Patterns of Cortical Synchronization in Isolated Dystonia Compared With Parkinson Disease

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IMPORTANCE Isolated dystonia and Parkinson disease (PD) are disorders of the basal gangliothalamocortical network. They have largely distinct clinical profiles, but both disorders respond to deep brain stimulation (DBS) in the same subcortical targets using similar stimulation paradigms, suggesting pathophysiologic overlap. We hypothesized that, similar to PD, isolated dystonia is associated with elevated cortical neuronal synchronization.

OBJECTIVE To investigate the electrophysiologic characteristics of the sensorimotor cortex arm-related area using a temporary subdural electrode strip in patients with isolated dystonia and PD undergoing DBS implantation in the awake state.

DESIGN, SETTING, AND PARTICIPANTS An observational study recruited patients scheduled for DBS at the University of California, San Francisco and the San Francisco Veterans Affairs Medical Center. Data were collected from May 1, 2008, through April 1, 2015. Findings are reported for 22 patients with isolated cervical or segmental dystonia (8 with [DYST-ARM] and 14 without [DYST] arm symptoms) and 14 patients with akinetic rigid PD. Data were analyzed from November 1, 2014, through May 1, 2015.

MAIN OUTCOMES AND MEASURES Cortical local field potentials, power spectral density, and phase-amplitude coupling (PAC).

RESULTS Among our 3 groups that together included 36 patients, cortical PAC was present in primary motor and premotor arm-related areas for all groups, but the DYST group was less likely to exhibit increased PAC (P = .008). Similar to what has been shown for patients with PD, subthalamic DBS reversibly decreased PAC in a subset of patients with dystonia who were studied before and during intraoperative test stimulation (n = 4). At rest, broadband gamma (50-200 Hz) power in the primary motor cortex was greater in the DYST-ARM and PD groups compared with the DYST group, whereas alpha (8-13 Hz) and beta (13-30 Hz) power was comparable in all 3 groups. During movement, the DYST-ARM group had impaired beta and low gamma desynchronization in the primary motor cortex.

CONCLUSIONS AND RELEVANCE Isolated dystonia and PD have physiologic overlap with respect to high levels of motor cortex synchronization and reduction of cortical synchronization by subthalamic DBS, providing an explanation for their similar therapeutic response to basal ganglia stimulation.
Isolated dystonia and Parkinson disease (PD) are both disorders of the basal gangliothalamocortical network. Increasing evidence suggests that the motor signs of PD are related to excessive synchronized oscillatory activity in the basal gangliothalamocortical network, manifested primarily by increased synchronization of population spiking to the motor beta rhythm. Isolated dystonia also may be associated with abnormalities in synchronized oscillations. Both disorders can be ameliorated by the same deep brain stimulation (DBS) paradigms, such as 100- to 200-Hz constant stimulation (DBS) paradigms, such as 100- to 200-Hz constant stimulation of the globus pallidus internus or subthalamic nucleus (STN). This empirical finding suggests similarities in the underlying brain circuit abnormalities in both disorders.

Previous studies used intraoperative electrocorticography (ECOG) in humans undergoing DBS implantation in the awake state to characterize specific patterns of neuronal synchronization in the arm-related area of the primary motor cortex (M1). Compared with other forms of invasive human recordings, such as basal ganglia local field potentials, ECOG potentials can compare the spectral characteristics of low-frequency rhythms, such as the dominant motor beta rhythm, across multiple diseases and extract a surrogate measure of population spiking from the ECOG power spectrum (ie, the amplitude of broadband high-frequency activity in the gamma range of 50-200 Hz). The most striking abnormality in patients with rigid akinetic PD compared with patients without PD is the excessive coupling of M1 broadband gamma activity to the phase of the beta rhythm. This coupling implies excessive phase locking of M1 neurons to the beta rhythm and may constrain the motor cortex into an inflexible pattern of activity such that initiation and execution of movement is impaired. This abnormality is reversed by acute therapeutic STN DBS. Furthermore, M1 broadband gamma activity at rest is elevated in PD, which is indicative of increased resting-state activity and consistent with functional imaging studies.

Herein we test the hypothesis that patients with isolated generalized dystonia show patterns in the M1 that are similar to patterns in patients with PD, with similar reversal by therapeutic DBS. Patients with dystonia may have physiologic endophenotypes that are also present in asymptomatic carriers of dystonia-predisposing genes or in the brain hemisphere contralateral to an asymptomatic body side. To resolve whether observed physiologic motifs reflect such an endophenotype (vs overtly manifesting motor signs), we separated patients with dystonia into those with clinically apparent arm involvement and those without arm involvement on the side contralateral to the ECOG recording in the arm area of the M1 (DYST-ARM and DYST groups, respectively). Although a prior study included a cohort with dystonia, that cohort only included patients with cranioocular dystonias without involvement of the arm contralateral to the ECOG recording.

Methods

Patient Selection

We recruited patients with isolated dystonia or idiopathic PD scheduled to undergo DBS surgery at the University of California, San Francisco or the San Francisco Veterans Affairs Medical Center for the study. Inclusion criteria for the PD group were rigidity and akinesia as the most prominent symptoms and a lack of dystonic symptoms in the upper body while not receiving medications. Written informed consent was obtained before surgery under a protocol approved by the institutional review boards of the University of California, San Francisco and the San Francisco Veterans Affairs Medical Center, and all patients were aware that the temporary subdural strip was used strictly for research purposes. Motor impairment was quantified for the DYST groups using the Burke Fahn Marsden Dystonia Rating Scale movement score or, for the PD group while not receiving medications, part III of the Unified Parkinson’s Disease Rating Scale. Forty-eight patients were initially included in the study, but 12 were excluded for reasons listed below; therefore, results are reported for 36 patients. Data were collected from May 1, 2008, through April 1, 2015.

Surgical Process and ECOG Strip Localization

To record cortical ECOG potentials, a 6-contact subdural ECOG strip was placed on the surface of the brain through the same burr hole used for the DBS implantation. The intended target location was the arm area of the M1, 3 cm from the midline and slightly medial to the hand knob. Recordings were performed at least 12 hours after stopping all antiparkinsonian and antidystonic medication therapies and at least 30 minutes after stopping propofol therapy. Data were collected before the DBS electrode implantation except for STN stimulation-related data. The DBS electrodes were placed in the STN as previously described.

The ECOG contact locations were confirmed anatomically using lateral fluoroscopy or intraoperative computed tomography fused to the preoperative planning magnetic resonance imaging with standard surgical planning software (Framelink, version 5.1; Medtronic, Inc). Median nerve somatosensory-evoked potentials (SSEPs) were recorded, and reversal of the first negative component of the cortical SSEP (N20) waveform indicated the M1 location. We found high concordance between anatomical and physiologic determinations of contact position with respect to the central sulcus (CS) (Figure 1A), but in case of discrepancy (10 patients), the SSEP location was used. Patients whose SSEPs did not show clear N20 reversal and who did not have computed tomography–confirmed ECOG strip location within 30 ± 5 mm from the midline were excluded from analysis (5 patients with dystonia and 3 with PD).

Signal Recordings

The ECOG potentials were recorded using an intraoperative electrophysiology recording system (Guideline 4000 [FHC] or MicroGuide Pro [Alpha Omega]). Recordings were obtained from 5 contacts differentially referenced to the most anterior sixth contact, with a scalp needle electrode as ground. Signals were band-pass filtered at 1 to 500 Hz, amplified, and sampled at a minimum 1000 Hz (Guideline 4000) or 3000 Hz (MicroGuide Pro), with additional notch filtering to remove power line artifacts. The Guideline 4000 system had slight attenuation up to 20 Hz owing to the slow rolloff characteristics of an intrinsic 1-Hz high-pass filter, which was compen-

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Figure 1. Study Methods

A. Images show placement of subdural 6-contact strip with 1-cm spacing between contacts, spanning the central sulcus (CS). B. Example of the electrocorticography (ECOG) signal, wrist accelerometer, and biceps electromyographic (EMG) signals. C. Placement of the ECOG strip is targeted approximately 3 cm from the midline, medial to the hand knob (unlabeled white arrowhead). D. Median nerve somatosensory evoked potential (SSEP) shows reversal of the N20 potential at the electrode contact pair spanning the primary motor cortex (CS-C6). E. Example of power spectral density from 1 patient obtained by transforming the cortical ECOG signal into the frequency domain during rest and the movement and stop phases of the elbow flexion-extension task. F. Interaction between low- and high-frequency rhythms in a schematic representation of phase-amplitude coupling (PAC). G. Each color data point is the phase-amplitude coupling index between the phase of the low-frequency band defined on the x-axis and the amplitude of the high-frequency band defined on the y-axis, extracted from the same ECOG potential. Mean beta-broadband gamma PAC was calculated by averaging the indices within the white box. CT indicates computed tomographic; LFP, local field potential; M1, primary motor cortex; MR, magnetic resonance; and SI, primary sensory cortex.

Behavioral Tasks

The ECOG potentials were recorded in 2 behavioral conditions. During rest, patients were instructed to relax with their eyes open for at least 30 seconds. During the movement task, patients performed flexion-extension of the elbow (3- to 5-second movement phase and 3- to 5-second stop phase, repeated 5 times) with slow deliberate movement to reduce the effect of velocity as a confounding variable. All patients underwent testing at rest, and all but 3 patients with dystonia and 5 patients with PD underwent the movement task. Muscle activity was recorded using surface electromyography from the contralateral anterior deltoid, biceps brachii, extensor carpi radialis (band-pass filtered at 20-1000 Hz, amplified, and sampled at 1 kHz), and a wrist accelerometer.

Signal Processing

Data analysis was performed using custom scripts in MATLAB (version R2014a; MathWorks). All recordings were downsampled to 1 kHz and visually inspected for electrical noise or signal loss; those portions were excluded. Patients whose recordings were excessively contaminated by noise or whose M1 signal root mean square was less than 10 μV were excluded from analysis (2 patients with PD were excluded for noise; 1 patient with dystonia and 1 patient with PD were excluded for low signal amplitude). The electromyographic and accelerometer recordings were analyzed using a semiautomated threshold detection method with visual confirmation to determine movement start and stop times. Movement and stop segments had to be at least 3 seconds long to be included in the analysis.

The ECOG potentials were rereferenced in a bipolar montage and assigned to one of the following 4 anatomical locations: M1 or precentral gyrus, CS, postcentral gyrus (SI), and premotor (II patients did not have premotor coverage; Figure 1). Data were analyzed in the frequency domain and log transformed for statistical comparison (Figure 1E). We calculated mean log-transformed power spectral density for multiple-
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Table. Patient Groups

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>No. of Patients</th>
<th>Age, Mean (SD), y</th>
<th>Sex, No. Female/Male</th>
<th>Side of ECOG Strip</th>
<th>Motor Score, Mean (SD)a</th>
<th>Arm Subscore, Mean (SD)b</th>
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<tbody>
<tr>
<td>DYST</td>
<td>14</td>
<td>55.9 (10.8)</td>
<td>8/6</td>
<td>4L/10R</td>
<td>12.8 (6.2)</td>
<td>0</td>
</tr>
<tr>
<td>DYST-ARM</td>
<td>8</td>
<td>50.4 (8.7)</td>
<td>5/3</td>
<td>4L/4R</td>
<td>29.5 (14.9)</td>
<td>5.1 (2.9)</td>
</tr>
<tr>
<td>PD</td>
<td>14</td>
<td>56.7 (10.0)</td>
<td>3/11</td>
<td>7L/7R</td>
<td>35.4 (17.7)</td>
<td>12.4 (5.7)</td>
</tr>
</tbody>
</table>

Abbreviations: DYST-ARM, isolated dystonia with arm symptoms contralateral to the ECOG side; DYST, isolated dystonia without arm symptoms contralateral to the ECOG side; ECOG, electrocorticography; L, left; PD, Parkinson disease; R, right.

a Indicates the arm subscore of the BFMDystonia Rating Scale (DYST groups) or the Unified Parkinson’s Disease Rating Scale part III (UPDRS-III) while not receiving medication (PD group).

b Indicates the Motor score of the Burke Fahn Marsden (BFM) Dystonia Rating Scale (DYST groups) or items 20 through 25 of the UPDRS III (PD group) on the arm contralateral to the side of the ECOG recording.

We calculated phase-amplitude coupling (PAC) between frequency bands (4–8, 8–13, 13–30, 30–50, and 50–200 Hz) and compared them among the patient groups.

We found differences in cortical beta and gamma power between isolated dystonia and Parkinson disease (PD) patients (Figure 1G). To obtain a beta-gamma interaction value specific to the symptom expression. In the awake resting state, we related PAC to the Motor score of the Burke Fahn Marsden (BFM) Dystonia Rating Scale ([UPDRS-III] while not receiving medication (PD group). We did not explore this finding systematically in the present study.

The mean PAC decreased approximately 80% during the movement phase (compared with the stop phase) for all 3 groups. This decrease was significant for the DYST group (P = .01) but was not significant for the PD group (P = .07). During the movement and stop phases of the movement task, we found no significant differences in mean PAC among the patient groups (Figure 4 in the Supplement).

Effect of Acute DBS on PAC in Dystonia

In 4 patients with dystonia, we evaluated the effect of DBS on cortical activity. A previous study showed that, in PD, therapeutic STN DBS reduces the PAC without a consistent effect on beta or gamma power (an example appears in Figure 3). In the present study, STN DBS also reduced the PAC in 2 patients in the DYST group (by 100% and 30%) and 2 patients in the DYST-ARM group (by 89% and 61%) (Figure 3). We had an insufficient number of cases to determine the effects of STN DBS on beta and gamma power (Figure 5 in the Supplement), but prior analyses of DBS in PD showed a reduction in PAC without a consistent change in power. Owing to intraoperative constraints, patients were not assessed for therapeutic benefit, but dystonia can demonstrate a very quick clinical response to STN DBS.

Resting Gamma Power- and Movement-Related Beta Power Decrease

A previous report revealed that the DYST group included 5 patients without an elevated PAC (empirically defined as the first quartile of all mean PAC values, 1.2 × 10−4), whereas the DYST-ARM and PD groups included only 1 patient each without an elevated PAC (P = .008, χ2 test). The PAC is generally stable over time (eFigure 3 in the Supplement), but we did not explore this finding systematically in this study.

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Elevated Cortical Synchronization in Dystonia and PD

Phase-amplitude coupling is a physiologic phenomenon important for information processing between and within cortical regions and is dynamically modulated during task performance. Motor cortex PAC can be detected in interictal recordings from patients with epilepsy undergoing long-term monitoring, suggesting a role in normal motor function. Previous studies showed that M1 PAC is exaggerated in patients with PD compared with patients without a movement disorder (epilepsy cohort) and is reduced by acute therapeutic DBS. These studies proposed that elevated cortical PAC is related to the expression of parkinsonian motor signs. Herein, we extend this model to isolated dystonia, offering an explanation for the fact that identical stimulation paradigms ameliorate both disorders. Because broadband gamma amplitude is a surrogate measure of population spiking, we interpret elevated coupling between the beta phase and broadband gamma amplitude as a manifestation of excessive synchronization of population spiking to the motor beta rhythm, a phenomenon also observed in the basal ganglia from single-unit and local field potential recording studies in PD.

Similarities in the pathophysiologic signatures of PD and dystonia are not surprising given the phenotypic overlap in motor...
symptoms observed clinically. Both disorders are characterized by slowness of movement (although bradykinesia is much more pronounced in PD), with a tendency for development of dystonia in PD (as a presenting sign or later as part of the clinical spectrum of motor fluctuations), and both disorders can coexist in rare dystonia-parkinsonism syndromes.22,23 Furthermore, dopaminergic deficiency can result in PD or dystonia (consider dopa-responsive dystonia and neuroleptic-induced dystonia), and striatal dopaminergic signaling pathways, fundamental to the pathophysiologic features of PD, have been strongly implicated in the development of dystonia.24 Although both disorders involve dysfunction in the basal gangliothalamocortical loop, additional undefined perturbations may bias the system toward a more parkinsonian or more dystonic phenotype.

Cortical Function in Dystonia

We differentiated dystonia based on the presence or absence of arm symptoms in the arm contralateral to cortical recordings to address whether electrophysiologic findings are endophenotypic (present in the brain of patients with dystonia independent of symptom expression) or if they correspond to symptom expression in the homologous body part. Prominent motor cortex PAC was observed in both dystonia cohorts, but it tended to be lower in the DYST group. A previous study5 reported low PAC in patients with cranio-cervical disease; however, in the present enlarged cohort, we detected several patients without arm symptoms who had increased PAC, in some cases of similar magnitude as PAC in PD and dystonia with arm symptoms. Elevated PAC may therefore be an endophenotype of the disease similar to excessive motor cortex plasticity shown in studies of transcranial magnetic stimulation.25 Alternatively, elevated PAC may have been caused by abnormalities in the neck region of the cortex (medial to the arm region), or some patients without overt arm dystonia may have had subclinical arm symptoms. For example, 1 patient in the DYST group had strong M1 PAC and reported that DBS resolved his purported arthritic hand pain and improved his handwriting, which suggests the presence of subclinical arm symptoms before surgery. This result highlights the difficulty of accurate symptom identification based only on visual observation.

Movement-related desynchronization of alpha-beta activity is a normal physiologic mechanism of motor function26-28 and was previously shown to be reduced in dystonia.7,10,29,30 Our results suggest that impaired desynchronization relates specifically to symptomatic expression. Beta activity in the motor system has been proposed to function in maintaining the existing motor state, requiring reduction to accomplish fluid movement.31,32 An inability to reduce beta activity at the onset of movement could thus produce action dystonia by inappropriately maintaining previous postures during the attempt movement.

Figure 3. Phase-Amplitude Coupling (PAC) in the Primary Motor Cortex in Deep Brain Stimulation of the Subthalamic Nucleus (STN DBS)

Color indicates PAC index for individual patients. Columns represent individual patients (all data were acquired after electrode implantation; poststimulation data for patient 13 in the DYST group were not obtained). DYST indicates isolated dystonia with no arm symptoms contralateral to the electrocorticography (ECOG) side; DYST-ARM, isolated dystonia with arm symptoms contralateral to the ECOG side; and PD, Parkinson disease.
Figure 4. Power Spectral Density (PSD) Analysis at Multiple Cortical Recording Locations at Rest and During Movement

A  PSD at rest

B  Change with movement

Change that occurs with movement is shown as the difference in log-transformed power spectra between the movement and stop phases of the movement task. Shaded areas are statistically different by 1-way analysis of variance (post hoc comparisons are described in text); the significant P value accounting for multiple comparisons is less than .003. We found no significant difference in broadband gamma modulation between groups. Eight patients did not have movement data. CS indicates central sulcus; DYST, isolated dystonia with no arm symptoms contralateral to the electrocorticography (ECOG) side; DYST-ARM, isolated dystonia with arm symptoms contralateral to the ECOG side; M1, primary motor cortex; PD, Parkinson disease; and S1, primary sensory cortex.

Gamma Band Activity as a Measure of Cortical Activation State

In ECOG recordings, broadband gamma band power (approximately 50-200 Hz) tracks local cortical function by increasing in amplitude in a highly topographic, task-specific manner when the relevant functional region is engaged. Gamma power is positively correlated with the functional magnetic imaging studies on resting-state metabolic activity in the M1 area have found to be elevated in positron emission tomography imaging in PD. In isolated dystonia, the results of functional imaging studies on resting-state metabolic activity in the M1 area are not consistent, but our findings suggest further pathophysiologic overlap between PD and isolated dystonia with respect to resting-state activation.

Limitations

Lack of a healthy control group, a difficulty inherent to invasive brain recordings in humans, precludes definitive labeling of a physiologic variant as abnormal. Previous ECOG work showed that patients without a movement disorder (eg, those with epilepsy undergoing interictal monitoring) have a lower PAC than patients with PD, so our finding of a similarly elevated PAC in dystonia is likely related to pathophysiologic mechanisms, but further studies are needed to confirm this finding in different cohorts. The range of clinical severity scores within each patient group was relatively narrow, and we did not find a correlation between clinical severity and any of the physiologic features that distinguished disease groups. Medication effects may not have fully washed out after overnight withdrawal and may have affected cortical activity, specifically in terms of modulating beta power. However, both dystonia groups received similar levels of benzodiazepines, so this effect is unlikely to be responsible for the observed differences.

Conclusions

Dystonia and PD are both disorders of high synchronization in the M1 area as assessed by coupling between broadband gamma activity and the phase of the motor beta rhythm; in both cases, this measure of neuronal synchronization is reduced by therapeutic DBS. This finding may account for the coexistence of dystonia and parkinsonism in several clinical syndromes and for the similarity in stimulation targets and stimulation settings that alleviate isolated dystonia and PD.

ARTICLE INFORMATION


Author Contributions: Drs Miocinovic and de Hemptinne had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Miocinovic, de Hemptinne, Starr.
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Additional Contributions:

Nicole Swann, PhD, Department of Neurology, University of California, San Francisco (UCSF) provided discussion and critical review of the manuscript. Nathan Ziman, BS, Department of Neurosurgery, University of California, San Francisco (UCSF) provided clinical data retrieval. Neither de Hemptinne, Starr, Miocinovic, de Hemptinne, Miocinovic, de Hemptinne, or Miocinovic helped with clinical data retrieval. Neither de Hemptinne, Starr, Miocinovic, de Hemptinne, Miocinovic, de Hemptinne, or Miocinovic contributed to data analysis, interpretation of the data, preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

References