s period during which the patient repeated the presented sentence in spoken voice while simultaneously modulating their brain activity by mentally moving the visually presented bar (in pink), corresponding to their real-time EEG-based activity during speaking, to the level of activity associated with their pre-recorded whisper (gray bar) (Fig. 1B,C). All patients were remotely monitored during all sessions and maintained two-way communication, if necessary. Short breaks were incorporated throughout the sessions, and the patients were allowed to notify the investigators to take breaks between the trials, if necessary.

All patients were followed up by telephone 1 week after the BCI intervention to collect feedback about the BCI effects on their voice symptoms.

LD Symptom Analysis

The effects of BCI intervention on LD symptoms were examined using a composite score of clinician-objective perceptual acoustic analysis and patient-

subjective evaluation of voice effort using visual analog scales (VAS), as described previously.[7,26] For this, all baseline and BCI sessions were audio-recorded in all patients, de-identified, randomized, and blindly perceptually rated for symptom severity by an experienced speech–language pathologist. LD-characteristic voice breaks were counted in each sentence; voice harshness/strain and breathiness were evaluated using VAS (0, none; 100, most severe). In addition, all patients completed a nine-point self-evaluation of voice and speech symptom severity (VAS: 0, no effort; 9, constant struggle) during all baseline and BCI sessions. The patients marked the score that reflected their symptom severity at the time of evaluation. Linear normalization was applied to clinician-objective and patient-subjective VAS scores to ensure data comparability, and the normalized data points in each patient were averaged to derive a composite VAS score of symptom severity.[7] Due to the cohort size, the related-samples Friedman's two-way analysis of variance (ANOVA) was used to examine the effect of BCI intervention on symptom severity at two-sided $P \leq 0.05$, with the follow-up post-hoc pairwise comparisons examining change in symptoms between the baseline on Day 1 and BCI sessions on Days 1–5.

EEG Signal Preprocessing, Artifact Removal, and Statistical Analysis

The EEG analysis followed the previously established pipeline.[21] Briefly, in each subject, the EEG signal was downsampled to 250 Hz and band-pass filtered using a zero-phase Hamming windowed-sinc FIR filter with cutoff frequencies at 1 and 60 Hz to remove DC offsets and high-frequency noise. To reduce power line noise at 60 Hz, a zero-phase Hamming windowed-sinc band-stop filter with cutoff frequencies at 55 and 65 Hz was used. Among 256 channels, the artifact-contaminated channels were identified using normalized kurtosis, followed by spherical interpolation to reconstruct rejected channels from the signal of neighboring electrodes, which led to a removal of a median of 39 (15.3%) interpolated channels per subject. The remaining artifacts were reduced using independent component (IC) analysis, and the resulting data were submitted to the ADJUST plug-in for automatic identification and removal of ICs associated with generic discontinuities, eye movement, facial muscle, and neck tension-related artifacts.[27] This processing led to the removal of a median of 41 (16.0%) ICs per subject.

Additionally, to rule out potential movement artifacts resulting from orofacial muscles during speaking, we used DeepLabCut (version 2.3.5) to analyze the motion tracking data from the front face videos recorded during the study. In each patient, an individual ResNet-50 network was trained on a total of 90 min of video recordings of the morning BCI sessions of Days 2–4. Ground truth was provided using 60 manually labeled frames. Orofacial markers were located on the chin, lower lip, and left and right mouth corners (Fig. 2). The trained networks were applied to the video recordings of the Day 1 calibration session and all BCI sessions throughout the week, totaling about 10 hr of video recording per patient. All samples with tracking confidence of $P < 0.6$ were removed using the default DeepLabCut threshold. The standard deviation of the distance from the center point of each marker, expressed in pixels, represented the direction-agnostic average amplitude of the movement, thereby capturing the extent of orofacial movements. Linear mixed-effects (LME) models per marker with Day as fixed factor and subjects as random factor found no significant effects for the chin marker ($F = 2.57$, $P = 0.16$), lower lip marker ($F = 1.96$, $P = 0.22$), right mouth corner ($F = 1.2$, $P = 0.45$), or left mouth corner ($F = 0.76$, $P = 0.59$). Thus, the absence of significant changes in orofacial motion throughout the study indicated minimal, if any, contamination of the EEG signal by orofacial motion artifacts as well as no systematic changes in movement patterns across the study due to BCI intervention.

The final EEG dataset included 94 a priori-selected, artifact-free channels, which spatially covered frontal, central, and parietal brain regions relevant to dystonia pathophysiology.[6,21,28–31] The signal from these electrodes was re-referenced to the common average to further reduce contamination.[32] Spectral analysis of each electrode was performed using Welch's power spectral density estimate using 50% overlapping Hamming windows (length 1 s). The size of the fast Fourier transform (FFT) was set to 250 points, resulting in a frequency resolution of 1 Hz. Spectral power was computed for a 1-s pre-trial baseline period and the subsequent task period (4 s for the baseline trial on Day 1; 5 s for each BCI trial). Single-trial baseline correction was performed by dividing the task power by the baseline power, converted to decibels (dB). Frequency bins were pooled to average spectral power of five frequency bands, including delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–50 Hz).

The Shapiro–Wilk test found that 17.2% of data were not normally distributed ($W \leq 0.85$, $P \leq 0.05$). Thus, an LME model with Day of intervention and frequency band as fixed factors and subjects as random factor was used to examine the main effects and their interactions at the overall statistical significance of $P \leq 0.05$. Post-hoc independent Wilcoxon signed-rank tests were performed between the baseline of Day 1 and the BCI sessions on Days 1–5 to determine differences from baseline in spectral topography at cluster-corrected $P \leq 0.05$. A cluster was defined as a group of contiguously neighboring significant electrodes; the cluster-based correction was performed with a

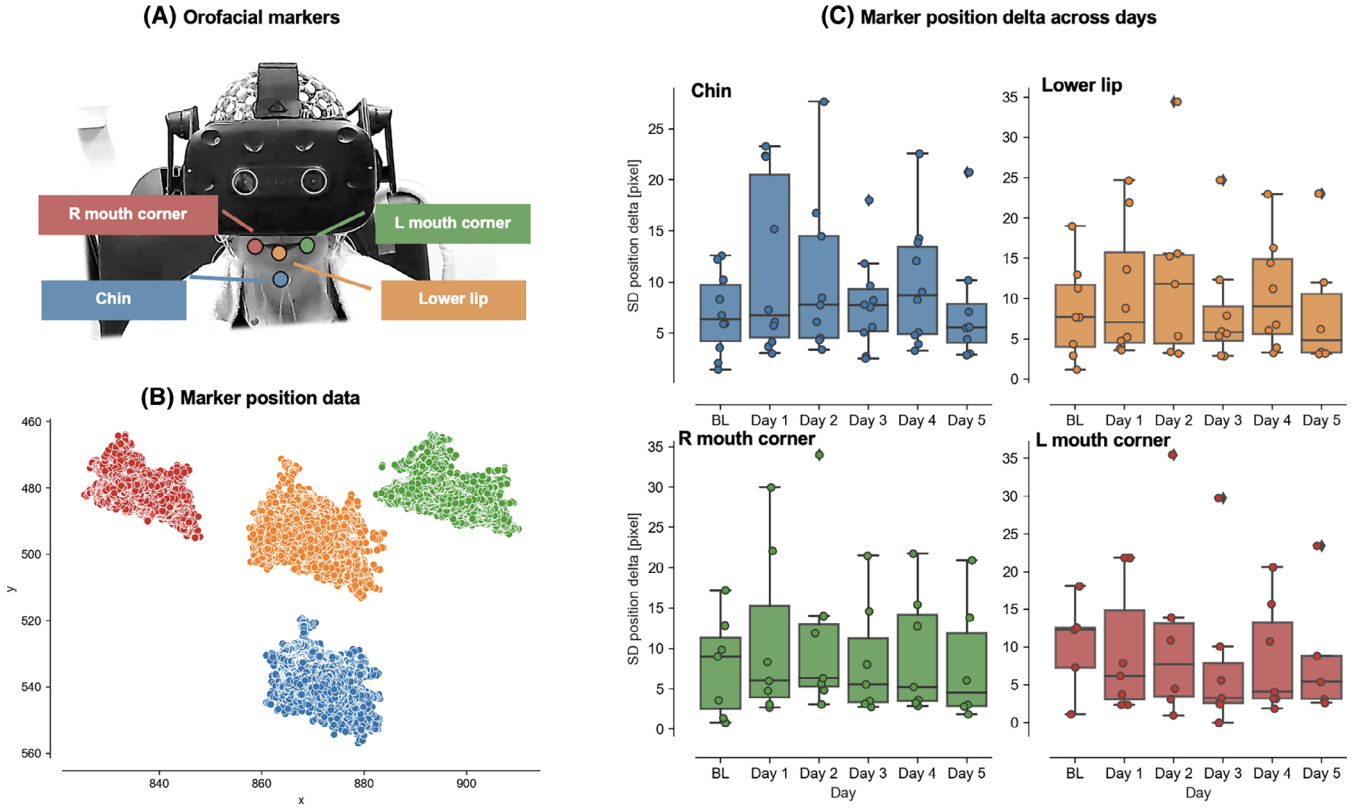

FIG. 2. (A) Orofacial markers. An overview of the positions of the orofacial markers, located on the chin, lower lip, left and right mouth corners, extracted from the frontal face videos of the baseline (BL) session of Day 1 and the brain–computer interface (BCI) sessions for each day (Days 1–5). (B) Marker position data. Examples of marker position data in a single subject and session. (C) Marker position delta across all days of BCI intervention. Median position variation across days for each orofacial marker shows no significant main effect of day. [Color figure can be viewed at wileyonlinelibrary.com]

significance set at ≥95% of the largest size of clusters in the randomly permutated data within each band.

To examine the extent of neurofeedback modulation throughout the BCI intervention, we computed the grand mean of the momentary neural feedback values by first averaging within each BCI 5-s trial production period and then averaging across all production trials per day in each patient, yielding one aggregated score per patient per day. An LME model with Day as fixed factor and subjects as random factor examined the overall effect of the neurofeedback score at $P \leq 0.05$, with post-hoc Tukey-adjusted pairwise comparisons assessing the differences between baseline and each day of intervention.

To evaluate the relationship between BCI-induced neural changes and LD clinical characteristics, we computed Spearman's rank correlation coefficients between spectral power modulations and clinical measures, including symptom severity on Days 1–5, LD duration, and age of onset, at two-sided $P \leq 0.01$ to correct for multiple comparisons.

Results

The Friedman's ANOVA of a composite clinician-objective and patient-subjective VAS score of symptom severity found a statistically significant effect of BCI training on LD symptoms ($t_5 = 19.3$, $P = 0.002$), with a significant reduction of voice symptoms on Days 1–5 from baseline ($t_9 = 2.6$–3.9, $P \leq 0.008$) (Fig. 3A). Notably, the average sound intensity throughout the experiment was consistent in all patients, without statistically significant changes between the first and last days of intervention (speech signal: 60.6 ± 2.4 dB vs. 59.9 ± 2.4 dB, $P = 0.25$; whisper signal: 49.5 ± 1.7 vs. 49.1 ± 1.8 dB, $P = 0.91$). In parallel, patients' controllability of the BCI neurofeedback was improved throughout the study, with a lower score indicating a better control closer to the personalized target level of asymptomatic whispering (Fig. 3B). The LME analysis of the BCI neurofeedback controllability found a significant main effect of day on neurofeedback score distributions ($F \leq 5.33$, $P < 0.002$), with a statistically significant improvement on Days 4 and 5 compared to Day 1 ($P \leq 0.01$).

The LME analysis of EEG activity throughout the BCI intervention found statistically significant main effects of Day and frequency band as well as Day × band interactions (all $P \leq 2 \times 10^{-16}$). Compared to Day 1 baseline (ie, prior to intervention), a statistically significant reduction of the left frontal delta power, including superior and middle frontal gyri, was found on Day 1 and the left

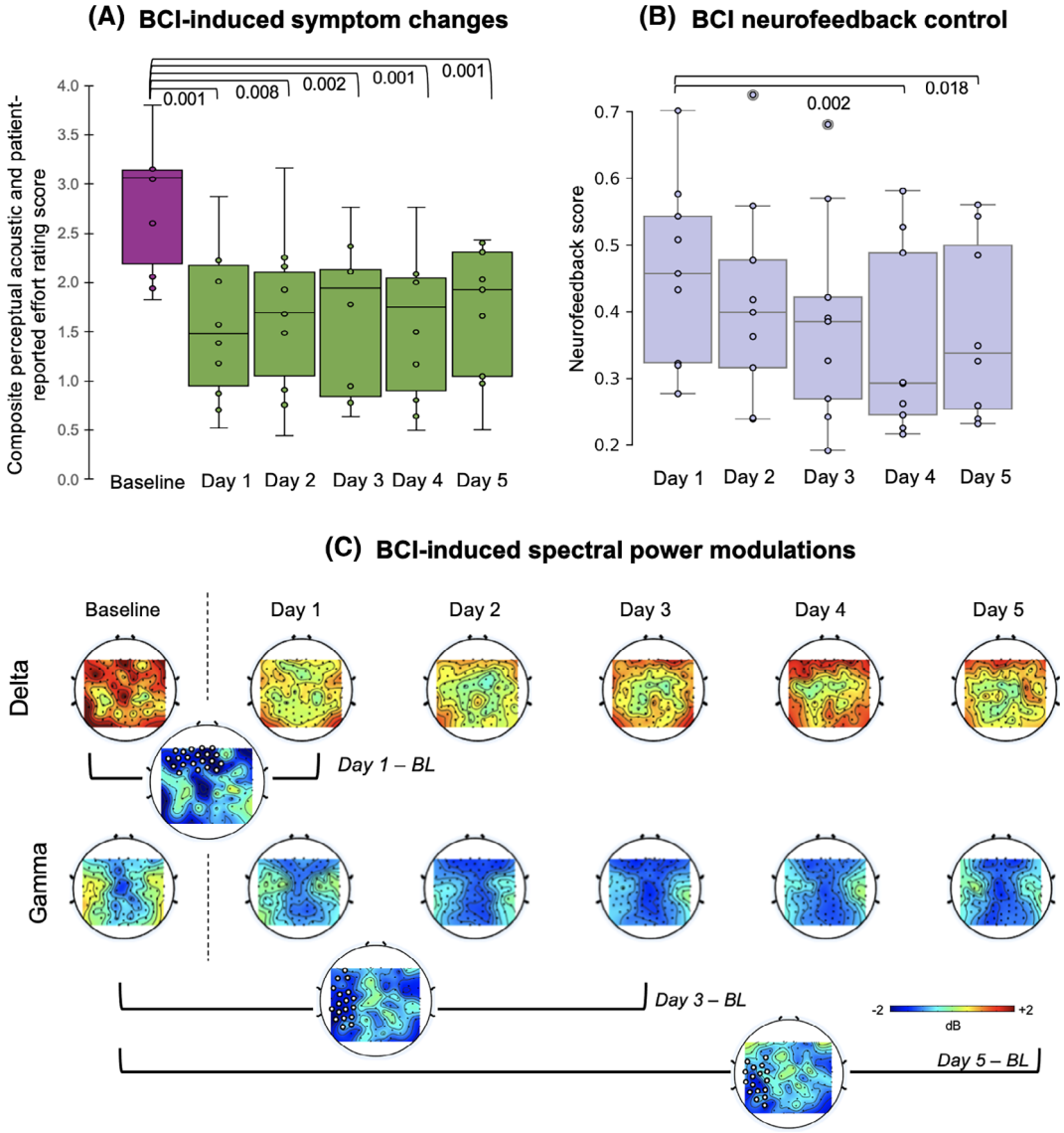

FIG. 3. (A) Brain–computer interface (BCI)-induced symptom changes. The boxplot graph shows the symptom severity measured as the composite score of clinician-objective perceptual acoustic analysis and patient-subjective voice effort rating at baseline and Days 1–5 of BCI intervention. Significant changes from baseline are shown with the *P*-value. (B) BCI neurofeedback control. The boxplot graph shows the neurofeedback score, reflecting the ability of the patient to control the visual neurofeedback bar associated with the momentary brain activity during symptomatic speaking. The lower the score, the better the controllability of the neurofeedback in decreasing brain activity during speaking to the level of asymptomatic whispering. (C) BCI-induced spectral power modulations. Statistically significant group-level differences in spectral power in the delta (Day 1) and gamma (Days 3 and 5) frequency bands during BCI intervention compared to baseline. Significant channels are shown in white circles. [Color figure can be viewed at wileyonlinelibrary.com]

central gamma power, including premotor, primary sensorimotor, and inferior parietal areas, on Days 3 and 5 (all corrected $P \leq 0.05$) (Fig. 3C).

There were no statistically significant correlations between significant spectral power changes and LD symptom severity, disorder duration, or the age of onset (all $R_S \leq 0.22$, $P \geq 0.11$). There were also no significant correlations between LD symptoms, duration, and age of onset (all $R_S \leq 0.37$, $P \geq 0.33$).

During the 1-week follow-up interview, 7/10 patients (70%) reported sustained positive effects of the BCI intervention on their voice, 2/10 patients (20%) reported that others had commented on their improved voice quality, and 9/10 patients (90%) reported the continuous use of individual mental strategies developed during the study to help maintain their symptom improvement.

Discussion

We developed and tested the first non-invasive, closed-loop, EEG-based, neurofeedback BCI for LD treatment. The personalized BCI intervention was

designed to recognize the individual neural signature associated with dystonic speech production. It incorporated real-time neurofeedback, presenting the patients with a visual guidance of their momentary brain activity as the difference between symptomatic speaking and asymptomatic whispering. The integrated VR scenes with different levels of audiovisual complexity modeled the real-life environments to enhance the patients' experience, maintain their high-level engagement during the study, and place them as close to realistic settings as experimentally possible.[25] Using neurofeedback and mental strategies, the patients actively engaged in the virtual avatar-guided self-training to modulate their individual neural activity during symptomatic speaking over the course of a 5-day BCI intervention, showing gradually and significantly improved controllability of the neurofeedback and significantly reduced LD voice symptoms. The BCI-induced symptom improvement was found to be sustained over a week after intervention in the majority of patients.

Importantly, the BCI effects were associated with a statistically significant reduction of left-hemispheric gamma and delta power in sensorimotor, inferior parietal, and prefrontal cortical regions compared with baseline. Alterations in these frequency bands have been previously reported along with aberrant functional coupling between primary motor and somatosensory cortical areas and between parietal cortex and cerebellum in different forms of focal dystonia.[33–36] In LD, we have identified increased gamma-band oscillations as a characteristic feature of disorder task-specificity, being selectively abnormal during symptomatic speaking but not during speech-related or unrelated asymptomatic behaviors, such as whispering and writing.[21] In line with earlier neuroimaging studies,[37,38] we have further shown that abnormal gamma oscillations originate from a distributed network of primary sensorimotor, premotor, and inferior parietal areas and are characterized by hyperfunctional reciprocal prefrontal-parietal connections. It has been postulated that parietal-premotor abnormalities may be of primary pathophysiological significance in LD and other task-specific dystonias.[5,6,39] Thus, the symptom reduction due to selective normalization of abnormal gamma-band hyperactivity in these cortical regions suggests that this closed-loop BCI neurofeedback intervention is capable of directly modulating the neural pathophysiology of LD. Moreover, left-sided BCI effects on brain activity denote their relevance to speech production, which is known for its left-hemispheric dominance.[40–42]

Conversely, the observed delta power modulations on Day 1 of BCI intervention may, in part, be explained by a cognitive load during initial familiarization with the experimental setup. It has been shown that changes in delta power are associated with high cognitive engagement in error- and performance monitoring,[43,44] which were more likely to be present at the beginning of the study when patients explored different mental strategies to control the visual neurofeedback. In addition, prefrontal alterations have been reported in LD and other forms of dystonia during sensory discriminatory and cognitive executive processing,[45–50] again pointing to the modulatory effects of BCI intervention on disorder pathophysiology.

The absence of statistically significant correlations between BCI-modulated brain activity and LD clinical characteristics substantiates our hypothesis that this closed-loop, neurofeedback-based intervention specifically targets the central pathophysiology of LD and is unlikely to be driven by the compensatory mechanisms following changes in symptom severity or other clinical features of the disorder. Likewise, the stability of speech sound intensity throughout the BCI intervention also indicates that the voice symptom improvement is likely due to modulation of the central pathophysiology leading to reduction of LD-characteristic vocal spasms, harshness, and breathiness, rather than changes in the loudness or other physical properties of the produced sound. Our comprehensive analysis of orofacial movements throughout the BCI intervention ruled out the presence of major motion confounders influencing neural activity or any changes in the pattern of orofacial movements due to BCI sessions, again pointing to the robustness of our findings. Notably, the comparable efficacy of the current BCI experimental paradigm in patients with a range of LD symptom severity (from mild to severe) and different disorder duration and age of onset substantially increases its translational potential as a novel therapeutic option for these patients. It is also worthwhile to note that the BCI setup was well received by the patients, as the majority demonstrated high levels of motivation during the intervention and proactively expressed eagerness to improve their controllability of neurofeedback and performance. Although patients wore the VR headset for approximately 2.5 hr a day, the integration of VR was not perceived as burdensome or hampering, but rather as engaging and beneficial compared with a conventional computer monitor-based alternative.

Study limitations should be acknowledged. Although this study was based on a moderate sample size, the recruited patients represented balanced LD demographics, with uniform distributions across sex, handedness, cognitive status, and post-botulinum toxin treatment interval, thus mitigating the potential challenges with the generalizability of the findings. While the cohort size and the single-blind design were appropriate for this first BCI intervention, future studies should consider a double-blind randomized trial in a larger cohort of LD patients, incorporating active and sham BCI sessions for enhanced statistical robustness,

accounting for potential placebo effects. Future studies should also consider longer follow-up assessments for the evaluation of the long-term sustainability of the BCI effects.

In conclusion, we have demonstrated the first-of-its-kind closed-loop BCI neurofeedback intervention for the treatment of isolated focal LD. The combination of personalized EEG modeling, real-time visual neurofeedback, and VR integration represents an effective approach to fostering a dynamic learning environment for LD symptom rehabilitation. The BCI intervention specifically targeting disorder pathophysiology shows significant potential as a novel treatment option for patients with LD and likely other forms of task-specific focal dystonia. ●

Author Roles: (1) Research Project: A. Concept and Design, B. Data Acquisition, C. Data Analysis; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique; (4) A. Supervision, B. Funding Acquisition.S.K.E.: 1A, 1B, 1C, 2A, 2B, 3A.
G.T.: 1B.
J.B.: 1B.
N.B.: 1B.
A.F.R.: 1C
K.S.: 1A, 1C, 2A, 2B, 2C, 3B, 4A, 4B.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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