DYSTONIA

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EDITED BY
John Robert Younce,
University of North Carolina at Chapel Hill, United States

*CORRESPONDENCE
Andrea A. Kühn,
andrea.kuehn@charite.de

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The chronical outcome monitoring in dystonia with deep brain stimulation (COMEDD) study protocol: a longitudinal evaluation of chronic electrophysiological biomarkers in patients with dystonia and deep brain stimulation therapy

Lucia K. Feldmann[1,2], Jonathan Kaplan[1], Ana Luisa de Almeida Marcelino[1,2], Daniel Schulze[3] and Andrea A. Kühn[1,4,5,6]*

[1]Movement Disorder and Neuromodulation Unit, Department of Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Berlin Institute of Health @ Charité, Charité University Medicine, Berlin, Germany, [3]Institute of Biometry and Clinical Epidemiology, Charité University Medicine, Berlin, Germany, [4]Berlin School of Mind and Brain, Charité University Medicine, Berlin, Germany, [5]NeuroCure Clinical Research Centre, Charité University Medicine, Berlin, Germany, [6]DZNE, German Center for Degenerative Diseases, Berlin, Germany

Introduction: Deep brain stimulation is an effective therapy for patients with isolated dystonia. In pallidal local field potential recordings, theta was identified as a biomarker for symptom severity, and beta as a transdiagnostic biomarker for bradykinesia. However, challenges remain: 1) programming can be a lengthy process, and to date there is no guidance by electrophysiological biomarkers; 2) temporal dynamics of stimulation effects, but also of stimulation-induced side-effects are not understood; 3) electrophysiological characteristics for dystonia subtypes or non-responders are unknown.

Materials and protocol outline: This is the protocol for an observational, prospective, long-term study for the systematic identification of electrophysiological pallidal biomarkers in patients with dystonia and a newly implanted sensing-enabled deep brain stimulation system. We expect a recruitment of 25–30 patients to be sufficient to track changes in chronic biomarkers and symptom severity. The protocol consists of two strategies for data collection in the same patient cohort over 12 months after deep brain stimulation surgery: 1) continuously recorded chronic peak biomarker activity with weekly home monitoring; 2) monthly in-hospital recordings of local field potential data at 250 Hz sampling rate during rest and motor activity and during stimulation ON/OFF. Two patients have completed the study protocol with an appointment adherence of 92%, underlining the feasibility of the study protocol.

Discussion: We here present a feasible, systematic protocol for identification of electrophysiological biomarkers in dystonia to establish electrophysiology-based guidance of therapy optimization in dystonia. Progress of the study can be followed in the study registration log: NCT07244549.

KEYWORDS

biomarkers, dystonia, electrophysiology, home monitoring, long-term follow-up

Introduction

Dystonia is a hyperkinetic movement disorder with an increased muscle tone that results in abnormal, often fixed postures, impaired voluntary movement, and sometimes tremor [1]. The clinical presentation is variable, ranging from focal, e.g., cervical dystonia to generalized dystonia with severe disability. Additional non-motor symptoms such as pain, impaired sleep quality, depression or compulsory behavior can add to the burden of disease. Dystonia affects patients of all age groups, making this one of the most common pediatric movement disorders.

Treatment of dystonia can be challenging, with limited pharmacological options. For more than 20 years, deep brain stimulation (DBS) to the globus pallidus internus (GPi) has been established as an effective treatment, resulting in dramatic and sustained symptom improvement [2–4]. However, not all patients benefit similarly, with approximately one third non-responders [4]. Clinical stimulation optimization can be a lengthy and challenging process, due to delayed effects. While standardized clinical algorithms [5] and algorithms based on anatomical localization [6] have been evaluated, electrophysiological biomarkers might provide further insights [7].

Besides the clinical efficacy, DBS implantation has also opened the opportunity to record intracranial electrophysiological activity from affected basal ganglia structures. Symptom specific patterns could be used as electrophysiological biomarkers for automated adjustment of DBS. With novel sensing-enabled devices, these biomarkers and their chronic dynamics have become accessible. In Parkinson's disease, beta band activity is known as a biomarker for bradykinesia [8]. With the sensing-enabled neurostimulators, biomarker stability [9, 10], and dynamics during stimulation [11, 12], as well as fluctuations around medication intake [13] and circadian periodicity [14] could be investigated, and now beta-based adaptive DBS is already used clinically in PD [15, 16].

In dystonia, low-frequency (LF) activity in the theta/alpha range is correlated with symptom severity [17–20] and is modulated by DBS [21]. Interestingly, with chronic stimulation, beta band activity increased, and patients developed bradykinesia, pointing towards a transdiagnostic biomarker [16]. Further, gamma band activity as a new biomarker for effective therapy states is of growing interest in PD [22], and has recently also been described in dystonia [23]. First case-reports in patients with dystonia have underlined the feasibility of chronic biomarker recordings in dystonia [7, 24, 25].

Understanding chronic biomarker dynamics could be crucial for DBS optimization in dystonia, as with the delayed stimulation effects, clinicians lack clinical observation as a guidance for the optimization. Biomarkers could inform and accelerate this often strenuous process. However, to date, no systematic chronic assessment of electrophysiological biomarkers in dystonia, especially during effective DBS, has been conducted. This would be of importance for the characterization of biomarkers for adaptive algorithms, and, more acutely, for electrophysiological guidance.

Study protocol

This study is a prospective, multi-center, observational study. At the moment of publication, three centers in Germany (Berlin, Hanover, Düsseldorf) are recruiting centers. Updates on recruitment, study centers, analysis plans etc., will be available in the study registration log on ClinicalTrials.gov, ID NCT07244549. The protocol outline is presented in Figure 1. The study duration is 12 months follow-up after the implantation of pallidal DBS electrodes and the Percept neurostimulator.

Clinical cohort

In this study, all patients with a diagnosis of isolated dystonia who receive DBS to the GPi and decide to select a Percept PC/RC (TM) (Medtronic, MN, United States) neurostimulator in one of the study centers are screened and contacted for participation.

Inclusion criteria are:

- Age 5–80 years
- Ability to give informed consent for the study, or in pediatric patients, legal guardian or parent willing to give informed consent
- Diagnosis of isolated dystonia, which may be focal, segmented or generalized
- Surgical intervention with DBS to the GPi is planned by clinical indication
- Decision to receive the sensing-enabled neurostimulator (Percept neurostimulator) PC/RC

Exclusion criteria are:

- Severe psychiatric disorders
- Other severe medical conditions, that may interfere with the successful participation in the study protocol
- No consent given

Patient and public involvement

Strategies and feasibility of home monitoring have been previously developed by us with a patient engagement program [26]. Throughout the piloting phase, patient feedback on the final set of questions has been obtained. Towards the end of the recruitment phase, a patient meeting will be organized to discuss the study results with the participants.

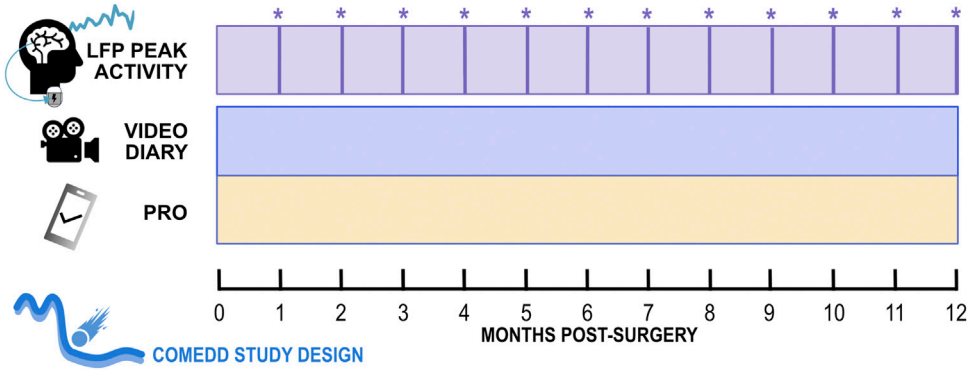

FIGURE 1
Schematic of COMEDD Study Protocol. The bars represent the parallel data acquisition over a time period of 12 months. The purple bar represents intracranial local field potential (LFP) recordings. While peak biomarker activity is recorded continuously, there are additional monthly recordings marked with an asterisk. Here, a short routine recording protocol is performed in the lab, including full LFP recordings during ON- and OFF-DBS states. Symptomatic home monitoring is performed continuously during the first 12 months. Here, patients are asked to perform video recordings (blue bar) and complete a patient-reported outcome questionnaire (yellow bar) (see Table 1) once per week.

Study protocol

For clinical characterization of the patients, the following scores aiming at motor- and non-motor symptoms are assessed at the first (month 0) and last (month 12) recording:

- Motor symptoms:
  - o Dystonia symptoms (also at the monthly in-hospital visits): Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS)
  - o bradykinetic symptoms: Unified Parkinson's Disease Rating Scale (UPDRS-III).
- Non-motor symptoms:
  - o Pain: TWSTRS-Pain
  - o Disability: TWSTRS-Disability
  - o Depression/Apathy: Beck's Depression Inventory (BDI), Starkstein Apathy Scale
  - o Obsession/Compulsion: Obsessive-Compulsive Inventory (OCI).

Chronic peak biomarker tracking and out-of hospital monitoring

Peak biomarkers are recorded continuously during the whole recording period, using the Chronic BrainSense function as previously described [14]. With this study, we aim to electrophysiologically characterize improvements in standard clinical care during the first post-operative year. This means that contact selection is determined by the clinical optimization procedure in the respective centers. Based on the clinical programming, peak biomarker power is tracked at a temporal resolution of one mean value every 10 min at an investigator-selected peak frequency ± 2.5 Hz in the clinically selected contacts. In one hemisphere, LF-activity will be tracked as a promising biomarker for dystonic symptom severity. Since technically, the minimal recordable center peak with the Percept IPG is 7.8 Hz, LF-activity in the range between 5.3 and 13 Hz can be recorded, depending on the selected peak. The second hemisphere is recorded at a peak frequency in the beta range (13–35 Hz) to assess for stimulation induced beta activity [16] increase over time. Decision which hemisphere will be used for which frequency band tracking will be made at the initial BrainSense set-up based on visual inspection of the automatically generated power spectra in the BrainSense Signal Test. If a clear LF peak <10 Hz is available in one hemisphere, we select the hemisphere with the highest peak for LF-tracking and the other hemisphere for beta-tracking. If no LF-peak is available, the hemisphere with the highest beta-peak is selected for beta-tracking, and the other hemisphere is set to 7.8 Hz. If no clear peaks are available selection is performed based on the previous criteria in the BrainSense Survey setting in the contact itself or adjacent contacts and assessment regarding severe artifact contamination is done. Ideally, this BrainSense setting is maintained during the entire recording period, but clinical optimization leading to change of stimulation contacts used, and thus also the recording configuration, may be necessary. Depending on patient preference, DBS is not activated during the first post-operative month. Because chronic biomarker tracking can only be performed if one of the two middle contacts/segments is used for clinical stimulation and if monopolar stimulation is used, some participants may be lost for chronic biomarker tracking over the course of the study duration. Figure 2B depicts exemplary simultaneous biomarker data recorded in one dystonia patient during chronic DBS for a week.

For correlation with clinical improvement, objective and subjective measures of symptom severity will be sampled weekly. Depending on the personal preferences and technical equipment of the participants, a paper-pencil version or a custom-made application through Virgobit UG, Münster, Germany, is provided. As a subjective assessment, we will use patient reported outcomes as per a questionnaire. The questions are presented in Table 1 and include 15 questions aiming at general wellbeing/functionality (2), non-motor symptoms such as neuropsychiatric symptoms, pain and sleep (7), motor-symptoms (4) and therapy efficacy (2). Reply options are evaluated on a 9-point-likert scale, or for question 8 with single choice from 4 options. The questions are oriented on clinical expertise, patient expertise (see above) and

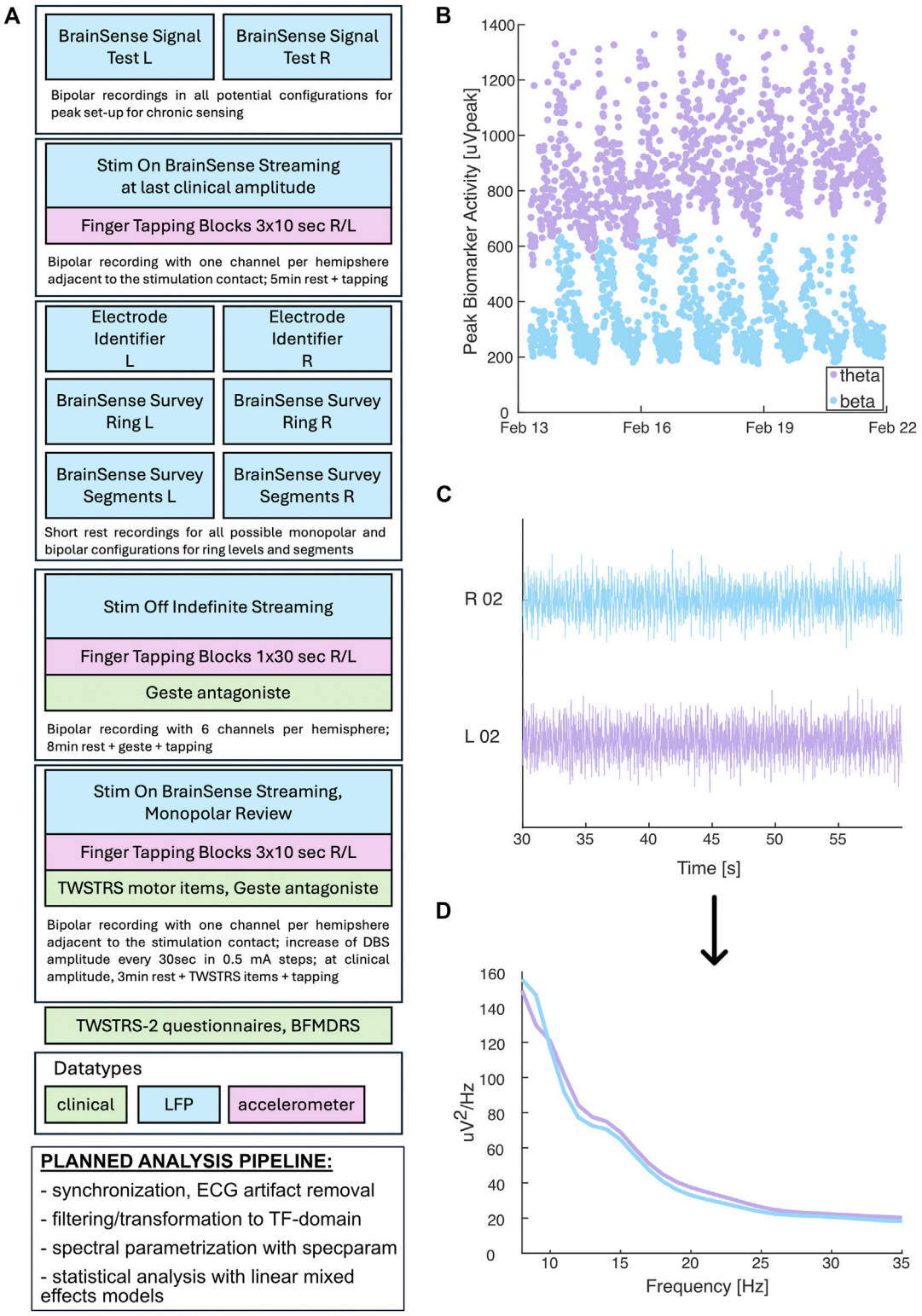

FIGURE 2
Exemplary data collection in a first patient. **(A)** Schematic and explanation of recorded data types at monthly recording visits (R: right; L: left; LFP: local field potential; Stim: stimulation), analysis plan (ECG: electrocardiogram; TF: time-frequency; specparam [27]); **(B)** Chronic BrainSense data collected out-of-hospital in 9 exemplary days 6 months post-surgery shows circadian fluctuations across investigated frequency bands (purple: theta, blue: beta. **(C)** Exemplary LFP recordings sampled at 250 Hz from the sensing-enabled channels Stim OFF (Indefinite Streaming mode) and power spectral representation **(D)**.

TABLE 1 Patient-reported outcome questionnaire.

Question number	Question	Reply options (on a 9 point-likert scale ex #8)
1	This week, I am generally feeling well	I fully disagree – I fully agree
2	This week, I am generally sad and feeling down	I fully disagree – I fully agree
3	This week, I feel...	Tired – energetic
4	This week, I feel self-confident/not embarrassed	I fully disagree – I fully agree
5	This week, I feel angry, frustrated or stressed	I fully disagree – I fully agree
6	On average, I can move well	I fully disagree – I fully agree
7	I am in pain/feel tight	I fully disagree – I fully agree
8	Pain is present during these amounts of awake time	0%–25%/25%–50%/50%–75%/75%–100%
9	I can walk well	I fully disagree – I fully agree
10	I can use my hands well	I fully disagree – I fully agree
11	My neck muscles are relaxed at the moment	I fully disagree – I fully agree
12	This week, my sleep quality on average is...	Very bad – very good
13	I can take care of myself (hygiene, everyday living)	I fully disagree – I fully agree
14	At the moment, my therapy effect is...	Very low – very good
15	At the moment, I have side effects	None-strong

previously published dystonia scales such as the Dystonia Non-Motor Symptoms Questionnaire (DNMSQuest) [28].

Additionally, as objective measures, patients record video diaries. In cervical dystonia, they record a short version of a video protocol similar to the TWSTRS [29], in generalized dystonia, patients or caregivers record whole-body videos at rest.

Monthly in-hospital recording visits

Figures 2A,C gives an overview over collected data types in in-hospital recordings. In-hospital recordings are high-resolution intracranial electrophysiological data recorded at monthly intervals in the electrophysiology laboratories at the participating clinical centers. Recordings during rest and voluntary movement, and ON and OFF DBS are performed. Voluntary movement is finger tapping recorded with an accelerometer. In cervical dystonia, bilateral electromyography of the Musculus sternocleidomastoideus is continuously recorded. A detailed schematic of the protocol is depicted in Figure 2A. In summary, there are four main types of recordings:

- During chronic DBS, with finger-tapping recorded in accelerometry
- During monopolar review (step-wise increase of stimulation amplitude per hemisphere), with finger-tapping recorded in accelerometry/clinical assessment of the TWSTRS
- OFF DBS, with finger-tapping recorded in accelerometry
- Short rest recordings (30–60 s) from various electrode configurations (bipolar/monopolar) OFF DBS.

If present in the participant, the *geste antagoniste* is also performed, both during DBS ON/OFF. During DBS ON, assessment of the TWSTRS is conducted, recorded and filmed. The overall protocol recording duration is approximately 1 hour.

For clinical characterization, at each visit, we assess the BFMDRS and TWSTRS at the clinically used stimulation amplitude.

Outcome measures

Primary outcome measures focus on the long-term modulation of electrophysiological biomarkers during continuous DBS.

- Suppression of LF-activity over time: We expect a suppression in LF-activity both in chronic peak biomarker recordings (maximum data amount 365 days * 144 mean values), and in monthly recordings (13 data points with high resolution electrophysiological data ON/OFF DBS). We expect this to correlate with clinical outcome parameters of improved dystonic symptoms in a) clinical dystonia scores (BFMDRS, TWSTRS) in-hospital, b) patient reported outcomes, c) automated video-based kinematic analysis, and thus, objective and subjective measures.
- Increase of beta band activity with chronic DBS: We expect an increase in beta band activity both in continuous biomarkers and high-resolution LFP recordings ON stimulation. We expect this to correlate with a deterioration in a) the bradykinesia items (especially 3.4) of the UPDRS-III and b) velocity in the monthly accelerometer recordings.

Secondary outcome measures focus on the symptomatic long-term dynamics and the validity of the home-monitoring.

- Subjective and objective measures of the home monitoring for dystonic symptoms correlate: We expect the subjective

assessment of the patients regarding motor symptoms, wellbeing and therapy effect to correlate with the objective measures of standardized clinical ratings and the automated kinematic analysis from the video diaries.
- Improvement of non-motor symptoms with chronic DBS: We expect an improvement of non-motor symptoms, such as pain, to correlate with an improvement in motor symptoms.

Exploratory outcomes involve a more detailed analysis of other frequency bands. Most prominently, we aim to elucidate if entrained gamma correlates with the clinically effective stimulation contacts and could thus support DBS optimization. With the longitudinal data set, we also plan to explore biomarker stability and localization.

Power and sample size

Studies in dystonia are restricted by the rarity of the disease. To date, electrophysiological studies in dystonia have shown significant effects in small sample sizes of 6–27 patients [16, 19, 21]. Longitudinal data in patients with dystonia has not yet been systematically recorded. However, in Scheller et al. [21], DBS effects and low-frequency modulation by chronic DBS are indirectly described. A power analysis was done by simulating a longitudinal mixed model in R based on the parameters from previous literature (version 4.4.2), with theta suppression as the predictor for changes in the BFMDRS. Scheller et al. [21] demonstrated a relationship between change in Burke Fahn Marsden Dystonia Rating Scale (BFMDRS) and low frequency activity that amounted to R squared marginal of 31%. For power simulation, we used the same analysis model (random intercept, random slope model) with a longitudinal intraclass coefficient of 0.75 and assumed no correlation between intercept and slope. As continuous recordings for 52 weeks are planned, given potential drop-outs and missed data points, "weekly means" of 35 measurements per patient over the course of the year-long observation period were simulated. To detect a significant relationship (strength: R squared marginal 31%) at a 5% alpha level and 80% power, N = 18 patients need to be measured. Since we also expect dropouts, we aim for a recruitment of 25–30 participants, with at least 18 patients with cervical dystonia. Since this is the most common dystonia type and we expect similar effects, we aim to perform a sub-analysis for this dystonia type, based on the overall power-estimation.

Feasibility

As of September 2025, two patients (1 female, 1 male, mean age 60 ± 5 years, both cervical dystonia) have completed the study. The attendance at study completion was 12/13 in-hospital recordings, resulting in a 92.3% attendance.

Of the currently active patients, recording compliance remains high. However, there are currently 18% dropouts, and some participants with reduced recording frequency because they are pediatric patients, or because of disability.

Data analysis

In this study a unique and large dataset will be acquired. Most analysis will be performed in Matlab (Mathworks, Natick, MA, USA)/Python using custom toolboxes such as Fieldtrip, Statistical Parametric Mapping (SPM12, UCL, London, United Kingdom), the perceive toolbox (https://github.com/neuromodulation/perceive/), the circa-diem toolbox [14], specparam [27], numpy, sci-py, and mne packages, and others, according to the developing research questions (see Figure 2B).

Regarding the electrophysiological long-term data, chronic dynamics, as previously described, will be analyzed regarding e.g., circadian periodicity. Overall biomarker peak changes and motor and non-motor PRO outcomes will be related in correlation analyses and linear mixed effects models. Videos will be rated by blinded clinicians and automatic video-based severity assessment [30] will be employed. These metrics will be used for correlation both with the subjective assessments and the electrophysiological data. The high-resolution longitudinal electrophysiological changes will be compared using common electrophysiological preprocessing with the ultimate goal to compare periodic and aperiodic components of spectral properties, as previously done within the group [9, 11, 12, 14, 31], finger tapping will be analyzed using the ReTap algorithm [32].

Ethics and dissemination

The study is conducted in compliance with the ethical standards set by the declaration of Helsinki and has been approved by the ethics committee of the Charité Universitätsmedizin Berlin under the IDs EA1/164/23 (piloting) and EA2/163/25. With this study, no additional clinical ethical or safety concerns are introduced for the participants. We use the *in-situ* devices for clinical therapy to record electrophysiological data and use non-invasive measures of motor activity. With the availability of a rechargeable IPG, battery usage through recordings is negligible. With monthly in-hospital recordings and weekly home monitoring, there is a high demand of organization and time spent with recordings for the participants. With a modular study design, participants can decide to decrease the recording frequency, but still stay in the study.

Discussion

With this study, we aim to close a knowledge gap in DBS care for dystonia and provide electrophysiological biomarkers, that can prospectively be used to steer DBS therapy decisions, and potentially adaptive algorithms.

Clinically, DBS is a long-term effective therapy for dystonia [4]. However, it is also known that DBS optimization can be a lengthy process with delayed therapy effects. With the opportunity of chronic biomarker recording, we here want to track if these delayed effects are reflected in delayed alterations in periodic or aperiodic biomarker changes. Importantly, to assess this, we collect weekly PRO for subjective assessment of therapy efficacy as well as videos for objectification with kinematic measures. With this, we also aim to elucidate at which time after start of stimulation DBS-induced bradykinesia develops [16]. With the repeated high-resolution LFP recordings ON and OFF DBS, we aim to investigate electrophysiological biomarkers for optimal clinical therapy, such as LF-activity [19, 21] and gamma [23] in a longitudinal approach and correlate them with anatomical

localization and symptomatic outcomes. Thus, we on the one hand aim to inform future studies on biomarker-guided DBS programming in dystonia, but also electrophysiologically characterize non-responders, as long-term studies confirmed approximately 30% non-responders [4]. If possible, we will also characterize pallidal signatures for different dystonia subtypes. Further, we aim to develop a home monitoring concept for dystonia combining objective and subjective measures that could be used beyond DBS, e.g., in patients treated with botulinumtoxin.

Overall, we hope that this study will contribute to a better understanding of the pathophysiology underlying dystonia and to a better clinical care for patients with dystonia.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics committee of the Charite. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants and/or the participants' legal guardians/next of kin.

Author contributions

LKF and AAK conceptualized the study. JK performed pilot recordings and LKF, AAK, and JK refined the protocol accordingly. AA provided expertise in pediatric movement disorders. DS performed the power size estimation. LKF and AAK provided funding for the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AAK declares that she is on the advisory board of Medtronic and Boston Scientific, and has received honoraria from Medtronic and Boston Scientific. LKF received honoraria for talks for Medtronic.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

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