VIEWPOINT

Brain–Computer Interfaces for Treatment of Focal Dystonia

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Isolated dystonia is a debilitating disorder that causes involuntary muscle contractions leading to abnormal, often repetitive, and sometimes painful movements. Typically, symptoms develop midlife and take a toll not only on the freedom of movement but also the various aspects of the individual's life, causing social embarrassment, derailed professional careers, chronic stress, psychiatric comorbidities, and increased suicidal risk.[1,2] Despite the significant progress made in the past decades toward understanding genetic, cellular, and neural mechanisms underlying dystonia pathophysiology, its treatment remains stagnant.[3,4] Therapeutic options are largely limited to temporary symptom management with botulinum toxin injections into the affected muscles; selective oral medications are nonexistent, and the off-label use of new drugs is restricted to trial-and-error explorations. Invasive neuromodulation with deep brain stimulation of globus pallidus and, more recently, magnetic resonance–guided focused ultrasound thalamotomy shows therapeutic benefits; however, only a fraction of patients with isolated dystonia undergoes brain surgery.[5,6]

The continuous gaps in the understanding of the ever-evolving complexity of dystonia pathophysiology were partly to blame for the lack of development of adequate treatments.[3,4] Traditionally, isolated dystonia was considered a basal ganglia disorder because of the predilection for striatal lesions to trigger dystonic symptoms.[7] According to the basal ganglia model of dystonia, an imbalance of the direct and indirect pathways was thought to underlie bottom-up abnormal decreases of intracortical inhibition and subsequent increases of cortical motor excitability.[8-10] Another model of dystonia has focused on the cerebellum, which was reported as one of the common sites of lesions causing secondary dystonia, proposing that cerebellar alterations may also be causal in the pathophysiology of isolated dystonia.[11,12] Although both the basal ganglia and cerebellum are critically important structures, clarifications of their involvement in dystonia pathophysiology have not yet, regrettably, led to breakthroughs in the treatment of these patients.

In parallel, advanced neuroimaging studies unveiled a more complex, larger-scale brain disorganization in dystonia. Following original studies that mapped the abnormal metabolic network in generalized dystonia,[9,13] recent research determined that focal dystonias are functional and structural neural network disorders where alterations in basal ganglia, cerebellar,

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and cortical sensorimotor and frontoparietal regions are critical components of the dystonic network[14,15] (Fig. 1). According to the currently prevailing network model of the disorder, the basal ganglia, thalamus, and cerebellum are at the core of network aberrations across all forms of dystonia. In parallel, phenotypically and genotypically different forms of dystonia are characterized by widespread but form-specific abnormalities in cortical regions responsible for multisensory processing, sensorimotor integration, and motor execution. Among these, the neural signature of task-specific dystonias, such as laryngeal dystonia, writer's cramp, or musician's dystonia, includes significant alterations in primary sensorimotor, premotor, and inferior parietal cortical areas compared with predominantly subcortical changes in non–task-specific dystonias, such as cervical dystonia or blepharospasm.[16,17]

Collectively, these studies expanded our understanding of dystonia pathophysiology beyond the basal ganglia and cerebellum, leading to the recommendation by the 2018 National Institutes of Health/National Institute of Neurological Disorders and Stroke Working Group on Dystonia Research Priorities to target well-defined network abnormalities that are commonly shared across different forms for the formulation of effective therapeutic strategies.[18] This Viewpoint outlines the consensus outcome of a multidisciplinary panel of experts from the fields of neurology, neurosurgery, neuroscience, speech sciences, engineering, and computer sciences who met within the framework of the Radcliffe Institute for Advanced Study at Harvard University in September 2020 to review the current state of knowledge of dystonia pathophysiology with the aim to formulate novel therapeutic interventions using advanced brain–computer interfaces (BCIs). The expert panel identified a well-known clinical phenomenon of task specificity in focal dystonias as a powerful pathophysiological feature that may successfully be targeted with BCIs and outlined the roadmap for implementing this neurotechnology for the treatment of patients with focal task-specific dystonias.

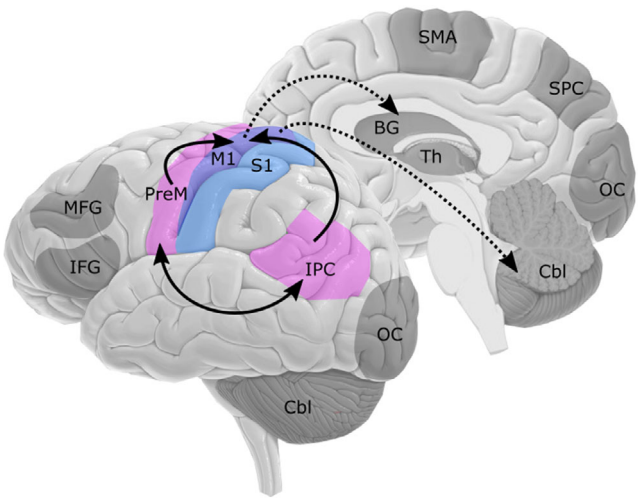

FIG. 1. Simplified schematic of functional and structural neural network alterations in focal dystonia. Colored areas depict cortical targets of neurofeedback brain–computer interface (BCI) intervention; gray areas depict other critical regions within the dystonic neural network. Alterations in inferior parietal (IPC) and premotor (PreM) cortex are thought to precede and influence those in the primary sensorimotor cortex (M1/S1). It is expected that BCI-based modulation of IPC-PreM activity leads to attenuation of M1/S1 activity, which, in turn, results in normalized M1/S1 output, including to the basal ganglia (BG) and cerebellum (Cbl). Solid black arrows indicate cortical sensorimotor modulation directly targeted by the proposed neurofeedback BCI intervention; dashed arrows indicate downstream effects resulting from cortical modulation. IFG, inferior frontal gyrus; MFG, middle frontal gyrus; OC, occipital cortex; SMA, supplementary motor area; SPC, superior parietal cortex; Th, thalamus.

BCIs and Neurofeedback Intervention

BCIs are devices designed to record brain activity, extract information from neural signals, and use this information to manipulate an effector.[19] Neural signals are translated into a control signal, which, in turn, drives an effector that is fed back perceptually to the user. Much of the pioneering BCI research has focused on providing new communication tools to patients with severe motor impairments (eg, locked-in syndrome) who progressively lose their ability for verbal and nonverbal communication.[20-23] Recently, the first closed-loop speech neuroprosthesis has been developed, which reconstructed, without delay, neural signals of imagined speech into an audio signal, allowing patients to hear what they imagined speaking.[24] Other prominent examples include deriving directional control signals to steer a computer cursor or robotic systems for giving autonomy to patients suffering from motor disabilities as a result of spinal cord injury and other conditions.[25,26] The key aspect of these BCIs is the closed-loop paradigm, where the feedback represents the momentary brain activity of the user and follows changes in neural activity associated with the given behavior. When provided with sufficient training, these adaptive BCIs enable the user to gain voluntary control over their neural activity and learn to self-regulate their brain activity.[19] Notably, neurofeedback serves as a form of endogenous neural stimulation,[27,28] helping the user refine momentary brain activity for the most optimal behavioral outcome.

Various BCIs have been studied for their potential in the rehabilitation of neurological disorders affecting the sensorimotor system,[27,29] such as restoring motor function following stroke,[30,31] Parkinson's disease,[32,33] and essential tremor.[34] Largely missing from this literature are BCIs for patients with isolated dystonia. To date, only one case report using the electroencephalography

(EEG)-based BCI has been published in a patient with writer's cramp.[35] Using visual feedback, this patient was trained to suppress abnormal cortical sensorimotor activity in the beta-frequency band during repetitive hand extensions. After 10 training sessions, the patient showed a significant reduction of dystonic symptoms, which was associated with decreased beta band event-related synchronization. Despite limited data, this proof-of-concept study pointed to the feasibility of BCIs for dystonia treatment.

Other relevant studies include the use of different feedback paradigms, eg, visual-haptic biofeedback, auditory grip force feedback, and reversal-learning tasks, for improved motor control in patients with focal hand dystonia and children with dystonia.[36,37] Although these feedback paradigms were not used as BCI components, these studies demonstrated that continuous sensorimotor training may translate into effective rehabilitation strategies for patients with dystonia, possibly by inducing plastic cortical reorganization and adaptation.[18]

A Roadmap for BCI-Based Therapeutic Strategies for Focal Task-Specific Dystonias

One of the prerequisites for effective implementation of neurofeedback BCIs for dystonia treatment is the targeting of the disorder's pathophysiological neural signature. Patients with task-specific focal dystonias are ideal candidates for developing personalized BCI protocols because of their unique clinical feature of a *selective* motor program impairment, which allows to reliably distinguish neural activity associated with symptomatic versus asymptomatic behaviors. In such BCIs, we define individual abnormal brain activity during symptomatic task production as the *disorder signature* and close-to-normal brain activity during an asymptomatic but relevant motor task as the *target signature*. Both disorder and target signatures are constructed based on EEG activity from cortical regions whose alterations are known to play an important role in task-specificity of focal dystonias. Specifically, prior studies have been consistent in showing abnormalities in premotor-parietal activity as one of the prominent neural features of task-specificity across different forms of focal dystonia.[38,39] Moreover, premotor-parietal alterations appear to *precede* and influence the output of dystonic activity by primary motor cortex.[40] We therefore anticipate that targeted modulation of premotor-parietal activity with the neurofeedback BCI would normalize the information flow from these regions to primary sensorimotor cortex, which, in turn, would attenuate motocortical hyperexcitability (first-order modulation) and subsequently reduce abnormal motocortical output within the larger dystonic network, including to subcortical structures, such as the basal ganglia and cerebellum (second-order modulation) (Fig. 1).

In this article, we outline a recommendation for a noninvasive, closed-loop neurofeedback BCI intervention paradigm in an example of laryngeal dystonia, isolated focal task-specific dystonia selectively affecting the production of voiced, but not whispered, speech. The integrated components of this BCI include: (1) a high-density EEG acquisition system, which records cortical activity for constructing individual neurofeedback and (2) a built-in machine learning (ML) platform consisting of a neural signal decoder and a neurofeedback controller that (3) provide visual feedback of ongoing EEG activity to the patient in near real time, eg, via a computer screen or virtual reality environment (Fig. 2A). Before the BCI intervention, the individual target signature is constructed based on the EEG recording of close-to-normal cortical activity during asymptomatic whisper. During the BCI intervention,

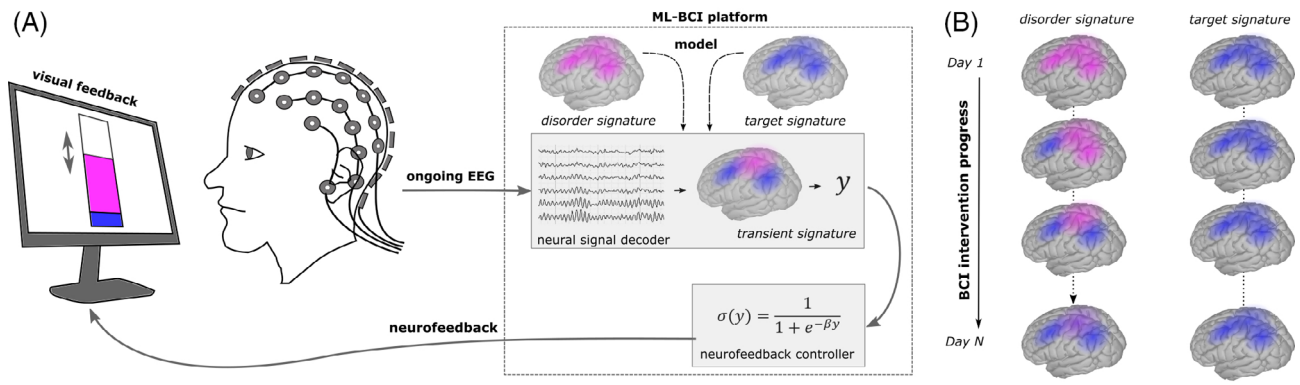

FIG. 2. (**A**) Overview of the neurofeedback BCI paradigm for treatment of focal task-specific dystonia, including a high-density EEG recording system, an ML-BCI platform, and a visual neurofeedback monitoring system. The ML-BCI platform transforms the momentary EEG activity into continuous visual neurofeedback that is based on the difference between the transient disorder signature and the target signature. While performing a symptomatic task, the patient actively regulates their brain activity to match the disorder signature to the target signature of a related but asymptomatic motor task. (**B**) Throughout the BCI training, the disorder signature is expected to gradually correspond to the target signature, which, in turn, is expected to be associated with clinically relevant symptom reduction. BCI, brain–computer interface; EEG, electroencephalography; ML, machine learning.

ongoing EEG activity during symptomatic speaking constitutes the individual disorder signature, which is continuously fed to the ML-BCI platform for computing the delta change from the target signature. The signal difference between disorder and target signatures is delivered to the patient in near real time as visual neurofeedback for guiding the dynamic learning process. That is, throughout the BCI intervention session, the patient learns to modulate their disorder signature associated with symptomatic speaking and normalize it to the level of the target signature associated with asymptomatic whisper (Fig. 2B). Such BCI-based modulation of brain activity is expected to translate to clinically relevant symptom reduction.

Similar neurofeedback BCI designs may be adapted for other forms of focal task-specific dystonia. For example, patients with writer's cramp may use their neural activity during symptomatic writing as the disorder signature and asymptomatic tapping as the target signature. Depending on the form of dystonia, personalized ML-BCI platforms should be calibrated based on individual alterations in EEG frequency bands and other pathophysiologically relevant neural and behavioral features. Other important methodological considerations include robust correction of EEG motion artifacts associated with the production of complex motor behaviors, eg, speaking or writing. In this context, the use of high-density EEG would allow to exclude peripheral, motion-prone electrodes during signal processing without compromising sufficient density of signal sampling from cortical regions of pathophysiological relevance. Moreover, high-density EEG effectively separates potential artifacts from relevant signal components using source and subspace reconstruction techniques.

To rigorously assess the outcome of neurofeedback BCIs and reduce the possibility of a training bias, the BCI interventions in patients with dystonia should consider the incorporation of a sham condition, eg, in the form of random neurofeedback. Longitudinal study designs are preferred to monitor changes in symptoms during and after BCI intervention. Finally, because of the lack of consensus on the outcome measures in dystonia, it is important to implement both objective and subjective evaluations using the clinician-administered standardized dystonia rating scales and patient self-ratings of their current state of symptoms, respectively.

Conclusion and Future Directions

Given the breadth of previous research on neurofeedback BCIs with promising outcomes in other neurological disorders, recent developments in neural decoding methods, existing computational capabilities for neural signal processing in near real time, and the current state of knowledge of clinical features and pathophysiology of dystonia, we propose that it is timely to develop and implement adaptive neurofeedback BCI interventions for the treatment of these patients. One such closed-loop BCI system that leverages the disorder's clinical and pathophysiological characteristics by targeting the task-specificity of focal dystonia is described earlier.

We recognize that patients with task-specific focal dystonias would likely receive greater benefits from the recommended BCI intervention paradigm than those with generalized or non–task-specific dystonias. We, however, expect this article to facilitate a broader discussion across the field for further development of BCIs in patients with various other forms of dystonia.

Future research should also be directed to ensuring the maintenance of BCI therapeutic benefits for the long-term clinical management of these patients. Although high-density EEG and other research-grade systems offer high precision for identifying clinically relevant pathophysiological features of significant therapeutic potential, they are challenging to use in the clinical setting. Therefore, building on the outcomes of research BCI studies, the ultimate goal should be to transfer the effective research technology to clinically applicable solutions. One such implementation may be the development of in-home-use portable devices with fewer electrodes and simplified setup procedures. Other opportunities may include developing implantable BCI devices or integrating the novel sensing deep brain stimulation systems (eg, Medtronic Percept PC) with neurofeedback BCIs for delivering patient-specific therapeutic benefits. ■

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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