Title

Elevated synchrony in Parkinson disease detected with electroencephalography

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Elevated Synchrony in Parkinson's Disease Detected with Electroencephalography

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Abstract

Objective—Parkinson's disease (PD) can be difficult to diagnose and treat. Development of a biomarker for PD would reduce these challenges by providing an objective measure of disease. Emerging theories suggest PD is characterized by excessive synchronization in the beta frequency band (~20 Hz) throughout basal ganglia-thalamo-cortical loops. Recently we showed with invasive electrocorticography (ECoG) that one robust measure of this synchronization is the coupling of beta phase to broadband gamma amplitude (i.e. phase amplitude coupling, PAC). Other recent work suggests that high frequency activity is detectable at the scalp using electroencephalography (EEG). Motivated by these findings, we tested whether beta-gamma PAC over sensorimotor cortex, recorded non-invasively with EEG, differs between PD patients Off and On medications, and healthy Control subjects.

Methods—Resting EEG was compared from 15 PD patients and 16 healthy control subjects. PD patients were tested On and Off medications on different days, in a counterbalanced order. For each dataset we calculated PAC and compared results across groups.

Results—PAC was elevated in the patients Off medications compared to On medications (p=0.008) and for patients Off medications compared to Controls (p=0.009).

Interpretation—Elevated PAC is detectable using scalp EEG in PD patients Off medications compared to On, and compared to healthy Controls. This suggests that EEG PAC may provide a non-invasive biomarker of the Parkinsonian state. This biomarker could be used as a control signal

for closed-loop control of deep brain stimulation devices, for adjustment of dopaminergic treatment, and also has the potential to aid in diagnosis.

Introduction

In Parkinson's disease (PD), one of the primary circuit abnormalities induced by striatal dopamine denervation is excessive synchronization of spike discharge to the dominant motor beta rhythm. This has been detected in humans from invasive recordings in patients undergoing or immediately following deep brain stimulation (DBS) implantation surgery. Manifestations of this excessive synchronization include oscillatory activity in basal ganglia single unit discharges[1-3], synchronization of basal ganglia spiking to local field potentials[4, 5], and more recently, exaggerated phase-amplitude coupling (PAC) detected by invasive subdural electrocorticography (ECoG) recordings[6, 7].

The excessive PAC in PD occurred preferentially between beta phase and broadband gamma amplitude. Broadband gamma amplitude is thought to reflect the spiking of populations of neurons, and is considered a surrogate for local neural activity[8-10]. Thus, elevated PAC is thought to reflect modulation of spiking activity by low frequency rhythms[11]. While PAC is a dynamic feature of healthy brain activity, responsive to changes in cognition and behavior[12], it may be elevated in cases of excessive synchrony, as in PD[6, 7]. In this report, we sought to test whether the excessive PAC previously observed in PD using ECoG is detectable using a non-invasive method: scalp electroencephalography (EEG). While traditional EEG analyses have focused on lower frequencies, recent work suggests it may be possible to detect higher frequency activity[13, 14]. Such a non-invasive method offers the advantage of being able to test healthy control subjects for comparison and circumvents potential confounds introduced by the intraoperative setting, effects of anesthesia, or residual effects associated with recent surgery. We tested PAC differences in EEG by comparing resting EEG data in PD patients on and off dopaminergic medications and relative to age-matched healthy control subjects.

Making a diagnosis of PD can be complex and is not always correct[15, 16]. Moreover, calibrating treatment (i.e. medication dosages and/or DBS settings) remains a challenge. Therefore there is an urgent need to develop an objective biomarker for PD. Here we present a putative biomarker for the hypersynchrony associated with PD that can be detected non-invasively via scalp EEG. Such a biomarker has the potential to be useful for closed-loop control of deep brain stimulator devices[17]. Additionally, scalp EEG metrics of altered neuronal synchronization in PD could be potentially recorded in the home environment and digitally sent to the treating physician, permitting objective manipulation of dopaminergic treatment regimens.

Methods

Participants

We re-analyzed data that were collected for a published study[18]. The data set consisted of EEG data from 15 PD patients (8 female, average age 63.2 years±8.2 years) on and off dopaminergic medications and 16 control subjects (9 female, average age 63.5±9.6 years).

All patients were being treated for Parkinson's disease by a movement disorders neurologist at Scripps clinic in La Jolla, CA. They all had mild to moderate disease (Hoehn Yahr 2 or 3) and an average disease duration of 4.5±3.5 years. Patients were well-matched to controls with respect to age, gender, and cognition (as measured by Mini-Mental State Exam (MMSE) and North American Adult Reading Test (NAART)). All participants were right-handed and provided written informed consent in accordance with the internal review board of the University of California, San Diego and the Declaration of Helsinki. See George et al. (2013)[18] for additional patient characteristics.

Procedure

Patients were tested both On and Off medications on separate days with the order of each day counter-balanced. For Off medications recordings no medications were taken for at least 12 hours prior to the visit. For the On medications recordings the normal medication schedule for each patient was maintained. Controls were tested once, using the same protocol. In addition to the rest recordings analyzed here, participants completed a number of clinical scales and another behavioral task, reported in George et al (2013)[18].

EEG recordings

During recordings, participants were seated comfortably, and told to relax with their eyes open while fixating on a cross presented on a computer screen. EEG data were collected for approximately 3 minutes using a 32-channel Biosemi ActiveTwo EEG system with a 512 Hz sampling rate. Eye blinks and movements were monitored with extra electrodes placed lateral to and below the left eye to monitor electro-oculogram. Electromyogram (EMG) was also recorded from the right first dorsal interosseous (FDI) muscle and analyzed for a control comparison of EMG PAC to EEG PAC as described below.

Preprocessing

EEG data were analyzed in Matlab using a combination of custom Matlab scripts and EEGLAB[19]. First, the mean of each channel was removed and then all data were re-referenced to the common average (excluding any channels with obvious noise). A high pass filter at 0.5 Hz was then used to remove the low frequency component of the signal (using a two-way FIR filter, eegfilt[19]). The data were then manually inspected for periods of artifact, which were marked for exclusion.

Finally, because we were especially concerned about the possibility of muscle activity contaminating the EEG signal, we re-referenced all the EEG data using a current-source density (CSD) procedure (CSDtoolbox, using a spherical spline with medium flexibility (m=3) [20-22]). CSD approaches allow increased isolation of the local electrophysiological signal. We also ran the same analyses using a common average reference and obtained similar results (described below).

Signal Processing

For our main analysis we focused on the two channels closest to M1 (C3 and C4). All analyses were performed on these two electrodes separately and then results were averaged.

The power spectral density (PSD) was computed on the longest artifact-free period of data using the Welch method (pwelch function in Matlab, 256 ms window, with 128 ms of overlap). PSD values were then normalized by subtracting the average log PSDs from 3-150 Hz, (excluding 60 Hz and harmonics) from the log PSDs of each frequency.

PAC was calculated using the Kullback-Leibler (KL)-based modulation index method, which has been previously described[6, 23]. In brief, the EEG signal from each channel was filtered separately to extract phase and amplitude at specified frequencies, using a two-way FIR1 filter (eegfilt.m with fir1 parameters[19]). To extract phase we filtered all frequencies ranging from 4-50 Hz (with a 2 Hz bandwidth) individually, and extracted the phase from this signal using a Hilbert transform. Similarly, for the amplitude component of the signal we filtered all frequencies ranging from 4-200 Hz (with a 4 Hz bandwidth) and extracted the amplitude from the filtered signal using a Hilbert transform. For each frequency pair, the distribution of the instantaneous amplitude envelope was computed for every 20° interval of the instantaneous phase, creating 18 phase bins. The mean amplitude for each bin was then normalized by the sum of the mean amplitudes for all bins, creating a distribution similar to a probability distribution. This was then compared to a uniform distribution using a Kullback-Leibler distance measure to derived the coupling ("modulation index (MI)")[23]. These steps are illustrated in Figure 1. The MIs for each frequency pair can then be displayed as a comodulogram (see Figure 2). For PAC calculations, the whole data file was analyzed, except segments containing artifacts. Periods with artifacts were extracted following filtering to avoid filtering artifacts due to sharp edges. There was no significant difference in the length of data included in the final analysis between groups (p>0.4). We also examined the preferred phase at which the coupling occurred (i.e. the phase of beta where the maximum broadband gamma modulation occurred). This is important because if the preferred phase occurred at the peak or the trough of the beta phase, this would be consistent with the presence of a 'sharp edge' in the signal, and could be an indication of spurious PAC[24].

Group statistics were performed to compare PD patients On and Off medications and patients Off medications to control subjects. A nonparametric Wilcoxon signed-rank (paired) test was used for the On versus Off medications comparison and a nonparametric Wilcoxon rank-sum (unpaired) test was used for the comparison of patients Off medications to Controls. Both tests were two-tailed. A PAC value was derived for each subject by averaging the comodulograms from the two electrodes closest to left and right M1 (C3 and C4) and averaging MI values over the beta range (13-30 Hz), for the phase frequency, and the broadband gamma range (50-150 Hz), for the amplitude frequency, for each subject individually. The exact frequency ranges selected were based on previous ECoG work[6]. Note that for ECoG, phase-coupled broadband power extended up to 200 Hz, but we choose to focus on activations below 150 Hz, due to the reduced signal amplitude for high frequencies in EEG[25], and the lower sampling rate in these data. Power analyses focused on the same ranges.

We also performed a parallel analysis of group differences in PAC after converting each subject's MI values to a z-score rather than comparing raw MI values across subjects. The z-score calculation was done by shifting the phase signal compared to the amplitude signal by

a random value, calculating the PAC, and then repeating with another random value 200 times to generate a surrogate distribution. This procedure should remove some forms of spurious coupling (i.e. those with a very consistent periodic profile, from electrical artifact, for instance). Results obtained with this approach were comparable to those using the raw MI values; therefore presented data use the raw MI values.

In the results below, for completeness, we report the statistical findings from our two control analyses: using a common average referencing scheme (rather than a CSD montage), and after converting each subject's MI values to a z-score. However, all figures are derived from our main analysis, using the CSD referencing scheme and the raw MI values. Additionally, the PSD analysis also used the CSD reference.

Controlling for Muscle Artifact

EMG contamination of the EEG signal can create sharp edges, which can result in non-neural coupling[24, 26]. To determine if EMG contamination corrupted our results, we analyzed EMG recorded from right FDI as an example of pure muscle activity. We used the FDI because this allowed us to examine EMG alone, without an EEG contribution. We re-referenced the EMG as a bipolar reference and ran all the same analyses for PAC described above. Importantly, because PAC driven by sharp edges can be characterized by increased coupling at the harmonics of the phase frequency, we extended the phase frequency range up to 150 Hz. To account for the possibility that EMG in the FDI is dissimilar from the EMG most likely to influence sensorimotor areas (i.e. EMG of facial muses, such as the temporalis) we also ran (using a CSD reference) the same analysis as we performed for the sensorimotor electrodes, for the electrodes closest to the temporalis muscle (F7 and F8). Again, we extended the phase frequency range up to 150 Hz for this analysis so that results would be comparable to the FDI analysis.

As an additional check for the possibility that EMG contamination may be driving group differences in PAC, we examined the topography of the PAC difference in EEG by computing the PAC for all EEG channels (using the CSD referencing scheme and raw MI values) and plotting the topography (topoplot, EEGLAB[19]) associated with the key group comparisons (patients Off compared to On medications and patients Off medications compared to Controls).

Results

Group Results

PAC—We found that PAC in PD patients was higher Off medications compared to On (p=0.008, two-tailed, paired, nonparametric, Wilcoxon signed rank test, See **Figure 2**), with 14 of the 15 patients showing the effect. This suggests that PAC may be a reliable, clinically useful, marker of medication state. This result was also significant if a common average reference was used instead of the CSD reference (p=0.007), or if individual subject results were first converted to a z-score prior to group statistics (p=0.005). PAC was also significantly higher in patients Off medications compared to healthy control subjects (p=0.009, two-tailed, unpaired, nonparametric, Wilcoxon rank sum test **Figure 2**). However,

this result was at the trend level if a common average reference scheme was used (p=0.055) or if individual subject results were first converted to a z-score (p=0.079). There was no significant difference between patients On medications and healthy controls (p=0.77). The preferred phase of the PAC was not at the peak or the trough of the beta phase for any group, using either the common average reference or the CSD reference. (It was most often ~70 degrees using the common average method.)

Spectral Power

We found no difference in beta power (13-30 Hz) for any comparison (p > 0.18, **Figure 3A-B**). This is consistent with previous work, using either EEG, MEG, or ECoG, which has not shown a consistent alteration of cortical beta power in PD[6, 18, 27-29]. Similarly, there were no differences in broadband gamma power (50-150 Hz, excluding 60 and 120 Hz) (p > 0.16, **Figure 3C-D**). A previous ECoG study has shown a relative elevation of broadband gamma in PD patients compared to other movement disorders[30]. In the present analysis the group differences in broadband gamma power were in this direction, but the results were not significant.

EMG

To address the concern that EMG may have contributed to the PAC difference we analyzed PAC in the FDI EMG, as an example of 'pure EMG', as well as the electrodes closest to temporalis muscle, which presumably have both EMG and EEG contributions.

Compared to sensorimotor EEG analyzed in the same way (**Figure 4A**), the FDI EMG comodulograms were characterized by strong coupling between broadband gamma to phase frequencies extending all the way down to the lowest frequency examined (4 Hz), and by strong harmonics in the coupling at many phase frequencies (**Figure 4E**). There also was no significant difference between groups in PAC recorded from the EMG (p > 0.09, **Figure 4F and G**, and in fact, there was a trend for higher EMG PAC On medications than Off, the opposite direction of the sensorimotor EEG results.)

We expect that the EEG over temporalis muscles contains both EMG and EEG contributions, and, consistent with this, the comodulograms have features similar to both sensorimotor EEG and FDI EMG (**Figure 4B-D**). However, there is no difference between the groups in these electrodes (p>0.59).

Topography

To help qualitatively characterize the PAC activity (and to reduce the possibility of an EMG contribution to our results), we plotted the topography from all channels for the key significant comparisons (patients On versus Off medications, and healthy Controls versus patients Off medications). If EMG signals were driving the PAC differences, we would expect the differences to be strongest over large muscle groups (i.e. nearest to frontalis and temporalis muscles), and not to have a topography consistent with a sensorimotor origin, as observed (**Figure 5**).

Single subject reliability of PAC as a diagnostic test

While PAC differences are apparent between patient groups (**Figure 2B**), we also assessed the potential sensitivity and specificity of EEG PAC as a diagnostic test in individual subjects. We derived a Receiver Operator Curve[31] (Stata software) for the comparison of patients Off medications to Control subjects (excluding one outlier from the control group, **Figure 2B**.) The area under the curve for this analysis was 0.83, suggesting some potential for diagnostic utility. To explore this possibility with a different approach, we calculated the effect size required (given the power of the comparison between patient's Off medications compared to controls in the present data, with one outlier excluded, and assuming a normal distribution in the population) to differentiate a single PD patient Off medications from the control subjects (calculated using G*Power software[32]). This comparison showed an effect size of 2.67 (Cohen's D) corresponding to a required MI value of 0.000829. Three out of 15 of the PD patients Off medications in this study surpassed this measure. This analysis indicates that the elevation in the EEG PAC signal in the PD patients compared to healthy controls in the current study is not demonstrable on a single subject basis, but only at the group level.

Discussion

We sought to develop a noninvasive measure of excessive neural synchronization in PD. Based on the finding from invasive ECoG recordings that beta-broadband gamma PAC in M1 is elevated in PD patients off medications[6], and recent work which suggests detection of high frequency activity by EEG may be possible[13, 14], we tested whether PAC from scalp EEG electrodes over M1 is also elevated in PD. In a group of 15 mild to moderate PD patients and 16 age-matched control subjects we found that M1 PAC is elevated in PD patients Off medications compared to On medications and compared to healthy Control subjects. Notably, 14 of 15 PD patients showed the pattern, highlighting the potential clinical utility of the method. Differences between groups were not detectable by spectral power in beta or gamma frequency bands.

Electrophysiological markers of PD

One consistent electrophysiologic abnormality in the motor system in PD is spike synchronization to beta phase[4, 5, 33]. In the cortex, this is manifest by excessive PAC in comparison to non-Parkinsonian disorders. This phenomenon was previously detected only using invasive subdural recordings[6, 7]. Here, we provide evidence that altered cortical PAC is a marker for the Parkinsonian state, using a *noninvasive* method, and show for the first time that this metric is reduced by anti-Parkinsonian medications within the same patients.

Another potential EEG biomarker for the excessive synchronization in the Parkinsonism state has been previously described: distributed EEG coherence in the beta range (~10-35 Hz)[34]. In that study, coherence was measured between all EEG contact pairs in PD patients and was found to be reduced with medications and DBS. That reduction with medications was replicated with the same dataset reported here, in a previous publication[18].

We suspect that the PAC detected here and the distributed coherence detected previously[18, 34] are related to the same underlying physiological process, namely, excessive beta synchronization and neural entrainment within and across structures in the motor network. While each method is sensitive to specific kinds of synchronization, in this context, the two methods may be detecting the same underlying process. The use of PAC, rather than distributed coherence, as a biomarker has the potential advantage of requiring fewer electrode contacts (here our main PAC results focused on the two electrodes closest to M1, rather than requiring electrodes distributed across the cortex), and being able to differentiate PD patients off medications from healthy control subjects, which, to our knowledge, has not been shown with distributed EEG coherence. Since PAC is different between unmedicated patients and controls, it suggests that PAC, perhaps in combination with other measures, could have clinical diagnostic utility.

In our data set, differences in PAC between PD patients and normal controls were significant, but not large enough to distinguish PD patients on an individual subject basis. Therefore, further refinements in recording or signal processing techniques are needed to be able to utilize this technique diagnostically. PAC is a dynamic process that changes with behavior and cognition[7, 35]. Therefore, it is possible that the short recordings utilized in this study may not have captured each patient's most representative PAC levels. A longer recording session, or measuring PAC at multiple visits, might improve sensitivity and signal stability at the individual level. Additionally defining PAC in a larger sample of control subjects would likely increase sensitivity, since the expected MI distribution would be better characterized.[32]

A noninvasive marker of the Parkinsonian state

While EEG has limitations compared to other methods like ECoG in terms of spatial resolution and signal to noise ratio it has an obvious advantage of being non-invasive, allowing both easy measurement in patients, even in the home, as well as comparisons to healthy populations.

The EEG PAC metric could be used to calibrate optimal medication dosages or medication frequency for a given patient. Scalp EEG metrics reflecting altered basal ganglia tone could be potentially recorded in the home environment and digitally sent to the treating physician permitting objective manipulation of dopaminergic treatment regimens. This approach parallels home monitoring for cardiac rhythm disorders or adjustment of medications for diabetes. Additionally, a recent ECoG study showed that therapeutic DBS acutely reduces cortical PAC[7], suggesting that this marker could also be used for physiology-based optimization of DBS settings in the clinic, or even to allow continuous device adjustment in real-time based on cortical activity, using a scalp contact for feedback control in closed-loop DBS. Other strategies for closed loop DBS using invasive subcortical signals have recently been described [17], but the use of EEG PAC has the advantage of utilizing a control signal recorded noninvasively.

Alternative interpretations

Here, we interpret increased beta phase-broadband amplitude coupling to be a manifestation of the synchronization of population spiking to the beta rhythm. However, other interpretations are possible. For instance, periodic sharp edges, either artifactual or physiological, will also produce high PAC values[24, 26]. One plausible physiological generator of PAC, which does not necessarily relate to changes in the relationship between spiking and ongoing rhythms, is a change in the shape of an oscillation such that the peak or trough becomes more 'spikey'[24]. These sources of PAC will sometimes remain even after a surrogate (statistical) correction. Thus, even though we conducted a test where we first converted each subject's PAC to a z-score, and obtained similar results, we cannot be sure that this removed all spurious coupling. However, that the preferred phase of coupling did not occur at the peak or the trough of the beta rhythm (as would be expected for a 'pure' sharp edge) argues against this interpretation.

The PAC signal could also represent contamination by EMG. Indeed, we have shown by analyzing both 'pure' EMG recorded from the FDI muscle and also the EEG electrodes over temporalis muscles that both recordings do show PAC, although the 'pure' EMG does appear to have a somewhat different frequency range. Nevertheless, based on the topography of the results, and the notable absence of group differences from the electrodes closest to the temporalis muscle, a more parsimonious explanation is that the PAC difference derives from sensorimotor cortex.

Conclusion

PD is characterized by excessive synchronization throughout thalamo-cortical-basal ganglia loops. There is substantial interest in developing biomarkers of this synchronization that could be used as potential signals to help improve PD treatments, for instance by providing a signal for closed loop control or for adjustment of medications. We have described one such marker: sensorimotor PAC, which is elevated in PD patients Off medications compared to On medications and compared to healthy Control subjects. This metric can be detected noninvasively using scalp EEG.

Acknowledgements

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A. Raw Signal

B. Filtered Signal
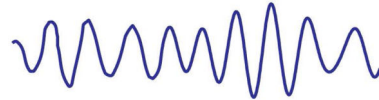
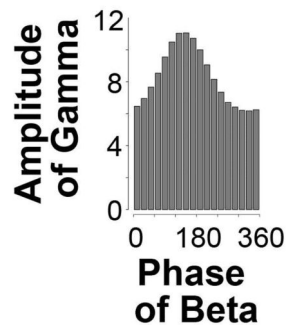low frequency (beta)   high frequency (gamma)
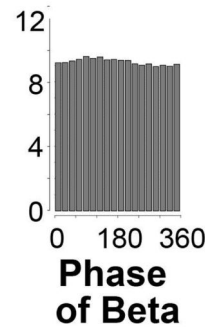
C. Extract Phase and Amplitude

low frequency phase   high frequency amplitude

D. Bin Amplitude by Phase

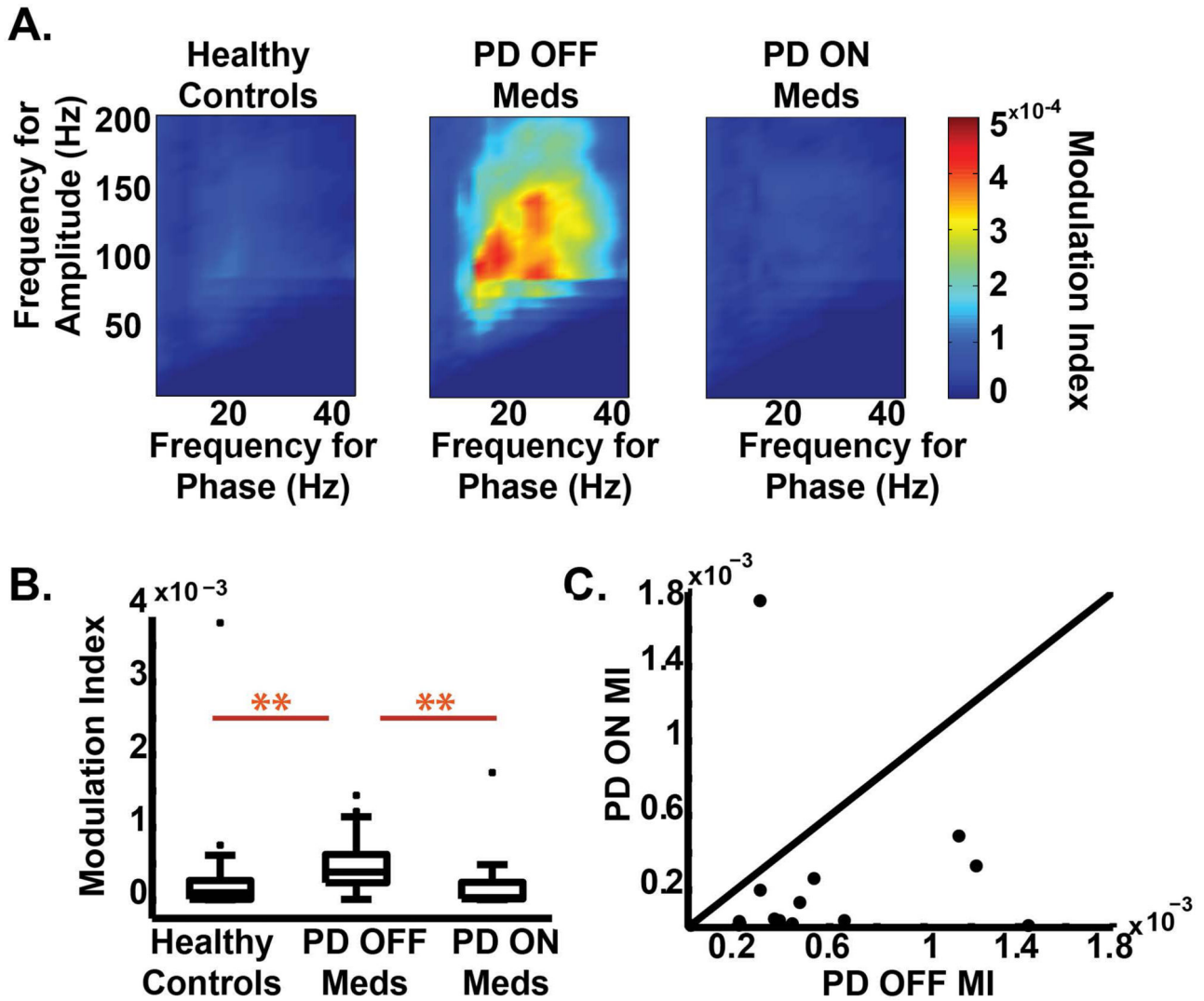**High Modulation Index**
(far from uniform)

Low Modulation Index
(closer to uniform)

Figure 1.
PAC calculation. The raw signal (A) for one electrode is first filtered (B) at both a lower frequency (for instance beta, left side), and a higher frequency (such as broadband gamma, right side). The lower frequency activity is thought to be important for long distance interactions throughout brain networks, [36, 37] whereas broadband gamma activity is more local and is thought to be a surrogate for neural firing[8, 10, 38]. The phase of the lower frequency activity and the amplitude of the higher frequency activity are then extracted using a Hilbert transform (C). Next the high frequency amplitude is binned according to low

frequency phase (D). This provides a way of quantifying the degree to which the broadband gamma amplitude ('spiking') is modulated by ongoing low frequency oscillation. This relationship between neuronal spiking and oscillations is probably a fundamental mechanism of neural processing[36] which is abnormal in PD[3-5]. PAC provides a mechanism to study this relationship without unit recordings[12].
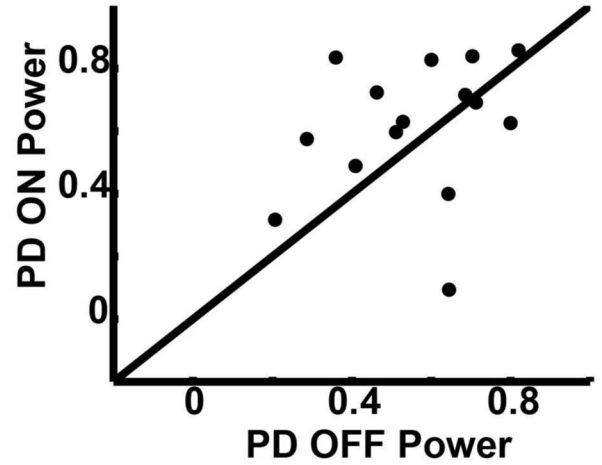
Figure 2.
A. Group comodulograms showing median modulation index across all subjects in each group. Prior to taking the median across subjects, comodulograms were averaged over EEG channels that correspond most closely to M1 (C3 and C4). Results are shown for each subject's raw modulation index (MI) values using a CSD reference, but results are similar if MI values are first converted to z-scores or if an average reference is used. B. Boxplots showing MI values averaged over beta (13-30 Hz) phase and broadband gamma (50-150 Hz) amplitude. There is a significant difference between PD patients On and Off medications (two-tailed, paired, Wilcoxon sign rank test, p=0.008) and between controls and PD patients Off medications (two-tailed, unpaired, Wilcoxon rank sum test p = 0.009.) Red asterisks represent significant comparisons (p < 0.01). C. Individual patients' MI values On and Off medications averaged over beta (13-30 Hz) phase and broadband gamma (50-150 Hz) amplitude. Each circle represents a patient.
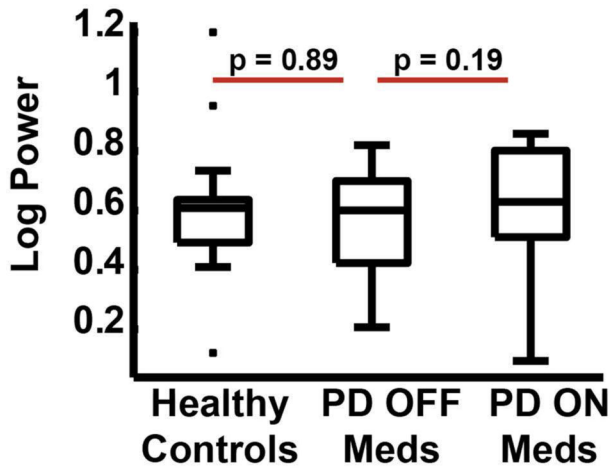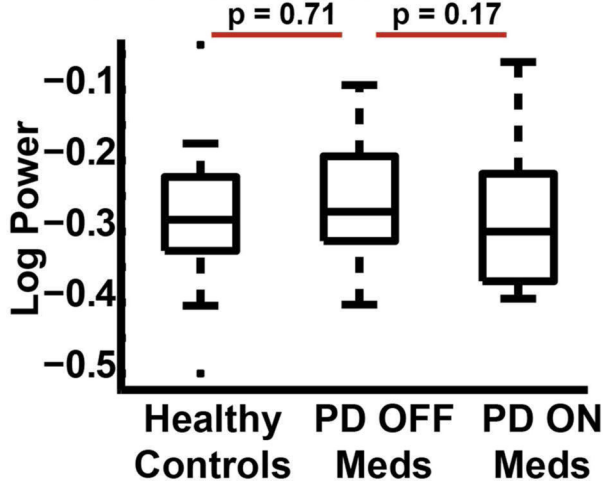
Figure 3.
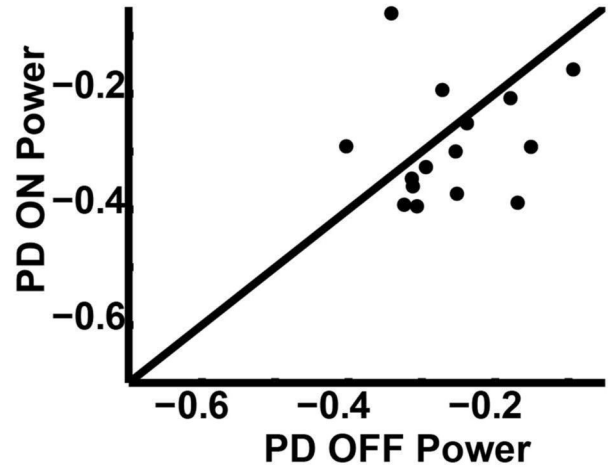Beta and Broadband gamma power for each group. A. Boxplots of average log beta power from 13-30 Hz. There is no significant difference between groups. B. Average log beta power for patients On versus Off medications. C. Boxplots of average log broadband gamma power from 50-150 Hz (excluding harmonics at 60 and 120 Hz). There is no significant difference between groups. D. Average log broadband gamma power for patients On versus Off medications.
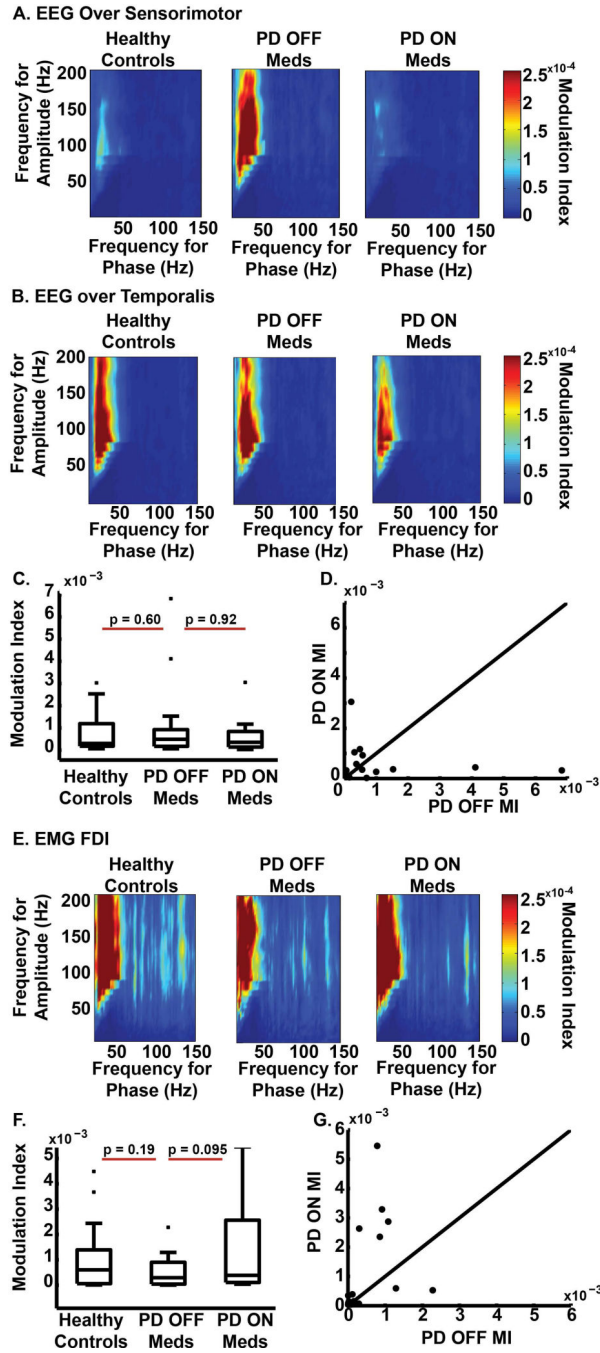
Figure 4.

Comparison of EEG and EMG Data. Because EMG picked up by EEG electrodes could generate non-neural PAC, we repeated the analysis we performed for sensorimotor EEG, but for the EEG electrodes closest to temporalis muscles (F7 and F8), and for bipolar EMG recorded from the right FDI muscle. A. Group comodulograms identical to Figure 2A except with the Phase Frequency extending to 150 Hz to allow visualization of harmonics at higher phase frequencies. B. Same as Figure 4A except showing the median across subjects of the EEG electrodes closest to temporalis muscles (F7 and F8), calculated with the CSD

reference and raw MI values. C. Boxplots of PAC averaged over beta (13-30 Hz) phase and broadband gamma (50-150 Hz) amplitude for the EEG electrodes closest to temporalis muscles. There are no significant differences between groups (p>0.59). D. Individual patients' MI values for the EEG electrodes closest to temporalis muscles, On and Off medications averaged over beta (13-30 Hz) phase and broadband gamma (50-150 Hz) amplitude. Each circle represents a patient. E. Same as Figure 4A except showing the median bipolar EMG across subjects. Note the PAC extends to the lowest phase frequencies examined and is present at the higher frequency harmonics. F. Boxplots of PAC averaged over beta (13-30 Hz) phase and broadband gamma (50-150 Hz) amplitude for the bipolar EMG signal. There are no significant differences (p>0.09). F. Individual patients' MI values for the bipolar EMG signal On and Off mediations averaged over beta (13-30 Hz) phase and broadband gamma (50-150 Hz) amplitude. Each circle represents a patient.
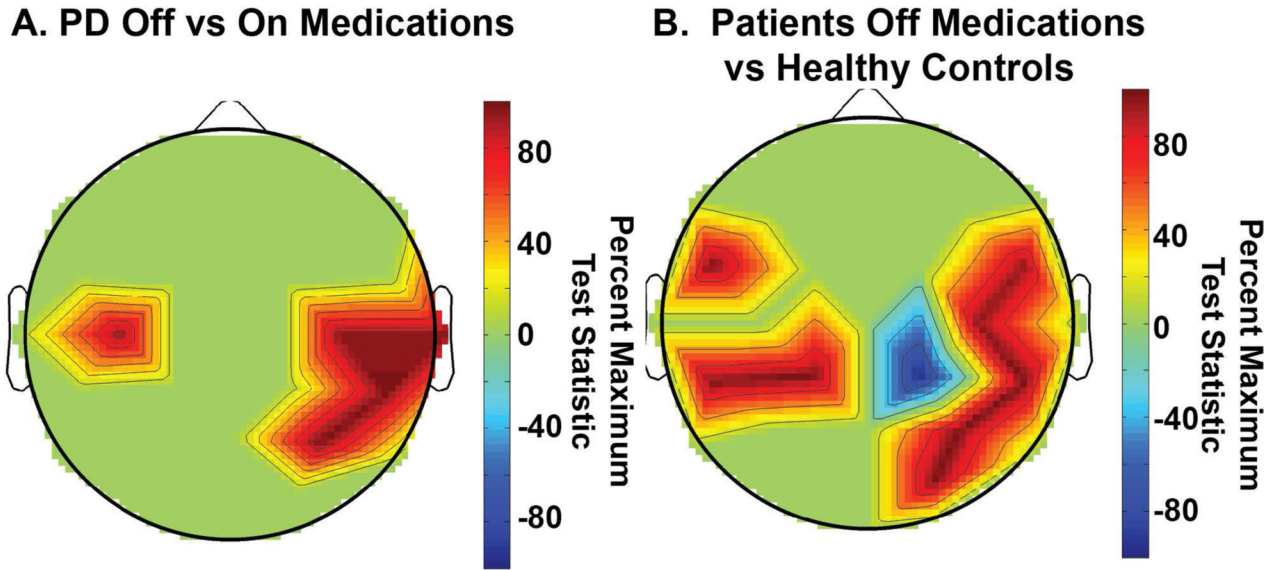
Figure 5.
Scalp Topography of Comparisons. We calculated PAC for all channels (using a CSD reference) and plotted the scalp topography for both the comparison of patients Off medications compared to patients On medications (A) and patients Off medications compared to controls (B). For the within patient comparison (A), paired tests were performed, and for the between group comparison (B), unpaired tests were performed. The normalized test statistic for each comparison is plotted for each electrode with a significant difference (p < 0.05; Wilcoxon sign-rank for A, Wilcoxon rank-sum for B). Test statistics for all non-significant tests were set to 0. For each comparison the test statistic for each electrode was normalized to the percent of the maximum test statistic for all channels. This normalization was to avoid confusion that might result from the different ranges of the rank sum versus signed rank test statistics.