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Research article

Why the clock ticks differently in Parkinson's disease: Insights from motor imagery and resting-state functional magnetic resonance imaging

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ABSTRACT

In Parkinson's disease (PD), an impaired perception of suprasecond time intervals has been reported. From a neurobiological perspective, dopamine is thought to be an important mediator of timing. Nevertheless, it is still unclear whether timing deficits in PD occur mainly in the motor context and are associated with corresponding striatocortical loops. This study attempted to fill this gap by investigating time reproduction in the context of a motor imagery task, and its neurobiological correlates in resting-state networks of basal ganglia substructures in PD.

Nineteen PD patients and 10 healthy controls therefore underwent two time reproduction tasks. In a motor imagery task, subjects were asked to walk down a corridor for 10 s and reproduce the time spent walking during motor imagery afterwards. In an auditory task, the subjects had to reproduce an acoustically presented time interval of 10 s. Subsequently, resting-state functional magnetic resonance imaging was performed and voxel-wise regressions were conducted between striatal functional connectivity and performance in the individual task at group level and compared between groups.

Patients significantly misjudged the time interval in the motor imagery task and an auditory task in comparison to controls. Seed-to-voxel functional connectivity analysis of basal ganglia substructures revealed a significant association between striatocortical connectivity and motor imagery performance. PD patients showed a different pattern of associated striatocortical connections as indicated by significantly different regression slopes for connections of the right putamen and left caudate nucleus.

In accordance with previous findings, our data confirm an impaired time reproduction of suprasecond time intervals in PD patients. Our data imply that deficits in time reproduction tasks are not specific to motor context but reflect a general time reproduction deficit. According to our findings, impaired performance in context of motor imagery is accompanied by a different configuration of striatocortical resting-state networks responsible for timing.

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1. Introduction

Perception of time is of outstanding importance for the interaction of subjects with their environment. The optimized response to stimuli and the processing thereof but also highly important functions such as motor control critically depend on an accurate temporal processing [1]. The subjective evaluation of perceived time intervals has traditionally been attributed to an 'internal clock', serving as an individual reference point [2]. Based on the Scalar Expectancy Theory (SET), processing of time intervals is conceptualised in three steps: time intervals are perceived by an internal clock, stored in memory, and finally a decision is made about their duration [3]. Various extensions of this model are still prevalent in the literature. However, the precise localization on where these processes take place awaits clarification.

Although the idea, that duration-tuned neural populations in the right supramarginal gyrus may encode subjective time experience has been put forward [1], the emerging picture rather favours complex processes involving numerous brain regions. In the last two decades, temporal processing has been linked to basal ganglia, the supplementary motor area (SMA), the inferior frontal gyrus (IFG), the parietal lobe, the temporo-parietal junction, the cerebellum and the insular cortex [1,4,5]. Another study by Coull [6] et al. could render evidence that impaired time perception is paralleled by decreased activity in the putamen and the SMA. At the neurotransmitter system level, the dopaminergic system thus seems to play a pivotal role in time processing.

The importance of dopaminergic signaling for timing is reflected not least in the fact that its manipulation can trigger a disturbed perception of time [7]. Hence amphetamines which increase dopamine concentrations in the synaptic cleft induce faster responses in peak interval paradigms [8], whereas D2-antagonists promote the overestimation of time intervals [9]. Accordingly, altered perception of time occurs in diseases of the dopaminergic system.

Nearly twenty years ago, Pastor et al. [2] for the first time reported 1) the underestimation of presented time intervals, and 2) an overproduction of time intervals in reproduction tasks in Parkinson's disease (PD). From the latter observations a slowness of the internal clock in PD can be inferred. Further studies revealed controversial results regarding an over- or underestimation of time intervals in PD with some studies showing a tendency to overestimate time intervals [2], and others advocating the opposite [10]. By performing motor imagery and time reproduction tasks in a study concerning executive functions in PD, Reuter et al. [11] showed that PD patients need more time for mental imagination of walking along distinct distances than for walking the same distances. Additionally, several studies report an association between disease severity and performance on time estimation and reproduction tasks with worse performance at advanced disease stages [2,11,12].

Inadequate processing of timing information can severely affect a patient's ability to respond to external stimuli, impair the independence in everyday life and can ultimately promote dangerous situations in which the patient is not able to evaluate time intervals appropriately (e.g. road traffic). Beyond that, impaired time perception can lead to restrictions in medical history if it is not possible for the patient to evaluate the timing of symptom occurrence and persistence adequately. Additionally, patient's compliance may be impaired since medication intake partly follows the patient's temporal estimation of symptoms.

Early observations of an improved performance after administration of levodopa/carbidopa at auditory stimuli presentation, hinted at a role for the dopaminergic system in impaired time processing in PD [2]. But an explanation how dopamine depletion modifies the functional activity of regions engaged in time processing and which basal ganglia substructures are involved, is still lacking. Given the evidence for dysfunction of dopamine deficient basal ganglia-cortical loops in timing deficits, we investigated time reproduction and ascertained its relation to striatocortical networks in PD patients.

2. Materials and methods

2.1. Study participants

Patients diagnosed with idiopathic PD according to recent clinical criteria [13] were recruited from our outpatient clinic, if they met the following criteria: Hoehn and Yahr (H&Y) stage I-III, no therapeutic changes within three months and age between 45 and 80 years. Exclusion criteria were history of structural cerebral damage (vascular events, tumors, etc.), severe depression according to Beck's depression inventory II (BDI-II scores >28) [14], signs of dementia according to the Parkinson Neuropsychometric Dementia Assessment (PANDA scores <14) [15] or severe motor complications (e.g., dyskinesias). Healthy controls were reached by advertising. Approval was obtained from the ethics committee of the Philipps-University of Marburg (ethical clearance number: 20/18). The study was carried out in conformation with the Declaration of Helsinki and all participants declared their written informed consent before participating.

2.2. Clinical and behavioral assessment

Along with the Unified Parkinson's Disease Rating Scale part III from the Movement Disorder Society (MDS-UPDRS-III) in the ON-state [16], levodopa-equivalent daily dose (LEDD) was calculated. As a measure of global cognitive performance, the PANDA was applied [15].

2.3. Walking, motor imagery and auditory control task

The motor imagery task and resting-state functional magnetic resonance imaging (fMRI) were performed at the Department for

Psychiatry and Psychotherapy of the University Hospital of Marburg, Germany. To account for performance bias, all tasks were instructed by the same researcher. PD patients were examined in the ON-state of dopaminergic medication.

- Walking task: Participants were instructed to walk along a corridor without visual obstacles for 10 s. The exact period was not communicated to the participant. The instructor gave the verbal sign "start" and "stop". This task was repeated three times to allow participants to familiarize her/himself with the distance.
- Motor Imagery Task: After the walking task, participants were instructed to stand at the corridor's entrance, close their eyes, and imagine the previously performed walking task. They were instructed to provide the verbal sign "start", when they initiated walking down the corridor and "stop" when they finished walking the learned memorized distance in their mind.
- Auditory Control Task: A 10 s time interval was presented with start and end delineated by a monofrequent tone. Afterwards participants were asked to reproduce the interval by giving the verbal signs "start" and "stop". The instructor measured the elapsed time with a stopwatch.

The sequence of the walking task followed by the motor imagery and auditory control task was performed twice to confirm or disprove potential learning effects.

2.4. Resting-state fMRI acquisition and analysis

MRI scanning was performed on a Trio Tim Syngo 3 T MR-scanner (Siemens, Erlangen) at the Department for Psychiatry and Psychotherapy of the University Hospital of Marburg, Germany. Patients were scanned in the "ON" state of dopaminergic medication under best clinical conditions. All but one of the patients were scanned at lunch time/in the early afternoon. Patients were positioned in the scanner and underwent structural MRI with the following parameters: repetition time (TR): 1900 m s, echo time (TE): 2.52 m s, voxel size: $1.0 \times 1.0 \times 1.0$ mm^3. For the subsequent fMRI measurement, subjects were instructed to keep their eyes opened and do not think about anything in particular. The eyes area was checked by camera throughout the measurement. The 8-min lasting multiband echo-planar imaging sequence [17] was characterized by the following parameters: 490 time points, TR 1040 m s, TE 30.0 m s, 3×3x3 mm^3 voxel size and 48 slices. MRI data preprocessing was carried out with the toolbox Conn v.18 b [18] and Statistical Parametric Mapping 12 software (https://www.fil.ion.ucl.ac.uk/spm/software/). The default preprocessing pipeline for fMRI data was applied, except for slice time correction: centering, realignment, direct segmentation and normalization, artifact detection tool (ART)-based scrubbing (www.nitrc.org/projects/artifactdetect/). Functional data were smoothed with a Gaussian filter of 5 mm full width at half maximum (FWHM) and further nuisance regression was applied by using the anatomical component-based noise correction (CompCor) method. In addition, linear detrending and band-bass filtering [0.01–0.1] was applied to functional data.

Seed-to-voxel functional connectivity maps were calculated for each subject for the following basal ganglia seeds obtained from Melbourne Subcortical atlas [19]: right and left anterior caudate nucleus, right and left posterior caudate nucleus, right and left anterior putamen, right and left posterior putamen. Multiple regressions were conducted voxel-wise with obtained seed-based connectivity maps and performance in the motor imagery task with age as covariate of no interest. Resulting maps were thresholded at $p < 0.05$ after correcting for multiple comparisons using the family-wise error (FWE) rate. In order to evaluate potential differences in the association between seed-based connectivity and performance between groups, voxel-wise comparison of regression slopes (one-way analysis of covariance (ANCOVA) covariate interaction) between the groups was performed (https://web.conn-toolbox.org/resources/documentation/manual). Cortical and cerebellar anatomical areas were identified based on the FSL Harvard-Oxford atlas and automated anatomical labeling atlas as implemented in CONN.

2.5. Statistical analysis

Motor imagery performance was determined as a relative deviation from the 10-s interval by subtracting the mean reproduced time (t) of both trials of the motor imagery task from the walking time of 10 s and dividing the absolute value by 10 ($(|10 - t|)/10$). The deviation of the reproduction of the auditory interval was calculated in the same way. A similar approach was adopted to calculate relative differences reflecting the degree of over- or underestimation ($(10 - t)/10$). Between-group differences in numeric variables were tested using Student's *t*-test or Mann-Whitney *U* test, depending on whether the criteria for parametric and non-parametric statistics were met. The same criteria were used to decide whether a Pearson or Spearman correlation was applied for testing for associations between clinical and behavioral variables. Group-Task interactions were tested with a mixed repeated measure design including a non-parametric permutation test implemented in the R package *ez* (https://rdocumentation.org/packages/ez/versions/4.4-0). Statistical analysis of demographical, clinical and behavioral data was performed using the statistic software R [20]. The code used to analyze behavioral and clinical data of the present study will be made freely available on GitHub.

3. Results

3.1. Demographics and clinical characteristics

Clinical, behavioral and neuroimaging data of 19 PD patients and 10 healthy controls were obtained (for demographic details cf. Table 1). Groups did not differ in terms of sex distribution, age and results of cognitive screening, and self-reported signs of depression. According to MDS-UPDRS part III, patients were moderately affected (27.1 ± 13.5) and received on average 544.3 ± 470.7 mg LEDD.

Nine patients were categorized as stage 1, six patients as stage 2 and four patients were categorized as stage 3 on Hoehn and Yahr scale. The mean disease duration was 6.1 ± 5.1 years. Our sample does not include participants with dementia or severe depression.

3.2. Motor imagery task

In the motor imagery task, PD patients misjudged the time interval significantly more than healthy controls ($t = -2.18$, df = 27, 95% confidence interval: [−20.7; −0.6], p = 0.038, cf. Fig. 1A). Although patients with right lateralized motor symptoms performed slightly better (less misjudgment), no significant differences were observed between left and right lateralized patients (cf. Supplementary material, Fig. S1). Furthermore, no significant associations of depressive mood (BDI-II), cognition (PANDA), disease severity (UPDRS-III, Hoehn & Yahr) or dopaminergic therapy (LEDD) with motor imagery performance were found in the patients' group or in the total cohort, except for a significant positive correlation with the subitem associative learning of the PANDA in PD patients ($\rho = -0.49$, p = 0.048).

3.3. Auditory task

In the auditory control task, there was a significant group difference in the misjudgment of the presented time interval (W = 50, 95% confidence interval: [−16.3; −0.2], p = 0.041, cf. Fig. 1B). PD patients misjudged the auditorily presented time interval significantly more than healthy controls.

3.4. PD patients exhibit a general reproduction deficit irrespective of task

Given that the majority of PD patients showed greater misjudgment in the motor imagery task compared to the control task (Fig. 1C), we analyzed group-dependent deficits with respect to the task (group-task interaction). The non-parametric permutation test analysis of the mixed repeated measure design revealed a significant main effect for group (p = 0.007), in the absence of any significant effect of task (p = 0.133) and group-task interaction (p = 0.908).

3.5. Neurobiological correlates of impaired time reproduction in the basal ganglia

To investigate possible links between functional connectivity of basal ganglia substructures and performance in the motor imagery task, voxel-wise regression analyses were performed between seed-to-voxel functional connectivity values and task performance, measured as the relative difference between the subjective reproduction and 10-s intervals. In both groups, significant associations were found between striatocortical functional connectivity and motor imagery task performance (Fig. 2A and B, Table 2).

For PD patients, performance in the motor imagery task was significantly related to functional connectivity between the right anterior putamen and the right precentral gyrus (PreCGr) as well as the right occipital fusiform cortex (OFusCr) (Fig. 2A, Table 2). In addition, connectivity between the left anterior putamen and the bilateral cerebellum was significantly associated with the motor imagery task performance. A significant relation to motor imagery was further found for connectivity between the right posterior putamen and the right supramarginal gyrus (SMGr) and left cerebellum and for the left posterior caudate and the right angular gyrus (AGr) in PD patients. For all these four striatal substructures with a significant association to motor imagery a negative regression slope was observed for this relation, indicating that time interval overestimation was paralleled by lower striatal connectivity and time interval underestimation occurred in the presence of a higher striatal connectivity in PD patients. By contrast, performance in the auditory control task was positively related to frontostriatal connectivity between the left anterior caudate and the right frontal pole (FPr) in PD patients, indicating that underestimation of auditorily perceived time intervals was associated with lower connectivity for this task (not shown).

Table 1
Demographic and clinical data of the cohort. Between-group differences in numeric variables were calculated by applying the Mann-Whitney *U* test or Student's t-test; comparisons of dichotomous variables were carried out via Fisher's test.

	PD patients (n = 19)	Healthy controls (n = 10)	Test-statistics	p-value
Sex (*m/f*)	12/7	8/2	OR = 0.44	0.431
Age (y)	62.1 ± 8.1	60.5 ± 9.1	$t = -0.47$	0.646
BDI-II	8.9 ± 6.3	6.4 ± 7.6	W = 71	0.279
PANDA	23.8 ± 3.7	24.5 ± 1.7	$t = 0.65$	0.521
LEDD (*mg*)	544.3 ± 470.7	–	–	–
MDS-UPDRS-III	27.1 ± 13.5	–	–	–
DD (y)	6.1 ± 5.1	–	–	–
Laterality L/R (n)	10/9	–	–	–
Hoehn & Yahr 1/2/3 (n)	9/6/4	–	–	–

Abbreviations: BDI-II = Beck's-Depression-Inventory; y = years; DD = disease duration; f = female; LEDD = levodopa equivalent daily dose; m = male; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; OR = odds ratio; PANDA = Parkinson Neuropsychometric Dementia Assessment.

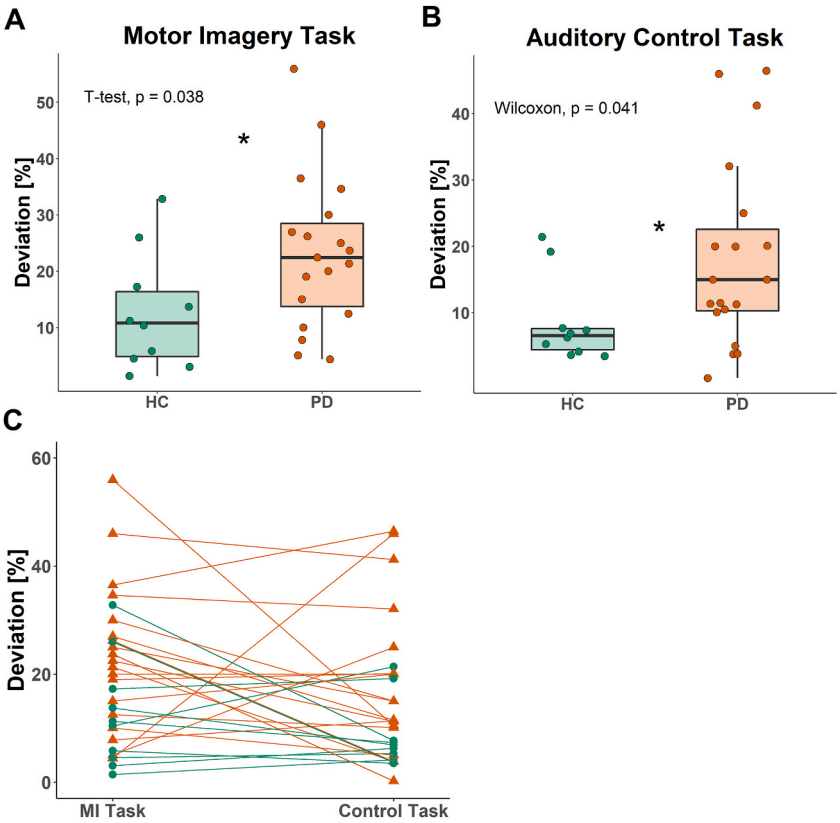

Fig. 1. Group comparison of performance in A) Motor Imagery Task and B) Auditory Control Task. Between-group differences in numeric variables were assessed by Student's t-test or Mann-Whitney *U* test. C) Direct relation between performance in motor imagery task and auditory control task for each individual. Abbreviations: HC = healthy controls; PD = Parkinson's disease; MI = motor imagery.

In the control group, performance in the motor imagery task was significantly associated with functional connectivity of the left and right posterior putamen with the SMA, the left precentral gyrus (PreCGl) and superior parietal lobe left (SPLl, Fig. 2B, Table 2). For both putamina positive regression slopes were observed, indicating that lower functional connectivity was paralleled by underestimation of the presented time interval, whereas an optimal time reproduction (around zero percent) was associated with a higher connectivity. For the auditory control task, no significant relation to striatocortical connectivity was observed in the healthy control group.

The voxel-wise comparison of regression slopes between the groups revealed a significant difference for the association between functional connectivity and motor imagery performance in the anterior and posterior right putamen and the left posterior caudate nucleus (cf. Fig. 3A–C, and Table 2). Cortical target areas showing significantly different association to motor imagery in PD included the posterior cingulate gyrus (Fig. 3A), the right precentral gyrus (PreCGr, Fig. 3B) and the right angular gyrus (AGr, Fig. 3C). Positive regression slopes were observed in the healthy control group and negative regression slopes were found in the PD group (cf. Corresponding plots in Fig. 3A–C right). Accordingly, lower striatocortical connectivity was accompanied by an underestimation of time intervals in healthy controls but an overestimation in the PD group. In contrast, higher striatocortical connectivity was associated with adequate time reproduction (near zero), with very high values correlating with minimal overestimation in healthy controls but underestimation in PD patients.

4. Discussion

The present study sought to investigate the relation between time reproduction in context of motor imagery and connectivity of basal ganglia substructures in 19 PD patients and 10 healthy control subjects. In accordance with previous findings, we confirm a significant impairment in the reproduction of suprasecond time intervals in PD patients, which was not specifically attributable to motor tasks. Instead, our data suggest generalized time reproduction deficits in PD without clear tendency towards interval over- or under reproduction. Seed-to-voxel analyses of striatal substructures rendered evidence for an altered pattern of timing associated striatocortical connections in PD patients for the right anterior and posterior putamen and the left posterior caudate nucleus.

In accordance with previous findings, we confirm a significant impairment in the reproduction of suprasecond time intervals in PD patients. Compared to previous studies examining time reproduction in PD, our paradigm sheds light on impaired time processing in

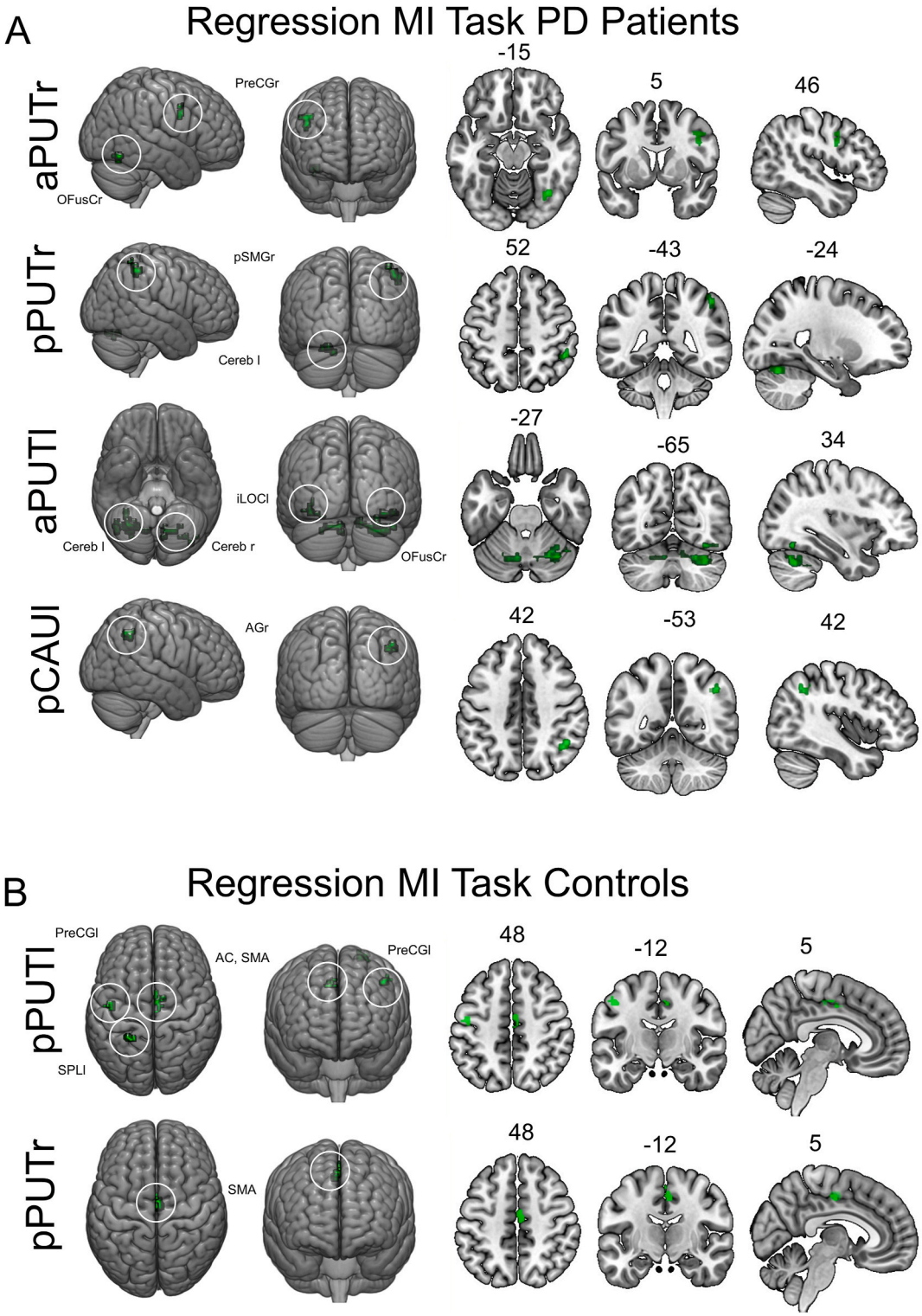

Fig. 2. Striatocortical functional connectivity networks with significant association to motor imagery task performance. Voxel-wise regressions were performed for all striatal subcompartments with motor imagery task performance (percentage deviation to 10 s interval) as variable of interest and age as covariate of no interest in A) PD patients and B) healthy controls in CONN. For all presented analyses, thresholds were set at $p_{FWE} < 0.05$ (two-tailed). Results are shown in render view and axial, coronal and sagittal slices with numbers above representing corresponding x-, y- or z-coordinates. Abbreviations: AC = anterior cingulum; AGr = right angular gyrus; aPUTl = left anterior putamen; aPUTr = right anterior putamen; Cereb = Cerebellum; HC = healthy controls; iLOCl = left inferior lateral occipital cortex; OFusCr = right occipital fusiform cortex; pCAUl

= left posterior caudate; PC = posterior cingulate gyrus; PD = Parkinson's disease; pPUTl = left posterior putamen; pPUTr = right posterior putamen; PreCGl = left precentral gyrus; PreCGr = right precentral gyrus; SMA = supplementary motor area; pSMGr = right supramarginal gyrus posterior division; SPLl = left superior parietal lobe.

Table 2
Results of voxel-wise regression analyses between motor imagery task performance and striatocortical functional connectivity. Voxel-wise regressions were performed for all striatal subcompartments with motor imagery task performance (percentage deviation to 10 s interval) as variable of interest and age as covariate of no interest in each group in Conn. Significant group differences in regression slopes were tested voxel-wise for all seeds to analyzed group:task interactions. For all presented analyses, thresholds were set at $p_{FWE} < 0.05$ assuming two-sided testing.

Group	Seed	Regions	size	t-value	P_{FWE}-value	MNI-coordinates
PD	aPUTr	PreCGr, MidFGr	76	5.53	0.035	52 2 38
		OFusCr, TOFusCr	71	7.28	0.048	36 -64 -16
	pPUTr	Cereb6 l, Cereb 1 l	134	6.12	0.002	−20 -70 -24
		pSMGr, SPLr, AGr	118	5.95	0.005	48 -46 50
	aPUTl	Cereb6 r, Cereb1 r	385	7.51	<0.0001	24 -60 -30
		Cereb1 l, Cereb6 l, Cereb2 l	129	5.64	0.002	−8 -66 -28
		OFusCr, iLOCr, ToFusCr	87	6.35	0.017	36 -64 -16
		iLOCl, OFusCl	72	4.97	0.044	−38 -78 -12
	pCAUl	AGr, sLOCr	98	5.57	0.010	46 -52 42
HC	pPUTl	AC, SMAr,	51	7.88	0.011	6 -16 48
		SPLl,	46	12.71	0.020	−24 -48 74
		PreCGl	41	11.01	0.037	−48 -12 48
	pPUTr	SMA, AC, PreCGr	84	8.99	<0.001	6 -16 48
Group:task	pPUTr	PC, PreCGr	88	5.65	0.043	4 -24 44
	aPUTr	PreCGr, MidFGr	109	7.84	0.012	46 2 38
	pCAUl	AGr, sLOCr	98	4.66	0.021	46 -52 38

Abbreviations: AC = anterior cingulum; AGr = right angular gyrus; aPUTl = left anterior putamen; aPUTr = right anterior putamen; Cereb = Cerebellum; FWE = family-wise error; HC = healthy controls; iLOCl = left inferior lateral occipital cortex; iLOCr = right inferior lateral occipital cortex; MidFGr = right mid frontal gyrus; OFusCl = left occipital fusiform cortex; OFusCr = right occipital fusiform cortex; PC = posterior cingulate gyrus; pCAUl = left posterior caudate; PD = Parkinson's disease; pPUTl = left posterior putamen; pPUTr = right posterior putamen; PreCGl = left precentral gyrus; PreCGr = right precentral gyrus; PostCGl = left postcentral gyrus; SMA = supplementary motor area; sLOCr = right superior lateral occipital cortex; SPL l = superior parietal lobe left; SPL r = superior parietal lobe right; pSMGr = right posterior division supramarginal gyrus; TOFusCr = right temporo-occipital fusiform cortex.

context of the imagination of movement. Since motor imagery could be perceived as more burdensome by patients due to impaired kinesthetic perception [11], stronger misperception in motor context was posited. Interestingly, since PD patients also misjudged the auditorily presented time interval, our data suggest that the deficits in time reproduction are not specific to motor tasks, but rather represent a generalized time reproduction deficit. However, there are controversial findings regarding over- or underestimation of time intervals in PD. Some studies propose a slowing of the internal clock [2], and others advocate for the opposite [10]. In line with these heterogenous results, we observed evidence for both phenomena in our cohort. The absolute difference between the reproduced time and the presented time of 10 s was significantly higher in PD patients in both tasks, but individually large under- and overestimations occurred.

Impaired time reproduction in PD could in general be related to physical impairment and bradykinesia or non-motor symptoms such as memory deficits and the underlying neurophysiological changes. In contrast to previous studies, we did not find an association between performance in time reproduction tasks and general motor impairment in PD patients [12]. Since other studies indicate a worse ability to imagine movements at more advanced disease stages in both states [11], the discrepancy is likely due to different experimental paradigms and differences in sample size. In addition, a link between impaired time reproduction and associative learning was observed in PD patients, highlighting the overall complex phenomenon of information integration necessary for adequate time perception.

A major strength of the current study are the observed neurobiological correlates which support a role for basal ganglia substructures and the extended sensorimotor network in the evaluation of suprasecond time intervals in this context. In line with our findings, a large body of evidence supports a role for a simultaneous activation of the basal ganglia, especially the putamen [21], and the SMA as important contributors of time perception and specifically motor timing [22].

While in healthy controls specifically the posterior putamina and their functional connectivity to the SMA were involved in motor imagery, PD patients showed a more widespread network, including the anterior putamina and the left posterior caudate nucleus and connections to the PreCGr, AGr, SMGr and bilateral cerebellum in our study. The latter regions have been assigned to time perception in previous studies [1,4,21]. Especially the right SMG has been recently reported in association to encoding of subjective timing and is likely to comprise duration-tuned neurons [1]. A specific role for the cerebellum in time processing, including motor timing, has been reported [22]. The fact that certain connections of the posterior putamen are involved in motor imagery in healthy controls and PD patients show a more widespread network, may indicate that this region, which is initially affected by the dopaminergic deficit in PD, loses its ability to process timing information adequately. In accordance with that, Coull et al. observed timing deficits and reduced blood-oxygenation-level-dependent signal activity in the putamen and SMA when examining the consequences of dopamine

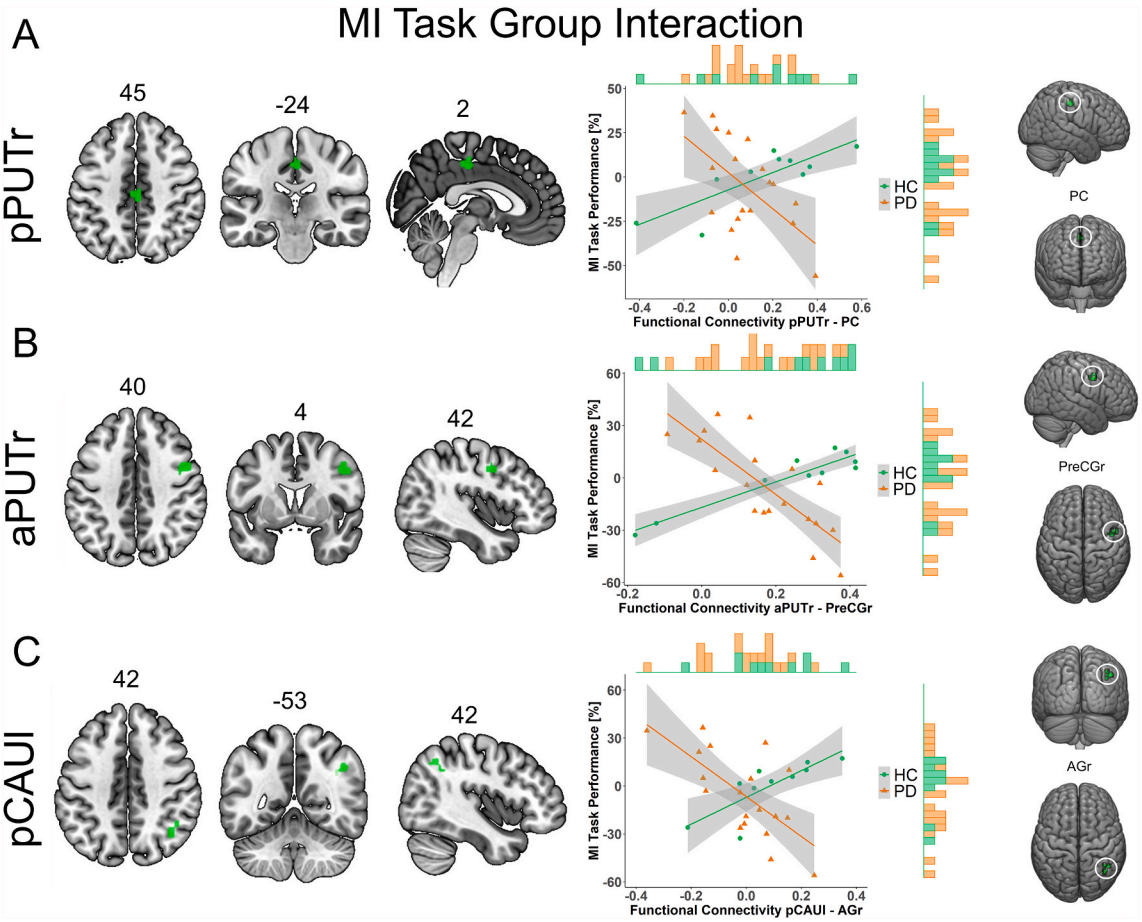

Fig. 3. Striatocortical functional connectivity networks with group differences in relation to motor imagery. Voxels with significant group differences in regression slopes between motor imagery task performance and seed-based connectivity of A) the right posterior putamen, B) the right anterior putamen and C) the left posterior caudate are shown in the left column. The right column shows regression plots for both groups for motor imagery task performance and the extracted connectivity values for voxels with significant group-differences obtained by voxel-wise comparison of regression slopes. Marginal histograms represent the frequency of the individual data sections in the respective group. Significant group differences in regression slopes were tested voxel-wise for all striatal seeds in CONN to analyze group:task interactions. For all presented analysis, thresholds were set at $p_{FWE} < 0.05$ (two-tailed). Results are shown in render view and axial, coronal and sagittal slices with numbers above representing corresponding x-, y- or z-coordinates. Abbreviations: AGr = right angular gyrus; aPUTr = right anterior putamen; HC = healthy controls; pCAUI = posterior caudate left; PC = posterior cingulate gyrus; PD = Parkinson's disease; pPUTr = right posterior putamen; PreCGr = right precentral gyrus.

metabolism via depleting the precursors phenylalanine und tyrosine in healthy subjects [6]. The observed involvement of additional striatal compartments in motor imagery performance in PD patients might be indicative for a compensatory adjustment; yet the confirmation of a corresponding process needs further clarification.

The results suggest that the striatum is an integrative structure that could be considered a central clock. In most recent models based on animal studies, ramp-like "climbing" activation patterns in different cortical areas are assumed to be responsible for duration representation and may arise as a result of reading activity patterns from this central clock [23]. From the negative regression slope observed in PD patients, one could hypothesize that aberrant synchronization of striatocortial activity (high connectivity) accelerates the internal clock and more asynchronous striatocortical activity (low connectivity) accompanies a slowed internal clock, whereas moderate connectivity enables accurate duration reproduction in healthy controls. An observation consistent with the Striatal Beat Frequency Theory, an extension of the SET which states that coincidence detection of oscillatory activity in striatocortical loops is responsible for interval timing [24]. Since the individual level of time reproduction in the auditory control task was related to frontostriatal circuits in PD patients and not to similar connections as motor imagery, different neurobiological changes inherent in striatal networks could underly their misjudgment, although similar deficits have been observed in both type of tasks.

4.1. Limitations

One major limitation of the present study is the small and unequal sample size. In addition, due to the separate behavioral testing

outside the scanner and resting-state fMRI measurements no distinct conclusions can be drawn concerning the activity at the moment the subjects were performing the task. However, resting-state fMRI offers better prerequisites for performing fMRI experiments in neurodegenerative disorders. Further studies with larger sample sizes and higher number of trials are required to confirm the present results and may include additional lengths of time intervals to investigate if there are interval-specific differences and comparisons between OFF- and ON-state. We have chosen the 10 s interval as it represents a compromise between detection of the difference and a feasible test duration in which the walking distance (twice the length of the corridor) could be covered. Thus, since the task was to walk down the corridor 5 times, we consider these repetitions to be already sufficiently stressful for patients with a movement disorder at the expense of a smaller number of repetitions. Since the effect sizes based on previous studies were expected to be high at 10 s intervals, we considered these repetitions to be suitable. Purely behavioral studies apply 10 trials per duration [2,25] but are not paired with a corresponding walking task and an imaging protocol that in total results in a relatively long study visit in our case. As stated in our limitations, future studies should conduct the presented approach in larger samples with more repetitions of the motor imagery task, which could be distributed over different exercise dates. Future projects should also investigate whether recently proposed models of time reproduction play a role in the observed deficits in PD, linking them to the perception of body states and cardiac innervation [26], which have already been shown to be altered in PD [27].

4.2. Conclusions

Here, we demonstrate that striatal substructures with early dopamine depletion in PD are part of functional connectivity networks associated with time reproduction performance in context of a motor imagery task in healthy subjects. According to our findings, the association between time reproduction and striatocortical connectivity is significantly altered in PD, indicating a disrupted configuration of networks responsible for timing.

Author contribution statement

Marina C. Ruppert-Junck: Analyzed and interpreted the data; Wrote the paper.
Lisa Torfah: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.
Vincent Hammes: Analyzed and interpreted the data.
Carsten Eggers, Franziska Maier, Andrea Greuel and Lars Timmermann: Conceived and designed the experiments.
David Pedrosa: Contributed reagents, materials, analysis tools or data; Analyzed and interpreted the data.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The contributing authors declare no conflicts of interest related to the content.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e14741.

Abbreviations

ANCOVA Analysis of covariance
AGr right angular gyrus
ART artifact detection tool
aPUTr right anterior putamen
BDI-II Beck's depression inventory II
CompCor component-based noise correction

fMRI	functional magnetic resonance imaging
FPr	right frontal pole
FWE	family-wise error
FWHM	full width at half maximum
HC	healthy controls
H&Y	Hoehn and Yahr
IFG	inferior frontal gyrus
LEDD	levodopa equivalent daily dose
PANDA	Parkinson Neuropsychometric dementia assessment
OFusCr	right occipital fusiform cortex
PC	posterior cingulate gyrus
pCAUl	left posterior caudate
PD	Parkinson's disease
pPUTl	left posterior putamen
pPUTr	right posterior putamen
PreCGl	left precentral gyrus
PreCGr	right precentral gyrus
SET	Scalar Expectancy Theory
SMA	supplementary motor area
SMGr	right supramarginal gyrus
SPLl	left superior parietal lobe
TE	echo time
TR	repetition time
MDS-UPDRS-III	Parkinson's Disease Rating Scale part III of the Movement Disorder Society

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