

# A shift from prospective to reactive modulation of beta-band oscillations in Parkinson's disease



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## ABSTRACT

Increased beta (13–30 Hz) oscillatory synchrony in basal ganglia–cortical circuits is a physiological characteristic of Parkinson's disease (PD). While the function of the beta rhythm is unknown, there is evidence that its modulation serves a predictive role, in preparation of future actions. We investigate the relation between predictive beta modulation and entrainment of brain oscillations in a task inviting behavioral entrainment by a regular task structure. MEG was recorded during a serial choice response task, in a group of 12 PD patients and 12 control subjects. In one condition, the reaction stimuli allowed for temporal preparation only (*random condition*), while in a second condition (*predictable condition*) the reaction stimuli allowed both temporal and effector preparation. Reaction times were identical between groups, and both groups benefited equally from the known effector side in the predictable condition. Analysis of oscillatory activity, by contrast, revealed marked differences between groups. In patients, the proportion of preparatory beta power desynchronization preceding the reaction stimuli was significantly smaller than in controls, while the proportion of beta desynchronization following the events was larger. In addition to this shift from prospective to reactive modulation of beta-band oscillations, patients showed a trend to reduced motor cortical pre-stimulus delta phase synchronization, and later gamma power synchronization than controls. Delta phase synchronization was, furthermore, significantly correlated with predictive beta desynchronization, supporting the relevance of hierarchical coupling between oscillations of different frequencies for the analysis of oscillatory changes in PD. Together, these features of task-related oscillatory activity indicate that entrainment fails to engender the same predictive mode of motor activation in PD patients as in healthy controls.

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## Introduction

It is well-established that basal ganglia dysfunction in Parkinson's disease (PD) is accompanied by an excess of oscillatory synchrony in the beta band (for reviews see Boraud et al., 2005; Hammond et al., 2007). This holds true for local field potentials in the basal ganglia and, less frequently observed, cortical beta oscillations measured by means of EEG or MEG (Crowell et al., 2012; Pollok et al., 2012). Correlations between clinical improvement and attenuation of STN beta power by dopaminergic medication and/or deep brain stimulation of the STN (Giannicola et al., 2010; Kühn et al., 2008; Ray et al., 2008) have suggested that high beta power may contribute to parkinsonian bradykinesia and rigidity. The possibility of a causal rather than epiphenomenal relation is supported by evidence that driving of cortical activity at beta frequencies slows down movement (Joundi et al., 2012; Pogosyan et al., 2009).

Within the context of research on the basal ganglia and PD, there is recent emphasis on beta modulation having an anticipatory role (Jenkinson and Brown, 2011; Oswal et al., 2012). Beta power is both down-regulated following a cue to prepare a movement, and up-regulated in anticipation of a postural challenge (Androulidakis et al., 2007a). Such features of beta activity underlie the proposal that beta activity in the basal ganglia and cortex may form an “internal likelihood index of the need for a novel voluntary action” (Jenkinson and Brown, 2011), driven by salient internal and external cues. The prospective nature of beta power modulation is a feature that beta oscillations share with slow brain potentials such as the readiness potential (RP) and the contingent negative variation (CNV). Indeed, both RP and CNV are sensitive to altered (movement) preparatory processes in PD (Cunnington et al., 1995; Jahanshahi et al., 1995; Praamstra and Pope, 2007; Praamstra et al., 1996a,b; Wascher et al., 1997).

The observation that compromised preparatory processes in PD are reflected in slow brain potentials as well as beta oscillations may be more than coincidental, especially if slow brain potentials are due to phase resetting of slow oscillations (Schroeder and Lakatos, 2009; Stefanics et al., 2010). A rapidly accumulating body of work has outlined a hierarchical coupling between oscillations of different frequencies

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(Canolty et al., 2006; Cravo et al., 2011; Lakatos et al., 2005, 2008). Slow oscillations in the delta frequency range have been shown to synchronize to environmental events that occur in a regular pattern. Faster oscillations, in turn, synchronize their phase and/or amplitude to the slow oscillations. Since alternating phases of neural oscillations correspond to low and high membrane excitability, the synchronization and hierarchical coupling could serve the purpose of bringing the relevant brain structures from which the oscillations originate into an optimal state for processing the stimuli to which they synchronize (Lakatos et al., 2005). Importantly, in any environment with events occurring at regular intervals, oscillatory synchronization may establish itself automatically, as it enables a more efficient rhythmic/predictive mode of attending compared to the continuous vigilant mode necessitated by an unpredictable environment (Cravo et al., 2013; Schroeder and Lakatos, 2009).

Against this background, the behavior of beta activity in cognitive or motor tasks with a regular task structure provides a means for addressing the following issues. Firstly, whether the presumed predictive nature of beta power modulation (Jenkinson and Brown, 2011) also applies when prediction is not driven by explicit knowledge, but the result of entrainment. Secondly, whether predictive modulation of beta power is linked to entrainment of slower and faster oscillations. In a previous EEG study, we already found evidence for altered entrainment in PD (Praagstra and Pope, 2007). However, this work described altered beta modulation in a qualitative fashion only, while analysis of slow brain activity was limited to time domain analysis using the CNV. Here, we employed MEG to readdress altered entrainment of oscillatory activity in PD patients, using a choice response task with a fairly fast rate of stimulus presentation to induce entrainment.

The aims of the study were, firstly, to confirm that PD specifically compromises *predictive* modulation of beta activity, i.e., attenuation of beta power *preceding* the reaction stimuli. Secondly, to examine hierarchical coupling of oscillatory activity, we evaluated whether altered beta modulation is associated with reduced synchronization of slow oscillations in the delta frequency range. Thirdly, we searched for signs of altered entrainment of gamma synchronization. Gamma activity is involved in movement production and is increased by dopaminergic medication (Alegre et al., 2005; Androulidakis et al., 2007b; Devos et al., 2006). Altered entrainment of gamma along with deficient entrainment of beta activity provides additional support for hierarchical coupling of oscillations. Finally, to gain a better perspective on the relation between oscillatory changes and anticipatory behavior, we contrasted a condition allowing only temporal preparation with a condition promoting both temporal and effector preparation. The latter condition enhanced the salience, in an implicit fashion, of the predictable task structure, perhaps eliciting entrainment in PD patients when it is not shown with just temporal predictability of response signals.

Although this study examines entrainment of MEG-recorded brain oscillations in conjunction with temporal and motoric entrainment of upper limb movements, our study also aims to contribute to the neurophysiology of (gait) cueing in PD. Translated to this domain, the results indicate that, in PD, rhythmic stimulation does not engender the same predictive motor activation as it does in healthy subjects.

## Materials and methods

### Participants

Participants were 12 PD patients (nine men; mean age  $\pm$  SD, 57  $\pm$  5 years) and 12 healthy control subjects (seven men; age 57  $\pm$  5 years). The control subjects were without history of neurological or psychiatric disease. The PD patients were of mild to moderate disease severity. In the PD group there were two left-handers and in the control group one, as determined by self-report. Left-handers were not excluded because the task involved both hands and MEG analyses were conducted in terms of contra- and ipsilateral hemispheres. All participants

had normal or corrected-to-normal vision. Participation was based on informed consent according to the Declaration of Helsinki and the study was approved by the local ethics committee (CMO Arnhem-Nijmegen). All patients were on dopaminergic medication and had a mean score of 26 ( $\pm$  6) on the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) (see Table 1). Disease duration ranged between 1 and 12 years (mean 6 years), with the most affected side being the right ( $n = 7$ ) and left ( $n = 5$ ). While all patients' motor symptoms were asymmetric, both sides were affected in all and asymmetry was modest. The reported analyses of behavioral and neurophysiological data do not differentiate between most and least affected sides, as there were no significant differences. The investigation and UPDRS rating were always performed in the morning, after overnight withdrawal of medication ( $>12$  h).

### Task and procedure

The experiment consisted of a choice response task to arrow stimuli presented on a screen, with the choice response being a left or right index finger button press. The critical experimental manipulations concerned the timing and the order of successive stimuli or trials. The response signals were presented at a relatively fast rate and fixed SOA (stimulus onset asynchrony), except for the last stimulus. The fast rate and fixed SOA were designed to induce temporal entrainment. The deviant final SOA, following trial series of variable length, helped to assess whether entrainment occurred. The predictability of a left or right hand response was manipulated by using two types of experimental blocks, presented in alternating fashion. In one version (the "random" condition), the order of the left and rightward pointing arrows was random. In the other version (the "predictable" condition), the response hand was predictable by alternating presentation of the left and rightward pointing arrows.

The experiment was divided in eight blocks of ~6 min each. Within each block, individual trials were presented in series of 11, 13, 15 or 17 consecutive trials and each block contained eight series. The variation in trial number served to prevent subjects from counting down to the end of the series. In each series, the SOA between successive reaction stimuli was always 1.5 s except for the last trial, which followed a SOA of 1.25 s or 1.75 s, that is 250 ms shorter (short deviant) or 250 ms longer (long deviant) than the preceding SOAs. Between each series there was a break of 19.875 s, 20.25 s, 20.625 s or 21 s. This was done in order to start the next series out of phase with the previous series. Between blocks there was a break of at least 1 min. The total number of series presented was 64, equally divided in random and predictable series. Responses to each stimulus were made with the left or right index finger, depending on the direction of the arrow.

The experiment was preceded by a short practice block that contained series from both conditions. Participants were not made aware of the regularity in SOA, the sequence-final deviant SOA, or the predictability of response hand in the predictable condition. The stimuli were presented with Presentation 14.9 software (Neurobehavioral Systems), using a liquid crystal display video projector, and back-projected onto a translucent screen with two front-silvered mirrors. Participants were seated comfortably in the MEG-chair with their eyes 75 cm from the screen. Response keys were attached to the armrests of the chair and subjects rested their fingers on the keys. Arrow stimuli were presented in white on a gray background for 300 ms. A fixation area was indicated by permanently displayed white brackets surrounding the central screen area where the arrow stimuli were presented. The brackets enclosed a square of  $7.2^\circ \times 6.1^\circ$  of visual angle; the arrows measured  $1.2^\circ \times 1.2^\circ$  of visual angle.

### MEG recordings

Ongoing brain activity was recorded using a whole-head MEG system with 275 axial gradiometers (VSM/CTF Systems, Coquitlam, BC) in

**Table 1**

Demographics and clinical characteristics of participating Parkinson patients. Levodopa was always used with dopadecarboxylase inhibitor carbidopa or benserazide.

Subject number	Age (years) and gender	Years since diagnosis	Most affected side	UPDRS motor score	Dominant hand	Medication (daily dose)
1	60, M	9	R	35	L	Levodopa 1400 mg
2	64, M	10	R	39	R	Levodopa 950 mg Entacapone 800 mg Pramipexole 0.875 mg
3	54, M	1	R	21	L	Levodopa 300 mg
4	52, F	5	R	24	R	Levodopa 450 mg
5	54, M	5	R	29	R	Levodopa 500 mg
6	59, M	11	R	22	R	Levodopa 450 mg Pramipexole 3.75 mg
7	61, M	10	R	21	R	Levodopa 550 mg
8	53, M	1	L	26	R	Levodopa 300 mg Trihexyphenidyl 6 mg
9	67, F	12	L	29	R	Levodopa 500 mg Pramipexole 3.75 mg Amantadine 200 mg
10	62, F	2	L	16	R	Levodopa 450 mg Pramipexole 1 mg
11	55, M	5	L	24	R	Ropinirole 4 mg Levodopa 500 mg
12	52, M	1	L	24	R	Levodopa 450 mg

a magnetically shielded room. During the experiment, we continuously measured head position relative to the sensor array using localization coils that were placed at the nasion and in the left and right ear canals. Furthermore, we recorded vertical electro-oculogram (EOG) from the supraorbital and infraorbital ridges of the left eye, and horizontal EOG from the bilateral canthi. MEG and EOG data were sampled at 1200 Hz.

#### Behavioral analyses

Reaction time analyses were performed on the responses following standard and deviant SOAs. For analysis of responses following standard SOAs, the first two trials of each series were discarded. In addition, we excluded trials with erroneous responses and outliers ( $\pm 3$  SD from the individual mean). Mean response times were determined for each condition separately. Differences in mean reaction times for standards were assessed using a mixed-design repeated measures analysis of variance (ANOVA) in SPSS version 19 (IBM Corp. Armonk, NY) with the between-subjects factor Group (controls vs. PD patients) and the within-subjects factor Predictability (random vs. predictable). An additional analysis assessed differences between reaction times for standards and deviants with a 3-level within-subjects factor SOA (short vs. standard vs. long).

#### MEG data preprocessing

MEG data were analyzed with MATLAB 7 (Mathworks, Natick, MA) using the open-source FieldTrip toolbox (Oostenveld et al., 2011). For the main analysis, epochs of 5000 ms (2000 ms pre-stimulus and 3000 ms post-stimulus) were extracted from the continuous data separately for both task conditions and response sides. Epochs were checked for artifacts using a semiautomatic routine detecting and rejecting trials containing muscle artifacts, slow drift, or SQUID (superconducting quantum interference device) jumps. After removal of artifacts, data were down-sampled to 300 Hz. Then, independent component analysis (ICA) was used to remove any remaining variance caused by eye blinks and heartbeat artifacts. Two control subjects and one PD patient showed a slow drift artifact which was removed by additional principal component analysis. As an extra check, the remaining data epochs were visually inspected and any remaining epochs with artifacts were removed manually. The remaining stimulus-locked datasets were submitted to time-frequency and statistical analyses.

From the axial gradiometer data, a planar gradient transform was calculated (Bastiaansen and Knösche, 2000). The planar representation simplifies the interpretation of the sensor-level data because it concentrates

the maximal activity above the source. Frequency decomposition was performed on the horizontal and vertical components of each channel, and these components were subsequently combined to obtain the oscillatory power at each synthetic planar channel. For all channels, time-frequency representations (TFRs) were calculated using a Fourier transform approach, applied to short sliding time windows across the entire length of the epochs, with a step-size of 50 ms. Before the Fourier transform, one or more tapers were multiplied to each time window and the resulting power estimates were averaged across tapers. The mean planar gradient power was estimated for all trials within a condition. For the frequencies 1–30 Hz (1 Hz frequency resolution), a single Hanning taper and an adaptive time window of four cycles for each frequency were used. For the frequencies 30–130 Hz, a fixed taper length of 250 ms was used (4 Hz frequency resolution, but increased to 2 Hz by spectral interpolation) as well as a frequency smoothing of  $\Delta f = 20$  Hz (Percival and Walden, 1993), resulting in four tapers. Percentage change in oscillatory power was defined as the relative change with respect to the mean of the epoch (1000 ms pre-stimulus to 2000 ms post-stimulus). The epoch length included two trials, enabling better comparison between predictable and random conditions.

Sources of beta activity were identified using a frequency-domain beam-forming approach on the axial sensor data. We contrasted the beta event-related desynchronization (ERD) (0–0.5 s post-stimulus) with the beta event-related synchronization (ERS) (0.6–1.1 s post-stimulus) activity for the beta frequency band (13–30 Hz). As the beam-former input required only one frequency, we used the center frequency of the beta band (22 Hz, resulting in 11 full cycles per time window). A realistic single-shell head model (Nolte, 2003) was created for all individuals using the brain surface from their individual segmented MRIs (11 out of 12 controls, 8 out of 12 PD patients) or a MNI template-MRI (Holmes et al., 1998). The brain volume of each individual was discretized to a grid with an 8 mm resolution and the lead field matrix was calculated for each grid point according to the head position in the system and the forward model. A spatial filter was then constructed for each grid point using the covariance and the lead field matrices. Source strengths were calculated for the ERD and ERS windows, after which these were contrasted and the location coordinates of maximal difference were saved for use in the analysis of delta phase.

#### MEG analyses

##### Beta activity

Since beta oscillatory activity (13–30 Hz) is most prominent in the sensorimotor system, and lateralizes with unimanual responses,

sensorimotor region ROIs were determined by a subtraction of beta activity associated with the left and right hand responses. This subtraction was performed across conditions and groups. Subsequently, the 20 sensors with the strongest beta modulation above each hemisphere were selected. After rejecting any sensors without a homologous sensor over the opposite hemisphere, this left two symmetric ROIs overlying the sensorimotor cortices each consisting of 18 sensors (see Fig. 3). In addition to analyses of beta power in sensorimotor ROIs, beta power was also analyzed across all sensors, using cluster-based non-parametric permutation tests (Maris and Oostenveld, 2007) in FieldTrip.

To study beta modulation over time, power values were averaged over the entire beta band and all sensors per ROI, creating contra- and ipsilateral time series of beta power. Time series for the left and right hand response conditions were combined by averaging the conditions separately for the contra- and the ipsilateral hemisphere. Modulation depth of beta power was defined as the difference between maximum post-stimulus desynchronization and synchronization. Differences in beta modulation depth were statistically tested using a mixed-design repeated measures ANOVA with between-subjects factor Group and within-subjects factors Predictability and Hemisphere. The amount of predictive beta modulation was defined as the percentage of desynchronization that occurred before stimulus onset, relative to the total desynchronization depth (difference between maximum pre-stimulus synchronization and post-stimulus desynchronization), and were both analyzed with the same ANOVA.

#### Gamma activity

For analysis of changes in gamma band power (60–90 Hz), two ROIs were identified in a similar way as for beta activity. First, a subtraction of activity associated with the left and right hand responses was performed to reveal the spatial distribution in a 350–550 ms post-stimulus time window. This subtraction was performed across conditions and groups. Since the distribution of gamma activity was captured reasonably well by the ROIs for beta power changes, these ROIs were optimized by removing three sensors at the ROIs medial border and adding three sensors at the lateral border, thus shifting the ROIs slightly laterally. This left two symmetric ROIs overlying the sensorimotor cortices each consisting of 18 sensors. After defining ROIs, the time course of gamma power was estimated by averaging spectral power across the frequency band and over all sensors of the ROI. Because of the relatively low signal-to-noise ratio of the gamma modulation, onset latencies of gamma ERS and peak gamma ERS were analyzed with a jackknifing procedure. In this procedure, every participant's gamma power trace over time was replaced by a subaverage across the other  $n - 1$  participants of the group, separately for controls and patients (Ulrich and Miller, 2001). Onset of gamma ERS was determined as the time point of minimal gamma power in the interval 400 ms pre-stimulus to 200 ms post-stimulus. The subsample gamma ERS onset latencies were submitted to a mixed-design ANOVA with between-subjects factor Group and within-subjects factor Predictability. The gamma ERS peak latency was defined as the time point of maximal gamma power in the interval 200–600 ms post-stimulus and was analyzed in the same way. To correct for the reduced variance of subsample gamma onset latencies due to the jackknifing procedure,  $F$ -values were adjusted according to Ulrich and Miller (2001).

#### Delta activity

Delta phase analysis was performed on spatially filtered data using a time-domain beam-former spatial filter (linearly constrained minimum variance). This beam-forming spatial filter for the previously stored locations of interest (the sensorimotor cortex, estimated by the source of beta activity) was used to filter the MEG data, separately for contra- and ipsilateral hemispheres. The LCMV spatial filter passed the activity at the location of interest with unit-gain, while optimally suppressing all other noise and other source contributions to the MEG data. Data

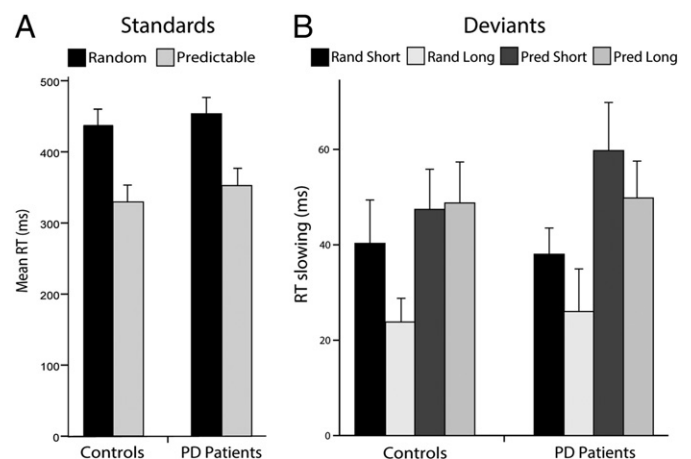
epochs (from 2 s pre-stimulus to 3 s post-stimulus) were band-pass filtered between 0.05 and 3 Hz using a finite impulse response least squares filter. Instantaneous delta phase values were calculated using the Hilbert transform of the band-pass filtered data. To test if any phase preference was present for the instantaneous phases at stimulus onset, Rayleigh's test for uniformity of phase data was used (Fisher, 1993). The strength of phase preference (entrainment) was acquired by calculating the intertrial coherence (ITC) over all trials within each individual. The ITC ranges from 0 to 1, where 0 means no phase consistency and 1 is perfect phase consistency. Rayleigh's test and ITC calculations were performed using the MATLAB circular statistics toolbox (Berens, 2009). All ITC values were submitted to a mixed-design ANOVA using between-subjects factor Group and within-subjects factors Predictability and Hemisphere. Pearson correlations were calculated in SPSS version 19 (IBM Corp. Armonk, NY) to test for any correlations between the amount of predictive beta modulation and the delta ITC.

## Results

### Behavioral data

Participants had to press a button with their left or right index finger after presentation of a left or right pointing arrow. The mean response times were approximately 100 ms faster in the predictable condition (controls:  $331 \pm 76$  ms, PD patients:  $353 \pm 80$  ms) compared to the random condition (controls:  $437 \pm 80$  ms, PD patients:  $454 \pm 80$  ms), yielding a significant main effect of Predictability ( $F(1,22) = 241.5$ ,  $P < 0.0001$ ) (see Fig. 1A). There was no significant difference between controls and patients across conditions ( $F(1,22) < 1$ ), nor was there an interaction between Group and Predictability ( $F(1,22) < 1$ ), indicating that both groups benefitted equally from effector predictability. Error rates were not different between groups in the random (controls: 3.5%, PD patients: 3.3% ( $F(1,22) < 1$ )) nor in the predictable condition (controls: 7.2%, PD patients: 2.7% ( $F(1,22) = 2.5$ ,  $P = 0.13$ )).

The deviant final SOAs led to violations of temporal expectation, inducing longer reaction times. An omnibus analysis across standards and deviants showed this effect to be significant ( $F(1,9,41.7) = 47.9$ ,  $P < 0.0001$ ) (see Fig. 1B). The reaction times to deviants were further analyzed separately, and reported in terms of the RT-increment relative to standards. There were no significant main effects or interactions involving the factor Group. There was, however, a significant main effect of Predictability ( $F(1,22) = 134.1$ ,  $P < 0.0001$ ). This was due to the mean response time increment following deviant SOAs being



**Fig. 1.** (A) Mean group reaction times following stimuli at the standard SOA in the random and predictable conditions. Values are in ms and error bars represent 1 standard-error-of-the-mean (SEM). Reaction times are averaged over the left and right hand responses. (B) Mean slowing in reaction time (relative to reaction time following standard SOA) for responses following short and long deviant SOAs.

significantly larger in the predictable than in the random condition. Thus, violations of temporal expectancy are more disruptive when not only the upcoming stimulus is temporally predictable, but also the effector is already prepared. There was a tendency for the cost of timing perturbations to be modulated by their direction, as reflected in a marginally significant effect of the direction of SOA deviance ( $F(1,22) = 3.1$ ,  $P = 0.09$ ). The difference between conditions was in the expected direction. As described by Grosjean et al. (2001), when an anticipated stimulus occurs earlier than expected, then its backward shift in time will be partly reflected in a longer RT, whereas a later presentation tends to shorten the RT.

### Oscillatory brain activity

#### Distribution of sensorimotor beta activity

Time–frequency analyses showed predominant movement-related modulations in the beta band. We first evaluated the distribution of the beta modulation, by quantifying beta power peak-to-peak from maximum desynchronization to maximum synchronization (see Fig. 3). The modulation of beta activity was maximal over the sensorimotor cortex contralateral to the response hand, and appeared to be more lateralized in the predictable than in the random condition (see Fig. 2). As shown in the time–frequency plots of Fig. 3, the modulation of beta power occurred over the full beta range from 13 to 30 Hz. The beta modulation followed a fixed pattern, with a reduction in beta power (desynchronization) before and during movement, and a subsequent increase in beta power (synchronization) shortly after movement.

#### Effects of effector predictability

A prominent feature in the time–frequency plots (Fig. 3) is an apparently earlier (contralateral) beta desynchronization in the predictable compared to the random condition. This was statistically evaluated by means of a cluster randomization analysis over all sensors. Beta power

(13–30 Hz) was compared between predictable and random conditions in a 200 ms pre-stimulus time window. The analysis confirmed that pre-stimulus beta power showed a stronger attenuation in the predictable than in the random condition in clusters overlying the sensorimotor cortex contralateral to the upcoming response hand (see Fig. 4). This was the case in controls for both left ( $P < 0.001$ ) and right hand ( $P < 0.001$ ) responses. This was likewise the case in PD patients for the left ( $P < 0.04$ ) as well as right hand ( $P < 0.003$ ) responses. This analysis demonstrates that the marked reaction time advantage in the predictable condition is indeed achieved, in both groups, on the basis of effector preparation as indexed by lateralized beta-band suppression.

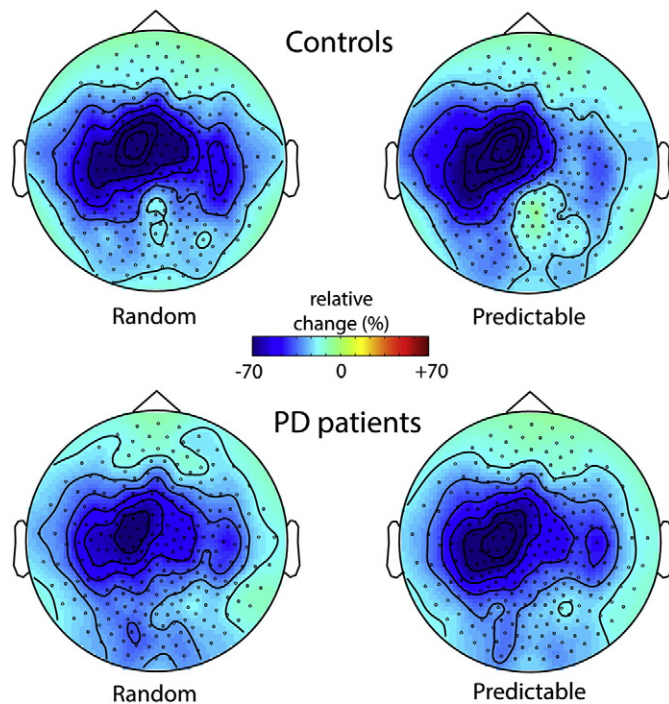
### Temporal dynamics of beta modulation

The time course of beta modulation shows a repeating pattern of beta desynchronization and synchronization. Since this oscillating pattern does not allow the definition of a pre-stimulus baseline, Fig. 5 shows the time series aligned to a baseline defined relative to the time of stimulus presentation. The modulation of beta power over time was analyzed in terms of two properties, the *modulation depth* as an indicator of the dynamic range of beta power changes and the amount of *predictive modulation* as an indicator of preparatory activity for an upcoming stimulus or response. These indices of beta modulation were deemed more appropriate for the analysis of beta activity during the relatively fast movement sequences, and yield more information on the temporal dynamics of the beta modulation, than an analysis in terms of beta-ERS and ERD relative to beta power in a resting period.

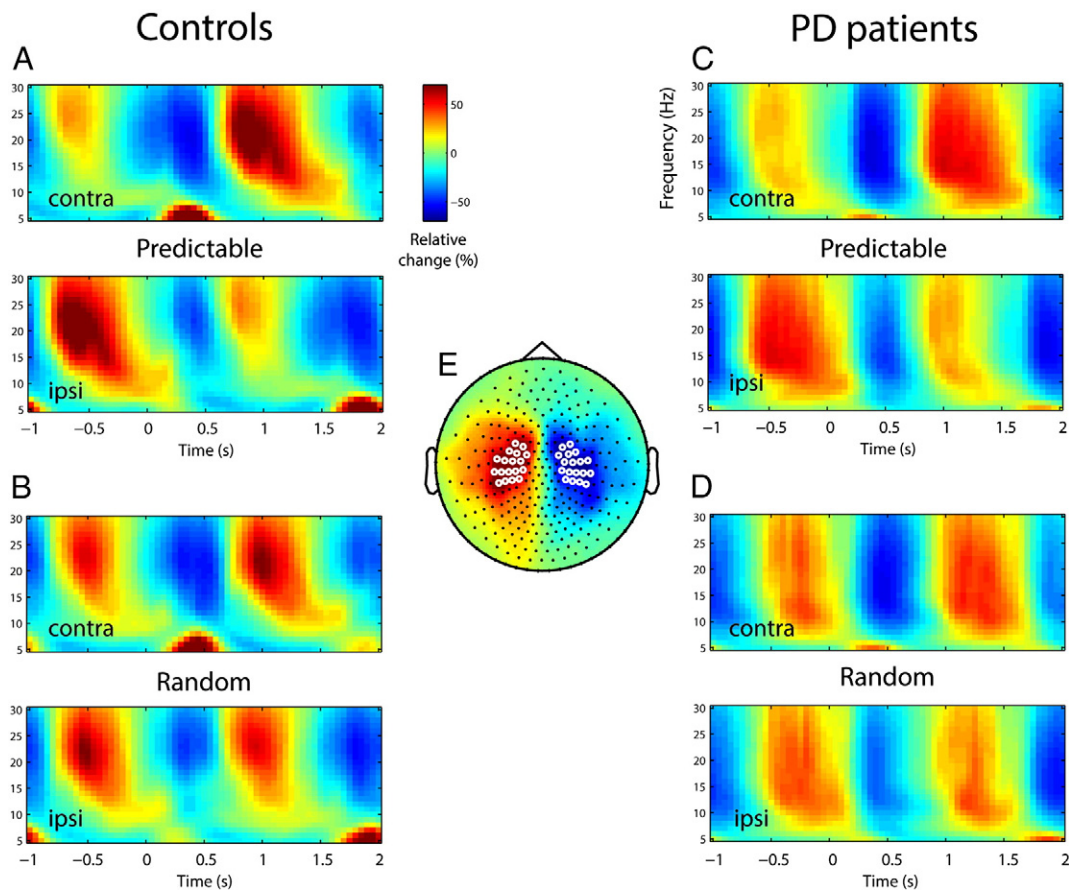
The modulation depth was significantly larger in the hemisphere contralateral than ipsilateral to the response hand, for all conditions and groups ( $F(1,22) = 62.7$ ,  $P < 0.0001$ ). There was also a significant interaction between Predictability and Hemisphere ( $F(1,22) = 15.1$ ,  $P < 0.001$ ), as the contralateral modulation depth was larger in the predictable than in the random condition. The ipsilateral modulation depth showed the opposite effect, being smaller in the predictable than in the random condition. No differences were found in modulation depth between groups ( $F(1,22) < 1$ ).

Predictive beta modulation was calculated as the percentage of beta modulation that occurred before stimulus onset compared to the total depth of the beta ERD (see Fig. 5). Analysis results for predictive beta modulation are summarized in Fig. 6. Across groups, there was significantly more predictive beta modulation in the hemisphere contralateral to the response hand than in the ipsilateral hemisphere ( $F(1,22) = 27.7$ ,  $P < 0.0001$ ) and there was an interaction between Hemisphere and Predictability ( $F(1,22) = 24.4$ ,  $P < 0.0001$ ). The interaction was explained by the fact that the difference in predictive beta modulation between hemispheres was larger in the predictable than in the random condition. Importantly, there was also a significantly lower predictive beta modulation in PD patients compared to controls across conditions ( $F(1,22) = 8.8$ ,  $P < 0.007$ ). No interactions were found involving the factor Group. Since there was no difference in the depth of the full ERD between groups ( $F(1,22) < 1$ ), the lack of predictive beta modulation in patients is made up for by a stronger reactive modulation, a feature which is evident in Fig. 5. By virtue of the definition of predictive beta modulation relative to the full ERD, the group difference in reactive beta modulation is identical to the difference in predictive beta modulation.

The altered contribution of predictive and reactive modulation to the total amount of task-related beta modulation was confirmed by an analysis of the instantaneous phase of contralateral beta power changes at stimulus onset. There was a significant difference between Predictability conditions ( $F(1,22) = 54.5$ ,  $P < 0.0001$ ), explained by beta power being further advanced towards the ERD trough of the modulation cycle, at stimulus onset, in the predictable compared to the random condition. The instantaneous phase of the beta power modulation at stimulus onset was also different between groups ( $F(1,22) = 5.5$ ,  $P < 0.03$ ), where beta power of controls was closer to the beta trough (maximal ERD) than for PD patients (see Fig. 7). This phase difference



**Fig. 2.** Distribution of the mean beta power modulation (% change), as measured from maximal ERD to maximal ERS. Topographies are averaged over the left and right hand responses by first mirroring the topographies of the left hand condition over the anterior–posterior axis and then averaging over the right and left hand conditions. Thus, the left hemisphere sensors are contralateral, and the right hemisphere sensors ipsilateral to the side of movement.



**Fig. 3.** Group mean time–frequency representations of oscillatory power changes, relative to the mean power over the epoch. Data of control subjects are on the left (predictable (A) and random (B) conditions). Data of PD patients are in the right column (predictable (C) and random (D) conditions). Time–frequency data are mean spectral power values over ROIs represented in (E). T = 0 indicates onset of the stimulus requiring a contralateral hand response.

in the cycle of beta power changes indicates that in control subjects more ERD is completed before stimulus onset than in PD patients. There were no interactions involving the factor Group. This additional analysis underscores that the difference in predictive beta modulation between patients and controls is not the result of our choice of baseline.

In order to verify the behavioral relevance of predictive beta modulation, we computed the correlation between predictive beta modulation and reaction time. The Pearson correlation (across groups), between predictive beta modulation in the hemisphere contralateral to the upcoming response hand and reaction time was significant in both the random ( $r = -0.54$ ,  $P < 0.01$ ) and the predictable ( $r = -0.46$ ,  $P < 0.03$ ) condition (see Supplementary Fig. 1).

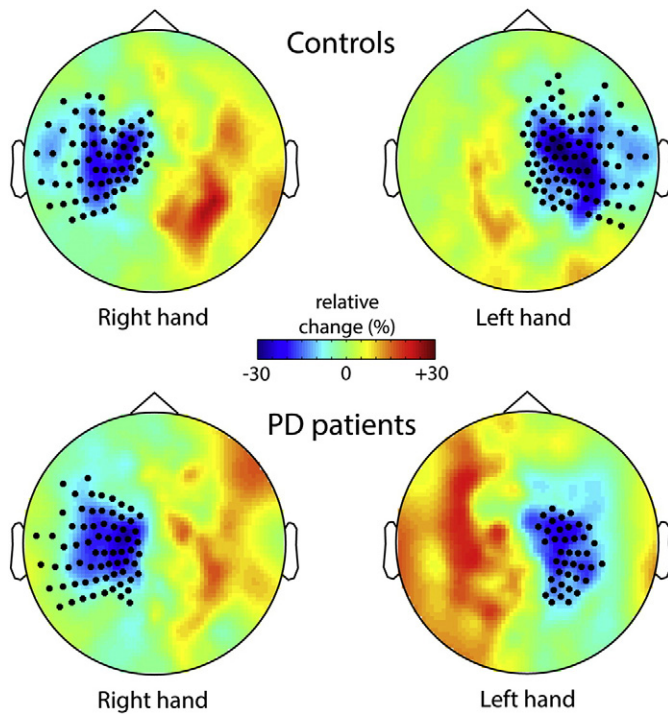
#### Spectral power in rest

Although it is unlikely that the task-related modulations of spectral power are influenced by differences in resting power between groups, we analyzed spectral power for all participants during rest, i.e. in-between the trial series. Spectral power was analyzed over the same ROIs as used in the analysis of task-related beta power. There was no difference in spectral power in rest between blocks of predictable or random arrow stimuli ( $P > 0.50$ , using a permutation test over all frequencies with 1000 randomizations). Hence the resting periods before predictable and random trial series were combined per participant. Spectral power during rest was compared between groups using a permutation test over all frequencies (1000 randomizations), and showed that there was only a significant difference in power in the theta band. That is, PD patients had higher power between 6.3 and 7.5 Hz ( $P < 0.05$ ). Additionally, mean spectral power over the alpha (8–12 Hz) and beta (13–30 Hz) bands was tested separately by using a one-way ANOVA with between-subjects factor Group. There was no difference

between groups in mean spectral power over the alpha ( $F(1,22) = 2.0$ ,  $P > 0.16$ ) or beta ( $F(1,22) = 1.7$ ,  $P > 0.20$ ) bands.

#### Temporal dynamics of gamma modulation

Given the more reactive nature of beta modulation in PD patients, we subsequently asked if the modulation of gamma power also had a more reactive profile. Gamma activity was studied over two clusters of 18 sensors symmetrically distributed over both hemispheres (see Materials and methods). Time–frequency representations of gamma power changes over the hemisphere contralateral to the response hand are shown in Fig. 8. Evaluation of the time–frequency spectra suggested that movement-related gamma activity in control subjects increased earlier than in PD patients, as can be seen in Figs. 8A and B. The time courses of beta and gamma power changes showed, as expected, an inverse relationship between beta and gamma power changes. Importantly, where the anticipatory decrease in beta power in controls was accompanied by an early slow increase in gamma power (Fig. 8C), the more reactive beta ERD in PD patients was accompanied by a similar reactive gamma ERS (Fig. 8D). The onset of gamma-ERS was evaluated with a repeated measures ANOVA, which confirmed a significant difference between groups in the form of an interaction between Predictability and Group ( $F(1,22) = 5.8$ ,  $P < 0.025$ ). The main effect of Group did not reach significance ( $F(1,22) = 3.4$ ,  $P = 0.1$ ). Post-hoc testing showed that in the predictable condition, the onset of gamma ERS was significantly later in patients than in controls ( $F(1,22) = 6.3$ ,  $P < 0.025$ ), while there was no difference in onset of gamma ERS in the random condition ( $F(1,22) < 1$ ). In contrast to the onset latency of the ERS rise, the time point of maximal gamma ERS did not differ between conditions ( $F(1,22) < 1$ ) and groups ( $F(1,22) < 1$ ). Nor was there a significant interaction.

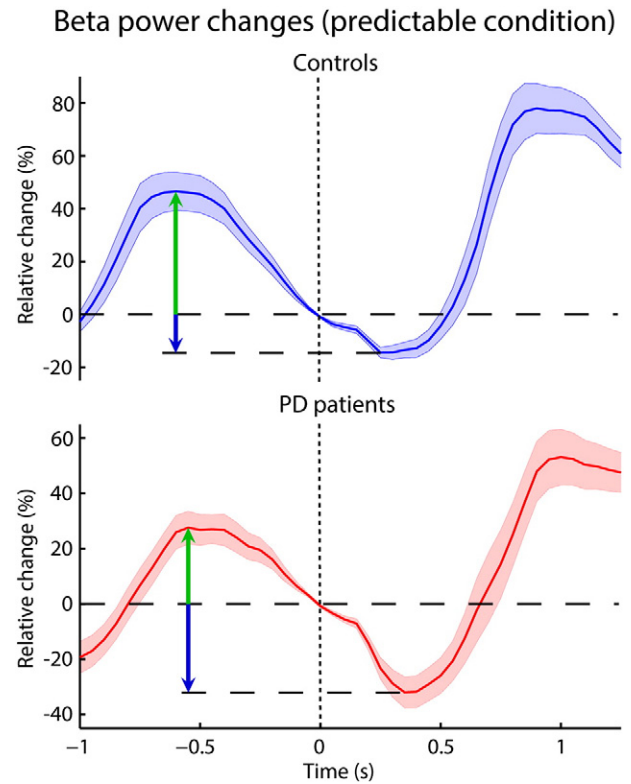


**Fig. 4.** Significant differences in group mean beta power changes between predictable and random conditions, measured in a 200 ms pre-stimulus window. Significant clusters of sensors in overlying areas with stronger beta ERD in the predictable compared to the random condition are marked with black dots. The color scale represents the difference in relative change (%) of beta power between conditions.

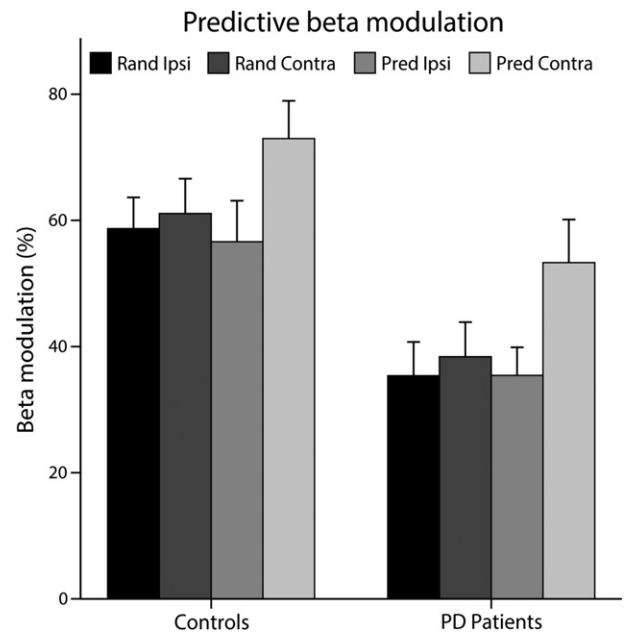
#### Phase entrainment of delta oscillations

As proposed by Lakatos et al. (2005), a rhythmic stream of stimuli will induce slow oscillations to align their high excitability phase with the occurrence of the stimuli. Therefore, the rhythmic task structure, with reaction stimuli occurring at a rate of 0.67 Hz, should allow for entrainment of slow oscillatory activity in the delta range (0.05–3 Hz). The distribution of delta activity matched a source in sensorimotor cortex. To evaluate synchronization of delta activity, a virtual channel in the motor cortex of both hemispheres was created by means of spatial filtering using beam-forming techniques (see Methods). Delta band oscillations extracted from this virtual channel were entrained to the rhythm of stimulation as shown by the significant non-uniformity of phase at stimulus onset (Rayleigh's test with  $P < 0.05$ , for both groups, conditions and hemispheres). Instantaneous delta phases (aligned to the preferred phase for all subjects) at stimulus onset in the motor cortex contralateral to the response hand are shown in Figs. 9A–D and show clear non-uniformity of delta phase distributions for both conditions and groups.

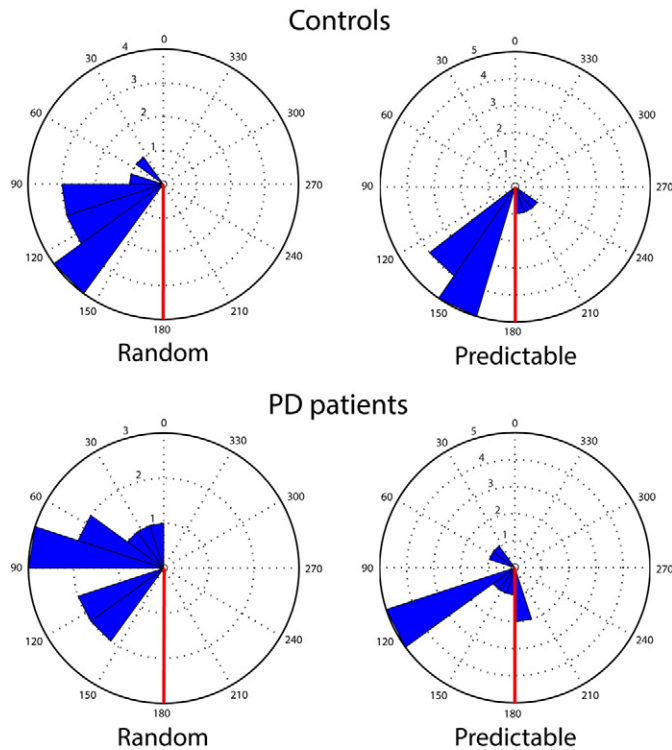
The intertrial phase coherence (ITC), a measure of phase entrainment, was calculated for both groups, conditions and hemispheres separately and submitted to a mixed-design ANOVA. Entrainment was significantly stronger in the predictable than random condition, yielding a significant main effect of Predictability ( $F(1,22) = 25.8, P < 0.0001$ ). There was a significant interaction between the factors Predictability and Hemisphere ( $F(1,22) = 5.0, P < 0.04$ ), and this interaction was explained by a larger difference in entrainment between hemispheres in the predictable than in the random condition, as shown in Fig. 9E. There was a trend of entrainment being stronger in controls than in PD patients, as evidenced by a marginally significant main effect of Group ( $F(1,22) = 4.1, P < 0.055$ ). In spite of the fact that the phase entrainment in the contralateral hemisphere in the predictable condition contributed most to this group difference, the three-way interaction Group by Predictability by Hemisphere did not reach significance ( $F(1,22) = 2.4, P = 0.11$ ).



**Fig. 5.** Time course of group mean beta power changes over the contralateral sensorimotor cortex ROI in the predictable condition. The traces represent power values over the entire beta band (13–30 Hz); the shaded margin represents  $\pm 1$  SEM. The predictive beta modulation was calculated as the percentage of beta ERD that occurred before stimulus onset, i.e. the change in power from pre-stimulus beta-ERS peak to  $t = 0$  (indicated by the vertical green line) relative to the full ERD depth and the change from pre-stimulus beta-ERS peak to post-stimulus beta-ERS trough (indicated by the vertical green plus dark blue line). Note that this calculation is independent of the baseline definition. To facilitate visual comparison of the pre- and post-stimulus changes in beta power between groups, the power traces are baselined at time point zero.



**Fig. 6.** Predictive beta modulation, i.e. the percentage of the beta ERD that occurs before stimulus onset, relative to the full depth of the ERD. The group mean percentage of predictive beta modulation (error bars represent  $\pm 1$  SEM) is shown for both groups in the random and predictable conditions, and ipsi- and contralateral hemispheres.



**Fig. 7.** Instantaneous phase (in degrees) of contralateral beta power changes at stimulus onset for both groups (control subjects and PD patients) and conditions (predictable and random). The red line indicates the beta trough (maximal ERD).

Based on the concept of hierarchical coupling of different oscillation frequencies, we hypothesized that the amount of predictive beta modulation could be related to the delta ITC. Both measures showed a strong contralateral predominance in the predictable condition. We therefore evaluated the correlation between predictive beta modulation with delta phase ITC for all participants, for both hemispheres and conditions. In the predictable condition, entrainment of delta phase in the motor cortex was, across groups, significantly correlated with the cortical

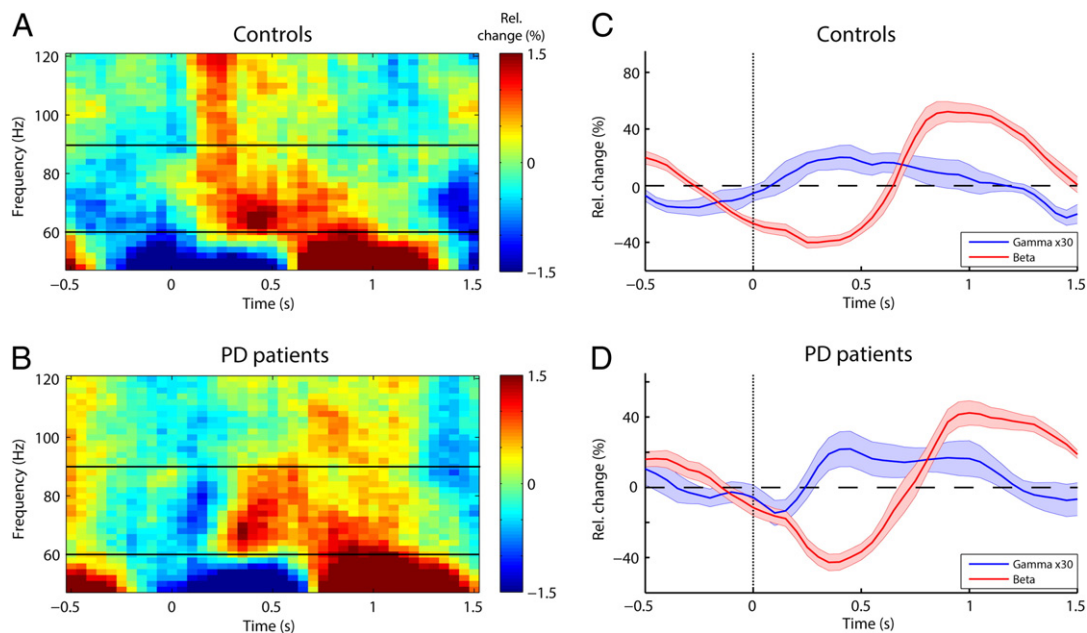
predictive beta modulation in the contralateral ( $r = 0.42$ ,  $P = 0.042$ ), but not in the ipsilateral hemisphere ( $r = 0.23$ ,  $P > 0.20$ ). In the random condition this correlation was, across groups, present both in the contralateral ( $r = 0.41$ ,  $P = 0.045$ ) and in the ipsilateral hemisphere ( $r = 0.45$ ,  $P = 0.026$ ) (see Supplementary Fig. 2). This pattern conforms to the Predictability by Hemisphere interaction that was found both for delta ITC and for predictive beta modulation, and suggests a possible joint role in preparation and interlinked entrainment of delta and beta oscillations by the regular task structure.

## Discussion

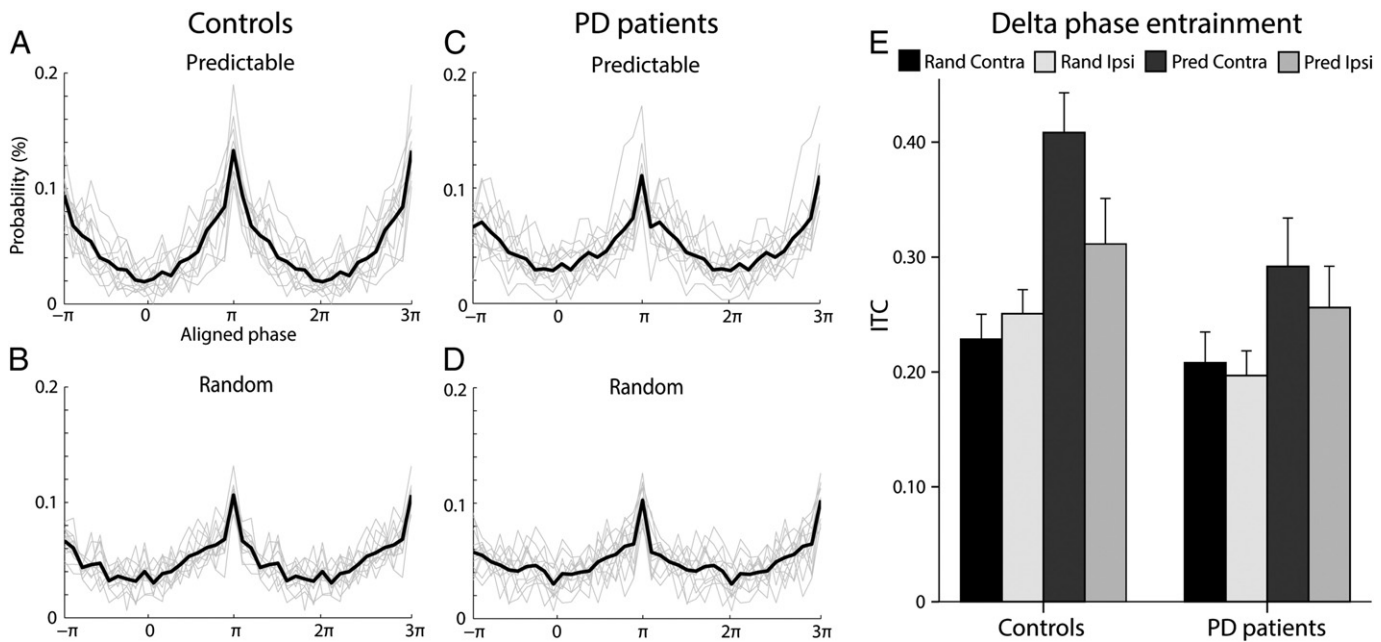
This study used a serial choice response task with a predictable task structure to investigate entrainment of oscillatory brain activity. A fast stimulus presentation rate, temporal predictability, and effector predictability invited advance preparation in an implicit fashion. The undemanding nature of the task resulted in an identical performance of PD patients and control subjects in terms of reaction time and error rate. Task-related beta-frequency oscillatory activity, however, showed a markedly different modulation profile in PD patients compared to control subjects. Associated changes in the delta frequency as well as the gamma frequency range suggest the relevance of hierarchical coupling between oscillations of different frequencies. The findings will be discussed in relation to the proposed prospective nature of beta power modulations, hierarchical coupling of oscillations, and gait rehabilitation based on entrainment with rhythmic cues.

## Behavioral data

Task performance was identical in control subjects and patients, including the benefit gained from the alternating responses in the predictable condition. Hence both groups took advantage of effector predictability. That temporal predictability influenced performance as well, is suggested by the fact that perturbations of the fixed interval (the sequence-final deviant SOAs) caused an increase in reaction time in both groups, as a sign of entrainment. The larger RT-increment in the predictable than in the random condition can perhaps be explained by the further advanced preparation in this condition, incurring an added cost of temporal adjustment. The identical behavioral



**Fig. 8.** Time–frequency representations of gamma activity over the contralateral sensorimotor ROI in the predictable condition. (A) Controls. (B) Patients. The analyzed gamma band (60–90 Hz) is indicated by horizontal black lines. (C) and (D) show the time courses of mean contralateral power changes, in the predictable condition, for the beta (13–30 Hz) band in red, and the gamma band (60–90 Hz), in blue (the traces are represented  $\pm 1$  SEM, indicated by the shaded areas). The traces are aligned relative to the mean across the epoch.



**Fig. 9.** Distribution of instantaneous delta phases (0.05–3 Hz) in the contralateral sensorimotor cortex at stimulus onset. Control subjects (A) and (B). PD patients (C) and (D). The light-gray lines represent the individual subjects and the black lines are the group mean. Phase preference (entrainment) of delta is clearly visible from all phase distributions. Distributions of all individual subjects were aligned by centering the most preferred phase for each individual at  $\pi$  (two cycles are shown). (E) Group mean delta phase entrainment (error bars represent 1 SEM) as measured by the inter-trial coherence for both hemispheres and conditions, for control subjects and PD patients.

performance of PD patients and control subjects is a fortuitous circumstance, allowing differences in neurophysiological measures to be more reliably attributed to altered physiology.

#### Temporal dynamics of beta oscillations

There is increasing evidence for the relevance of excessive beta synchronization to the motor symptoms of PD. Key characteristics of beta power attenuation in the peri-movement time window are influenced by dopaminergic medication (Devos et al., 2006; Doyle et al., 2005; Kühn et al., 2009) and by subthalamic nucleus (STN) stimulation (Giannicola et al., 2010; Kühn et al., 2008; Ray et al., 2008). Moreover, suppression of hypersynchronous beta activity, by medication or STN stimulation, is associated with improved motor performance (Devos et al., 2006; Doyle et al., 2005; Kleiner-Fisman et al., 2003; Ray et al., 2008; Rodriguez-Oroz et al., 2005). Changes in beta activity resulting from dopaminergic medication and/or STN stimulation include an earlier onset of beta-ERD and larger amplitude of beta-ERD preceding and during a self-paced voluntary movement (Devos et al., 2003; Doyle et al., 2005). The relevance of such observations is underscored by the fact that, in reaction time tasks, the onset of beta-ERD and beta power in the STN correlates with reaction time (Williams et al., 2005).

Of specific interest here, beta oscillatory power in PD is not only studied in the peri-movement time window, but also studied during the delay between a warning cue and an imperative signal (Oswal et al., 2012, 2013; Williams et al., 2003). Similar to the behavior of beta activity at the cortical level (Androulidakis et al., 2007a; Gould et al., 2011; van Ede et al., 2011; van Wijk et al., 2009), delay period beta power in the STN is modulated in an anticipatory fashion, based on the information provided by the cue and the anticipated response associated with the imperative signal. Like peri-movement beta activity, delay-period beta oscillatory power is influenced by dopaminergic medication, showing greater reactivity on medication (Oswal et al., 2012). These findings thus support that an important aspect of beta reactivity consists in the presetting of processing resources for future action (Jenkinson and Brown, 2011).

Whereas the above studies manipulated the information provided by the warning signal in an explicit way, our experimental paradigm

influenced anticipatory activity in an implicit fashion. Firstly, the regular interval between reaction stimuli enabled temporal preparation and preparation of both response alternatives in the random condition. Secondly, the alternation of response sides in the predictable condition provided a salient but implicit cue to also prepare for the expected response side. Both manipulations produced the effects we expected. Across conditions, beta power started to reduce well before the next stimulus, yielding a preparatory beta-ERD. This preparatory ERD was larger and displayed a stronger ipsi-contralateral asymmetry in the predictable condition, due to effector selective preparation. Preparatory effects, expressed in the percentage of the beta-ERD occurring before stimulus presentation, were significantly smaller in PD patients than in control subjects. Importantly, the reduced preparatory beta-ERD was manifested as a main effect of Group, thus was not affected by whether the response side was predictable or not. This means that the reduced preparatory beta-ERD represents a deficit in predictive timing or reduced engagement of preparatory processes. Possibly as the result of a larger reactive ERD, the reduced predictive ERD in patients did not produce slower reaction times. The behavioral significance of predictive beta-ERD is nevertheless upheld by the significant modulation by Predictability and by a significant correlation with reaction time.

In spite of existing evidence for a role of beta oscillations in predictive timing and anticipation of future actions (Arnal and Giraud, 2012; Jenkinson and Brown, 2011), one might ask whether the reduced prospective beta-ERD is not primarily due to a sluggish return to baseline or attenuated post-movement beta rebound in PD patients. This alternative account can be rejected for several reasons. Firstly, it is difficult to reconcile with the preserved modulation depth of beta power. Secondly, due to the especially pronounced lateralization of beta-ERS it predicts differences between the predictable and the random condition on the basis of trial repetition. Such an interaction of group by condition, for predictive beta-ERD, was not there. Thirdly, this account would predict that the deficit in predictive beta-ERD is ameliorated with longer intertrial intervals. A reanalysis of data from Praamstra and Pope (2007) (see Addendum) demonstrates that this is not the case. This reanalysis shows a robust deficit in predictive beta-ERD in patients, not recovering with longer intertrial intervals.

### Temporal dynamics of gamma oscillations

Movement execution is accompanied by changes in the beta band, but there are also transient changes in gamma band (60–90 Hz) activity (for a review see [Cheyne, 2013](#)). An increase in gamma power (ERS) is usually seen in the primary motor cortex contralateral to the response hand during movement and this change in gamma power has a more focussed spatial distribution than changes in beta power ([Pfurtscheller et al., 2003](#)). The observed gamma ERS is highly stable over time ([Cheyne and Ferrari, 2013](#)) and occurs irrespective of whether the movement is cued or self-paced ([Muthukumaraswamy, 2010](#)). Important here, gamma power can already increase prior to movement ([Donner et al., 2009](#)). Several studies have shown that gamma activity is also affected in PD, as they show reduced gamma power in rest ([Stoffers et al., 2007](#)), a more bilateral gamma ERS in STN LFPs ([Androulidakis et al., 2007b](#)), reduced gamma-mediated interregional coupling ([Herz et al., 2014b](#)), and an increased coupling between beta phase and gamma amplitude in the primary motor cortex ([de Hemptinne et al., 2013](#)). Reduced gamma power in PD can be restored using dopaminergic medication, and the increase in gamma power correlates with improvement in motor symptoms ([Alegre et al., 2005](#); [Androulidakis et al., 2007b](#); [Devos et al., 2006](#); [Litvak et al., 2012](#)).

In line with the literature, we find a gamma ERS during movement execution in both conditions of the experiment. In the predictable condition this gamma ERS starts significantly earlier in control subjects than in PD patients, whereas in the random condition there is no difference in onset between groups. Interestingly, the temporal profile of gamma power is very similar to the temporal profile of the beta power changes, as shown in [Fig. 8](#). This similarity in temporal profile combined with the significant differences in onset times lends further support to the interpretation that PD patients do not engage in a prospective processing mode. The recent suggestion of coupling between beta and gamma oscillations ([de Hemptinne et al., 2013](#)) could also be relevant for the closely matched time courses in our data. The matched time courses of gamma-ERS and beta-ERD are also reminiscent of the reciprocal relationship between gamma and beta LFP power in the STN region ([Fogelson et al., 2005](#)).

### Entrainment of delta oscillations in motor cortex

The use of a fixed temporal interval between stimuli in the current study enables slow oscillatory activity in the delta band (0.05–3 Hz) to entrain to the stimulus rhythm, in the form of phase resetting of slow oscillations to external events. The entrainment of slow oscillations may serve the purpose of bringing relevant brain structures into an optimal state for processing the stimuli to which they synchronize ([Lakatos et al., 2008](#); [Schroeder and Lakatos, 2009](#)) and can occur not only in the sensory cortices but also in the frontal, parietal and central areas of the cortex ([Besle et al., 2011](#)). Several studies have shown that entrainment is beneficial for stimulus processing as it leads to enhanced sensitivity to (near-threshold) sensory stimuli ([Cravo et al., 2013](#); [Henry and Obleser, 2012](#); [Monto et al., 2008](#); [Saleh et al., 2010](#)), can suppress distracting stimuli ([Gomez-Ramirez et al., 2011](#); [Schroeder and Lakatos, 2009](#)), and lead to faster reaction times ([Stefanics et al., 2010](#)).

In this study we find entrainment of delta oscillations in the motor cortex, measured by phase consistency over trials. In the random condition the entrainment is, as expected, equal for both hemispheres. Since the upcoming response side is unpredictable in this condition, both hemispheres need to be brought into an optimal state for stimulus processing and response preparation. In the predictable condition, however, there was significantly more entrainment in the hemisphere contralateral to the response hand than in the ipsilateral hemisphere, suggesting that participants make use of the implicit effector predictability. The same Predictability by Hemisphere interaction characterized the predictive beta modulation. Previous work has indeed shown

hierarchical coupling between oscillations of different frequencies, for example between delta phase and theta power ([Lakatos et al., 2005](#)), theta phase and beta power ([Cravo et al., 2011](#)) or theta phase and gamma power ([Canolty et al., 2006](#)). We hypothesized that delta phase might be related to beta amplitude and that stronger entrainment of delta oscillations would lead to higher motor readiness, reflected in lower beta power. This was confirmed by the computed correlation between predictive beta modulation and pre-stimulus delta phase entrainment. The obtained correlation is in line with results of [Saleh et al. \(2010\)](#), who suggested that delta phase and beta amplitude work together to enhance sensitivity to predictable and task-relevant visual cues.

Recently it has been suggested that the contingent negative variation (CNV) actually might reflect entrained delta oscillations ([Besle et al., 2011](#); [Lakatos et al., 2013](#)), a proposition strongly supported by data in [Stefanics et al. \(2010\)](#). If this is the case, the tendency to reduced entrainment of delta oscillations that we find here is in line with earlier findings regarding the CNV in PD. Previous studies show that the CNV is reduced or absent in PD patients during implicit timing tasks ([Cunnington et al., 1995](#); [Praagstra and Pope, 2007](#)), but not when PD patients are explicitly instructed to take advantage of the predictable timing of reaction stimuli ([Cunnington et al., 1999](#)). While we considered that the predictable condition in the present study might have a similar effect as explicit instruction (see Introduction), this was clearly not the case, neither for delta ITC nor for predictive beta modulation. Our data thus add to growing evidence for lack of spontaneous entrainment in PD. An interesting early piece of evidence is the observation that the CNV is even more affected in PD than the readiness potential, recorded with self-paced movements ([Ikeda et al., 1997](#)).

### Rhythmic cueing and entrainment of oscillatory activity

Although our study used upper limb responses, the results have relevance to cueing in PD. There are numerous reports that rhythmic cueing improves gait in Parkinson's disease ([Morris et al., 1996](#); [Nieuwboer et al., 2007](#); [Rochester et al., 2009](#); [Thaut et al., 1996](#); [van Wegen et al., 2006](#); [Willems et al., 2006](#); for review see [Nombela et al., 2013](#)), but rhythmic cues can also improve upper limb movements ([Vercruysse et al., 2012](#)). The underlying mechanisms of cueing are not clear, however. The most explicit views hold that external cues facilitate movement on the basis of a recruitment of lateral premotor areas compensating for deficient activation of the medial premotor cortex, effectively bypassing basal ganglia–medial premotor cortex circuits ([Cunnington et al., 1995](#); [Rochester et al., 2007](#)). This view does not have strong support. A recent meta-analysis of functional imaging studies in PD showed that neither increased lateral nor decreased medial activation are consistent findings ([Herz et al., 2014a](#)). Neuroimaging studies in healthy human subjects do also not support a strong segregation between brain activations associated with internally vs. externally cued movements ([Ballanger et al., 2006](#); [Cunnington et al., 2002](#); [Jahanshahi et al., 1995](#); but see [Debaere et al., 2003](#)). Finally, cell recordings in the basal ganglia of primates do not reveal selective involvement of the basal ganglia in internally generated movements ([Mink and Thach, 1991](#); [Turner and Anderson, 2005](#)).

Recent fMRI work on rhythm perception by [Grahn and Rowe, 2009](#) further corrects the above view on two counts. These studies demonstrated that the lateral premotor cortex and the putamen are preferentially activated by rhythms with a strong beat, and that the activation serves the prediction of beat timing in a sequence of stimuli. Hence, if rhythmic cueing relies on the lateral premotor cortex, then this route is not likely to “bypass the basal ganglia”, and serves moreover a predictive mode of motor activation instead of the presumed reactive mode. It has been pointed out already that these data, in fact, raise an important paradox, because if rhythm perception depends on the basal ganglia, how can rhythm improve movement in PD patients ([Chen et al., 2009](#); [Nombela et al., 2013](#))?

The present data reinforce this paradox by the demonstration of oscillatory entrainment with beta-ERD occurring predominantly before reaction stimuli (predictive beta-ERD) in healthy control subjects, contrasting with an entrainment pattern of predominantly reactive beta-ERD in PD patients. This finding suggests that if repetitive external stimulation supports movement in PD, it does not do so by recruiting a control system that is left unaffected by the disease. Nor can it be claimed that it invokes a more automatic mode of activation (Nombela et al., 2013). Note that the data do not discount the possibility that rhythmic cues can be beneficial. A salient aspect of both current data and previous data acquired in a similar paradigm (Praagstra and Pope, 2007) is the preserved depth of the beta power modulation in PD patients, achieved through a higher reactive beta-ERD. This contrasts with the commonly reported reduction of beta ERD and ERS in PD (Degardin et al., 2009; Devos et al., 2003; Doyle et al., 2005; Heinrichs-Graham et al., 2013; Oswal et al., 2012; Pfurtscheller et al., 1998). In combination with PD patients' normal reaction times, this raises the interesting possibility that facilitatory effects of rhythmic or repetitive stimuli in PD are mediated by an enhancement of beta modulation depth.

## Conclusion

Abnormal beta oscillatory activity in basal ganglia–cortical circuits is a known biomarker of PD, with possible pathophysiological significance. We report several new findings with respect to beta activity in PD. The observed shift from a prospective to a reactive modulation of beta power supports the notion that dynamic modulation of beta oscillatory power serves a predictive function (Jenkinson and Brown, 2011; Oswal et al., 2012) and that it is precisely this function which is compromised in PD. We further establish a correlation between predictive beta modulation and phase synchronization of slow delta oscillations. This correlation fits the emerging concept of hierarchical coupling between different oscillation frequencies (Lakatos et al., 2005; Schroeder and Lakatos, 2009), also supported, albeit weaker, by the similarity in time course of beta-desynchronization and gamma-synchronization. The concept of hierarchical oscillatory coupling entails a possible link between the known attenuation of slow brain potentials in PD (Cunnington et al., 1995; Jahanshahi et al., 1995; Praagstra and Pope, 2007; Praagstra et al., 1996a,b; Wascher et al., 1997) and abnormal beta and gamma oscillatory synchrony. It is important to note, however, that the here presented evidence is merely correlational. What also needs further investigation is why predictive beta modulation in PD, the reduction of which indicates a deficit in predictive timing or reduced engagement of preparatory processes, remains sensitive to effector predictability, corresponding with a preserved behavioral benefit. Possibly, the normal performance of patients is not just due to the non-demanding nature of the task, but the result of reduced predictive beta-ERD being compensated by increased reactive beta-ERD, enabled by the rhythmic task structure. If that is the case, the conclusion is warranted that entrainment fails to engender the same predictive mode of motor activation in PD patients as in healthy controls, but that there is still a performance-enhancing effect of entrainment.

## Addendum

For the purpose of comparison with the data of the present paper, beta power modulation in Praagstra and Pope (2007) was reanalyzed. The reanalysis concerned the differentiation of beta-ERD in a predictive and a reactive component, by means of the index described in the Methods. We refer to the original paper for further information concerning the participants (10 PD patients, 12 control subjects), task and EEG data acquisition and analysis. In contrast to the present experiment, the task had two different SOA lengths of 1500 and 2000 ms. There was no manipulation of effector (choice) predictability. Beta

**Table 2**

Predictive beta modulation in the study of Praagstra and Pope (2007). Long and short SOAs refer to intervals of 2000 and 1500 ms respectively.

Condition and hemisphere	Control subjects (% $\pm$ 1 SD)	PD patients (% $\pm$ 1 SD)
Long SOA contralateral	59 $\pm$ 16	35 $\pm$ 18
Long SOA ipsilateral	58 $\pm$ 21	34 $\pm$ 18
Short SOA contralateral	45 $\pm$ 19	25 $\pm$ 18
Short SOA ipsilateral	45 $\pm$ 21	22 $\pm$ 19

power values were measured from symmetrical ROIs, each consisting of five electrodes, overlying the left and right motor cortices.

Across groups, the modulation depth of beta power was influenced solely by Hemisphere, being of higher amplitude contra- than ipsilateral to the side of movement ( $F(1,20) = 17.2$ ,  $P < 0.0001$ ). There was no between groups difference in modulation depth ( $F(1,20) < 1$ ).

Predictive modulation of beta power was higher with long than with short SOAs ( $F(1,20) = 32.0$ ,  $P < 0.0001$ ). Between groups, predictive beta modulation was considerably smaller for patients, as shown in Table 2, resulting in a significant effect of Group ( $F(1,20) = 9.5$ ,  $P < 0.006$ ). There were no interactions involving the factor Group.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2014.06.039>.

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