Hyper-synchrony despite pathologically-reduced beta oscillations in patients with Parkinson’s disease: A pharmaco-magnetoencephalography study

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Abstract

Parkinson’s disease (PD) is a progressive debilitating neurodegenerative disorder clinically manifest by motor, posture and gait abnormalities. Human neurophysiological studies recording local field potentials within the subthalamic nucleus and scalp-based electroencephalography have shown pathological beta synchrony throughout the basal ganglia-thalamic-cortical motor network in PD. Notably, suppression of this pathological beta synchrony by dopamine replacement therapy or deep-brain stimulation has been associated with improved motor function. However, due to the invasive nature of these studies, it remains unknown whether this “pathological beta” is actually stronger than that observed in healthy demographically-matched controls. We used magnetoencephalography (MEG) to investigate neuronal synchrony and oscillatory amplitude in the beta range and lower frequencies during the resting-state in patients with PD and a matched group of patients without neurologic disease. Patients with PD were studied both in the practically-defined drug “OFF” state, and after administration of dopamine replacements. We found that beta oscillatory amplitude was reduced bilaterally in the primary motor cortices of un-medicated patients with PD compared with controls. Administration of dopaminergic medications significantly increased beta oscillatory activity, thus having a normalizing effect. Interestingly, we also found significantly stronger beta synchrony (i.e., hyper-synchrony) between the primary motor cortices in un-medicated patients with PD compared with controls, and that medication reduced this coupling which is in agreement with the intra-operative studies. These results are consistent with the known functionality of the basal ganglia-thalamic-cortical motor circuit, and the likely consequences of beta hyper-synchrony in the subthalamic nucleus of patients with PD.

Keywords: cortex, oscillations, magnetoencephalography, MEG, resting-state
1. Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer’s disease, affecting an estimated 1-2% of adults in the United States (National Institute of Neurological Disorders and Stroke, 2011). Disease pathobiology is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) resulting in muscle rigidity, resting tremor, hypo- or brady-kinesia, instability, and muscle weakness (Jankovic 2008). Currently, there is no disease ameliorating therapies and symptomatic improvements rely primarily on the replenishment of lost dopamine (Stacy 2009) or by deep-brain stimulation (DBS). Moreover, there are no biomarkers available that can definitively diagnose PD, and there are a number of different disorders with Parkinson’s-like symptoms. Thus, a greater understanding of the basic pathophysiology of disease is needed to help facilitate improved diagnostics and treatment strategies.

In the human brain, eight-to-twelve intrinsic functional networks have been identified in resting-state functional MRI (fMRI) and magnetoencephalography (MEG) recordings (Brookes et al. 2011c; Calhoun et al. 2008; Hillebrand et al. 2012). One of these is the sensorimotor network, which includes the bilateral primary motor and somatosensory cortices and the supplementary motor area, or SMA (Brookes et al. 2011c; Calhoun et al. 2008; Hillebrand et al. 2012). Notably, recent resting-state MEG analyses have determined that local neuronal ensembles of the sensorimotor network primarily oscillate at the beta (14-30 Hz) frequency (Brookes et al. 2011b; Hillebrand et al. 2012), and that brain regions within this network exhibit high inter-regional phase-locking (i.e., coupling) in the beta-band. This is in agreement with a study that used independent components analysis (ICA) to identify the dominant oscillatory frequencies of each of the 8-12 major intrinsic brain networks, and found that neuronal activity
in the sensorimotor cortices and the SMA was strongest in the beta rhythm and that the regions
were significantly coupled at rest (Brookes et al. 2011b). It is well-known that the SMA and
motor cortices are structurally connected through direct lateral connections (Ashe et al. 2006;
DeLong and Wichmann 2007; Nachev et al. 2008; Tanji 1994) and through the basal ganglia-
thalamo-cortical loop (McFarland and Haber 2000). Other components of this loop include the
subthalamic nucleus (STN), which receives input from the primary motor cortices, SMA, and
premotor cortical areas, and provides excitatory output to the globus pallidus internus (GPi),
substantia nigra pars reticulata (SNpr), and globus pallidus externus (GPe). Meanwhile, the GPi
and SNpr receive inhibitory projections from the GPe and putamen, and ultimately provide
inhibitory feedback to thalamic nuclei, which in turn modulate all components of the cortical
motor network (Figure 1; (DeLong and Wichmann 2007)). This circuit is responsible for
coordinating motor output via the spinal cord and mediates motor control. Importantly, it also
contains the specific locus of degeneration in PD (i.e., the SNpc; (DeLong and Wichmann 2007).
Thus, understanding how PD affects this motor circuit, as well as how it is modulated by
treatment, is a critical step for improving symptom management and developing physiological
markers of PD.

Interestingly, hyper-synchrony of neuronal responses in the same 14-30 Hz beta range
has been found during intra-operative evaluation of the effects of DBS on the STN in PD (Brown
and Brown 2011; Kuhn et al. 2008; Weinberger et al. 2006). The most common finding is
pathological hyper-synchronization (i.e., coherence) of neurons within the STN and between
cortical motor neurons and those in the STN of patients, both of which are partially arrested by
DBS and/or dopamine replacement therapy. Such observations have been critical to
understanding the therapeutic mechanisms of DBS and the underlying pathophysiology. In addition, these observations have been coalesced into the so-called Oscillation Model of PD, which postulates that beta oscillations become hyper-synchronous in the STN of patients with PD and that this impairs motor function by modulating other structures in the motor network toward a state of excessive synchrony (Hutchison et al. 2004). However, it is important to recognize that all of the involved patients had severe PD and that none of these studies included any type of control group, which greatly complicates interpretation of these findings in the context of healthy brain physiology. Essentially, the degree of beta synchrony was interpreted as abnormal in these studies because dopaminergic medications and/or DBS decreased beta coupling between the STN and motor cortex (and within the STN itself) while improving motor function (Brown 2007; 2003; Cassidy et al. 2002; Hammond et al. 2007; Hirschmann et al. 2013; 2011; Jenkinson and Brown 2011; Kuhn et al. 2008; Weinberger et al. 2006), but in the absence of data from healthy controls one can only speculate about the whether the degree of beta synchrony was in fact abnormal in the patients with PD prior to administration of dopamine medication and/or DBS. In other words, it has been inherently assumed that the effect of these treatments is to “normalize” neuronal responses (i.e., becoming more like a healthy brain), which is not necessarily the case as these treatments could modulate different neural parameters that have some form of compensatory net effect on the motor system.

To date, only a few studies have examined spontaneous beta activity (i.e., oscillatory amplitude and/or synchrony) in patients with mild to moderate PD and included a control group (Bosboom et al. 2006; Stoffers et al. 2007). Stoffers et al. (2007) recorded resting-state MEG oscillatory activity in patients with PD, both on and off dopaminergic medication, compared to healthy controls and found that patients with PD had significantly reduced lower-beta activity
and significantly higher theta and alpha activity in almost every MEG sensor. However, overall these MEG studies have limited their analyses to the sensor-level (Bosboom et al. 2006; Pollok et al. 2012; Stoffers et al. 2007) which, regrettably, provides spatially nonspecific results often complicating interpretation. Nonetheless, based on these studies, there is no indication that patients with PD have beta “hyper-synchrony” in motor regions relative to healthy controls, nor stronger amplitude beta oscillations as some studies have reported the opposite (i.e., weaker cortical beta in patients; Stoffers et al. 2007). These data stand in contrast to what has been predicted based on the intra-operative studies, and highlight a significant disconnect for interpreting prior invasive and noninvasive neurophysiological studies of spontaneous neural activity in PD. On the other hand, paradoxically, there is substantial agreement between invasive and noninvasive studies of beta oscillatory activity during movement tasks in patients with PD (Brown 2007; Buhmann et al. 2003; Cassidy et al. 2002; Heinrichs-Graham et al. 2013; Kuhn et al. 2008; Salenius et al. 2002; Weinberger et al. 2006).

Based on such gaps, we used spatially-filtered MEG to assess resting neurophysiological activity in the motor network of patients with mild to moderate PD, both off and on their dopaminergic medication, and in demographically-matched controls. We hypothesized that patients with PD would exhibit abnormally reduced oscillatory activity throughout the motor network compared to healthy controls, and that these abnormalities would be restricted to the beta frequency. In addition, we predicted abnormally-high levels of beta synchrony (i.e., hyper-coupling) between regions of the motor network in unmedicated patients with PD. Finally, we hypothesized that the administration of dopaminergic medication would normalize beta oscillatory activity and synchrony, with the medicated patients exhibiting neuronal responses closer to those of healthy controls. We propose that by understanding how neuronal dynamics
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Differ between un-medicated patients with PD and healthy controls, therapeutic techniques can be better optimized toward normalizing these dynamics and not rely solely on measures of symptom improvement, which are often more categorical (i.e., non-quantitative) in nature.

2. Methods

2.1 Subject selection

Eighteen adults with PD (4 females) and 17 age-, sex-, and educationally-matched adults (5 females) without PD were enrolled. Participants with PD were recruited from local neurology clinics and the regional chapter of the American Parkinson Disease Association, while participants without PD were recruited from the local community. All participants except one control were right-handed. All participants with PD had been prescribed their current dosage of regularly monitored dopamine replacement therapy for at least 2 months prior to study enrollment (see Table 1), and had showed a satisfactory clinical response to the particular medication(s). Motor impairments were measured by a certified rater using the Unified Parkinson’s Disease Rating Scale (UPDRS) in both the practically-defined “off” state (i.e., following at least a 12-hour withdrawal of dopamine replacements) and in the “on” state (i.e., after administration of typical medication regimen). Exclusionary criteria included any medical illness affecting CNS function, presence of any neurological or psychiatric disorder (besides PD), history of head trauma, and current substance abuse. After complete description of the study to participants, written informed consent was obtained following the guidelines of the University of Nebraska Medical Center’s Institutional Review Board. Complete demographics and UPDRS scores are provided in Table 1.
Three patients with PD and two controls were excluded from data analysis due to major dental artifacts, large or repetitive head movements, tremor-related (or exasperated) artifacts, MEG malfunctions, or related problems. Mean ages of the fifteen patients with PD and fifteen controls that were included in the analysis were 63.1 years for patients (range: 52-76 years) and 66.3 years for controls (range: 50-85) at enrollment. This difference was not significant. Mean patient UPDRS-III scores for the included patients were 29.92 in the “off” state and 23.69 in the “on” state, which was a significant improvement ($t(13)=3.69; p=.003$).

To ensure that any medication effects observed in this study were not a result of a possible time-of-day effect, four healthy, right-handed adult males (mean age: 31.4 years, range 24-39) were recorded using the same protocol described below. These participants were recorded in the early and late morning for three consecutive days.

2.2 Experimental Paradigm

All participants were scheduled early in the morning (e.g., 07:30-8:00), and for the participants with PD, after at least a 12-hour withdrawal from dopamine replacement medication. Prior to starting the task, each participant entered the magnetically-shielded room and was seated in the MEG chair. During the task, participants were instructed to relax, remain still, and fixate on a centrally-presented cross hair for one continuous six-minute block of awake, eyes-open rest. Patients with PD were then moved to the patient waiting area and were administered their regular dosage of antiparkinsonian medication. About 75 minutes after administration, these patients returned to the MEG chamber and completed a second six-minute recording of eyes-open rest. Dual-plane accelerometers were attached to the proximal portion of the participant’s left and right index fingers and sampled with the MEG data, which allowed us to precisely monitor...
for movement and/or tremor artifacts throughout the recording. The resulting time series were
differenced to account for any discrepancies in the positioning of the accelerometers between
subjects and sessions, and subsequently the standard deviation (i.e., movement; any variation
from zero) was calculated. These data were examined using independent-samples t-tests for
patient/control comparisons and paired-samples t-tests for medication effects.

2.3 MEG Data Acquisition

All recordings were conducted in a one-layer magnetically-shielded room (MSR) with
active shielding engaged. Neuromagnetic responses were sampled continuously at 1 kHz, with
an acquisition bandwidth of 0.1 – 330 Hz, using a 306-sensor Elekta Neuromag system with 204
planar gradiometers and 102 magnetometers (Elekta, Helsinki, Finland). Using MaxFilter
(v2.1.15; Elekta), MEG data from each session and subject were individually-corrected for head
motion, coregistered to structural MRI, and subjected to noise reduction using the signal space
separation method with a temporal extension (tSSS; (Taulu and Simola 2006; Taulu et al. 2005).

2.4 MEG Coregistration & Structural MRI Processing

Prior to MEG measurement, four coils were attached to the subject’s head and the
locations of these coils, together with the three fiducial points and scalp surface, were recorded
with a 3-D digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA).
Once the subject was positioned for MEG recording, an electric current with a unique frequency
label (e.g., 322 Hz) was fed to each of the coils. This induced a measurable magnetic field and
allowed each coil to be localized in reference to the sensors throughout the recording session.
Since coil locations were also known in head coordinates, all MEG measurements could be
transformed into a common coordinate system. With this coordinate system (including the scalp
surface points), each participant’s MEG data was coregistered with structural T1-weighted MRI
data prior to source space analyses. Structural MRI data were aligned parallel to the anterior and
posterior commissures and transformed into the Talairach coordinate system (Talairach and

2.5 MEG Source & Connectivity Analyses

Following tSSS and head-motion correction, the sensor-level time series was divided into
epochs of 4096 ms duration (4096 points) and artifact rejection was performed using a fixed
threshold method supplemented with visual inspection. Artifact-free epochs were transformed
into a regional source model per participant via inverse spatial filtering using the Brain Electrical
Source Analysis software (BESA version 6.0; see Figure 2; [Becker et al. 2013; Franzen et al.
2013; Scherg et al. 2002; Wilson et al. 2013]). Only data from the 204 gradiometer sensors were
used for calculation of the source model. Essentially, a 29-point grid with dual orthogonal
orientations per point was constructed, and spatial filtering was performed by creating a linear
inverse operator of the lead field matrix \( L = (l_1, l_2, \ldots, l_n) \), which contained the lead field vector of
each source orientation in the model. Briefly, we can denote the MEG signals from the
individual sensors by the matrix \( U \) (sensors * samples) and state that \( U \) is the linear overlap
coming from the source regions (i.e., \( U = L \ast S + \text{noise} \)), with each source region having an
unknown level of activity over time \( (s_i, \text{row i in source time series matrix } S) \). The unknown
levels of brain activity \( S \) can then be reconstructed by inverting matrix \( L \) (i.e., \( S = L^{-1} \ast U - L^{-1} \ast \text{noise} \)), with \( L^{-1} \) being a spatial filter that reconstructs the magnitude of source activity in brain
area \( i \) over time \( (s_i) \) while suppressing activity from all other brain areas. We used regularization
(1%), based on the truncated singular value decomposition approach, to prevent the weights in
the inverse spatial filter operator \( (L^{-1}) \) from becoming too large and enhancing the MEG
background noise. Such regularization does cause minor smearing of activity amongst the
sources, but the overall effect is negligible (Becker et al. 2013; Franzen et al. 2013; Wilson et al. 2013). Each resulting source waveform represents activity in a cortical volume near 2 cm$^3$

After transformation into source space, the current-amplitude (nAm) time series for each of the two orthogonal orientations per source were transformed into the frequency domain using Fourier analyses (i.e., 4096 data points per window). Average spectra across the six minute recording were then computed for each orientation per brain region by averaging the ~90 Fourier-transformed epochs. Subsequently, for each of the 29 dual-orientation regional sources, the orientation with the strongest amplitude (broad-band) was individually identified for each participant as the dominant orientation for that brain region, and the respective current-amplitude time series (per region) was used for the connectivity (i.e., phase coherence) analyses. Briefly, given our hypotheses, we extracted the zero-lag phase-locking value (PLV) using the method described by Lachaux et al. (1999) for the dominant orientation of only the sources corresponding to the left and right motor cortex and the left and right SMA. The signals were band-pass filtered at ±2.0 Hz, and their convolution was computed using a complex Gabor wavelet centered at the target frequency. We extracted the phase of the convolution for each time bin, frequency, trial and source pair and then averaged these values across the frequency bands of interest and across trials to derive the PLV, which was then collapsed across the entire epoch to estimate the average PLV per source pair per frequency. Thus, the PLV reflects the intertrial variability of the phase difference between source pairs across the entire epoch. Values close to 1 indicate strong synchronicity with only minute differences in phase across the time series, whereas values close to 0 indicate substantial phase variation between the 2 signals across time, and thus, low synchronicity (connectivity) between the two regions.
2.6 Statistical Analyses

We first examined local spectral amplitude, within the four traditional frequency bands of quantitative electroencephalography (qEEG; i.e., delta: 1-4 Hz, theta: 4-7 Hz, alpha: 8-14 Hz, and beta: 14-30 Hz), among the four brain regions that comprise the resting-state cortical motor network (left/right primary motor cortex and left/right SMA; (Brookes et al. 2011b; Calhoun et al. 2008; Hillebrand et al. 2012) using a mixed-model ANOVA. Initially, we evaluated group differences using an omnibus mixed-model ANOVA with brain region and frequency-band as within-subjects fixed factors, and group (un-medicated PD, controls) as a between-subjects random factor. To investigate the effect of dopamine replacement therapy, we ran a separate repeated-measures ANOVA with brain region, frequency band, and medication status (on/off medication) as within-subject factors. Follow-up t-tests were performed to determine the locus of significant main effects and interactions, as appropriate. All statistical analyses were two-tailed and conducted in SPSS (Release 21.0.0).

3. Results

All participants were able to complete the task. As described in section 2.1 of the Methods, three patients with PD and two controls were excluded from data analysis. To ensure there were no group differences in inadvertent movements during MEG, we examined the bilateral accelerometer signals. There were no significant differences (p-values ranged from 0.3 to 0.7) in the standard deviations of the finger accelerations between the patients and controls, nor between unmedicated and medicated patients with PD, which confirms that movement during MEG was equivalent between groups and between medication states in patients.
3.1 Amplitude Analysis

To investigate the relationship between disease state and spectral amplitude, an omnibus 4 x 4 x 2 ANOVA with location (four regions) and frequency (four bands) as within-subjects fixed factors, and group as a between subjects random factor was conducted. Results showed a significant main effect of region, $F(3,84) = 4.340$, ($p = .007$) and frequency band, $F(3,84) = 398.536$, ($p < .001$), as well as a significant region-by-frequency band interaction, $F(9,252) = 3.857$, ($p < .001$), frequency-by-group interaction, $F(3,84) = 4.113$, ($p = .009$), and a region-by-frequency-by-group three-way interaction, $F(9,252) = 1.875$, ($p = .056$). Post-hoc t-tests were conducted to probe the frequency-by-group interaction, which showed that unmedicated patients with PD had significantly reduced beta amplitude across brain regions compared to controls, $t(28) = 2.032$, ($p = .05$). No other frequencies were significantly different between groups. Post-hoc independent samples t-tests were also conducted to probe group differences in each frequency band and region. These tests showed that unmedicated patients with PD had reduced beta oscillatory activity in both the left primary motor cortex, $t(28) = 2.213$, ($p = .035$) and right primary motor cortex, $t(28) = 2.963$, ($p = .006$; see Figure 3). No other differences in the amplitude of neuronal activity were significant. Note that we did not evaluate the main effect of brain region because of the potential for partial volume effects (i.e., differences in the sensitivity of the imaging device to neural activity in different brain regions) that are always a concern in neuroimaging and bioimaging in general.

To evaluate the effect of dopamine replacement therapy on resting-state oscillations, a repeated-measures 4 x 4 x 2 ANOVA with location (four regions), frequency (four bands), and medication status (off/on medication) was conducted. We observed a significant effect of frequency, $F(3,42) = 162.867$, ($p < .001$) and medication status, $F(1,14) = 6.378$, ($p = .024$), as
well as a significant frequency-by-medication status interaction, $F(3,42) = 7.661, (p < .001)$. Follow-up paired-samples t-tests showed significant increases ($p < .05$) following dopamine administration across all four bands in the left SMA and the left primary motor cortex (see Table 2 and Figure 3). In contrast, increased resting-state amplitude in the right SMA post-medication was restricted to the beta frequency $t(14) = 2.925, (p = .011)$, and only a marginal increase in beta activity following medication was detected in the right primary motor cortex, $t(14) = 1.941, (p = .073)$. No other results were significant, although there were trending differences in all other frequency bands in the right motor cortex ($p < .10$). Follow-up testing was conducted to evaluate whether dopamine normalized cortical beta oscillations, and these tests were affirmative; we found no significant differences between healthy controls and medicated patients (left primary motor cortex: $t(28) = .531, p = .600$; right primary motor cortex: $t(28) = 1.240, p = .225$).

To ensure that the medication effects were, in fact, due to the administration of dopaminergic medication and not a result of a possible time-of-day effect, we evaluated resting state amplitudes in the same cortical motor areas in four healthy adult males. These participants were recorded in the early and late morning for three consecutive days (unpublished results). Amplitudes were extracted for each frequency band and source, using exactly the same methods as the current study, and then averaged across the three days for each source, frequency band, and time. An omnibus 4x4x2 ANOVA was conducted with location (four regions), frequency (four bands) and time-of-day (early/late morning) as within-subjects factors. Importantly, our results showed that there was no main effect of time ($p=.776$), no time-by-region interaction ($p=.932$), no time-by-frequency interaction ($p=.702$), and no three-way interaction ($p=.748$). Thus, it is unlikely that our medication effect was confounded by the time-of-day difference between pre- and post-medication scans.
3.2 Phase Synchrony Analysis

Given the beta oscillatory amplitude results, we focused connectivity analyses on the primary motor cortices. Independent-samples t-tests of zero-lag PLV’s showed that beta synchronicity between the left and right primary motor cortices was significantly stronger in unmedicated patients with PD relative to healthy controls ($t(28) = 2.385, p = .024$); synchronicity in the theta ($p = 0.379$) and alpha ($p = 0.438$) bands were not significant. Further, there were no significant differences between groups in the synchronicity between primary motor cortices and the SMA in any frequency band. Finally, administration of dopaminergic medication decreased beta synchronicity between the left and right primary motor cortices in patients with PD, but this effect was not significant ($p = 0.578$; Figure 4).

4. Discussion

We examined resting-state neurophysiological activity in the motor network of patients with PD before and after dopamine replacement therapy, and compared these data to a group of matched controls without neurologic disease. We found that unmedicated patients with PD exhibit significantly decreased beta oscillations compared to controls in the bilateral motor cortices, and that this difference is largely normalized following dopamine replacement, meaning that after medication administration there was no longer a statistical difference between neural activity in controls and patients with PD. Furthermore, despite decreased beta oscillatory activity in the primary motor cortices, patients with PD exhibit significantly higher synchronicity between the left and right motor cortex, which is also restricted to the beta frequency and partially normalized by dopamine replacement therapy. Below, we discuss the implications of these findings for understanding how PD affects the striatal-thalamo-cortical motor loop, as well
as how dopaminergic medication might function to normalize the activity in the motor network of patients with PD.

We found that resting-state beta activity in the bilateral primary motor cortices was significantly reduced in un-medicated patients with PD compared to controls, and that administering dopamine replacement therapy normalized beta oscillatory amplitude in these same cortical regions. In addition, dopamine replacement resulted in broad-band increases (i.e., delta, theta, alpha, and beta) in oscillatory amplitude across the cortical motor system, especially in the left hemisphere, though there were also trending effects (p’s < .09) in the right primary motor cortex. At first glance, these results may seem surprising since the most common findings from invasive (intra-operative) studies of patients with PD have been beta hyper-synchronization within the STN and/or between the STN and motor cortices (i.e., the oscillation model of Parkinson’s; (Brown 2007; 2003; Cassidy et al. 2002; Hammond et al. 2007; Hirschmann et al. 2013; 2011; Jenkinson and Brown 2011; Kuhn et al. 2008; Weinberger et al. 2006). However, examination of the excitatory and inhibitory pathways throughout the striatal-thalamic-cortical motor circuit (Figure 1) shows that the STN provides excitatory input to the GPi and the SNpr, which in turn provide strong inhibitory drive to thalamic neurons that project to the motor cortices, including both primary motor and the SMA. Thus, given the network architecture, the expected outcome of hyper-synchrony in the STN would be pathological inhibition of the thalamus, which would strongly reduce excitatory drive to the cortex and thereby may encourage local hyper-synchronization of cortical neurons (DeLong and Wichmann 2007). Furthermore, previous research has demonstrated that dopamine replacement therapy reduces beta synchronization in the STN (Priori et al. 2004). Given the previously-described relationship between the STN and the cortical motor areas, it is logical that dopaminergic modulation of the
STN would ultimately reduce the inhibitory drive to the thalamus, which would “release” the thalamus to stimulate motor cortical neurons and thereby increase resting-state beta oscillations.

Similarly, degeneration of neurons in the SNpc, which is the hallmark feature of PD would cause a similar inhibition of cortical beta activity, although this effect would be mediated through a different cortical pathway. Degeneration of the SNpc would decrease the inhibitory drive to the GPi and SNpr and, through these means, increase inhibition of thalamic neurons via the GPi and SNpr, resulting in reduced excitatory output of thalamic neurons projecting to the motor cortices, and hence reduced beta amplitude in the cortex (Figure 1). Wichmann and Delong (2003) tested this hypothesis using PET imaging in macaques infected with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP), which causes severe nigrostriatal degeneration. They found increased activity in the GPi and SNpr, as well as a decreased activity in the thalamus. Thus, hyper-synchrony in the STN and/or reduced SNpc activity would ultimately reduce resting-state beta oscillatory amplitude in motor cortices. Such a reduction and the subsequent increase in cortical beta oscillations following dopamine replacement therapy may serve as a reliable measure of motor circuit functionality and treatment efficacy in patients with PD.

Our results also showed frequency-dependent beta hyper-synchrony between the bilateral primary motor regions, which was marginally reduced with dopaminergic medication. From strictly a MEG signal-processing perspective, there is a positive relationship between amplitude and phase synchrony (a.k.a., phase coherence) due to the increased signal-to-noise ratio that results from increased local oscillatory amplitude (Brookes et al. 2011a; Schoffelen and Gross 2009). Consequently, the significantly reduced beta amplitude observed in un-medicated patients would have biased the phase-synchrony computation toward lower values in this group. Despite this, unmedicated patients had significantly stronger beta synchrony relative to controls between
the left and right primary motor cortices, which is even more compelling given that the
synchrony values were clearly biased against this conclusion. These results compliment previous
findings (Baudrexel et al. 2011; Brown and Williams 2005; Pollok et al. 2013; Salenius et al.
2002; Silberstein et al. 2005; Williams et al. 2002) that showed increased coherence throughout
the striatal-thalamic-cortical motor network in patients with PD. Our results are also consistent
with a recent study showing that the degree of cortico-cortical coupling between primary motor
cortices and the SMA was positively correlated with disease duration (Pollok et al. 2013). Many
of these studies have posited that this increased coherence could act as a compensatory
mechanism resulting from a breakdown in the motor circuit. However, Brown (2007) suggested
that a loss of functional segregation within the parallel loops between the basal ganglia and
cortex may be the primary source of pathological beta synchrony throughout the motor circuit.
This loss of functional segregation leads to hyper-synchrony within the cortex (as found in the
current study), between the cortex and subcortical structures, and within the basal ganglia itself
(2007). Alternatively, we hypothesize that the decreased excitatory drive from the thalamus
might lead to increased functional connectivity between the cortical motor regions, as their
bidirectional reciprocal inputs may create a closed loop in the absence of thalamic inputs.
Although speculative, this would be consistent with our previous study, which showed that un-
medicated patients with PD are unable to properly suppress beta activity in the primary motor
cortex during movement planning (Heinrichs-Graham et al. 2013). Future multiunit recording
studies, perhaps using the MPTP model, could test these alternatives by recording cortical, basal
ganglia, and thalamic neural populations (simultaneously) in the un-medicated and medicated
state. A strong negative relationship between the amplitude of neural activity in the thalamus and
the cortical synchrony would support our view, whereas widespread changes in coupling (pre- to
post-medication) would support the loss of functional segregation theory. Finally, unlike other studies (Silberstein et al. 2005), we did not observe a significant change in cortico-cortical synchronicity following administration of dopaminergic medication, although coupling did decrease post-drug and became more like controls. It is important to note, however, that Silberstein and colleagues were studying patients that were undergoing DBS implantation, and thus were much more severe.

In conclusion, this study is the first to demonstrate that beta oscillatory amplitude in the primary motor cortices is significantly reduced in un-medicated patients with PD relative to healthy controls, and that this effect is normalized following dopamine replacement therapy; in other words, there was no longer a statistical difference in cortical activity between controls and patients with PD. In addition, this study showed beta hyper-coupling between the left and right primary motor cortex in un-medicated PD relative to controls, which was reduced but not eliminated by dopaminergic medications. Before closing, there are a few limitations to the study that warrant discussion. Foremost, while our results compliment previous neurosurgical findings regarding amplitude and synchronicity in the STN and other subcortical structures of patients with PD, we were unable to compute an accurate time series for these subcortical structures using resting-state MEG, and as such a concrete relationship between cortical and subcortical oscillations and synchrony could not be derived. This limitation is due to subcortical structures, especially the STN, being extremely small, the fact that magnetic field strength falls off with the square of the distance from the current source, and the rather poor signal-to-noise ratio of resting-state recordings (relative to task-based MEG). That said, other noninvasive neuroimaging methods would also be unable to derive these measures; fMRI lacks the temporal resolution to compute synchrony and the spatial precision to accurately estimate activity in the STN, and EEG
imaging also lacks the spatial resolution to resolve these small structures. Thus, while limited, MEG remains one of the most capable noninvasive tools for probing cortical and subcortical neurophysiology. Secondly, when discussing connectivity in the context of electrophysiology, it is important to keep in mind that there are several different measures that can be used to quantify connectivity, each with its own strengths and weaknesses. Coherence, for example, is a functional connectivity measure that does not separate the differential effects of phase and amplitude on the computed values, and can be biased by small amplitude changes (Lachaux et al. 1999). Measures of the phase-locking value (PLV), which was used in the current analysis, are susceptible to linear mixing due to volume conduction, while other calculations, such as the phase-lag index (PLI) are relatively immune to this problem (Schoffelen and Gross 2009; Stam et al. 2007). While the PLV is relatively more affected by volume conduction, it is unlikely that this significantly contributed to our results for at least reasons. For one, volume conduction should have been relatively equal between the patients and controls, thus any effect on the PLV would not have produced the group differences that we observed. Second, our results showed a decreased amplitude response in our patients with PD along with an increase in the PLV, which is contrary to what would have been expected if our results were a result of volume conduction or signal leakage. Basically, an increase in oscillatory amplitude, reflective of a larger or more synchronous population of active neurons, would actually result in more volume conduction and give an artificially-high PLV, which is opposite to what was observed in this study. Nonetheless, it is important to recognize that volume conduction is an important consideration when computing connectivity in electrophysiology data. Another limitation is that we did not divide our patient population into symptom-specific subgroups. As such, there may be underlying
physiological differences between, for example, tremor-dominant patients with PD and bradykinesia-dominant patients with PD.

Despite these limitations, this study is the first to show reductions in cortical beta amplitude within motor circuits of patients with PD compared to healthy controls, and as such provides an avenue by which therapeutic methods can be evaluated. Essentially, rather than simply judging efficacy by the degree of reduction in symptomatology within individual patients, new therapies can be gauged by their capacity to normalize neuronal activity to that of healthy individuals. Moreover, such neurophysiological response patterns may also be diagnostically informative. For example, a recent electrocorticography study suggested that patterns of cortical oscillatory activity could distinguish between PD, primary dystonia, and essential tremor (Crowell et al. 2012). However, this study was unable to utilize a control group (i.e., electrocorticography is invasive), and overall such applications remain a relatively distant goal for noninvasive methods.

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**Disclosures:**

The authors have no conflicts of interest to disclose.
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Atypical coupling between posterior regions of the default mode network in attention-


**Figure Legends**

**Figure 1.** Motor Circuit Components of Importance to PD. Black arrows indicate inhibitory (gamma-aminobutyric acid [GABA]–ergic) connections; gray arrows indicate excitatory (glutamatergic) connections. Cortex includes the cortical motor areas: primary motor, SMA, premotor areas, and cingulate motor areas GPe: external segment of the globus pallidus; GPi: internal segment of the globus pallidus; SNpc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; STN: subthalamic nucleus; (Adapted from Delong and Wichmann, 2007).

**Figure 2.** Representation of the Regional Source Model. For each participant, a 29-node (grid-point) model with dual orthogonal orientations was used to estimate regional neuronal activity during the resting-state MEG recording using inverse spatial filtering. The model can be seen above overlaid on a structural MRI, with the yellow sources representing the cortical motor regions which were of primary interest in the current study. The same 3D rendition is shown in both the left and right panels, although the orientation of the image differs between the two panels to facilitate visualization of the spatial location of each source. The non-yellow color is only meant to aid in visually distinguishing the regional sources. Note that the regional sources are spaced equidistant apart and that each represents activity over an extended cortical area (i.e., > 1 cm³). Thus, the time series of each node reflects the average neuronal activity over that brain region, and not the amount of activation at a precise neuroanatomical coordinate (e.g., a voxel in MNI space). Following spectral analyses, the current amplitude (in nAm) from the dominant orientation of each source was used for statistical analysis.
Figure 3. Beta Oscillatory Amplitude Differences in the Primary Motor Cortices. Amplitude (in nAm) is shown on the y-axis, while region is denoted along the x-axis. Significant differences between unmedicated patients with PD (black) and healthy controls (white) were restricted to the beta band in the left ($p = .035$) and right ($p = .006$) primary motor cortices; data from medicated patients appears in gray. Administration of antiparkinsonian medication increased the amplitude of beta activity in the left ($p = .024$) and right ($p = .011$) primary motor cortices. A similar pattern of changes following medication was detected in the left and right SMA (not shown, see Table 2). Error bars indicate one standard error of the mean.

Figure 4. Phase Synchrony Between the Left and Right Primary Motor Cortices. Phase-locking values are shown on the y-axis while frequency band is denoted on the x-axis. Data for healthy controls is shown in white, un-medicated patients with PD in black, and the data for medicated patients with PD appears in gray. Un-medicated patients with PD showed significantly stronger beta synchrony between the left and right primary motor cortices than did healthy controls. While beta synchrony was reduced following medication, this reduction was not significant.
### Table 1. Clinical and Demographic Characteristics.

<table>
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<tr>
<th>Subject ID</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Disease Duration (yrs)</th>
<th>Affected Side (R/L)</th>
<th>PD Medications (type, dose)</th>
<th>UPDRS III off</th>
<th>UPDRS III on</th>
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<td>R</td>
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<td>--</td>
<td>R</td>
<td>Pram (1.5 mg), CD/LD (25/100 mg)</td>
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</tbody>
</table>

Pram = pramipexole, CD/LD = carbidopa/levodopa, Aman = amantadine

* denotes participants who were excluded from analysis due to major dental artifacts, large or repetitive head movements, or tremor-related (or exasperated) artifacts
**Table 2. Medication Amplitude Effects.**

<table>
<thead>
<tr>
<th>Region</th>
<th>Frequency</th>
<th>Pre-Medication Amplitude (nAm)</th>
<th>Post-Medication Amplitude (nAm)</th>
<th>$t$</th>
<th>$p$</th>
</tr>
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<tbody>
<tr>
<td>Left Primary Motor Cortex</td>
<td>Delta</td>
<td>32.96(2.24)</td>
<td>37.37(2.12)</td>
<td>2.17</td>
<td>.047</td>
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<tr>
<td></td>
<td>Theta</td>
<td>30.91(3.06)</td>
<td>35.62(3.13)</td>
<td>2.62</td>
<td>.020</td>
</tr>
<tr>
<td></td>
<td>Alpha</td>
<td>52.22(4.54)</td>
<td>58.83(3.92)</td>
<td>3.54</td>
<td>.003</td>
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<tr>
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<td>Beta</td>
<td>111.63(6.24)</td>
<td>125.03(5.73)</td>
<td>2.54</td>
<td>.024</td>
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<tr>
<td>Left SMA</td>
<td>Delta</td>
<td>33.35(2.67)</td>
<td>38.05(2.32)</td>
<td>2.27</td>
<td>.040</td>
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<tr>
<td></td>
<td>Theta</td>
<td>31.07(3.36)</td>
<td>35.63(2.65)</td>
<td>3.06</td>
<td>.008</td>
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<tr>
<td></td>
<td>Alpha</td>
<td>47.75(3.79)</td>
<td>56.27(3.78)</td>
<td>2.30</td>
<td>.037</td>
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<td>Beta</td>
<td>116.02(10.04)</td>
<td>135.24(9.73)</td>
<td>2.54</td>
<td>.024</td>
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<td>Right Primary Motor Cortex</td>
<td>Delta</td>
<td>34.11(3.22)</td>
<td>38.17(2.32)</td>
<td>1.82</td>
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<td>Theta</td>
<td>33.79(5.33)</td>
<td>36.81(3.37)</td>
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<td>.068</td>
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<tr>
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<td>Alpha</td>
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<td>61.60(5.20)</td>
<td>1.97</td>
<td>.068</td>
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<td>131.85(9.34)</td>
<td>2.93</td>
<td>.011</td>
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<tr>
<td>Right SMA</td>
<td>Delta</td>
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<td>36.91(2.91)</td>
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<td>.126</td>
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<td>110.59(9.46)</td>
<td>125.65(37.91)</td>
<td>1.94</td>
<td>.073</td>
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</table>

*Note.* Significant increases in amplitude from pre- to post-medication are shown in bold. Amplitude values are shown as mean(SE).