OXFORD

Social Cognitive and Affective Neuroscience, 2023, **18**(1), 1–11

DOI: https://doi.org/10.1093/scan/nsac040
Advance Access Publication Date: 8 June 2022
Original Manuscript

The dopaminergic system supports flexible and rewarding dyadic motor interactive behaviour in Parkinson's Disease

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Abstract

Studies indicate that the dopaminergic system (DAS) supports individual flexible behaviour. While flexibility is quintessential to effective dyadic motor interactions, whether DAS mediates adaptations of one's own motor behaviour to that of a partner is not known. Here, we asked patients with Parkinson's Disease (PD) to synchronize their grasping movements with those of a virtual partner in conditions that did (Interactive) or did not (Cued) require to predict and adapt to its actions. PD performed the task during daily antiparkinsonian treatment ('On' condition) or after drug-withdrawal ('Off' condition). A group of healthy individuals also served as control group. In the Interactive condition, PDs performed better and found the interaction more enjoyable when in 'On' than in 'Off' condition. Crucially, PD performance in the 'On' condition did not differ from that of healthy controls. This pattern of results hints at the key role of the DAS in supporting the flexible adaptation of one's own actions to the partner's during motor interactions.

Key words: behavioural flexibility; social behaviour; interpersonal motor interactions; Parkinson disease; dopamine; motivation

Introduction

Parkinson's Disease (PD) is a neurodegenerative disorder characterized by a dopamine depletion in the striatum, affecting the functioning of the fronto-striato-thalamo-cortical circuits, resulting in motor, cognitive and motivational deficits (Zgaljardic *et al.*, 2003). A feature that characterizes cognitive and motor domains in PD is inflexible behaviour. At a cognitive level, PD inflexibility results in a deficit in set-shifting, that is the ability to reorganize behaviour according to the task demands (Cools *et al.*, 1984; Downes *et al.*, 1989; van Spaendonck *et al.*, 1995). This difficulty also extends to non-rule-based tasks requiring action reprogramming, that is the ability to switch from an expected to a less expected movement (Galea *et al.*, 2012).

Behavioural flexibility is of crucial relevance when individuals need to coordinate their actions with that of a partner. In these situations, individuals need to predict and monitor their partner's actions by continuously updating their expectations about them (Vesper *et al.*, 2010). Indeed, when interacting with others we often need to implement new motor plans in response to their unpredicted behaviours (e.g. motor errors) to avoid undesired consequences. Behavioural studies show that mechanisms similar to the ones at play when performing errors (like post-error slowing, Laming, 1979; Ullsperger and Danielmeier, 2016; Fusco *et al.*, 2022), also occur when observing someone else performing an error (Wang *et al.*, 2016; Weller *et al.*, 2018) and when interacting with another individual, in response to his/her errors (Sacheli *et al.*, 2021). Moreover, studies show that the same electrocortical signatures (e.g. increase in theta oscillations originating in frontal regions) associated to the execution of errors (Luu *et al.*, 2004) and to the observation of one's own avatar committing an error (Pavone *et al.*, 2016; Pezzetta *et al.*, 2018; Spinelli *et al.*, 2018) also appear when interacting with a virtual partner, in conditions requiring prediction and monitoring of its actions (Moreau *et al.*, 2020, 2022). Interestingly, frontal theta oscillations have been proposed to depend on dopaminergic activity (Parker *et al.*, 2015) although the role of dopamine in supporting the emergence of theta oscillations related to the activity of the performance monitoring system is still poorly investigated (Singh *et al.*, 2018).

Received: 14 December 2021; **Revised:** 21 April 2022; **Accepted:** 7 June 2022

The role of the dopaminergic system (DAS) in supporting socio-emotional behaviour has been tested in studies on PD patients (McNamara and Durso, 2003; Sprengelmeyer *et al.*, 2003; Kawamura and Koyama, 2007; Péron *et al.*, 2009; Bodden *et al.*, 2010; Santangelo *et al.*, 2012; Fabbri *et al.*, 2018; Ponsi *et al.*, 2021). Interestingly, the ability of PD patients in performing actions in a social context has also been explored in dopamine depletion studies in which PD patients show difficulties in modulating action kinematics based on the social (compared to individual) context in which the action takes place (Straulino *et al.*, 2015, 2016a, 2016b).

Crucially, the role of dopamine (and the related functionality of fronto-striato-thalamo-cortical circuits) has never been investigated during interpersonal motor interactions where individual behaviour needs to be dynamically integrated with the movements of a partner. These situations require flexible cognitive and motor behaviour as well as the motivation to engage in an interaction and offer the possibility to study PD patients' abilities in ecological but still highly controlled scenarios. To address this issue, in the present study PD patients were tested in 'On' and 'Off' conditions along with a group of healthy controls (HCs) while required to grasp a bottle-shaped object (that could be grasped in two different parts, i.e. an upper or a lower part via a precision and a power grip, respectively) as synchronously as possible with a virtual partner in two separate conditions, namely: (i) a Cued condition, in which participants knew in advance where they had to grasp the object and (ii) an Interactive condition, asking participants to coordinate their action according to the virtual partner's movement by either imitating or complementing its movement (requiring on-line prediction and monitoring of the virtual partners' actions). We tested the hypothesis that the DAS plays a role in orchestrating the mechanisms necessary to successfully interact with a partner. Thus, we predicted that, after controlling for individual's ability to perform the task in the Cued condition, PD patients in the 'Off' condition would show difficulties in performing the task in the Interactive condition and would be less motivated during the interaction compared to when performing the task in the 'On' condition.

Methods

Participants

Eighteen patients affected by Parkinson's Disease (hereafter referred to as PD) were involved in the study. The sample size was selected thanks to a prospective power analysis performed with the software More Power (Campbell and Thompson, 2012). We inserted as expected effect size the partial eta squared value (0.40) observed in (Candidi *et al.*, 2017) where the same task employed here was used to study the ability to perform motor interactions in patients with higher-order motor difficulties. The analysis indicates that a $2 \times 2 \times 2 \times 2$ within-subject design, a power of 0.85 and a partial eta squared of 0.40 (as computed from Candidi *et al.*, 2017), requires a sample size of 16 participants.

All participants had normal or corrected-to-normal vision and were naive as to the purpose of the experiment. Patients were recruited for the study according to the following inclusion criteria: (i) diagnosis of idiopathic PD (United Kingdom Parkinson's Disease Society brain bank criteria, UPDRS; (Fahn and Elton, 1987); (ii) absence of dementia (Mini Mental State Examination, MMSE above or equal to 25); (iii) absence of other neurological and psychiatric diseases; (iv) taking daily doses of dopamine or a dopamine agonist (L-Dopa equivalent doses are reported in Table 1).

Two patients were excluded from the final sample, see Supplementary Information for details.

The final sample included 16 patients (12 males, 4 females, group average age $= 70.13 \pm 8.56$ years; group average years of education $= 12.19 \pm 3.45$; group average MMSE $= 29.25 \pm 0.68$). Socio-demographic and clinical characteristics of patients who participated in the study are reported in Table 1.

Moreover, 16 HCs were involved in the study as a control group. One HC was not included because he had only one accurate trial in one experimental condition of the motor interaction task. The final sample of HCs comprised 15 participants (9 males, 6 females, group average age $= 70.3 \pm 7.58$ years; group average years of education $= 12.87 \pm 3.54$; group average MMSE $= 28.73 \pm 1.44$). Age, years of education and MMSE scores did not differ between the PD and HCs groups ($P = 0.94$, $P = 0.59$ and $P = 0.57$, respectively).

Table 1. Socio-demographic and clinical characteristics of PD patients

Participants	Gender	Age	Education	Months of illness	UPDRS_ON	UPDRS_OFF	H&Y_ON	H&Y_OFF	MMSE	MMPSE	L_Dopa_ equivalents
1	m	83	8	264	17	22.5	2	2	29	31	870
2	m	59	13	108	17.5	41	2	2.5	29	31	650
3	m	77	13	84	10	41	2	2.5	29	28	750
4	f	71	13	84	19	41	2.5	2.5	30	31	550
5	m	82	8	24	20.5	27	2	2	29	25	312.5
6	f	64	13	156	10	61.5	2	3	29	30	650
7	m	57	18	36	17.5	35.5	2	2	28	31	400
8	m	68	18	144	13	43	2	2.5	29	32	950
9	m	72	13	30	17	35.5	2	2	30	30	425
10	m	73	13	24	20	38	2	1.5	30	30	750
11	m	78	13	288	25.5	40	2.5	2.5	30		650
12	m	60	13	84	23	40	2	2	30	31	725
13	m	79	5	204	18	20	2	2	29	25	400
14	m	69	13	120	14.5	40	2	2.5	30	27	600
15	f	72	13	156	8	35	2	2.5	29	29	600
16	f	58	8	276	35	38	2.5	2.5	28	31	810
Means		70.1	12.2	130.1	17.8	37.4	2.1	2.3	29.3	29.5	630.8

HCs were recruited for the study according to the following criteria: (i) absence of neurological and psychiatric diseases, (ii) absence of psychological and cognitive disorders, (iii) absence of medications with psychotropic action and (iv) MMSE above or equal to 25.

Patients were tested in three different experimental sessions over 3 different days. During the first day they completed a neuropsychological assessment under their daily dopaminergic treatment (factor condition). See Supplementary Information for indication on the neuropsychological assessment and Supplementary Table S1 for all the test results. After this first session, patients were tested in two experimental conditions that were performed on different days, always at the same time of the day, with an intersession interval of 15 days. In the 'Off' Condition patients performed the experimental tasks in the morning, after 18 h of drug withdrawal. In the 'On' Condition they were examined 60 min after their first morning therapeutic dose of levodopa and/or dopamine agonists. The condition was counterbalanced across patients so that half of them performed the first experimental session in 'On' Condition and the other half in 'Off'. HCs performed the task in a single session, after which they were administered the MMSE.

Moreover, to ascertain the efficacy of the dopaminergic medication in improving extrapyramidal motor symptoms, PD patients were administered the UPDRS-Part III (Fahn and Elton, 1987) (a 27-items scale where each item is evaluated on a 5-point Likert scale, ranging from 0 to 4) and the Hoehn and Yahr (Hoehn and Yahr, 1967) (this scale identifies eight illness stages, indicated with the following numbers: 0-1-1.5-2-2.5-3-4-5) scales in both 'On' and 'Off' conditions (see Table1).

The experimental protocol was approved by the ethics committee of the Fondazione Santa Lucia and was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki and later amendments. Participants gave their written informed consent to take part in the study. For indication about the Neuropsychological assessment performed see Supplementary Information.

Experimental task

Stimuli

The stimuli of the motor interaction task were the same used in previous studies (Sacheli *et al.*, 2015a, b, 2018; Candidi *et al.*, 2017; Gandolfo *et al.*, 2019; Era *et al.*, 2020a, 2020b; Moreau *et al.*, 2020; Fini et al., 2021). They consisted of ten grasping movements performed by a virtual partner (five precision and five power grips). See Supplementary Information for details.

Motor interaction task

Participants were requested to perform a well-validated and controlled motor interaction 'Joint-Grasping task' (Sacheli *et al.*, 2015a, 2015b; Candidi *et al.*, 2017; Gandolfo *et al.*, 2019; Era *et al.*, 2020a, 2020b; Moreau *et al.*, 2020; Fini et al., 2021, Figure 1).

In this task, participants' goal can only be achieved by predicting and monitoring the virtual partner's movements and, therefore, adapting to them in real-time in order to grasp an object in synchrony with the virtual partner. Participants sat at a rectangular table, where a bottle-shaped object was located in front of them. The object could be grasped on two different parts: its lower part through a whole-hand grasp (power grip) and its upper part through a thumb-index precision grip (Movement Type factor). The virtual partner was presented on a monitor positioned on the table, behind the bottle-shaped object (Figure 1). Participants started each trial with their right hand positioned over a start-button on the table, and their index finger and thumb touching each other. In different blocks, participants were required to: (i) online monitor the movement of their partner so as to select whether to perform a precision grip or a power grasping based on the movement of the partner as they were asked to perform an opposite or same action compared to that of their partner (Interactive coordination condition) or (ii) follow an auditory instruction, indicating to perform a precision grip or a power grasping regardless of what movement their partner performed (Cued coordination condition), thus without the necessity to predict and monitor the partner's actions. In both coordination conditions, participants were instructed to grasp the bottle-shaped object as synchronously as possible with their virtual partner and did so by performing complementary or imitative actions with respect to it (Interaction type factor). In the imitative condition, participants grasped the same portion of the object as the virtual partner. In the complementary condition, instead, participants grasped the bottle-shaped object on different parts (the virtual partner grasped the lower part via power grip, and the participants grasped the upper part via precision grip, or vice-versa) (Figure 1). In order to promote the need to monitor the virtual partner's actions in the entire experiment, in 36% of trials the virtual partner performed a movement change by switching from a power grasp to a precision grip (or vice versa) during the reaching phase of the movement (Movement correction factor). In each session, participants performed one 44-trial Interactive Imitative, one 44-trial Interactive Complementary, and one 44-trial Cued Imitative and one 44-trial Cued Complementary block (in a counterbalanced order across participants) each comprising half power and precision grips. Thus, participants performed 14 No-Correction and 8 Correction trials (22 power and 22 precision grips) in each condition of the following 2×2×2 design: 2 (Interactive/Cued) ×2 (Complementary/Imitative)×2 (Precision/Power grip). Stimuli presentation and randomization were controlled by

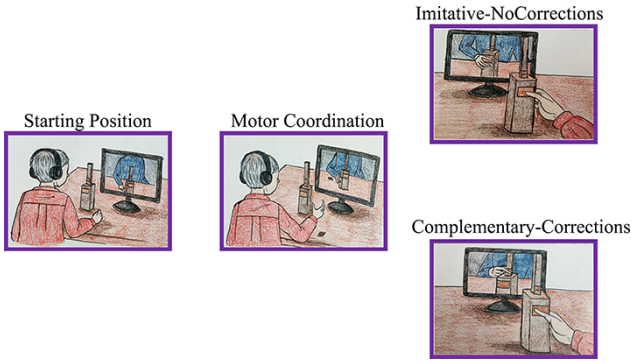

Fig. 1. Illustration of the motor interaction task. Participants were instructed to grasp the object as synchronously as possible with the virtual partner. In the Interactive condition, they were asked to coordinate their action according to the virtual partner's movement as to imitate or complement the movement of the partner (requiring prediction and monitoring of the virtual partners' actions). To increase the need to continuously monitoring the virtual partner's actions, in 36% of the trials the virtual partner performed an unexpected trajectory change from grasping the upper part of the bottle to the lower part, or vice-versa. In the upper part of the illustration participants coordinate their action to perform Imitative Power grips (NoCorrection condition), while in the lower part of the illustration participants are required to perform complementary action with respect to the virtual partner and the virtual partner changes its action from a Power to a Precision grip (Correction condition).

E-Prime2 software (Psychology Software Tools Inc., Pittsburgh, PA). The experimental protocol never lasted more than 45 min to avoid exceeding the time-window of the effect of the dopaminergic therapy. For information about kinematics recordings and their data analyses please see Supplementary Information.

Subjective reports.

At the end of the motor interaction task, participants were asked to answer three questions: (i) to what extent they found the motor interaction to be easy, (ii) to what extent they found it to be enjoyable and (iii) to what extent they found it to be satisfactory. Answers were indicated using a visual analogic 0–100 scale (VAS) in which 0 corresponded to 'not at all' and 100 to 'extremely'.

Experimental design and statistical analysis

We excluded from the analyses the trials in which participants (i) missed the touch-sensitive markers, preventing from recording their responses, (ii) did not respect their Imitative/Complementary or Up/Down instructions, (iii) behavioural values that fell 2.5 s.d.s above or below each individual mean for each experimental condition (outlier trials) (on average, excluded trials of Grasping Asynchrony = 7.7± 5.15% of total).

Statistical approaches

Behavioural measure. We considered as main behavioural measure Grasping Asynchrony (GAsynchr), i.e. the absolute value of time delay between the participant's and virtual partner's touch-time on the bottle-shaped object.

We subtracted from each individual's mean in the Interactive conditions the corresponding individual's means in the Cued conditions. This way, we indexed the participants' ability to perform the motor interaction task (requiring predicting and monitoring the virtual partner's actions), net of their baseline ability in performing precision and power grasping actions as measured in the Cued condition (not requiring predicting and monitoring the virtual partner's actions). To test whether the Condition factor (On/Off medication) influenced the Grasping Asynchrony in the Cued trials, before running the analysis on the subtraction (Interactive minus Cued), we run a *t*-test between Grasping Asynchrony in the 'On' and 'Off' Condition only in the Cued trials. Results showed no significant difference between 'On' and 'Off' Condition [$t(14) = -0.66$, $P = 0.52$], indicating that the Condition factor had no effect on Grasping Asynchrony in the Cued trials. We then subtracted from each individual's mean of Grasping Asynchrony in the Interactive conditions the corresponding individual's means in the Cued conditions. Grasping Asynchrony' data were normally distributed, thus we run three different sets of ANOVAs: (i) a within-participants ANOVA to compare performance of PD patients in the motor interactions task between 'On' and 'Off' Conditions. This ANOVA had Condition (On/Off)× Interaction type (Complementary/Imitative)× Movement Type (Precision/Power grip)× Movement correction (Correction/NoCorrection) as within-subject factors; (ii) a mixed ANOVA, to compare performance of PD patients in 'On' Condition and of HCs in the motor interactions task. This ANOVA had Group (PD_On/HCs) as between-subjects factor and Interaction type (Complementary/Imitative)× Movement Type (Precision/Power grip)× Movement correction (Correction/NoCorrection) as within-subject factors; (iii) a mixed ANOVA to compare performance of PD patients in 'Off' Condition and of HCs at the motor interactions task. This ANOVA had Group (PD_Off/HCs) as between-subjects factor and Interaction type (Complementary/Imitative)× Movement Type (Precision/Power grip)× Movement correction (Correction/NoCorrection) as within-subject factors. Raw means and standard deviations of Grasping Asynchrony are reported in Table 2. All tests of significance were based on an α level of 0.05. Post hoc tests were performed using the Newman–Keuls method when appropriate. Statistical analyses were performed using Statistica 8 software (StatSoft). For all the analyses of the other behavioural and kinematics measures (reaction times, movement times, accuracy, maximum grip aperture and maximum wrist height) see Supplementary Information.

Subjective reports. Because of normality violations, we compared the subjective reports of 'On' and 'Off' Conditions by means of separate Wilcoxon tests for each question. Moreover, we compared the subjective reports of 'On' Condition and HCs, and 'Off' Condition and HCs by means of separate Mann–Whitney U-tests for each question.

UPDRS and Hoehn and Yahr (H&Y). We compared the UPDRS and H&Y scores of 'On' and 'Off' Condition by means of paired sample *t*-tests.

Correlations between behavioural performance, neuropsychological tests and subjective experience during the task. In order to correlate patients' ability to interact and their neuropsychological profile and the subjective experience associated to the appreciation of the interaction, we created an index of patients' ability to interact with the virtual partner by subtracting the grand mean of Grasping Asynchrony in the 'On' Condition from the grand mean of the 'Off' Condition. We then run correlational analyses between this index and the neuropsychological tests assessing executive functions, the UPDRS change associated to the condition ('Off' minus 'On'), and changes in the subjective measure of how much patients enjoyed the motor interaction task due to the condition ('Off' minus 'On').

Results

Description of all significant effects of condition (On/Off) in the within-subject analyses and of Group (PD_Off/PD_On/HCs) in the between-subject analyses of behavioural (i.e. Grasping Asynchrony) and subjective variables (i.e. subjective reports)

Grasping asynchrony

In brief, the within-PD (On/Off) ANOVA revealed a significant main effect of Condition indicating worse performance in the 'Off' compared to the 'On' Condition. This result indicates that in the Interactive trials patients in the 'Off' Condition achieved a worse performance compared to when they were in the 'On' Condition, net of their ability to perform grasping movements in the Cued trials. The between-group ANOVA comparing PD patients in 'On' Condition and HCs showed that the main effect of Group was not significant indicating that participants' performance did not differ between the 'On' Condition and HCs group. Conversely, in the between-group ANOVA comparing PD patients in 'Off' Condition and HCs, the main effect of Group was significant indicating that participants' performance was worse in the 'Off' Condition compared to HCs (see below).

Table 2. Raw means and standard deviations of Grasping Asynchrony in PD 'On' and 'Off' Conditions

	Interactive								Cued							
	Complementary				Imitative				Complementary				Imitative			
	NoCorrection		Correction		NoCorrection		Correction		NoCorrection		Correction		NoCorrection		Correction	
	Precision grip	Power grip	Precision grip	Power grip	Precision grip	Power grip	Precision grip	Power grip	Precision grip	Power grip	Precision grip	Power grip	Precision grip	Power grip	Precision grip	Power grip
Off																
Mean (ms)	363.80	596.60	500.40	598.10	352.50	365.50	385.30	576.60	190.30	279.60	157.10	266.70	176.10	193.20	182.10	235.50
s.d. (ms)	240.50	276.50	231.70	211.10	170.80	231.70	182.70	266.70	52.23	173.90	93.98	188.30	79.90	63.02	60.34	129.00
On																
Mean (ms)	306.90	466.80	422.80	496.50	324.90	300.30	326.70	449.20	171.20	235.80	134.00	200.80	182.30	216.90	202.50	205.60
s.d. (ms)	172.40	244.00	187.70	220.40	175.20	205.40	129.70	169.50	63.40	155.10	115.30	127.50	108.30	120.20	95.44	197.00

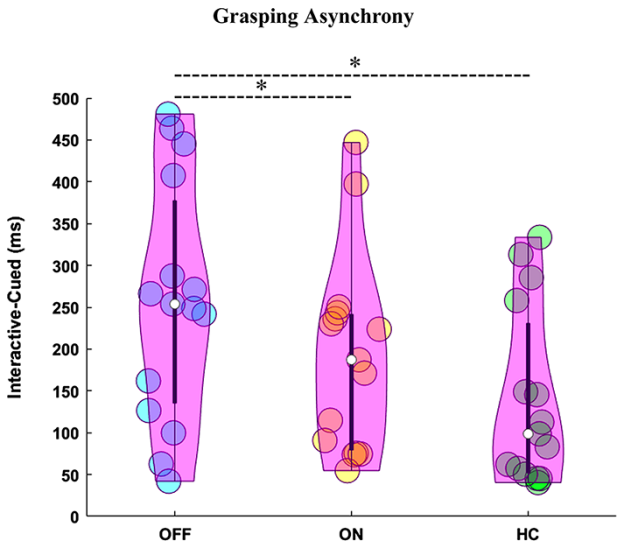

Fig. 2. Participants' performance in the motor interaction task. PD patients in 'Off' Condition achieved worse performance compared to themselves in 'On' Condition and to HCs. PD patients in 'On' Condition, instead, did not differ from HCs. Violin plots display box plots, data density and single subjects' values (dots).

Within-subject ANOVA comparing PD patients in 'On' and 'Off' conditions. The ANOVA on Interactive minus Cued values of Grasping Asynchrony with factors Condition (On/Off), × Interaction type (Complementary/Imitative)× Movement Type (Precision/Power grip)× Movement correction (Correction/NoCorrection) showed a significant main effect of Condition [$F(1, 14) = 6.84$, $P = 0.02$, $\eta p^2 = 0.33$] indicating worse performance (higher Grasping Asynchrony) in the 'Off' ($M = 257.3$, $SE = 36.9$) compared to the 'On' ($M = 193.12$, $SE = 30.$) Condition (Figure 2). This result indicates that when controlling for the patient's ability to perform power and precision grasps in the Cued trials (i.e. requiring to perform grasping actions in synchrony with the virtual partner following an instruction indicating what action to perform, thus not requiring to predict and monitor the virtual partner's actions as in the Interactive condition) patients in 'Off' Condition achieved a worse performance compared to when they were in 'On' Condition.

The Condition factor did not interact significantly with any other factor (all $Ps > 0.2$).

See Table 3 for all the other significant main effects and interactions.

Between-subjects ANOVA comparing PD patients in 'On' condition and HCs. The ANOVA on Interactive minus Cued values of Grasping Asynchrony with factors Group (PD_On/HCs) × Interaction type (Complementary/Imitative)× Movement type (Precision/Power grip)× Movement correction (Correction/NoCorrection) showed that the main effect of Group was not significant [$F\ (1,\ 28) = 1.8$, $P = 0.19$, $\eta p^2 = 0.06$] indicating that participants' performance did not differ between the 'On' Condition and HCs group (Figure 2). The Group factor did not interact significantly with any other factor (all $Ps > 0.10$). See Table 3 for all the other significant main effects and interactions.

Between-subjects ANOVA comparing PD patients in 'Off' condition and HCs. The ANOVA on Interactive minus Cued values of Grasping Asynchrony with factors Group (PD_Off/HCs),× Interaction type (Complementary/Imitative)× Movement Type

Table 3. Significant main effects and interactions of the ANOVAs on Grasping Asynchrony

Within-subject ANOVA Comparing PD patients in 'On' and 'Off' Conditions				
Effect	F	df	P	η^2
Main effect of Condition	6.84	1.14	0.02	0.33
Main effect of Interaction type	13.9	1.14	0.002	0.5
Main effect of Movement correction	15.23	1.14	0.002	0.52
Main effect of Movement Type	11.46	1.14	0.004	0.45
Interaction Interaction type × Movement correction × Movement Type	21.65	1.14	<0.001	0.6
Between-subjects ANOVA Comparing PD patients in 'On' Condition and HCs				
Effect	F	df	P	η^2
Main effect of Interaction type	23.7	1.28	<0.001	0.46
Main effect of Movement correction	38.59	1.28	<0.001	0.58
Main effect of Movement Type	13.76	1.28	<0.001	0.33
Interaction Movement correction × Movement Type	6.66	1.28	0.015	0.19
Interaction Interaction type × Movement correction × Movement Type	39.72	1.28	<0.001	0.59
Between-subjects ANOVA Comparing PD patients in 'Off' Condition and HCs				
Effect	F	df	P	η^2
Main effect of Group	6.65	1.28	0.015	0.19
Main effect of Interaction type	10.14	1.28	0.003	0.27
Main effect of Movement correction	27.56	1.28	<0.001	0.5
Main effect of Movement Type	13.45	1.28	0.001	0.32
Interaction Interaction type × Movement correction × Movement Type	77.92	1.28	<0.001	0.74

(Precision/Power grip)× Movement correction (Correction/NoCorrection) showed a significant main effect of Group [$F(1, 28) = 6.65$, $P = 0.015$, $\eta p^2 = 0.19$] indicating worse performance in the 'Off' Condition (M = 257.3, SE = 32.53) compared to the HCs (M = 138.67, SE = 32.53) group (Figure 2). The Group factor did not interact with any other factor (all *P*s >0.054). See Table 3 for all the other significant main effects and interactions.

Subjective reports

In brief, patients reported the interaction was more enjoyable in the 'On' Condition compared to the 'Off' Condition. Patients did not differ in the 'On' Condition compared to the 'Off' Condition in how much they found the interaction to be easy and satisfactory. Patients in the 'On' Condition reported the interaction was less enjoyable compared to HCs and found it to be more difficult. Patients in the 'On' Condition did not differ from HCs in how much they found the interaction to be satisfactory. Patients in the 'Off' Condition reported the interaction was less enjoyable compared to HCs and found it less satisfactory. Patients in the 'Off' Condition did not differ from HCs in how much they found the interaction to be easy. (See below).

Wilcoxon tests comparing PD patients in 'On' and 'Off' conditions

Wilcoxon tests showed a marginal significance when comparing how much patients enjoyed the interaction with higher values in 'On' (M = 77.56, s.d. = 18.80) than 'Off' (M = 62.69, s.d. = 27.26) Condition (Z= 1.96, $P = 0.05$) (Figure 3). Patients did not differ in the 'On' Condition compared to the 'Off' Condition in how much they found the interaction to be easy (Z = 1.03, $P = 0.3$) and satisfactory (Z = 0.83, $P = 0.4$).

Mann–Whitney U-tests comparing PD patients in 'On' condition and HCs

Mann–Whitney U-tests showed that patients in the 'On' Condition (M = 77.56, s.d. = 18.80) enjoyed the interaction significantly less (Z = –2.08, $P = 0.037$) compared to HCs (M = 90.40, s.d. = 13.39) (Figure 3) and found it to be more difficult (M 'On' = 76.75, s.d. =19.17, M HCs = 87.47, s.d. = 15.98) (Z = –2.02, $P = 0.037$). Patients in the 'On' Condition did not differ from HCs in how much they found the interaction to be satisfactory (Z = –1.8, $P = 0.07$).

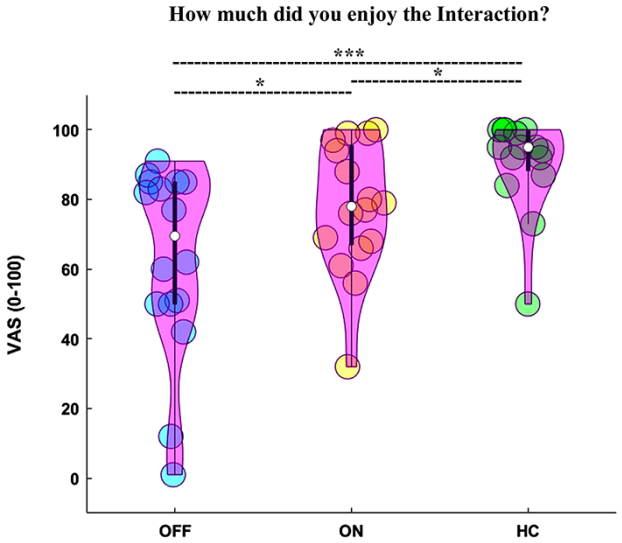

Fig. 3. Subjective motivation during the motor interaction task. PD patients in 'Off' Condition reported to enjoy the interaction less, compared to themselves in 'On' Condition and to HCs. Both PD patients in 'Off' and 'On' Condition enjoyed the interaction less compared to HCs. Violin plots display box plots, data density and single subjects' values (dots).

Mann–Whitney U-tests comparing PD patients in 'Off' condition and HCs

Mann–Whitney U-tests showed that patients in the 'Off' Condition (M = 62.69, s.d. = 27.26) enjoyed the interaction significantly less (Z = –3.7, $P < 0.001$) compared to HCs (M = 90.40, s.d. = 13.39) (Figure 3) and found it less satisfactory (M 'Off' = 77.25, s.d. =23.38, M HCs = 94.73, s.d. = 4.96) (Z = –2.92, $P = 0.003$). Patients in 'Off'

Condition did not differ from HCs in how much they found the interaction to be easy ($Z = -1.3$, $P = 0.19$).

UPDRS and H&Y

UPDRS scores were significantly higher in 'Off' ($M = 37.44$, s.d. = 9.37) compared to 'On' ($M = 17.84$, s.d. = 6.58) Condition ($t(15) = -6.25$, $P < 0.001$). Similarly, a significant difference emerged also in the H&Y scores between 'Off' ($M = 2.28$, s.d. = 0.17) and 'On' ($M = 2.08$, s.d. = 0.36) Condition ($t(15) = -3.31$, $P = 0.035$). These results confirm the efficacy of the dopaminergic medication in improving patients' extrapyramidal symptoms.

Correlations between behavioural performance, neuropsychological tests and subjective experience during the task

No correlation resulted to be significant (all $Ps > 0.03$, correct P value: $0.05/8 = 0.006$).

Discussion

The main result of the present study is that, after controlling for the individual's ability to perform a reach-to-grasping motor task in non-interactive conditions (i.e. Cued, control, condition), PD patients in 'Off' medication state showed difficulties in performing the task in an Interactive condition compared to PD patients in 'On' state. Moreover, their performance was lower than that of HCs, independently from whether the virtual partner performed a Correction or a NoCorrection trial. PD patients in 'On' state, instead, did not differ from HCs in their performance in the Interactive condition, suggesting that dopaminergic medication facilitates PD patients' ability to successfully coordinate with a virtual partner when predictions and monitoring of its actions are needed. Moreover, while both PD patients in 'Off' and 'On' states reported enjoying the interaction with the virtual partner less than HCs, PD patients in 'Off' state also reported enjoying the motor interaction less compared to when in 'On' state. These results indicate a role of the DAS in supporting motor coordination abilities during interpersonal motor interactions. These abilities are based on prediction and monitoring of the partner's actions, as well as on integration of predictions concerning one's actions and those of the partner and likely rely on the activity of a variety of brain regions. Previous studies highlight the engagement in motor interaction tasks of fronto-parietal regions (Novembre *et al.*, 2014; Hadley *et al.*, 2015; Sacheli et al., 2015a; Sacheli *et al.*, 2018; Era *et al.*, 2018, 2020a; Moreau *et al.*, 2020; Dumas *et al.*, 2020; Boukarras *et al.*, 2022), including the primary motor cortex (Novembre *et al.*, 2014), the dorsal premotor cortex (Hadley *et al.*, 2015), the temporo-parietal junction (TPJ, Decety and Lamm, 2007; Era *et al.*, 2020a) and the anterior intra-parietal sulcus (aIPS, Sacheli et al., 2015a; Era *et al.*, 2018, 2020a; Sacheli *et al.*, 2018), implicated in sensorimotor transformations (Freund, 2001) and motor simulation (Aglioti *et al.*, 2008; Panasiti *et al.*, 2017; Özkan *et al.*, 2019), and also the medial-frontal cortex and the medial parietal cortex (Moreau *et al.*, 2020; Ninomiya *et al.*, 2020 for a study in the monkey) implicated in performance monitoring (Cohen *et al.*, 2008; Fattori *et al.*, 2015). Besides the role of fronto-parietal regions in supporting interpersonal motor interactions, also subcortical structures have been suggested to play a role in social behaviour (Straulino *et al.*, 2016b). Here we suggest that the functionality of the corticostriatal circuits based on dopaminergic activity supports the ability to flexibly adapt one's own motor behaviour to a partner's action during interpersonal motor interactions.

Role of the Dopaminergic system in action monitoring and programming during motor interactions

Successfully interacting with others requires planning one's own actions and flexibly adapting them based on prediction and monitoring of the interactor's actions (Bekkering *et al.*, 2009; Vesper *et al.*, 2010). In the task employed in the present study, the inclusion of the Correction condition (in which the virtual partner unexpectedly changed the performed action, from a power to a precision grip or vice-versa) boosted the need for participants to monitor the virtual partner's actions also when no change in its behaviour would happen (NoCorrection condition). In fact, a previous study using the very same experimental task showed that an increase in the activity of the performance monitoring system (indexed by an increase in midfrontal theta activity) occurred not only when healthy participants interacted with a virtual partner performing unexpected changes of its actions but also when these changes did not occur (NoCorrection condition, Moreau *et al.*, 2020), suggesting that interactive conditions require an increased monitoring activity. This is in line with the idea that midfrontal theta power may play a role not only in reactive cognitive control, that is the detection and resolution of cognitively demanding events after their onset (specific of the Interactive-Correction trials), but also in proactive cognitive control, that is the anticipation and prevention of cognitively demanding events before they occur (Common to both Interactive-Correction and Interactive-NoCorrection trials) (Braver, 2012). In a recent study (Boukarras *et al.*, 2022), we showed that delivering frontal theta tACS while participants were engaged in interpersonal motor interactions, improved their coordination abilities in both Correction and NoCorrection trials, suggesting that frontal theta tACS might have boosted endogenous neural oscillations that facilitated proactive cognitive control. Moreover, midfrontal theta oscillations have been proposed to depend on dopaminergic activity (Parker *et al.*, 2015) and to be altered in PD patients (Singh *et al.*, 2018).

PD patients are characterized by cognitive difficulties (Robbins and Cools, 2014), including an altered activity of the performance monitoring system (Falkenstein *et al.*, 2001; see Pezzetta *et al.*, 2021 for a review). Behaviourally, PD patients in 'Off' medication state present difficulties in tasks requiring to flexibly adapt to changes in stimulus–response requirements (task-set shifting, Cools *et al.*, 2001) and in tasks requiring action reprogramming in response to unexpected events happening in a predictable sequence of events (Galea *et al.*, 2012). In both contexts, dopaminergic medication restored the patient's performance (Cools *et al.*, 2001; Galea *et al.*, 2012). Similarly, a study in healthy participants shows that the pharmacological block of dopamine receptors results in altered programming of a new motor response to an unpredictable event happening in a predictable sequence (Bestmann *et al.*, 2014). These authors suggest that, in line with the active inference model (Friston *et al.*, 2012), dopamine would play a role in balancing the weight attributed to top–down prior expectations (in this case responding to a predictable event) and bottom–up sensory information (the current event), allowing for efficient and flexible responses to unexpected sensory events (Galea *et al.*, 2012; Bestmann *et al.*, 2014).

In the present study PD patients in 'Off' state showed difficulties in coordinating with a virtual partner which could or could not change its action during the interaction. Conversely, dopaminergic medication improved PD patients' ability to perform the motor interaction task, as behavioural performance of PD patients in 'On' state did not differ from the one of HCs. Patients needed

to continuously monitor the virtual partners' action to efficiently interact with it, reproducing a real-life interactive context. We suggest that reduction of dopamine level in 'Off' state and the resulting dysfunction in the fronto-striato-thalamo-cortical circuits may result in difficulties in programming effective and flexible motor behaviour during interpersonal interactions. Thus, that dopaminergic medication influenced interactive abilities in both Interactive Correction and NoCorrection trials in our study may suggest that it affected proactive cognitive control, known to be impaired in PD patients (Bonnin *et al.*, 2010) and required in interpersonal motor interactions (Boukarras *et al.*, 2022).

Role of the Dopaminergic system in visuo-motor integration during motor interactions

Programming effective and flexible motor behaviour during interpersonal interactions also requires the integration of predictions regarding executed and observed actions (Vesper *et al.*, 2010; Era *et al.*, 2019). PD patients have difficulties in visuo-motor control during individual manual tasks, emerging before motor symptoms (Hocherman and Giladi, 1998) and depending on sensorimotor processing deficits (Chen *et al.*, 2016). Moreover, dopaminergic medication in PD patients improves visuomotor control, by improving the sensorimotor system' ability to anticipate error signals and consequently plan adaptive responses in advance (Chen *et al.*, 2016). Dopaminergic medication in PD patients also modulates the activity of cortical regions implicated in motor functions, including the parietal cortex, resulting in higher activity of bilateral parietal cortices during motor tasks (Mattay *et al.*, 2002). Anatomical studies have shown that the basal ganglia are connected to several cortical areas subserving different cognitive functions (Middleton and Strick, 2000). Interestingly, studies with monkeys have shown that the basal ganglia are connected to the area AIP (Clower *et al.*, 2005), that is the homologous of the human anterior intraparietal sulcus (aIPS) in the monkey. More specifically, since the aIPS is known to play a role in controlling reaching movements (Tunik *et al.*, 2007; Desmurget *et al.*, 2009) and coding for reaching goals (Hamilton & Grafton, 2006), the aIPS might communicate relevant signals with the basal ganglia to control reaching movements and plan their goal. The aIPS, indeed, has been shown to play a causal role, together with the functionally connected network, in integrating predictions of one's own and others' complementary actions during interpersonal motor interactions in the very same task used in the present study (Sacheli et al., 2015a; Era *et al.*, 2018, 2020a; Sacheli *et al.*, 2018).

In the present study, the fact that PD patients in 'Off' medication state achieved a worse performance in the Interactive condition compared to PD patients in 'On' state suggests that the altered functioning of fronto-striato-thalamo-cortical circuits in PD patients in 'Off' state may result in altered inputs to the aIPS and thus in altered integration of predictions about to-be-performed and observed actions that are fundamentally important for interpersonal motor interactions.

Role of the Dopaminergic system in encoding motivation during motor interactions

Interacting with others seems to be a rewarding experience (Godman, 2013). Tellingly, reward-related brain regions, including the ventral striatum, are activated when individuals engage in direct eye contact (Schilbach *et al.*, 2010; Pfeiffer *et al.*, 2014) and cooperate with other individuals (Rilling *et al.*, 2002). Moreover, dopaminergic neurons play a central role in reward-seeking behaviour (Wise, 2004; Mazzoni *et al.*, 2007). The rewarding experience associated to social interactions may motivate individuals towards efficient interactions. As far as motor interactions are concerned, using the very same interactive task used in the present study, we have shown that participants achieve a better performance when interacting with a low status individual when they have an implicit preference towards them (Boukarras *et al.*, 2021) and that individuals perform better during motor interactions when interacting with someone whose help is highly needed (when guessing abstract compared to concrete concepts, Fini *et al.*, 2021). These results suggest that individuals' motivation during motor interactions influences the success of the interaction itself. In the present study PD patients in 'Off' medication state reported enjoying the interaction less compared to PD patients in 'On' state. Thus, PD patients in 'Off' state were possibly less motivated during the interaction. The same PD patients in 'Off' state reported no differences compared to when they were in 'On' state and compared to HCs concerning the perception of task difficulty. That PD in 'Off' state found the interaction less enjoyable is in line with previous studies, showing that PD patients in 'Off' state do not differentiate their motor behaviour based on the social (compared to individual) context in which they act, differently from what is observed in HCs and in PD patients in 'On' state. These results suggest that dopamine levels may influence individuals' motivation during social interactions and thus shape the way they act in social contexts (Straulino *et al.*, 2015, 2016a, 2016b). It has been suggested that motivation and cognitive control may interact in promoting successful goal-directed behaviour. More specifically, reward incentives seem to especially improve proactive, anticipatory (Goschke and Bolte, 2014; Mäki-Marttunen *et al.*, 2019) cognitive control. Dopamine is suggested to play a key role in the motivation-cognitive control interaction, modulating the activity of both striatum and prefrontal cortex (Yee and Braver, 2018). We may thus hypothesize that higher motivation during motor interactions contributed to better performance during our motor interaction task. However, we did not find a correlation between higher motivation and behavioural performance in 'On' compared to 'Off' state. It is worth noting that subjective motivation was only measured at the end of the motor interaction task and was thus not measured separately for the Interactive condition, in which we found the effect of dopaminergic medication on task performance. Thus, we run the correlation between a generic improvement in the task (Collapsing Cued and Interactive trials) and the higher motivation in 'On' compared to 'Off' state. This may explain why we did not observe a correlation between the two indexes. Moreover, in the present study we did not manipulate reward in the interaction task, differently from previous studies in which a relation between cognitive control and motivation was observed (Yee and Braver, 2018). Thus, future studies are needed to better explore the role of dopamine in modulating relationship between motivation and behavioural performance during interpersonal motor interactions.

Conclusions

We investigated, for the first time to the best of our knowledge, the role of the DAS in supporting PD patients' ability to coordinate their action with a virtual partner. The main results are that PD patients in 'Off' state performed worse, and enjoyed the interaction less, compared to HCs and to their own performance in 'On' state. Conversely, dopaminergic medication improved patients' ability to perform the motor interaction task and resulted in a more enjoyable experience. These results indicate that the ability to flexibly adapt one's own motor behaviour to a partner's action

during interpersonal motor interactions may depend not only on the isolated activity of fronto-parietal regions but also on the functionality of dopaminergic corticostriatal circuits. Future studies are needed to directly investigate the influence of dopamine on the functioning of corticostriatal circuits during interpersonal motor interactions.

Acknowledgements

We thank Anna Bianco for the drawings in Figure 1. We thank BrainTrends for building the experimental set-up. BrainTrends has no financial or intellectual conflict of interest in connection with the manuscript. We thank Gaetano Tieri, Virtual Reality Lab, Unitelma Sapienza for implementing the virtual partner.

Funding

V.E. was supported by the Fondazione Umberto Veronesi and by the BE-FOR-ERC Grant from Sapienza University of Rome; M.C. was supported by the Italian Ministry of Health (Ricerca Finalizzata, Giovani Ricercatori 2016, n. GR-2016-02361008) and Sapienza University (Progetti di Ricerca Grandi 2020); S.M.A. was supported by the European Research Council (ERC) Advanced Grant 2017, Embodied Honesty in real world and digital interactions (eHONESTY, 789058) and by the PRIN grant (Italian Ministry of University and Research, Progetti di Ricerca di Rilevante Interesse Nazionale, Edit. 2017, Prot. 2017N7WCLP).

Conflict of interest

The authors declare no competing financial interests.

Supplementary data

Supplementary data are available at *SCAN* online.

Data availability statement

Data are available at https://osf.io/nsd4q/.

Author contributions

V.E., M.C and S.M.A. conceived the original idea, V.E., M.C. and S.M.A. designed the experimental paradigm, S.Z. and S.T. recruited the patients and performed the neuropsychological assessment, A.P. recruited the patients and performed the neurological assessment, V.E., S.D. and C.P. collected and processed the data, V.E. performed statistical analyses, V.E., R.P., M.C. and S.M.A. interpreted the results, V.E., M.C., R.P. and S.M.A. prepared the original version of the manuscript, all the authors revised the manuscript and approved its final version, M.C., A.C., G.A.C., S.M.A. supervised the project.

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