



Effects of rhythmic stimulus presentation on oscillatory brain activity: the physiology of cueing in Parkinson's disease



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ABSTRACT

The basal ganglia play an important role in beat perception and patients with Parkinson's disease (PD) are impaired in perception of beat-based rhythms. Rhythmic cues are nonetheless beneficial in gait rehabilitation, raising the question how rhythm improves movement in PD. We addressed this question with magnetoencephalography recordings during a choice response task with rhythmic and non-rhythmic modes of stimulus presentation. Analyses focused on (i) entrainment of slow oscillations, (ii) the depth of beta power modulation, and (iii) whether a gain in modulation depth of beta power, due to rhythmicity, is of predictive or reactive nature. The results show weaker phase synchronisation of slow oscillations and a relative shift from predictive to reactive movement-related beta suppression in PD. Nonetheless, rhythmic stimulus presentation increased beta modulation depth to the same extent in patients and controls. Critically, this gain selectively increased the predictive and not reactive movement-related beta power suppression. Operation of a predictive mechanism, induced by rhythmic stimulation, was corroborated by a sensory gating effect in the sensorimotor cortex. The predictive mode of cue utilisation points to facilitation of basal ganglia-premotor interactions, contrasting with the popular view that rhythmic stimulation confers a special advantage in PD, based on recruitment of alternative pathways.

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1. Introduction

There is evidence that rhythmic cues can improve gait in patients with Parkinson's disease (PD) (for review see Keus et al., 2007; Nombela et al., 2013; Spaulding et al., 2013). Recent studies, however, have shown that PD patients are impaired in rhythm perception, especially of beat-based rhythms with strong temporal regularity (Grahn and Brett, 2009). This deficit might have its basis in the involvement of the basal ganglia in rhythm perception and production, as suggested by neuroimaging studies (Grahn and Rowe, 2009, 2013) and by neural recordings in monkey basal ganglia (Bartolo et al., 2014; Bartolo and Merchant, 2015; Merchant et al., 2015). The impairment in rhythm perception and its presumed basis in basal ganglia dysfunction raise the question how rhythm can improve movement in PD patients (Chen et al., 2009; Nombela et al., 2013; Te Woerd et al., 2014).

An important element of the recent evidence for basal ganglia involvement in rhythm perception is that putamen activity and associated putamen-premotor interaction during rhythm perception are engaged in a predictive fashion (Grahn and Rowe, 2009, 2013; Merchant et al., 2015). Notably, relevant putamen-premotor interactions include interactions with the supplementary motor area but also with the

lateral premotor cortex. The predictive engagement of putamen-lateral premotor cortex circuits by rhythm processing underscores the significance of the question how rhythm improves movement in PD. This is because this predictive engagement contradicts the popular view that the lateral premotor cortex supports compensation in PD due to a mode of processing that is more externally driven than requiring internal generation and prediction (Cunnington et al., 1995, 2001; Jahanshahi et al., 1995; Samuel et al., 1997; Sabatini et al., 2000; Debaere et al., 2003; Vercruyssen et al., 2012).

To investigate the physiological basis of rhythmic stimulation benefits in PD, we recorded movement-related brain activity during a choice response task with rhythmic and non-rhythmic modes of stimulus presentation, using magnetoencephalography (MEG) in 15 PD patients and 15 control subjects. There is increasing recognition that brain oscillations tend to entrain to environmental regularities and that this physiological mechanism may underlie behavioural advantages conferred by such regularities (Schroeder and Lakatos, 2009). Hence we analysed slow brain oscillations in the frequency range of the stimulus presentation rate. Of key interest was, furthermore, the response of the sensorimotor beta rhythm, which is a known pathophysiological marker of PD (e.g. Gatev et al., 2006; Hammond et al., 2007; Pollok et al., 2012; Brittain and Brown, 2014), and which is hypothesised to represent an internal likelihood index for pending voluntary action (Engel and Fries, 2010; Jenkinson and Brown, 2011). The magnitude of the

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movement-related beta amplitude modulation, commonly attenuated in PD (e.g. Devos et al., 2003; Doyle et al., 2005; Heinrichs-Graham et al., 2014), was expected to demonstrate a gain with rhythmic stimulus presentation. Crucially, to evaluate whether such a gain is due to the adoption of a more predictive mode of control, as opposed to reactive responding, movement-related beta suppression was separated into a predictive and a reactive phase, occurring before and after a reaction stimulus, respectively (Praamstra and Pope, 2007; Te Woerd et al., 2014). Fig. 1 outlines the different outcome scenarios based on this distinction.

2. Methods

2.1. Participants

Participants were 15 PD patients (10 men; aged 61 ± 5 years) and 15 healthy subjects (9 men; aged 61 ± 5 years). Control subjects were without history of neurological or psychiatric disease. PD patients were of mild to moderate disease severity (see Table 1). 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 $28 (\pm 7)$ on the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) (see Table 1). The investigation and UPDRS rating were performed in the morning, after overnight withdrawal of medication (>12 h).

2.2. Task and procedure

The experiment consisted of a serial choice response task to arrow stimuli presented on a screen, with the response being an index or middle finger button press, depending on the direction of the arrow. The ordering of left and rightward arrows was always random. The critical

experimental manipulation concerned the temporal predictability of successive stimuli, which was manipulated by using two types of blocks. In one version (the “rhythmic” condition), the SOA (stimulus onset asynchrony) between successive stimuli was always 1.5 s. In the other version (the “non-rhythmic” condition), the SOA between successive stimuli varied between 1 and 2 s (in 0.1 s steps, with the majority being 1.5 s ($\sim 40\%$)). Subjects used one hand during each block, starting the first block with their dominant hand and switching to the other hand for the next block. Half the subjects started with the rhythmic, the other half with the non-rhythmic condition. Rhythmicity was alternated every two blocks, such that all subjects first performed one condition with both hands before switching to the other condition.

The experiment was divided in eight blocks of ~ 5 min each, containing 160 stimuli per block. Each block was preceded by a 20 s resting period during which ongoing brain activity was recorded. In order to make an unbiased comparison between conditions, only the 1.5 s intervals from the non-rhythmic condition were used for analyses and an equal number of stimuli from the rhythmic condition. The experiment was preceded by a short practice block and participants were instructed to press the correct button as swift as possible, and were not made aware of the rhythmicity manipulation. Stimuli were presented with Presentation 14.9 software (Neurobehavioral Systems), using a liquid crystal display video projector, and back-projected onto a translucent screen in the magnetically shielded room. Participants were seated in the MEG-chair with their eyes 75 cm from the screen, and response pads attached to the armrests of the chair. Stimuli were presented in white on a grey background for 300 ms. The fixation area was permanently indicated by 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.

2.3. MEG recordings

Ongoing brain activity was recorded using a whole-head MEG system with 275 axial gradiometers (VSM/CTF Systems, Coquitlam, BC) in a magnetically shielded room. During the experiment, we continuously measured head position relative to the sensor array using localisation coils that were placed at the nasion and in the left and right ear canals. Vertical electro-oculogram (EOG) was recorded from the supra- and infraorbital ridges of the left eye, and horizontal EOG from the bilateral canthi. MEG and EOG data were sampled at 1200 Hz.

2.4. Behavioural analyses

Reaction time analyses were performed on the responses to the visual cues. We excluded trials with erroneous responses and discarded trials in which the response was too slow (>900 ms). Mean response times were determined for each condition separately. Differences in reaction time variability, at the individual subject level, were determined by using the coefficient of variation (ratio of standard deviation to the mean response time). As musical training could influence the experimental outcomes (Grahn and Rowe, 2009), all subjects filled out the subpart ‘musical training’ of the Goldsmiths Musical Sophistication Index (v1.0) (Müllensiefen et al., 2014). All correlations between reaction time and other behavioural or neurophysiological markers are calculated by means of a (parametric) Pearson correlation, and are listed with uncorrected p-values. However, if a correlation does not survive a Bonferroni correction for multiple comparisons, this is explicitly mentioned.

2.5. MEG data preprocessing

MEG data were analysed with MATLAB (2011b) (Mathworks, Natick, MA) using the open-source FieldTrip toolbox (Oostenveld et al., 2011). For the main analyses, epochs of 5000 ms (3000 ms

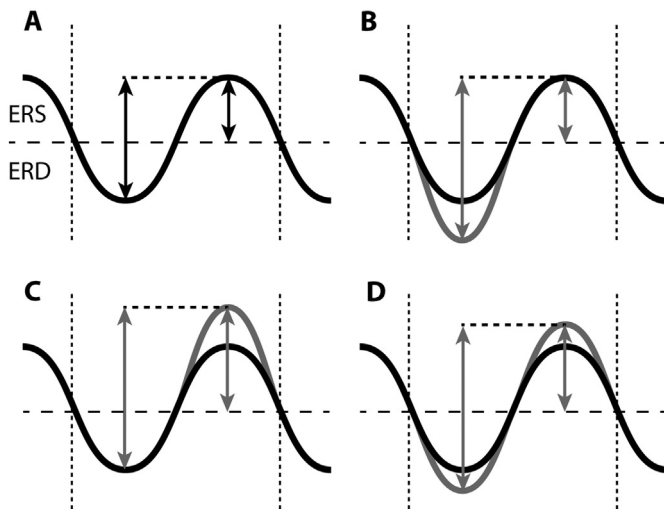


Fig. 1. Possible outcome scenarios of changes in beta power modulation as a result of rhythmic vs. non-rhythmic stimulus presentation. (A) Typical time course of beta power in a serial reaction task with stimuli presented at time points indicated by vertical lines. A decrease of beta power relative to baseline is called event-related desynchronisation (ERD). An increase of power is called event-related synchronisation (ERS). Movement preparation and execution is accompanied by a beta ERD (movement-related beta suppression). This suppression can be divided in a predictive and a reactive part. Predictive beta suppression is calculated as the power change from pre-stimulus ERS-peak to stimulus-onset (shown by the right arrow in A) relative to the modulation depth (from pre-stimulus ERS-peak to subsequent ERD-trough; left arrow in A). Rhythmic stimulus presentation is expected to increase the beta modulation depth. (B) This increase might be mediated by a stronger desynchronisation, producing higher amplitude reactive beta suppression. (C) Alternatively, it might be mediated by a stronger synchronisation, indicating a predictive mode of cue utilisation and yielding higher predictive beta suppression. (D) An increase in beta modulation may also consist of increased synchronisation and desynchronisation phases.

Table 1
Demographic and clinical characteristics of participating Parkinson patients. UPDRS motor score was determined directly after the experiment. Levodopa was always used with a dopadecarboxylase inhibitor.

Subject number	Age (years) and gender	Years since diagnosis	Most affected side	UPDRS motor score	Dominant hand	Medication (daily dose)
1	66, M	13	R	37	R	Levodopa 1000 mg Entacapone 800 mg Pramipexol 1 mg
2	63, M	10	R	30	R	Levodopa 700 mg
3	66, M	6	L	40	R	Levodopa 700 mg Pramipexol 1.125 mg
4	56, M	3	R	22	R	Levodopa 300 mg
5	53, M	2	L	27	R	Levodopa 700 mg
6	61, M	14	R	24	L	Levodopa 500 mg Pramipexol 3.75 mg
7	54, F	6	R	33	R	Levodopa 800 mg
8	68, F	15	L	30	R	Levodopa 850 mg Pramipexol 3.75 mg Amantadine 200 mg
9	63, F	5	L	14	R	Levodopa 600 mg Pramipexol 1.5 mg
10	66, M	2	L	22	R	Levodopa 300 mg
11	55, F	4	L	25	R	Levodopa 600 mg Pramipexol 0.375 mg
12	56, M	7	R	33	R	Levodopa 500 mg
13	69, M	5	L	25	R	Levodopa 300 mg Pramipexol 1.125 mg
14	58, F	7	L	19	R	Levodopa 300 mg Ropinirol 6 mg Selegiline 10 mg Amantadine 200 mg
15	62, M	6	R	32	L	Levodopa 900 mg Entacapone 800 mg Ropinirol 2 mg Amantadine 200 mg
Mean (\pm SD)	61 \pm 5	7 \pm 4		28 \pm 7		

pre-stimulus and 2000 ms post-stimulus) were extracted from the continuous data separately for both task conditions and response sides. After removal of trials containing muscle artefacts, slow drift, or SQUID (superconducting quantum interference device) jumps, data were down-sampled to 600 Hz. Independent component analysis was used to remove any remaining variance caused by eye blinks and heart-beat artefacts. As an extra check, the remaining data epochs were visually inspected and any remaining epochs with artefacts were removed manually. The remaining stimulus-locked epochs were submitted to time-frequency and statistical analyses. For more details about the pre-processing, we refer to [Te Woerd et al. \(2014\)](#). All statistical analyses presented here were performed using SPSS version 19 (IBM Corp. Armonk, NY) unless stated otherwise.

2.6. MEG analyses

2.6.1. Beta activity

Since beta oscillatory activity (13–30 Hz) is most prominent in the sensorimotor system, and lateralises with unimanual responses, sensorimotor regions of interest (ROI) were determined by a subtraction (across conditions and groups) of beta activity associated with the left and right hand responses. Subsequently, the 25 channels with strongest beta modulation above each hemisphere were selected and those without a homologous sensor over the opposite hemisphere rejected. This resulted in two symmetric ROIs overlying the sensorimotor cortices with 19 sensors each.

Differences in oscillatory power in the ROIs between conditions were investigated by means of cluster-based non-parametric permutation tests ([Maris and Oostenveld, 2007](#)) in FieldTrip. To study beta power changes 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 pre-stimulus ERS and subsequent ERD trough. The amount of predictive beta modulation was defined as the change in beta power from maximum pre-stimulus ERS to the time of stimulus onset, relative to the modulation depth. The baseline against which beta power changes were measured was defined by the mean power of the analysis epoch, effectively the same as the mean power across the whole measurement session ([Tan et al., 2014a](#)). The results were verified with an alternative baseline, i.e., the resting power before the start of experimental blocks.

2.6.2. Delta activity

For the analyses of delta phase entrainment, the source of beta activity was identified using frequency-domain beam-forming source estimation ([Gross et al., 2001](#)). We contrasted the beta ERD with the beta ERS activity using two 500 ms time windows centred on the time points of maximal post-stimulus ERD and ERS. As the beam-former input required only one frequency, we used the 20 Hz frequency (resulting in 10 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 MRI (if available) or an MNI template-MRI ([Holmes et al., 1998](#)). The brain volume of each individual was discretised to a grid with a 10 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 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. Delta phase analyses were performed on spatially filtered data using a time-domain beam-former source estimation ([Van Veen et al., 1997](#)). This beam-forming spatial filter for the stored location of

interest (the contralateral motor cortex) was used to filter the MEG data. The LCMV spatial filter passed the activity at the location of interest with unit-gain, while optimally suppressing all other noise and source contributions to the MEG data. To allow the estimation of phase at low frequencies, we expanded each data epoch with mirror (time-reversed) images of itself. This procedure increased the length of each epoch to ~16.7 s (resulting in a ~0.067 Hz frequency resolution) while preserving data continuity (Cohen, 2014). The strength of phase preference was acquired by calculating the intertrial phase coherence (ITPC) over all trials within each individual in the frequency range 0.13–10 Hz. Evoked power was investigated by averaging all epochs and submitting the averaged epoch to time-frequency analysis using a single Hanning taper and an adaptive window of three cycles for each frequency in the range 0.13–10 Hz. As a strong ITPC at the task rhythm (~0.67 Hz) could also be caused by evoked activity from stimulus presentation, we calculated the power of evoked activity at 0.67 Hz for all subjects and conditions and used a repeated measures ANOVA to test for differences between conditions and groups. For the analysis of instantaneous phase, all epochs were band-pass filtered between 0.05 and 3 Hz using a finite impulse response least squares filter. Phase values were calculated using the Hilbert transform of the band-pass filtered data. To test if any phase preference was present at stimulus onset, Rayleigh's test for uniformity of phase data was used (Fisher, 1993). Rayleigh's test and ITC calculations were performed using the MATLAB circular statistics toolbox (Berens, 2009).

3. Results

3.1. Behavioural data

Participants had to respond as fast as possible to arrow stimuli presented on screen. Mean response times to all intervals were faster in the rhythmic than non-rhythmic condition (controls: 401 ± 49 ms vs 422 ± 43 ms; PD patients: 460 ± 82 ms vs 486 ± 81 ms), yielding a significant main effect of Rhythmicity ($F_{1,28} = 45.6, P < 0.0001$) (see Fig. 2). Mean response times of control subjects were faster than those of PD patients, as indicated by a main effect of Group ($F_{1,28} = 6.6, P = 0.016$). However, both groups benefitted equally from rhythmicity, as there was no interaction between Rhythmicity and Group ($F_{1,28} < 1$). The amount of musical training was not different between groups ($F_{1,28} = 1.4, P = 0.25$), and did not correlate with reaction time benefit ($r = 0.11, P = 0.55$).

3.2. Oscillatory brain activity

3.2.1. Phase entrainment of delta oscillations

Since the rhythmic stimuli allow for entrainment of slow oscillations, we analysed phase synchronisation in the delta band (0.05–3 Hz) using a virtual channel located in the contralateral motor cortex. Oscillatory delta-band activity was entrained to the reaction stimuli as shown by analyses of phase-consistency over trials (Fig. 3). Delta-band oscillations showed a significant phase preference at stimulus onset (Rayleigh's test for non-uniformity with $P < 0.05$, for both groups and conditions). The instantaneous phases of delta at stimulus onset (aligned to the preferred phase for all subjects) in the motor cortex are shown in Fig. 3A. Phase synchrony was significantly stronger (as represented by the modulus length, Fig. 3D) in the rhythmic than non-rhythmic condition, yielding a main effect of Rhythmicity ($F_{1,28} = 6.7, P = 0.015$). Overall, phase synchrony was stronger in healthy controls than PD patients ($F_{1,28} = 7.8, P = 0.009$), but there was no interaction between the factors Rhythmicity and Group. The strength of delta phase synchrony correlated with response speed, but only in the rhythmic ($r = -0.41, P = 0.024$; uncorrected p-value, does not survive multiple comparison correction) and not in the non-rhythmic condition ($r = -0.21, P = 0.27$), supporting a behavioural benefit of entrainment of slow oscillations in conditions of rhythmic stimulus presentation, that is absent with non-rhythmic presentation (cf. Cravo et al., 2013).

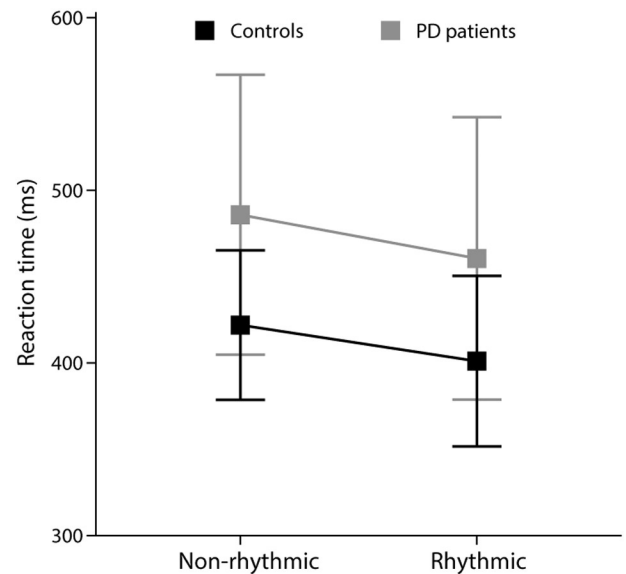


Fig. 2. Group mean response times for both groups in the non-rhythmic and rhythmic conditions. Error bars represent 1 standard deviation, and all reaction times are averaged over left and right hand responses.

Relevant to the interpretation of phase synchrony is whether it is due to alignment of endogenous slow oscillations as opposed to a stimulus-evoked effect. The fact that there was no increase in power at the task rhythm (0.67 Hz) (Fig. 3C), suggests that the strong ITPC values at this frequency (Fig. 3B) reflect the entrainment of endogenous oscillations. This is supported by the fact that evoked power (at the task rhythm) at stimulus onset was stronger in the non-rhythmic than rhythmic condition for both groups ($F_{1,28} = 28.2, P < 0.001$) (Fig. 3F), while the ITPC effect showed a trend in the opposite direction ($F_{1,28} = 3.1, P = 0.09$) (Fig. 3E).

Together, these results show that phase synchronisation across conditions was weaker in patients than in controls. Entrainment, i.e., elevated phase synchronisation with rhythmic stimulus presentation, was the same in both groups. The behavioural relevance of this entrainment was supported by a correlation with reaction time.

3.2.2. Distribution of sensorimotor beta activity

Time-frequency analyses of data from the ROI-sensors 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 desynchronisation to subsequent maximum synchronisation. The modulation of beta activity was maximal over the motor cortex contralateral to the response hand, as seen in Fig. 4.

As shown in the time-frequency plots of Fig. 5, 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 before and during movement, and a subsequent increase in beta power shortly after movement termination. These power changes were, for both groups, stronger in the rhythmic than non-rhythmic condition, as shown by two clusters of stronger desynchronisation and one of synchronisation ($P < 0.032$ for all clusters).

3.2.3. Rhythmicity and beta modulation depth

The modulation depth was significantly larger in the rhythmic than in the non-rhythmic condition ($F_{1,28} = 25.0, P < 0.0001$), and was larger in the hemisphere contralateral than ipsilateral to the response hand, for both groups ($F_{1,28} = 153.3, P < 0.0001$) (see Fig. 6A-B). More importantly, there was no interaction between Group and Rhythmicity ($F_{1,28} < 1$). This means that the increase in modulation depth was

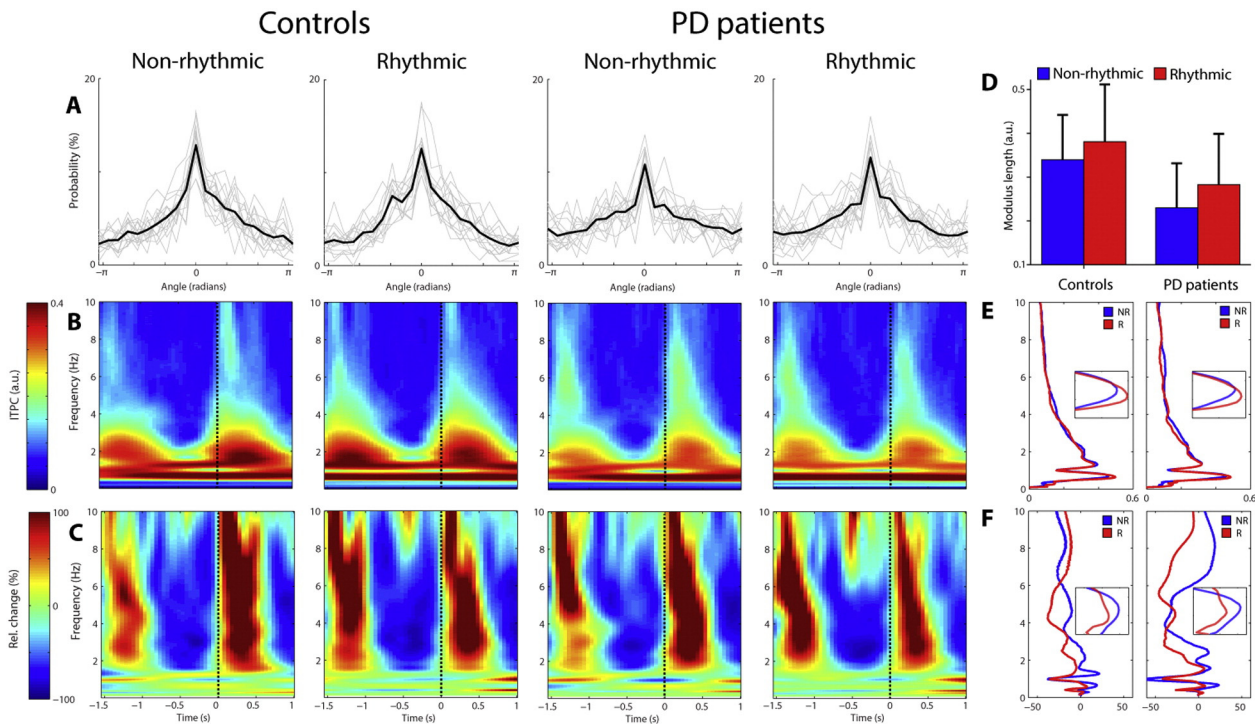


Fig. 3. Phase entrainment analyses in a virtual channel located in the motor cortex contralateral to the response hand (all results are averaged over all trials and response hands). (A) Distributions of instantaneous delta phase at stimulus onset (aligned to the preferred phase of each subject). The light grey traces show all individual subjects, and the black traces are the group means. Intertrial phase coherence (ITPC) values (B) and evoked (ERF) power (C) are shown for both groups and conditions. (D) Overview of modulus lengths resulting from the phase distributions in (A) for both groups and conditions. ITPC values (E) and evoked power (F) at stimulus onset for both conditions (non-rhythmic in blue, rhythmic in red) and groups (controls in left panel and PD patients in right panel). Insets show the ITPC and evoked power around the stimulation frequency (0.67 Hz) at stimulus onset.

equal for both groups. Also, in both groups, the increase in modulation depth was solely caused by a stronger ERS phase (as shown by the difference between conditions in Fig. 5), with similar spatial distribution for both groups (Fig. 6D).

Figs. 5 and 6 show an apparent reduction in modulation depth in PD patients, but there was not a significant difference between groups ($F_{1,28} = 2.2, P = 0.15$). The apparent difference between the group averages could be due to greater variability in reaction times in the patient compared to the control group, leading to poorer alignment of ERD and ERS phases. This mechanism cannot explain the between-conditions effect, as reaction time variability was similar between conditions. The difference between rhythmic and non-rhythmic condition can neither be explained by a difference in reaction time variability (between conditions) at the individual subject level. This was established by computing for each subject and condition the coefficient of variation. A Group by Rhythmicity analysis of this coefficient revealed no significant difference between groups ($F_{1,28} = 1.7, P = 0.20$), nor a difference between conditions ($F_{1,28} = 1.8, P = 0.19$).

To rule out any effects due to the choice of baseline, the same analyses were repeated with data baselined to a 20 s resting period before the start of each block (Fig. S1). These analyses showed the same results as presented here, and confirmed that the increase in beta modulation depth was exclusively due to a higher amplitude synchronisation phase.

The behavioural relevance of the increased modulation depth was underscored by a significant correlation between beta modulation depth in the contralateral hemisphere and reaction time (across groups), in both the non-rhythmic ($r = -0.46, P = 0.011$) and rhythmic condition ($r = -0.50, P = 0.005$) (Fig. S2).

3.2.4. Predictive beta modulation

Predictive beta modulation was calculated as the percentage of beta modulation that occurred before stimulus onset (beta power change from maximal pre-stimulus ERS to stimulus onset) compared to the total beta modulation depth (beta power change between maximal

ERS and subsequent maximal ERD). By definition, this means that a stronger ERS will lead to an increase in predictive beta modulation (assuming the ERD remains the same), while a stronger ERD phase leads to a decrease in predictive modulation. Across groups, the predictive beta modulation was higher in the rhythmic than non-rhythmic condition ($F_{1,28} = 28.7, P < 0.0001$), which agrees with the higher amplitude ERS phase in the rhythmic condition. The predictive beta modulation was higher in the contralateral than ipsilateral hemisphere ($F_{1,28} = 52.6, P < 0.0001$) and significantly lower in PD patients than in healthy controls ($F_{1,28} = 4.9, P = 0.035$). There were no interactions involving the factors Group, Rhythmicity or Hemisphere.

There was a significant correlation (across groups) between predictive beta modulation in the hemisphere contralateral to the upcoming response hand and reaction time, in both the non-rhythmic ($r = -0.55, P = 0.002$) and rhythmic condition ($r = -0.72, P < 0.001$) (Fig. S2). The correlation between the between-conditions difference of both the predictive modulation and reaction time was also significant ($r = 0.46, P = 0.01$), meaning that the speeding of reaction time correlates with the increase in predictive beta modulation. Since we found a correlation between reaction time and both the contralateral modulation depth and predictive beta modulation, we used partial correlations to find out which of the two best explained reaction time. There was a significant partial correlation between predictive beta modulation and reaction time, regressing out modulation depth, in both conditions (non-rhythmic: $r = -0.48, P = 0.009$; rhythmic: $r = -0.66, P < 0.001$). Partial correlations between modulation depth and reaction time, regressing out predictive beta modulation, showed a trend towards significance in both conditions (non-rhythmic: $r = -0.36, P = 0.057$; rhythmic: $r = -0.35, P = 0.06$). These findings indicate that both modulation depth and predictive modulation of contralateral beta oscillatory power are related to reaction time, the latter more robustly.

Based on previous studies showing a coupling between delta and beta oscillatory activity in rhythmic tasks, we investigated the

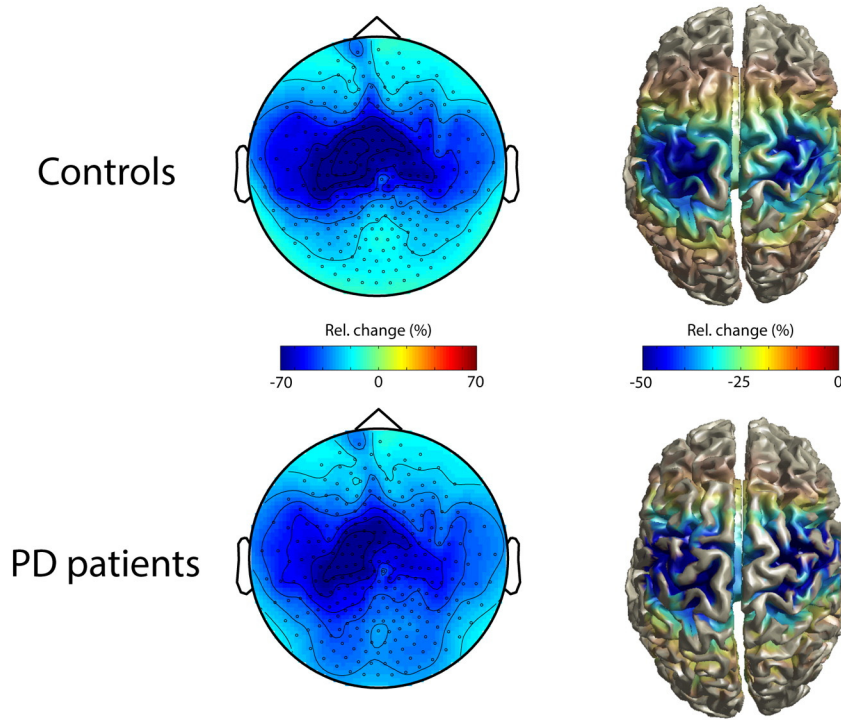


Fig. 4. Spatial distribution of the beta power modulation (in % change), measured from maximal post-stimulus ERD to maximal ERS, at the sensor level (left panel) and projected onto an MRI-derived cortical surface (right panel). The topographies are averaged over both conditions and response hands (by first mirroring the topographies of the left hand condition over the anterior–posterior axis and then averaging over the right and left hand conditions), but separately for both groups (scaling of the PD group is increased by 10% for illustrative purposes). Thus, the left hemisphere sensors are contralateral, and the right hemisphere sensors ipsilateral to the side of movement.

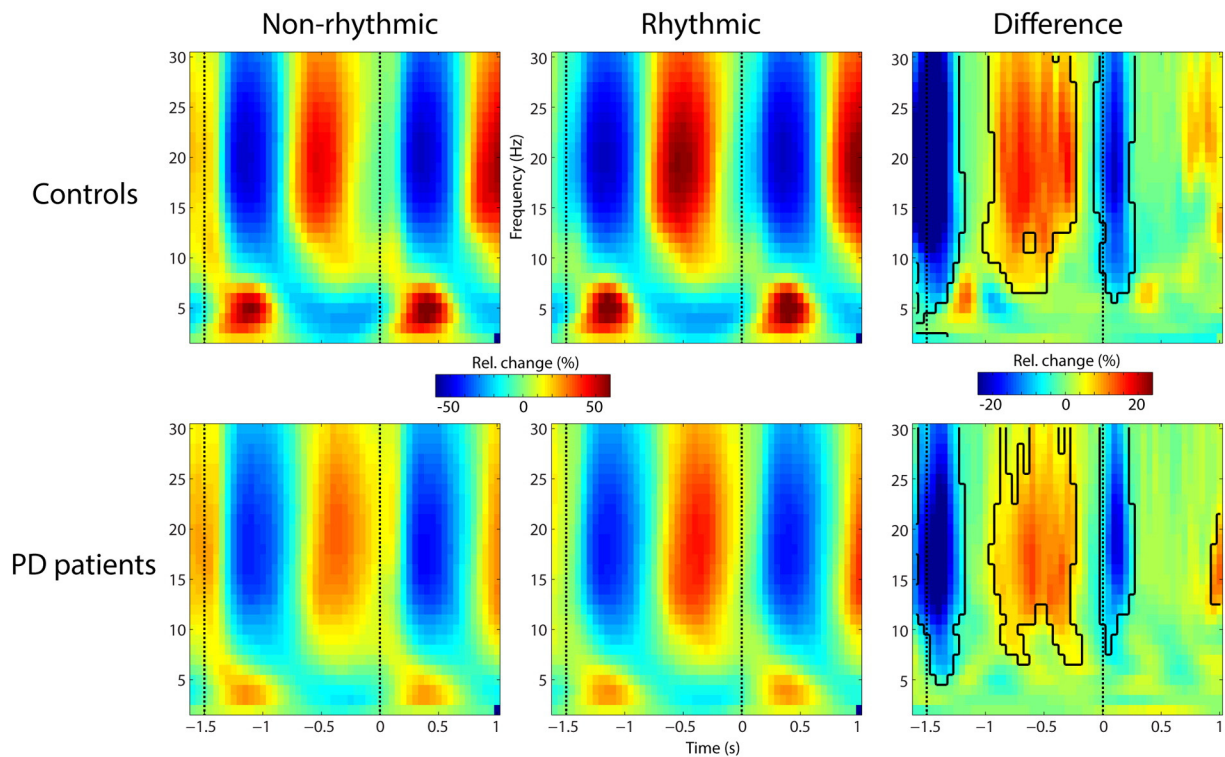


Fig. 5. Time-frequency representations of the changes in spectral power in the contralateral sensorimotor area ROI (see Fig. 6C) for controls and PD patients in both the non-rhythmic and rhythmic conditions. The vertical dotted lines indicate stimulus onset. The power difference (rhythmic minus non-rhythmic) between conditions is represented in the right-most column. Black solid lines surround time-frequency clusters that are significantly different ($P < 0.05$) between conditions, as tested by means of a cluster-based nonparametric permutation test. Note, there are two significant clusters of beta ERD, of which the first is due to averaging of trials with non-equal SOAs preceding the standard 1.5 s interval in the non-rhythmic condition. The second cluster of ERD represents a sensory gating effect (see Section 3.2.5).

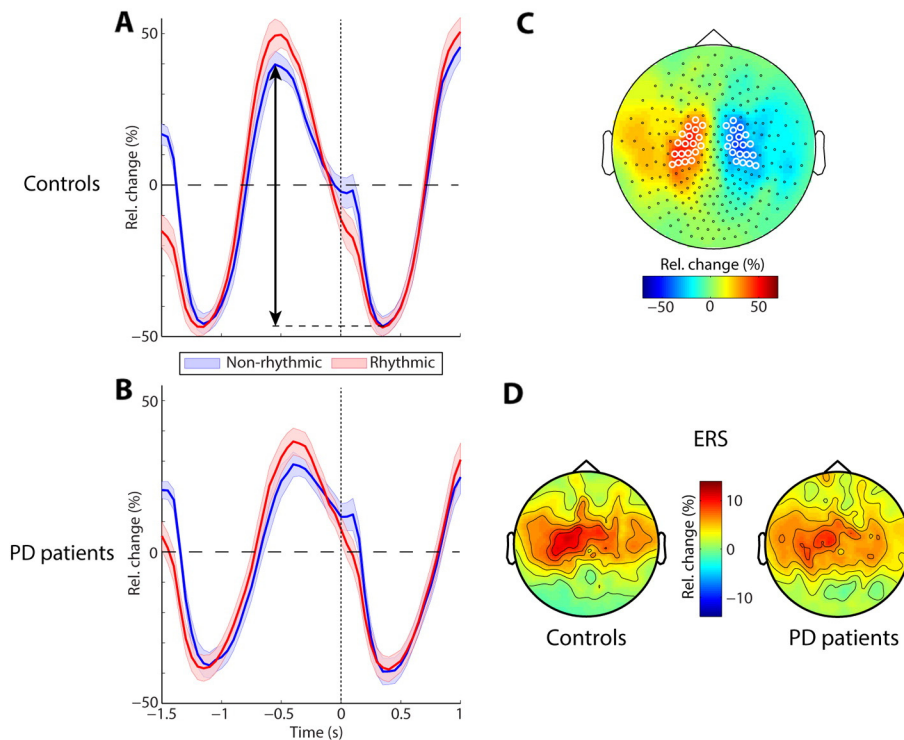


Fig. 6. The group mean beta power changes over time, averaged across all beta frequencies (13–30 Hz) and all sensors overlying the ROI contralateral to the response hand (in C). Beta power traces are shown for controls (A) and PD patients (B) in the non-rhythmic (blue traces) and rhythmic (red traces) conditions. Beta modulation depth is equal to the difference between maximal pre-stimulus ERS and subsequent ERD trough (shown by the black arrow). Shaded areas around the mean beta power traces represent the SEM, and the vertical dotted line indicates stimulus onset. Topography of the difference in beta power between conditions is shown in (D), during a 200 ms-window around the ERS peak (averaged across both hands, 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).

correlation between the strength of delta phase entrainment and the amount of predictive beta modulation. This correlation was significant in the rhythmic ($r = 0.38$, $P = 0.041$), but not in the non-rhythmic condition ($r = 0.09$, $P = 0.65$), supporting that phase-amplitude coupling of delta and beta oscillations may contribute to the behavioural advantage observed in the rhythmic condition.

3.2.5. Modulation of stimulus-evoked beta activity

In both groups, the beta power in the non-rhythmic condition briefly increased at a fixed latency of ~100 ms after stimulus onset, showing a small peak. In the rhythmic condition this peak reduced to a mere notch. The peak and notch correspond in time with a robust peak of beta synchronisation over posterior areas, at which location there was no amplitude difference between conditions. The short latency and temporal coincidence with posteriorly distributed beta synchronisation of high amplitude indicate that the central beta modulation concerns a modulation of stimulus-evoked beta activity. Importantly, the reduced beta power in the rhythmic condition reveals a gating of sensory input to sensorimotor areas due to further advanced movement preparation in this condition (Seki and Fetz, 2012). Within the sensorimotor cortex ROI, the size of the beta power difference between rhythmic and non-rhythmic conditions was identical between groups ($F_{1,28} = 1.5$, $P = 0.23$). Analysis of this between-conditions effect across all sensors revealed a cluster of sensors in which beta power was significantly lower in the rhythmic compared to non-rhythmic condition for both controls ($P < 0.001$) and PD patients ($P < 0.001$). This effect displayed a focus over the contralateral sensorimotor cortex. The gating effect corroborates that the gain in beta modulation depth, the elevated beta-ERS, and the increased predictive beta suppression express increased preparatory activity due to a predictive mode of cue utilisation.

4. Discussion

The main results of this study are, first, that PD patients benefit from a rhythmic compared to a non-rhythmic presentation of stimuli, both in terms of reaction time, entrainment of slow oscillations, and properties of beta oscillatory activity. Second, the entrainment of slow oscillations and the increase in modulation depth of beta oscillatory activity in PD patients, under a rhythmic stimulation regime, are identical to those in healthy control subjects. Third, the increase in modulation depth of beta oscillatory activity is, both in patients and controls, entirely due to an increased beta ERS phase that improves the predictive movement-related beta suppression, reflecting a predictive mode of cue utilisation. Fourth, the beneficial effect of rhythmic stimulus presentation on reaction time, phase synchronisation of slow oscillations and predictive beta suppression, in both groups, are found against the backdrop of an overall significant group difference on these measures, with patients demonstrating slower reaction times, poorer phase synchronisation and smaller predictive beta suppression.

There is growing recognition of the role of temporal prediction in human behaviour (e.g. Large and Jones, 1999; Schwartz and Kotz, 2013; Calderone et al., 2014). One form of temporal prediction is based on environmental regularity, mediated by endogenous neural oscillations that align to regular external events (Schroeder and Lakatos, 2009). This alignment occurs in such a way that timing of low and high excitability phases of neural oscillations are optimised to the processing of relevant events (Lakatos et al., 2008; Henry and Obleser, 2012). Entrainment of neural oscillations to the temporal structure of a task has demonstrated effects in a variety of behaviours and analyses of oscillatory entrainment are beginning to be applied to neurological and psychiatric disorders (Praagstra and Pope, 2007; Lakatos et al., 2013; Calderone et al., 2014; Leong and Goswami, 2014; Te Woerd et al., 2014). In PD such analyses have added relevance due to the wide application of rhythmic cueing in rehabilitation.

Investigations and reviews on cueing in PD frequently refer to compromised basal ganglia-cortical loops involving (pre-)SMA, resulting in impaired timing and impaired generation of internal cues for the sequencing of actions (Cunnington et al., 1995; Rochester et al., 2007; Nombela et al., 2013). External cues would improve motor function on the basis of increased activity of the lateral premotor cortex, probably supported by greater reliance on cerebellar-thalamocortical circuits, bypassing basal ganglia-thalamocortical loops (Cunnington et al., 1995, 2001; Samuel et al., 1997; Rochester et al., 2007; Yu et al., 2007; Sen et al., 2010; Vercruyse et al., 2012; Benoit et al., 2014). This view on cueing, assuming a shift in activation from medial to lateral premotor cortex and, subcortically, a shift from basal ganglia to cerebellum (Hughes et al., 2010), has also been criticised, however. It has been noted that there is no preferential involvement of the basal ganglia in internally generated movements (Turner and Anderson, 2005; Ballanger et al., 2006), and that functional specialisation of medial and lateral premotor cortex for internally and externally cued movements is relative (Jahanshahi et al., 1995; Cunnington et al., 2002; Ballanger et al., 2006; Gowen and Miall, 2007). In a recent meta-analysis of imaging studies in PD, moreover, no evidence was found for a shift in activation from medial to lateral premotor areas (Herz et al., 2014a). Imaging studies comparing on and off states, furthermore, have shown that relative overactivation of lateral premotor cortex in PD is a feature of the off state only, eliminated by dopaminergic therapy which restores activity and connectivity of the SMA (Rowe et al., 2010; Michely et al., 2015). EEG studies using this approach revealed a similar pattern in restored oscillatory coupling of the SMA with prefrontal, premotor and motor cortex (Herz et al., 2014b, 2014c).

Recent work on rhythm perception has given an intriguing new perspective on this discussion. Grahn and Brett (2009) found impaired perception of beat-based rhythms in PD. Perception of such rhythms does indeed rely on activation of putamen-premotor circuits with both SMA and lateral premotor cortex (Grahn and Rowe, 2009; Geiser et al., 2012), with the putamen activation specifically serving beat prediction (Grahn and Rowe, 2013). As pointed out in the introduction, this raises an important question with respect to rhythmic cueing: if PD patients are impaired in the perception of beat-based rhythms with strong temporal regularity, how can they benefit from rhythmic cueing (Chen et al., 2009; Nombela et al., 2013)? A closely linked question, not addressed before, is whether a benefit, if it is there, preserves the predictive nature of putamen-premotor involvement in rhythm processing or takes a different, more reactive form.

Based on the available evidence on movement-related beta activity, we hypothesised that a behavioural benefit of rhythmic stimulus presentation should be accompanied by an increase of beta power modulation depth in PD. We were specifically interested in whether such an increase is due to a gain in synchronisation or a gain in desynchronisation (see Fig. 1). Previously, we have observed a preserved modulation depth in PD, but with a shift from predominantly predictive to more reactive modulation. That is, relative to control subjects patients demonstrated little beta desynchronisation before the reaction stimuli, but a much larger desynchronisation after the stimulus, possibly in compensation (Praagstra and Pope, 2007; te Woerd et al., 2014). In a direct comparison of rhythmic and non-rhythmic stimulus presentation, this puts key significance on the sign of a gain in modulation depth. An increase in the *synchronisation* phase, with concomitant increase of predictive beta modulation fits the predictive nature of basal ganglia involvement in rhythm processing (Grahn and Rowe, 2009, 2013), and would provide an argument for rhythmic cueing to facilitate impaired basal ganglia-cortical communication. A qualitatively different increase in the *desynchronisation* phase, by contrast, would be an argument for beneficial effects of rhythmic stimulation to be based on mechanisms that perhaps bypass the basal ganglia. That is, preparatory adjustments enabled by rhythmic stimulus presentation may involve motor preparation, but also the presetting of stimulus processing mechanisms (Requin et al., 1991; Müller-Gethmann et al., 2003; SanMiguel et al., 2013).

When the latter form of preparation predominates, an increase in beta modulation depth may be reactive only.

The effects of rhythmic stimulus presentation were unambiguous. The gain in modulation depth was of the same size in patients and controls. In addition, the gain was entirely due to stronger synchronisation in both groups, which resulted in a significantly increased predictive beta suppression. Both these features are in agreement with the predictive nature of basal ganglia involvement in rhythm processing. Importantly, the sensory gating effect, which was of equal amplitude in patients and controls, provides strong confirmation of a predictive mode of cue utilisation. Finally, the topographic distribution of the beneficial effects of rhythmic stimulation was identical between groups. This combination of results strongly suggests that the neural mechanism by which rhythmic stimulation facilitates movement is the same for patients and control subjects.

Serendipitously, the selective modulation, by temporal regularity, of the ERS phase of the movement-related beta amplitude modulation closely resembles a recently described effect on beta-ERS of movement errors in a visuomotor adaptation task (Tan et al., 2014a). The authors found a negative correlation between error size and amplitude of the beta-ERS phase, leading to the hypothesis that this beta-ERS effect serves the trial-to-trial modification of an internal model that guides future movement. In our experiment, the difference between actual and expected (mean or most frequent) interstimulus interval may also have acted as an error signal, influencing the beta-ERS modulation. The resemblance of the effects on beta-ERS is important for several reasons. Firstly, beta-ERS was hitherto understood as related to an idling state of the motor cortex or to sensory afferent processing (Pfurtscheller et al., 1996; Cassim et al., 2001). The proposed relation to updating of an internal model establishes a conceptual link between the amplitude of beta-ERS and predictive beta suppression. That is, following successful performance post-movement beta-ERS will be higher than after an error, and act to preserve the set of motor commands that achieved the last response (Tan et al., 2014a). Conversely, reduced beta-ERS following an error provides the flexibility that is necessary for motor adjustments on the next trial (Brittain and Brown, 2014). Naturally, these different states yield different degrees of preparedness, expressed in predictive beta suppression. Secondly, Tan et al. (2014b) obtained similar effects in the subthalamic nucleus (STN) of (medicated) Parkinson patients, and complemented this observation with analyses of information exchange between STN and cortex. These analyses revealed an STN-driven coupling to the sensorimotor cortex after large errors which correlated with subsequent behavioural adjustment. This demonstrates that even in advanced PD the basal ganglia maintain a significant degree of involvement in adaptive behaviour and, most relevant here, are able to support the beta modulation we observe in this study. Note that we do not imply that the beta ERS effect reported by Tan et al. has the same underlying mechanism as the modulation we observe. The important resemblance is the association between ERS amplitude and preparation for a subsequent trial.

Returning to rhythm processing and entrainment in PD, there is a general view that basal ganglia and cerebellum represent different timing systems, beat-based and duration-based, respectively (Teki et al., 2011; Merchant et al., 2015). The distinction may explain why beat-based rhythms activate putamen-premotor circuits and rhythms without temporal regularity the cerebellum (Grahn and Rowe, 2013). However, a case has been made that the two systems do not operate independently, but in a coordinated fashion (Teki et al., 2012; Cope et al., 2014). In the unified timing model of these investigators, the basal ganglia are an obligatory component, required for duration-based as well as beat-based timing. Moreover, temporal prediction within a beat-based context is designated as a function crucially relying on the basal ganglia (Cope et al., 2014). Clearly, from the perspective of this model, our finding of a predictive mode of cue utilisation in PD supports that the benefit of rhythmic stimulus presentation involves the basal ganglia, and calls the notion

of a simple shift from basal ganglia-thalamocortical to cerebellar-thalamocortical pathways, as the basis for rhythmic cueing, into question.

5. Conclusion

There is a longstanding notion that PD patients do not optimally exploit advance information or easily engage in advance preparation, instead adopting a more reactive mode of responding. In line with this notion, the movement-related suppression of beta power in serial reaction tasks is predominantly reactive in PD patients and more prospective in healthy subjects (Praagstra and Pope, 2007; Te Woerd et al., 2014). The present data show, however, that rhythmic vs. non-rhythmic stimulus presentation produces the same gain in beta modulation depth in patients and controls, exclusively due to a higher amplitude beta-ERS phase that increases the predictive, but not the reactive beta power suppression. Supported by recent work in areas of motor learning and timing, the results point to a facilitatory effect of rhythmic stimulation on basal ganglia-premotor cortex interaction, in patients and controls alike. This outcome echoes the conclusion of Ballanger et al. (2006), stating that benefits of external cues reflect general properties of the motor system, rather than being due to recruitment of ancillary structures compensating for deficient basal ganglia-cortical projections. A limitation is that we used visual stimuli only, at a presentation rate slightly slower than optimal for inducing entrainment. However, with stimulus modality and frequency optimised to induce strong entrainment, the observed predictive mode of cue utilisation is more likely to be strengthened than to be reversed.

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