RESEARCH ARTICLE

Early-Stage Parkinson's Patients Show Selective Impairment in Reactive But Not Proactive Inhibition

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ABSTRACT: Background: It is well known that a deficit in inhibitory control is a hallmark of Parkinson's disease (PD). However, inhibition is not a unitary construct, and it is unclear whether patients in the early stage of the disease (Hoehn and Yahr stage 1) exhibit a deficit in outright stopping (reactive inhibition), a deficit in the ability to shape their response strategies according to the context (proactive inhibition), or both.
Objective: We assessed whether PD patients at Hoehn and Yahr stage 1 show a global or selective impairment in inhibitory control. As it has been suggested that inhibition relies upon a right-lateralized pathway, we tested whether left-dominant PD patients suffered from a more severe deficit in this executive function than right-dominant PD patients.
Methods: Via a reaching stop-signal task, we assessed both proactive and reactive inhibition in 17 left-dominant PD and 17 right-dominant PD patients and in 24 age-matched participants.
Results: We found that reactive inhibition was more impaired in PD patients than in healthy participants. However, proactive inhibition was not affected. Furthermore, we found no differences between left-dominant PD and right-dominant PD patients.
Conclusions: For the first time, we found evidence for a deficit of reactive inhibition in the early-stage PD patients in the absence of evidence for deficits in proactive inhibition. These findings have clinical relevance as they provide critical insights on the time course of the disease. In addition, we confirmed, on a population of PD patients at Hoehn and Yahr stage 1, previous results showing that the onset of the disease does not affect inhibition.

Key Words: inhibitory control; lateralization; reaching arm movement; stop signal task; symptoms asymmetry

Decision making is driven by the evaluative representations of possible future scenarios.[1,2] However, given that the outcomes of actions cannot be fully predicted, decisions bear a certain degree of uncertainty. Sometimes, actions must be stopped on the fly to avoid catastrophic consequences because of the occurrence of random events. Therefore, response inhibition represents a key component of executive control, which allows behavioral flexibility in a continually changing world.

It is well known that patients with Parkinson's disease (PD) experience a severe deficit in inhibitory control[3-9] (for a review, see ref. 10, which dramatically impacts their ability to pursue future-oriented goals. Given its importance, it has been posited that response inhibition performance could be a sensitive outcome measure for diagnosis and progression of PD.[11]

However, at present there are some major gaps in our knowledge of how inhibitory control changes according to the stage and the features of PD. First, with only 1 exception,[12] there are no studies on PD patients in the earliest stage of the disease. In the study by Vriend and colleagues,[12] 20 drug-naïve PD patients (de novo) were tested with a stop-signal task during functional magnetic resonance imaging scanning. Only 1 component of inhibitory control, that is, reactive inhibition (the ability to stop a response outright when a

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stop instruction is presented) was measured, and the behavioural performance of patients was not significantly different with respect to that of age-matched healthy controls. These results cannot be considered conclusive as the number of trials was rather low, and proactive inhibition, that is, the ability to flexibly adapt the motor strategy according to constraints embedded in the current context, was not measured. Second, there is another salient aspect that has been overlooked in the vast majority of previous work (see ref. 6 for an exception). In a great number of cases, cardinal symptoms (rigidity, bradykinesia, resting tremor, and postural changes) of PD develop unilaterally either on the left or the right side of the body.[13,14] Motor symptoms become bilateral at later stages of the disease. The unilateral onset of PD is a result of the asymmetric depletion of dopaminergic cells in the substantia nigra pars compacta, which affects the functioning of the hemisphere contralateral to the predominantly affected side of the body.[15,16] Because it has been hypothesized that inhibitory control of manual movements relies on a right-lateralized frontal–basal ganglia–thalamic pathway,[17] it follows that lateralized PD patients are an ideal population in which to test the role of the right hemisphere in action countermanding. Recently, Mirabella and colleagues[6] compared inhibitory performance of right-dominant and left-dominant PD patients (RPD and LPD, respectively) in the middle stage of the disease (Hoehn and Yahr stages 2 or 3), and they did not find any difference in either reactive or proactive inhibition between LPD and RPD patients even though the patients were impaired with respect to healthy controls. The authors concluded that inhibition does not rely solely on the right hemisphere but on cooperation between the 2 hemispheres.[6] An objection to this result is that the absence of difference in inhibitory control between RPD and LPD patients could be ascribed to the fact that even though symptoms in these patients were pronounced asymmetric, both hemispheres were affected.

Hence, the aim of the present work is twofold. First, we want to assess whether reactive, proactive, or both types of inhibition are already affected at the very early stage of PD. Second, we want to retest whether LPD patients have a worse inhibitory control than RPD patients using a population of patients whose symptoms are limited to 1 side of the body.

To achieve these goals, we gave a reaching version of the stop-signal task to PD patients at Hoehn and Yahr stages 1 or 1.5, that is, with motor symptoms restricted either to the left or to the right side of the body, and to age-matched and education-matched healthy participants to collect normative data. The stop-signal task consists of a pseudorandom intermix of trials. In most of them, the participants have to execute an action to respond to go-signals (no-stop trials), whereas in a minority of trials they have to suppress the preplanned action if a stop-signal follows the go-signal (stop trial). The reaching-arm version of this task allows the simultaneous assessment of reactive and proactive inhibition.[6,18] The former is quantified by the time it takes to cancel an action, the stop-signal reaction time (SSRT), which is estimated using the race model.[19] The latter is computed by evaluating the "context effect."[5–7,18] This phenomenon consists of a change of motor strategy for the execution of the same reaching-arm movement executed under 2 different contexts: when participants are aware that unexpectedly a stop signal could be presented versus when they are aware that it would never be shown. Operationally this comparison is realized by contrasting the reaction times (i.e., the time to initiate a response; reaction time [RT]) and the movement times (i.e., the time to execute the motor response; movement time [MT]) of arm reaches during no-stop trials versus those measured during the execution of the same movements in the context of a simple RT task (go-only trial). It has been repeatedly shown that in healthy participants, go-only trials RTs are shorter and MT are longer than in no-stop trials.[18] In contrast, in advanced PD patients[5,6] or patients with unilateral deep brain stimulation,[7] this optimization of costs and benefits (shorter RTs are compensated by longer MTs and vice versa) is impaired. This seems to be a very sensitive tool for assessing proactive control (but see ref. 20 for an alternative experimental design).

We hypothesized that reactive inhibition at the early stage of PD would be selectively impaired while proactive inhibition would be preserved because PD patients in this stage should be less cognitively impaired than in later stages of the disease. On the grounds of our previous results,[6,7] we do not foresee any differences between RPD and LPD patients.

Materials and Methods

Participants

From the outpatients of the Parkinson's unit of the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Neuromed Hospital, we recruited 34 idiopathic PD patients with lateralized motor symptoms (Hoehn and Yahr stages 1 or 1.5). Half of them had left-sided symptoms, and the other half had right-sided symptoms. In both groups, 10 were drug-naïve, whereas 7 were under stable treatment with the administration of levodopa and dopamine agonists (see Tables S1 and S2 of Supplemental Data 1). All patients were right-handed as assessed by the Edinburgh Handedness Inventory[21] and had normal or corrected-to-normal vision. Patients were excluded if they showed (1) presence of severe sensory deficits or any other neurological disease besides PD, as assessed by a standard

neurological examination; (2) overt signs of dementia (Mini-Mental State Examination <24) and/or severe tremor; or (3) symptoms of impulse control disorder[22] (as it has been shown that PD patients with impulse control disorder are significantly faster at stopping initiated motor actions than PD patients without impulse control disorder symptoms[23]). Motor symptoms were rated using the Unified Parkinson's Disease Rating Scale part 3 (UPDRS3). Demographic and clinical characteristics across the 2 groups of patients did not statistically differ (see Table 1 and Supplemental Data 1).

Finally, to have a baseline measure of inhibitory control, we enrolled 24 healthy right-handed participants with normal or corrected-to-normal vision and without a history of neurological diseases. The average age of the controls and their education were not statistically significantly different from those of the 2 groups of PD patients (Table 1).

All participants provided written informed consent. All the procedures were approved by the Institutional Ethics Committee of IRCCS Neuromed Hospital and were performed following the ethical standards laid down in the Declaration of Helsinki. Data will be freely available from the Open Science Framework platform (https://osf.io/tyc43/).

Tasks

Both PD patients and controls performed the go-only task and the reaching version of the stop-signal task previously described.[7] (Those patients on dopaminergic drugs were always tested in *on* therapy.) The go-only task was an RT task aimed at measuring RTs and MTs of reaching-arm movements in a context in which the participants knew that they would never be required to cancel a pending action (Fig. 1). In go-only trials, the participants had to reach and hold a central stimulus until it disappeared and, simultaneously, a peripheral target appeared 18.6 degrees of visual angle to the right (go-signal). To give a correct response, participants had to reach the target as quickly as possible and to hold it until they heard an acoustic signal, which was presented at a variable delay of 300 to 400 milliseconds (*in step of 50* milliseconds). The stop-signal task consisted of a pseudorandom mix of no-stop and stop trials (Fig. 1). No-stop trials were the same as go-only trials, whereas in stop trials the central stimulus reappeared at a variable delay after the go-signal (stop-signal delay [SSD]) before the onset of the movement acting as the stop-signal. In this instance, the participants were instructed to cancel the preplanned movement response toward the peripheral target. The length of the SSD was changed using a staircase procedure depending on the stopping performance[24] with a 50% performance criterion. If participants succeeded in inhibiting the response, then stopping was made more difficult by increasing the SSD by 39.9 milliseconds (3 refresh rates); otherwise, the SSD decreased by the same amount of time. The starting value of the SSD was 119.7 milliseconds (9 refresh rates).

As people automatically tend to postpone their response to make inhibition on stop trials easier, we verbally informed participants that the probability of stopping would approximate to 50%, irrespective of their strategy. We also impose a maximum RT for no-stop trials, that is, whenever the RTs were >800 milliseconds, no-stop trials were aborted (overreach trial). Overreach trials were kept for the final analysis to avoid cutting the right tail of the RT distribution, and on average they accounted for 3.6%, 3.8%, and 4.8% of the total no-stop trials in RPD patients, LPD patients, and controls, respectively.

Importantly, whereas controls performed the 2 tasks using the right (dominant) arm, the patients also performed them using the left arm. Sessions in which the patients used the right arm were counterbalanced with sessions in which they had to employ the left arm. In the left version of the task, the peripheral target appeared on the horizontal plane to the left of the central stimulus. All of the participants completed 4 blocks of 108 stop-signal trials (432 trials) and about 90 go-only trials with the dominant arm. Patients performed the same amount of trials using the left arm. Therefore, each patient performed

TABLE 1. Demographic and clinical features of participants

	Age	Education, y	Handedness	Hoehn & Yahr	UPDRS3, total	UPDRS3, limbs of affected side	LEDD, mg	MMSE	Months since diagnosis
RPD	57.6 (6.8)	13.3 (3.3)	87.6 (12.5)	1 (0)	14 (3.9)	10.5 (3.6)	200.3 (172.3)	27 (1.8)	17.1 (10.2)
LPD	61.6 (5.6)	11.8 (3.8)	90 (11.7)	1.1 (0.2)	14.9 (5.1)	12.3 (4)	140.7 (100.8)	28.2 (2.1)	15.3 (10.7)
Controls	58.8 (6.9)	13.2 (4.6)	86.7 (13.7)						

For each group, the average value (± standard deviation) of age, years of education, and handedness (measured according to Olfied 1971)[21] are given. In addition, just for RPD and LPD, the average value (± standard deviation) of Hoehn & Yahr scores (indicating the stage of Parkinson's disease), total score of the UPDRS3 (for those patients who were under pharmacological treatment, the UPDRS3 was measured after the assumption of the habitual dose of levodopa), partial score of the UPDRS3 related to the limbs of the affected side, LEDD (the value refers to those patients that were not drug naïve), MMSE score, and months since diagnosis are provided. The ages of control participants and their education were not statistically significantly different from those of Parkinson's disease patients (see Table S3, Supplemental Data 1). None of the clinical features of RPD patients differed from those of LPD patients (see Table S3, Supplemental Data 1).
UPDRS3, Unified Parkinson's Disease Rating Scale part 3; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental Examination; RPD, right-dominant Parkinson's disease patients; LPD, left-dominant Parkinson's disease patients.

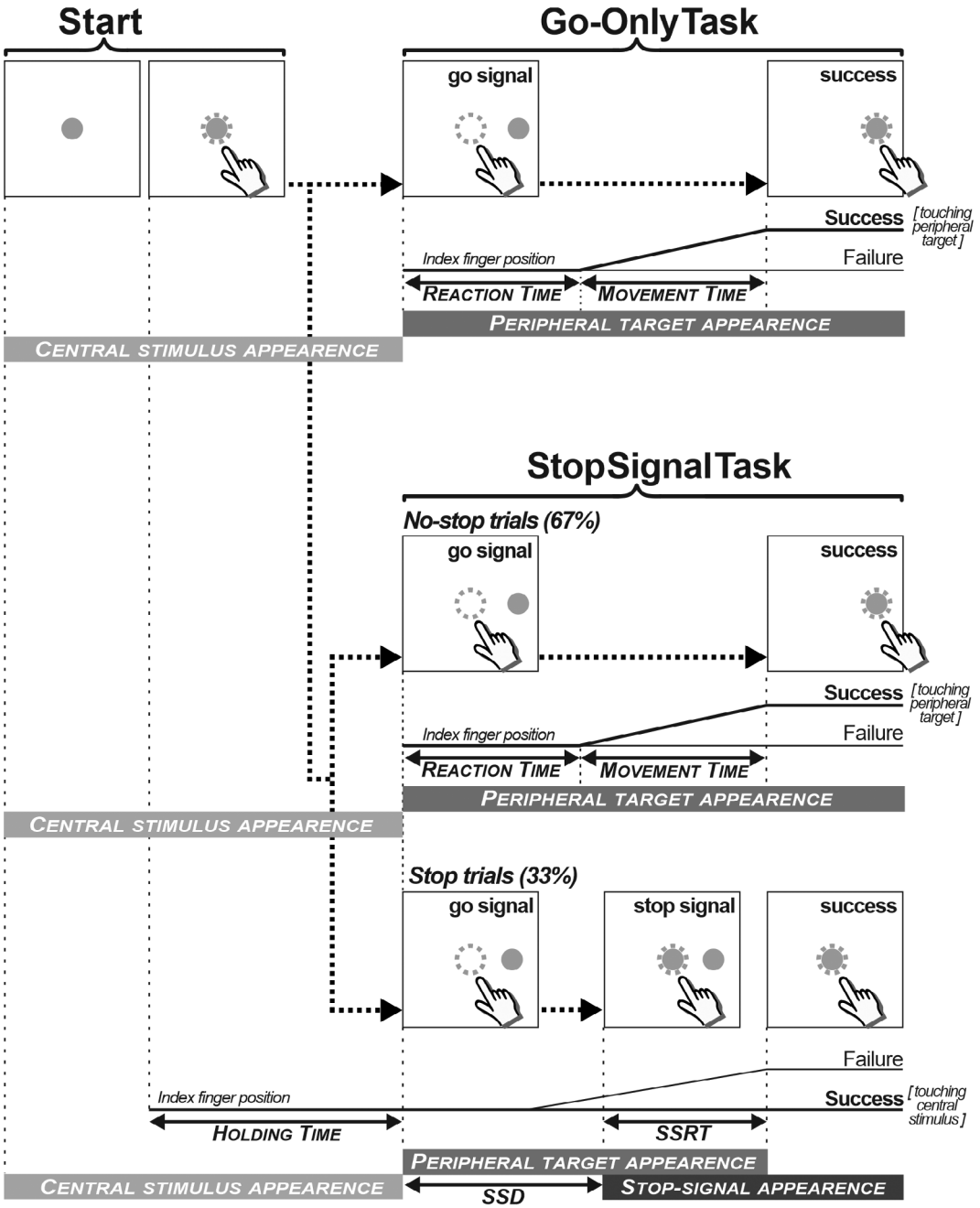

FIG. 1. Experimental tasks (go-only and stop-signal task). Participants were seated in a silent room so that their eyes were about 40 cm away from the touchscreen and they could comfortably reach the stimuli projected on the touchscreen (MicroTouch, 3M, Saint Paul, MN, USA; sampling rate 200 Hz). The go-only task consisted of only 1 type of trial (go-only), whereas the stop-signal task consisted of a pseudorandom mix of no-stop (67%) and stop trials (33). All trials began with the appearance of a central stimulus, which participants had to reach and hold with the index of the right (dominant) arm for a variable period of 500–800 milliseconds (patients also performed the task with the left arm). Successively, the central stimulus disappeared, and a target appeared 18.6 degrees of visual angle (dva) to the right (or to the left, when patients employed the left arm), acting as a go-signal. In the go-only and the no-stop trials, participants had to reach and hold the peripheral target for 300–400 milliseconds. In contrast, in the stop trials, the central stimulus (stop-signal) reappeared at a variable delay after the go signal (stop-signal delay, SSD), and participants were instructed to suppress the preplanned movement. To score a success, participants had to keep the index finger on the stop signal for 300–400 milliseconds. Otherwise, the trial was scored as a failure. Correct responses were signaled by auditory feedback. The dotted circle (blind to the participants) indicates the size of the tolerance window for the touches (5 dva of diameter). CORTEX, a free, noncommercial software package, was used to control stimulus presentation and to collect behavioral responses. Visual stimuli consisted of red circles (2.434 cd/m^2) with a diameter of 4 dva presented against a dark background of uniform luminance (<0.01 cd/m^2). The temporal arrangements of stimulus presentation were synchronized with the personal computer monitor (17-inch, cathode-ray tube noninterlaced) refresh rate (75 Hz, 640 × 480 resolution).

~1040 trials. Resting periods were allowed between blocks whenever requested. Before starting the task, ~50 practice trials were given to familiarize the participants with the apparatus.

Data Analyses

RTs, MTs, and the SSRTs were taken as behavioral parameters. RTs were computed as the time interval between the go-signal presentation and the onset of movement. MTs were computed as the time interval between the movement onset and the moment in which the peripheral target was touched. Trials with RTs shorter/longer than the mean ± 3 standard deviations (SDs) were considered outliers and discarded. Overall, 1.8%, 1.6%, and 1.1% of the data were eliminated in RPD patients, LPD patients, and controls, respectively.

Reactive inhibition was measured via the SSRT,[19,25] which was estimated using the integration method as this method provides the best estimate when proactive slowing occurs[26] (Supplemental Data 2). Proactive inhibition was assessed by comparing the RTs and the MTs of no-stop trials versus those of go-only trials.[18]

We assessed the assumption of normality of the distributions of RTs, MTs, and SSRTs using the Shapiro-Wilk test. As this assumption was satisfied in all cases but 2 (i.e., the RTs of go-only trials of LPD and controls), we employed different types of analysis of variance (ANOVA) to assess changes in RTs, MTs, and SSRTs given that parametric tests are more robust than the corresponding nonparametric tests. Bonferroni corrections were applied for all multiple comparisons. For each ANOVA, we quantified the effect size in terms of the partial eta-squared (η_p^2; values of 0.01, 0.058, and 0.139 indicate small, medium, and large effects, respectively), whereas for the *t* test we quantified it using Cohen's d (values of 0.2, 0.5, and 0.8 indicate small, medium, and large effects, respectively). To quantify the strength of null hypotheses, we calculated the Bayes factors (BF_{10}) with an *r* scale of 0.707[27] (BF_{10} values <0.33 and <0.1 provide moderate and robust support, respectively, for a null hypothesis compared to the alternative hypothesis). Finally, cumulative distributions of RTs and MTs in no-stop and go-only trials were compared using 2-sample Kolmogorov-Smirnov tests. χ^2-tests were used to determine whether there were significant differences between the occurrences of the context effects.

Results

First, we assessed whether (1) the staircase algorithm worked similarly well in our populations of patients and controls and (2) the assumption about the stochastic independence between the go process and the stop process[19,25] was fulfilled. As both conditions were satisfied, we concluded that our estimates of the overall speed of inhibition (SSRT) were accurate (Table 2 and Supplemental Data 3).

Reactive Inhibition: PD Patients Have Longer SSRTS Than Controls

As shown in Table 2 and Figure 2A, the average SSRTs of PD patients were longer than the average SSRT of controls. A 1-way ANOVA (levels: RPD, LPD, and controls) revealed a main effect, and the following post hoc tests showed that controls inhibit their movement significantly faster than both RPD and LPD patients (Table 3). In contrast, the SSRT of RPD and LPD patients was similar. The values of the BF_{10} provided further support for the null hypotheses, strengthening the conclusion that RPD and LPD patients do not show significant differences in reactive inhibition.

Proactive Inhibition: No Difference Between PD Patients and Controls

Proactive inhibition was measured quantifying the context effect following both a within-subject approach and 2 different population approaches.[6,7]

First, we assessed the occurrence of the context effect in each participant checking whether the individual cumulative distributions of RTs and MTs were significantly different via the 2-sample Kolmogorov-Smirnov test. After that, we computed the percentage of participants who exhibited a simultaneous decrease in RTs and increase in MTs in no-stop trials with respect to go-only trials. As shown in Figure 2B, the percentage of

TABLE 2. Summary of behavioral values for RPD and LPD patients and controls during the stop-signal task and the go-only task when the right arm was employed

	RPD	LPD	Controls
Mean SSD	256.6 ± 90.2	239.9 ± 83.6	257.5 ± 99.8
P (failure)	0.51 ± 0.06	0.52 ± 0.06	0.50 ± 0.03
SSRT	239 ± 22.8	241.4 ± 21.8	220.0 ± 26.1
RT no-stop trials	505.1 ± 89.4	492.4 ± 85.9	499.51 ± 94.8
RT stop-failure trials	399.4 ± 76.9	397.9 ± 56.9	406.44 ± 84.8
RT go-only trials	272.8 ± 48.8	257.5 ± 42.8	305.39 ± 87
MT no-stop trials	594.3 ± 130	490 ± 97.7	425.36 ± 104.3
MT go-only trials	658.8 ± 123.1	563.1 ± 112.1	495.78 ± 132.3
Accuracy go-only trials	0.92 ± 0.04	0.87 ± 0.08	0.92 ± 0.08
Accuracy no-stop trials	0.90 ± 0.10	0.91 ± 0.06	0.90 ± 0.08

Accuracy is defined as the ratio between the number of trials correctly executed and the total number of trials delivered, given by the sum of trials correctly executed, trials in which participants missed the target, trials in participants remained still on the central stimulus for more than 2 seconds, and trials in which they did not hold the central stimulus or the target for the requested amount of time. In all cases the average value across the samples (± standard deviation) is reported.

RPD, right-dominant Parkinson's disease patients; LPD, left-dominant Parkinson's disease patients; SSD, stop-signal delay; SSRT, stop-signal reaction time; RT, reaction time; MT, movement time; P (failure) probability of failing to perform a stop trial.

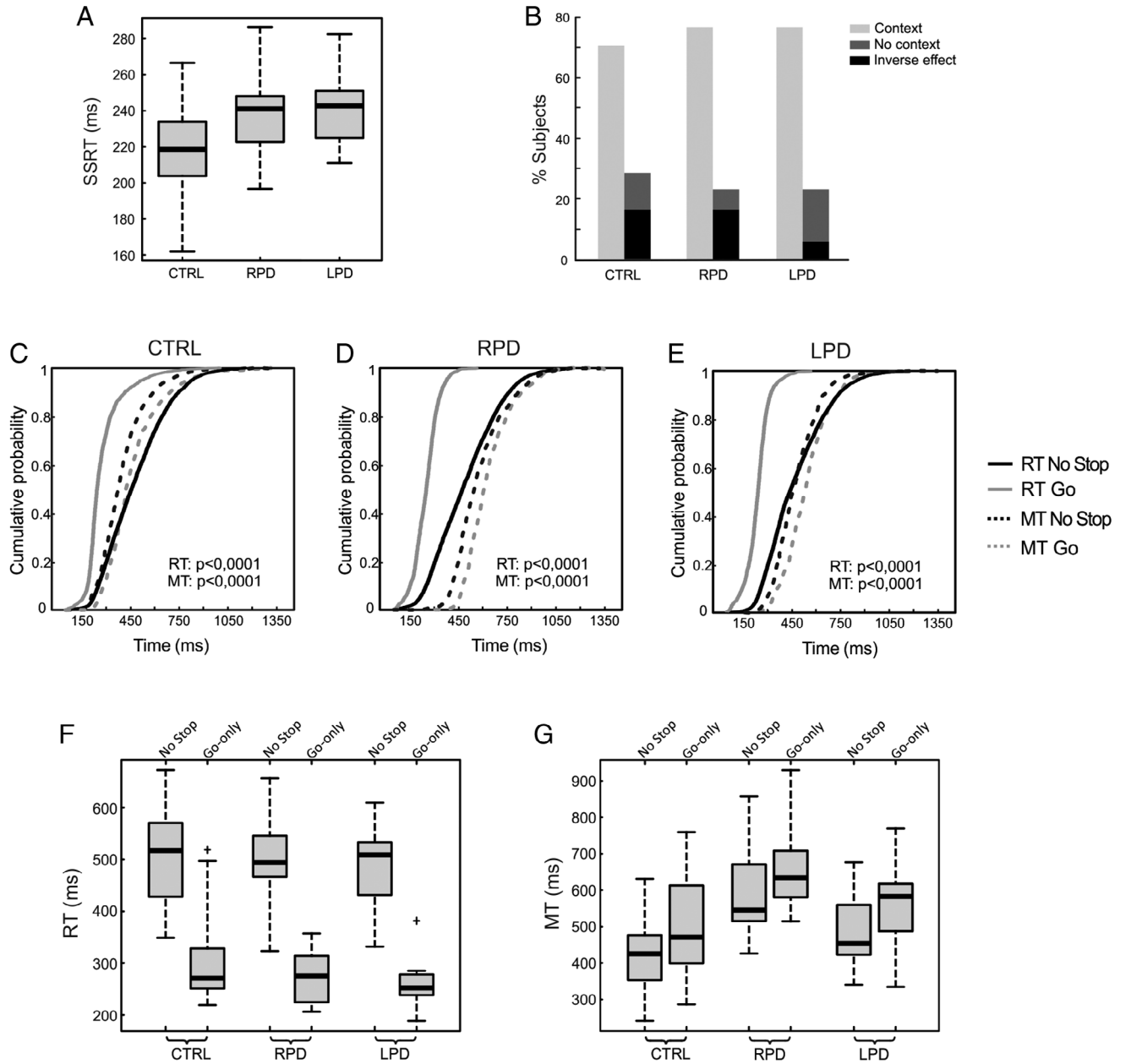

FIG. 2. Inhibitory control for right-dominant PD patients (RPD; n = 17), left-dominant PD patients (LPD; n = 17), and controls (CTRL; n = 24) when the right arm was employed. (**A**) Reactive inhibition. Box plots of stop signal reaction times (SSRT). (**B**) Proactive inhibition: context effect in each participant (within-subject approach). Percentage of age-matched controls, RPD patients, and LPD patients showing either (1) simultaneously a significant increase in reaction times (RTs) and a significant decrease in movement times (MTs) in no-stop trials with respect to go-only trials ("context"), (2) a significant lengthening of both RTs and MTs in no-stop trials with respect to go-only trials ("reversed context"), or (3) a significant increase in RTs in no-stop trials with respect to go-only trials, but MTs of no-stop trials were not different from those of go-only trials ("no context"). (**C**) Proactive inhibition: cumulative distributions (population approach). Cumulative distributions of RTs (solid lines) and MTs (dotted lines) of controls for go-only trials (gray) and no-stop trials (black). These cumulative distributions were obtained by collapsing together the cumulative distributions of RTs and MTs of no-stop and go-only trials of single participants. The *P* value of the 2-sample Kolmogorov–Smirnov test is reported. (**D**) Same representation as in (**C**) for RPD patients and (**E**) for LPD patients. (**F**) Proactive inhibition: average values of RT and MT (population approach). Box plot of RTs and (**G**) of MTs of no-stop and go-only trials in controls, RPD patients, and LPD patients. In all box plots, the boundary of the box closest to 0 indicates the first quartile, a thick black line within the box marks the median, and the boundary of the box farthest from 0 indicates the third quartile. Whiskers indicate values 2.2 times the interquartile range below the first quartile and above the third quartile. Outliers are represented by crosses.

participants showing a context effect (70.8%) was not significantly different from either that of RPD patients (76.5%, $\chi^2[1] = 0.64$, $P = 0.42$) or that of LPD patients (76.5%, $\chi^2[1] = 0.64$, $P = 0.42$). Furthermore, the percentage of occurrences in RPD and LPD patients was the same. Second, to evaluate the context effect at the population level, we combined data from single participants to create cumulative population distributions of RTs and MTs of go-only trials and no-stop trials. As Figure 2C–E shows, qualitatively the 2 experimental paradigms had opposite effects on RTs and MTs in all 3 groups of participants given that all had significantly

TABLE 3. Results of the statistical analysis of SSRT, RT, and MT across RPD, LPD, and controls when the right arm was employed

	Value of Parameters	*P* Values	Effect Size	BF_{10}
One-way ANOVA: group (RPD, LPD, controls)				
Main effect: group	$F_{2,55} = 5.03$	***0.01***	$\eta_p^2 = 0.15$	5.45
Post hoc test: RPD vs. controls	$t_{39} = 2.4$	***0.047***	d = 0.77	2.86
Post hoc test: LPD vs. controls	$t_{39} = 2.76$	***0.02***	d = 0.88	5.52
Post hoc test: RPD vs. LPD	$t_{32} = -0.32$	1	d = 0.11	0.34
Two-way ANOVA (factors: group [RPD, LPD, and controls]; trial type [RT no-stop trials, RT go-only trials])				
Main effect: group	$F_{2,55} = 0.88$	0.42	$\eta_p^2 = 0.03$	0.12
Main effect: trial type	$F_{1,55} = 340.6$	***<0.001***	$\eta_p^2 = 0.86$	<0.001
Interaction: group × trial type	$F_{2,55} = 1.37$	0.26	$\eta_p^2 = 0.05$	0.28
Two-way ANOVA (group [RPD, LPD, and controls]; trial type [MT no-stop trials, MT go-only trials])				
Main effect: group	$F_{2,55} = 11.49$	***<0.001***	$\eta_p^2 = 0.29$	<0.001
Main effect: trial type	$F_{1,55} = 36.18$	***<0.001***	$\eta_p^2 = 0.39$	5.98
Interaction: group × trial type	$F_{2,55} = 0.044$	0.96	$\eta_p^2 = 0.002$	0.14
Post hoc test: RPD vs. controls	$t_{39} = 4.56$	***<0.001***	d = 1.44	389.6
Post hoc test: LPD vs. controls	$t_{39} = 1.99$	0.053	d = 0.63	1.46
Post hoc test: RPD vs. LPD	$t_{32} = 2.69$	***0.01***	d = 0.92	4.63

Post hoc tests (pairwise comparisons) had an adjusted alpha level corrected according to Bonferroni. Statistically significant results are reported in bold and italics. Bayes factors report the ratio between the null versus the alternative hypothesis (BF_{10}), η_p^2, Cohen's d.
SSRT, stop-signal reaction time; RT, reaction time; MT, movement time; RPD, right-dominant Parkinson's disease patients; LPD, left-dominant Parkinson's disease patients; ANOVA, analysis of variance.

longer RTs and shorter MTs in no-stop trials than in go-only trials (2-sample Kolmogorov-Smirnov test, all $P < 0.0001$). Finally, we compared the average values of RTs and MTs via 2-way mixed-design ANOVAs (between-subjects factor, group [controls, RPD, LPD]; within-subjects factor, trial type [RT/MT no-stop trials, RT/MT go-only trials]). We found that the RTs of no-stop trials were significantly longer than those of go-only trials (Table 3). No other effects were found (Fig. 2F). The analysis of MTs showed both the main effect of trial type and group (Table 3). The former result was because of the fact that participants had longer MTs when executing go-only trials than when performing no-stop trials (Fig. 2G). The latter effect was because RPD patients were significantly slower than LPD patients and controls.

If the context effect truly represents an optimization of the motor strategy and not a simple speed–accuracy tradeoff phenomenon,[28] that is, the fact that faster responses tend to induce more errors, then accuracy during no-stop trials have to be similar to that of go-only trials. This was the case (Table 2 and Supplemental Data 4).

These results suggest that proactive inhibitory control did not differ across participants.

Reactive Inhibition Does Not Differ Among PD Patients With and Without Dopaminergic Treatment

As reported previously, both in the LPD and RPD groups, 7 patients of 17 were under dopaminergic treatment. As it has been suggested that dopaminergic treatment improves inhibitory control in early-stage PD patients, but not in moderate to advanced patients,[29] we assessed whether those patients of our sample who were under drug therapy had a better reactive inhibition with respect to drug-naïve patients. As reported in Supplemental Data 6, we did not find any difference between treated and untreated patients. Therefore, the deficit in reactive inhibitory control does not seem to be related to the administration of medications.

Inhibitory Control Does Not Change According to the Arm Employed for Task Execution

To probe further the hypothesis of the hemispheric lateralization of inhibition, we tested the following predictions: if inhibitory control is right-lateralized, it follows that RPD patients, who have the left and not the right hemisphere compromised, should exhibit better inhibitory control over both right and left arm movements than LPD patients. To this end, we compared reactive and proactive inhibition across both arms and the 2 groups of PD patients. As shown in Supplemental Data 5, we did not find any difference either between RPD and LPD patients or between the arm used in the task. Thus, at least in right-handed PD patients, at the behavioral level there are no overt signs of right lateralization of inhibitory control.

Correlations Between Behavioral Parameters of the Stop-Signal Task and the UPDRS3 Score

To assess whether symptom severity, measured on the UPDRS3, correlates with behavioral parameters

characterizing the performance in the stop-signal task (i.e., the SSRTs, the RTs, and the MTs), we computed the values of the Spearman's correlation coefficient. We did not find any significant correlation (not shown). This is probably because the items of the UPDRS3 scores measure motor skills such as speech, tremor, rigidity, leg movements, and the stability of posture, which are poorly or not related to the feature measured with the experimental paradigm employed in this study.

Discussion

We found a selective deficit of inhibitory control in early-stage PD patients, as they exhibit an impairment of reactive inhibition with respect to healthy controls but, at the same time, patients have an intact proactive inhibition. In our opinion, as we discuss next, these results might potentially be exploited in the post-diagnostic phase by clinicians to assess the course of the disease. We confirmed once again the absence of hemispheric specialization of inhibitory control in PD patients with unilateral symptoms.

Early-Stage PD Is Characterized by the Selective Impairment of Inhibitory Control Components

Our findings indicate that the 2 neuropsychological domains of inhibitory control, reactive and proactive inhibition, have different sensitivity to dopaminergic degeneration. In the early stage of the disease, PD patients are less capable of stopping an action outright. However, they keep the ability to shape their behavioral strategies according to the available contextual cues. This might have high relevance for assessing the clinical progression of the disease. In everyday life, proactive control is tuned to one's short-range, medium-range, and long-range goals, which are retrieved from long-term memory according to the current needs. Being able to manage these needs allows a person to feel self-confident and less anxious in most situations. Consistent with this reasoning, it has been claimed that proactive inhibition plays a key role in psychiatric disorders such as anxiety and depression, whereas deficits in reactive inhibition could be more involved in diseases characterized by poor urge control.[30] In the first stages of PD, patients exhibit decreased motor control, but they are less likely to develop anxiety or depression, 2 psychiatric disorders that frequently occur in the more advanced phase.[31,32] The impairment of proactive control could represent the primary trigger for developing such disorders, and it might be used as a biomarker signaling the beginning of the more advanced phase of the disease. In principle, this could help the clinician to set the appropriate drug therapy. Clearly, to make an accurate prediction about proactive inhibition it is essential to have a reliable tool for measuring it. In our view, the experimental approach exploited here has such a feature because it does not conflate inhibitory control with other executive functions such as working memory or attention as other task do, for example, the conditional stop task.[33] However, these considerations are hampered by the fact that our performance-based measures did not correlate with the scores of the UPDRS3 scale, and we did not collect questionnaire-based measures of impulsivity. Therefore, on the one hand, the link between the clinical features of the disease and our measures of inhibitory control must be taken cautiously. On the other hand, it is known that the correlation between questionnaire-based impulsivity and performance-based measures tend to be poor.[34,35] In our opinion, this is because rating scales are based on a verbal description of behaviors, whereas performance-based tests capture implicit/automatic aspects of cognitive processes associated with movement control. If this intuition is proven to be correct, then performance-based measures might represent a better tool for assessing at least some clinical aspects of the disease than standard clinical ratings. Surely further studies are needed to test these hypotheses.

Another noteworthy feature of our results is that even though reactive inhibition of PD patients in the early stages is compromised with respect to controls, their average SSRT (mean = 240.2 milliseconds, SD = 21.9 milliseconds) is shorter, that is, participants were more proficient in outright stopping than were more advanced PD patients (Hoehn and Yahr stages ~2.3; mean = 258.2 milliseconds, SD = 39.7 milliseconds[6]) and unilateral deep brain stimulation patients either in ON or OFF stimulation (mean = 256.1 milliseconds, SD = 34.4 milliseconds[7]).

In conclusion, we found evidence that the impairment of inhibitory control in PD patients has a progression. In the early stages, the deficit in reactive inhibition is milder than in the most advanced stage, whereas proactive inhibition is intact.

Inhibitory Control Is Not Right Lateralized in PD Patients

The unilateral development of motor symptoms is a distinctive feature of PD[13,14] (for reviews, see refs. 36 and 37). However, whether RPD and LPD patients have different cognitive profiles is still a matter of debate. Some have found a correlation between the side of motor onset and a specific pattern of cognitive profiles,[38] whereas some others claimed a lack of difference in cognitive symptoms between RPD and LPD in the earliest stages, suggesting that eventual differences emerge with disease progression.[39,40] These studies, however, are based on clinical scales and questioners, and this might limit the generalizability of their results. The most consistent performance-based evidence suggest that RPD patients tend to have a specific impairment in some language domains,[36] whereas

LPD patients show visuospatial impairments[41,42] and impaired vocal emotion processing.[43,44] All of these functions have clear lateralization in healthy subjects, suggesting that lateralized PD patients represent a good model to assess whether inhibitory control relies on a right-lateralized network.[17] We hypothesized that, if this was the case, than LPD patients should be more impaired than RPD patients in both proactive and reactive inhibition. Although it has already been shown that this is not the case,[6,7] previous findings were based on PD patients in whom both hemispheres were affected, although the symptoms were still very asymmetric. This objection motivated the present study in which we fully confirmed the absence of significant differences between RPD and LPD with unilateral symptoms, that is, patients with major or exclusive damage of the left or right hemisphere, respectively. As both groups of patients were less skilled than healthy controls in reactive inhibition, and as it has been shown that bilateral[4,45] but not unilateral deep brain stimulation[7] restores reactive inhibitory control to a near-normal level, we concluded that this executive function requires the cooperation of both hemispheres.

Conclusions

Our findings shed light on the evolution in time of the inhibitory deficit in PD. We suggest that these features could potentially provide critical insights into the state of the disease. We confirmed our previous results showing no difference in inhibitory control between LPD and RPD patients,[6,7] hence indicating that, at least in these patients, this executive function relies on the cooperation between the 2 hemispheres.[4,5]

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References

1. Seligman ME, Railton P, Baumeister RF, Sripada C. Navigating into the future or driven by the past. Perspect Psychol Sci 2013;8(2):119–141.
2. Mirabella G. Should I stay or should I go? Conceptual underpinnings of goal-directed actions. Front Syst Neurosci 2014;8:206.
3. Gauggel S, Rieger M, Feghoff TA. Inhibition of ongoing responses in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75(4):539–544.
4. Mirabella G, Iaconelli S, Romanelli P, et al. Deep brain stimulation of subthalamic nuclei affects arm response inhibition in Parkinson's patients. Cereb Cortex 2012;22(5):1124–1132.
5. Mirabella G, Iaconelli S, Modugno N, Giannini G, Lena F, Cantore G. Stimulation of subthalamic nuclei restores a near normal planning strategy in Parkinson's patients. PLoS ONE 2013;8(5):e62793.
6. Mirabella G, Fragola M, Giannini G, Modugno N, Lakens D. Inhibitory control is not lateralized in Parkinson's patients. Neuropsychologia 2017;102:177–189.
7. Mancini C, Modugno N, Santilli M, et al. Unilateral stimulation of subthalamic nucleus does not affect inhibitory control. Front Neurol 2018;9:1149.
8. Wylie SA, van Wouwe NC, Godfrey SG, et al. Dopaminergic medication shifts the balance between going and stopping in Parkinson's disease. Neuropsychologia 2018;109:262–269.
9. Obeso I, Wilkinson L, Jahanshahi M. Levodopa medication does not influence motor inhibition or conflict resolution in a conditional stop-signal task in Parkinson's disease. Exp Brain Res 2011;213(4):435–445.
10. Jahanshahi M, Obeso I, Baunez C, Alegre M, Krack P. Parkinson's disease, the subthalamic nucleus, inhibition, and impulsivity. Mov Disord 2015;30(2):128–140.
11. MacDonald HJ, Byblow WD. Does response inhibition have pre- and postdiagnostic utility in Parkinson's disease? J Mot Behav 2015;47(1):29–45.
12. Vriend C, Gerrits NJ, Berendse HW, Veltman DJ, van den Heuvel OA, van der Werf YD. Failure of stop and go in de novo Parkinson's disease—a functional magnetic resonance imaging study. Neurobiol Aging 2015;36(1):470–475.
13. Toth C, Rajput M, Rajput AH. Anomalies of asymmetry of clinical signs in parkinsonism. Mov Disord 2004;19(2):151–157.
14. Uitti RJ, Baba Y, Whaley NR, Wszolek ZK, Putzke JD. Parkinson disease: handedness predicts asymmetry. Neurology 2005;64(11):1925–1930.
15. Huang WS, Lin SZ, Lin JC, Wey SP, Ting G, Liu RS. Evaluation of early-stage Parkinson's disease with 99mTc-TRODAT-1 imaging. J Nucl Med 2001;42(9):1303–1308.
16. Marek KL, Seibyl JP, Zoghbi SS, et al. [123I] beta-CIT/SPECT imaging demonstrates bilateral loss of dopamine transporters in hemi-Parkinson's disease. Neurology 1996;46(1):231–237.
17. Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J Neurosci 2007;27(14):3743–3752.
18. Mirabella G, Pani P, Ferraina S. Context influences on the preparation and execution of reaching movements. Cogn Neuropsychol 2008;25(7-8):996–1010.
19. Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: a model and a method. J Exp Psychol Hum Percept Perform 1984;10(2):276–291.
20. Criaud M, Longcamp M, Anton JL, et al. Testing the physiological plausibility of conflicting psychological models of response inhibition: a forward inference fMRI study. Behav Brain Res 2017;333:192–202.
21. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9(1):97–113.
22. Voon V, Hassan K, Zurowski M, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology 2006;67(7):1254–1257.
23. Claassen DO, van den Wildenberg WP, Harrison MB, et al. Proficient motor impulse control in Parkinson disease patients with impulsive and compulsive behaviors. Pharmacol Biochem Behav 2015;129:19–25.
24. Levitt S, Gutin B. Multiple choice reaction time and movement time during physical exertion. Res Q 1971;42(4):405–410.
25. Boucher L, Stuphorn V, Logan GD, Schall JD, Palmeri TJ. Stopping eye and hand movements: are the processes independent? Percept Psychophys 2007;69(5):785–801.
26. Verbruggen F, Chambers CD, Logan GD. Fictitious inhibitory differences: how skewness and slowing distort the estimation of stopping latencies. Psychol Sci 2013;24(3):352–362.
27. Rouder JN, Speckman PL, Sun D, Morey RD, Iverson G. Bayesian t tests for accepting and rejecting the null hypothesis. Psychon Bull Rev 2009;16(2):225–237.
28. Fitts PM. The information capacity of the human motor system in controlling the amplitude of movement. J Exp Psychol 1954;47(6):381–391.

29. Manza P, Schwartz G, Masson M, et al. Levodopa improves response inhibition and enhances striatal activation in early-stage Parkinson's disease. Neurobiol Aging 2018;66:12–22.

30. Aron AR. From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. Biol Psych 2011;69(12):e55–e68.

31. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Arbizu J, Gimenez-Amaya JM. The basal ganglia and disorders of movement: pathophysiological mechanisms. News Physiol Sci 2002;17:51–55.

32. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol 2009;8(5):464–474.

33. Swann N, Tandon N, Canolty R, et al. Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. J Neurosci 2009;29(40):12675–12685.

34. Shuster J, Toplak ME. Executive and motivational inhibition: associations with self-report measures related to inhibition. Conscious Cogn 2009;18(2):471–480.

35. Toplak ME, West RF, Stanovich KE. Practitioner review: do performance-based measures and ratings of executive function assess the same construct? J Child Psychol Psychiatry 2013;54(2):131–143.

36. Verreyt N, Nys GM, Santens P, Vingerhoets G. Cognitive differences between patients with left-sided and right-sided Parkinson's disease. A review. Neuropsychol Rev 2011;21(4):405–424.

37. Riederer P, Jellinger KA, Kolber P, Hipp G, Sian-Hulsmann J, Kruger R. Lateralisation in Parkinson disease. Cell Tissue Res 2018; 373(1):297–312.

38. Amick MM, Grace J, Chou KL. Body side of motor symptom onset in Parkinson's disease is associated with memory performance. J Int Neuropsychol Soc 2006;12(5):736–740.

39. Poletti M, Frosini D, Pagni C, et al. The relationship between motor symptom lateralization and cognitive performance in newly diagnosed drug-naive patients with Parkinson's disease. J Clin Exp Neuropsychol 2013;35(2):124–131.

40. Pellicano C, Assogna F, Cravello L, et al. Neuropsychiatric and cognitive symptoms and body side of onset of parkinsonism in unmedicated Parkinson's disease patients. Parkinsonism Relat Disord 2015;21(9):1096–1100.

41. Karadi K, Lucza T, Aschermann Z, et al. Visuospatial impairment in Parkinson's disease: the role of laterality. Laterality 2015;20(1): 112–127.

42. Harris JP, Atkinson EA, Lee AC, Nithi K, Fowler MS. Hemispace differences in the visual perception of size in left hemiParkinson's disease. Neuropsychologia 2003;41(7):795–807.

43. Garrido-Vasquez P, Pell MD, Paulmann S, Strecker K, Schwarz J, Kotz SA. An ERP study of vocal emotion processing in asymmetric Parkinson's disease. Soc Cogn Affect Neurosci 2013;8(8): 918–927.

44. Stirnimann N, N'Diaye K, Jeune FL, et al. Hemispheric specialization of the basal ganglia during vocal emotion decoding: Evidence from asymmetric Parkinson's disease and (18)FDG PET. Neuropsychologia 2018;119:1–11.

45. van den Wildenberg WP, van Boxtel GJ, van der Molen MW, Bosch DA, Speelman JD, Brunia CH. Stimulation of the subthalamic region facilitates the selection and inhibition of motor responses in Parkinson's disease. J Cogn Neurosci 2006;18(4):626–636.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.