

DISSERTATION

Movement Decoding for electrophysiology-based intelligent
adaptive deep brain stimulation in Parkinson's disease

Bewegungsdekodierung für elektrophysiologisch gestützte
intelligente adaptive tiefen Hirnstimulation bei der Parkinson-
Krankheit

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List of abbreviations

DBS	Deep Brain Stimulation
aDBS	Adaptive Deep Brain Stimulation
PD	Parkinson's Disease
ET	Essential Tremor
LFP	Local Field Potentials
ECoG	Electrocorticography
EEG	Electroencephalography
STN	Subthalamic Nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
BCI	Brain-Computer Interfaces
MRI	Magnetic Resonance Imaging
fMRI	Functional Magnetic Resonance Imaging
CT	Computed Tomography
XGBOOST	Extreme Gradient Boosting
SPoC	Source Power Comodulation

Abstract

Deep Brain stimulation is an effective treatment for movement disorders such as Parkinson's disease or essential tremor. Current therapy protocols do not adjust in real-time to the present need for treatment but instead rely on constant stimulation parameters. A novel concept called intelligent adaptive deep brain stimulation triggers stimulation based on decoding of a predefined state, such as movement, in a demand-driven way. Invasive Brain Computer Interfaces were previously presented for decoding behavioral states both using local field potential recordings from depth electrodes, primarily in movement disorder patients, and using electrocorticographic signals in epilepsy patients. Future brain implants may successfully treat different movement disorders using both modalities. A systematic brain signal decoding comparison of the two recording sites within patients was lacking. In this work, we analyzed invasive intraoperative recordings from Parkinson's disease patients undergoing deep brain stimulation therapy. Subthalamic local field potentials and simultaneous electrocorticographic signals were recorded while the patients were performing a hand-gripping force task. We used these signals to develop a real-time-enabled feature estimation and decoding framework and investigated different hyperparameter-optimized machine learning approaches for the prediction of movement strength. We identified optimal temporal, spatial, and oscillatory decoding components. Our analysis showed for the first time that movement decoding performances of cortical recordings were superior to subcortical ones using different machine learning methods. We found that gradient-boosted decision trees showed the best performances for electrocorticographic recordings, while Wiener filters were optimal for subthalamic signals. Models from single electrode contacts were better performing than methods that combine data from multiple contacts. Decoding performances were negatively correlated to Parkinson's disease-specific symptom scores. Previously, subthalamic beta oscillations were reported to reflect Parkinson's disease symptom severity, here we found that decoding performances were negatively correlated to elevated subthalamic beta oscillations. Additionally, we developed a movement decoding network that predicted contact-specific movement decoding performances using functional and structural connectivity profiles. In conclusion, we propose a computational framework based on invasive neurophysiology for brain signal decoding and highlight interactions of decoding performances with Parkinson's disease symptom states, pathological symptom biomarkers, and whole-brain

connectivity. This thesis, therefore, constitutes a significant contribution to the development of intelligent personalized medicine for adaptive deep brain stimulation.

Zusammenfassung

Tiefe Hirnstimulation ist eine effektive Behandlung von Bewegungsstörungen wie bei der Parkinson-Krankheit oder dem Essentiellen Tremor. Derzeitige Protokolle passen sich nicht in Echtzeit dem aktuellen Behandlungsbedarf an, sondern beruhen auf konstanten Stimulationsparametern. In einem neuen Therapieverfahren, der „intelligenten adaptiven tiefen Hirnstimulation“, wird die Stimulation bedarfsgerecht anhand eines vordefinierten Zustands, wie beispielsweise der Bewegung, angepasst. Invasive Brain Computer Interfaces konnten in vorigen Studien Verhaltenszustände mit elektrophysiologischen Aufnahmen dekodieren. Hier wurden entweder lokale Feldpotentiale, abgeleitet von Elektroden in tiefen Hirnregionen bei Patient*innen mit Bewegungsstörungen, oder elektrokortikographische Signale, bei Epilepsie-Patient*innen, verwendet. Beide Signal-Modalitäten könnten für zukünftige Hirnimplantate genutzt werden. Ein systematischer Vergleich der jeweiligen Dekodierleistung wurde bei denselben Patient*innen bisher nicht durchgeführt. Hier analysierten wir deshalb intraoperative Aufzeichnungen subthalamischer lokaler Feldpotentiale und gleichzeitige elektrokortikographische Ableitungen von Parkinson-Patient*innen während der Implantation des tiefen Hirnstimulators. Die Patient*innen führten Handbewegungen mit unterschiedlicher Greifkraft aus. Mittels echtzeitfähiger Feature Berechnung und Dekodierung untersuchten wir verschiedene Hyperparameter-optimierte maschinelle Lernverfahren zur Vorhersage der Bewegungsstärke. Wir identifizierten optimale temporale, oszillatorische und lokalisationspezifische Parameter der Dekodierung. Unsere Studie zeigt zum ersten Mal, dass die Dekodierleistung von kortikalen gegenüber subkortikalen Signalen anhand von verschiedenen maschinellen Lernmethoden deutlich überlegen war. Gradient-boosted decision trees waren für elektrokortikographische Aufzeichnungen die beste Dekodiermethode, während Wiener Filter für subthalamische Signale am geeignetsten waren. Modelle aus einzelnen Elektrodenkontakten zeigten bessere Dekodierleistungen als Modelle die Daten mehrerer Kontakte kombinierten. Die Dekodierleistung korrelierte negativ mit der Parkinson-Symptomschwere, und korrelierte zusätzlich negativ mit erhöhten subthalamischen Beta-Oszillationen, von denen bereits berichtet wurde, dass sie den Parkinson-Schweregrad widerspiegeln. Zusätzlich entwickelten wir ein Netzwerk für die Vorhersage der kontaktspezifischen Dekodierleistungen anhand von funktionellen und strukturellen Konnektivitätsprofilen. Zusammenfassend stellen wir ein computerbasiertes, neurophysiologisches Framework für die invasive Hirnsignal-Dekodierung vor. Wechselwirkungen der Dekodierleistung wurden mit der

Parkinson-Symptomschwere, elektrophysiologischen Biomarkern pathologischer Symptome und der Konnektivität des gesamten Gehirns identifiziert. Diese Dissertation unterstützt daher die Entwicklung intelligenter, personalisierter Medizin für die adaptive tiefe Hirnstimulation.

1. Introduction

1.1 Invasive brain signal decoding

Neuronal data can be recorded invasively using different techniques that comprise distinct temporal and spatial resolutions. Electrocorticographic (ECoG) recordings measure the summed activity of neurons across multiple neocortical layers from the exposed cortical surface. Local field potentials (LFP) record extracellular electrical potentials around neurons inside the brain (1). Invasive brain-computer interfaces (BCI) using these recordings were recently successfully demonstrated for different clinical applications in humans (2,3). In the first landmark studies, prosthetic devices were effectively controlled by microelectrode array recordings in the primary motor cortex of patients with tetraplegia (4), and speech was decoded using ECoG recordings in a paralyzed patient with anarthria (5). ECoG recordings were mostly acquired from epilepsy patients and LFP recordings from movement disorder patients undergoing deep brain stimulation (DBS) therapy. Both recording modalities have been used to decode different behavioral states, such as movement (6,7). A BCI decoding comparison of ECoG and LFP recordings was, however, not conducted yet.

1.2 Deep brain stimulation and Parkinson's disease

DBS is a neurosurgical procedure that involves implanting electrodes into the depth of the brain. The electrodes are connected to a neurostimulation device implanted in the chest of the patient that can deliver electrical pulses for chronic invasive neurostimulation. DBS is an established therapy with high efficacy for movement disorders such as Parkinson's disease (PD) (8,9). PD is primarily characterized by bradykinesia (slowness of movement) and rigidity or rest tremor, or both (10). Additionally, many non-motor symptoms can be present (10). Symptoms are related to the loss of dopaminergic neurons in the substantia nigra. Initial treatment includes the medication levodopa, which brings with it hyperkinetic side effects, including dyskinesia (involuntary muscle activations). Medication can therefore induce cyclic "on-off" transitions, alternating between hyper- and hypokinetic states (11). Due to the progressive loss of dopaminergic neurons, medication efficacy may diminish over time. Even in stages of advanced PD symptoms, DBS can be a highly effective treatment option. Stimulation parameters can be adjusted to account for patient individual side effects. The DBS target location in PD is the subthalamic nucleus

(STN). This nucleus is located in the basal ganglia, and needs to be localized precisely for DBS therapy to hit the so-called stimulation “sweet spot” for optimal therapeutic outcome (12). Magnet resonance imaging (MRI) was previously used to estimate optimal connectivity to predict DBS outcome in PD (13).

DBS electrodes can also be used to record LFP activity patterns that have been shown to reflect PD motor signs. Previous studies identified a correlation between STN beta frequency (8 – 35 Hz) power and motor impairment (14). Furthermore, it was found that beta activity in PD patients is not static, but appears in transient episodes of elevated band power, called bursts. The higher likelihood of beta bursts with longer duration was shown to positively correlate with PD symptom severity (15).

Despite STN-DBS was proven to be highly effective alleviating PD symptoms, stimulation-induced side effects remain, such as dyskinesia or psychiatric impairments (16,17). Adaptive deep brain stimulation (aDBS) aims for demand-driven stimulation, and thus tries to alleviate side effects (18,19). Stimulation may be adapted based on either a single biomarker, such as subthalamic beta oscillations, or a decoded brain state, such as movement presence or movement strength, in the following called vigor (20). Movement actuated aDBS was previously demonstrated in essential tremor (ET) patients (21) but could potentially also alleviate symptoms in PD due to the progressive loss of dopamine and its relation to movement (22).

1.3 Invasive decoding of movement using local field potentials and electrocortigraphy with machine learning

DBS implantation offers the unique opportunity to measure LFP signals from the stimulation target, such as the STN in PD. DBS therapy is an established treatment option with high efficacy but could be further improved by adapting stimulation in combination with a clinical BCI. In addition to LFP recordings, ECoG electrodes could be implanted to further optimize decoding of a relevant brain state. Movement is such a state that is affected by motor system disorders.

STN-LFP gripping force decoding was demonstrated by Tan *et al.* using first-order linear models with beta and gamma features (23). The combination of previous time points within a Wiener cascade filter was further recommended for force decoding using STN-LFP signals. On the contrary, ECoG movement classification of individual fingers, acquired from epilepsy patients, could be achieved with highest performance using

gradient-boosted decision trees with the eXtreme Gradient Boosting (XGBOOST) framework (24). Movement could further be decoded in essential tremor patients using ECoG signals with linear classification methods (21). An analysis investigating the optimal decoding strategies for both recording methods, including a decoding performance comparison in the same patients, was however not conducted yet.

Additionally, electrode placement and channel selection for optimal decoding of invasive recordings remains an open research question. EEG recordings are acquired through standardized montages, whereas locations and counts of invasive electrode contacts can differ across patients.

Because human invasive recordings are rare and have high importance for clinical research, data acquisition is only possible through invasive treatment options such as DBS for patients suffering from severe diseases. The implantation of additional ECoG electrodes is currently only approved for research purposes. Therefore, there exist only a few reports investigating BCI applications using ECoG and simultaneous LFP recordings. Usually, not more than 5 patients were recruited for comparable studies (21,25).

1.4 Research questions

The development of new invasive adaptive therapies, that further alleviate symptoms and reduce side effects, requires investigation of optimal recording locations and methods for best decoding. Movement-actuated aDBS could be performed using depth LFP, ECoG recordings, or a combination of both (25). The optimal machine learning strategies of decoding movement vigor, for ECoG and STN-LFP recording locations need to be investigated. Additionally, identification of the brain location with the best BCI decoding performance is required for the design of optimal future aDBS systems.

Parkinson's disease patients show different symptom severities. A potential relationship between decoding performances of movement gripping force and symptom scores could improve the development of future decoding methods.

STN-LFP beta activity was identified as an invasive electrophysiological biomarker for PD symptom severity (26). The associations between STN beta bursts and cortical and subcortical decoding performances would be required to understand the mechanisms of beta oscillations with respect to vigor decoding and Parkinson's disease.

Additionally, it remains to be determined if brain-wide network measures can explain variance in decoding performances. An underlying optimal decoding network could guide ECoG electrode placements for future BCI applications.

Generally, the associations between optimal high-performing machine learning-based invasive decoding approaches and electrophysiological, pathological, and connectomic correlates constitute the main research objectives of this thesis.

1.5 Hypotheses

- ECoG signals show higher hand gripping force decoding performances than STN-LFP signals in PD patients undergoing DBS surgery.
- Novel complex machine learning methods outperform linear methods for electrophysiology based decoding of gripping force.
- Number of features and channel counts have significant impact on decoding performance.
- Higher motor symptom severity is associated with increased beta activity during movement and accompanied by lower movement decoding performance in PD.
- Whole-brain MRI connectivity measures derived from individual channel locations can predict channel specific decoding performances across subjects.

2. Methods

2.1 Data acquisition / electrophysiological recordings

The data for this retrospective study were intraoperative recordings from 11 Parkinson's disease patients undergoing bilateral subthalamic deep brain stimulation therapy (29,30). The ECoG electrode setup varied between patients. Left or right hemispheres were recorded with electrode strips of different contact numbers. Clinical scores, age, gender, and electrode contact counts are displayed in Table 1.

Table 1: Patient characteristics

N	Gender	UPDRS total	Hemi-sphere	Age [years]	Move-ments	Disease duration [years]	ECoG strip contact number left	ECoG strip contact number right
1	Male	28	R	60.3	128	10.7	n.a.	6
2	Male	27	L+R	51.2	464	14	28	28
3	Male	33	L+R	53.8	213	7.2	8	8
4	Male	31	L+R	44.2	285	10.1	8	8
5	Male	32	2L+2 R	63.6	381	13.1	28+8	28+8
6	Male	52	L	59.6	84	5.9	6	n.a.
7	Male	55	L	71.6	161	1.4	6	n.a.
8	Male	50	L	52.5	131	8.7	6	n.a.
9	Male	62	L+R	66.8	547	9.8	6	6
10	Male	48	L	67.9	86	17.1	6	n.a.
11	Female	31	R	69	205	10.4	n.a.	6

From Merk *et al.*, 2022 (31)

Within the operating room, ECoG and STN-LFP recordings were acquired during a movement task (32). The task included Go/No-Go cues and visualized feedback of the applied movement gripping force strength. Gripping force was measured using a grip-dynamometer (Biometrics Ltd.). During the recordings, patients varied the applied gripping force according to the experimental setup. STN-LFP recordings were acquired using four contact clinical DBS leads from Medtronic (layout: 1x4, contact area: 5.89 mm²). ECoG recordings were acquired from Ad-Tech electrodes using six (layout: 1x6;

contact area: 12.56 mm²), eight (layout: 1x8, contact area: 12.56 mm²), or 28 contacts (layout: 2x16, contact area: 3.14 mm²); for additional specifications see supplementary file 1A “Electrode details” in the original publication (31). Data was measured using a Ripple-grapevine amplifier at 40 kHz and further downsampled at 1 kHz. The reference electrode of the differential amplifier was placed in the scalp, and the ground electrode on the shoulder. Referential montages are common in low signal amplifiers to obtain high input impedances and therefore minimize leakage currents (33). The localization of ECoG electrode contacts involved the use of pre-operative MRI scans, intra-operative fluoroscopy, and post-operative CT scans. This process was previously explained in detail (34). Essentially, the images obtained from the three scans were aligned to the 3D skull, and the location of each electrode contact was estimated by projecting the fluoroscopic image to the cortical surface. The Lead-DBS software (12) was utilized to localize DBS electrodes. In this case, the pre-operative MRI and post-operative CT scans were co-registered and normalized to "MNI 2009b NLIN ASYM" space. The DBS electrode artifacts were then identified through visual inspection as part of the Lead-DBS default pipeline.

2.2 Signal processing and feature extraction

Normalization is a preprocessing step that is usually performed using all trial or session data. Here, we aimed to simulate real-time recordings, which implies that it would be a confound to use the total trial data for normalization. Therefore, data was replayed using a batch-wise data stream with a sampling rate of 10 Hz. For every batch, data was preprocessed using a compatible sliding window preprocessing and feature estimation pipeline that we developed as part of this thesis. The z-score normalization and feature estimation of a given sample was hence performed solely on the 10 s preceding time window in real time. To obtain localized activity from the tissue spatially close to the recording contacts, STN-LFP channels were bipolar re-referenced to the adjacent channels. ECoG channels were common average re-referenced (Figure 1).

Oscillatory features have been previously used for successful movement decoding (6,35,36). In this study, band-power was calculated in the following frequency bands: θ (4–8 Hz), α (8–12 Hz), β (13–35 Hz), low β (13–20 Hz), high β (20–35 Hz), low γ (60–80 Hz), all γ (60–200 Hz), and high-frequency activity (90–200 Hz). Band-power was obtained using a finite impulse response (FIR) bandpass filter, and variance was

calculated in frequency band-specific time windows ($\theta = 1000$ ms, α and $\beta = 500$ ms, $\gamma = 100$ ms). This allowed for feature estimation without losing temporal specificity.

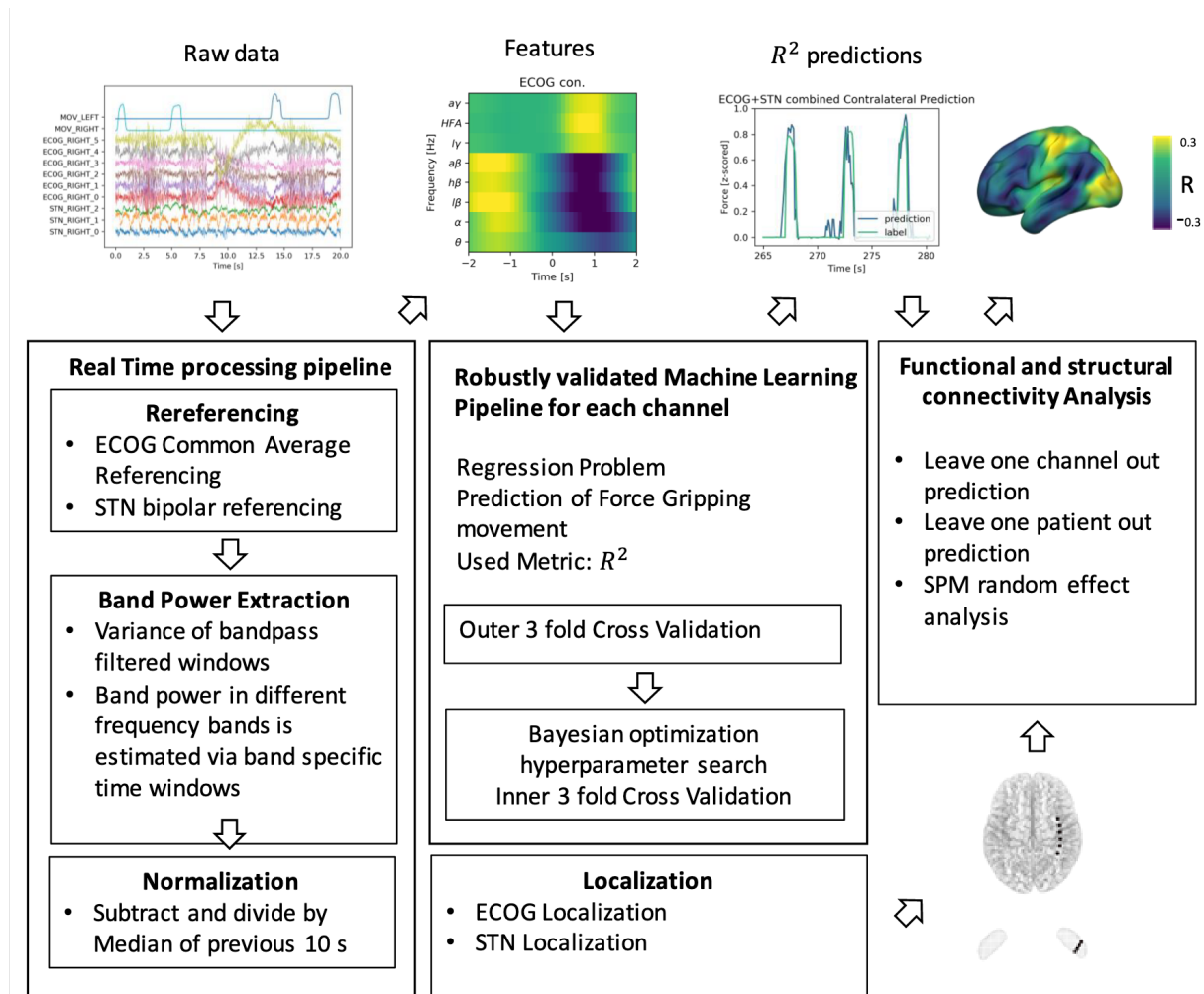


Figure 1: Schematic visualization of the processing pipeline. Data preprocessing is followed by band-power feature estimation and real-time-enabled feature normalization. Hyperparameter-optimized nested cross-validation was used to obtain decoding performances for every electrode contact. Connectivity was then estimated to identify a movement decoding network. Modified from Merk *et al.*, 2022 (31).

2.3 Feature estimation and decoding framework: *py_neuromodulation*

The development and publication of the above-described feature estimation pipeline is one of the main aims and achievements of this thesis. The toolbox is made publicly available as a Python framework called *py_neuromodulation* (37). Beyond oscillatory activity, the implemented feature modalities were extended for temporal waveform shape (38,39), characterization of the spectral aperiodic component (40), non-linear dynamics (41), connectivity measures (42), and others. This framework provides different pre- and postprocessing routine wrappers from established libraries (43), and can be used for

decoding without individual patient training and real-time applications. Neuromodulation applications for different brain disorders, such as epilepsy or treatment-resistant depression, can be conducted with the provided feature estimation pipeline.

2.4 Machine learning methods

Different machine learning methods are suitable for invasive brain signal decoding. In an extensive review article we summarized promising machine learning architectures (20). In this study, different linear and non-linear machine learning methods were compared for cortical and subcortical recordings. Linear methods, such as linear regression and Wiener filters, as well as non-linear methods, such as neural networks or XGBOOST (27), were compared for movement hand-gripping force performances. The continuous output predictions were evaluated using the R^2 coefficient of determination:

$$R^2(y, \hat{y}) = 1 - \frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{\sum_{i=1}^n (y_i - \bar{y})^2}$$

True hand-gripping force labels are denoted here with y and predictions with \hat{y} for n samples. Performances were clipped at the lower threshold of zero since the R^2 metric can be negative in case of worse-than-chance predictions. Using nested 3-fold cross-validation, channel-specific performances were evaluated. In the inner 3-fold cross-validation, optimal hyperparameter sets were investigated through Bayesian optimization, and in the outer validation loop, the parameters were applied to predict test set targets. For the performance report, the best channel per patient was then selected to allow for a post-hoc comparison of the location and performance of best channels between ECoG and STN-LFP within subjects.

2.4.1 Linear models

Linear models capture linear dependencies between features and the respective target. To prevent overfitting, elastic net regularized linear regression models were used. l_1 and l_2 regularization parameters were both uniformly sampled between zero and one using Bayesian optimization. Wiener filter methods were previously used for STN-LFP gripping force decoding (7). The intuition is here that time-lagged samples contain contributing information for target prediction in addition to features of the current sample. This time lag was investigated using a grid search, with a time range of 100 ms to 1000 ms preceding the current sample in steps of 100 ms. The optimal time lag was subsequently also

used for non-linear methods. Linear machine learning architectures were implemented using the scikit-learn framework (43).

2.4.2 Neural Networks

Neural networks consist of several layers of connectionist neurons. Dot product multiplications of inputs and weights are fed through commonly non-linear activation functions to the next layer. Neural networks with only a single hidden layer were shown to be universal function approximators (44). In combination with convolutional, recurrent, or attention layers, neural networks were used in end-to-end learning and successfully applied to movement and motor imagery decoding applications using ECoG recordings (45,46). In this manner, features do not need to be calculated beforehand. Feature estimation, selection, and engineering are directly learned by the model, given a sufficient dataset size. In this work, the dataset size was insufficient for end-to-end learning methods because each recording session lasted only a few minutes. Accordingly, the same features used for the other tested model architectures were fed to neural networks. The following hyperparameter search was therefore not exhaustive, but rather a pragmatic search for investigating performances from very basic neural network architectures. The number of hidden layers was sampled between one and three, with one to ten hidden dense layer neurons for each hidden layer. Sigmoidal and hyperbolic tangent activation functions were both tested. Parameter configurations were optimized through the Adam algorithm (47). The TensorFlow framework was used to implement neural network training and evaluation (48).

2.4.3 Gradient-boosted decision trees using XGBOOST

Many commonly used algorithms for competitive machine learning are based on decision trees. The basic idea is that a tree is set up of sequential decision nodes. Label predictions are obtained through the resulting leaf nodes. Central hyperparameters are the maximum tree depth, the node splitting criterion, and the minimum required samples within a leaf node. To obtain higher generalization, multiple decision trees can be built in parallel through a process called bagging. This method is used in random forests or extra tree models (49). Each tree is constructed using samples from the same distribution. On the other hand, gradient-boosted decision trees make use of misclassified labels from previous trees to construct new ones sequentially. This concept is used in the XGBOOST (eXtreme Gradient Boosting) framework (27). XGBOOST is commonly used as a default

choice for many decoding problems and was made popular on competitive machine learning platforms such as Kaggle (50). To obtain the optimal XGBOOST hyperparameters, the maximum number of trees was uniformly sampled between one and 100, the learning rate of each tree was log uniformly sampled between 10^{-5} and one, and the gain parameter specifying the node splitting criterion was sampled uniformly between one and ten.

2.4.4 Source Power Comodulation

The previously mentioned machine learning models were all based on single-channel data. Source Power Comodulation (SPoC) is a method capable of extracting spatial information by utilizing all channels (51). This method linearly projects bandpass-filtered sensor data into source space. It makes the assumption that source time traces linearly correlate with the target signal. Internally, a generalized eigenvalue problem is being solved by maximizing the correlation between the target and the predicted target. It holds the advantage of interpretability of spatial patterns, that linearly project source to sensor time traces. A single spatial filter for each frequency band was chosen, followed by either an elastic net or XGBOOST regression model. We used XGBOOST to test the hypothesis that non-linear source-to-target methods perform better than linear ones.

2.5 Hyperparameter tuning using Bayesian optimization

Since all implemented machine learning models contain different model parametrization choices, the sweet spot of optimal hyperparameters must be investigated. Common methods of finding optimal hyperparameters are grid search, random search, and Bayesian optimization. Grid search iterates through a predefined set of hyperparameters but suffers a high computational cost. Random search explores random hyperparameter configurations but does not make use of previously explored states. Bayesian optimization is an iterative method for exploring optimal parameter sets (52). Using a surrogate function, a probabilistic prior for maximum likely hyperparameters is sampled, instead of directly sampling hyperparameters because of the computationally expensive model train and test evaluation. In this implementation, ten iterations were used with a Matern kernel. The parameter set maximizing the within 3-fold cross-validation is used for evaluation on the outer cross-validation test set.

2.6 Analysis of beta bursts

Movement-related performances were previously shown to correlate with STN-LFP beta activity (28,53). Higher Parkinson's disease symptom severity was also characterized by elevated STN beta burst duration (15). Therefore, we aimed to investigate the relationship between beta bursts and movement decoding performances. Low and high beta bursts were calculated using the 75th percentile threshold (28). The mean time spent in burst was calculated for motor preparation ([-1 to 0] s around movement onset) and motor execution ([0 to 1] s around movement onset) and correlated with PD symptom severities (UPDRS-III total scores) and decoding performances.

2.7 Prediction of decoding performances using MRI networks

A decoding performance-specific MRI network was developed using functional and structural MRI connectomes of 74 Parkinson's disease patients (Parkinson's Progression Markers Initiative [PPMI]; <https://www.ppmi-info.org/>). A spherical seed was first placed at the ECoG location for each electrode contact. From this seed location, functional and structural whole-brain fingerprint profiles were calculated using Lead-DBS (12). Functional connectivity was estimated through the temporal correlation of fMRI resting state activity of the seed voxel to all other brain voxels. Structural connectivity was obtained through fiber tracking using diffusion-weighted imaging. Since each contact had an assigned decoding performance, the whole-brain decoding performance R-Map was calculated in the following manner: for each brain voxel a Spearman's rho correlation between the decoding performance vector and the corresponding fingerprint voxel vector was calculated. This process was repeated in a leave-one channel and leave-one patient out cross-validation and allowed for computation and statistical validation of a decoding performance-specific network. The approach was previously applied and validated for different correlates (54,55). To investigate the structural connectivity profile, fiber tracts traversing the originating recording seed location were first estimated using the fiber filtering Lead-DBS tool (56). Next, fiber tracts were identified that could significantly predict decoding performances across patients. For each fiber tract, decoding performances originating from connected and unconnected contacts were statistically compared using a two-sample t-test. Fiber tracts were then color coded with the corresponding t-value and correlated with each contact's decoding performance.

2.8 Statistical analysis

All statistical tests were computed using non-parametric Monte-Carlo sampled permutation tests with a significance value of $\alpha = 0.5$. Correlation values were reported using Spearman's rho correlation coefficient. For fiber filtering visualization, the significance value was corrected for a false discovery rate.

2.9 Open science

All raw data were formatted into the Brain Imaging Data Structure (BIDS) standard for intracranial electroencephalography (57). Raw data was made publicly available (<https://doi.org/10.7910/DVN/IO2FLM>). The dataset furthermore reached from the date of publication (May 27, 2022) close to 10000 downloads (58). The code required for analysis and figure reproduction is publicly available at a GitHub repository (https://github.com/neuromodulation/ECoG_vs_STN) (59). For these efforts to facilitate open science, this publication received the Charité Berlin Institute of Health Open Data Reuse Award (60).

2.10 Adherence to method guidelines and sample size

We adhered to the guidelines of “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) to ensure reproduction of all conducted analyses. The main analysis in this work was the comparison of ECoG and STN-LFP regression correlation performances. A type 1 error would therefore indicate a performance difference when both recording sites result in the same performances, and a type 2 error would result from equal predicted performances while both actually differ. The required sample size was calculated using a power analysis. Under the assumption of a t-distribution, the type 1 error was set to 0.05, and the required statistical power to 0.8. ECoG performances were estimated to have a mean coefficient of determination of 0.4 and STN-LFP of 0.2. The variances of both distributions were assumed to be 0.1, indicating a Cohen's d effect size of 2. The minimum required sample size resulted then in 4.22. The sample size of this 11 PD patient cohort therefore met the power analysis requirements. An a-priori sample size evaluation of intracranial data using a power analysis can however be challenging due to the high uncertainty of the underlying distribution. To circumvent bias, permutation tests without distribution assumptions were therefore used within this analysis.

The intraoperative acquisition of awake human intracranial data is in general a unique opportunity, which is only made possible through the invasive treatment of DBS. Human invasive recordings therefore have high value, with exceptional signal-to-noise ratio and overall higher quality than non-invasive recordings. Sample sizes of studies including ECoG and subcortical brain recordings for movement disorders are generally small, since ECoG electrode implantation is only utilized for research purposes. The sample size used in this work is higher than the sample sizes reported in the literature on cortical and subcortical movement decoding. Opri *et al.* reported embedded movement classification for cortical and thalamic recordings for 3 essential tremor patients (21), and Gilron *et al.* decoded motor cortical and subthalamic motor states in 5 Parkinson's disease patients (25).

3. Results

3.1 Real-time processing and feature estimation

Cued gripping force-aligned spectral changes reproduced previously described time-frequency characteristics (Figure 2 A) (32,61). The calculated features represented spectral changes in the specified eight frequency bands (Figure 2 B). Contralateral spectral changes were stronger than ipsilateral ones, and ECoG responses were more prominent than STN-LFP changes. Linear models were further analyzed for frequency band-specific contributions and showed the strongest coefficients for beta and gamma frequency bands. The computed features were then used to evaluate linear models and Wiener filters. Since Wiener filter performances peaked at a time lag of 500 ms, features preceding up to that time lag were stacked for the subsequent machine learning analysis.

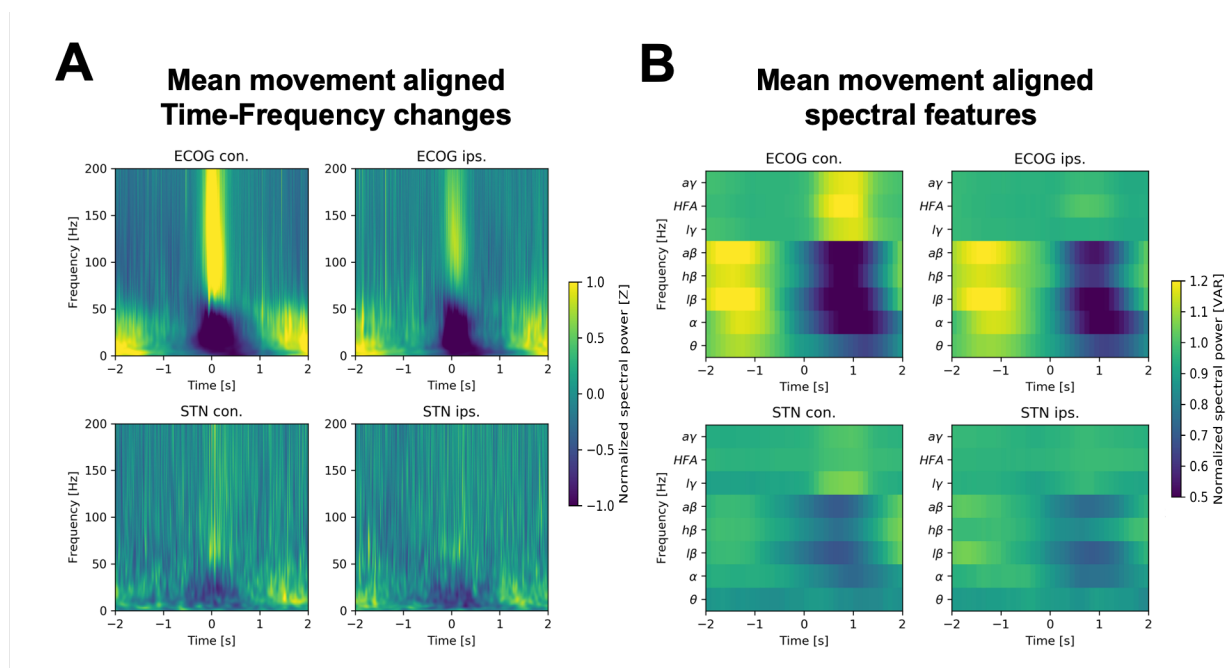


Figure 2: Time-frequency visualization and estimated spectral features. Movement-induced spectral changes for Morlet wavelet time-frequency transformation (A), and estimated band power features for ECoG and STN-LFP contra- and ipsilateral movements (B). Modified from Merk *et al.*, 2022 (31).

3.2 Machine learning model performance comparison

Decoding performances were compared for different machine learning models. Hyperparameters for every model were identified through Bayesian optimization. The best contact per electrode was selected using nested cross-validation. ECoG decoding performances were stronger than STN-LFP performances for all tested machine learning architectures

(Figure 3 A+B). To test for a performance gain if multiple spatially distinct electrode contacts were used in combination, Source Power Comodulation utilizing all channel data was evaluated (51). Best ECoG performances were achieved using XGBOOST, whereas linear Wiener filters performed best for STN-LFP recordings. The best ECoG channels in combination with the best STN-LFP channels were tested, as well as all ECoG and all STN-LFP channels combined (Figure 3 C+D). Best performances were achieved with individual ECoG channels for contra- and ipsilateral movement predictions. All ECoG and all STN-LFP channels combined had a slight performance gain over all ECoG channels combined. STN-LFP performances showed also statistically above-chance performance (contralateral $p=0.025$, ipsilateral $p=0.028$). In the supplementary materials from the original publication, group-wise performances for each machine learning architecture were reported (31).

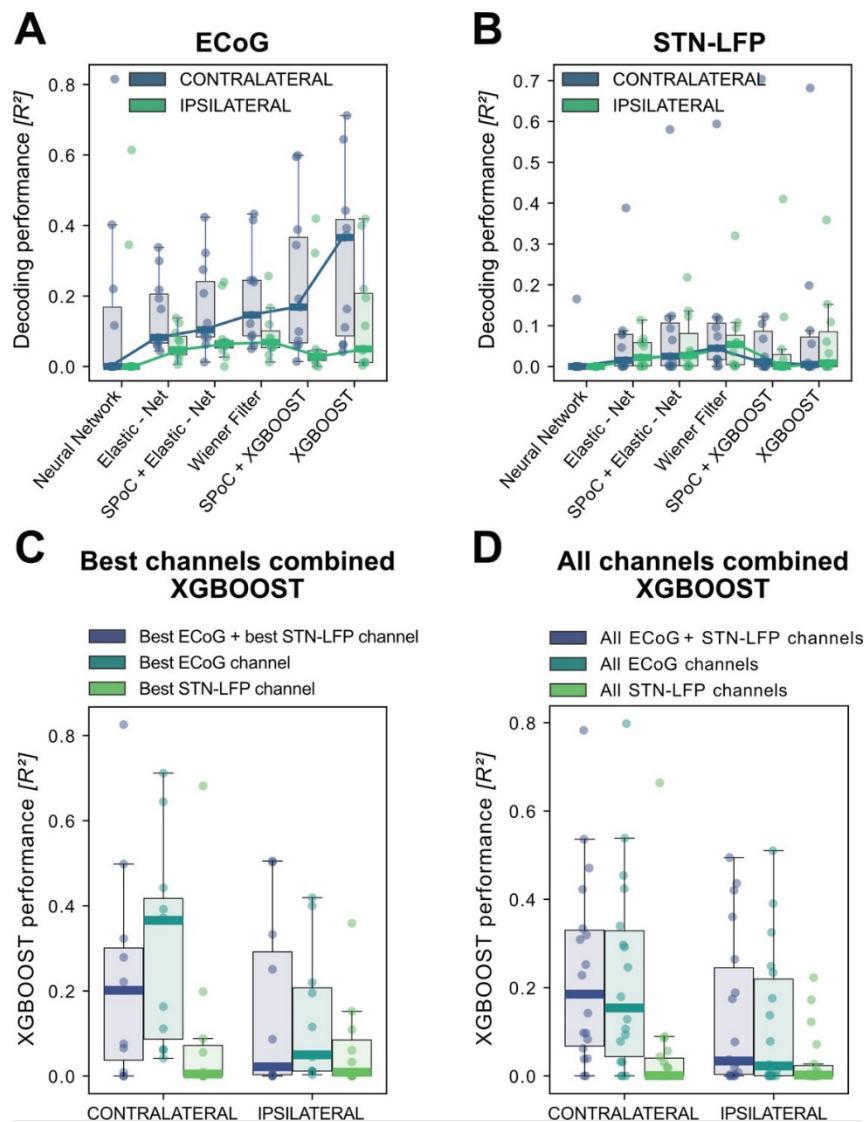


Figure 3: Machine learning model, recording site, and channel selection comparison. Single-channel ECoG recordings using XGBOOST were superior to STN-LFP recordings, different channel combinations, and other model architectures. ECoG recordings strongly outperformed STN-LFP performances (A+B). Non-linear methods showed highest performances for ECoG recordings, while linear Wiener filters performed best for STN-LFP recordings. Individual channel performances were superior to combinations of the best ECoG and STN-LFP channels (C) and all channels combined (D). From Merk *et al.*, 2022 (31).

3.3 Correlation of decoding performances with clinical scores and STN-LFP beta burst activity

We correlated XGBOOST decoding performances and Parkinson's disease symptom severity, measured by the UPDRS-III total score. ECoG and STN-LFP best channel decoding performances, averaged for contra- and ipsilateral movements, showed significant negative correlations with UPDRS-III scores (ECoG $\rho=-0.55$, $p=0.039$ and

STN-LFP $\rho=-0.55$, $p=0.042$). The correlation between best channel force predictions and UPDRS-III showed further a significant negative correlation that was temporally specific to the movement but not resting phase (31), highlighting the potential relationship between data-driven model performances and pathological or physiological states. This disease-specific relation was also investigated by correlating decoding performances to STN-LFP beta activity, since beta activity was previously shown to reflect pathological symptom states (26,62). We found a positive correlation between UPDRS-III and time spent in low beta bursts during movement preparation ($[-1$ to $0]$ s around movement onset) and execution ($[0$ to $1]$ s around movement onset) (Figure 4 A). ECoG performances showed a strong correlation with mean time spent in STN-LFP beta bursts during motor preparation and execution (motor preparation $\rho=-0.76$, $p=0.004$, motor execution $\rho=-0.71$, $p=0.005$) (Figure 4 B+C). The distributions of beta bursts for an exemplary good and poor performer are shown in Figure 4 C. For the good ECoG performance subject, there was almost no STN beta bursting activity during movement (mean time spent in burst during motor preparation = 142 ms, mean time spent in burst during movement execution = 9 ms). For the poor ECoG performance subject, the mean burst duration during movement was significantly longer (mean time spent in burst during motor preparation = 268 ms, mean time spent in burst during movement execution = 143 ms).

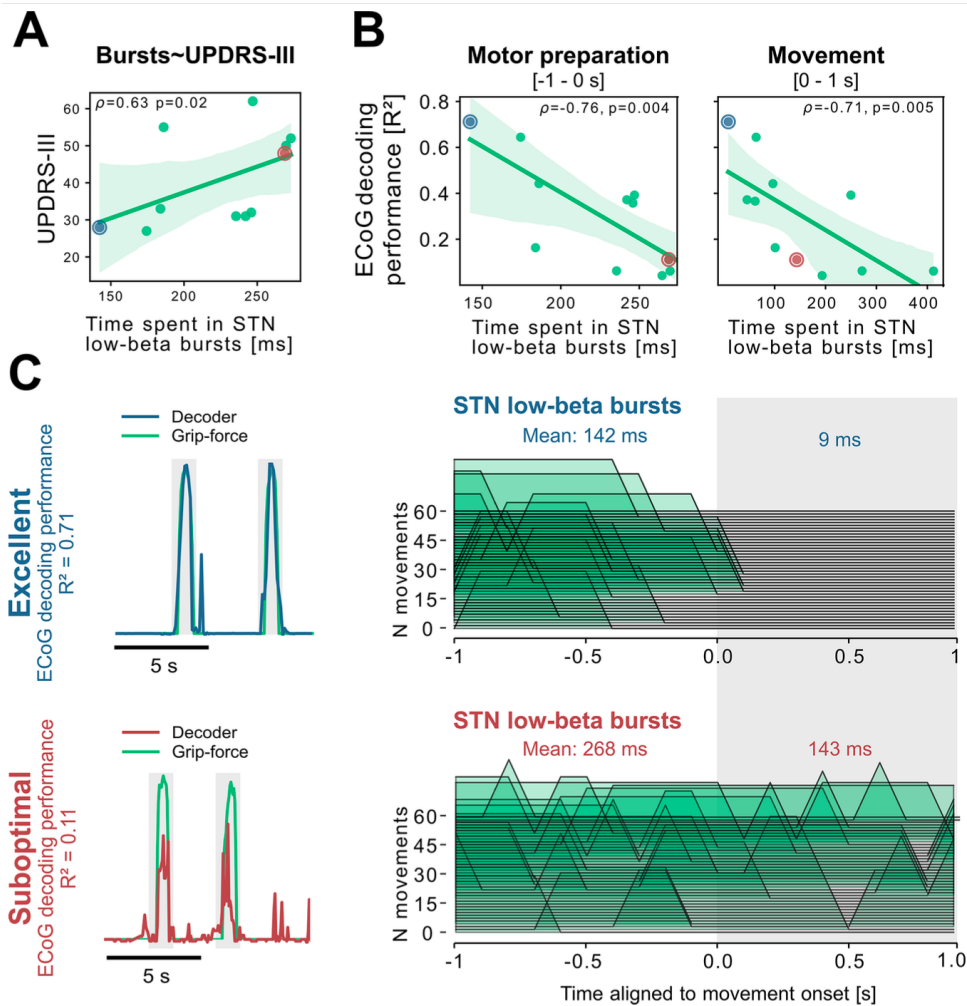


Figure 4: Relation of ECoG performances and STN-LFP beta bursts. UPDRS-III total scores were positively correlated to STN-LFP time spent in bursts (A). ECoG performances showed a negative correlation with time spent in STN-LFP bursts during the motor preparation and movement execution phase (B). Exemplary good and poor ECoG time trace predictions are displayed with the respective STN-LFP burst durations. Higher ECoG performances accompanied lower STN-LFP bursting during movement preparation and execution. From Merk *et al.*, 2022 (31).

3.4 Functional and structural connectivity predicts decoding performances

The spatial distribution of decoding performances of ECoG and STN-LFP electrode contacts was further investigated and displayed on the cortex and STN surfaces (Figure 5 A). Using linear mixed effect models, with the subject as a random effect, we found a significant correlation between decoding performances and electrode contact distance to the motor cortex hand-knob area ($\beta=-0.002$, lower confidence interval (CI)=-0.003, upper CI=-0.001, $R^2=0.57$, $p<0.001$). The STN-LFP contact distance to the dorsolateral STN did not show a significant correlation. Testing for the same relationship across patients did not show a significant relation between ECoG contact performances and hand-knob area distances. Therefore, we used an MRI network-based approach to

test if decoding performances could be predicted by connectivity related to the respective recording contact locations. Using the PPMI connectome, structural diffusion imaging and functional connectivity profiles were estimated for every ECoG recording contact. Significant fiber tracts across the whole cohort (Figure 5 B) and the optimal decoding R-Map (Figure 5 C) showed a clear connectivity cluster around the motor cortex. Structural connectivity fiber-tracts could significantly predict performances using leave one channel and patient out cross-validation approaches (leave one channel out $\rho=0.38$, $p<0.0001$; leave one patient out $\rho=0.24$, $p<0.0004$) (Figure 5 D). Functional connectivity could also predict left-out decoding performances using the same validation approaches (leave one channel out $\rho=0.37$, $p<0.0001$; leave one patient out $\rho=0.25$, $p<0.0004$) (Figure 5 E).

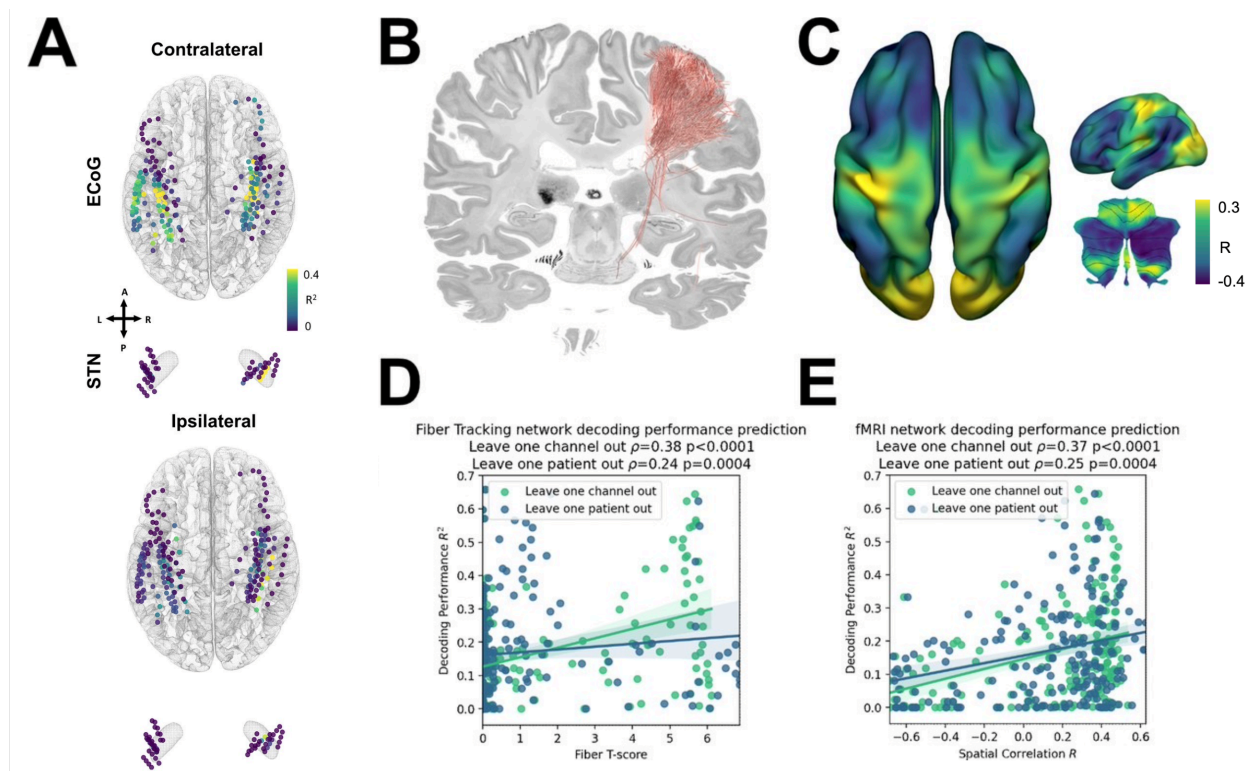


Figure 5: Functional and structural connectivity predicts decoding performances. Cortical and subcortical electrode locations are color-coded by XGBOOST decoding performances. Cortical performances showed a clear relation to motor cortical areas (A). Decoding performance-specific structural (B) and functional (C) network profiles were estimated and could predict performances in leave-one channel and subject out cross-validation (D+E). Modified from Merk *et al.*, 2022 (31).

4. Discussion

4.1 ECoG recordings are superior to STN-LFP signals and benefit from non-linear machine learning methods

In this work, we first systematically compared ECoG and STN-LFP movement decoding performances across different machine learning methods, investigated the influence of pathophysiological activity, and identified whole-brain networks that characterize optimal decoding performances. We highlight that ECoG recordings showed higher movement decoding performances than STN-LFP signals for different machine learning methods. STN-LFP recordings did not benefit from non-linear complex machine learning models. The previously reported Wiener filter method was also found to yield best performances for STN-LFP signals (7). In contrast, a strong decoding performance gain could be achieved with ECoG recordings. These results can be explained by the strong differences in amplitude and signal-to-noise ratio between ECoG and STN-LFP signals (63). We expect that ECoG BCI decoding methods would benefit from utilizing more complex non-linear architectures in the future. In contrast to EEG research, ECoG electrode layouts and contact locations usually differ across patients. Here, we identified that the best decoding could be achieved first using only a single electrode contact, and second using the gradient boosted decision tree machine learning method with the XGBOOST framework. XGBOOST is a common architecture in tabular datasets, utilizing different feature modalities without extensive need for feature preprocessing and hyperparameter tuning (27). Although not tested in this work, end-to-end deep learning could in the future outperform machine learning methods with a larger training dataset size. However, when limited training data is available, as presented in the intra-operative recording setting, a feature estimation pipeline with a regularized machine learning architecture could be a strong baseline model for many BCI applications. This pipeline could potentially also meet embedded hardware storage and computing power requirements (64,65).

4.2 Decoding performances show disease-specific correlations

The negative correlation of UPDRS-III and ECoG or STN-LFP decoding performances showed that the tested machine learning models were not independent of the underlying PD symptom states. Clinical scores could therefore potentially be used as features to improve behavioral decoding. However, a static score could not improve model

predictions in a within-patient validation setting. Yet, in the context of multi-subject or multi-cohort decoding, disease-specific symptom scores could be integrated either directly as additional features or lead to the clustering of symptom-specific model groups. The presented relationship between STN-LFP beta oscillations and ECoG decoding performances also highlights that beta oscillations reflected PD symptom severity in this cohort. Previously, it was shown that transient decreases in striatal beta activity correlated positively with phasic dopamine currents (66). Therefore, this result could point towards a relationship between the obtained decoding performances and basal ganglia dopamine levels.

4.3 Functional and structural connectivity predicts decoding performances

The presented network-guided approach to predict decoding performances could be further used in different applications. For example, it could guide the placement of sensing electrodes for brain-computer interfaces. In this way, motor cortical areas could be combined with brain regions encoding kinematic-associated information for decoding improvement. When electrode locations for a new patient are precisely determined, the decoding contact could also be selected by the strongest correlation with a decoding performance specific connectivity network. This method thus enables across-patient decoding without individual patient training. Alternatively, a grid with standardized electrode contact positions was demonstrated for across-patient movement decoding (67). Using this approach, data from individual patient electrodes was interpolated onto the common grid space. A performance comparison of the R-Map single channel selection and common grid point interpolation approaches remains to be investigated for future BCI applications.

4.4 Conventional and machine learning-based adaptive deep brain stimulation

In addition to the presented methodological developments of invasive decoding, we discuss in the following potential applications of the presented framework for aDBS. Adaptive stimulation protocols using a single biomarker were previously demonstrated in PD, and in the following called conventional aDBS (68). Since elevated subthalamic oscillatory power in the beta band was shown to correlate with PD symptom severity and medication-induced symptom alleviation (26,62), stimulation was triggered based on STN signal amplitude power in the beta frequency band. This approach relies on switching

stimulation on when beta power crosses a certain threshold (Figure 6 A). In a different study, stimulation-induced speech impairments were improved through single biomarker aDBS with the same clinical efficacy using only half stimulation ON time compared to continuous DBS (69). Beta-based aDBS holds, however, the limitation that beta oscillations are involved in different physiological states. For example, beta activity is altered in a diurnal cycle and during movement execution (28,70). In a beta oscillation triggered aDBS setting, stimulation would therefore be actuated not only specific to a disease state but might interfere with healthy physiological states such as movement or sleep.

Machine learning based decoding, such as this presented movement vigor decoding framework, can be used to predict different pathological and physiological states (71,72). The presence of multivariate features and non-linear dependencies, motivate machine learning methods for brain state decoding also using recordings from multiple brain sites (Figure 6 B) (20). In addition to depth recordings from the stimulation electrode, ECoG recordings were shown to encode relevant physiological and pathological states (35,73,74). Therefore, ECoG could be included as an additional recording modality for aDBS. In recent studies with essential tremor patients, machine learning models were used to decode movement using thalamic LFP (75) and ECoG recordings (21). When the presence of movement was detected, stimulation was triggered.

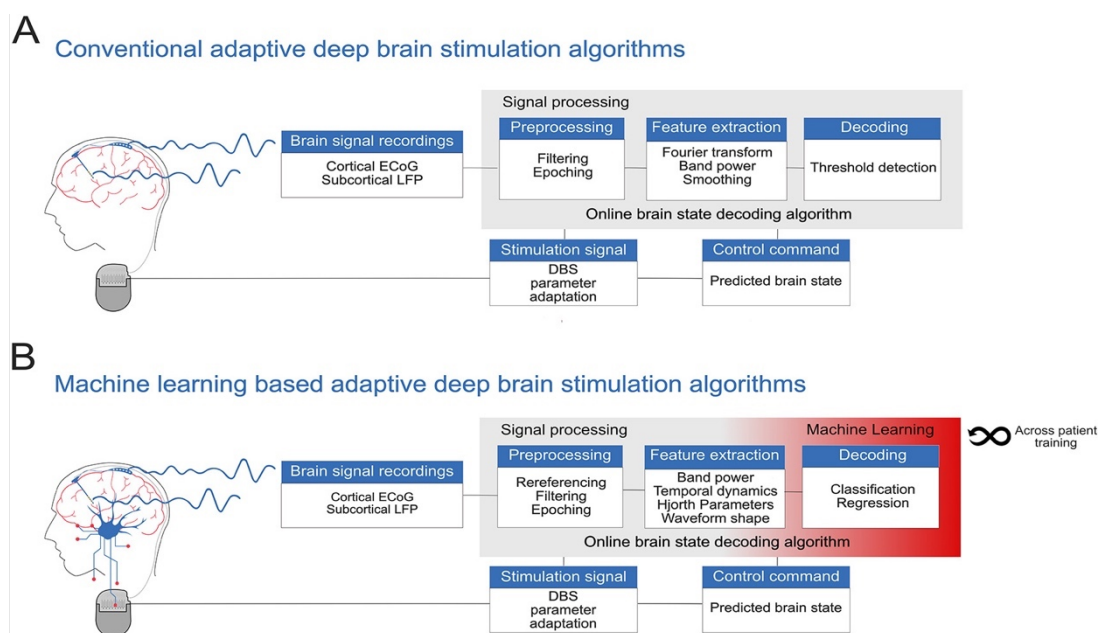


Figure 6: Comparison of conventional and machine learning-based adaptive deep brain stimulation. (A) Conventional aDBS relies on adapting stimulation based on a single biomarker state, such as subthalamic beta power. If a predefined threshold is crossed, DBS stimulation parameters

are adapted. (B) In machine learning-based aDBS, brain states are predicted using multimodal features. Here different pathological and physiological states can be decoded. The model architecture can in addition include current stimulation parameters. Data from different patients can be used for decoding without individual patient training. From review article “Machine learning based brain signal decoding for intelligent adaptive deep brain stimulation” Merk and Peterson *et al.*, 2022 (20).

Intelligent aDBS systems could also simultaneously integrate information from multiple decoded states. Non-linear relationships between different feature modalities and recording sites could be included to trigger stimulation (20). The same neural features would be included in different models to decode multiple states. For example, STN-LFP beta oscillations were in this study not only predicting ECoG decoding performances but were also strong contributing features for the prediction of movement vigor itself. Additionally, they were previously shown to be involved in many conditions, such as working memory and several sensorimotor functions (76). The different roles of beta oscillations could therefore be disentangled for aDBS paradigms capable of decoding multiple pathological and physiological states.

4.5 Movement-actuated adaptive deep brain stimulation for Parkinson’s disease

Gilron *et al.* showed recently that mobile and immobile PD states could be detected using motor cortical and subthalamic LFP recordings (25). aDBS systems could therefore act on these slow fluctuating symptom states, but symptoms could potentially also be alleviated on a faster time scale based on stimulation when single movements are detected. In this work we provided a framework for decoding movement vigor. Da Silva *et al.* recently demonstrated in mice that firing rates of dopaminergic neurons in the substantia nigra were shown to peak before movement initiation (22). Movement vigor and firing rates correlated positively, and stimulation activation could initiate movements. In PD, movement symptoms are present due to the progressive loss of dopaminergic neurons. Since dopaminergic neurons were shown to be involved in movement, symptoms could potentially be alleviated based on stimulation that is actuated in proportion to movement vigor. This novel approach could be combined with STN beta-based aDBS to account for different pathological symptoms that are present in PD.

4.6 Limitations

The present analyses were based on a cohort of 11 PD patients with only a single female individual. In a previous study, the rate of men diagnosed with PD was reported twice as high compared to women (77), not reporting whether gender was self-identified. Future studies therefore need to test the presented findings in a gender and sex-assigned-at-birth balanced manner.

Sample sizes in movement disorder cohorts with ECoG recordings are often limited due to the potential additional risk of infections during electrode implantation (78). Furthermore, the recordings are purely performed for research purposes and are not necessary for DBS therapy. Therefore, cohort sizes of comparable movement disorder studies including ECoG recordings reported similar or lower subject numbers (7,21,25). In the future, collaborations will be necessary to facilitate across-subject and cohort model validations. In adherence to open-science practices, we therefore made an effort for computational reproduction and made all data and analysis code publicly available (Raw data: <https://doi.org/10.7910/DVN/IO2FLM>, GitHub repository: [https://github.com/neuromodulation/ECoG vs STN](https://github.com/neuromodulation/ECoG_vs_STN)) (58–60).

Despite that the presented pipeline represents data streams in a real-time compatible setup, a different limitation of this study is that model evaluations were done offline. In addition, the intraoperative recording durations were in the order of a few minutes. The presented neural network models might therefore not generalize across the non-shuffled cross-validation due to the limited data set duration. With a larger training dataset size, performances of end-to-end learning architectures with more model parameters would likely outperform different feature estimation and machine learning model-based pipelines. In a within-hospital recording setting, however, this scenario remains challenging. Alternatively, when data is being streamed from patients' homes (25), machine learning and deep learning methods could be continuously adapted and improved.

In addition, naturalistic movement decoding models could be trained without a specific movement type. Here, data was obtained retrospectively from a Go/No-Go cued task, therefore, the shown associations remain to be investigated for self-initiated movements.

5. Conclusions

This study bridges invasive neurophysiology in Parkinson's disease, machine learning-based movement decoding, and whole brain structural and functional connectome-based decoding. Identifying the movement state could be beneficial for different aDBS paradigms for Parkinson's disease. Here, we provided a framework for real-time enabled feature estimation and highlighted that the strongest movement vigor decoding performances were obtained with single ECoG channel recordings. STN-LFP recordings could also predict movement vigor above chance level but clearly showed inferior performances. Different machine learning architectures were investigated, and XGBOOST strongly outperformed all tested models. ECoG performances showed a negative correlation with Parkinson's disease symptom scores and with time spent in STN-LFP beta burst activity before and after movement initiation. Therefore, this analysis highlights the advantages and limitations of utilizing data-driven decoding models. Furthermore, whole-brain connectivity profiles were investigated that could predict performances in a leave-one channel and subject out cross-validation. In conclusion, we demonstrated a machine learning comparison for invasive neural movement decoding from different recording sites and highlighted additional advantages of ECoG electrode placement for aDBS in addition to stimulation depth electrodes. The presented decoding performances were analyzed in detail: we identified pathological, oscillatory, and network-associated predictors that should be incorporated into the design of future BCI applications.

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Statutory Declaration

"I, Timon Merk, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic "Movement Decoding for electrophysiology-based intelligent adaptive deep brain stimulation in Parkinson's disease" (German: "Bewegungsdekodierung für elektrophysiologisch gestützte intelligente adaptive tiefen Hirnstimulation bei der Parkinson-Krankheit"), independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date

Signature

Declaration of your own contribution to the publications

Timon Merk contributed the following to the below listed publications:

Publication 1: **Merk T**, Peterson V, Lipski WJ, Blankertz B, Turner RS, Li N, Horn A, Richardson RM, Neumann WJ, **Electrocorticography is superior to subthalamic local field potentials for movement decoding in Parkinson's disease**, *eLife*, 2022

Contribution:

I conceptualized the study together with my supervisor Prof. Dr. Wolf-Julian Neumann. I standardized and preprocessed the already acquired data. I did all methodological analysis of machine learning, clinical and beta-burst correlation, and predictive network estimation. I created all figures and tables of the publication, wrote the original draft, and conducted all analysis for the revision.

Signature, date and stamp of first supervising university professor / lecturer

Signature of doctoral candidate

Excerpt from Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2020** Selected Editions: SCIE,SSCI
 Selected Categories: **"BIOLOGY"** Selected Category Scheme: WoS
Gesamtanzahl: 93 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	BIOLOGICAL REVIEWS	17,047	12.820	0.019750
2	Physics of Life Reviews	1,942	11.025	0.003280
3	CURRENT BIOLOGY	78,289	10.834	0.116100
4	BIOSCIENCE	22,560	8.589	0.012470
5	eLife	68,113	8.140	0.287820
6	PLOS BIOLOGY	39,598	8.029	0.059920
7	BMC BIOLOGY	8,577	7.431	0.015750
8	Communications Biology	4,996	6.268	0.016030
9	PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B- BIOLOGICAL SCIENCES	56,921	6.237	0.055730
10	Science China-Life Sciences	6,307	6.038	0.006960
11	BIOLOGICAL RESEARCH	2,563	5.612	0.002270
12	BIOELECTROCHEMISTRY	6,107	5.373	0.004870
13	PROCEEDINGS OF THE ROYAL SOCIETY B- BIOLOGICAL SCIENCES	64,652	5.349	0.061070
14	FASEB JOURNAL	54,279	5.191	0.044390
15	Current Opinion in Insect Science	3,455	5.186	0.008610
16	Biology-Basel	2,726	5.079	0.003990
17	QUARTERLY REVIEW OF BIOLOGY	4,781	4.875	0.000920
18	Life Science Alliance	1,208	4.591	0.004260
19	COMPUTERS IN BIOLOGY AND MEDICINE	9,751	4.589	0.011860
20	Biology Direct	2,265	4.540	0.002430
21	Geobiology	2,793	4.407	0.003600
22	BIOESSAYS	11,559	4.345	0.011680
23	ASTROBIOLOGY	4,963	4.335	0.005570
24	SAUDI JOURNAL OF BIOLOGICAL SCIENCES	6,487	4.219	0.007240
25	EXCLI Journal	2,642	4.068	0.002870
26	Interface Focus	2,863	3.906	0.004480
27	Life-Basel	1,851	3.817	0.003870
28	Biology Letters	12,880	3.703	0.016230
29	JOURNAL OF EXPERIMENTAL BIOLOGY	40,334	3.312	0.026860
30	JOURNAL OF BIOLOGICAL RHYTHMS	4,128	3.182	0.003270
31	YALE JOURNAL OF BIOLOGY AND MEDICINE	2,938	3.026	0.003300



Electrocorticography is superior to subthalamic local field potentials for movement decoding in Parkinson's disease

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Abstract Brain signal decoding promises significant advances in the development of clinical brain computer interfaces (BCI). In Parkinson's disease (PD), first bidirectional BCI implants for adaptive deep brain stimulation (DBS) are now available. Brain signal decoding can extend the clinical utility of adaptive DBS but the impact of neural source, computational methods and PD pathophysiology on decoding performance are unknown. This represents an unmet need for the development of future neurotechnology. To address this, we developed an invasive brain-signal decoding approach based on intraoperative sensorimotor electrocorticography (ECoG) and subthalamic LFP to predict grip-force, a representative movement decoding application, in 11 PD patients undergoing DBS. We demonstrate that ECoG is superior to subthalamic LFP for accurate grip-force decoding. Gradient boosted decision trees (XGBOOST) outperformed other model architectures. ECoG based decoding performance negatively correlated with motor impairment, which could be attributed to subthalamic beta bursts in the motor preparation and movement period. This highlights the impact of PD pathophysiology on the neural capacity to encode movement vigor. Finally, we developed a connectomic analysis that could predict grip-force decoding performance of individual ECoG channels across patients by using their connectomic fingerprints. Our study provides a neurophysiological and computational framework for invasive brain signal decoding to aid the development of an individualized precision-medicine approach to intelligent adaptive DBS.

Editor's evaluation

This paper evaluates movement decoding from intracranial brain recordings in patients with Parkinson's disease. Interestingly, the authors demonstrate that cortical recordings (electrocorticography) outperform subthalamic nucleus in decoding grip force. This work will be of interest to brain computer interface, movement disorder, motor control, and general neurophysiology communities.

Introduction

Subthalamic deep brain stimulation (DBS) for Parkinson's disease (PD) is one of the most successful neurotechnological advances in translational neuroscience to date. In addition to its clinical utility, DBS has provided unique insight into the neurophysiology of movement disorders (Cagnan et al., 2019; Krauss et al., 2021). PD has been associated with increased beta synchronization and beta bursts in the basal ganglia (Kühn et al., 2006; Neumann et al., 2016; Kehnemouyi et al., 2021) and exaggerated phase amplitude coupling and waveform sharpness asymmetry in cortex (de Hemptinne et al., 2015; Cole et al., 2017). Symptom severity in the OFF medication state was shown to correlate with resting beta power in the STN across patients (Kühn et al., 2006; Neumann et al., 2016). Such observations have inspired the idea of adaptive DBS (aDBS), where electrophysiological signals are used to change stimulation parameters in response to evolving clinical states (Little et al., 2013; Beudel and Brown, 2016; Tinkhauser et al., 2017; Swann et al., 2018; Piña-Fuentes and van Dijk, 2019; Velisar et al., 2019; Hwang et al., 2020; Petrucci et al., 2020). In a series of seminal papers it was shown that significant clinical benefit and reduced side-effects could be achieved, when stimulation was triggered by beta power (Little et al., 2013; Velisar et al., 2019). Machine-learning for aDBS applications can integrate multivariate feature sets for adaptive DBS control beyond beta power. First trials on machine learning based movement classification to trigger adaptive DBS either using electrocorticography (ECoG) or subcortical local field potentials (LFP) in essential tremor have shown promising results (Opri et al., 2020; He et al., 2021). In the future, smart implants may become available that combine invasive brain signal decoding with real-time stimulation adaptation, toward a precision medicine approach to adaptive DBS in PD and other brain disorders. However, the identification of optimal decoding strategies and the characterization of relevant factors with impact on decoding performance remains and unmet need. With the present study, we address this by a thorough investigation grip-force decoding that is motivated by the well-described relationship of vigor, movement velocity, bradykinesia, and dopamine in Parkinson's disease (Turner and Desmurget, 2010; Yttri and Dudman, 2016; Lofredi et al., 2018). We use state-of-art machine learning algorithms with multimodal invasive neurophysiology and whole-brain connectomics in PD patients undergoing DBS electrode implantation. Our results highlight the utility of cortical vs. subcortical signals to accurately decode grip-force and establish a link between decoding performance and motor impairment in PD. Finally, we investigate brain networks from ECoG recording locations with normative structural and functional connectomics and demonstrate the predictive power of connectomic fingerprints for brain signal decoding.

Results

Real-time processing and feature definition

We analyzed sensorimotor ECoG and subthalamic LFP data recorded intraoperatively from 11 PD patients undergoing DBS implantation during performance of a Go/No-Go based cued grip-force task (Figure 1A). Individual electrode localizations in Montreal Neurological Institute (MNI) space are shown in Figure 1B with typical responses (Kühn et al., 2004; Androulidakis et al., 2007; Kondylis et al., 2016; Lofredi et al., 2018) in Figure 1C aligned to onset of grip force (total $n=2685$, on average $n=244 \pm 149$ STD movements per patient, see Figure 1—figure supplement 1 for more detail on grip-force variability). For the use in machine-learning models, band power feature time-series were extracted in a real-time BCI compatible implementation (Figure 1D) streamed in virtual packets of 100ms length at a sampling rate of 1000 Hz to mimic the online application. Variance as a measure of amplitude of rereferenced, band-pass filtered raw data segments was extracted at 10 Hz with an adaptive window length from 1000 to 100ms of past data for eight oscillatory features [θ (4–8 Hz), α (8–12 Hz), β (13–35 Hz), low β (13–20 Hz), high β (20–35 Hz), low γ (60–80 Hz), high-frequency activity (HFA) (90–200 Hz) and all γ (60–200 Hz)]. All features were normalized to the median of the past 10 s to compensate for potential signal changes over time. The target variable was continuously measured grip-force (z-scored for each recording session), which was cleaned from noise and baseline drift (Xie et al., 2018).

Including preceding signals up to 500 ms before the decoded sample improves grip-force decoding performance

A linear model analysis of all eight oscillatory features per channel was used to investigate the contributing band power correlations for time-points simultaneous to and preceding target samples

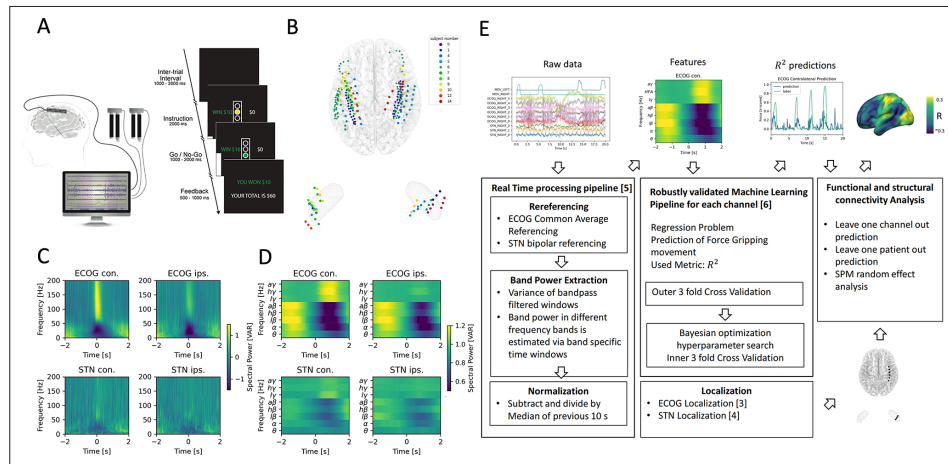


Figure 1. Movement induced spectral changes are more dominant for ECoG than STN-LFP signals for a grip force task before and after a machine learning feature signal processing pipeline. **(A)** ECoG, STN, and gripping force were recorded simultaneously during performance of a Go / No-Go task. **(B)** Individual ECoG and STN electrodes were localized and transformed into in Montreal Neurological Institute (MNI) space (**Figure 1—source data 1**). Note that ECoG strip designs varied slightly between patients (see **Supplementary file 1a**), leading to varying dimensions of overall input feature matrices. The number of ECoG channels (average $n=9.45 \pm 11.15$ STD per hemisphere) is higher compared to the number of STN LFP channels ($n=3$). **(C)** Mean spectral power of all ECoG and STN channels for contra- and ipsilateral movements showed typical movement induced spectral changes (**Figure 1—source data 2**). **(D)** Virtual streaming of data packets secured real-time compatible processing and normalization to extract time-frequency modulations into discrete feature time-series. Mean features of all ECoG and STN channels are visualized (**Figure 1—source data 3**). **(E)** Schematic flow chart of the implemented real-time enabled feature extraction, machine learning evaluation and functional and structural connectivity analysis pipeline.

The online version of this article includes the following source data and figure supplement(s) for figure 1:

Source data 1. ECoG and STN electrode localizations.

Source data 2. Mean ECoG and STN spectral power.

Source data 3. Mean ECoG and STN features.

Figure supplement 1. Analyzed movements show variability in maximum amplitude and velocity.

of continuous grip-force measurements. **Figure 2A** shows the weight distributions of multivariable linear models of the best performing channels per subject. Since each cortical or STN electrode has multiple channels, only the best channel per electrode is selected for this visualization. As the interpretability of coefficients in multivariable models is limited (*Haufe et al., 2014*), we have further visualized the normalized coefficients of univariate models for each relative time-point and frequency band in **Figure 2B**. Next, to investigate the cumulative performance contribution of preceding time points for optimal feature construction, all frequency bands were concatenated while continuously increasing the cumulative number of premovement time-points (from -100 to -1000 ms) and each set was subjected to training a Wiener Filter. The respective best channel R^2 performances are shown in **Figure 2C**. A performance saturation becomes visible when concatenating 5 time-points from 500ms (prior to target sample) to 0ms (target sample), resulting in an optimal input vector of 8 frequency bands with 5 time-points (=40 features) for further analyses.

XGBOOST outperforms other machine learning models for grip-force decoding

In order to build a grip-force decoder, different machine learning (ML) algorithms were tested in a large-scale Bayesian Optimization hyperparameter search (see **Supplementary file 1B** for a list of hyperparameters for each model). Elastic - Net regularized Linear Models, Neural Networks and Gradient Boosted trees (XGBOOST) (*Chen and Guestrin, 2016*) were tested for each channel for contra- and ipsilateral movements. XGBOOST was included as it can learn non-linearities and has

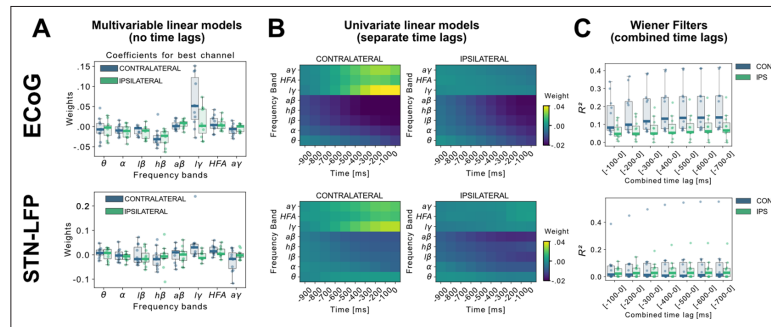


Figure 2. Linear Models and Wiener Filters reveal temporally and spectrally specific coefficient distributions with grip-force decoding performance gain by including signals preceding the target sample by up to 500ms. **(A)** Multivariable linear model coefficients trained only from the instantaneous sample (0 time lag with respect to decoded target sample) including all frequency bands from best channels per patient resemble movement induced spectral changes with beta desynchronization and gamma synchronization (**Figure 2—source data 1**). ECoG derived coefficients yield higher absolute values than STN-LFP derived coefficients. **(B)** Univariate frequency and time lag specific Linear Models were trained and visualized to improve interpretability of average coefficients in the absence of interactions (**Figure 2—source data 2**). Low γ (60–80 Hz), HFA (90–200 Hz), and all γ (60–200 Hz) bands show stronger positive associations for contralateral over ipsilateral movements. Moreover, stronger associations are visible for ECoG over STN-LFP signals for β , HFA, and γ bands. **(C)** Wiener Filters can integrate multiple time-steps in Linear Models leading to an incremental performance gain when signals are included preceding the current target sample by up to 500ms (**Figure 2—source data 3**).

The online version of this article includes the following source data for figure 2:

Source data 1. Best channel Linear Model coefficients trained from instantaneous sample.

Source data 2. Univariate Linear Model coefficients of single frequency band and time lag.

Source data 3. Wiener Filter multiple time-step comparison.

advantages over other models with respect to feature selection. To further utilize potential information derived from spatial patterns, the Source Power Comodulation (SPoC) framework (*Dähne et al., 2014*) was used in combination with Elastic - Net or XGBOOST predictors. Each model was informed by 40 features (8 specific frequency bands concatenated at 5 time-points ranging from $t = -500$ ms to $t=0$ ms to the target sample) per channel and evaluated via rigorously cross-validated test-set predictions ranked by R^2 coefficients of determination. **Figure 3** shows performance outcomes for the different machine learning methods, with overall best results achieved by XGBOOST from ECoG signals (see **Supplementary file 1c** for further details). Contralateral ECoG strips had significantly higher decoding performances than ipsilateral ones (contralateral $R^2 = 0.31 \pm 0.24$, ipsilateral $R^2 = 0.13 \pm 0.16$, $p=0.02$). Given the relatively low decoding performances for STN-LFP, we applied permutation tests to confirm that performance was above chance (contralateral $p=0.025$, ipsilateral $p=0.028$). Corroborating the model choice in previous literature, highest STN performances were achieved with the Wiener Filter method for contra- and ipsilateral movements (*Shah et al., 2018*). Importantly, varying combinations of multiple ECoG and/or STN channels did not lead to significant performance advantages (**Figure 3 C+D**), which is important for the utility and design of machine learning enabled implantables.

Grip-force decoding performance is correlated with PD motor impairment and subthalamic beta burst dynamics

To investigate potential sources of bias from patient specific information on grip-force decoding performance, we performed Spearman's correlations with the grand average from all contra- and ipsilateral decoding performances. Averaging was necessary to obtain one value per patient. Age ($\rho = -0.16$, $p=0.32$), disease duration in years ($\rho = 0.31$, $p=0.17$) and number of movements ($\rho = -0.41$, $p=0.11$) and movement variability ($\text{Rho} = -0.49$, $p=0.06$) did not reveal significant correlations.

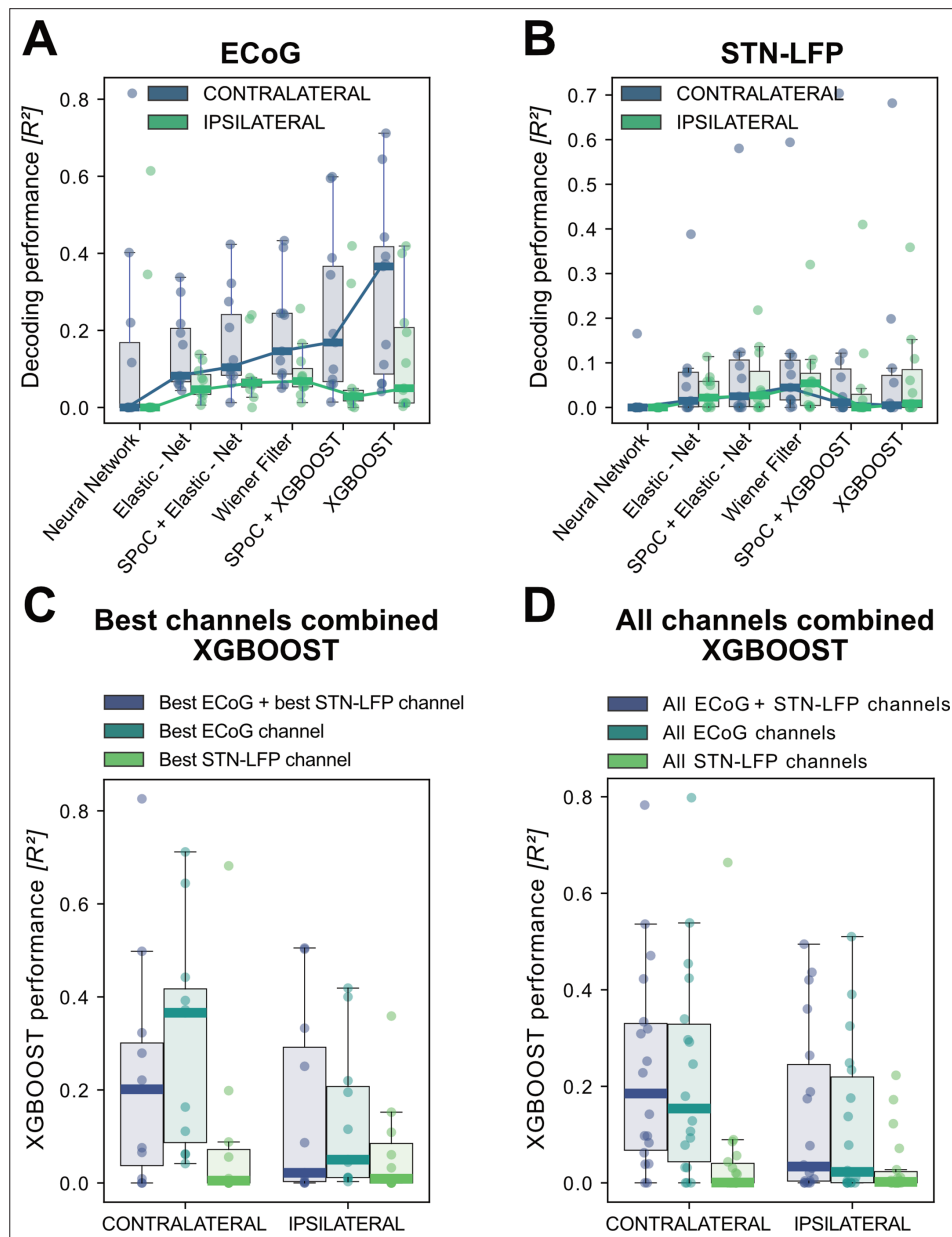


Figure 3. XGBOOST outperforms other machine learning methods for ECoG based grip-force decoding. Based on the presented real-time compatible signal processing pipeline Neural Networks, Elastic - Net regularized Linear Models, Wiener Filters and extreme Gradient Boosting (XGBOOST) regression models were tested. Mean R^2 test-set grip-force decoding performances are shown for the best channel per patient after 10 rounds of Bayesian Optimization of hyperparameters with nested cross-validation for ECoG (A) and STN-LFP (B) (Figure 3—source data 1). The same pipeline Figure 3 continued on next page

Figure 3 continued

was subjected to spatial feature extraction approach using all available channels of an electrode for each patient with Source Power Comodulation (SPoC). Best ECoG (A) performances were obtained by XGBOOST regressors. STN-LFP signals (B) did not exhibit performance gain when applying advanced machine learning methods. The mean ECoG vs. STN XGBOOST performance differences of contralateral $\Delta R^2 = 0.21 \pm 0.18$ and ipsilateral $\Delta R^2 = 0.069 \pm 0.08$ movements, indicate the higher grip-force decoding performance of ECoG over STN signals. The mean test-set prediction performances were higher for ECoG than for STN-LFP signals across all patients, for both contra- and ipsilateral movements. Best ECoG channels outperformed best STN-LFP channels and the combination of best channels from both ECoG and STN-LFP (C) (Figure 3—source data 2). When combining multiple channels, performances improve through the combination of ECoG and STN-LFPs (D), but the performances remain below individual best ECoG channels as depicted in (C). For combined ECoG +STN – LFP training, the model learned specific combinations between both feature locations and failed to select only the best ECoG features due to overfitting.

The online version of this article includes the following source data for figure 3:

Source data 1. Cross-validated ECoG and STN machine learning model performances for single channels.

Source data 2. Cross-validated combined and best-channel XGBOOST performances for best ECoG and STN channels.

Source data 3. Cross-validated XGBOOST performances for multichannel models based on ECoG, LFP and combined ECoG-LFP channels.

We further investigated whether motor impairment related to the hypodopaminergic state in PD can explain differences in grip-force decoding across patients. Therefore, we correlated preoperative OFF medication total UPDRS-III scores, which revealed negative correlations for best ECoG ($\rho = -0.55$, $p = 0.039$) and STN-LFP ($\rho = -0.55$, $p = 0.042$) channels (Figure 4 A+B). Combined ECoG and STN channel performance also showed significant correlations ($\rho = -0.54$, $p = 0.045$), as well as combined ECoG ($\rho = -0.55$, $p = 0.045$) and combined STN-LFP performances ($\rho = -0.61$, $p = 0.024$). To test whether the correlation measure was corrupted by outliers, we repeated the analysis using the robust percentage-bend correlation (Pernet et al., 2012) which replicated the significant association between UPDRS total score and mean contra -and ipsilateral channel performance for ECoG ($r = -0.62$, $p = 0.04$) and STN ($r = -0.7$, $p = 0.016$). This correlation was temporally specific to decoding of ongoing grip-force, indicative of the models' underestimation of motor output (Figure 4C). Thus, the lower decoding performance in patients with more severe symptom severity could not be attributed to changes in decoder output in the absence of movement or temporal imprecision. This has practical implications and highlights the importance of investigating interactions between disease and machine learning approach for neural implants.

To better understand the relationship of PD pathophysiology and grip-force decoding performance, we have further investigated associations between cortical and subthalamic beta burst dynamics. We follow the methodology of previous reports that demonstrated that the time spent in beta burst correlates with impairment of movement kinematics (Torrecillos et al., 2018). Beta bursts were defined as threshold crossings of the beta feature vector above the 75th percentile of the baseline period. Following the previous finding that specifically the time-spent in low-beta but not high-beta bursts was correlated with PD motor impairment (Lofredi et al., 2019), we investigated these bands separately for the motor preparation period (-1-0 s with respect to movement onset) and movement execution period (0-1 s following movement onset). To uncover a potential relationship of the beta-burst metric with PD pathophysiology, we performed correlations with UPDRS-III total scores. Significant correlations were found between UPDRS-III and low-beta bursts in STN-LFP signals during motor preparation ($\rho = 0.63$, $p = 0.02$; Figure 5A) and movement execution ($\rho = 0.56$, $p = 0.04$; data not shown), but not for the high-beta band ($p > 0.05$). Conversely, for ECoG high-beta but not low-beta burst dynamics during motor preparation but not movement periods were significantly correlated with UPDRS-III total scores ($\rho = 0.55$, $p = 0.04$). In summary, we provide evidence that both subthalamic and cortical beta burst dynamics relate to PD motor sign severity with subthalamic low-beta bursts showing the most robust correlations, both during motor preparation and movement periods.

To relate these findings to movement decoding performance from cortex, we correlated the grand average XGBOOST grip-force decoding performances from ECoG channels (as above for UPDRS-III) with high- and low-beta burst dynamics in both ECoG and STN-LFP signals. ECoG based grip-force decoding performance was significantly correlated with subthalamic low-beta burst dynamics during motor preparation ($\rho = -0.76$, $p = 0.004$) and movement execution ($\rho = -0.71$, $p = 0.005$; Figure 5B). Subthalamic burst dynamics in the high-beta band also correlated with ECoG decoding performances during movement ($\rho = 0.71$, $p = 0.007$) but not motor preparation. Cortical burst dynamics from ECoG

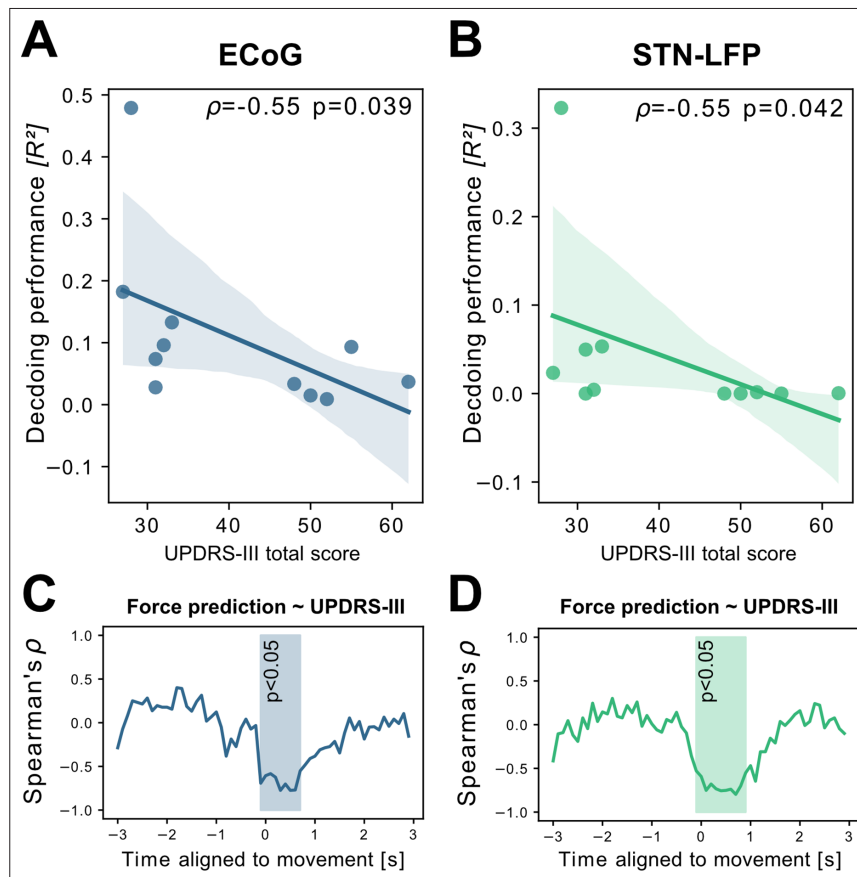


Figure 4. Grand average grip-force decoding performances correlate inversely with preoperative PD motor sign severity. UPDRS-III scores show significant negative correlations with patient-wise XGBOOST grip-force decoding performance averages for (A) ECoG ($\rho = -0.55$, $p = 0.039$) and (B) STN-LFP signals ($\rho = -0.55$, $p = 0.042$) (Figure 4—source data 1). The temporal specificity of this correlation is revealed through movement aligned sample-wise correlations of average force prediction model output with UPDRS-III scores across patients (cluster based corrected significant segments are displayed shaded) (C+D) (Figure 4—source data 2).

The online version of this article includes the following source data for figure 4:

Source data 1. ECoG and STN single channel performances and UPDRS ratings.

Source data 2. ECoG and STN Force prediction UPDRS correlation.

signals did not reveal significant correlations with ECoG-based grip-force decoding performances. Relevant correlations alongside exemplar burst visualizations and corresponding grip-force decoding traces are shown in Figure 5.

Brain mapping of grip-force decoding performance from invasive cortical and subthalamic recordings

The spatial distributions of decoding performance on cortex and STN for contra- and ipsilateral movements are shown in Figure 6. To evaluate the relevance of recording location with respect to decoding performance, we calculated correlations of performance measures with a priori defined implantation

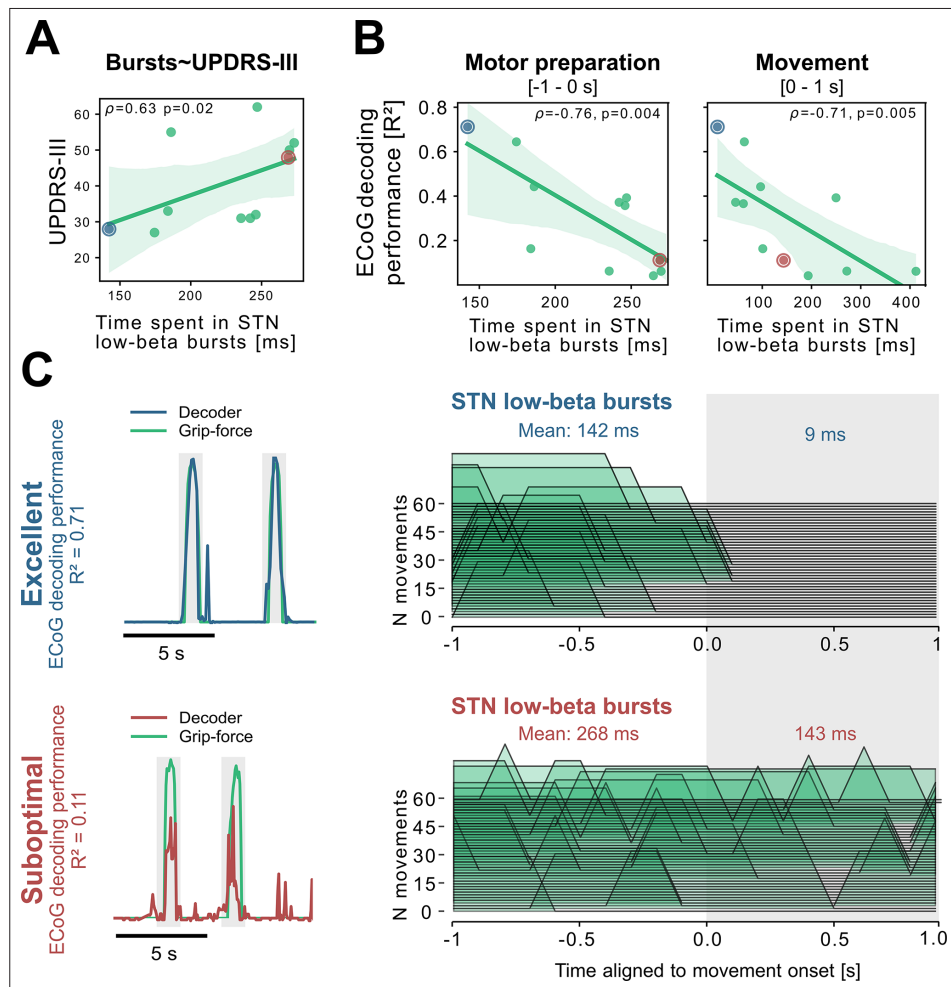


Figure 5. Subthalamic low-beta bursts relate to PD motor impairment and are associated with lower ECoG decoding performance. UPDRS-III scores are significantly correlated with time spent in subthalamic low-beta bursts in the motor preparation period (A) and during movement (not shown). Average XGBOOST decoding performance correlated inversely with time spent in subthalamic low-beta bursts during motor preparation and movement performance (B) (Figure 5—source data 1). Patient examples with excellent ($R^2=0.71$; blue) and suboptimal ($R^2=0.11$; red) performances are highlighted in (B) and shown in further detail in (C) (Figure 5—source data 2). Note the difference in decoder output with respect to the original grip-force trace (left panel) and the differences in burst frequencies and durations across movement repetitions (right panel) in the motor preparation and movement execution (grey shaded area) period.

The online version of this article includes the following source data for figure 5:

Source data 1. Time spend in low-beta burst performance and UPDRS correlation.

Source data 2. Movement onset aligned low-beta bursts for two subjects.

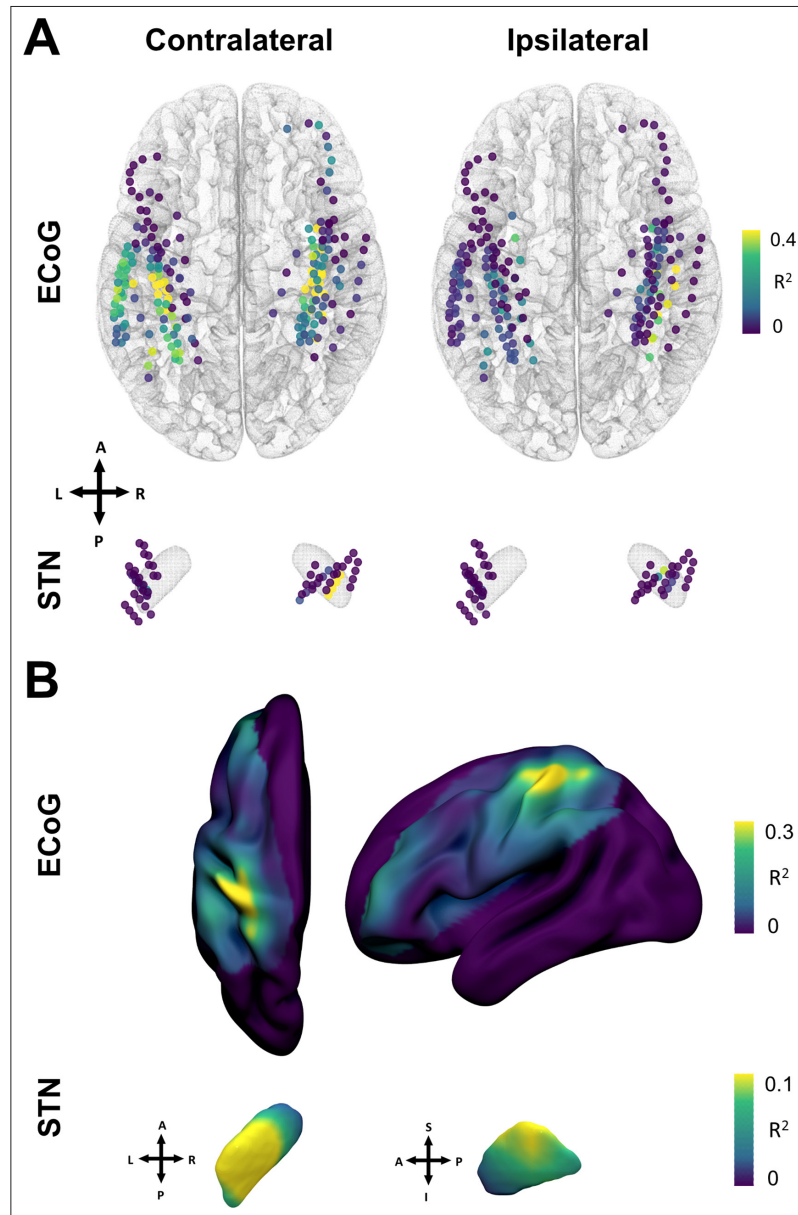


Figure 6. Grip-force decoding performances spatially peak in sensorimotor cortex and the dorsolateral STN. **(A)** Channels are color coded for individual XGBOOST grip-force regression performances per channel. Performance differences shown are in favor of ECoG over STN and contralateral over ipsilateral recording locations for movement decoding. (*Figure 6—source data 1*) **(B)** Spatial interpolation across all contacts projected to the

Figure 6 continued on next page

Figure 6 continued

left hemisphere shows peak performances in sensorimotor cortex. STN interpolated decoding performance peaks in the dorsolateral portion of the STN, in proximity to the best therapeutic target (Caire *et al.*, 2013).

The online version of this article includes the following source data for figure 6:

Source data 1. Single channel XGBOOST coordinates and performances.

targets, namely the dorsolateral STN (Caire *et al.*, 2013; Horn *et al.*, 2017a) and the hand-knob of the precentral gyrus (Mayka *et al.*, 2006). Linear mixed effects models showed a significant within-subject relation for contralateral ECoG decoding performances ($\beta = -0.002$, Lower CI = -0.003 , upper CI = -0.001 , $R^2 = 0.57$, $p < 0.001$), but not STN locations ($p > 0.05$). The dependent variable was the decoding performance, the fixed effect was the distance to hand knob area or dorsolateral STN respectively, and the random effect the subject. Repeating the analyses across electrodes and patients in a cross-validated manner revealed no significant predictive value ($p > 0.05$). Thus, Euclidean distance to hand knob area for ECoG and therapeutic target for STN was significantly correlated with decoding performance within patients, but could not predict decoding performance across channels or patients.

Whole-brain connectomics can aid the discovery of brain networks underlying the neural encoding of grip-force

The ability to account for decoding performances for invasive electrodes may soon become as important as accounting for variance in stimulation effects, as bidirectional clinical brain computer interfaces will rely both on electrical sensing and stimulation. Recently, network mapping of neurostimulation targets has shown utility to predict variance in clinical outcomes following DBS (Horn *et al.*, 2017b; Horn and Fox, 2020; Li *et al.*, 2020). Here, we extended the same framework to predict variance in grip-force decoding performance observed from single channels, using the XGBOOST grip-force decoding results. In this approach – termed *prediction network mapping* – we calculated functional and structural connectivity *fingerprints* by projecting each recording location to a group connectome that was acquired in a cohort of PD patients. These fingerprints denote to which other brain areas each site is connected to. Using a discriminative fiber tracking analysis, (Baldermann *et al.*, 2019; Li *et al.*, 2020) we analyzed the predictive value of structural connectivity from ECoG recording locations (for an exemplar case see Figure 7A) for XGBOOST decoding performance. Therefore, diffusion imaging derived whole-brain fiber connectome data traversing to more than 20% of recording locations were used (Figure 7B). The specific fiber distributions included structural projections spanning sensory, motor and prefrontal cortex, and could significantly predict decoding performance of left out channels ($\rho = 0.38$, $p < 0.0001$; thresholded at a false discovery rate $\alpha = 0.05$) and patients ($\rho = 0.37$, $p < 0.0001$) in a cross validated manner (Figure 7D). Next, we created spatial models of optimal decoding performance for functional connectivity (R-Maps are shown in Figure 7C). This model led to significant predictions of decoding performance in leave-one-channel-out ($\rho = 0.37$, $p < 0.0001$) and leave-one-subject-out cross validations (functional connectivity $\rho = 0.37$, $p < 0.0001$) (Figure 7E). The results were further validated with voxel-wise correlations using the statistical parametric mapping (SPM) framework (see Materials and methods for further details). Models such as the two presented here could be generalized to all BCI applications and used to identify brain networks that encode specific behavioral and clinical target variables.

Discussion

Bidirectional brain computer interfaces will revolutionize the treatment of previously intractable brain disorders with brain signal decoding based adaptive neuromodulation. DBS provides a unique platform to trailblaze neurophysiological approaches, disease-specific modulation and computational strategies for brain signal decoding for next-generation brain implants. Here, we investigated clinical and computational strategies for grip-force decoding as a representative and pathophysiologically relevant behavioral target variable. We used multimodal invasive neurophysiology time-series data in PD patients undergoing DBS electrode implantation. Our findings can be broken down into four advances to the field: (1) we developed a new decoding approach based on multispectral time-concatenated band-power measures, subjected to Bayesian optimized extreme gradient boosted

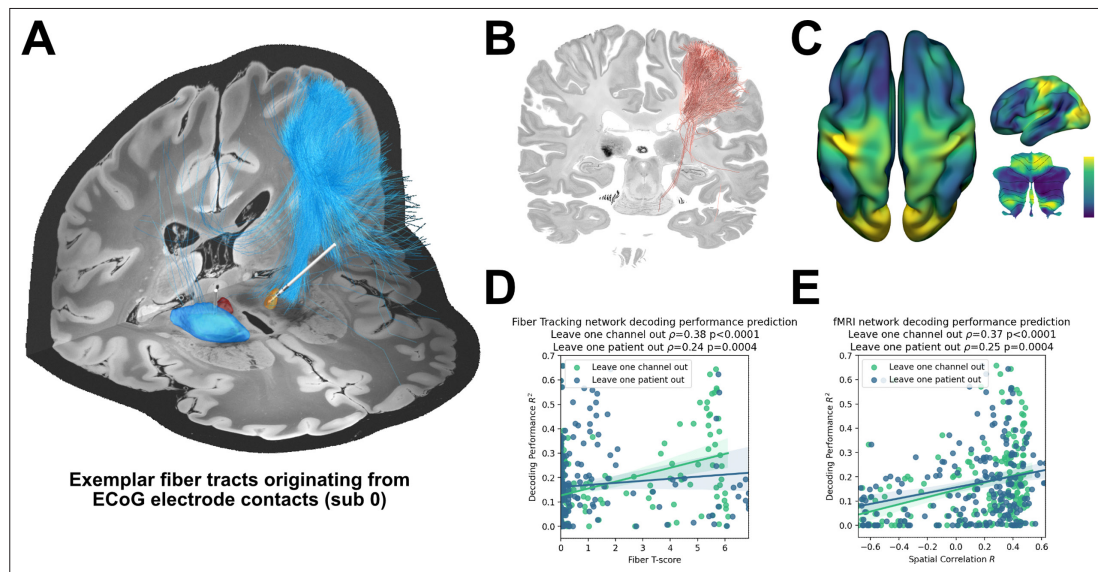


Figure 7. Structural and functional movement decoding network analysis reveals cerebellar as well as sensorimotor cortical decoding capacity. (A) Visualization of fibers originating from the ECoG recording locations of subject 1. (B) Decoding performance across all subjects and channels significant fiber tracts are displayed. All ECoG contacts were projected to the left hemisphere. For every fiber a t-test statistic between connected and unconnected brain regions was calculated. Only significant fibers, indicating structural connectivity to grip-force decoding performance, are shown. (C) The optimal R-Map is shown for the cortical surface as well as cerebellum for fMRI functional connectivity. Fingerprints were calculated between the functional connectivity of every electrode contact to all other voxels. The R-Map was then calculated as a correlation between individual contact fingerprints and the contact specific R^2 decoding performance. (D) Fiber tracking connectivity predicts grip-force decoding performance (leave one channel out cross validation $\rho = 0.38$, $p < 0.0001$, leave one patient out cross validation $\rho = 0.24$, $p = 0.0004$) (Figure 7—source data 1). Here, each individual point represents a statistic of connected and unconnected fibers of each contact or patient. The previously calculated fiber statistic within each cross-validation fold could thus predict the channel or patient specific performance. (E) Functional connectivity predicts decoding performance (leave one channel out cross validation $\rho = 0.37$, $p < 0.0001$, leave one patient out cross validation $\rho = 0.25$, $p = 0.0004$) (Figure 7—source data 2). The spatial correlation between individual fingerprints and the cross-validation specific R-Map, predicts left out decoding performances.

The online version of this article includes the following source data and figure supplement(s) for figure 7:

Source data 1. Fiber Tracking network decoding performance prediction.

Source data 2. fMRI network decoding performance prediction.

Figure supplement 1. 'Prediction Network Mapping' allows for prediction of machine learning decoding performances using functional and structural connectivity.

ensembles (XGBOOST): this outperformed traditional linear model-based methods and may be generalized to all brain signal-based regression problems. (2) Next, we demonstrate that electrocorticography signals outperform subthalamic LFP for grip-force decoding, supporting the utility of additional ECoG in adaptive DBS research for PD patients. (3) Our findings link PD motor impairment, PD pathophysiology with deterioration in decoding performance, highlighting a potential impairment in movement coding capacity through subthalamic low-beta bursts during motor preparation and execution periods. (4) Finally, we could significantly predict how well a specific recording site would perform to decode grip force based on brain connectivity. This novel framework (termed prediction network mapping) can be used in future implants to identify connectomic networks from which brain sensing can predict symptoms and behavior.

Limitations

Our analysis is retrospective in nature and the data were obtained in context of a Go/No-Go task, which may have implications on the generalizability of the findings in the application during naturalistic

Table 1. Subject characteristics.

N	Gender	UPDRS total	Hemisphere	Age	Movements	Disease duration [years]	ECoG Strip Contact Number Left	ECoG Strip Contact Number Right
0	Male	28	R	60.3	128	10.7	0	6
1	Male	27	L+R	51.2	464	14	28	28
2	Male	33	L+R	53.8	213	7.2	8	8
3	Male	31	L+R	44.2	285	10.1	8	8
4	Male	32	2L+2 R	63.6	381	13.1	28+8	28+8
5	Male	52	L	59.6	84	5.9	6	0
6	Male	55	L	71.6	161	1.4	6	0
7	Male	50	L	52.5	131	8.7	6	0
8	Male	62	L+R	66.8	547	9.8	6	6
9	Male	48	L	67.9	86	17.1	6	0
10	Female	31	R	69	205	10.4	0	6

behavior. All model training and evaluations were conducted offline. Nevertheless, we took meticulous care to exclude any circularity in processing and machine learning applications. To this date, such circularities are overlooked in some movement decoding papers with filtering, normalization and time frequency transformation across entire sessions, thus reaching into the future from the point of the individually decoded sample. Ridding our analysis from data that would be unavailable in a real-time setting as reported in this study, leads to worse performances, but gives a more realistic estimate of model performance in the clinical use-case. While gripping is a relevant motor skill for human behavior, our findings are restricted to the decoding of grip-force and may have limited generalizability to other movements. The overall number of patients in this study is low. This may have limited a more detailed analysis of bias and other factors, beyond the described correlation of clinical symptom severity, subthalamic beta burst dynamics, electrode location and connectomics. Most importantly, the signal to noise ratio may further impact decoding accuracies differently for ECoG and LFP signals. This could in part explain why decoding from ECoG signals may benefit more from complex and non-linear model architectures. The comparability of ECoG and LFP recordings was further affected by the higher number of available ECoG channels, when compared to only three bipolar LFP channels. However, the large effect size of superior decoding performances with ECoG may indicate that this bias does not relevantly impact the interpretation of our findings. An additional limitation was the relatively small amount of available data per patient, which was constrained by the intraoperative setting (see *Table 1*). For deep learning approaches, we expect better performances with increased dataset sizes, which may become available, either through externalized extraoperative recordings (*He et al., 2021*) or sensing enabled implantable devices (*Opri et al., 2020; Gilron et al., 2021*). Importantly, our finding that decoding performances from single contacts outperform multi-electrode models may be a consequence of a combination of short recording durations in this study, suboptimal computational model selection and the fact that sensorimotor cortex and STN are part of the same circuit that is synchronized in oscillations. While we have made an effort to accommodate models that are optimized for spatio-spectral feature learning, and we are confident that these cannot outperform single channel approaches in this dataset, future studies should cautiously reinterrogate this issue in larger datasets, for example by implementing neural networks optimized for this purpose (*Peterson et al., 2021*). Finally, we should acknowledge that the exploration of the neural feature space in this study was non-exhaustive, and further raw data features, such as the local motor potential (*Mehring et al., 2004*), waveform shape features (*Cole and Voytek, 2017*), and aperiodic signal components (*Wilson et al., 2022*) could further improve decoding performances in future movement decoding studies.

Decoding grip force based on invasive electrophysiology

Our study defines a novel computational strategy to decode grip-force based on ECoG and LFP in patients undergoing DBS for PD. It explores defined oscillatory feature sets and compares machine-learning models with varying complexity, from linear models to artificial neural networks and regression trees. ECoG-based movement decoding of varying movement types has been previously investigated in epilepsy patients that underwent electrophysiological monitoring (Leuthardt et al., 2004) through which local motor potentials and gamma band activity were highlighted as informative features (Gunduz et al., 2016). First analyses based on STN-LFPs in PD patients have shown that Wiener Filter architectures can be successfully used for grip-force decoding (Tan et al., 2016; Shah et al., 2018). The present study extends these previous reports to a continuous non-trial-based decoding approach. Furthermore, a direct comparison of ECoG and LFP performance with relation to systematic machine learning methods was lacking. Our findings indicate that sensorimotor ECoG recordings are more informative than LFP recordings from the STN for grip-force decoding. While this finding is robust, we should acknowledge that the size and shape of electrodes (see [Supplementary file 1a](#)) and the spatial orientation and size of the neural architectures that are sampled are not directly comparable across these methods. Thus, it is difficult to derive the relative importance of the different brain regions for grip-force and vigor processing in motor control from this comparison. Instead, we interpret our result as a practical demonstration of the greater utility of ECoG signals for movement decoding. The results in this study are based on extracted band-power features and show superior performances with XGBOOST, when compared to other model architectures and algorithms. More specifically, best performances were obtained for Bayesian optimized XGBOOST models trained on data from single ECoG channels without additional benefit from channel combinations or combined ECoG and STN channel sets. In the future, this machine learning approach can be adopted to extend the clinical utility of invasive brain stimulation approaches for other brain disorders, e.g. through decoding of tics or obsessive compulsive behavior in neuropsychiatric DBS indications.

Towards machine-learning-based adaptive stimulation in Parkinson's disease

Adaptive DBS (aDBS) has the potential for significant innovation in movement disorders (Starr, 2018). For Parkinson's disease, different control policies of subthalamic beta band activity are now tested in clinical trials to improve the treatment for patients with akinetic rigid dominant PD (<https://clinicaltrials.gov/> Identifier: NCT04681534, NCT04547712) (Little et al., 2013; Arlotti et al., 2018; Velisar et al., 2019). Beyond subthalamic beta power, ECoG recordings were previously used to successfully decode the presence of dyskinesia through elevated levels of gamma band synchronization. This could be used to reduce stimulation intensity to alleviate medication and stimulation induced dyskinesia (Swann et al., 2018). Such single biomarker approaches have the advantage that pathophysiological mechanisms may be the direct target of intervention, while machine learning based decoding methods derive correlates of symptoms and behavior indirectly through learning potentially noisy correlations (Neumann et al., 2019). Therefore, single biomarker based aDBS presents an optimal starting point for investigating the clinical utility of aDBS in controlled study designs. However, single biomarkers alone cannot account for the diverse and complex set of clinical signs of PD and behavior, for example during gait (Molina et al., 2021; Thenaisie et al., 2022), speech, and tremor (Hirschmann et al., 2013; Hirschmann et al., 2017). Here, a versatile decoding based control algorithm may further improve clinical outcome for these patients in the future (Neumann et al., 2019; Merk et al., 2022a). Indeed, machine learning-based decoding has been successfully described in first translational breakthrough studies (Opri et al., 2020; Gilron et al., 2021; He et al., 2021). In a complementary approach, we focused on direct grip-force decoding, motivated by the hypothesis that future aDBS studies increasing DBS amplitude during periods of higher movement vigor may advance the successful treatment of bradykinesia in PD. While our previous findings indicate that relative amounts of beta can still signal bradykinesia during movement, (Lofredi et al., 2019; Feldmann et al., 2021) further positive control parameters could keep stimulation proportional to intended movement vigor. Moreover, recent reports that beta power correlates negatively with phasic dopamine release may further substantiate the idea of movement/kinematics based STN stimulation to support intrinsic movement related dopamine signals (Schwerdt et al., 2020). We may speculate that DBS constitutes a network modulation that is similar to dopamine transients by suppressing local

firing of the subthalamic nucleus (Milosevic et al., 2018) and shifting the balance of basal ganglia from indirect to direct pathway activity. As highlighted above it was recently shown in non-human primates that phasic decreases in beta in the basal ganglia are correlated to phasic dopamine signals during movement (Schwerdt et al., 2020). Thus, in order to support the intrinsic dopaminergic capacity of PD patients, future machine learning based aDBS approaches could be complemented by algorithms that inform the stimulation on behavioral and motor adjustments to mimic intrinsic phasic dopamine signals. Previous studies have successfully decoded the presence of movement using cortical beta activity (Opri et al., 2020) which could also become a viable treatment option in PD. However, getting an estimate of movement vigor that is through the prediction of grip-force may complement advanced aDBS control policies, as multivariate models emerge for the next-generation of neurotherapeutics.

Notably, the proposed adaptive stimulation would require a fast algorithmic adaptation of stimulation to ongoing behavior. This could be combined with additional slower adaptations in response to medication or sleep cycles. Specifically for PD, beta-activity-based adaptive stimulation can be well suited to track the patient's overall symptom state (Tinkhauser and Moraud, 2021) while more rapid stimulation adaptations based on vigor can follow fast kinematic changes. The utility of vigor-based stimulation and the combination of this approach with additional slower adaptation algorithms, require further proof-of-concept studies before the clinical utility can be foreseen. In our study, we demonstrate that motor symptom severity itself can have direct and negative effects on decoding performance, which we should keep in mind during clinical decision making. Previous studies have shown that the presence of beta bursts correlated with motor performance in cortex (Little, 2019) and STN (Torrecillos et al., 2018), which could degrade decoding performance (Khawaldeh et al., 2020). Our study replicates and extends these findings, as we show a direct correlation between movement related beta burst dynamics and PD motor sign severity. More importantly, our results show that the amount of time the STN is bursting in the low-beta band, during motor preparation and movement execution is inversely correlated with ECoG based grip-force decoding performance. An obvious interpretation of this finding is that excessive synchronization in the STN may impair flexible motor control by decreasing information coding capacity and neural entropy as previously suggested in animal studies (Mallet et al., 2008; Cruz et al., 2009) and recently suggested for subthalamic beta bursts (Velasco et al., 2022). Again based on the inverse relationship of beta activity and dopamine signaling. Dopamine was shown to precede and invigorate future movement (da Silva et al., 2018). If subthalamic beta bursts indicate phasic decreases in dopaminergic innervation, we could expect a loss of invigoration and reinforcement of ongoing neural population activity in the cortex – basal ganglia – thalamic loop, which offers an elegant explanation for the lower decoding performance from ECoG signals in the absence of obvious cortical activity patterns.

Beyond beta bursts our findings indicate general impact of motor symptoms in the hypodopaminergic state on machine learning based kinematic decoding capacity. This highlights the conceptual relevance of disease specific interactions with computational models. Interestingly, in the hypodopaminergic state, the model output underestimated the grip force extent produced by the patients. This could reflect a loss of neural vigor representations related to insufficient dopaminergic modulation (Turner and Desmurget, 2010). In the future, we will have to account for the individual impact of disease specific changes in brain signals that affect decoding performance. Further, our results corroborate the notion that dopamine plays a key role in coding and modulating neural representations of movement kinematics in the human brain.

Connectomics can aid the discovery of brain networks underlying encoding of clinical and behavioral target variables

Decoding performance for clinical BCI may be drastically improved when adjusting brain signal recording sites to the underlying interconnected network that is relevant for encoding of the specific target behavior. For instance, when decoding language or speech, one could envision that recordings at either Broca's or Wernicke's region could be helpful, but a combination of both could be optimal. The two regions form a network with direct connections via the Arcuate Fascicle. In the present study, we have leveraged multisite recordings from various electrode locations across patients to identify the network that would be most informative for grip force decoding. For this endeavor, we adapted two existing methods that are able to isolate (i) connected voxels and (ii) connected fiber tracts (Horn

et al., 2017b; Li et al., 2020) associated with a specific target metric (such as grip-force decoding performance in the present case). While Euclidean distance to motor target, i.e. hand knob area for ECoG and therapeutic target for STN, was significantly correlated with decoding performance within-subject, this simplistic notion could not predict decoding performance across channels or patients. Thus, proximity to landmarks alone does not reliably help the identification of optimal recording sites. Given the complexity and vast distribution of movement related brain areas, from cerebellum to frontal cortex to parietal cortex, it may not be surprising that whole-brain connectomics outperform single region of interest based distance metrics for predicting informative recording locations. The development of a connectomic identification of optimal decoding locations has important implications in clinical adoptions of BCI technology. Preoperative identification of brain networks would allow the design of optimal electrode architectures and targeted implantation to cover strategic nodes of distributed networks for decoding of clinical variables and behavior. Moreover, connectomic approaches can inform the optimal spatial feature selection of pretrained machine learning models to facilitate brain signal decoding without the requirement for individual (re-)training. Importantly, the connectomic models that we used can be trained based on multiple dimensions of input-output relationships, for example for decoding of behavior like grip-force, but also for decoding clinical signs, such as tremor or mood disturbances. Thus, when implanting a high-density ECoG grid, connectomic analyses can generate target specific contact combinations, for example focusing on primary cortex for tremor and supplementary motor area for motor intention and bradykinesia. Our results highlight the utility of whole-brain connectomics to predict machine learning-based brain signal decoding performance that can be generalized to any bidirectional clinical brain-computer interface use-case. In the future, neurosurgeons may not target individual sensing locations in isolation, but instead determine optimal implant trajectories in accordance with whole-brain connectomic fingerprints for optimal BCI performance.

Conclusion

Our analysis from PD patients undergoing DBS implantation showed that ECoG recordings outperform STN-LFP recordings for grip-force decoding throughout different machine learning methods, with XGBOOST showing the highest performance. Parkinsonian motor sign severity and subthalamic low-beta bursts were associated with loss of decoding performance, indicating a specific link between PD pathophysiology, kinematic coding capacity and motor impairment. To investigate the spatial relationship of ECoG decoding performances in the brain, we have formalized a connectomic framework that could cross-predict decoding performances across recording sites and patients, based on underlying whole brain MRI connectivity patterns. Our findings highlight the utility of ECoG for intelligent adaptive stimulation in PD, corroborate the role of PD symptom severity in kinematic coding and pave the way for connectomic neurosurgery for machine learning-based brain signal decoding. We hypothesize that future neurotechnological treatments may have the potential to outperform traditional drug regimes, due to a key advantage in the temporal and spatial precision of therapeutic delivery towards a precision medicine approach for intelligent adaptive DBS (*Neumann et al., 2019; Neumann and Rodriguez-Oroz, 2021; Merk et al., 2022a*).

Materials and methods

Participants

The current study is based on previously published data (*Alhourani et al., 2020*). In brief, subthalamic LFP and subdural ECoG recordings were simultaneously acquired from 11 PD patients. The patients were subjected to bilateral STN-DBS lead implantation, as proposed by standard clinical indications criteria. In accordance with protocol #PRO13110420, approved by the Institutional Review Board of the University of Pittsburgh, informed consent for all patients was obtained prior to any surgical procedure. The subject characteristics are detailed in **Table 1**. UPDRS Part III scores for the off-medication conditions were collected in a time period of 1–3 months prior to surgery by movement disorder neurologists. Dopaminergic medications were withheld for at least 12 hr before intraoperative testing.

Behavioral paradigm

The behavioral task performed for this study was previously described (*Kondylis et al., 2016; Alhou-rani et al., 2020; Fischer et al., 2020*) and it is schematically shown in *Figure 1A*. The task included Go/No-Go cues with randomized inter-trial interval durations. Feedback durations were adjusted based on grip force reaction times. In the present analyses, time-series were virtually streamed as continuous data to simulate real-time grip-force decoding, irrespective of task trials. Subjects were fully awake, and no anesthetic agents were administered for at least 1 hr before the task procedure. No medication was given during the task. The task paradigm was implemented using the Psychophysics Toolbox (*Brainard, 1997*) on a portable computer. The trials consisted of a simultaneous presentation of a yellow traffic light in the center of a screen, and a cue on one side indicating which hand the subject should use for the subsequent response of squeezing the handgrip. The cue remained on screen for 1000–2000ms, followed by the traffic light changing either green or red, signaling a 'go cue' and 'no-go cue', respectively. Subjects performed the task for a cumulative total time of 10–25 min. As the present study focuses on grip-force decoding performance based on the electrophysiological signals, all sessions containing valid movements were merged per subject for further analysis. To validate that the used grip-force label in our data varies not only between two movement states, but constitutes a relevant regression problem with varying force amplitude and velocity, all movement maximum amplitudes and velocity traces are visualized in the *Figure 1—figure supplement 1*.

Electrophysiological recordings

Subdural electrode strips were implanted temporarily through standard frontal burr holes located near the coronal suture and aimed posteriorly to the hand knob motor cortex region. Strip targeting has been previously described and was based on markings of stereotactically defined overlying scalp locations (*Kondylis et al., 2016*). STN-DBS electrodes were implanted bilaterally, targeting the dorsolateral motor area of the STN. ECoG data were recorded intra-operatively using six-contact (left n=5 patients, right n=3), eight-contact (left n=3, right n=3) and twenty-eight-contact (left n=2, right n=2) strip electrodes. The electrode details are shown in *Supplementary file 1a* and all ECoG and STN electrodes are plotted in *Figure 1B* (mean number of electrode contacts were 10.18 ± 11.29 for left and 8.9 ± 12 for right hemispheres). A referential montage was used in which the reference electrode was placed in the scalp and a ground electrode was placed in the skin overlying the acromion process. ECoG and STN signals were filtered (0.3–7.5 kHz), amplified, and digitized at 30 kHz using a Grapevine neural interface processor (Ripple Inc). Force signals were digitally recorded simultaneously with the ECoG and STN-LFP signals. LFPs from the STN were recorded using the clinical DBS lead (model 3389, Medtronic) from all four contacts and referenced offline in a bipolar montage. All signals were resampled to 1 kHz for offline analysis. To investigate the variability of grip-force as a potential bias for decoding performance, we calculated the variance of peak force across movement repetitions.

Electrode localization

Subdural electrode reconstructions were obtained by aligning pre-operative MRI, intra-operative fluoroscopy, and postoperative CT. Representative images of this technique were previously shown in detail (*Randazzo et al., 2016*). In short, the CT and MRI were co-registered using mutual information using the SPM software library and rendered onto 3D skull and brain surfaces using Osirix (v7.5) (*Rosset et al., 2004*) and Freesurfer (v5.3) software packages (*Dale et al., 1999*), respectively. These surfaces and the fluoroscopy images were then aligned according to common points: stereotactic frame pins, implanted depth electrodes, and skull outline positions (*Randazzo et al., 2016*). The parallax effect of the fluoroscopic images was accounted for using the obtained distance from the radiation source to the subject's skull. Succeeding the surface-to-fluoroscopic image orientation alignment, a 3D location for each electrode contact was projected from the fluoroscopic image to the cortical surface. Deep brain stimulation electrode locations were reconstructed using the advanced neuroimaging pipeline defined by Lead-DBS using default settings (*Horn et al., 2019*). In brief, preoperative MRI and postoperative CT scans were co-registered and normalized to MNI 2009b NLIN ASYM space. Electrode artefacts were visually identified and marked to obtain MNI coordinates of DBS electrode contacts. All electrode localizations are visualized in *Figure 1B*.

ECoG and LFP preprocessing and feature extraction

The entire preprocessing pipeline used in the present study was optimized for real-time performance and inspired by the Berlin Brain Computer Interface (Blankertz, 2006). Processing was performed in Python using custom code based on MNE-python (Gramfort et al., 2013), mne_bids (Appelhoff et al., 2019) and pybv (<https://pybv.readthedocs.io/en/stable/>). All raw data files were saved in the iEEG-BIDS structure (Holdgraf et al., 2019). To account for baseline drifts, the force traces were cleaned using a normalization approach presented for previous ECoG finger trajectory decoding (Xie et al., 2018). A real-time data stream of untouched electrophysiological raw data was emulated to ensure that all processing that can impact decoding is performed in a real-time compatible manner. Referencing was performed online (i.e. after streaming virtual data packets). All LFP recordings were referenced bipolarly, against the adjacent contacts (0–1, 1–2, 2–3 with contact 0 being the lowest by convention of the manufacturer). Throughout the manuscript, we adopt the clinical usage of electrodes (also named 'leads') and contacts from the DBS realm. During preprocessing (in pseudo real time), we derive three bipolar STN-LFP channels from four adjacent contacts in one DBS electrode (also called 'lead'). We also follow this nomenclature for ECoG, where we call the entire strip an 'electrode'. ECoG electrodes in our dataset can have varying number of contacts (see [Supplementary file 1a](#)). ECoG recordings were referenced by subtracting the common average of all ECoG electrodes, therefore the number of channels per ECoG electrode is equal to the number of contacts per strip. To facilitate computationally efficient real-time enabled algorithms, time frequency decomposition for the machine learning analysis was conducted by bandpass filtering in the θ (4–8 Hz), α (8–12 Hz), β (13–35 Hz), low β (13–20 Hz), high β (20–35 Hz), all γ (60–200 Hz), low γ (60–80 Hz) and high-frequency activity, (90–200 Hz) frequency bands. Overlapping broad β and γ bands were added in addition to subbands to enable the investigation of distinct interactions within these frequency bands (Figure 1C). To estimate band specific activity, different time durations were used for bandpass filtering with longer time segments for lower frequencies, and shorter time segments for higher frequencies (θ =1000ms, α and β bands = 500ms, γ = 100ms). To get an estimate of amplitude of the activity in the filtered signals, variance was extracted in intervals of 1 s in a sliding window of 100ms resulting in a time resolution of 10 Hz. All variance estimates were normalized by subtracting and dividing by the median in a sliding window of 10 s to account for differences in impedance and proximity to the source before subjecting the data to the machine learning analysis. All features were clipped as an artifact rejection mechanism when they exceeded a normalized value of $[-2, 2]$. The used normalization is fully compatible with a real-time prediction approach, as data acquired in the future do not influence the present predictions. See Figure 1E for an outline of the methods pipeline. For the purpose of visualization, Morlet wavelets (7 cycles) were used to demonstrate the entire time-frequency decomposition (Figure 1C).

Machine learning training and evaluation

A rigorous nested cross-validation approach was implemented. An outer threefold cross validation split the data into folds of two third training and one third test set. For each individual channel, a Bayesian Optimization hyperparameter search (Frazier, 2018) was then conducted for 10 rounds using the training set only. For each round the training data was trained and tested in an inner threefold cross-validation with 80% training size. Post-hoc assessment confirmed convergence in performance after a maximum of 5 rounds in all recordings. The mean R^2 coefficient of determination of every test set estimate of the outer cross-validation was used as the performance measure as defined below:

$$R^2(y, \hat{y}) = 1 - \frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{\sum_{i=1}^n (y_i - \bar{y})^2}$$

Since the R^2 metric can be lower than zero for predictions that are worse than constant predictions, we used a lower threshold at zero to make performances comparable for the purpose of visualization. The input features for every model were all eight previously described frequency bands. In order to test the contribution of time points preceding the decoded target sample, frequency band features of different time points were concatenated and compared with respect to their decoding performance. The present study investigated commonly used and promising linear and non-linear machine learning

algorithms, specifically elastic net regularized linear models, linear Wiener filters, neural networks, gradient boosted decision trees (XGBOOST) and source power comodulation.

Linear models

Linear models can capture underlying feature dependencies and reveal those as correlations in each weight parameter. Input features are multiplied by a weight coefficient. The dot product of the weight vector \mathbf{w} and feature vector \mathbf{x} is then shifted by the bias b . The feature vector in this analysis is the vector of all frequency bands for a single time point. The prediction label y is the baseline corrected gripping force. For a linear regression the activation function is linear, is defined as follows:

$$y = \mathbf{w}\mathbf{x} + b$$

To prevent overfitting, regularization in the form of l_1 and l_2 norm is commonly used. Here we tested different parameters of the elastic-net (enet) regularization (Zou and Hastie, 2005), which is a combination of the l_1 and l_2 norm specified by the regularization hyperparameters α and ρ , respectively. The objective function of the enet model follows:

$$\min_{\mathbf{w}} \frac{1}{2n_{\text{samples}}} \|\mathbf{X}\mathbf{w} - \mathbf{y}\|_2^2 + \alpha\rho \|\mathbf{w}\|_1 + \frac{\alpha(1-\rho)}{2} \|\mathbf{w}\|_2^2$$

where \mathbf{X} is a matrix of dimension $n \times m$ whom i^{th} row is the feature vector \mathbf{x} of size m and \mathbf{w} is the solution vector, which, due to the l_1 sparse regularization term, most of the coefficient will be expected to be zero. For hyperparameter-search, α and ρ were both sampled from a uniform distribution ranging from zero to one. Since elastic nets are solved using gradient descent, the maximum training iteration also needs to be specified. Here an iteration number of 1000 has been used. The implementation was done using the scikit learn Python package (Pedregosa, 2011).

Wiener filters

Tan et al. described the use Wiener filters in the application of force estimation from STN-LFP signals (Shah et al., 2018). Here, the output y is a weighted sum of features in the time and frequency domain in the weight matrix \mathbf{W} . I frequency band features are used together with J lags. For the regression analysis the activation function is kept linear, as follows:

$$y(n) = \sum_{j=0}^J \sum_{i=0}^I w_{ij} x_i(n-j)$$

This equation has a closed form solution, known as the normal equation (Proakis and Monolakis, 1996). Wiener filters essentially implement a multivariable linear model with multiple time-steps. Using Wiener filters, we tested the contribution of different concatenated time-steps of brain signals preceding the decoded target sample. This provides insight about the optimal feature length in the time domain.

Neural networks

We have further investigated the utility of artificial neural networks. While linear models and Wiener filters may underfit the data, neural networks can be very complex and have a higher risk to overfit with increasing complexity. The ideal model architecture finds a balance between under and overfitting to the training dataset. In this context not only single weight correlations of band features could contribute to force decoding performances, but a richer representation of feature invariances in combinations of different frequency bands may be learned by additional layers and units of the model. The architecture of neural networks is derived from linear models with non-linear activation functions, which are referred to in this context as units. Multiple units are combined in different layers with different activation functions.

Explicitly, the output y of the i^{th} unit in layer l is the weighted sum of activations of the previous layer units y_k^{l-1} with weights w_{ik}^l ,

$$y_i^l = f^l \left(\sum_k w_{ik}^l y_k^{l-1} + b_i^l \right)$$

Neural networks are trained through a cost function using a gradient descent algorithm. Hyperparameters were adjusted in order to prevent over- and underfitting (Geman *et al.*, 1992). Here, neural networks were tested with at least one hidden layer. The input nodes of this layer were in the hyperparameter search uniformly sampled in a range of 1–10. The number of hidden dense layers were sampled from a range of 1–3 layers. The hidden dense layer neurons were uniformly sampled in a range of 1–10. Sigmoidal and hyperbolic tangent activation functions were tested in the hidden layers. After each hidden layer a batch normalization layer and a dropout layer with a factor of 0.2 was added. The output activation function was set linear. The used training algorithm was the Adam optimizer (the learning rate was sampled from a log uniform distribution from 0.0001 to 0.01, β_1 was set to 0.9, β_2 to 0.999 and ϵ to 0.999). The Adam optimizer improves backpropagation such that each weight parameter is adapted according to its first and second momentum (Kingma and Ba, 2015). Each neural network was trained using 1,000 epochs with a batch size of 100. The loss function was set to the mean squared error. To prevent overfitting, the training set was further split into train and validation set with 80% train. The validation dataset was then used for early stopping with a patience parameter of 10 epochs. The model with lowest validation error is then used for test set prediction. Due to poor performances, the inner cross-validation was left out for the neural network training sequence. Neural Networks were implemented using the TensorFlow framework (Abadi, 2016).

Gradient boosted trees using the XGBOOST framework

A common problem with neural networks is the high dependency on the provided set of features and potential to learn spurious input-output associations. In this analysis, a feature vector of all 8 frequency bands concatenated for 5 time points requires a Wiener Filter with 40 weights. In an architecture-like neural networks all these features are contributing to the overall force prediction, nevertheless not all weight parameters are promising. Decision Tree algorithms overcome this problem naturally by implementing optimization of input feature use in their architecture. Thus, decision trees and random forests, first described by Breiman, 2001, were proven to be a robust, accurate and successful tool for solving machine learning tasks, including classification, regression, density estimation and manifold learning or semi-supervised learning (Gall and Lempitsky, 2013). Random forests are an ensemble method consisting of many decision trees. A decision tree is a statistical optimal data segregation method, that is only controlled by conditional sequences. Different implementations were proposed on top of Decision Trees. AdaBoost (Schapire, 2009) is an adaptive learning algorithm that builds up successive decision trees iteratively. By that an ensemble of multiple weighted weak learners are combined to yield a strong estimator. Gradient Boosting is built using the same concept. According to Empirical Risk Minimization it fits each decision tree based on the residuals of a defined objective function. This objective function is typically based on an error loss and a regularization term. The model is initialized using a constant value. In an iterative process, the new trees are added to the model up till the maximum defined estimators are reached. Here, the scalable tree boosting framework XGBOOST (Chen and Guestrin, 2016) was used. In this analysis the number of boosting rounds is set to 10. The depth of each tree is sampled uniformly in a range from 1 to 100. When adding new trees to the model the parameter learning rate η is scaling the contribution of each tree prediction and is sampled here log uniformly from of the range $[10^{-5}, 1]$. Regularization in Gradient Boosted Trees is controlled by different factors. One of the factors is the minimum splitting loss γ . For every decision tree, new nodes were added only if the gain metric was above γ . It is here sampled from a uniform distribution between 1 and 10. Hyperparameters for all used machine learning methods are listed in detail in *Supplementary file 1b*.

Source power comodulation

A state-of-the-art movement prediction approach is the source separating framework called Source Power Comodulation (SPoC) (Dähne *et al.*, 2014). Oscillatory sources are here extracted based on their power comodulation with the force gripping target. SPoC was implemented using the MNE framework (Gramfort *et al.*, 2013). Thus, discriminant neural sources are made visible. In this context, the band-power at each frequency band of interest was calculated by taking the logarithm of the variance of the projected signal in the source space. For sake of comparison, only one spatial filter was used for feature computation at each frequency band. In the same manner as before, a Wiener filter was then applied in order to resample time lags up to 500ms. Here again, the band power

features are then used as input features. A Bayesian Optimization hyperparameter search was also here implemented for both the enet model as well as the XGBOOST framework with the aforementioned parameters.

Hyperparameter search: Bayesian optimization

All models underwent an extensive hyperparameter search using Bayesian optimization. A common problem using machine-learning algorithms is finding the optimal hyperparameter settings given a certain architecture. *Grid search* exhaustively tries out all provided hyperparameters while *Random search* only draws random parameters from the given hyperparameter distributions. Sampling the error loss function can be computationally expensive. Bayesian Optimization formulates this problem into an optimization problem. Here, a cost function is minimized given a set of hyperparameters. Instead of sampling from the objective cost function, a probabilistic model is defined. The hyperparameters minimizing the negative expected improvement are selected given a multinomial Gaussian process using a Matern kernel. Those parameters are then used to sample from the respective regressor in the given dataset. The resulting error is used to update the gaussian process distribution and given the maximum expected improvement, the next best hyperparameter set is drawn. This process is repeated for the elastic net, neural networks and XGBOOST architecture for 10 iterations. For every round, a threefold cross validation is used in order to prevent overfitting. Given log-uniform distributions a wide range of hyperparameters can thus be sampled in a computationally efficient manner. The implementation was done using the scikit-optimize framework (<https://scikit-optimize.github.io/stable/>). **Supplementary file 1b** lists the hyperparameters subjected to Bayesian optimization. The chosen methodology is non-exhaustive and primarily serves the comparison of variance in decoding explained by the recording location of the signal (ECoG vs. STN), motor symptom severity (UPDRS-III), beta bursts and brain networks. It further gives an intuition about the potential of more complex and elaborate machine learning methods for brain computer interfaces.

Definition of best model and best channels

Previous studies have repeatedly demonstrated that using a single optimal channel in the STN is advantageous over using all available channels (*Shah et al., 2018*). Most importantly, addition of more channels leads to decreased generalization and higher risk of overfitting with little performance benefit. Based on these results and to account for varying numbers of available electrode contacts, one channel with optimal decoding performance on the cross-validation test set was chosen per patient to quantify and compare decoding performance for the ECoG and STN analysis across patients. Since hyperparameter optimization is implemented only within each inner cross validation fold, any circularity and data leakage is circumvented. A robust decoding performance estimate is thus obtained through left out testing data only.

Analysis of beta bursts during motor preparation and movement execution periods

To investigate a potential relationship between grip-force decoding performance and beta burst activity, we have adopted a previously validated approach to movement related burst analyses (*Torre-cillos et al., 2018; Lofredi et al., 2019*). Therefore, the beta feature time-series were used and a threshold constituting the 75th percentile of the rest periods were calculated. Next, threshold crossings of at least 100ms lengths in the motor preparation (−1–0 s with respect to movement) and movement execution (0–1 s with respect to movement execution) were marked as bursts. In previous reports, the most informative metric was the 'time spent in burst' which is calculated as the sum of burst durations in the time period of interest. This metric is directly proportional to the burst probability at a given time-point. All burst analyses were repeated for the low-beta and high-beta bands in ECoG and STN-LFP. The times spent in bursts were correlated with UPDRS-III and ECoG based decoding performances.

Prediction Network Mapping with whole-brain connectomics

To investigate whether decoding performance from different recording locations can cross-predict decoding performances across patients, we developed a whole-brain connectomics based approach. Therefore, ECoG electrode recording locations were projected to normative structural and functional

MRI data (Parkinson's Progression Markers Initiative [PPMI]; <https://www.ppmi-info.org/>) using Lead-DBS software in Matlab (<https://www.lead-dbs.org/>). (Horn et al., 2019) The PPMI connectomes of patients with PD (n = 74) was priorly computed (Ewert et al., 2018) and has been used in context of DBS multiple times (Horn et al., 2017c; Neumann et al., 2018; de Almeida Marcelino et al., 2019; Lofredi et al., 2021). No patient-specific diffusion or functional MRI was required for this analysis. Seeding from each recording site resulted in connectivity profiles (fingerprints) that were expressed as voxel-wise whole-brain volumes for functional and structural connectivity and a set of streamline connections for structural connectivity. We have adapted three previously published methods leveraging normative connectomes as predictive models.

First, fiber streamlines representative of structural connectivity between ECoG channels and all other brain areas were isolated and assigned with a 'Fiber T-score', associating XGBOOST decoding performance with the fiber tracts connectivity from respective ECoG recording locations across patients using mass-univariate two-sample t-tests between R^2 scores in connected vs. unconnected recording locations. Only fibers with significant t-scores surviving FDR correction at an alpha level 0.05 were considered further. Next, T-values were used as weights in an aggregated fiber score to predict out of training sample channel and patients' performances. Next, functional connectivity maps were used to generate an 'R-Map', a connectivity model which is associated with optimal decoding performance, by performing voxel-wise correlations of connectivity and decoding performance from recording locations. The connectomic fingerprint from each recording location can then be assigned a spatial correlation coefficient that may have predictive value for the underlying decoding performance. The predictive value of these two methods were confirmed using 'leave-one-channel-out' and 'leave-one-subject-out' cross-validation. Finally, statistical parametric mapping was used to confirm the described correlations of structural and functional connectivity using linear-mixed effects models. In a voxel-wise approach, structural connectivity between ECoG channels and all other brain areas was calculated using Lead Mapper (<https://www.lead-dbs.org/>). Statistical voxel-wise correlation between decoding performance and structural and functional connectivity, separate mixed effects models, with a subject based random effect, were corrected for multiple comparisons with random field theory as implemented in the Statistical parametric mapping (SPM12) toolbox (<https://www.fil.ion.ucl.ac.uk/spm/>). Functional connectivity strengths between recording sites and sensorimotor cortex (peak coordinate x = -38, y = -22, z = 72), parietal lobe (x = 6, y = -32, z = 82), striatum (x = -34, y = -24, z = 26) and cerebellum (x = 18, y = -50, z = -50 and x = -22, y = -52, z = -54) accounted for decoding performance. Similarly, for structural connectivity, a significant cluster in the sensorimotor region (x = -44, y = -18, z = 70) correlated with high decoding performance. All connectivity analyses were performed using ECoG recording locations with contralateral R^2 performances (Figure 1E). A schematic illustrating the different steps of functional and structural prediction network mapping can be found in Figure 7—figure supplement 1.

Statistical analysis

Results are stated as mean \pm standard deviation. All significance testing was performed using two-sided Monte-Carlo permutation tests and bootstrapping. p-Values were obtained by shuffling value positions and determining the resulting original rho value percentile in the distribution of surrogate combinations. Spearman's correlations were performed because of small sample size and varying distributions. Clinical correlations were performed using preoperative UPDRS-III total scores. To test for the temporal specificity of the clinical correlation with decoding performance, we performed sample-wise correlations of decoding output with UPDRS-III total scores across subjects. Multiple comparisons were corrected by adjusting the significance threshold α to the false discovery rate (Benjamini and Hochberg, 2016).

Data availability

All raw data in BIDS for iEEG format are openly available through the Harvard Dataverse (<https://doi.org/10.7910/DVN/IO2FLM>). Code and derived source data for the reproduction of all figures and the machine learning and statistical analysis are provided through GitHub (https://github.com/neuromodulation/ECoG_vs_STN; Merk, 2022b; copy archived at [swh:1:rev:09d3ea5b846681d28edb26943b4315ae5f5a37dd](https://www.swh.io/rev/09d3ea5b846681d28edb26943b4315ae5f5a37dd)).

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Timon Merk, Conceptualization, Formal analysis, Funding acquisition, Methodology, Software, Visualization, Writing – original draft, Writing – review and editing; Victoria Peterson, Formal analysis, Methodology, Software, Writing – review and editing; Witold J Lipski, Investigation, Methodology, Writing – review and editing; Benjamin Blankertz, Funding acquisition, Writing – review and editing; Robert S Turner, Funding acquisition, Supervision, Writing – review and editing; Ningfei Li, Software, Writing – review and editing; Andreas Horn, Methodology, Resources, Software, Writing – review and editing; Robert Mark Richardson, Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review and editing; Wolf-Julian Neumann, Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review and editing

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Ethics

Human subjects: The patients were subjected to bilateral STN DBS lead implantation, as proposed by standard clinical indications criteria. In accordance with protocol #PRO13110420, approved by

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Decision letter and Author response

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Additional files

Supplementary files

- Supplementary file 1. Electrode details, Bayesian optimization hyperparameters and best subject performances. (a) Electrode Details (b) Bayesian Optimization Hyperparameters (c) Best channel R^2 performances.
- Transparent reporting form

Data availability

All raw data in BIDS for iEEG format are openly available through the Harvard Dataverse (<https://doi.org/10.7910/DVN/IO2FLM>). Code and derived source data for the reproduction of all figures and the machine learning and statistical analysis are provided through GitHub (https://github.com/neuromodulation/ECoG_vs_STN, copy archived at [swh:1:rev:09d3ea5b846681d28edb26943b4315ae5f5a37dd](https://www.swh.io/rev/09d3ea5b846681d28edb26943b4315ae5f5a37dd)).

The following dataset was generated:

Author(s)	Year	Dataset title	Dataset URL	Database and Identifier
Merk T, Peterson V, Lipski W, Blankertz B, Turner RS, Li N, Horn A, Richardson RM, Neumann WJ	2022	Replication Data for: Electrocorticography is superior to subthalamic local field potentials for movement decoding in Parkinson's disease	https://doi.org/10.7910/DVN/IO2FLM	Harvard Dataverse, 10.7910/DVN/IO2FLM

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Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

Publication list

1. **Merk T**, Peterson V, Lipski WJ, Blankertz B, Turner RS, Li N, Horn A, Richardson RM, Neumann WJ. Electrocorticography is superior to subthalamic local field potentials for movement decoding in Parkinson's disease. *eLife*. 2022 May 27;11:e75126. (Impact Factor 2022: 8.71)
2. **Merk T**, Peterson V, Köhler R, Haufe S, Richardson RM, Neumann WJ. Machine learning based brain signal decoding for intelligent adaptive deep brain stimulation. *Experimental Neurology*. 2022 May 1;351:113993. (Impact Factor 2022: 5.62)
3. Peterson V, **Merk T**, Bush A, Nikulin V, Kühn AA, Neumann WJ, Richardson RM. Movement decoding using spatio-spectral features of cortical and subcortical local field potentials. *Experimental Neurology*. 2023 Jan 1;359:114261. (Impact Factor 2022: 5.62)
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5. Yin Z, Jiang Y, **Merk T**, Neumann WJ, Ma R, An Q, Bai Y, Zhao B, Xu Y, Fan H, Zhang Q, Qin G, Zhang N, Ma J, Zhang H, Liu H, Shi L, Yang A, Meng F, Zhu G, Zhang J. Pallidal activities during sleep and sleep decoding in dystonia, Huntington's, and Parkinson's disease. *Neurobiology of Disease*. 2023 May 3;106143. (Impact Factor 2022: 7.04)
6. Koutris A, Siozos T, Kopsinis Y, Pikrakis A, **Merk T**, Mahlig M, Papaharalabos S, Karlsson P. Deep Learning-Based Indoor Localization Using Multi-View BLE Signal. *Sensors*. 2022 Jan;22(7):2759. (Impact Factor 2022: 3.85)
7. Babakhani P, **Merk T**, Mahlig M, Sarris I, Kalogiros D, Karlsson P. Bluetooth Direction Finding using Recurrent Neural Network. In: 2021 International Conference on Indoor Positioning and Indoor Navigation (IPIN). 2021. p. 1–7. (Impact Factor 2021: 1.2)

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