NeuroImage: Clinical 20 (2018) 448–457

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

The significance of brain oscillations in motor sequence learning: Insights from Parkinson's disease

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ARTICLE INFO

Keywords:
Implicit motor learning
Oscillatory beta activity
SRTT
Interference
Magnetoencephalography (MEG)
Motor control

ABSTRACT

Motor sequence learning plays a pivotal role in various everyday activities. Motor-cortical beta oscillations have been suggested to be involved in this type of learning. In Parkinson's disease (PD), oscillatory activity within cortico-basal-ganglia circuits is altered. Pathologically increased beta oscillations have received particular attention as they may be associated with motor symptoms such as akinesia. In the present magnetoencephalography (MEG) study, we investigated PD patients and healthy controls (HC) during implicit motor sequence learning with the aim to shed light on the relation between changes of cortical brain oscillations and motor learning in PD with a particular focus on beta power. To this end, 20 PD patients (ON medication) and 20 age- and sex-matched HC were trained on a serial reaction time task while neuromagnetic activity was recorded using a 306-channel whole-head MEG system. PD patients showed reduced motor sequence acquisition and were more susceptible to interference by random trials after training on the task as compared to HC. Behavioral differences were paralleled by changes at the neurophysiological level. Diminished sequence acquisition was paralleled by less training-related beta power suppression in motor-cortical areas in PD patients as compared to HC. In addition, PD patients exhibited reduced training-related theta activity in motor-cortical areas paralleling susceptibility to interference. The results support the hypothesis that the acquisition of a new motor sequence relies on suppression of motor-cortical beta oscillations, while motor-cortical theta activity might be related to stabilization of the learned sequence as indicated by reduced susceptibility to interference. Both processes appear to be impaired in PD.

1. Introduction

Complex movements such as riding a bike or playing a musical instrument are composed of sequences of single mostly simple movements. Therefore, our capacity to learn new motor sequences is essential for many activities of daily living. The initial acquisition of skills is characterized by performance improvement followed by motor consolidation which refers to stabilization of skills, i.e. reduced susceptibility to interference, and 'off-line' improvement without further practice (Karni et al., 1998; Robertson et al., 2004, 2005). An established measure of motor sequence learning is the *serial reaction time task* (SRTT) which involves a repeated sequence of button presses (Nissen and Bullemer, 1987). In this task, learning is reflected in a reaction time (RT) decrease over the course of training. Since participants are usually not aware of the embedded sequence, the SRTT allows the induction of implicit learning.

Neuroimaging studies suggest the involvement of primary motor, premotor, dorsolateral prefrontal cortices, the basal ganglia and the cerebellum in motor sequence learning (Destrebecqz et al., 2005; Doyon et al., 2009; Grafton et al., 1995; Hardwick et al., 2013). Furthermore, there is converging evidence that motor and cognitive functions are accompanied by synchronized oscillatory activity at different frequencies proposing a mechanism of functional integration within brain networks (Buzsáki and Draguhn, 2004; Schnitzler and Gross, 2005; Varela et al., 2001). Movement execution is associated with a typical pattern of beta (13–30 Hz) power suppression (i.e., power decrease) prior to and during movement execution followed by a rebound (i.e., power increase) after movement termination (Pfurtscheller

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https://doi.org/10.1016/j.nicl.2018.08.009
Received 22 May 2018; Received in revised form 20 July 2018; Accepted 7 August 2018
Available online 10 August 2018

and Lopes Da Silva, 1999). Regarding motor sequence learning in particular, motor-cortical beta and alpha oscillations (8–12 Hz) are suggested to be relevant in healthy younger adults (Pollok et al., 2014; Zhuang et al., 1997). More specifically, stronger beta power suppression has been linked to superior learning of a motor sequence (Pollok et al., 2014). Similarly, transcranial alternating current stimulation (tACS), assumed to interact with oscillations in a frequency-dependent manner (Helfrich et al., 2014; Thut et al., 2012), was found to facilitate acquisition (Pollok et al., 2015) as well as retrieval of a motor sequence (Krause et al., 2016) when applied over the primary motor cortex at 20 Hz. These findings strengthen the role of beta oscillations in motor sequence learning.

In Parkinson's disease (PD), oscillatory activity in the cortico-basal-ganglia circuits is altered. More specifically, beta activity in the subthalamic nucleus (STN) has been found to be pathologically exaggerated and could be linked to motor impairment such as akinesia and rigidity (Beudel et al., 2017; Jenkinson and Brown, 2011; Kühn et al., 2006, 2009; Neumann et al., 2016; reviewed by Hammond et al., 2007; Oswal et al., 2013; Schnitzler and Gross, 2005). Importantly, such alterations seem to be a feature of the whole cortico-basal-ganglia loop (reviewed by Hammond et al., 2007; Oswal et al., 2013). Along these lines, a non-invasive study using magnetoencephalography (MEG) to investigate cortical beta activity in PD reports an association between motor-cortical beta power during isometric contraction and motor impairment (Pollok et al., 2012). Relating to beta oscillations and its reactivity to voluntary movement in PD, it has been further demonstrated that beta power suppression during transient movement is pathologically reduced in cortical areas associated with motor processing (Heinrichs-Graham et al., 2014).

Taken together, suppression of motor-cortical beta oscillations has been suggested to be linked to successful motor sequence learning in healthy participants and beta oscillations in cortico-basal-ganglia circuits are altered in PD. Furthermore, a considerable set of studies reports impaired motor sequence learning in PD patients as compared to healthy older adults (Muslimovic et al., 2007; Stephan et al., 2011; Wilkinson et al., 2009; reviewed by Ruitenberg et al., 2015; but see Kelly et al., 2004; Smith et al., 2001 for intact learning). Therefore, the present MEG study investigated PD patients and healthy controls (HC) during training on a SRTT to elucidate the relation between changes of beta oscillations and motor learning abilities in PD. We hypothesized that PD patients exhibit less beta power suppression during the SRTT than HC and, concomitant with that, diminished motor sequence learning. Although we were particularly interested in beta oscillations, we performed complementary analyses at theta (4–7 Hz), alpha and gamma frequencies (30–90 Hz) since motor and cognitive processes have been shown to be closely linked to oscillatory brain activity at these frequencies as well (for an overview see Herrmann et al., 2016).

2. Material and methods

2.1. Participants

Twenty PD patients and 20 HC participated in this study. Exclusionary criteria involved tremor-dominant PD, dementia (*Mattis Dementia Rating Scale* (MDRS; Mattis, 1988) score ≤ 130), clinically relevant depression (*Beck Depression Inventory* (BDI-II; Hautzinger et al., 2006) score ≥ 18) or other psychiatric and neurological disorders besides PD. One patient was additionally diagnosed with ataxia several months after testing. Since SRTT performance and oscillatory power values were within two standard deviations of the group mean, we did not exclude these data. Patients remained on their regular anti-parkinsonian medication (for mean daily levodopa equivalent dose (LED; Tomlinson et al., 2010) see Table 1) during study participation to minimize general motor impairment. Motor impairment was characterized by the *Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale*, part III (MDS-UPDRS III; Goetz et al., 2008). In none of the PD patients, tremor prevailed.

For each patient, a sex- and age-matched HC was tested. All participants were right handed (Edinburgh Handedness Inventory; Oldfield, 1971) and had normal or corrected-to-normal vision. To rule out that potential differences in motor sequence learning between groups were influenced by short-term memory deficits, verbal and visuospatial short-term memory was assessed in all participants by means of the *Digit span* (von Aster et al., 2006) and *Block-Tapping-Test* (Schellis, 1997). The study was approved by the local ethics committee (study no. 4792) and is in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation and received monetary compensation. Characteristics of PD patients and HC are shown in Table 1.

2.2. Experimental paradigm: SRTT

The SRTT was introduced as a measure of RT and participants were not informed of the sequence embedded in the task. A nonmagnetic custom-made response box with four response keys anatomically aligned to the right hand was used. Each key corresponded to one of four horizontally aligned bars presented on a back projection screen. All participants were instructed to rest the fingers of their right hand on the response buttons and to press as quickly as possible the corresponding button as soon as one of the bars changed from dark to light blue. RT was defined as the interval between color change and button press onsets. The next bar was presented 2 s after the correct response. In case of incorrect button presses, the bar remained light blue until participants responded correctly. The sequence used was an eight-item sequence (ring-index-thumb-middle-ring-middle-thumb-index finger of the right hand).

After a short practice session of 12 randomly varying bars, the experimental phase comprising five blocks started. The first block served as baseline (*Random*) and consisted of ten repetitions of eight randomly varying bars. To enable learning, the sequence was repeated 15 times (*Training on the sequence*). Then, ten repetitions of the sequence were presented serving as *end of acquisition* (*EoA*). To examine whether randomly presented bars interfered with the learned sequence, ten repetitions of eight randomly varying bars (*Interference*) were followed by ten repetitions of the sequence (*SIn*). Stimulus timing and response recording was controlled by E-Prime® software version 2 (Psychology Software Tools, Sharpsburg, PA, USA). For an overview of the task design, see Fig. 1.

To assess whether explicit learning occurred, participants were asked at the task's end whether they had noticed anything significant. If they were aware of a sequential pattern, they were asked to recall it. Three participants in each group were able to recall at least half of the sequence correctly. For reasons of statistical power, all participants were included in the following analyses.

2.3. Statistical analyses of behavioral data

Analyses were performed using IBM SPSS 24 (IBM Corporation, Armonk, NY, USA). For each block of interest (*Random*, *EoA*, *Interference*, *SIn*), we calculated individual mean RTs. RTs below and above two standard deviations of the respective mean were excluded (patients: 4.9 ± 2.1%; HC: 4.0 ± 0.9% of all trials). Kolmogorov-Smirnov tests revealed no significant deviation from Gaussian distribution (all $p > .05$). Analyses of variance (ANOVA) on mean RT with *block* (*Random* vs. *EoA* vs. *Interference* vs. *SIn*) as within- and *group* (HC vs. PD patients) as between-subjects factor were conducted. *Post-hoc* tests were calculated using two-tailed *t*-tests. In case of violation of sphericity assumptions, Greenhouse-Geisser correction was applied.

To account for motor impairment in PD as indicated by generally slower RTs, we further computed percentage RT gains for motor sequence acquisition ((*Random* − *EoA*) / *Random* × 100) and susceptibility to interference ((*Interference* − *SIn*) / *Interference* × 100) and

Table 1
Characteristics of Parkinson's disease patients and healthy controls.

Demographics and cognitive and affective screening measures								
Group	n	Gender (male/female)	Age	Years of Education	MDRS	BDI-II	Digit Span	Block-Tapping-Test
Patients	20	9/11	52.85 (± 6.88)	14.68 (± 2.82)	141.90 (± 1.48)	7.21 (± 4.48)	8.45 (± 1.70)	5.45 (± 0.70)
Controls	20	9/11	54.05 (± 7.71)	16.25 (± 4.08)	142.55 (± 1.23)	2.50 (± 4.08)	8.50 (± 2.01)	5.05 (± 0.69)

Clinical characteristics of patients			
Side of Impairment (right/left)	Disease Duration (months)	Daily LED (mg)[a]	MDS-UPDRS III
10/10	66.85 (± 36.40)	550.81 (± 265.03)	20.85 (± 6.30)

Demographics and screening measures are presented as group means (standard deviation (SD)). MDRS = Mattis Dementia Rating Scale; BDI-II = German version of the Beck Depression Inventory; LED = levodopa equivalent dose; MDS-UPDRS III = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale motor score on medication.

[a] Note that only one PD patient was treated solely with Levodopa, all other patients (also) received dopamine agonists and/or monoamine oxidase B inhibitors.

compared them between groups using independent-samples *t*-tests.

To investigate whether SRTT performance was related to clinical characteristics in PD, correlations involving LED using Pearson's *r* and correlations involving MDS-UPDRS III using Spearman's ρ were calculated. Bonferroni corrections for multiple testing were applied.

2.4. MEG data acquisition

Neuromagnetic brain activity was recorded during task execution using a 306-channel whole-head MEG system with 204 planar gradiometers and 102 magnetometers (Elekta Neuromag, Helsinki, Finland). The data was sampled at 1 kHz with a bandwidth of 0.1–330 Hz.

Four head position indicator (HPI) coils were fixed to each participant's scalp and HPI coil positions and anatomical landmarks (nasion, left, and right preauricular points) were digitized (Polhemus Isotrak, Colchester, Vermont, USA). Vertical electrooculogram was recorded during the SRTT. Structural MRIs were acquired (3 T Siemens-Magnetom, Erlangen, Germany) after the MEG session. MRIs were aligned with the MEG coordinate system using HPI coils and anatomical landmarks.

2.5. MEG data processing

Data of the gradiometers only were analyzed with the Matlab-based FieldTrip toolbox (Oostenveld et al., 2011) using Matlab R2015a (Mathworks, Natick, MA, USA). The data were segmented into epochs of 1500 ms pre to 2000 ms post button press onset and were filtered using 200 Hz low-pass and 1 Hz high-pass filter. Line noise was removed using band-stop filter with a width of 2 Hz centered at the line frequency of 50 Hz and its harmonic at 100 Hz and data was demeaned. By visual inspection, trials containing sensor jumps or muscle artifacts were rejected from further analyses. A nearest-neighbors approach was used to interpolate data of broken channels by the mean signal of the neighboring channels. A principal component analysis was applied to correct for further artifacts. For each subject, components associated with eye blinks or cardiac signals were removed (mean number of components = 3.53; SD = 0.60).

Time-frequency representations of power were computed using fast Fourier transformation. For frequencies ≤30 Hz, we used an adaptive sliding time window with a width of five full cycles of the respective frequency f ($\Delta t = 5/f$) multiplied by a Hanning taper. The time window moved in steps of 50 ms and the frequency resolution was $1/\Delta t$. For frequencies > 30 Hz, we used a multi-taper approach (sliding time window of 500 ms length) with four orthogonal Slepian tapers resulting in a frequency smoothening of ± 5 Hz. Spectral power was calculated for vertical and horizontal gradiometers separately and was then combined. Due to strong muscle artifacts, one participant of each group was excluded from analyses of frequencies > 30 Hz. Power changes were defined as relative change with respect to the mean of the complete epoch length according to previous studies (Pollok et al., 2014; te Woerd et al., 2014, 2015).

2.6. Statistical analyses of MEG data

First, we investigated whether oscillatory activity differed significantly between groups prior to learning during *Random*. To this end, we averaged the activity across the respective frequencies (theta, alpha, beta, and gamma) and computed cluster-based non-parametric

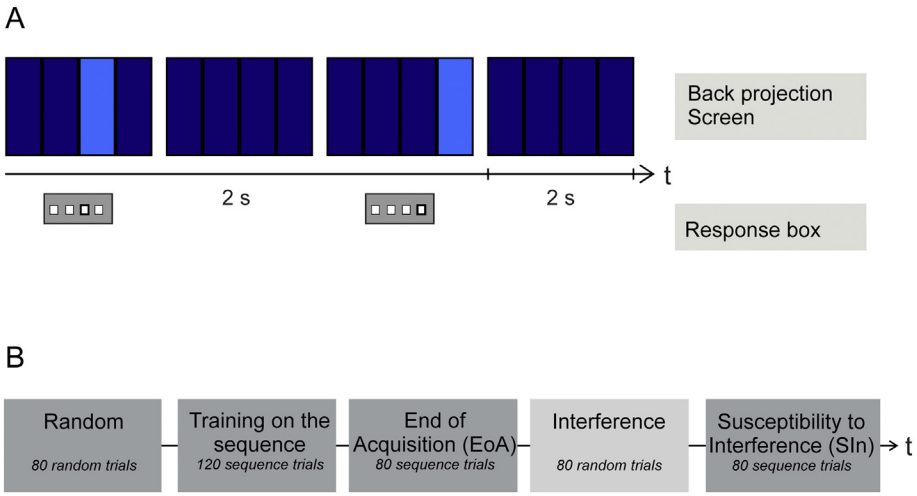

Fig. 1. Overview of task design. (A) Sequence of events in two exemplary SRTT trials. The response keys of the response box were spatially mapped to four bars presented on the back projection screen. Participants were instructed to press the corresponding button as soon as one of the bars changed from dark to light blue. The interval between the correct response and the next trial was set to 2 s. (B) SRTT procedure. Neuromagnetic brain activity was recorded during the entire task. During *Random*, ten repetitions of eight randomly varying bars were presented. To enable acquisition of a motor sequence, an eight-item sequence was presented 15 times (i.e. *Training on the sequence*). The end of acquisition (*EoA*) comprised ten repetitions of the sequence. For the assessment of susceptibility to interference, ten repetitions of eight randomly varying bars were presented (*Interference*) and followed by ten repetitions of the introduced sequence (*SIn*).

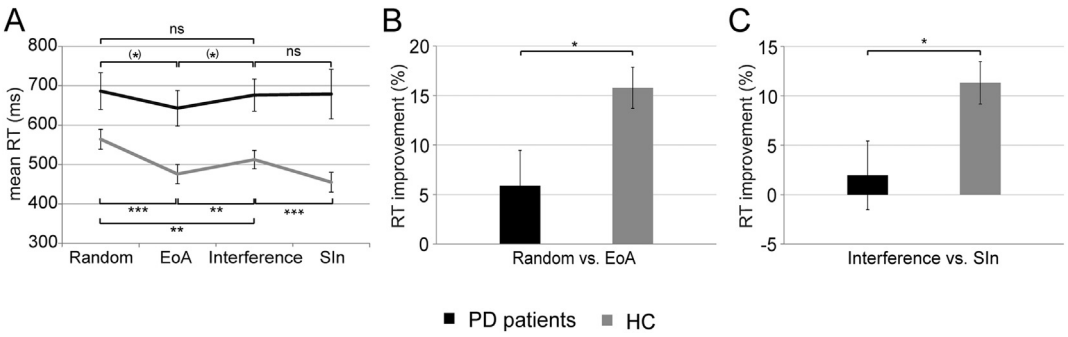

Fig. 2. Behavioral results. (A) Mean RTs of blocks of interest in PD patients and HC. Percentage RT gains in HC and patients from (B) *Random* to *EoA* reflecting sequence acquisition and from (C) *Interference* to *SIn* reflecting susceptibility to interference. Note that greater RT improvement from *Interference* to *SIn* reflects *less* susceptibility to interference. Error bars indicate standard error of the mean (SEM); *** $p < .001$; ** $p < .01$; * $p < .05$; (*) $p = .06$; ns = not significant; End of Acquisition (EoA); sequence trials after interference (SIn).

permutation tests (Maris and Oostenveld, 2007) in FieldTrip. This statistical approach effectively controls for multiple comparisons across time points and channels. Analyses were performed for a time interval of 750 ms pre to 1500 ms post button press onset in a selection of 32 channels covering left and right primary sensorimotor cortices (S1/M1; Pollok et al., 2014; Fig. 3). Further, cortical sources of alpha and beta power modulation (maximal rebound to suppression) were identified using *Dynamic Imaging of Coherent Sources* (DICS; Gross et al., 2001) implemented in FieldTrip. For beta activity, we contrasted two time windows of 500 ms centered on the time points of maximal beta power suppression and rebound, respectively. 20 Hz was chosen as center frequency (spectral smoothening of ± 5 Hz) which resulted in 10 full cycles per time window. We created a realistic, single-shell brain model (Nolte, 2003) based on the individual anatomical MRI or on a MNI template ($n = 10$). Forward solution for each participant was estimated using a regular 3D grid with 1 cm resolution in MNI space which was warped onto the individual anatomy. A lead-field matrix was computed for each grid point according to the MEG head position and forward model. Using the cross-spectral density and lead-field matrices, a common spatial filter was constructed on both time windows (suppression and rebound) for each grid point. The spatial filter was then applied to beta power suppression and rebound epochs and contrasted. For each group, source reconstructed oscillatory power was averaged across participants and visualized on the cortical surface of the MNI template brain. The same steps were applied for alpha activity, using a center frequency of 10 Hz (spectral smoothening of ± 2 Hz) resulting in five full cycles per time window.

To examine differences in oscillatory activity relating to motor sequence acquisition and susceptibility to interference between groups, we calculated the difference in oscillatory activity between *EoA* and *Random* as well as between *SIn* and *Random*. We compared these contrasts of interest between groups by means of cluster-based permutation tests for the same time interval and frequencies (averaged across theta, alpha, beta, and gamma, respectively) as described above with Monte Carlo randomization controlling for multiple comparisons across time points and channels. Since motor-cortical areas have been suggested to play a pivotal role in motor sequence learning, statistical analyses were performed in the S1/M1 channel selection (Pollok et al., 2014; Fig. 3). Additionally, we used the same cluster-based approach to conduct complementary analyses including all sensors. Resulting clusters with p-values $< .05$ were considered significant.

3. Results

Mean years of education, MDRS scores, and verbal short-term memory did not differ between PD patients and HC (all $p > .13$). Patients tended to exhibit better visuospatial short-term memory ($p = .07$). Although PD patients scored significantly higher on the BDI-II (median = 6.50) than HC (median = 2.00; U = 73; z = −3.46; $p = .001$), none of the patients exhibited clinically relevant depression. Furthermore, BDI-II scores were not significantly correlated with SRTT performance in neither group (all $p > .20$).

3.1. Behavioral data

The ANOVA revealed significant main effects of *block* ($F(2.5, 94.8) = 8.69$; $p < .001$) and *group* ($F(1, 38) = 10.43$; $p = .003$) with slower RTs in patients than in HC (see Fig. 2A). A significant *group* by *block* interaction ($F(2.5, 94.8) = 4.21$; $p = .01$) indicated significantly faster RTs at *EoA* as compared to *Random* ($t(19) = -6.68$; $p < .001$) and *Interference* ($t(19) = -3.25$; $p = .004$) in HC. In patients, we found only a trend towards faster RTs at *EoA* as compared to *Random* ($t(19) = -2.00$; $p = .06$) and *Interference* ($t(19) = -2.00$; $p = .06$). Additionally, HC were significantly faster during *Interference* than *Random* ($t(19) = -3.39$; $p = .003$) suggesting unspecific RT improvement while RTs did not differ significantly in patients ($p = .71$). Furthermore, HC were significantly faster during *SIn* than *Interference* ($t(19) = -5.22$; $p < .001$) indicating that they were not susceptible to interference. In patients, no significant difference emerged ($p = .93$). As the standard error of the mean as depicted in Fig. 2A appears to be relatively large in the PD patients group, especially during *SIn*, it is possible that this null finding in PD patients might be driven by pronounced improvement of RT from *Interference* to *SIn* in some patients combined with marked slowing of RT in others. To further investigate and quantify individual performance in PD patients, we calculated the confidence interval from RTs during *Interference* and examined whether individual mean RTs of PD patients during *SIn* fall within or outside the limits of this interval. RTs of two PD patients were outside this interval (i.e. below the limits) although their RTs were within limits during *Interference*. Additionally, one PD patient whose RT was below the limits of the interval during *Interference* exhibited a mean RT within the limits of the interval during *SIn*. Thus, we assume that the majority of patients did not show pronounced RT deviations from *Interference* to *SIn*. Further evidence for this assumption was revealed by the observation that RT gains from *Interference* to *SIn* did not differ significantly from zero in PD patients ($t(19) = 0.56$; $p > .58$).

The analysis of percentage RT gains revealed significantly less gain in RT from *Random* to *EoA* in patients as compared to HC ($t(38) = -2.39$; $p = .02$; Fig. 2B) indicating diminished motor sequence acquisition in the former group. Significantly smaller RT gains from *Interference* to *SIn* in patients ($t(38) = -2.30$; $p = .03$; Fig. 2C) indicated higher susceptibility to interference in PD patients as compared to HC.

Correlational analyses linking clinical characteristics to SRTT performance revealed no significant results (all $p \geq .16$).

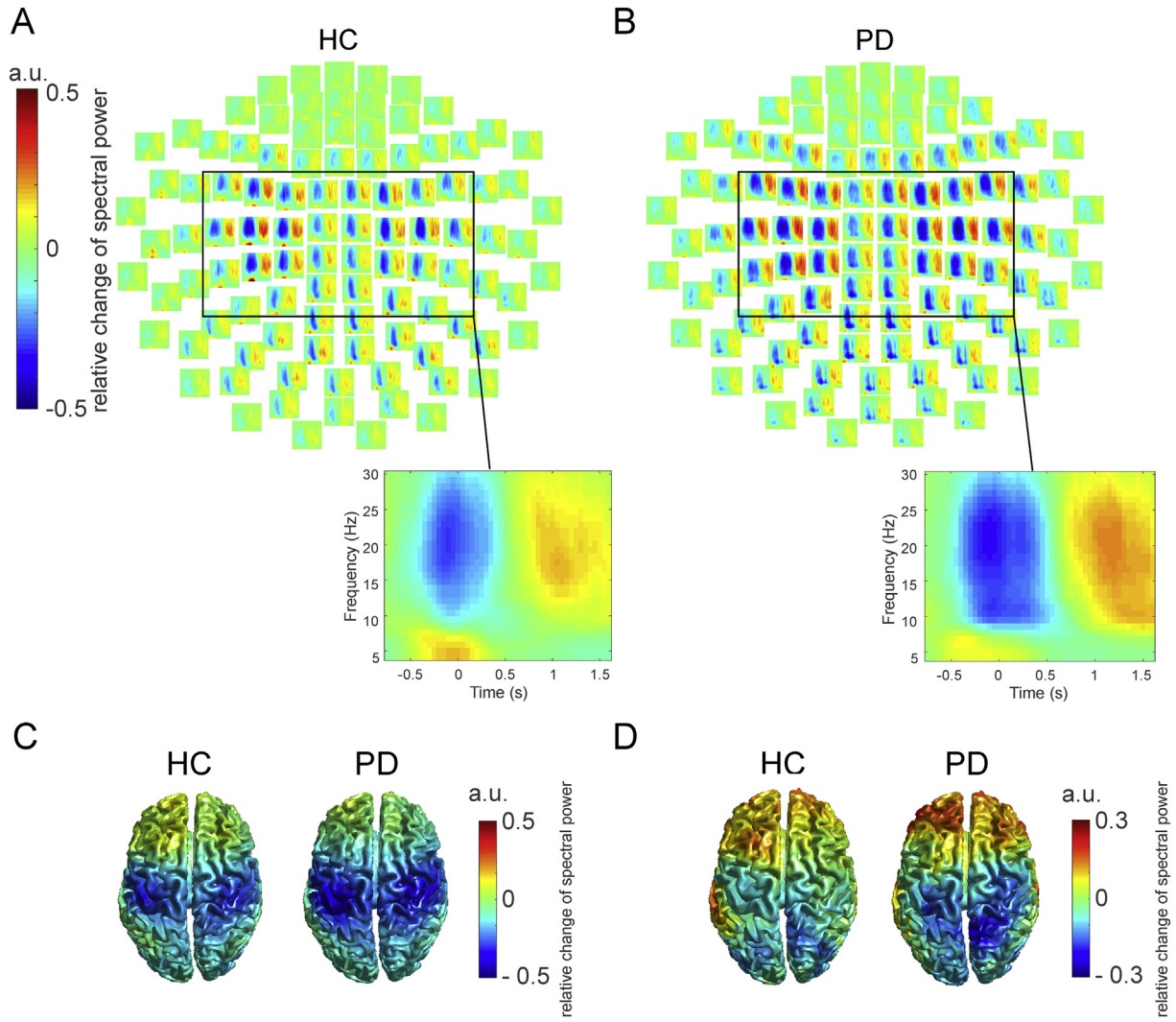

Fig. 3. Oscillatory activity at frequencies ≤30 Hz during *Random*. Sensor plot of 102 combined planar gradiometers showing time-frequency representations of power expressed as relative change to baseline averaged across (A) HC and (B) PD patients. Inserts indicate spectral power averaged across the channel selection covering S1/M1 in each group. Warm colors indicate an increase, cold colors a decrease in power. Button press onset was at 0 s. Color bar placed at the far left applies to all plots. Source reconstruction of (C) beta and (D) alpha power modulation, measured from maximal rebound to maximal suppression averaged over each group (left panel: HC, right panel: PD patients) projected onto the MNI template brain.

3.2. MEG data

After preprocessing of the data including artifact rejection, the two groups did not differ in the number of trials subjected to MEG data analyses (mixed-design ANOVA: all $p \geq .18$).

3.2.1. Group differences during Random

Oscillatory activity in frequencies ≤30 Hz is shown in Fig. 3A and B. Descriptively, both groups showed the expected beta power suppression before and during button press followed by a rebound. Modulation of alpha power appeared to be especially pronounced in PD patients. In addition, theta power increased relative to baseline approximately 400 ms prior to button press. Cortical sources of beta and alpha power modulation are illustrated in Fig. 3C and D. Beta power modulations were most pronounced in bilateral pericentral regions, while alpha power modulations were less focal.

Statistical analyses in sensors covering motor-cortical areas revealed no significant group differences at beta frequencies. However, significant differences between PD patients and HC emerged at alpha frequencies which were most pronounced between 350 ms prior to and 500 ms after button press ($p = .003$) and between 1100 and 1500 ms after button press ($p = .02$; Fig. 4) suggesting significantly stronger alpha power suppression as well as rebound in PD patients as compared to HC. At theta and gamma frequencies, no significant group differences emerged.

3.2.2. Group differences over the course of the SRTT

Fig. 5A and C show differences in oscillatory activity between blocks in frequencies ≤30 Hz. For *EoA* as compared to *Random*, statistical analyses between groups revealed a significant difference between groups at beta frequencies in the S1/M1 channel selection ($p = .048$; Fig. 5B) most pronounced between 450 and 350 ms prior to button press suggesting less beta power suppression during *EoA* relative to *Random* in patients than in HC. Noteworthy, this difference was most pronounced in motor areas ipsilateral to the moving hand. Complementary analyses including all sensors resulted in a difference at beta frequencies most pronounced between 450 and 250 ms prior to button press trending towards significance ($p = .06$). In other frequency bands, no significant differences emerged.

For *SIn* as compared to *Random*, statistical analyses between groups revealed a significant difference at theta frequencies in S1/M1 channels ($p = .02$; Fig. 5D) most pronounced between 50 ms prior to and 150 ms

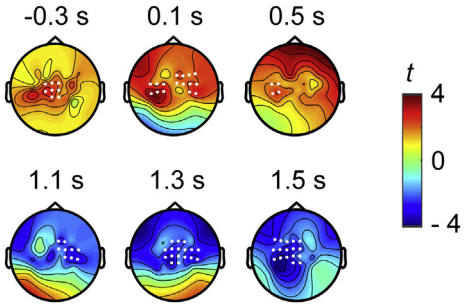

Fig. 4. Results of statistical group comparisons during *Random*. Results of the cluster-based permutation test (HC vs. PD patients) comparing oscillatory activity in the S1/M1 channel selection averaged across the alpha frequency band prior to learning during *Random*. Clusters showing differences between groups ($p < .05$) are indicated by white circles. Warm colors indicate stronger decrease, cold colors stronger increase in power in patients than in HC. For illustrative reasons, only a selection of time points is shown. Color bars placed at the far right apply to all cluster plots.

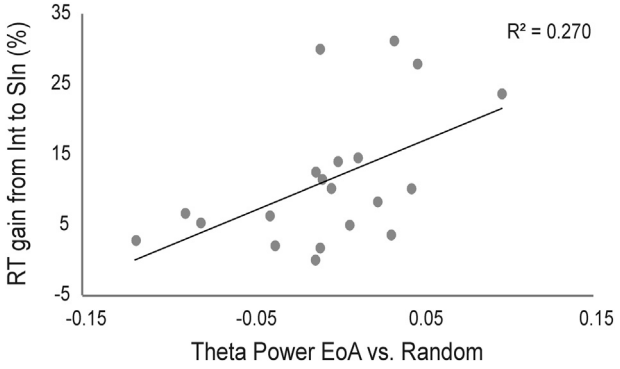

Fig. 6. Correlation between theta power changes and susceptibility to interference in HC. Changes in motor-cortical theta activity (*EoA* vs. *Random*) in a time window of 800 ms surrounding button press onset was significantly correlated with percentage RT gains from *Interference* to *SIn*. For the interpretation of the results, it is important to highlight that larger RT gains from *Interference* to *SIn* indicate *less* susceptibility to interference. End of Acquisition (EoA); Interference (Int); sequence trials after interference (SIn).

after button press contralateral to the moving hand suggesting less theta power increase from *Random* to *SIn* in patients. In other frequency bands, no significant differences emerged.

Although results of cluster-based permutation tests do not provide information on the exact temporal extent, the observed group difference in the theta frequency band appeared to be rather short-lived. To further validate the functional role of theta activity for susceptibility to interference, we conducted additional correlational analyses. To this end, we extracted individual theta power values from a time window of 800 ms surrounding button press in which theta activity was most pronounced during task performance (see time-frequency representations of power, Fig. 3) for *Random*, *EoA* and *SIn*. We then correlated the change in theta power from *Random* to *EoA* and *SIn*, respectively with

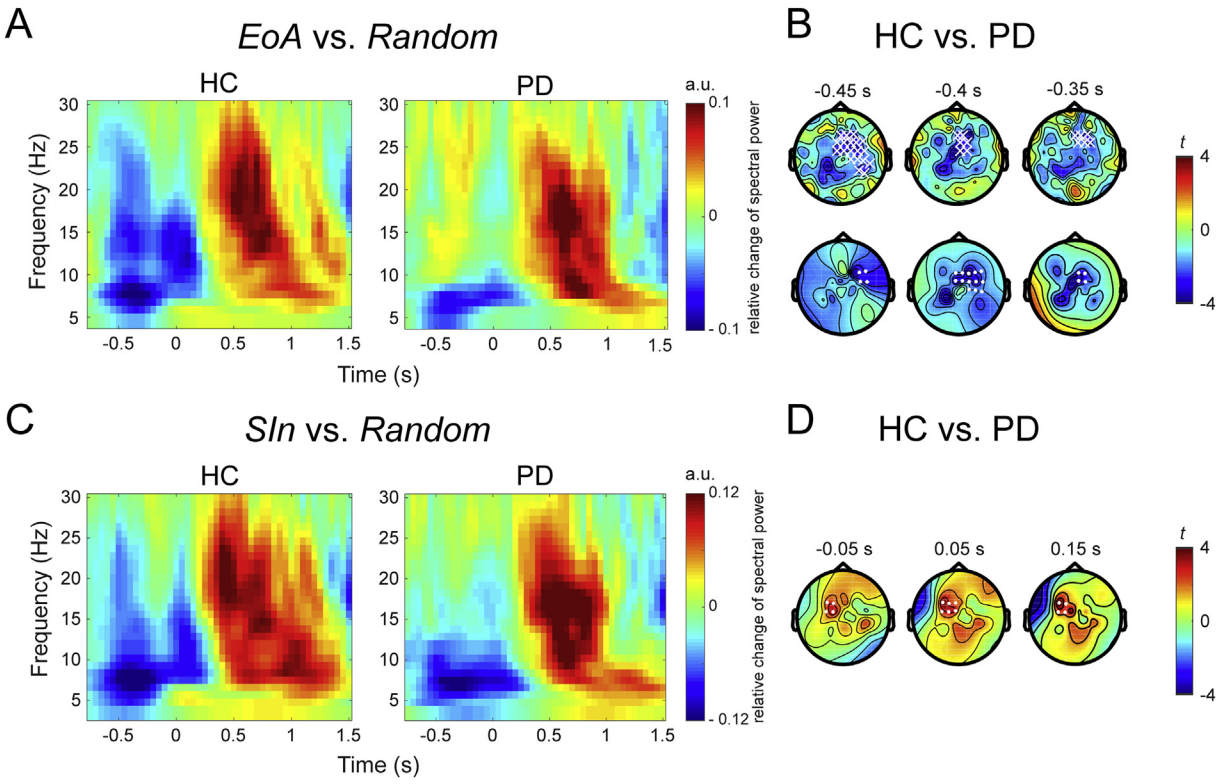

Fig. 5. Oscillatory activity at frequencies ≤30 Hz over the course of the SRTT. Time-frequency representations of power for the contrasts of interest (A) *EoA* vs. *Random* and (C) *SIn* vs. *Random* averaged across the S1/M1 channel selection in HC (left) and PD patients (right). Cold colors indicate stronger decrease in power during *EoA/SIn* than *Random*. Warm colors indicate stronger increase in power during *EoA/SIn* than *Random*. Button press onset was at 0 s. Color bar placed at the right applies to HC and patients. Results of statistical analyses (HC vs. PD patients) for the contrasts of interest (B) *EoA* vs. *Random* averaged across beta frequencies (13–30 Hz) including all channels (top) and the S1/M1 channel selection (bottom) and for (D) *SIn* vs. *Random* averaged across theta frequencies (4–7 Hz) for the S1/M1 channel selection. Clusters that show a difference between groups ($p < .05$) are indicated by white circles. White Xs indicate clusters with $p = .06$. Cold colors indicate less decrease (in B) and warm colors less increase in power (in D) in patients than in HC from *Random* to *EoA* or *SIn* in the respective frequency bands. Color bars placed at the far right apply to all cluster plots. Please note that the cluster in (B) for all channels was most pronounced between 450 and 250 ms prior to button press onset. For illustrative reasons, we kept the displayed time interval equal for the top and bottom row. End of Acquisition (EoA); sequence trials after interference (SIn).

the percentage RT gain from *Interference* to *SIn* representing susceptibility to interference. This rather large time window of 800 ms was chosen to ensure that the observed effects indeed reflect oscillatory theta activity. As changes in theta power did not deviate significantly from Gaussian distribution (Kolmogorov-Smirnov tests: all $p > .07$), we calculated Pearson's correlation coefficients. Correlational analyses for each group revealed a significant correlation between theta power changes from *Random* to *EoA* and RT gain from *Interference* to *SIn* in HC ($r = 0.52$; $p = .04$; Bonferroni corrected; Fig. 6) but not in PD patients ($p > .50$). Correlational analyses involving theta power changes from *Random to SIn* failed to reach significance, both in HC and in PD patients (all $p > .27$).

4. Discussion

The present MEG study investigated PD patients and healthy participants while performing a SRTT with the right hand to elucidate the relation between beta oscillations and motor learning. The data indicate reduced motor sequence acquisition and higher susceptibility to interference in PD patients as compared to HC. Diminished acquisition in patients as compared to HC was paralleled by less motor-cortical beta power suppression supporting the relevance of beta activity to motor sequence learning. Additionally, we found less increase in theta activity in PD patients as compared to HC paralleling susceptibility to interference. Interestingly, changes in theta activity over the course of the SRTT were significantly correlated with reduced susceptibility to interference in HC only. These results provide first evidence for the significance of theta oscillations in stabilizing newly acquired movement patterns.

4.1. Oscillatory activity prior to motor sequence learning

Both PD patients and HC showed the established pattern of movement-related alpha and beta power modulation during *Random*. However, statistical analyses revealed significant differences between groups at alpha frequencies. More specifically, the data suggest stronger alpha power suppression as well as rebound in sensors covering motor-cortical areas in PD patients than in HC. As alpha oscillations have been related to attentional information processing and automatic motor control (Klimesch, 2012; Klostermann et al., 2007; Pollok et al., 2009; Zhuang et al., 1997) this difference may reflect the need for greater attentional resources and control mechanisms in PD. Contrary to alpha frequencies, beta power modulation prior to learning did not differ significantly between groups in sensors covering motor-cortical areas. However, at a descriptive level, time-frequency representations of power as well as source reconstruction (Fig. 3) may suggest more widespread beta power modulation in patients which could reflect the recruitment of a larger brain network for task performance in PD. The present (null) finding at beta frequencies deviates from results of a previous study reporting *diminished* beta power suppression prior to and during basic finger movements in PD (Heinrichs-Graham et al., 2014). It is important to note, that the previous study examined patients OFF medication. As PD patients in the present study were tested ON their regular dopaminergic medication, it is beyond the scope of the study to determine whether these differences are related to specific task requirements or rather relate to differences in medication at the time of testing. However, since beta power modulation may be dopamine-dependent (Doyle et al., 2005; Litvak et al., 2012; Oswal et al., 2012, 2013), different findings likely relate to different levels of levodopa.

4.2. Alterations in motor sequence learning in PD patients as compared to HC

The present data suggest that motor sequence acquisition is diminished in PD patients as compared to HC. This is in line with several studies reporting impaired or reduced motor sequence acquisition in PD (reviewed by Ruitenberg et al., 2015). In addition to sequence-specific gain, HC showed unspecific RT improvement from *Random* to *Interference*. Since RTs during *SIn* and *EoA* were significantly faster than during *Interference*, sequence-specific improvement was more pronounced than unspecific gain.

Apart from motor sequence acquisition, we further examined susceptibility to interference immediately after acquisition of the sequence. This process has rarely been studied in PD but needs to be taken into account to understand different processes involved in motor sequence learning (Doyon, 2008; Marinelli et al., 2017). Our analyses suggest higher susceptibility in patients than in HC indicating that not only acquisition but also early stabilization processes are altered in PD.

In contrast to a previous study by Muslimovic et al. (2007) in which medicated PD patients with more severe clinical symptoms tended to show worse sequence learning, we found no significant link between symptom severity and motor sequence learning in the present patient sample. However, as the correlation between symptom severity and learning impairment reported by Muslimovic et al. (2007) was rather weak, the sample size of the present study might have been too small to replicate this finding.

4.3. The functional significance of oscillations in motor sequence learning

4.3.1. Beta oscillations

During *EoA* as compared to *Random*, we observed significantly less beta power suppression in PD patients than in HC most pronounced prior to button press which was paralleled by diminished sequence acquisition in PD. Interestingly, beta activity has been related to the "maintenance of the current motor and cognitive state" (Engel and Fries, 2010) suggesting that increased beta activity might promote the maintenance of a current task set at the expense of flexible control strategies. Accordingly, beta power suppression has been assumed to represent an anticipatory control mechanism related to the prospective control of motor (or cognitive) readiness (Brittain and Brown, 2014; Engel and Fries, 2010; Jenkinson and Brown, 2011; Oswal et al., 2012). The present finding of less beta power suppression accompanied by reduced motor sequence acquisition in PD patients is in line with these assumptions. Furthermore, our results fit nicely with the hypothesis that beta power suppression might represent a neurophysiological marker of functional reorganization of motor areas associated with motor (sequence) learning (Boonstra et al., 2007; Pollok et al., 2014). Unfortunately, as our data does not allow causal conclusions regarding the role of beta oscillations, we cannot determine whether beta power suppression relates to learning itself or rather represents the execution of automatized movements as a result of learning progression. Similarly, one might further argue, that reduced beta power suppression over the course of the task as observed in PD patients might reflect slowing of movement execution in general unrelated to motor sequence learning. But, as our results show that beta power suppression prior to learning during *Random* was not reduced in PD patients as compared to HC, the observed differences in beta power suppression over the course of the task rather relate to alterations in motor learning performance than to movement slowing.

Group differences in beta power suppression were most pronounced in motor regions *ipsilateral* to the responding right hand. We are aware that results of cluster-based permutation tests do not provide information on the exact spatial extent of the effect. Nevertheless, differences between PD patients and healthy older adults in beta oscillations ipsilateral to the effector have been reported before. For example, Meziane et al. (2015) found symmetrical beta power suppression in sensorimotor areas during a reaching task in healthy older adults but not in PD patients supporting the assumption that loss of hemispheric lateralization may be one characteristic of an aging, healthy motor system (Vallesi et al., 2010). Thus, older adults may need more extensive recruitment of (bilateral) sensorimotor areas than young adults to achieve optimal performance levels (Meziane et al., 2015). This compensatory

mechanism may be deficient in PD.

Determining the mechanisms by which beta activity contributes to skill acquisition is beyond the scope of the data. However, previous studies revealed a link between increased beta oscillations and decreased cortical excitability (McAllister et al., 2013; Noh et al., 2012). It is therefore tempting to speculate that beta power suppression reflects an increase in cortical excitability which promotes plastic changes in training-related neural networks. Consistent with this interpretation, impaired (motor-)cortical plasticity is already apparent in early PD (Koch, 2013).

4.3.2. Theta oscillations

Beyond beta activity, we found significantly less theta power increase from *Random* to *SIn* in patients than in HC. This finding was paralleled by higher susceptibility to interference in patients at the behavioral level. Since prior to learning no significant group differences at theta frequencies emerged, the data may provide a piece of evidence that theta oscillations contribute to susceptibility to interference, at least in healthy older volunteers. This assumption was further supported by the significant correlation between theta power changes from *Random* to *EoA* and RT gain from *Interference* to *SIn* – representing reduced susceptibility to interference – in HC. Interestingly, this result further fuels the idea that susceptibility to interference after the end of training relies on neurophysiological changes occurring during acquisition already. In general, theta oscillations have been linked to executive processes and declarative memory functions (Brier et al., 2010; Burke et al., 2014; Klimesch et al., 1997, 2001; Sauseng et al., 2005). Furthermore, the implication of theta oscillations in the induction of local synaptic plasticity indicates their mnemonic function (Larson and Lynch, 1989; Orr et al., 2001; Pavlides et al., 1988) and may propose a functional mechanism of these oscillations in sequence learning possibly impaired in PD. Alternatively, it has been hypothesized that cortical theta synchronization might represent one mechanism coordinating sensory and motor brain activity to facilitate learning (Caplan et al., 2003). Therefore, theta rhythms might be involved in learning, especially when sensorimotor integration is necessary (Bland, 1986; Bland et al., 2007; Bland and Oddie, 2001; Caplan et al., 2003; Cruikshank et al., 2012). More specifically related to sequence learning, beneficial effects of theta power increases on early consolidation of explicitly acquired motor sequences were found in a recent neurofeedback study (Rozengurt et al., 2016). This finding indicates that theta oscillations are involved in early consolidation in explicit learning. The present data add to this evidence by suggesting an involvement of theta oscillations also in implicit learning.

4.4. Caveats

In the present study we make assumptions about oscillatory activity at the cortical level. Evidently, the basal ganglia have been suggested to play a key role in successful learning of a motor sequence (e.g., Doyon et al., 2009; Ruiz et al., 2014). However, as deep brain activity is not easily measured from the scalp (Cohen et al., 2011), implications about the involvement of the basal ganglia are beyond the scope of the study.

We observed slower RTs in patients than in HC during *Random* already although patients were tested ON medication. Thus, an effect of general motor impairment cannot be excluded. But, as symptom severity was not significantly correlated with RTs, observed performance differences on the SRTT likely reflect diminished sequence learning rather than impairment of motor performance. Additionally, one might wonder whether motor characteristics such as tremor might have influenced the present MEG results. However, as we excluded tremor-dominant PD patients during recruitment, we assume this to be a minor issue that cannot account for the present findings.

Fatigue effects might be greater in PD contributing to observed group differences in motor sequence learning. However, as patients were not significantly slower at *SIn* as compared to *Random* ($p > .81$) such effects may play a minor role. Furthermore, PD patients may have difficulties in exploring optimal task solutions and maintaining mental effort and motivation (Schneider, 2007; Vakil et al., 2014). We did not assess motivational aspects during participation, which makes it difficult to rule out such influences. However, patients tended to perform better on a visuospatial short-term memory task than HC arguing against a pivotal role of motivational factors. Finally, we cannot exclude the possibility that PD patients might have reached similar performance levels as HC with more extensive training. This issue has to be addressed in future studies applying more sequence repetitions.

4.5. Conclusion

The present findings provide evidence for altered motor sequence acquisition and susceptibility to interference in PD. Behavioral deficits were paralleled by aberrant beta and theta activity in PD patients supporting their role in sequence acquisition and stabilization of newly acquired movement patterns.

Authors' roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique

S.N.M.: 1A, 1B, 1C, 2A, 2B, 3A.
V.K.: 1C, 2C, 3B.
M.S.: 1A, 3B.
C.J.H.: 1B, 2C, 3B.
B.P.: 1A, 2A, 2C, 3B.

Declarations of interests

None.

Acknowledgments

The authors would like to express their gratefulness to all participants of the study. We further thank Erika Rädisch for the acquisition of structural MRIs. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. S.N.M. has received a travel grant from the German Academic Exchange Service (DAAD). C.J.H. has received a travel grant from Abbott.

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