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Canonical Correlation to Estimate the Degree of Parkinsonism from Local Field Potential and Electroencephalographic Signals

Teresa H. Sanders¹, Annaelle Devergnas^{2,3}, Thomas Wichmann^{2,3,4}, and Mark A. Clements¹

¹Georgia Institute of Technology, Atlanta, GA

²Yerkes National Primate Research Center

³Udall Center of Excellence in Parkinsons Diseases Research

⁴Dept. Neurology, School of Medicine, Emory University, Atlanta, GA

Abstract

In this study, modulation index (MI) features derived from local field potential (LFP) recordings in the subthalamic nucleus (STN) and electroencephalographic recordings (EEGs) from the primary motor cortex are shown to correlate with both the overall motor impairment and motor subscores in a monkey model of parkinsonism. The MI features used are measures of phase-amplitude cross frequency coupling (CFC) between frequency sub-bands. We used complex wavelet transforms to extract six spectral sub-bands within the 3–60 Hz range from LFP and EEG signals. Using the method of canonical correlation, we show that weighted combinations of the MI features in LFP or EEG signals correlate significantly with individual and composite scores on a scale for parkinsonian disability.

I. Introduction

Deep brain stimulation (DBS) is a highly effective treatment for parkinsonism that involves the implantation of an electrode into specific brain regions (often the subthalamic nucleus (STN)). The electrode is used to apply small-amplitude electrical pulses produced by an implanted battery-driven impulse generator. Typically, DBS therapy is continuously administered, without regard for the presence or absence of parkinsonian signs or symptoms. The recent realization that the implanted DBS electrodes can also be used to record local field potentials (LFPs) [1] in humans has led to interest in pursuing approaches to modulate DBS based on measurements of brain activity [2]. Use of such closed-loop DBS approaches could lead to significant savings in battery power of the implanted pulse generator devices, as they could potentially be switched off or run with reduced duty cycles for periods of less severe parkinsonism. One potential brain signal that could (in principal) be used for feedback would be LFPs recorded from the site of DBS (for instance, the STN). While generally promising, the use of such LFPs would obviously be complicated during stimulation, because of the presence of strong electrical stimulation artifacts. Other brain signals that could be used in closed-loop DBS approaches are encephalographic recordings (EEGs). In fact, we have shown previously that phase-amplitude cross-frequency-coupling measures from EEGs recorded in the primary motor cortex (M1) correlate with the overall degree of parkinsonism in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model

of primate parkinsonism [3]. Other recent studies have shown that EEG phase-amplitude coupling measures return to more normal patterns during and shortly after therapeutic STN DBS treatments in human parkinsonian patients [4]. As an extension of our previous work, this study examines the accuracy with which the severity of parkinsonism can be estimated from STN-LFPs and M1 EEGs.

II. Methods

A. General methods

We recorded EEG and STN-LFP signals in two MPTP-treated monkeys while they transitioned from the normal to a moderately parkinsonian state. From the recorded signals, we calculated modulation indices (MIs) [5–8] which are measures of phase-amplitude cross frequency coupling (CFC) between frequency sub-bands within EEGs or LFPs. Using canonical correlation [9], we maximized the correlation between these features and the parkinsonism rating scores (a validated measure of the severity of parkinsonism), and identified the EEG and LFP features that correlated most strongly with the parkinsonism scores. The canonical correlation weightings were then used to create parkinsonism rating estimates from the LFP and EEG features. Finally, the normalized root mean square differences between the estimates and the observation-based ratings of the severity of parkinsonism were calculated.

B. Animals, surgical procedures

Two rhesus monkeys (*Macaca mulatta*, 6–10 kg) were used for this electrophysiological experiment. The animals were housed in pairs, with ad libitum access to food and water. All experiments were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the United States Public Health Service policy on the humane care and use of laboratory animals. All studies were approved by the Institutional Animal Care and Use Committee of Emory University. After initial behavioral conditioning, the animals were surgically prepared for chronic recordings, by affixing standard metal recording chambers to their skull with dental acrylic that gave us access to the left STN, using a sagittal approach (36 from the vertical). Head fixation bolts were also embedded into the acrylic. In addition, we implanted multiple epidural EEG electrodes over M1 and the supplementary motor area in both hemispheres. For the purpose of this report, we focus on signals that were subsequently recorded from the left M1.

C. MPTP treatment

After completion of the recordings in the normal (baseline) state (see following section), the animals were rendered progressively parkinsonian through weekly administration of MPTP (0.3–0.6mg/kg im). Monkey 1 received 21 injections (9.4mg/kg total), Monkey 2 received 26 injections (10.2mg/kg total) before developing stable motor signs of parkinsonism. To assess the degree and stability of the MPTP induced motor disability, one of the investigators (AD) carried out a 15 minute observation of the animals behavior every week, preceding that week's MPTP injection, so as to maximize the time from the injection done in the previous week. During this observation, motor impairment was scored (rating bradykinesia, freezing, extremity posture, frequency of arm movements, and finger dexterity) as well as trunk

posture, home cage activity, and balance. Composite scores were formed from the individual impairment scores and ranged from 0 (baseline) to 16 (moderate parkinsonism).

D. Recordings and arousal scoring

Prior to the MPTP injections, LFP and EEG baseline signals were recorded on 2 consecutive days for Monkey 1 and on 8 days for Monkey 2. During the MPTP-treatment period, LFPs and EEGs were recorded once weekly, on the same day as, or the day after the behavioral assessments mentioned above. The dorsal sensorimotor portion of the STN was targeted for LFP recordings [10]. LFPs were recorded with bipolar electrodes (SNEX-100, Rhodes Medical Instruments Inc, CA). M1 EEGs were recorded as bipolar signals using the epidural electrodes over the left M1. EEGs, LFPs, and video images of the animals face were recorded simultaneously for all sessions. The EEGs and LFPs were amplified, bandpass filtered (0.3–1000Hz), sampled at 1000Hz and stored on a hard drive using a data acquisition interface (Power 1902 and 1401; CED, Cambridge, UK) and commercial software (Spike2, CED) for later down-sampling and off-line analysis. Because the state of arousal strongly influences the spectral content of EEGs and STN-LFPs, the animals state of arousal during recording was scored offline using the Spike2 sleepscore script (www.ced.co.uk; 10s epochs). Each epoch was labeled as representing wakefulness, drowsiness or light sleep, based on EEG features and the face videos. Only epochs scored as wakefulness were used. Wakefulness was defined as a period of time during which the monkey was attentive to its environment, with eyes open and showing low-amplitude mixed-frequency EEG.

E. Complex continuous wavelet transform

All algorithms for the subsequent data analysis steps were implemented in a combination of Matlab (Mathworks, Natick, MA) scripts and C++. We used wavelet methods to decompose the LFP and EEG signals. Wavelet methods are appropriate for this type of analysis, because wavelet bases allow representation of signals that vary in both frequency and duration. For this study, we chose to use the complex continuous wavelet transform in order to facilitate extraction of accurate phase information. First, the LFP and EEG signals for each 10s epoch were z-scored (standard scored), using the mean and standard deviation of the same epoch. The z-scored data was then downsampled by a factor of 4 prior to computing the complex Morlet wavelet transform (CWT) coefficients, $X_w(c, n)$,

$$X_w(c, n) = \frac{1}{\sqrt{c}} \int_{-\infty}^{\infty} x(t) \psi^* \left(\frac{t-n}{c} \right) dt$$

where “c” represents the scale factors and “n” represents the time points at which the CWT coefficients are evaluated. For this study, $c = 1:512$, $n = 1:2500$, and ψ is the complex Morlet wavelet.

Previous studies have documented parkinsonism-related changes in theta-, beta- and gamma-bands in LFP and EEG signals [1, 2, 4, 11–13]. In order to capture effects in these and neighboring bands, composite signals were created by pooling the wavelet coefficients

corresponding to each of the following wavebands: delta (3–4Hz), theta (5–7 Hz), alpha (8–11 Hz), low beta (12–19 Hz), high beta (20–30 Hz), and gamma (31–60 Hz).

F. Cross frequency coupling and modulation index

Cross frequency coupling (CFC) is defined as the interaction between oscillations in multiple frequency bands and can include phase-amplitude, phase-phase, or amplitude-amplitude coupling. Phase-amplitude coupling analysis has uncovered features of interest in several recent studies, particularly event-related theta band phase modulation of gamma band amplitudes [7], and beta band phase modulation of both narrowband gamma band oscillations in STN and broadband gamma band oscillations in M1 [4]. For this work, phase-amplitude coupling was calculated by averaging the amplitude in the modulated frequency band corresponding to phase values for the modulating frequency band. We used phase values from $0-2\pi$, divided into 18 equal width phase bins. Note that, since our correlation analysis method weights the CFC features to optimize the overall correlation with increasing parkinsonism, any increased (decreased) CFC feature magnitudes due to larger (smaller) frequency band widths did not impact the overall results. In order to facilitate comparisons of phase-frequency coupling over time, various measures have been developed. We used the MI calculation proposed by Tort [8] based on the Kullback-Leibler divergence between two distributions:

$$D_{KL}(P||Q) = \sum_i \ln \left(\frac{P(i)}{Q(i)} \right) P(i).$$

where $P(i)$ indicates the uniform distribution that occurs when the amplitudes are distributed randomly across all phases, and $Q(i)$ indicates the distribution obtained by normalizing the phase-amplitude coupling calculated as described above. The two-sided divergence was used, i.e., $D_{KL}(P||Q) + D_{KL}(Q||P)$, in order to give a symmetric measure of the deviation from the uniform distribution. This measure is more indicative of true sinusoidal modulation than other methods, such as height differences, which only measure the distance between two points on the distribution (usually the minimum and maximum).

MI's were calculated for each 10s epoch. Next, the MI's were averaged across all epochs within a file. These average MI's from each file were used to correlate with the motor scores as described in the next section.

G. Canonical correlation

The goal of canonical correlation is to choose a set of weights $\mathbf{a}$ and $\mathbf{b}$ that maximize the correlation between samples from two vectors of random variables, $\mathbf{X}$ (e.g., MI features) and $\mathbf{Y}$ (e.g., motor scores).

The function to be maximized can be written:

$$\rho = \frac{\mathbf{a}' \sum_{XY} \mathbf{b}}{\sqrt{\mathbf{a}' \sum_{XX} \mathbf{a} \mathbf{b}' \sum_{YY} \mathbf{b}}}. \quad (1)$$

where Σ_{XX} , Σ_{YY} are the covariance matrices for X and Y respectively, and Σ_{XY} is the covariance matrix between X and Y .

Observing that the solution is not affected by scaling, the optimization problem can be solved by maximizing the numerator in (1) subject to:

$$a' \sum_{x \in X} a = 1 \quad (2)$$

$$b' \sum_{y \in Y} b = 1 \quad (3)$$

The maximization problem can be solved in multiple ways with the most common approaches using either singular value decomposition alone [14] or in combination with QR factorization (decomposition of a matrix A into a product $A=QR$ of an orthogonal matrix Q and an upper triangular matrix R), as done in this study.

III. Results

Our analysis included 5373 10s epochs of data recorded on 13 days over the 6 months during which Monkey 1 progressed from the baseline (normal) state to a state of moderate parkinsonism. For Monkey 2, the analysis included 5779 10s epochs recorded over a similar progression from baseline to moderate parkinsonism.

For each monkey, the weightings that resulted in maximum correlation between the motor scores and the modulation indices were calculated. For both monkeys, the weighted combination of LFP modulation indices correlated well with the composite motor score ($p < 0.0001$), as well as subscores for balance and bradykinesia ($p < 0.01$), and freezing ($p < 0.001$). Figure 1 shows the weighted motor scores and LFP MIs for Monkey 1 for each recording file. Figure 2 shows the relationship between the weighted sum of the MIs and the balance motor scores for Monkey 2. The weighted combination of EEG MIs also correlated well with the composite motor scores ($p < 0.001$) and subscores ($p < 0.01$). For both monkeys, the optimally weighted canonical correlation between the EEG MIs and the composite motor scores were similar to those between the LFP MIs and the composite motor scores, (for Monkey 1, 0.9428 and 0.9205, respectively; for Monkey 2, 0.9000 and 0.9185, respectively). The EEG MIs and the LFP MIs were also highly correlated with each other (optimally weighted canonical correlation of 1.0 for Monkey 1 and 0.9856 for Monkey 2, $p < 0.0001$). Note that the raw STN-LFPs and EEGs are different from each other in appearance and uncorrelated (cross correlation coefficients < 0.05).

While modulation indices from particular frequency bands did not appear to be associated with individual motor component scores, there were several frequency bands that correlated well with multiple motor scores, and many frequency bands that interacted with each other to form the most highly weighted modulation indices. In particular, two LFP (phase/amplitude) modulation indices, (12–19 Hz/12–19 Hz) and (8–11 Hz/12–19 Hz), yielded statistically significant correlation with both composite motor scores and subscores.

Table 1 summarizes the accuracy of the motor score estimates calculated using the LFP and EEG MIs as compared to the motor scores. The comparison includes both the full LFP MI estimates as well as the estimates obtained using the subset of two statistically significant LFP MIs mentioned previously. The entries in the table are $1 - \text{NRMSE}$ (normalized root mean square error):

$$1 - \frac{\sqrt{\frac{\sum (\text{estimated score}(i) - \text{actual score}(i))^2}{n}}}{(\text{max score} - \text{min score})}$$

The asterisks indicate the statistical significance of the canonical correlation underlying each estimate.

IV. Discussion and conclusions

We have shown that canonical correlation methods can be used to estimate parkinsonian motor scores from STN-LFP and M1 EEG MIs. This finding provides further support that parkinsonism is associated with changes in cross-frequency coupling patterns that can be detected both in cortex and in associated basal ganglia areas. The high correlation between the MI features from simultaneous STN-LFPs and M1 EEGs, and the ability to estimate parkinsonism motor scores and subscores using weighted MI features from STN-LFP and EEG signals, are new findings. These results suggest that EEG signals could be used for the detection of the severity of parkinsonism, and possibly as control signals for on-demand DBS [2, 13]. As stated above, the advantage of using EEG measurements rather than the more frequently considered LFPs from the DBS electrodes is that EEG signals are less prone to show stimulation artifacts so that monitoring of parkinsonism may be accomplished not only when the DBS pulse generator is off, but also during stimulation.

It is a limitation of the current analysis that the parkinsonism estimate is based on the full data set and that we achieved our results by studying relatively long data segments (multiple 10s epochs of data within each recording file). Predicting parkinsonism in a test set using weights calculated from a training set, and examining whether shorter epochs suffice to predict the degree of parkinsonism will be of interest in future studies.

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Fig. 1. Comparison between measured composite motor scores (dashed line) and motor scores estimated from the sum of the optimally weighted LFP MIs (solid line) for Monkey 1.

Fig. 2. Distributions of the sum of the optimally weighted LFP MIs (composite modulation index) for each of the measured balance motor scores (x-axis) for Monkey 2. For each box, the central mark is the median, while the edges of the box are the 25th and 75th percentile.

TABLE I

Accuracy of Motor Scores Estimated using Weighted Modulation Indices.

Motor Score Type	Monkey 1				Monkey 2			
	All STN LFP MIs	All EEG MIs	2 LFP MIs: (12–19 Hz/12–19 Hz) and (8–11 Hz/12–19 Hz)		All STN LFP MIs	All EEG MIs	2 LFP MIs: (12–19 Hz/12–19 Hz) and (8–11 Hz/12–19 Hz)	
Composite	0.89 ****	0.92 ****	0.77 ****		0.87 ****	0.86 ****	0.87 ***	
Subscores:								
Balance	0.86 **	0.90 ****	0.72 *		0.88 ****	0.85 ****	0.87 ****	
Freezing	0.88 ****	0.91 ****	0.75 **		0.89 ****	0.84 **	0.87 ****	
Bradykinesia	0.89 ****	0.90 ****	0.80 ****		0.86 **	0.86 **	0.86 *	
Home Cage Activity	0.91 ****	0.90 ****	0.79 ****		0.84 ^{ns}	0.85 *	0.82 *	

*p < .05,

**p < .01,

***p < .001,

****p < .0001