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Pre-stimulus beta power modulation during motor sequence learning is reduced in 'Parkinson's disease

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ABSTRACT

Beta oscillations within motor-cortical areas have been linked to sensorimotor function. In line with this, pathologically altered beta activity in cortico-basal ganglia pathways has been suggested to contribute to the pathophysiology of Parkinson's disease (PD), a neurodegenerative disorder primarily characterized by motor impairment. Although its precise function is still discussed, beta activity might subserve an anticipatory role in preparation of future actions. By reanalyzing previously published data, we aimed at investigating the role of pre-stimulus motor-cortical beta power modulation in motor sequence learning and its alteration in PD. 20 PD patients and 20 healthy controls (HC) performed a serial reaction time task (SRTT) in which reaction time gain presumably reflects the ability to anticipate subsequent sequence items. Randomly varying patterns served as control trials. Neuromagnetic activity was recorded using magnetoencephalography (MEG) and data was re-analyzed with respect to task stimuli onset. Assuming that pre-stimulus beta power modulation is functionally related to motor sequence learning, reaction time gain due to training on the SRTT should vary depending on the amount of beta power suppression prior to stimulus onset. We hypothesized to find less pre-stimulus beta power suppression in PD patients as compared to HC associated with reduced motor sequence learning in patients. Behavioral analyses revealed that PD patients exhibited smaller reaction time gain in sequence relative to random control trials than HC indicating reduced learning in PD. This finding was indeed paralleled by reduced pre-stimulus beta power suppression in PD patients. Further strengthening its functional relevance, the amount of pre-stimulus beta power suppression during sequence training significantly predicted subsequent reaction time advantage in sequence relative to random trials in patients. In conclusion, the present data provide first evidence for the contribution of pre-stimulus motor-cortical beta power suppression to motor sequence learning and support the hypothesis that beta oscillations may subserve an anticipatory, predictive function, possibly compromised in PD.

1. Introduction

The investigation of oscillatory brain activity within the context of sensorimotor functions has revealed a typical pattern of modulation in the beta band (13–30 Hz) time-locked to voluntary movement: A decrease in beta power (i.e., beta power suppression) prior to and during movement execution followed by a transitory increase after movement termination, known as rebound (Pfurtscheller and Lopes da Silva, 1999). Parkinson's disease (PD) is a common neurodegenerative disorder particularly characterized by motor symptoms such as bradykinesia and muscular rigidity although other impairments including cognitive functions have been demonstrated as well (Dubois and Pillon, 1997; Kalia and Lang, 2015; Svenningsson et al., 2012). Interestingly, in PD, beta activity has been found to be pathologically altered. Such alterations have been particularly observed in the subthalamic nucleus (STN) of PD patients undergoing surgery for deep brain stimulation (DBS) but also in motor-cortical areas (Brown et al., 2001; Hammond et al., 2007; Heinrichs-Graham et al., 2014;

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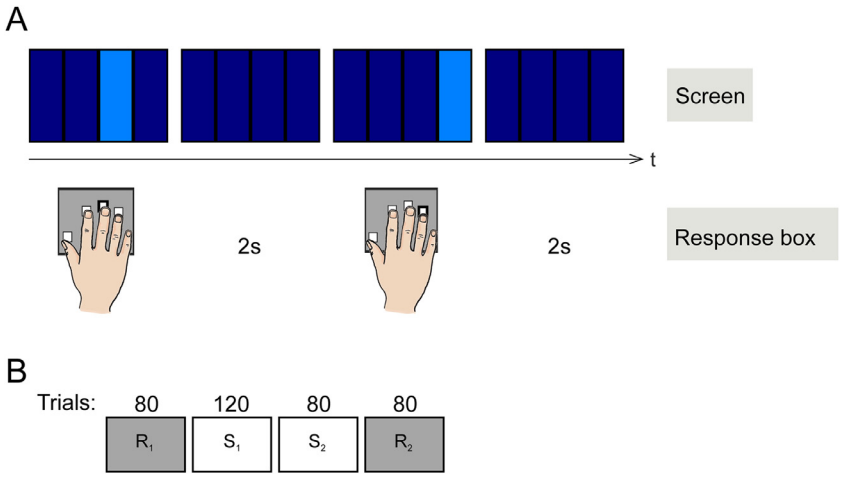

Fig. 1. Experimental setting. (A) Four horizontally aligned bars presented on a back-projection screen were spatially mapped to four response keys on a button box. Participants were instructed to press the respective response button as soon as one of the bars changed from dark blue to light blue. The response-to-stimulus interval was set to 2 s. (B) The SRTT consisted of sequential (S) and random control (R) trials. During training on the sequence (S_1), the sequence was repeated 15 times. Sequences during the subsequent test block (S_2) as well as random patterns prior to (R_1) and after sequence trials (R_2) were repeated ten times, respectively. MEG was recorded during the entire SRTT procedure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Oswal et al., 2013a; Pollok et al., 2012; Schnitzler and Gross, 2005). For example, planning of simple finger movements has been related to reduced beta power suppression in motor-cortical areas in PD patients as compared to healthy participants, suggesting a link between altered beta modulation and motor control in PD (Heinrichs-Graham et al., 2014).

The modulation of beta activity has further been associated with motor sequence learning in healthy volunteers (Pollok et al., 2014). More specifically, Pollok et al. (2014) applied a *Serial Reaction Time Task* (SRTT), a well-established motor learning paradigm involving responses to stimuli at different locations following a sequential regularity (Nissen and Bullemer, 1987). In this study, superior learning reflected by larger reaction time (RT) gain as training on the task proceeded was linked to stronger beta power suppression (Pollok et al., 2014). In PD, evidence for diminished motor sequence learning on tasks such as the SRTT exists (for a review, see Ruitenberg et al., 2015). We recently investigated whether altered motor sequence learning on the SRTT in PD is linked to altered beta modulation (Meissner et al., 2018). Supporting the role of beta activity in motor sequence learning, PD patients indeed exhibited less beta power suppression over the course of the task which was paralleled by diminished learning.

Similar to a vast amount of studies investigating oscillatory activity related to motor control in general, both of the introduced motor learning studies concentrated data analyses on activity time-locked to the motor response (Meissner et al., 2018; Pollok et al., 2014). However, it has been stressed that beta activity already prior to stimuli signaling the need for a specific motor response might be of behavioral relevance for planning and preparation of the required response (Meziane et al., 2015; Perfetti et al., 2011). Further emphasizing the need to investigate pre-stimulus beta power modulation and to differentiate between pre- and post-stimulus modulation, there is converging evidence that despite generally preserved modulation depth, pre-stimulus modulation of beta power is attenuated in PD (Praamstra and Pope, 2007; te Woerd et al., 2014). In contrast, its modulation after stimulus onset has been observed to be enhanced, indicating a shift from a prospective to a more reactive mode of motor control in PD (Praamstra and Pope, 2007; te Woerd et al., 2014). Taken together, these findings support the assumption that beta activity may subserve a prospective control function related to the anticipation of an upcoming response (Brittain and Brown, 2014; Engel and Fries, 2010; Jenkinson and Brown, 2011; Oswal et al., 2012), a function possibly compromised in PD (te Woerd et al., 2014). This again raises the question whether pre-stimulus beta activity may also relate to motor sequence learning on the SRTT – a task in which faster RTs as training on the task proceeds presumably reflect the anticipation of upcoming items of the sequence. To investigate this, we reanalyzed previously published magnetoencephalography (MEG) data for which PD patients and healthy older controls (HC) performed a SRTT (Meissner et al., 2018). The data was analyzed with respect to the onset of SRTT stimuli. Based on previous results (e.g., te Woerd et al., 2014), we expected to find less pre-stimulus beta power suppression in PD patients. Given that pre-stimulus beta power is functionally related to motor sequence learning, RT gain due to training on the SRTT should vary depending on beta power modulation prior to stimulus onset.

2. Material and methods

2.1. Participants

Twenty PD patients and 20 age- and sex-matched HC participated in the study. Exclusionary criteria involved tremor-dominant PD, dementia (Mattis Dementia Rating Scale (MDRS; Mattis, 1988) score $\leq$130), clinically relevant depression (Beck Depression Inventory (BDI-II; Hautzinger et al., 2006) score $\geq$18) or other psychiatric and/or neurological disorders. Patients remained on their regular anti-parkinsonian medication during study participation. For detailed characteristics of participants including clinical information, see Meissner et al. (2018). The study was approved by the local ethics committee of the Medical Faculty of the Heinrich-Heine-University Dusseldorf (study no. 4792) and is in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to study participation and received monetary compensation.

2.2. Motor sequence learning: SRTT

The SRTT was introduced as a simple RT task with participants not being informed about the embedded eight-digit sequence (ring-index-thumb-middle-ring-middle-thumb-index finger). Four horizontally aligned bars were presented on a back-projection screen. Each bar corresponded to one of four response buttons on a custom-made response box. Participants were instructed to press as quickly as possible the corresponding button with the respective finger of the right hand once one of the bars changed from dark to light blue (Fig. 1A). RT was determined by measuring the interval between color change and button press onsets. The response-stimulus interval was set to 2 s. In case of incorrect responses, bars remained light blue until participants responded correctly.

To familiarize themselves with the buttons of the response box, all participants conducted a short practice session of 12 randomly varying trials. The experimental phase of the SRTT consisted of a training block of 15 sequence repetitions (S_1) followed by a test block of ten sequence repetitions (S_2). Ten repetitions of eight randomly varying trials before (R_1) and after sequence blocks (R_2) served as control condition for unspecific RT improvement (Fig. 1B). Stimulus timing and response

recording were controlled by E-Prime® software version 2 (Psychology Software Tools, Sharpsburg, PA, USA).

2.3. Statistical analyses of behavioral data

Analyses were performed using IBM SPSS 25 (IBM Corporation, Armonk, NY, USA). Whenever necessary, the sequential Bonferroni procedure was applied to correct for multiple comparisons (Holm, 1979). To determine the RT gain in sequence relative to random trials, we calculated a learning index by dividing RTs during sequence trials by those during random ones ($S_{1+2}/R_{1+2;}$ Values two standard deviations (SD) below or above the respective group mean were excluded from further analyses (2 patients; 1 HC)). Values <1 indicate RT gain during sequence as compared to random trials. Kolmogorov-Smirnov tests revealed no significant deviations from Gaussian distribution (all $p \geq .20$). Group comparison was assessed using a two-tailed independent-samples *t*-test. In addition to comparing learning indices between groups, we conducted one-sample *t*-tests for PD patients and HC to investigate whether learning indices differed significantly from 1 and thereby indicate significant RT gains in sequence trials in both groups. Effect sizes were computed using Cohen's *d* (Cohen, 1988).

To investigate whether learning indices were related to dopaminergic medication (daily levodopa equivalent dose (LED; Tomlinson et al., 2010)) or motor impairment (Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale, part III (MDS-UPDRS III; Goetz et al., 2008)) in patients, correlations involving LED using Pearson's *r* and correlations involving MDS-UPDRS III using Spearman's ρ were calculated.

2.4. MEG data

2.4.1. Data acquisition and preprocessing

Neuromagnetic brain activity was recorded during the SRTT using a 306-channel whole-head MEG system with 204 planar gradiometers and 102 magnetometers (Elekta Neuromag, Helsinki, Finland). Four head position indicator (HPI) coils were fixed to each participant's scalp and HPI coil positions and anatomical landmarks (nasion and pre-auricular points) were digitized (Polhemus Isotrak, Colchester, Vermont, USA). Vertical electrooculogram was recorded in order to detect eye blinks. For 30 participants, structural magnetic resonance images (MRIs) were acquired in a separate session (3 T Siemens-Magnetom, Erlangen, Germany). Off-line analyses were restricted to gradiometers and carried out using the MATLAB-based open source toolbox FieldTrip (Oostenveld et al., 2011). Continuously recorded data were segmented into epochs of 2000 ms pre- to 2000 ms post-stimulus onset. Data were demeaned and filtered using 200 Hz low-pass and 1 Hz high-pass filters. Trials with sensor jumps or muscle artifacts were rejected from further analyses after visual inspection of the data. A principal component analysis was then applied to correct for further artifacts. Components associated with eye blinks or cardiac signals were removed (mean number of components ± SD: 3.53 ± 0.60).

2.4.2. Time-frequency analyses

Groups did not differ in number of trials subjected to analyses (all $p > .11$). Time–frequency representations of power ($\leq$30 Hz) for sequence and random trials were computed using fast Fourier transformation. We used an adaptive sliding time window with a width of four full cycles of the respective frequency f ($\Delta t = 4/f$) multiplied by a Hanning taper. The time window moved in steps of 50 ms and the frequency resolution was $1/\Delta t$. Spectral power was calculated for vertical and horizontal gradiometers and was then combined. As no clear baseline could be defined during the task, power changes were measured against a baseline defined by the mean of the full epoch length according to previous studies (Meissner et al., 2018; Pollok et al., 2014; te Woerd et al., 2015, 2014).

In a first step, we studied group differences in beta power modulation during sequence test trials (S_2). To this end, oscillatory activity was averaged across the beta band and cluster-based, independent-samples *t*-tests with Monte Carlo randomization controlling for multiple comparisons were computed (Maris and Oostenveld, 2007). Analyses were performed for a time window ranging from 1500 ms pre- to 1500 ms post-stimulus onset. Since motor-cortical areas have been shown to be relevant for motor sequence learning, sensors covering left and right sensorimotor cortex (S1/M1) were selected and used for statistical analyses. This selection was determined a priori and was mainly based on a previous study investigating oscillatory activity in channels covering the left primary sensorimotor cortex during motor sequence learning in young healthy adults (Pollok et al., 2014). However, to account for rather bilateral and wider recruitment of the motor-cortical network in the aging brain (Quandt et al., 2016; Vallesi et al., 2010), we extended the original selection by adding a sensor located posterior to it as well as by adding the respective channels covering the right, ipsilateral hemisphere. To exclude the possibility that significant group differences were present already prior to learning, beta power changes during random trials prior to sequence training (R_1) were compared between groups using the same statistical approach. Resulting clusters with *p*-values < 0.05 were considered significant.

For illustrative purposes, cortical sources of beta power modulation for sequence test trials (S_2) and random trials prior to training on the sequence (R_1) were identified by means of *Dynamic Imaging of Coherent Sources* (DICS; Gross et al., 2001). To this end, we contrasted two time intervals of 500 ms centered on maximal beta power suppression and maximal (pre-stimulus) beta power increase for R_1 and S_2, respectively. The center frequency was 20 Hz (spectral smoothening of ± 5 Hz) resulting in 10 full cycles per time window. A realistic, single-shell brain model (Nolte, 2003) was created based on the individual anatomical MRI or on a MNI template ($n = 10$). Then, forward solution was estimated for each participant using a regular 3D grid (1 cm resolution) in MNI space which was warped onto individual anatomy. We computed a lead-field matrix for each grid point according to MEG head position and the forward model. A common spatial filter was constructed for suppression and beta peak time windows for each grid point using the cross-spectral density and lead-field matrices. This spatial filter was then applied to suppression and peak epochs and contrasted. Source reconstructed beta power was averaged across participants of each group for R_1 and S_2 and visualized on the cortical surface of the MNI template brain.

2.4.3. Pre-stimulus beta power modulation during the SRTT

As potential group differences resulting from time-frequency analyses may simply relate to differences in modulation depth, we further examined the percentage of beta power modulation prior to stimulus onset relative to the total modulation depth. The strength of this approach has been demonstrated previously (e.g., Praamstra and Pope, 2007; te Woerd et al., 2015, 2014). In a first step, we averaged activity across the beta band and the channels covering left and right S1/M1, respectively. We then determined the percentage of pre-stimulus beta power suppression relative to the total suppression depth from maximum pre-stimulus beta power to maximum beta power suppression (te Woerd et al., 2015, 2014, see Fig. 2 for a schematic representation) for sequence (S_1 and S_2) and random trials (R_1 and R_2). Differences in the percentage of pre-stimulus beta power suppression relative to the full suppression depth were tested by means of a mixed design analysis of variance (ANOVA) with within-subjects factors *hemisphere* (left vs. right) and *condition* (sequence vs. random) and between-subjects factor *group* (HC vs. PD patients). Effect sizes were calculated using partial eta squared (η^2_p).

2.4.4. Pre-stimulus beta power modulation during sequence training and its relation to learning

In a last step, we aimed to determine the predictive value of the

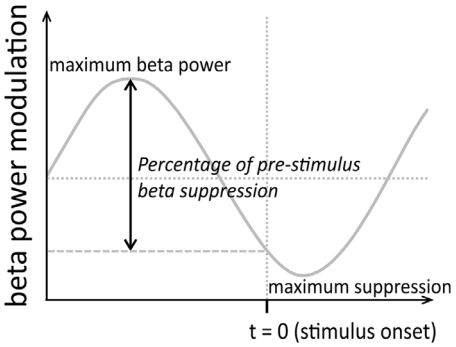

Fig. 2. Schematic representation of the percentage of pre-stimulus beta power modulation relative to the full modulation depth. The trace illustrates the time course of beta power changes during one SRTT trial. For data analyses, we calculated the percentage of pre-stimulus beta power suppression, thus the change in beta power from maximum pre-stimulus beta power to stimulus onset ($t = 0$) as indicated by the black arrow relative to the full suppression depth (i.e., from maximum pre-stimulus beta power to maximum beta power suppression).

ability to suppress beta power prior to stimulus onset. Therefore, linear regression analyses involving the percentage of pre-stimulus beta power suppression relative to the full suppression depth during sequence training (S_1) and subsequent RT advantage in sequence as compared to random trials were conducted. The percentage of pre-stimulus beta power suppression of the left S1/M1 during S_1 was used as predictor, since previous data support the particular relevance of the contralateral hemisphere to motor learning (Pollok et al., 2014). However, as the aging motor system has been suggested to be characterized by a loss of hemispheric lateralization, we additionally correlated the percentage of pre-stimulus beta power suppression relative to the full suppression depth of the left and the right hemisphere with each other, since such a correlation would play a role in the interpretation of regression analysis outcomes. As dependent variable for the regression analyses, the learning index at test trials was used (i.e., RTs during S_2/R_2). Values two SD below or above the respective group mean were excluded from analyses (1 PD patient, 1 HC). Analyses were conducted for each group separately.

3. Results

3.1. Behavioral data

The independent-samples *t*-test on learning indices revealed significantly higher values in PD patients as compared to HC ($t(35) = -2.1$; $p = .04$; Cohen's $d = 0.68$; Fig. 3) indicating *smaller* RT gains in sequence relative to random trials in the former group. Additional one-sample *t*-tests indicated that learning indices differed significantly from 1, both in PD patients ($t(17) = -2.21$; $p = .04$; Cohen's $d = 0.52$) and HC ($t(18) = -5.87$; $p < .001$; Cohen's $d = 1.35$). For absolute mean RTs for all PD patients and HC, please see Supplementary Figure S1 as well as our previous publication for more detail (Meissner et al., 2018). Correlational analyses between clinical characteristics in PD patients and learning indices revealed no significant results (all $p > .40$).

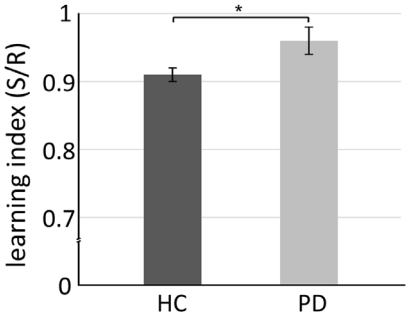

Fig. 3. Behavioral data. Standardized learning indices indicating RT gain during sequence (S_1 and S_2) relative to random trials (R_1 and R_2) during the SRTT in HC and PD patients. Please note that *lower* learning indices indicate *greater* RT gain during sequence relative to random trials. Indices are presented as group means and error bars indicate standard error of the mean (SEM). * $p < .05$.

3.2. MEG data

3.2.1. Time-frequency analyses

Fig. 4 displays oscillatory activity in frequencies ≤30 Hz as well as cortical sources of beta power modulation prior to (R_1) and after sequence training during sequence test trials (S_2). Time-frequency analyses revealed the expected pattern of beta power modulation which was strongest over both left and right sensorimotor areas (Fig. 4A and C) and occurred over the entire beta range from 13–30 Hz (Fig. 4B).

Statistical analyses on beta power changes during S_2 revealed significant differences between groups most pronounced between 250 ms pre- to 250 ms post-stimulus onset (negative cluster; $p = .007$; for topographical representations, see Supplementary Figure S2), indicating that PD patients exhibited less beta power suppression as compared to HC prior to stimulus onset. Additionally, significant differences between groups emerged most pronounced between 700 and 1300 ms after stimulus onset (positive cluster; $p = .004$) suggesting stronger, prolonged post-stimulus beta power suppression in patients as compared to HC (see Fig. 4D for group differences in oscillatory activity including the beta frequency range during S_2). For random trials prior to sequence training, no significant group differences emerged, neither prior to nor post stimulus onset (R_1: all $p \geq .10$).

3.2.2. Pre-stimulus beta power modulation during the SRTT

The mixed design ANOVA on the percentage of pre-stimulus beta power suppression relative to the full suppression depth revealed significant main effects of *condition* ($F(1,38) = 5.40$; $p = .03$; $\eta^2_p = 0.12$) and *hemisphere* ($F(1,38) = 28.66$; $p < .001$; $\eta^2_p = 0.43$), indicating a larger percentage of pre-stimulus beta power modulation in sequence than in random trials and in the left as compared to the right hemisphere. Furthermore, a significant main effect of *group* ($F(1,38) = 10.72$; $p = .002$; $\eta^2_p = 0.22$) emerged, revealing a significantly smaller percentage of pre-stimulus beta power suppression relative to the full suppression depth in patients as compared to HC. All interactions, including the *condition* by *group* interaction ($F(1,38) = 2.05$; $p = .16$; $\eta^2_p = 0.05$), failed to reach significance (all other $p \geq .22$).

Although the mixed design ANOVA did not reveal evidence for a significant interaction involving the factor *group*, the effect size (η^2_p) of the *condition* by *group* interaction roughly corresponds to a medium effect (small effect: $\eta^2_p = 0.01$; medium effect: $\eta^2_p = 0.059$; Cohen, 1988; Miles and Shevlin, 2001). Therefore, we decided to conduct additional exploratory repeated-measures ANOVAs on the percentage of pre-stimulus beta power suppression relative to the full suppression depth for PD patients and HC separately. In patients, this ANOVA yielded a significant main effect of *hemisphere* ($F(1,19) = 6.95$; $p = .02$; $\eta^2_p = 0.27$) revealing a larger percentage of pre-stimulus beta power modulation in the left hemisphere as compared to the right one. However, the main effect of *condition* and the *hemisphere* by *condition* interaction were not significant (all $p \geq .44$; $\eta^2_p \leq 0.03$). In HC, significant main effects of both *hemisphere* ($F(1,19) = 27.78$; $p < .001$; $\eta^2_p = 0.59$) and *condition* ($F(1,19) = 6.19$; $p = .02$; $\eta^2_p = 0.25$) emerged, indicating not only a larger percentage of beta power modulation prior to stimulus onset in the left as compared to the right hemisphere but also in sequence than in random trials. The *hemisphere* by *condition* interaction was not significant ($F(1,19) = 0.004$; $p = .95$;

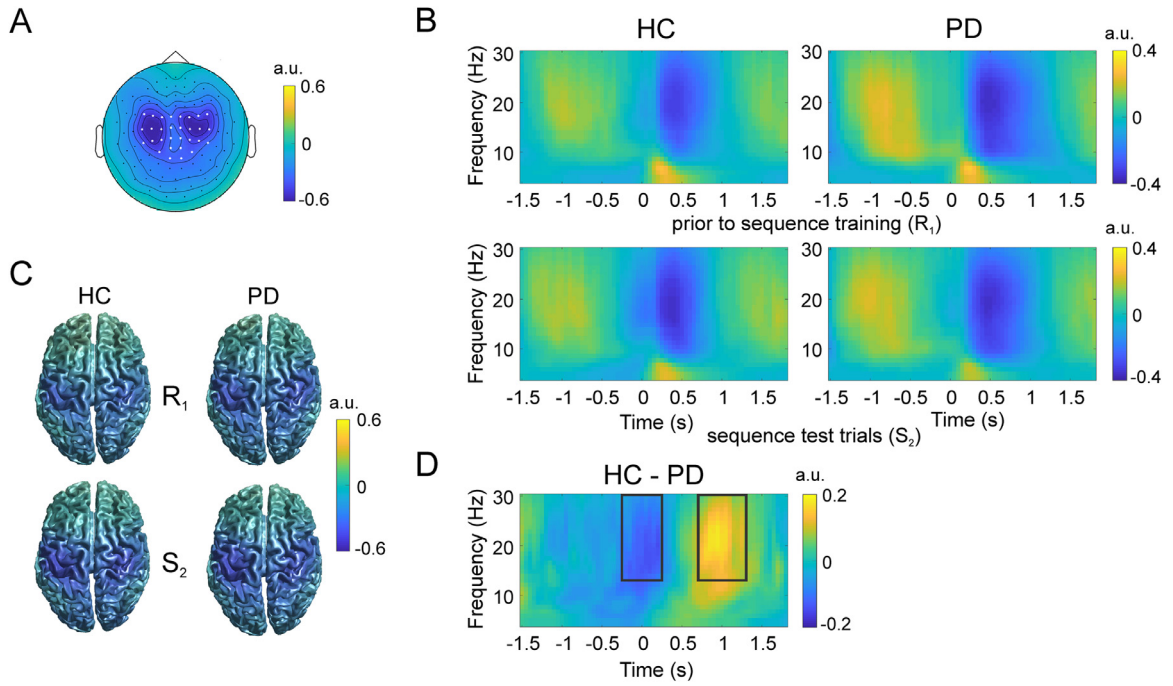

Fig. 4. Oscillatory activity during the SRTT. (A) Exemplary illustration of the distribution of oscillatory beta power modulation (13–30 Hz; prior to sequence learning (R_1)) as measured from maximum pre-stimulus beta power to maximum beta power suppression. White dots show channels covering left and right sensorimotor areas (S1/M1) further used for statistical MEG analyses. (B) Time-frequency representations of oscillatory power in frequencies ≤30 Hz for channels covering S1/M1 during random (R_1; top) and sequence test trials (S_2; bottom) in HC (left) and PD patients (right). Warm colors indicate an increase, cold colors a decrease in power relative to baseline. Stimulus onset is defined as $t = 0$ on the x-axis. The expected movement-related beta power modulation with a decrease in power (i.e., suppression) before and during movement as well as subsequent beta power increase is observable across the whole beta range from 13–30 Hz. Please note that due to our stimulus-locked analysis strategy, the beta power increase of the previous trial also appears as pre-stimulus beta power increase of the current trial. (C) Source reconstruction of beta power modulation, measured from maximal pre-stimulus beta power to maximal beta power suppression for random (R_1; top) and sequence test trials (S_2; bottom) averaged across HC (left) and PD patients (right) projected onto the MNI template brain. Beta power modulation was strongest over left and right sensorimotor areas. (D) Group differences (HC vs. PD patients) in oscillatory activity (≤30 Hz) for channels covering S1/M1 during sequence test trials (S_2). A schematic illustration of significant group differences in the beta frequency band during S_2 resulting from cluster-based permutation tests is given by black rectangles. Cold colors indicate less decrease in beta power in PD patients as compared to HC (first rectangle), warm colors indicate stronger decrease in beta power in PD patients as compared to HC (second rectangle). For cluster plots with a detailed topographic representation, see Supplementary Figure S2.

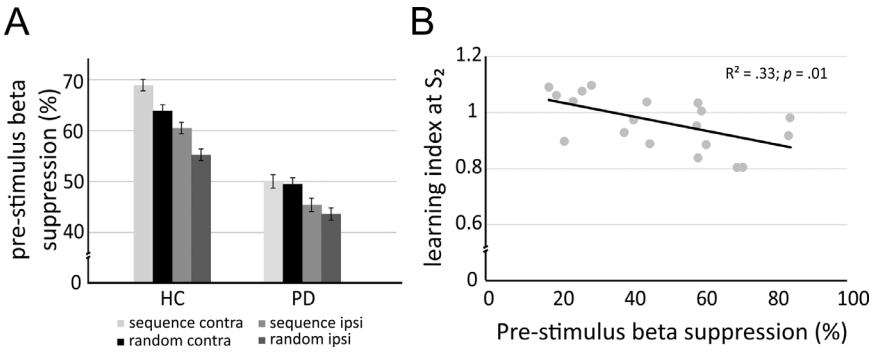

Fig. 5. The percentage of pre-stimulus beta power modulation and its association with the learning index at test trials. (A) The percentage of pre-stimulus beta power suppression in left (contralateral) and right (ipsilateral) motor-cortical areas during sequence and random trials in HC and PD patients. Values are presented as group means and error bars indicate SEM reflecting within-subjects variability (O'Brien and Cousineau, 2014). (B) The percentage of pre-stimulus beta power suppression in left motor-cortical areas during sequence training (S_1) significantly predicted the subsequent learning index at test trials (i.e., S_2/R_2) in PD patients. Please note that *lower* learning indices indicate *greater* RT gain in sequence relative to random trials.

$\eta^2_p < 0.01$). Fig. 5A displays the respective group means for sequence and random trials in each hemisphere.

3.2.3. Pre-stimulus beta power modulation during sequence training and its relation to learning

In a final step, linear regression analyses were conducted to elucidate the predictive value of pre-stimulus beta power suppression for motor sequence learning. In PD patients, the percentage of pre-stimulus beta power suppression relative to the full suppression depth in the left S1/M1 during sequence training (S_1) significantly predicted subsequent learning indices at test trials (RTs at S_2/R_2; standardized $\beta = -0.57$; $R^2 = 0.33$; $p = .01$; Fig. 5B). This result suggests that the ability to suppress beta oscillations prior to stimulus onset during sequence training is linked to learning-related RT gain in subsequent sequence trials. In HC, the regression analysis did not reveal significant effects (standardized $\beta = -0.22$; $R^2 = 0.05$; $p = .38$; Supplementary Figure S3). Additional analyses correlating the percentage of pre-stimulus beta power suppression in the left with the one in the right hemisphere revealed strong correlations, both in patients ($r = 0.83$; $p < .001$) and in HC ($r = 0.87$; $p < .001$).

4. Discussion

With the present study, we aimed to elucidate the functional role of pre-stimulus beta activity in motor sequence learning and its possible alteration in PD. We reanalyzed previously published MEG data of PD

patients and HC recorded during the SRTT with a focus on beta modulation time-locked to the onset of SRTT stimuli. At the behavioral level, we observed less RT gain in sequence relative to random trials in PD patients than in HC. Nevertheless, PD patients showed significant sequence-specific gains in RT as well, indicating reduced but basically preserved motor sequence learning in PD patients. This finding fits nicely with numerous studies reporting altered motor sequence learning in PD (Muslimovic et al., 2007; Stephan et al., 2011; Wilkinson et al., 2009; for a review, see Ruitenberg et al., 2015). Analyses of MEG data revealed that during the SRTT, PD patients exhibited reduced beta power suppression *prior* to stimulus onset as compared to HC. Further exploratory within-group analyses indicated that whereas the amount of beta power suppression occurring prior to stimulus onset did not differ significantly between sequence and random trials in PD patients, it was larger during sequence trials in HC. Although especially the latter findings have to be interpreted with caution due to their exploratory character, the present data provide first evidence for the hypothesis that pre-stimulus beta power modulation may contribute to motor sequence learning. Further strengthening this assumption and the behavioral relevance of pre-stimulus beta power modulation, the ability to suppress beta power prior to stimulus onset during sequence training made a significant contribution to predicting subsequent RT advantage in sequence relative to random trials in PD patients.

As reported previously, movement-related beta power modulation suggested to be linked to motor sequence learning in healthy volunteers (Pollok et al., 2014) has been shown to be altered in PD (Meissner et al., 2018). In addition to studying oscillatory activity time-locked to movement onset, the SRTT further allows to investigate oscillatory activity time-locked to stimuli indicating the next sequence item. Behaviorally, RT improvement during training on the task presumably reflects the anticipation of upcoming items of the sequence. The investigation of stimulus-locked activity during the SRTT might therefore allow to identify the oscillatory signature which may serve as a marker for an anticipatory function of motor control going beyond “pure” motor activity. Previous data showed attenuated pre-stimulus beta power suppression during a simple choice response task in PD with a shift from a prospective to a more reactive mode of motor control (Praamstra and Pope, 2007; te Woerd et al., 2015, 2014). Based on these findings, we examined pre-stimulus motor-cortical beta activity in PD patients as compared to HC during the SRTT to investigate its functional relevance to motor sequence learning. The present time-frequency analyses revealed the expected pattern of beta power modulation associated with voluntary movement during random and sequential trials of the SRTT. In PD patients, beta power suppression prior to stimulus onset was reduced in sequence test trials. It is important to keep in mind that – as reported in more detail in our previously published study on the same dataset (Meissner et al., 2018) – PD patients exhibited generally slower RTs than HC during random trials already prior to sequence training. Therefore, one might argue that significant group differences in oscillatory beta activity might simply reflect unspecific movement slowing related to motor impairment rather than representing differences in motor sequence learning in PD. However, control analyses comparing beta power changes in random trials prior to sequence training between groups did not reach significance rendering this assumption less likely. Furthermore, general motor impairment was not significantly related to task performance in PD patients. Taken together, the present findings on pre-stimulus beta power modulation extend previously reported results of movement-related beta power suppression in a motor learning task (Pollok et al., 2014) and its alteration in PD (Meissner et al., 2018), and provide first evidence for a functional role of pre-stimulus beta power modulation in motor sequence learning.

Additional support for the latter assumption comes from our analyses on the percentage of pre-stimulus beta power suppression relative to the full suppression depth conducted to control for possible effects of modulation depth. We found that the percentage of pre-stimulus beta power suppression was not only significantly smaller in random as compared to sequence trials but also generally reduced in PD patients as compared to HC. Although we realize that the *condition* by *group* interaction failed to reach significance, its effect size (η^2_p) corresponds to a medium effect (Cohen, 1988; Miles and Shevlin, 2001).We therefore decided to conduct additional analyses for each group separately. However, it is important to keep in mind, that their results have to be interpreted with caution due to their exploratory character and require further investigation and replication with larger samples sizes. Nevertheless, these analyses may give a hint that the pattern of pre-stimulus beta power modulation in motor-cortical areas during sequence and random trials in PD patients might indeed differ from that observed in HC: whereas there was no significant difference in the percentage of pre-stimulus beta power suppression relative to the full suppression depth between sequence and random trials in patients, this percentage was significantly larger in sequence than in random trials irrespective of the hemisphere in HC. These findings may simply reflect less efficient response preparation during sequence trials in PD. However, alternative interpretations are also conceivable. Previous work pointed out, that a stronger post-movement beta power increase may also increase prospective, pre-stimulus beta power suppression in the subsequent trial (te Woerd et al., 2015). Interestingly, such a post-movement beta power increase has been suggested to reflect a trial-to-trial modification of an internal model informing future actions (Tan et al., 2014). One might therefore speculate, that stronger pre-stimulus beta power suppression in sequence as compared to random trials as observed in the present study may provide evidence for the formation of an internal model of the sequence during motor sequence learning in HC.

The result of the linear regression analysis conducted on the present data provides further evidence for the behavioral relevance of beta power modulation prior to stimulus onset. More specifically, this analysis confirmed that the percentage of pre-stimulus beta power suppression relative to the full suppression depth in contralateral motor-cortical areas during sequence training significantly contributed to subsequent RT gain in sequence relative to random trials in patients. However, as additional analyses revealed a strong correlation between pre-stimulus beta power suppression in the contra- with the one in the ipsilateral hemisphere, we cannot completely exclude the possibility that the ipsilateral hemisphere might also contribute to observed RT gains in sequential trials, especially since the loss of hemispheric lateralization with bilateral recruitment of sensorimotor areas has been suggested to be one characteristic of an aging motor system (Meziane et al., 2015; Vallesi et al., 2010). Within the group of HC, a significant relation was not obtained. This difference in findings might at least to some extent be explained by the more variable neurophysiological pattern observed in patients (and a relatively low variability in the data of HC, respectively: $SD_{HC} = 15$; $SD_{PD} = 21$; see also Supplementary Figure S3) that might result in a stronger and statistically significant association between the two variables in the patient group (Goodwin and Leech, 2006). Taken together, those PD patients who showed rather strong pre-stimulus beta power suppression – and therefore exhibited a neurophysiological pattern more similar to that in HC – also exhibited larger learning indices.

Interestingly, Ruiz and colleagues (2014) revealed in an explicit sequence learning study that anticipatory beta power suppression in the STN in PD patients at sequence boundaries (i.e., the first and the last sequence item) is related to better performance, while stronger beta power suppression before within-sequence items seems to be associated with poorer performance (Ruiz et al., 2014). Similarly, it is conceivable that in the present study, the movement related to the first sequence item (i.e., when the pattern has yet to emerge) differs fundamentally from the one related to the following sequence items. Unfortunately – unlike in the case of *explicit* sequence learning in which the sequence boundaries are very well set as participants are informed about the specific sequence they have to perform prior to the experiment – it is difficult to pinpoint the individual sequence boundaries in implicit

learning paradigms such as the SRTT as they may differ between participants; especially as the embedded sequence is presented repeatedly without any breaks between the items of the current and the subsequent sequence. This assumption is indirectly supported by one of our former studies in which several participants who recognized a repeating pattern were asked to reproduce the sequence. Interestingly, these participants did not necessarily begin the reproduction of the sequence with the first item of the sequence as defined by us (Meissner et al., 2016). Nevertheless, future MEG and electroencephalography studies in PD patients implementing explicit rather than implicit forms of motor sequence learning paradigms could help to provide more fine-grained insights into motor sequence learning and its underlying dynamics at the motor-cortical level.

Our data are consistent with current theories proposing an anticipatory, predictive nature of beta power modulation (Jenkinson and Brown, 2011; Oswal et al., 2013b, 2012). Some results fueling this assumption stem from studies on beta activity in PD patients undergoing STN-DBS surgery (e.g., Oswal et al., 2012). Similarly, motor-cortical beta activity has been reported to be modulated in an anticipatory fashion as well (Androulidakis et al., 2007; Perfetti et al., 2011). Interestingly, a shift to a rather reactive mode in PD has been proposed (Meziane et al., 2015; Praamstra and Pope, 2007; te Woerd et al., 2015, 2014). This assumption is supported by the present finding of stronger beta power suppression several hundred milliseconds after stimulus onset in patients as compared to HC. It is nevertheless important to keep in mind that with the present study design, it is not possible to clearly separate whether beta activity relates to anticipatory processes or task-specific response preparation. However, results of a previous study support the former interpretation (Oswal et al., 2012). More precisely, warning cues signaling the need for an upcoming action – being it motor or cognitive – were followed by beta power suppression, independent of the specific nature of the upcoming action. Thus, modulation of beta activity can be dissociated from task-specific response preparation and appears to particularly reflect an anticipatory function (Oswal et al., 2012). Further evidence for this hypothesis comes from studies investigating oscillatory beta activity during language or tactile tasks (Li et al., 2017; van Ede et al., 2010), suggesting pre-stimulus modulation of beta activity to represent one mechanism underlying anticipatory language processing (Li et al., 2017), or the expectation of tactile stimuli (van Ede et al., 2010). Remarkably, in the latter study, expectation-induced modulation of beta activity prior to predictable tactile stimuli occurred independent of whether sensory events were attentive or not (van Ede et al., 2010). Our data linking pre-stimulus beta modulation to behavioral performance during the SRTT in which repetition of the embedded sequence implicitly invites anticipatory processes further add to the proposed anticipatory function of beta activity even in implicit tasks. This function is possibly compromised in PD.

Beyond its contribution to a better understanding of the functional significance of pre-stimulus beta activity and the neurophysiological dynamics of motor sequence learning, the present data may also be of clinical relevance. Importantly, our results suggest that although motor sequence learning is reduced in PD patients as compared to HC, it is nevertheless preserved to some extent. As motor rehabilitation is often characterized as a “re-learning” process and is therefore based on the assumption that practice leads to improvement of motor skills, the preservation of motor (sequence) learning is essential for successful rehabilitation in PD (Abbruzzese et al., 2016; Krakauer, 2006; Nieuwboer et al., 2009). Furthermore, a better understanding of the neurophysiological dynamics linked to (poorer) behavioral performance is not only required to disentangle the pathophysiological mechanisms underlying this movement disorder but may also help to further unravel therapeutic strategies and approaches specifically targeting these altered neurophysiological dynamics to improve learning in future studies.

It is important to note that PD patients remained on their regular antiparkinsonian medication during study participation to minimize the effects of general motor impairment on motor sequence learning. Thus, we cannot exclude the possibility that medication may have affected the present findings as well. However, time-frequency analysis during random trials prior to learning did not result in significant differences between groups. Additionally, reduced beta power modulation prior to stimulus onset has been reported in PD patients tested OFF medication as well (Praamstra and Pope, 2007; te Woerd et al., 2015, 2014). Therefore, we would argue that the present findings are not just driven by alterations related to antiparkinsonian medication.

5. Conclusion

The present results indicate that pre-stimulus beta power suppression is not only reduced in PD patients as compared to healthy volunteers during a motor sequence learning task, but it also significantly predicts sequence learning-related RT gains. The present data provide first evidence for the functional significance of pre-stimulus beta activity in motor sequence learning and are well in line with its suggested anticipatory, predictive function, possibly compromised in PD.

Declaration of Competing Interest

None.

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Authors’ roles

S.N.M.: Study concept, design, and organization, acquisition, analysis and interpretation of data, writing the first draft of the manuscript; V.K.: Acquisition and interpretation of data, critical revision of the manuscript for intellectual content; M.S.: Study concept, critical revision of the manuscript for intellectual content; C.J.H.: Study organization, critical revision of the manuscript for intellectual content; B.P.: Study concept and design, analysis and interpretation of data, critical revision of the manuscript for intellectual content.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102057.

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