Parkinsonism and Related Disorders 65 (2019) 210–216

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Excessive phase synchronization in cortical activation during locomotion in persons with Parkinson's disease

Yael Miron-Shahar[a], Jan W. Kantelhardt[b], Adam Grinberg[c], Sharon Hassin-Baer[d,e,f], Ilan Blatt[e], Rivka Inzelberg[g,h,i], Meir Plotnik[c,h,j,k,*]

[a] School of Graduate Studies, Neuroscience Department, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel
[b] Institute of Physics, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
[c] Center of Advanced Technologies in Rehabilitation, Sheba Medical Center, Tel Hashomer, Israel
[d] Movement Disorders Institute, Sagol Neuroscience Center and Department of Neurology, Sheba Medical Center, Tel-Hashomer, Israel
[e] Department of Neurology, Sheba Medical Center, Tel-Hashomer, Israel
[f] Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel
[g] Department of Neurology and Neurosurgery, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel
[h] Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel
[i] Department of Applied Mathematics and Computer Science, the Weizmann Institute of Science, Rehovot, Israel
[j] Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel
[k] Gonda Brain Research Center, Bar Ilan University, Ramat-Gan, Israel

ARTICLE INFO

Keywords:
Parkinson's disease
Electroencephalography
Interhemispheric phase synchronization
Gait
Bimanual movements

ABSTRACT

Introduction: Parkinson's disease (PD) is characterized by gait disturbances, which become severe during the advanced stages of the disease. Though gait impairments in Parkinson's disease have been extensively described in terms of spatiotemporal gait parameters, little is known regarding associated patterns of cortical activity. The objective of the present study is to test if interhemispheric synchronization differs between participants with PD and healthy elderly controls (NPD). We analyzed electroencephalography (EEG) signals recorded during bilateral movements, i.e., locomotion and hand tapping.

Methods: Fifteen participants with PD ('OFF' their anti-parkinsonian medications) and eight NPD were assessed during quiet standing, straight-line walking, turning, and hand tapping tasks. Using a 32-electrode EEG array, we quantified the synchronization in periodic cortical activation between the brain hemispheres (interhemispheric phase synchronization; inter-PS). Theta, alpha, beta, and gamma bands were evaluated.

Results: In all bands, inter-PS was significantly higher for the PD group as compared with the NPD group during standing and walking ($p < 0.001$) and during bimanual tasks ($p = 0.026$).

Conclusions: Persons with PD exhibit increased inter-PS as compared with NPD participants. These findings support previous evidence from animal studies, that bilateral cortical hypersynchronization emerges from the asymmetric neural degeneration that is at the base of the disease. Future studies should elucidate the long-term temporal development of this hypersynchronization and its clinical relevance (e.g., can it 'serve' as prodromal marker?).

1. Introduction

Debilitating gait disturbances are common among persons with Parkinson's disease (PD), evidently resulting from complex interactions at all levels of the central nervous system (for review, e.g. Ref. [1]). This study is a first stage in a comprehensive project to delineate the relation between various physiological processes and gait disturbances in PD. The study focuses on bihemispheric cortical phase synchronization as expressed in electroencephalography (EEG) signals. We hypothesize that interhemispheric synchronization will be elevated in PD as compared to healthy elderly controls (non-PD = NPD). We focus on movements that involve bilateral brain activation (i.e., locomotion and bimanual hand tapping).

1.1. Background and rationale

During walking, hierarchical supraspinal regions including cortical (i.e., primary motor and prefrontal cortices and premotor/

* Corresponding author. Center of Advanced Technologies in Rehabilitation, Rehabilitation Hospital, Chaim Sheba Medical Center, Tel Hashomer, 5265601, Israel.
E-mail address: meir.plotnik@sheba.health.gov.il (M. Plotnik).

https://doi.org/10.1016/j.parkreldis.2019.05.030
Received 1 January 2019; Received in revised form 21 May 2019; Accepted 21 May 2019

supplementary motor area) and subcortical structures (pontomedullary reticular formation, mesencephalic and cerebellar locomotor regions and the basal ganglia (BG)) send descending control signals to spinal central pattern generators (CPGs) to modify the stereotyped locomotor pattern [1,2].

The contribution of cortical areas to gait in PD have been the focus of a handful of EEG studies (e.g. Refs. [3,4]) These primarily addressed the enigmatic phenomenon of freezing of gait (FOG) (for review on FOG see Ref. [1]). Although motion-induced EEG artifacts constitute a major challenge, recent technological developments highlighted the feasibility of EEG recording during walking [5]. EEG allows to measure cortical activity changes with fine temporal resolution. EEG is also an efficient method for monitoring synchronized cortical activity expressed in different frequency bands. Specifically, the beta band is considered to represent the maintenance of an existing ('status quo') sensorimotor and cognitive state [6]. In contrast, cortical gamma activity was shown to increase during voluntary movement [7].

Recent years' findings from studies associating cortical activity with the activity of the subthalamic nucleus (STN) draw the attention to the presence of simultaneous hyper EEG activity, in particular of the motor areas, associated with dopaminergic loss [8,9]. Ahn et al. revealed higher levels of cortical phase synchronization (PS) for beta band oscillations in PD participants as compared with healthy controls [8]. Elevated PS in PD was particularly pronounced when EEG leads were placed over different hemispheres, reflecting a prominent role for interhemispheric PS (inter-PS). Nevertheless, the dynamics of inter-PS in PD remains largely unknown, since interhemispheric communication during gait, which involves bilateral brain activation, was hardly studied [10].

The present study focuses on interhemispheric cortical dynamics in PD using EEG PS [11]. The rationale behind our study hypothesis (see above) is based on the following: (1) PD-related neural impairments and symptomatology have asymmetric presentations [12] associated with an asymmetrical depletion of dopamine (DA) in the substantia nigra [13] and (2) previous observations form animal models e.g. Ref. [14], demonstrated a longitudinal development of bicortical synchronization following unilateral (i.e., asymmetric) subcortical damage. Thus, we postulated that interhemispheric hypersynchronization will evolve in PD, since there is also an asymmetric dopaminergic loss.

2. Methods

2.1. Participants

PD participants were recruited from the Movement Disorders Institute at Sheba Medical Center.

Inclusion criteria for PD participants were age over 50 years, diagnosis of idiopathic PD [15], current levodopa treatment, ability to walk unassisted for at least 100 m during OFF state, and ability to understand verbal instructions. Exclusion criteria were the presence of significant comorbidities (i.e., previous brain surgery, any surgery within the previous 6 months, peripheral neuropathy, spinal stenosis, stroke, amputation, or major depression - based on the neurologist report) or major orthopedic problems. Inclusion criteria for NPD were age over 50 years and ability to walk independently. Exclusion criteria for NPD were any neurological disease and the presence of any clinical condition that may affect gait.

The study was approved by the Sheba Medical Center Committee for Human Experimentation. Following screening for eligibility, 25 participants (17 PD, 8 NPD) agreed to participate and gave written informed consent prior to study initiation. Two PD participants were unable to complete the assessment protocol.

2.2. Recording equipment

To collect EEG signals: A portable EEG system (MicroMed®, Mogliano-Veneto, Italy) consisting of a 32-channel montage was used to record naturally-occurring electrical activity (Fig. 1). Sampling rate was 2048 Hz, and a notch filter of 50 Hz was applied. In addition, video recordings synchronized with the EEG were made for all motor trials. Post-hoc analysis of the video was used to annotate the EEG data in reference to the performed activity.

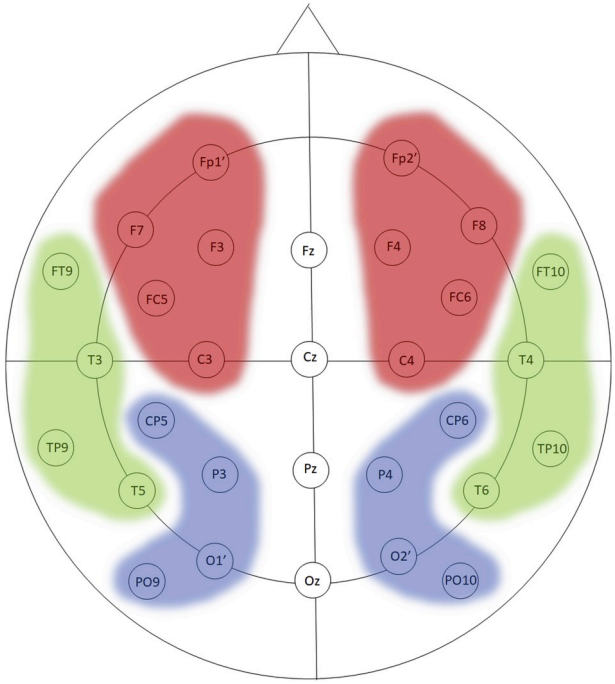

Fig. 1. EEG recording Montage. A 32 channel EEG montage (reference electrode on C7 spinous process and ground electrode on the left mastoid process, both does not appear). The EEG leads were attached to the skull using conductive gel. The array was kept in place by a bandage. All cables were lumped together and connected to a data logger box attached to the subject's hip. The following combinations were considered as covering different brain lobes: Frontal left (FP1, F3, F7, FC5, C3), Frontal right (FP2, F4, F8, FC6, C4), Parietal-occipital left (CP5, PO9, P3, O1), Parietal-occipital right (CP6, PO10, P4, O2), Temporal left (FT9, T3, TP9, T5), Temporal right (FT10, T4, TP10, T6).

2.3. Experimental procedure

All participants were assessed in the morning hours. PD participants were examined while in the OFF medication state. Since the timing of the experiment with reference to the last antiparkinsonian medications intake might influence cortical activity, we aimed at starting our measurements exactly 12 h after the last medication intake for each patient. The experimenter (YSM) interviewed the participant about his/her regular evening hour for consumption of medicines, and set the time of the appointment accordingly, taking into account that preparations and fixing the EEG electrodes and other equipment would last about 1–1.5 h. One day prior to the experiment, the participant was contacted by phone, and these details were confirmed. On the day of the experiment, the last medication consumption hour (on the previous evening) was recorded based on the report of the participant and/or his/her care giver.

Upon arrival, the recording equipment was connected to the participant. The motor trials consisted of gait-related tasks and upper limb motor tasks. The rationale for including these two types of tasks was to compare natural alternating movements of the lower limbs (i.e., walking) with alternating hand tapping. During the performance of these tasks, the participant was often asked if s/he needed to rest and was allowed to sit and rest as needed. After completing the motor trials, the participants responded to questionnaires for cognitive and clinical

evaluation.

2.3.1. Gait-related tasks

The gait-related tasks were performed along a corridor 16 m long and two meter wide. The participant walked back and forth at a comfortable pace along 16 m long and 2 m wide corridor between two cones placed 12 m apart for five minutes.

Three gait-related tasks were defined:

(1) **Standing still** without moving while gazing forward for 1 min. This period served as a 'baseline' for both the gait trials and the upper limb trials (see below); (2) **Walking** in a straight line; and (3) **Turning.** Rationale for the choice of gait tasks: It has been shown that turns were associated with increased frontal lobe activation in PD [16]. Thus as a secondary hypothesis we propose that bihemispheric synchronization will also be stronger in relation to this walking task, in particular in the frontal lobe.

2.3.2. Upper limb bimanual movement tasks

After completing the gait trials and a short rest period, the participant stood in front of an elevated table and performed hand tapping tasks with his/her palms. Prior to each task, the experimenter demonstrated the task the participant was to perform and verified that the participant understood the task. The following two tasks were performed for at least one minute each: (1) **Alternating tapping**; (2) **Simultaneous tapping**. Rationale for the choice of the bimanual tasks: Since simultaneous hand tapping involves identical bilateral motor activity, we hypothesized that interhemispheric synchronization will be increased across cohorts, during the performance of this task, in particular in the frontal lobe.

2.4. Questionnaires for cognitive and clinical evaluation

The following questionnaires were administered:

(1) Demographic characteristics [age, gender, years of formal education, height and weight; body-mass-index (BMI) was calculated].
(2) PD motor impairment was evaluated by the motor part (III) of the Unified Parkinson's Disease Rating Scale (UPDRS) [17].
(3) Screening for cognitive impairment by the Montreal Cognitive Assessment (MoCA). This brief questionnaire has been validated in Hebrew [18] and is suitable for individuals with PD [19].
(4) Subjective measure of FOG symptom severity by the New FOG Questionnaire (see more details in the Supplementary Material).

2.5. Data processing

2.5.1. EEG preprocessing

In preparation for preprocessing, EEG data were annotated according to video viewing and parsed into relevant segments:

(1) **Walking in a straight line –** segments were included after removing turns, stops and any FOG episodes (if present; from 10 s before to 5 s after a freezing episode was excluded).
(2) **Turns –** segments containing the 180° turn around the cones (see above) were included unless a FOG episode occurred during the turn.
(3) Each of the **upper limb** tasks (i.e., alternating, simultaneous tapping) was analyzed as a separate segment.

EEGLAB tools [20] were used to preprocess the data. Full account on preprocessing is provided in the Supplementary Material.

2.5.2. Phase synchronization (PS)

The primary outcome measure was the PS coefficient. For full description see Supplementary Material. This coefficient was calculated for the following spectral bands (i.e., after applying fast Fourier transform, FFT, a filter, and an inverse FFT): theta (3.9–7.8 Hz), alpha (7.8–15.6 Hz), beta (15.6–31.2 Hz) and gamma (31.2–62.4 Hz). The calculated PS index ranges from 0 to 1, representing none to maximal synchronization, respectively.

Inter-PS was calculated separately in each band for all right-left electrode pairs (169 pairs) and separately for pairs over frontal (25 pairs), parieto-occipital (16 pairs) and temporal (16 pairs) lobes (Fig. 1). Finally, these coefficients were averaged over the full duration of the relevant segment (e.g., turning or walking). Then an average over all similar segments (e.g., all turns) was calculated as a weighted mean based on the duration of each segment.

2.6. Statistical analysis

Statistical analysis was performed using SPSS Statistical software (IBM, Armonk, NY, USA). Significance level was set at $\alpha = 0.05$. Data for inter-PS were log transformed, as they were not normally distributed for all bands, lobes and groups. Analysis of variance (ANOVA) was used to evaluate differences in inter-PS (transformed) among the two *groups* (between-groups factor, GROUP: NPD vs PD) and across the three gait-related tasks (within-groups factor, TASK: standing vs. Walking a straight line vs. turns). This ANOVA was run separately for each band for all electrode pairs and for the electrode pairs covering each lobe. To control for multiple comparisons, a Bonferroni correction was applied to the obtained significance levels. Identical analyses were performed with the upper limbs movement tasks (alternating tapping vs. simultaneous tapping) as the within-groups TASK factor. Since sex and MOCA scores were different between the PD and NPD (see *results*), these were entered as covariates to the ANOVA models.

3. Results

3.1. Characteristics of study participants

Demographic, motor and clinical characteristics of the 23 participants are shown in Table 1. Participants with PD were not significantly different from NPD participants regarding age, BMI and years of formal education. PD participants had lower MoCA scores (22.4 ± 4.0 versus 25.8 ± 2.3, $p = 0.029$), and there were proportionately more males in the PD group (male/female: 12/3 versus 3/5, $p = 0.042$).

3.2. PS during gait-related tasks

3.2.1. Whole brain inter-PS

Inter-PS was significantly higher in the PD group than in the NPD group in all bands (theta: $F(1,18) = 14.13$, $p = 0.001$; alpha: $F(1,18) = 16.65$, $p = 0.001$; beta: $F(1,18) = 16.08$, $p = 0.001$; gamma: $F(1,18) = 13.23$, $p = 0.002$).

Fig. 2 (top) depicts the time dependence of PS values from a single PD participant and a typical NPD participant during ~4 min of

Table 1
Participant characteristics in each group (mean ± SD).

	PD ($n = 15$)	NPD ($n = 8$)	p-value[a]
Gender (male/female)	12/3	3/5	0.042
Age (years)	67.7 ± 8.0	63 ± 8.5	0.099
BMI (kg/m^2)	26.1 ± 4.1	25.1 ± 3.1	0.401
Education (years)	13.4 ± 4.2	15.3 ± 2.7	0.253
MoCA score	22.4 ± 4.0	25.8 ± 2.3	0.029
Disease duration (years)	10.5 ± 4.7	n/a	–
UPDRS motor score ("Off")	17.8 ± 7.0	n/a	–

SD: standard deviation; **PD**: Parkinson's disease; **NPD**: Non-PD healthy control; **BMI**: body-mass index; **MoCA**: Montreal Cognitive Assessment; **UPDRS**: Unified Parkinson's Disease Rating Scale.
[a] Mann-Whitney *U* test, with the exception of Chi-Square for gender.

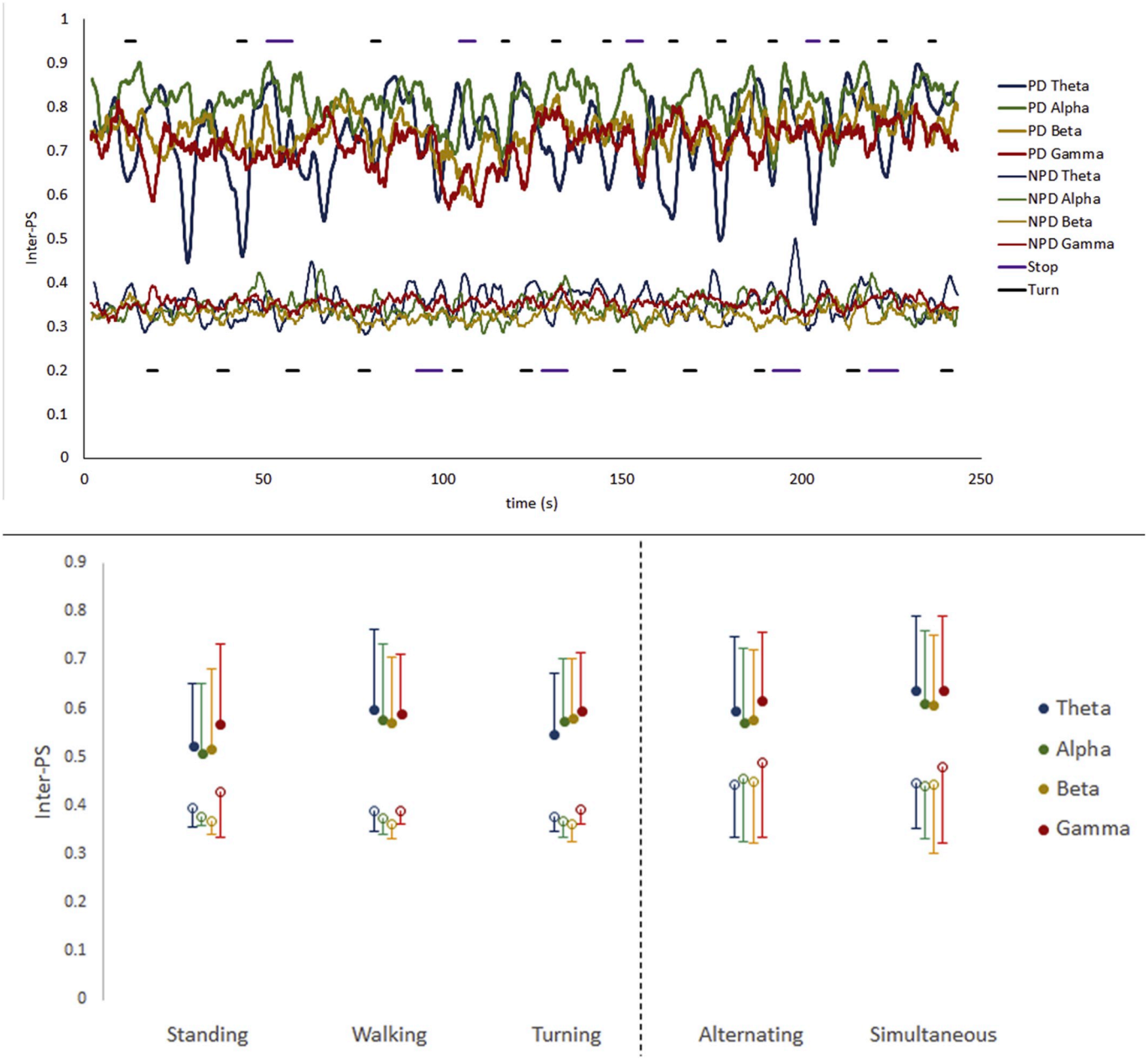

Fig. 2. Top- Representative inter-PS values during the course of ~4 min walking from one participant with PD (top four thick traces) and one NPD participant (bottom four thin traces). It can be seen that across all EEG bands, inter-PS values are higher for the PD participant. Annotations of periods of spontaneous stops (purple horizontal bars) and 180° turns at the edges of the corridor (black horizontal bars) are indicated above and below the inter-PS traces for the PD participant and the NPD participant, respectively). **Bottom**: Group means for whole brain inter-PS values in lower limb (left) and upper limb (right) tasks for the various EEG bands (see key; PD: filled circles; NPD: open circles). Error bars: SD. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

walking. It can be seen that fairly stable dynamics are maintained throughout the task, with the PD participants showing higher whole-brain inter-PS values.

There was no significant TASK effect on whole brain inter-PS in either group ($F(2,36) \leq 2.39$; $p \geq 0.137$). Fig. 2 (bottom left) A depicts the PS values for the gait-related tasks.

3.2.2. Inter-PS between homologous lobes

Inter-PS values were compared between the groups for the left-right electrode pairs over frontal, parieto-occipital and temporal lobes (recall Fig. 1). The upper part of Table 2 summarizes the statistical results for left-right inter-PS for each lobe and band during gait-related tasks. A significant GROUP effect, i.e., higher inter-PS values were evident in PD vs. NPD participants for all lobes and bands ($F(1,18) \geq 6.56$; $p \leq 0.020$). No significant TASK effect was found for any of the lobes and bands. ($F(2,36) \leq 3.83$; $p \geq 0.052$). Descriptive statistics for each condition are provided in Tables A-C of the Supplementary Material.

3.3. Inter-PS during bimanual upper limb motor tasks

3.3.1. Whole brain inter-PS

Fig. 2 (bottom right) summarizes the whole brain inter-PS results for the GROUP and TASK effects for upper limb tasks. Inter-PS was significantly higher in the PD group as compared with the NPD group in the theta and gamma bands ($F(1,18) = 7.49$, $p = 0.014$ and $F(1,18) = 4.80$, $p = 0.042$, respectively), but not for the alpha and beta

Table 2
Left-right inter-PS for homologous lobes.

Gait related tasks				
Lobes	Bands			
	Theta	Alpha	Beta	Gamma
Frontal	7.29, **$p = 0.015$**	6.56, **$p = 0.020$**	10.39, **$p = 0.005$**	7.87, **$p = 0.012$**
Parieto-Occipital	8.68, **$p = 0.009$**	13.24, **$p = 0.002$**	11.45, **$p = 0.003$**	9.16, **$p = 0.007$**
Temporal	9.31, **$p = 0.007$**	9.64, **$p = 0.006$**	10.53, **$p = 0.004$**	8.38, **$p = 0.010$**
Upper-limb tasks				
Lobes	Bands			
	Theta	Alpha	Beta	Gamma
Frontal	3.37, $p = 0.083$	2.21, $p = 0.154$	3.42, $p = 0.081$	4.18, $p = 0.056$
Parieto-Occipital	4.48, **$p = 0.048$**	4.65, **$p = 0.045$**	2.90, $p = 0.106$	2.95, $p = 0.103$
Temporal	12.84, **$p = 0.002$**	4.76, **$p = 0.043$**	3.53, $p = 0.076$	4.76, **$p = 0.043$**

Each cell contains F (d.f.: 1,18)* and p values for the GROUP effect. Significantly ($p < 0.05$; bold). *In the gait tasks there were missing data for one PD participant during the turning task. In the upper limb tasks there was missing data for one of the NPD participants.

bands ($F(1,18) = 3.63$, $p = 0.073$ and $F(1,18) = 3.95$, $p = 0.062$, respectively). There was no significant TASK effect ($F(1,18) \leq 2.87$, $p \geq 0.107$).

3.3.2. Inter-PS for homologous lobes

The lower part of Table 2 summarizes the results for each lobe and band during upper limb tasks. The largest differentiation between the groups (i.e., higher inter-PS in the PD group) was evident for the parieto-occipital and temporal lobes. No significant TASK effect was found for each of the lobes and bands ($F(1,18) \leq 3.58, p \geq 0.075$). Descriptive statistics for each condition are provided in Tables D-F of the Supplementary Material.

Finally, we conducted an exploratory post-hoc analysis to examine the association between FOG symptoms and cortical phase synchronization using the PS metric. Full account on this underpowered analyses is provided in the Supplementary Material. Briefly, the analysis provides initial support on the fact that the FOG symptom is associated with increased inter-PS in the frontal lobe, in particular during turning.

4. Discussion

Our analyses indicate that individuals with PD have increased interhemispheric synchronization compared with healthy elderly adults. These findings are consistent for all EEG bands in the gait related tasks, and for the theta and gamma bands in the upper limb motor tasks. However, we did not find evidence that turning, nor simultaneous hand tapping are associated with increased interhemispheric PS in PD or in healthy participants.

4.1. Evidence for interhemispheric hypersynchronization in PD

The present findings are consistent with those obtained in unilateral 6-hydroxydopamine (6-OHDA) rat models of PD [14], simulating dopaminergic deficiency asymmetry [14]. These studies have shown that interregional cerebral hypersynchronization developed in parallel with functional deterioration (e.g., decrease in walking speed).

In persons with PD who were implanted with subthalamic nucleus (STN) stimulating electrodes, movement related bilateral cortico-cortical inter-PS was attenuated when the stimulators were ON as compared to the OFF condition. This reduction in PS during STN stimulation was correlated with an amelioration in symptoms' severity as measured by the UPDRS [21,22].

While our study, like the rat studies [14], shows evidence of interhemispheric hypersynchronization, it is not possible to elucidate the temporal order of hypersynchronization onset across different cerebral regions. Invasive human studies recording cortical activity with EEG simultaneously with STN local field potentials and neuronal units provide a snapshot from one point in time that does not allow inferences about longitudinal changes over time (e.g. Refs. [7,9,23]).

Ahn et al. [8] reported that the dynamics of STN synchronization in the beta band are correlated with the dynamics of beta band synchronization between motor and frontal cortices bilaterally. However, these results were obtained during STN-DBS surgery in PD patients relatively long after disease onset (i.e., 9.90 ± 4.07 years from diagnosis), meaning that their observations reflect end results of neural processes over extended durations.

4.2. Bihemispheric synchronization during bimanual movements

The increase in inter-PS in PD during bimanual movements is supported by fMRI studies, where unilateral hand movements reflect an increased activity in several brain areas, including M1 ipsilateral to the moving hand [24]. Further, it is of relevance to differentiate between simultaneous and alternating motor tasks as they are presumably generated by simultaneous and alternating activations of motor areas. Walking would be an example of a lower limb alternating task. Notably, our findings did not reveal a difference between simultaneous or alternating upper limb activations. In contrast, a previous fMRI study comparing young and elderly adults performing anti-phase (alternating) and in-phase (simultaneous) visually directed finger movements revealed greater connectivity in the dominant hemisphere for the anti-phase compared to the in-phase task in young adults only [25]. We believe that the apparent inconsistency between these previous findings and those of the present study may be related to differences in the used motor tasks (visually driven versus not) and by uncertain equivalence of fMRI 'connectivity' and EEG-based PS.

4.3. Neural synchronization in the EEG beta band

Beta band oscillations are typically observed within motor system-related cortical and subcortical structures [26]. Further, it is well-established that beta activity in the BG is elevated in patients with PD and linked to the severity of their motor impairment [27]. Excessive beta activity has been demonstrated in the striatum, STN, GPi, motor [28] and frontal cortices [8] of PD patients, regardless of the side of predominant symptoms. In the present study, we demonstrated that during locomotion, PD and NPD participants were indeed differentiated by the frontal inter-PS, especially in the beta range (as well as in other bands, see below). Clinically, bilateral coherence in the lower beta range in the STN is significantly correlated with motor symptom severity in PD [27]. Various studies have examined the correlation between STN-based signals and cortical EEG signals in the beta bands in PD participants [8,9,29]. Furthermore, coherence of the beta band has been previously observed between STN and the frontal lobe [29], in bilateral STN, and between the STN and ipsilateral/contralateral motor cortex [9]. Notably, longer beta bursts were correlated with more advanced motor impairment. Recently, rather explicit evidence has shown the link between the degree of power modulation within high beta frequency bands in the STN and stepping abnormalities [30].

In keeping with the hypothesis concerning the role of the beta band-related activity in preserving the motor and cognitive status quo, abnormal (i.e., hyper) synchronization results in diminished flexibility [6], which is more prominent in PD + FOG.

Our study provides supportive evidence, albeit underpowered, that increased inter-PS in the frontal lobe is associated with patients who

suffer from the FOG symptom (c.f., Supplementary Material). This evidence is in line with the hypothesis concerning the role of beta band-related activity in preserving the motor and cognitive status quo, abnormal (i.e., hyper) synchronization results in diminished flexibility [6], i.e., characteristics which are consistent with the FOG symptom.

4.4. Neural synchronization in other EEG bands

The present study systematically explores interhemispheric phase synchronization at the whole brain level as well as between homologous lobes.

Unlike for the beta band, interregional cortical EEG synchronization was sparsely described in the literature and hardly reported on even for healthy participants. Interregional EEG phase locking between motor areas (intra- and interhemispheric) was increased in the delta and theta bands in elderly healthy adults as compared to young adults [31].

In PD, while preforming manual tasks, increased fronto-central synchronization was observed in the theta and alpha bands [32]. Further, in PD, interregional cortical EEG synchronization was reported in the context of FOG. For example Handojoseno et al. [33], reported on freezing-related higher spectral density in the theta, alpha and high beta bands, as well as on effective connectivity between frontal-parietal-occipital lobes in these EEG bands (see also our initial findings on increased frontal lobe inter-PS among PD + FOG in the Supplementary Material).

In the non-motor realm, in healthy individuals, eliciting emotions (by video and/or audio stimuli) was found to increase intra-hemispheric (more on the right side), interregional, and interhemispheric frontal lobe synchronization in the alpha, beta and gamma bands [34]. Furthermore, interregional theta band synchronization was associated with decision making, i.e., shortly before a subject chooses to select one action over another [35].

Indeed, exploring phase synchronization of diverse EEG bands, is of importance in view of their attributed roles of within the preparation/evolution of a motor act. However, with the presently available heterogeneous and sparse evidence on interregional neural synchronization, it would be highly speculative to propose a comprehensive view on its characterization and function as reflected by EEG in different bands (i.e., PS in the present study), in general and specifically in PD. While increased interhemispheric beta PS in PD might be consequential to increased subcortical beta activity, can the increased interhemispheric PS, in other bands, be a subsequent outcome of the beta synchronization?

4.5. Limitations, future directions and potential clinical implications

Source localization, as well as directionality and connectivity between different lobes/brain areas, were beyond the scope of this study. Advanced analyses like these may further elucidate the related neural processes. In addition, future studies should inspect the direct effect of L-dopa on inter-PS by testing the participants both during the OFF and ON periods.

If indeed inter-PS develops over time in response to asymmetric subcortical neural damage, we suggest that inter-PS may prove a valuable biomarker reflecting disease progression in PD and may also serve as an index of interventional efficacy. Therefore, future EEG studies with data sampled over the course of the disease, beginning at diagnosis or even at the prodromal stage, may be of benefit for elucidating the evolution of interregional cortical hypersynchronization in PD.

Acknowledgements

The authors would like to thank the participants for their time and effort. Special thanks to Drs. Simon Israeli-Korn and Gilad Yahalom in their help in recruiting participants, and to Ms. Musaiee for technical assistance. We also thank Dr. Glen M Doniger for critical review of the manuscript. This study was supported in part by the Israel Science Foundation grant # 1657-16, the Israel Ministry of Health grant # 3000-14527; the German Israel Foundation (GIF) grant # I- 1298-415.13/2015 and the German Science Foundation (DFG) grant KA 1676/4.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.05.030.

Summary declaration of interest statement

This work is broadly related to a pending patent application (US2014/0303508). MP is one of the inventors listed on that application. No other potential conflict of interests are declared.

References

[1] J.G. Nutt, B.R. Bloem, N. Giladi, M. Hallett, F.B. Horak, A. Nieuwboer, Freezing of gait: moving forward on a mysterious clinical phenomenon, Lancet Neurol. 10 (8) (2011) 734–744.
[2] A. Frigon, The neural control of interlimb coordination during mammalian locomotion, J. Neurophysiol. 117 (6) (2017) 2224–2241.
[3] A.A. Handojoseno, M. Gilat, Q.T. Ly, H. Chamtie, J.M. Shine, T.N. Nguyen, Y. Tran, S.J. Lewis, H.T. Nguyen, An EEG study of turning freeze in Parkinson's disease patients: the alteration of brain dynamic on the motor and visual cortex, Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE, IEEE, 2015, pp. 6618–6621.
[4] A.M. Handojoseno, J.M. Shine, M. Gilat, T.N. Nguyen, Y. Tran, S.J.G. Lewis, H.T. Nguyen, Prediction of Freezing of Gait Using Analysis of Brain Effective Connectivity, IEEE, 2014, pp. 4119–4122.
[5] A.A. Handojoseno, J.M. Shine, T.N. Nguyen, Y. Tran, S.J. Lewis, H.T. Nguyen, Using EEG spatial correlation, cross frequency energy, and wavelet coefficients for the prediction of Freezing of Gait in Parkinson's Disease patients, Engineering in Medicine and Biology Society (EMBC), 2013 35th Annual International Conference of the IEEE, IEEE, 2013, pp. 4263–4266.
[6] A.K. Engel, P. Fries, Beta-band oscillations—signalling the status quo? Curr. Opin. Neurobiol. 20 (2) (2010) 156–165.
[7] J.-S. Brittain, P. Brown, Oscillations and the basal ganglia: motor control and beyond, Neuroimage 85 (2014) 637–647.
[8] S. Ahn, S.E. Zauber, R.M. Worth, T. Witt, L.L. Rubchinsky, Interaction of synchronized dynamics in cortex and basal ganglia in Parkinson's disease, Eur. J. Neurosci. 42 (5) (2015) 2164–2171.
[9] K. Kato, F. Yokochi, M. Taniguchi, R. Okiyama, T. Kawasaki, K. Kimura, J. Ushiba, Bilateral coherence between motor cortices and subthalamic nuclei in patients with Parkinson's disease, Clin. Neurophysiol. 126 (10) (2015) 1941–1950.
[10] C.C. Charalambous, M.G. Bowden, D.L. Adkins, Motor cortex and motor cortical interhemispheric communication in walking after stroke: the roles of transcranial magnetic stimulation and animal models in our current and future understanding, Neurorehabilitation Neural Repair 30 (1) (2016) 94–102.
[11] n. Rosenblum, n. Pikovsky, n. Kurths, Phase synchronization of chaotic oscillators, Phys. Rev. Lett. 76 (11) (1996) 1804–1807.
[12] R. Djaldetti, I. Ziv, E. Melamed, The mystery of motor asymmetry in Parkinson's disease, Lancet Neurol. 5 (9) (2006) 796–802.
[13] P.A. Kempster, W.R. Gibb, G.M. Stern, A.J. Lees, Asymmetry of substantia nigra neuronal loss in Parkinson's disease and its relevance to the mechanism of levodopa related motor fluctuations, J. Neurol. Neurosurg. Psychiatry 52 (1) (1989) 72–76.
[14] B.N. Jávor-Duray, M. Vinck, M. van der Roest, E. Bezard, H.W. Berendse, T. Boraud, P. Voorn, Alterations in functional cortical hierarchy in hemiparkinsonian rats, J. Neurosci. 37 (32) (2017) 7669–7681.
[15] A.J. Hughes, S.E. Daniel, L. Kilford, A.J. Lees, Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J. Neurol. Neurosurg. Psychiatry 55 (3) (1992) 181–184.
[16] I. Maidan, H. Bernad-Elazari, E. Gazit, N. Giladi, J.M. Hausdorff, A. Mirelman, Changes in oxygenated hemoglobin link freezing of gait to frontal activation in patients with Parkinson disease: an fNIRS study of transient motor-cognitive failures, J. Neurol. 262 (4) (2015) 899–908.
[17] S. Fahn, R.L. Elton, Unified Rating Scale for Parkinson's Disease, Recent Developments in Parkinson's Disease, Macmillan, florham park. new york, 1987, pp. 153–163.
[18] M. Lifshitz, T. Dwolatzky, Y. Press, Validation of the Hebrew version of the MoCA test as a screening instrument for the early detection of mild cognitive impairment in elderly individuals, J. Geriatr. Psychiatry Neurol. 25 (3) (2012) 155–161.
[19] D.J. Gill, A. Freshman, J.A. Blender, B. Ravina, The montreal cognitive assessment as a screening tool for cognitive impairment in Parkinson's disease: screening tool for cognitive impairment, Mov. Disord. 23 (7) (2008) 1043–1046.
[20] A. Delorme, T. Mullen, C. Kothe, Z. Akalin Acar, N. Bigdely-Shamlo, A. Vankov, S. Makeig, EEGLAB SIFT, NFT BCILAB, ERICA, New tools for advanced EEG

processing, Comput. Intell. Neurosci. 2011 (2011) 1–12.
[21] P. Silberstein, A. Pogosyan, A.A. Kühn, G. Hotton, S. Tisch, A. Kupsch, P. Dowsey-Limousin, M.I. Hariz, P. Brown, Cortico-cortical coupling in Parkinson's disease and its modulation by therapy, Brain 128 (6) (2005) 1277–1291.
[22] D. Weiss, R. Klotz, R.B. Govindan, M. Scholten, G. Naros, A. Ramos-Murguialday, F. Bunjes, C. Meisner, C. Plewnia, R. Krüger, A. Gharabaghi, Subthalamic stimulation modulates cortical motor network activity and synchronization in Parkinson's disease, Brain 138 (3) (2015) 679–693.
[23] A. Singh, A. Plate, S. Kammermeier, J.H. Mehrkens, J. Ilmberger, K. Bötzel, Freezing of gait-related oscillatory activity in the human subthalamic nucleus, Basal Ganglia 3 (1) (2013) 25–32.
[24] S. Papegaaij, W. Taube, S. Baudry, E. Otten, T. Hortobágyi, Aging causes a reorganization of cortical and spinal control of posture, Front. Aging Neurosci. 6 (2014).
[25] S. Kiyama, M. Kunimi, T. Iidaka, T. Nakai, Distant functional connectivity for bimanual finger coordination declines with aging: an fMRI and SEM exploration, Front. Hum. Neurosci. 8 (2014).
[26] B.C.M. van Wijk, W.-J. Neumann, G.-H. Schneider, T.H. Sander, V. Litvak, A.A. Kühn, Low-beta cortico-pallidal coherence decreases during movement and correlates with overall reaction time, Neuroimage 159 (2017) 1–8.
[27] P. Brown, Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease, Mov. Disord. 18 (4) (2003) 357–363.
[28] A. Galvan, A. Devergnas, T. Wichmann, Alterations in neuronal activity in basal ganglia-thalamocortical circuits in the parkinsonian state, Front. Neuroanat. 9 (2015).
[29] V. Litvak, A. Jha, A. Eusebio, R. Oostenveld, T. Foltynie, P. Limousin, L. Zrinzo, M.I. Hariz, K. Friston, P. Brown, Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease, Brain 134 (2) (2011) 359–374.
[30] P. Fischer, C.C. Chen, Y.-J. Chang, C.-H. Yeh, A. Pogosyan, D.M. Herz, B. Cheeran, A.L. Green, T.Z. Aziz, J. Hyam, S. Little, T. Foltynie, P. Limousin, L. Zrinzo, H. Hasegawa, M. Samuel, K. Ashkan, P. Brown, H. Tan, Alternating modulation of subthalamic nucleus beta oscillations during stepping, J. Neurosci. 38 (22) (2018) 5111–5121.
[31] N. Rosjat, L. Liu, B.A. Wang, S. Popovych, T. Tóth, S. Viswanathan, C. Grefkes, G.R. Fink, S. Daun, Aging-associated changes of movement-related functional connectivity in the human brain, Neuropsychologia 117 (2018) 520–529.
[32] S.J. Palmer, P.W.-H. Lee, Z.J. Wang, W.-L. Au, M.J. McKeown, θ, β but not α-band EEG connectivity has implications for dual task performance in Parkinson's disease, Park. Relat. Disord. 16 (6) (2010) 393–397.
[33] A.M.A. Handojoseno, M. Gilat, L. Quynh Tran, H. Chamtie, J.M. Shine, T.N. Nguyen, Y. Tran, S.J.G. Lewis, H.T. Nguyen, An EEG Study of Turning Freeze in Parkinson's Disease Patients: the Alteration of Brain Dynamic on the Motor and Visual Cortex, IEEE, 2015, pp. 6618–6621.
[34] Y. Dasdemir, E. Yildirim, S. Yildirim, Analysis of functional brain connections for positive–negative emotions using phase locking value, Cognitive neurodynamics 11 (6) (2017) 487–500.
[35] T. Womelsdorf, M. Vinck, S.L. Leung, S. Everling, Selective theta-synchronization of choice-relevant information subserves goal-directed behavior, Front. Hum. Neurosci. 4 (2010) 210.