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Sensorimotor EEG Activity During Brain-Computer Interface Therapy Predicts Motor Function in Parkinson's Disease

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ABSTRACT: Parkinson's disease (PD) is associated with motor impairment and altered sensorimotor oscillatory activity. Brain computer interface (BCI) based neurorehabilitation may provide both therapeutic benefits and a means to assess underlying neurophysiology. In this study, we investigated whether people with PD (pwPD) can effectively use a motor imagery (MI) based BCI and whether MI related neurophysiological markers allow prediction of motor function at the individual subject level.
Electroencephalography (EEG) data were analyzed from pwPD performing BCI therapy based on MI, functional electrical stimulation and visual feedback using a 3D avatar. PwPD achieved a mean BCI accuracy of 74%, which was not related to motor symptom severity as quantified by the Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) Part III. Using cross validated regression models, beta band event related (de)synchronization (ERD/S) during MI of all four limbs reliably predicted MDS-UPDRS Part III on an individual subject level.
These findings demonstrate that pwPD can control an MI based BCI independent of motor impairment severity and extend existing literature beyond group level differences by identifying beta ERD/S as an individualized neurophysiological marker of motor function in PD.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease and is characterized by a progressive loss of dopaminergic neurons in the substantia nigra, resulting in reduced dopamine levels [1]. PD is also one of the major causes of disability worldwide and has shown the fastest increase in prevalence and impairment among neurological diseases in recent years [2,3].
People with PD (pwPD) experience a range of motor symptoms, including rigidity, bradykinesia, postural instability, tremor, as well as speech and swallowing impairments. In addition, non-motor symptoms are common and include sensory and psychiatric disorders, cognitive impairment and dementia, depression, anxiety, autonomic dysfunction, gastrointestinal disorders, and excessive daytime sleepiness [4].
Brain-computer interfaces (BCIs) have been shown to facilitate motor function improvements after stroke [5–9] and have also shown promise in multiple sclerosis [10]. As BCIs are based on recording brain activity, utilizing electroencephalography (EEG) for example, they provide a unique opportunity to track neurophysiological activity continuously throughout the course of therapy.
This is particularly relevant for PD, as numerous studies have linked motor function to changes in oscillatory activity over the sensorimotor cortex and the subthalamic nucleus (STN). However, most of this work has relied on group-level analyses, such as comparisons between pwPD and healthy controls [11,12], comparisons between on- and off-drug states [13–16], or correlations with motor function [13]. While informative, such analyses provide limited insight into predictive power at the individual patient level [17,18]. More recently, there has been a shift toward cross-validated and predictive approaches, with Kurbatskaya et al.[19] demonstrating good performance in differentiating pwPD from controls in a multi-site study, and Waldthaler et al.[20] predicting disease progression from baseline neurophysiological features.
With respect to PD, action observation as well as motor imagery (MI) have been shown to be beneficial for motor function [21]. In addition, also functional electrical stimulation (FES) has shown encouraging results in improving motor function [22]. These approaches target motor networks that are known to be affected in PD. However, the key neurophysiological correlate of MI, namely event-related desynchronization (ERD), is reduced in pwPD [23], raising the question to what extent MI-related brain activity can be reliably exploited for therapeutic and diagnostic purposes in this population.
Here, we show that pwPD can nevertheless use sensorimotor rhythm based BCIs relying on MI, proprioceptive feedback via FES, and visual feedback via a realistic 3D avatar. Furthermore, we extend the existing evidence beyond group-level analyses by demonstrating that ERD during MI constitutes an individualized neurophysiological marker of motor function in pwPD for the first time.

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MATERIALS AND METHODS

Participants and Study Design

The study was approved by the Ethikkommission der Medizinischen Fakultät der JKU (1367/2023) and written informed consent was provided before participation.

Fifteen pwPD, participated in a BCI treatment comprising 24 therapy sessions, across 4 weeks. Throughout the entire BCI treatment, participants' medication (levodopa or dopamine agonists) remained unchanged and all sessions were conducted in the on-status. Participants' functional state was evaluated during pre- and post-assessments, which were performed at the same time of date within each patient (see Fig. 1A). The Pre1 assessment was performed one week before the first therapy session, whereas Pre2 was performed one to three days before the first therapy session. Two post-assessments were conducted, with Post1 performed one to three days after the last therapy session and Post2 performed two weeks after the last therapy session.

BCI System

Participants trained with a BCI system based on MI, FES and a realistic 3D avatar providing visual feedback (recoveriX, g.tec medical engineering GmbH, Austria). EEG was recorded using a wireless EEG system (g.Nautilus PRO, g.tec medical engineering GmbH, Austria), and stimulation was delivered using an FES stimulator (g.Estim FES, g.tec medical engineering GmbH, Austria). The EEG montage comprised 16 electrodes covering the sensorimotor cortex (FC3, FCZ, FC4, C5, C3, C1, CZ, C2, C4, C6, CP3, CP1, CPZ, CP2, CP4, and PZ) and reference and ground electrodes were placed on the right earlobe and AFZ, respectively.

Throughout the BCI treatment, participants performed right hand versus left foot MI during odd sessions and right foot versus left hand MI during even sessions, with approximately six sessions per week. Fig. 1B illustrates the MI trial structure. Each trial started with an attention beep, followed by a visual and auditory cue indicating the side for MI. Both visual feedback and proprioceptive feedback via FES were provided 1.5 s after the cue. One BCI session consisted of three runs (i.e., blocks), each containing 40 MI trials per side, with the first run of each session used for calibration. Further details regarding the BCI system, including FES parameters and signal processing, can be found elsewhere [10,24].

EEG and Behavioral Data

As the study is still ongoing, the present analysis focuses on EEG data recorded during eight therapy sessions (i.e., four per MI paradigm). To enable across-participant comparisons, the EEG data were adjusted for participants' more and less affected side based on their MDS-UPDRS III in Pre2 [25]. Specifically, the MI tasks were redefined to reflect more and less affected hand and foot MI, assuming that the right side was the more affected side. For participants whose left side was more affected, electrode positions were swapped pairwise between hemispheres (e.g., C3 ↔ C4).

With respect to the behavioral data, the Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) Part III [26,27] was used, as it is the primary outcome measure of the study. Further, it represents the gold standard for assessing motor symptoms in PD and is recommended by the Movement Disorder Society. It evaluates rigidity, bradykinesia, postural stability, tremor, and other motor symptoms. Scores range from 0 to 132 points, with higher scores indicating greater motor impairment. For simplicity and readability, the MDS-UPDRS Part III is referred to as MDS-UPDRS III going forward and reflects the score obtained during the Pre2 assessment, as this assessment is closest to the early therapy sessions.

All processing steps were performed in MATLAB (The MathWorks Inc., United States), and all filters were implemented as zero-phase Butterworth digital filters.

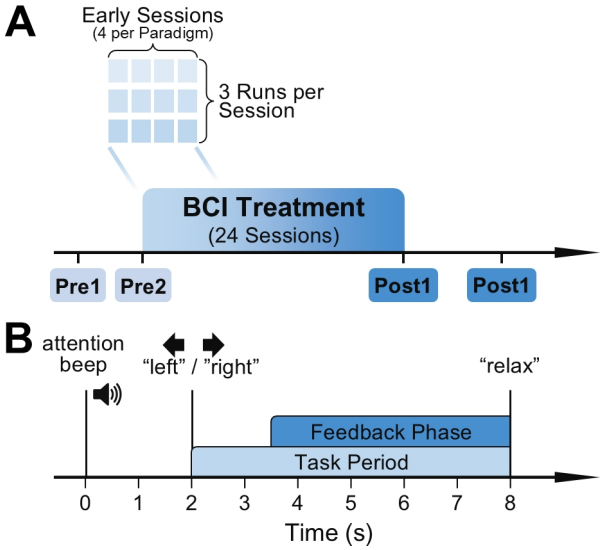

Figure 1: (A) Time course of BCI treatment with the first 4 sessions per paradigm being used for analysis. (B) Time course of a single motor imagery trial.

EEG Preprocessing

ERD/S features from the first eight therapy sessions were extracted for each subject, resulting in a total of 360 BCI runs. Raw EEG data were first notch-filtered at 50 Hz using a second-order notch filter. A trial rejection procedure was then applied to reduce the influence of potential artifacts. Specifically, the data were bandpass-filtered from 1 to 40 Hz using a fourth-order filter and epoched from 0 to 8 s (see Fig. 1B). For each MI trial, log-transformed power values were extracted and z-score normalized across trials. Trials were rejected if any channel exhibited an absolute z-score ≥ 3.

Feature Extraction and Epoching

After notch-filtering and rejection of bad trials, the EEG data were common average referenced. Log-transformed power was extracted for the mu (8–12 Hz) and beta (13–30 Hz) frequency bands using fourth-order bandpass filters as they are related to motor function

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and are modulated during MI, motor execution, action observation, and passive movement [28,29]. Power was estimated using 1 s windows with a 50 ms step size. After epoching from 0 to 8 s, the baseline period from 0 to 2 s was subtracted, resulting in ERD/S features reflecting average power changes in decibels (dB) for the time windows. Finally, ERD/S features were averaged across trials to obtain a robust estimate of subjects' ERD/S.

Predictive Analyses

To reduce dimensionality, multicollinearity, and allow for interpretable results, a subset of ERD/S features was selected. For spatial subsampling, nine regions of interest (ROI) were defined. The premotor cortex was represented by FC3, FCZ, and FC4, the primary motor cortex by C3, CZ, and C4, and the primary somatosensory cortex by CP3, CPZ, and CP4 [30–32]. Temporal subsampling was performed by selecting the following 1 s windows: 2–3 s, 3–4 s, 4–5 s, 5–6 s, 6–7 s, and 7–8 s. The final feature set comprised 432 features, corresponding to 9 ROIs × 6 time windows × 2 frequency bands × 4 MI tasks.

A cross-validated regression analysis was used to assess whether ERD/S patterns could predict subjects' motor function as quantified by MDS-UPDRS III. The model consisted of a support vector machine (SVM) regressor with a Gaussian kernel. Input features were standardized, the kernel scale was automatically determined using MATLAB's heuristic optimization, and the box constraint was fixed at 1.0 to reduce overfitting. Model performance was evaluated using 10 repetitions of a 5-fold cross-validation procedure due to the relatively small sample size. Pearson's *r* was used as the performance metric.

To examine the predictive contribution of individual MI tasks and frequency bands (mu, beta, and mu+beta), the following feature subsets were constructed: (1) all MI tasks, (2) more affected hand MI, (3) more affected foot MI, (4) less affected hand MI (5) less affected foot MI.

Empirical P-values were computed for each of the 15 feature subsets (5 MI conditions × 3 frequency band conditions) to estimate the probability that observed model performances occurred by chance, according to Lee et al.[33]. A permutation approach was applied, generating 1,000 null models by randomly shuffling the target variable. For each permutation, the full 10×5 cross-validation procedure was repeated, resulting in 1,000 performance estimates under the null hypothesis of no association between features and the target variable. The resulting 15 *P*-values were corrected for multiple comparisons using the false discovery rate procedure [34]. Above-chance performance was defined as $P < 0.05$.

RESULTS

In the current sample, pwPD were able to control the BCI system with MI accuracies of 74.7% (SD = 7.4) for more affected hand versus less affected foot MI and 74.6% (SD = 10.2) for more affected foot versus less affected hand MI. These two accuracies were significantly correlated ($r = 0.712$, $P = 0.0029$), indicating that patients achieved similar MI performance irrespective of the MI paradigm. Importantly, MI accuracy during both MI tasks was independent of subjects' MDS-UPDRS III score in Pre2 ($P > 0.05$, respectively). Note that, MDS-UPDRS III scores did no differ significantly between the two pre-assessments ($P = 0.46$).

Fig. 2 shows the obtained model performances for the respective feature subsets and indicates which model performance corresponds to a corrected P-value of 0.05. All models that exclusively utilized beta ERD/S performed above chance level, whereas none of the models that exclusively utilized mu ERD/S performed above chance level. When combining mu and beta ERD/S, model performance slightly deteriorated on average and dropped below chance level when ERD/S during less affected hand MI was used. Overall, ERD/S predicted subjects' motor function similarly well across the different MI tasks.

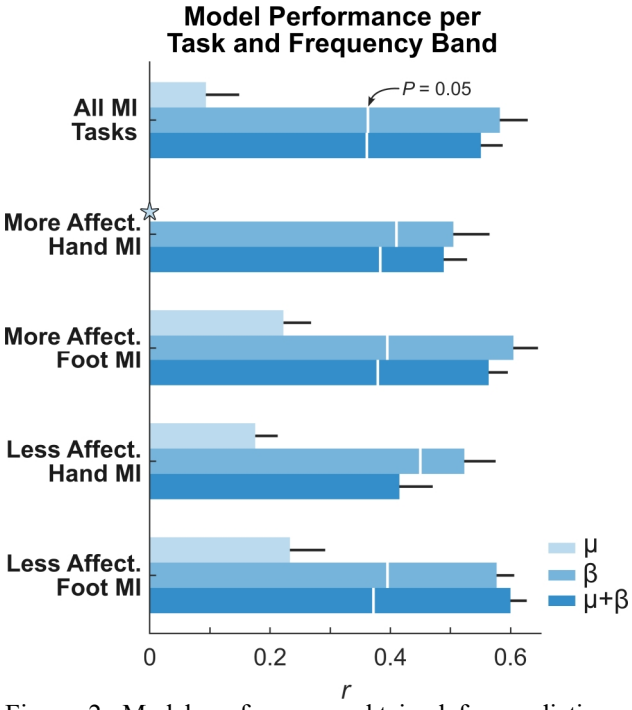

Figure 2: Model performance obtained for predicting MDS-UPDRS III score based on subsets of event-related (de)synchronization (ERD/S) features. Performance is quantified by Pearson's *r* and obtained in a 10×5 cross-validation. Bars and errorbars reflect the mean and standard error of the mean, respectively. Star indicates the model performance for mu ERD/S features during more affected hand motor imagery (MI): -0.26 (SEM = 0.05).

Investigating the relationship between beta ERD/S and MDS-UPDRS III during the respective MI tasks revealed statistically significant effects for both more and less affected hand MI, as well as strong and statistically significant correlations (see Fig. 3). ERD/S was extracted from the electrode location (C3, CZ, or

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C4) expected to exhibit the strongest ERD during the respective MI tasks. For example, C3 is expected to show the strongest ERD during more affected hand MI, whereas CZ is expected to show the strongest ERD during both more and less affected foot MI due to its topographical position. Across all conditions, stronger ERD (i.e., more negative ERD/S values) was associated with better motor function, reflected by lower MDS-UPDRS III scores. Importantly, this relationship cannot be attributed to differences in task engagement, as classification accuracy did not differ between more and less affected patients ($P > 0.2$, respectively).

Finally, three subjects have so far completed the BCI treatment and the Post1 assessment (see Tab. 1). All subjects showed improvements in MDS-UPDRS III scores, with S2 and S3 exceeding the minimally clinically important difference [35]. These findings provide encouraging preliminary evidence for the study going forward.

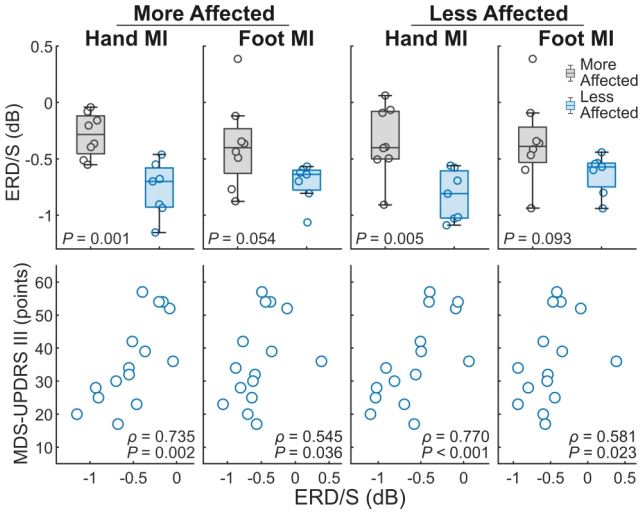

Figure 3: Relationship between beta event related (de)synchronization (ERD/S) and MDS-UPDRS III scores across motor imagery (MI) tasks. ERD/S is shown for the electrode expected to exhibit maximal ERD (e.g., Cz for foot MI and C3 for more affected hand MI). The upper panel shows subjects stratified by MDS-UPDRS III, and the lower panel shows correlations between ERD/S and MDS-UPDRS III.

Table 1: BCI accuracy for early (first 8) and late (last 8) therapy sessions and Pre2- and Post1 MDS-UPDRS III

	Accuracy (%)		UPDRS III (points)	
Subject	**Early**	**Late**	**Pre2**	**Post1**
S1	80.9	79.0	34	32
S2	73.2	73.0	54	40
S3	77.7	79.9	23	15

DISCUSSION

In this study, we investigated the relationship between ERD/S during BCI therapy and the motor functional state of pwPD. To this end, we utilized EEG data from the first eight BCI sessions and MDS-UPDRS III scores obtained during the Pre2 assessment.

The predictive analyses using cross-validated regression models showed that beta ERD/S is a strong predictor of motor function in pwPD. Specifically, stronger ERD during MI was robustly associated with better motor function as quantified by MDS-UPDRS III. Similar observation have been reported previously, including movement-related ERD being: modulated by drug status (on versus off medication) [13–16], correlated with motor symptoms [13] and reduced in pwPD compared to healthy controls [11,12]. Building upon these findings, the present results demonstrate that beta ERD during MI even allows inference of motor function at the individual subject level, during on-drug status.

Beta ERD/S was as a markedly stronger predictor of motor function than mu ERD/S. This contrasts with findings in stroke patients, where both frequency bands were shown to contribute to functional outcomes [25]. This difference is consistent with PD motor symptoms being closely linked to increased beta synchronization at rest and with beta activity being strongly modulated by dopaminergic medication and STN-DBS, both of which enhance motor-related ERD and improve motor function [15,16,36,37].

Another notable observation was that the limb used for the MI task did not substantially influence the predictive power of beta ERD. Specifically, MI of both the more and less affected hand and foot provided sufficient information to allow robust prediction of patients' motor function. This suggests that beta ERD reflects a more global marker of motor impairment in pwPD rather than being strictly limb-specific.

The current findings are based on ERD/S patterns extracted during BCI therapy and therefore provide insight into subjects' motor functional state during and across the course of the BCI treatment. An advantage of this approach is that no additional or time-consuming recording sessions are required. At the same time, the findings should be interpreted in the context of MI combined with FES feedback [38]. Future studies in PD should therefore investigate the relationship between ERD/S and motor function across MI, motor execution, passive FES, and may compare its predictive performance to resting state power using a randomized cross-over design.

Finally, three patients have so far completed the full BCI therapy and the Post1 assessment, all of whom showed an improvement in motor function, with two exceeding the minimally clinically important difference. In addition, participants tolerated the BCI therapy well and no adverse events were observed. Taken together, these preliminary results are encouraging with respect to the feasibility and safety of BCI therapy for pwPD.

CONCLUSION

In the present study, we showed that pwPD can control an MI based BCI system independent of motor symptom severity. Furthermore, we demonstrated that beta ERD/S during BCI therapy based on MI, FES and visual feedback enables prediction of motor function in pwPD at the individual subject level. Beta ERD/S

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predicted motor function irrespective of the MI task performed. Taken together, these findings extend previous group-level observations by identifying beta ERD/S as an individualized neurophysiological marker of motor impairment that can be assessed during ongoing BCI therapy.

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