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Testing the dopamine overdose hypothesis in action control: A study in people with Parkinson's disease

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Abstract

Prior work on patients with Parkinson's disease (PD) has shown that the administration of dopaminergic medication in the early to intermediate stages of PD benefits (motor) functions associated with the dopamine-depleted dorsal striatal circuitry but may 'overdose' and interfere with (cognitive) functions associated with the relatively intact ventral striatal circuitry. The present study aimed to elucidate this so-called *dopamine overdose hypothesis* for the action control domain. Using a within-subject design in a sample of 13 people with PD, we evaluated the effect of dopaminergic medication on two cognitive processes underlying goal-directed behaviour, namely action selection and initiation through event binding and conflict adaptation. We also investigated whether individual differences in the magnitude of medication effects were associated across these processes. Results showed no indications that dopaminergic medication affects action selection and initiation or conflict adaptation in PD patients. Additionally, we observed no correlations between both cognitive processes nor between individual differences in medication effects. Our findings do not support the notion that dopaminergic medication modulates action control processes, suggesting that the dopamine overdose hypothesis may only apply to a specific set of cognitive processes and should potentially be refined.

KEYWORDS
action control, dopamine, movement, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder associated with dopamine (DA) depletion in the striatum. It is characterized primarily by motor deficits such as resting tremor, bradykinesia and rigidity, but many patients additionally experience problems in non-motor domains (e.g. cognition, emotion, sleep; for reviews see Dirnberger & Jahanshahi, 2013; Schapira et al., 2017). While patients generally take DA medication to relieve their motor symptoms, there are indications that such medication can at the same time hinder various cognitive processes including those underlying action control (Duthoo et al., 2013; Ruitenberg et al., 2016, 2021). This set of findings may be captured by the *DA overdose hypothesis* (Cools et al., 2001; for a review, see Vaillancourt et al., 2013). The hypothesis is based on the asymmetrical decline of DA levels in the dorsal versus ventral striatum in the relatively early stages of PD. In the early to moderate stages of the disease, DA depletion is evident in the dorsal striatum and associated cortical areas. In contrast, DA levels in the ventral striatum and associated areas remain relatively intact and only start to reduce in later stages of the disease. Consequently, while dopaminergic medication restores the DA level in the dorsal striatal circuitry and remediates associated functions, it overdoses the intact DA level in the ventral striatal circuitry and impairs functions relying on (networks involving) this structure.

Successful motor performance is typically not only dependent on the ability to physically generate accurate movement but also on action control processes that allow for the maintenance of goal-directed behaviour in the face of uncertain and/or changing contexts (McDougle et al., 2016; Prinz et al., 2009; Ruitenberg et al., 2015). Two core cognitive processes underlying goal-directed action are (i) the intentional selection of a goal-directed action and (ii) the shielding of the selected action against potent but irrelevant information of response tendencies (i.e. conflict adaptation). As we will outline below, exploring the effect of dopaminergic medication on these two action control processes in the same sample of people with PD can provide clear empirical tests on core assumptions and predictions from the DA overdose hypothesis in this domain. In brief, the overdose hypothesis predicts that intentional selection benefits from DA medication as this process relies on brain areas that are part of the dorsal striatal circuitry (Melcher et al., 2008), while conflict adaptation is predicted to be negatively affected as it relies on brain areas that are part of the ventral striatal circuitry (Botvinick et al., 2001, 2004; Grandjean et al., 2013). To the best of our knowledge, such combination of goal-directed action control tasks has never been examined within a single sample of people with PD.

Intentional action selection

A prominent perspective on how people intentionally select and initiate actions builds on the notion that associations (i.e. bindings) form between an action and its specific perceptual outcomes (Dignath et al., 2019; Frings et al., 2020; Hommel, 2004, 2019; Hommel et al., 2001). According to the *Binding and Retrieval in Action Control* framework (BRAC; Frings et al., 2020) and the *Theory of Event Coding* (TEC; Hommel et al., 2001), the perceptual and motor features of an event become integrated through experience and are bound together in so-called *event-files*. The binding of these features (i.e. visuomotor binding) into such unitary representations is a basic process, and it has been proposed that event files allow for the control of intentional behaviour. Specifically, the intentional selection and initiation of a goal-directed action is enabled by the (intentional) retrieval and activation of particular anticipated and desired effects—this co-retrieves and activates the corresponding action features via stored event files (Hommel & Wiers, 2017).

One specific and robust empirical observation supporting the above perspective on action control stems from studies using the event-file task (sometimes also called S1R1-S2R2 task; for a review, see Frings et al., 2020). In this task, people perform an arbitrary response (R1) following a stimulus presentation (S1)—thus creating an event file (E1). Immediately after, a second imperative stimulus (S2) is presented to which the participant must respond (R2) based on predefined stimulus–response rules for S2. In healthy adults, R2 performance is typically impaired when the perceptual stimulus features repeat (i.e. S1 = S2) while the required action changes (i.e. R1 ≠ R2), or when the action repeats (i.e. R1 = R2) while the stimulus changes (i.e. S1 ≠ S2), as compared to when the stimulus and required action both repeat or both change (Frings et al., 2020; Hommel, 2004; Ruitenberg & Koppelmans, 2021). The performance decline in partial changes as compared to full/absent changes is attributed to the need to break down the previously stored event file (E1) as some but not all of its ingredients should be re-used for the second S2-R2 event (Fournier & Gallimore, 2013; Hommel, 2004, 2019; Mattson et al., 2012). As stimulus and action features are assumed to be integrated in a unitary representation, reactivation of one feature also activates the other features with which it is associated. Hence, re-encountering a specific feature leads to the re-activation of the entire event file it was recently part of, and current stimulus–response rule execution is hindered in the case of partial overlap—thus resulting in suboptimal selection and initiation.

Colzato et al. (2012) investigated the effect of dopaminergic medication on such event binding in a group of PD patients, who performed the task once ON and once OFF their medication. Results showed that the performance difference between partial changes and full/absent changes (known as the *partial repetition cost*; PRC) was larger when patients were ON their medication than when they were OFF medication. In line with the notion that event binding is associated with brain areas that are part of the dorsal striatal circuitry (Melcher et al., 2008), these findings suggest that the retrieval and updating of S-R events in PD patients is positively affected by medication.

Conflict adaptation

The second action control process core to the present study is conflict adaptation, which refers to the modulation of attentional settings and adjustment of ongoing behaviour in response to changing situational demands, to maintain goal-directed behaviour. In the lab, conflict adaptation can be studied via conflict paradigms where relevant and irrelevant stimulus features (e.g. ink colour and word meaning in the Stroop task) trigger responses that are either the same without causing conflict (i.e. congruent trials) or in competition with each other yielding conflict (i.e. incongruent trials)—with people typically performing worse on the latter. Prior work has shown that this so-called congruency effect is modulated by previous trial congruency (i.e. *congruency sequence effect*; for a review, see Duthoo et al., 2014) and by the relative proportion of congruent and incongruent trials (i.e. list-wide *proportion congruency effect*; for a review, see Bugg & Crump, 2012). Specifically, the congruency effect is typically reduced after an incongruent trial and in settings with higher proportions of incongruent trials than congruent trials. These observations are often taken to indicate that humans possess a set of adaptive control processes that dynamically adjust processing selectivity in response to changes in the environment or the detection of conflict, with the goal of resolving this conflict and/or preventing subsequent occurrences of conflict (Braem et al., 2019).

Two prior studies tested the effect of dopaminergic medication on conflict adaptation in people with PD. In line with the notion that this function is thought to rely on brain areas that are part of the ventral striatal circuitry (Botvinick et al., 2001, 2004; Grandjean et al., 2013), Duthoo et al. (2013) found that DA medication impaired transient conflict adaptation as reflected in the congruency sequence effect in PD. In contrast, Ruitenberg et al. (2019) found no indications that dopaminergic medication modulated more sustained conflict adaptation as indicated by the proportion congruency effect in PD. This discrepancy led to the proposition that transient, reactive control that has been linked to the congruency sequence effect may be differently affected by dopaminergic medication than more sustained, proactive

cognitive control processes that are at play in the list-wide proportion congruency effect (Ruitenberg et al., 2019), yet this has not been examined further. Here, we therefore assess another hallmark of transient conflict adaptation, namely the item-specific proportion congruency (ISPC) effect (Jacoby et al., 2003), to test the idea that reactive control processes would be sensitive to dopaminergic medication status. The ISPC effect refers to the observation that the congruency effect is typically reduced for items that are mostly presented in an incongruent manner as compared to items that are mostly presented in a congruent manner.

The present study

In the current study, we thus explore the effect of dopaminergic medication on action selection and initiation through event binding and conflict adaptation in order to further test predictions from the DA overdose hypothesis and thereby to replicate and extend prior work. By measuring two action control processes within the same group of individuals with PD we can test the generality of the DA overdose effect. More specifically, we used a within-subject design in which people with PD perform the action selection and initiation through event binding and conflict adaptation tasks once ON and once OFF their regular medication. We hypothesized that (1) intentional action selection and initiation as reflected in the PRC is enhanced by dopaminergic medication, whereas (2) reactive, transient conflict adaptation as reflected in the ISPC effect is impaired by dopaminergic medication. Finally, whereas prior studies mostly evaluated action control components in isolation (for a review, see Ruitenberg et al., 2021), our within-subject design allowed us to explore whether modulating effects of dopaminergic medication on action control are *associated within* individuals. Such an intraindividual association of medication effects would point towards a shared underlying DA mechanism for action control components, whereas the absence of an association could be taken as an indication that they are relatively independent.

METHODS

Participants

Our sample consisted of 13 patients diagnosed with mild to moderate-stage PD (aged 45–75 years, M = 61, 8 M/5 F; Hoehn and Yahr stages 1–2; Hoehn & Yahr, 1967). We also compared their performance to that of a sample of 53 healthy control (HC) subjects who completed the same experimental tasks as part of a prior larger study (Ruitenberg & Koppelmans, 2021). The HCs were in the same age range as the PD group (aged 45–75 years, M = 59, 20 M/33 F) and also matched the PD group in terms of gender, $\chi^2(1) = 2.42$, $p = .12$, and general cognitive abilities as assessed by the MoCA (see below), $t(64) = 0.28$, $p = .78$. According to Annett's (1970) Handedness Inventory 10 PD patients and 51 HCs could be classified as right-handed (the remaining participants were left-handed). All participants reported to have good eyesight (i.e. no colour blindness; corrective glasses or contact lenses were permitted). Written informed consent was obtained from all participants. PD patients received a compensation of €25 per test session for their participation; HCs were not compensated. The study was approved by the Ethical Board of the local University Hospital.

Experimental tasks

The experimental tasks used in this study have been described in detail and visualized in Ruitenberg and Koppelmans (2021). Stimulus presentation, timing and response registration were controlled by E-Prime © 2.0 software, running on a Dell Latitude E5540 laptop computer. Responses were given on a standard qwerty computer keyboard connected to the laptop.

In brief, we used the event-file task to assess action selection and initiation through event binding. In this task, participants were instructed to respond to two successive stimuli (S1 and S2) that varied in shape and colour. The first response (R1) was cued before S1 presentation, by either a left or a right arrow. Upon presentation of S1, participants had to respond in line with the direction of the arrow, irrespective of the stimulus that was presented. The second response (R2) was based on a predefined decision rule related to the shape of S2 (i.e. colour was an irrelevant stimulus feature). Participants were presented 10 practice trials, after which they completed five experimental blocks of 32 trials each. The main outcome measure for this task is the so-called partial repetition costs (PRC; see Hommel, 2004; Hommel et al., 2011). The subject-specific PRC for the task-relevant visuomotor binding between shape and response is calculated as the difference between the mean RT for partial repetitions (shape repeated and response alternated, or vice versa) and the mean RT for complete repetitions and alternations (shape and response both repeated or both alternated). Larger PRC values represent stronger, less flexible binding. For the sake of completeness, we used similar calculations to determine PRCs for the binding between colour and response (task-irrelevant visuomotor binding) and between shape and colour (visuoperceptual binding).

To assess conflict adaptation, we used the Stroop task in which participants were instructed to respond to the ink colour of stimuli consisting of colour words displayed in a specific ink colour. Stimuli consisted of eight colour words (red, yellow, green, blue, violet, orange, pink and brown) that were used as words as well as ink colours (the Dutch words were 'rood', 'geel', 'groen', 'blauw', 'paars', 'oranje', 'roze' and 'bruin'). Two different subsets of four colours each were used (set 1: red–yellow–violet–brown, set 2: green–blue–pink–orange; *cf.* Geukes et al., 2015), such that individuals with PD who completed two test sessions performed the task with a different subset on each session to avoid learning effects. Participants were presented 16 randomly ordered practice trials (50% congruent) and then completed four experimental blocks of 160 trials each. For half of the stimuli across the experiment, the relevant and irrelevant stimulus features (i.e. ink colour and word meaning) triggered responses that are either the same without causing conflict (i.e. congruent trials), whereas in the other half they were in competition with each other yielding conflict (i.e. incongruent trials). This means that across the entire task, the proportion of (in)congruent stimuli was 50%. Importantly, however, we manipulated the proportion of (in)congruent trials of individual items in the task such that some words were in a congruent word-colour combination on 80% of the trials (i.e. multiple congruent items), while others were presented in such a congruent combination on only 20% of the trials (i.e. multiple incongruent items). This allowed us to evaluate the ISPC effect, a hallmark indicator of conflict adaptation (Jacoby et al., 2003). The ISPC effect is calculated by subtracting the difference in performance between incongruent and congruent trials on 20% congruent items from the difference on 80% congruent items; larger ISPC values represent more conflict adaptation.

Procedure

At the start of the test session participants were informed about the procedure and provided written informed consent. They completed a short interview, the experimental tasks, and several paper-and-pencil questionnaires. We used the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) and the Dutch Reading Test for Adults (the Dutch version of the National Adult Reading Test; Schmand et al., 1992) to assess participants' global cognitive abilities and verbal intelligence, respectively. We also screened participants for signs of clinical depression using a Dutch translation of the Beck Depression Inventory-II (BDI-II-NL; Beck et al., 1996). PD patients also completed a series of additional assessments. We used Dutch translation of the Profile of Mood States (POMS) questionnaire to control for differences in mood state between the two medication states and test sessions. Furthermore, we used the PDQ-8 (Jenkinson et al., 1997) to evaluate patients' quality of life, as well as the FOG-Q (Giladi et al., 2009) and the WOQ-9 (Stacy et al., 2006) to determine whether patients experienced freezing of gait and wearing off (i.e. end-of-dose effects), respectively. Finally, we used the Unified Parkinson's

Disease Rating Scale (UPDRS) motor subscale to assess motor symptoms. For the PD patIents, the MoCA, POMS and UPDRS were administered during both sessions, whereas the other questionnaires were administered during the first session only.

As mentioned above, PD patients performed the experimental tasks during two sessions, allowing us to evaluate the effect of dopaminergic medication. ON medication, patients were tested on average 2.3 h (*SD* = 1.8; range 0.5–7 h) following their last medication intake. When assessed OFF medication, testing took place after overnight withdrawal from patients usual medication (*M* = 17.5 h, *SD* = 3.6; range 13–26 h). Previous work has shown that after a 12 h withdrawal period levodopa blood plasma concentrations are reduced to zero (Crevoisier et al., 2003; Gasser et al., 1999). The order of medication status at the two sessions was counterbalanced, with seven patients first being tested ON medication, and six other patients first performing the tasks OFF their medication. The sessions were separated on average by 8.2 days (range 5–17 days).

Data processing

For the PRC analyses, we filtered out incorrect responses to S2 as well as responses >2000 ms or <200 ms (*cf.* Colzato et al., 2012). For the ISPC analyses, we excluded the first trial of each block, as well as error and post-error trials. We also excluded trials when the RT exceeded the mean RT by more than 3 standard deviations. This was done separately for each proportion and congruency condition for each participant and additionally per medication status for each patient.

To analyse differences in PRCs and the ISPC effect between PD patients ON versus OFF medication as well as between patients and controls, we used both the more traditional null-hypothesis significance testing approach (NHST; via SPSS software, version 26.0; IBM Corp, 2019) and a Bayesian approach with default prior settings (via JASP software, version 0.14.0; JASP Team, 2020). Table 1 presents the RTs for each of the conditions in our experimental tasks as well as the PRC and ISPC effects separately for the PD patients ON versus OFF medication and controls. As the analyses on PRCs and the ISPC

TABLE 1 *Event-file task*: Mean ± *SD* RTs (in ms) for responses to the second stimulus as a function of the relationship between the responses (repetition vs. alternation from R1 to R2) and the task-relevant stimulus shape (repetition vs. alternation from S1 to S2). *Stroop task*: Mean ± *SD* RTs (in ms) for responses to congruent and incongruent stimuli as a function of proportion (80% vs. 20% congruent). The rightmost column shows the mean ± *SD* partial repetition cost (PRC in ms) and item-specific proportion congruency effect (ISPC in ms).

Event-file task					
	Response repeated		**Response alternated**		
DA status	**Shape repeated**	**Shape alternated**	**Shape repeated**	**Shape alternated**	**PRC**
HC	647 ± 134	699 ± 133	656 ± 134	665 ± 128	21 ± 76[a]
PD_{OFF}	681 ± 258	724 ± 269	666 ± 254	697 ± 286	6 ± 67
PD_{ON}	692 ± 226	759 ± 270	693 ± 257	714 ± 262	23 ± 76
Stroop task with ISPC manipulation					
	80% Congruent items		**20% Congruent items**		
DA status	**Congruent**	**Incongruent**	**Congruent**	**Incongruent**	**ISPC**
HC	1000 ± 226	1187 ± 291	1057 ± 271	1081 ± 273	163 ± 126[a,b]
PD_{OFF}	1159 ± 584	1427 ± 584	1298 ± 553	1357 ± 684	210 ± 156[a]
PD_{ON}	1126 ± 333	1435 ± 603	1230 ± 451	1246 ± 497	293 ± 258[a,b]

[a]Significantly different from zero; $p < .05$.

[b]Significant group difference; $p < .05$.

effect below could have obscured patterns of main and interaction effects regarding these conditions, the Supporting Information presents the results of analyses that evaluated the effects of condition in each experimental task.

RESULTS

Clinical and neuropsychological assessments

The demographic and clinical characteristics of the PD patients are listed in Table 2. Scores on the Reading Test indicated that IQ estimates were within the normal range and did not differ between patients (M = 117.62, SD = 11.76) and controls (M = 119.34, SD = 6.93), $t(64) = 0.51$, $p = .62$. Scores on the BDI indicated that none of the participants showed signs for severe depression. Within the patient group, 10 participants (77%) in our sample scored in the minimally depressed range, two (15%) scored in the mildly depressed range, and 1 (8%) scored in the moderately depressed range. Within the HC group, 48 (91%) participants scored in the minimally depressed range and five (9%) scored in the mildly depressed range. Scores on the MoCA showed that all PD patients scored above the cut-off score of 21 during any of the test sessions (total range 22–30), meaning that none showed indications for PD-dementia (Dalrymple-Alford et al., 2010). Within-subject comparison of the MoCA scores of the patients tested ON their medication (M = 27.08, SD = 1.71) and OFF their medication (M = 27.46, SD = 2.54) showed no significant effect of medication status on cognitive ability ($p = .46$). For HCs, scores of all participants (M = 27.43, SD = 1.87, total range = 24–30) were above the cut-off score of 23 for healthy cognitive ageing (Carson et al., 2018).

As listed in Table 2, twelve patients were treated with levodopa, in eleven cases coupled to a monoamine oxidase-B (MAO-B) inhibitor (ten rasagiline, one safinamide) and in one case coupled to pramipexole, a DA agonist. Of the patients that took a MAO-B inhibitor, seven also received to a DA agonist (five ropinirole, two pramipexole) and one patient additionally received entacapone, a catechol-O-methyl transferase (COMT) inhibitor. Finally, one patient was not treated with levodopa, but received rasagiline. We calculated the levodopa equivalent dose (LED) to compare patients who were on different medication regimens (see Tomlinson et al., 2010). To assess patients' motor symptoms, we used the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) during both the ON and OFF medication test sessions. UPDRS scores indicated that medication significantly alleviated motor symptoms (M = 10.38, SD = 6.12 ON medication, and M = 19.00, SD = 11.85 OFF medication), $t(12) = 4.68$, $p = .001$, $d = 0.512$. Finally, within-subject comparison of patients' scores on the POMS questionnaire show that scores did not differ significantly as a function of medication status (ON M = 15.85, SD = 11.87 vs. OFF M = 15.92, SD = 10.23; $p = .96$) or test session (T1 M = 16.31, SD = 10.84 vs. T2 M = 15.46, SD = 11.29; $p = .59$), thus excluding the possibility of a mood state confound.

Action selection and initiation through event binding

As detailed in the method section, the PRC for the binding between shape and response (task-relevant visuomotor binding) was determined based on responses to the second stimulus.[1] Figure 1a shows this PRC for each participant as well as the mean PRC per group. We first ran one-sample t-tests on the

[1]To evaluate whether medication affected simple responses to the first stimulus, we ran paired samples t-tests on patients' mean RTs (correct trials only) and proportion of correct responses in the ON and OFF medication states. Responses did not differ significantly between performance ON and OFF medication in terms of RTs (465 vs. 461 ms, $p = .79$) nor accuracy (.89 vs. .85, $p = .10$). We also ran two independent samples t-tests on RTs and proportion of correct responses to evaluate whether patients and controls performed differently. Results showed that RTs to the first stimulus did not differ significantly between HCs (455 ms) and PD patients ON medication (465 ms, $p = .72$), nor PD patients OFF medication (461 ms, $p = .82$). Similarly, there were no significant effects for accuracy ($PD_{ON} = .89$, $PD_{OFF} = .85$, HC = .88; $ps > .46$).

TABLE 2 Demographic and clinical characteristics of the PD patients

Subject	Age (years)	Gender	Disease duration (years)	Most affected side[a]	Handedness[b]	H&Y stage	Subtype[c]	LED (mg/day)	Medication type	FOG-Q	PDQ-8	WOQ-9	UPDRS[d]	
													ON	OFF
#1	69	M	14	L	L*	1	TD	500	Levodopa, DA-A	2	5	3	8	13
#2	67	M	6	R	R	1	AR	660	Levodopa, MAO-B, DA-A	6	6	2	10	15
#3	73	F	8	R	R	1	TD	560	Levodopa, MAO-B, DA-A	0	1	1	3	6
#4	55	M	9	R	R*	1	AR	1220	Levodopa, MAO-B, DA-A	11	4	6	7	10
#5	54	F	2	R	R	1	TD	400	Levodopa, MAO-B	1	5	1	7	6
#6	46	M	4	L	L*	2	TD	400	Levodopa, MAO-B,	3	5	5	23	44
#7	53	F	8	L	R	1	TD	650	Levodopa, MAO-B, DA-A	1	2	0	9	17
#8	74	M	7	B	R	2	TD	1060	Levodopa, MAO-B, DA-A, COMT	18	7	6	19	36
#9	68	M	11	L	L*	2	AR	1200	Levodopa, MAO-B, DA-A	10	13	3	18	31
#10	63	F	14	R	R*	2	TD	500	Levodopa, MAO-B	5	14	4	6	22
#11	71	M	4	L	R	2	TD	1100	Levodopa, MAO-B	4	10	7	13	24
#12	45	M	3	L	R	1	Mixed	100	MAO-B	0	9	0	8	10
#13	52	F	4	L	R	1	AR	660	Levodopa, MAO-B, DA-A	1	4	6	4	13
Mean ± SD	61 ± 10		7.2 ± 4					693.1 ± 348.2		4.8 ± 5.3	6.5 ± 3.9	3.4 ± 2.5	10.4 ± 6.1	19.0 ± 11.9

Abbreviations: COMT, catechol-O-methyl transferase inhibitor; DA-A, dopamine agonist; FOG-Q, freezing of gait questionnaire; H&Y, Hoehn and Yahr rating scale; LED, levodopa equivalent dose; MAO-B, monoamine oxidase-B inhibitor; PDQ-8, Parkinson's disease quality of life; UPDRS, Unified Parkinson's Disease Rating Scale; WOQ-9, wearing off questionnaire.

[a]Dominant side of motor symptoms: L = left, R = right, B = bilateral.

[b]Dominant hand according to Annett's (1970) Handedness Inventory; *denotes that the other (non-dominant) hand was used for the tasks.

[c]Classification according to the method of Kang et al. (2005): AR, akinetic–rigid; TD, tremor dominant.

[d]Significant difference ON vs. OFF; $p = .001$.

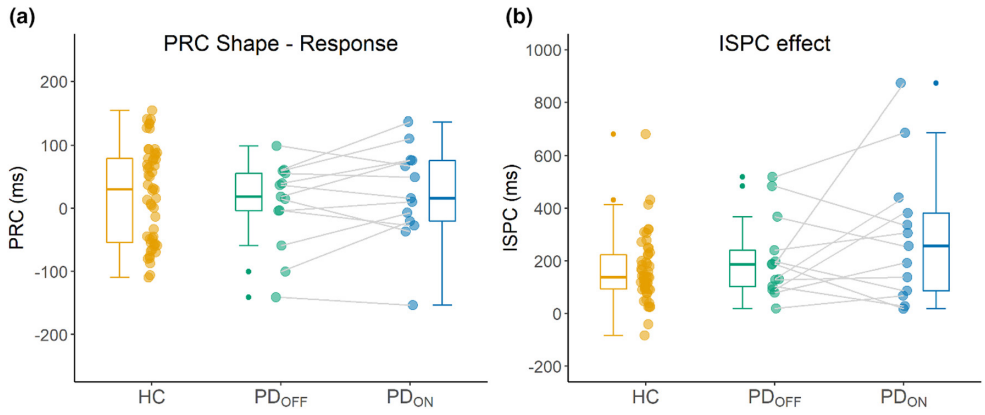

FIGURE 1 (a) Mean PRC (in ms) related to task-relevant visuomotor binding between Shape and Response for the HCs, PD_{OFF} patients and PD_{ON} patients. (b) Mean ISPC effect (in ms) for the HCs, PD_{OFF} patients and PD_{ON} patients

task-relevant visuomotor PRC between shape and response in each group and medication state to evaluate whether it differed from zero. Results showed that the PRC was significant for participants in the HC group, $t(52) = 2.06$, $p = .044$, $d = 0.28$, $BF_{10} = 1.05$, but not for PD patients in the ON or OFF medication states ($ps > .30$, BFs_{10} between 0.29 and 0.45).

To examine the effect of medication on PRCs within the PD patients, we ran a paired samples *t*-test on PRCs in the ON and OFF medication states. Results showed that medication did not significantly affect the PRC ($p = .19$, $BF_{10} = 0.61$). Next, we ran two independent samples *t*-tests to compare the PRC between HCs and patients ON or OFF medication, respectively. Results showed no differences between HC and patients (ON: $p = .96$, $BF_{10} = 0.30$; OFF: $p = .49$, $BF_{10} = 0.36$). Finally, for completeness, we also evaluated PRCs for the binding between colour and response (task-irrelevant visuomotor binding), and between shape and colour (visuoperceptual binding; see Figure S1). Results of paired samples *t*-tests showed that medication did not significantly affect these PRCs ($ps > .24$, BFs_{10} between 0.52 and 0.61). We also found no differences between participants in the HC and PD groups (HC vs. PD_{ON}: $ps > .20$, BFs_{10} between 0.46 and 0.58; HC vs. PD_{OFF}: $ps > .36$, BFs_{10} between 0.31 and 0.43).

Conflict adaptation

The ISPC effect for each participant as well as the mean ISPC effect per group are illustrated in Figure 1b. We first ran one-sample *t*-tests on the ISPC effect in each group and medication state to evaluate whether it differed from zero. Results showed that the ISPC effect was significant for participants in the HC group, $t(52) = 9.46$, $p < .001$, $d = 1.30$, $BF_{10} > 100$, as well as the PD patients ON medication, $t(12) = 4.09$, $p = .001$, $d = 1.14$, $BF_{10} = 28$ and OFF medication, $t(12) = 4.87$, $p < .001$, $d = 1.35$, $BF_{10} = 89$.

Next, we ran paired samples *t*-tests to examine the effect of medication status on patients' ISPC effects. Results showed that medication did not significantly affect the ISPC effect ($p = .24$, $BF_{10} = 0.29$). Finally, we ran two independent samples *t*-tests to evaluate whether the ISPC effect differed between HCs and patients ON or OFF medication, respectively. Results of a *t*-test comparing PD_{ON} patients and HCs showed that the ISPC effect was larger in the PD_{ON} than the HC group (293 vs. 163 ms), $t(64) = -2.64$, $p = .01$, $d = -0.82$, $BF_{10} = 4.68$. Importantly, this group difference survives a correction for multiple comparisons between the PD and HC groups as well as within the PD group (i.e. adjusted alpha threshold of 0.016). Results of a similar *t*-test comparing PD_{OFF} patients and HCs showed no significant difference ($p = .25$, $BF_{10} = 0.52$).

Correlations between medication effects

Results of correlation analyses showed that the PRC and ISPC effect were not significantly correlated within the HC group, nor PD patients ON or OFF their medication (*r*s between −.014 and −.19, *p*s > .53). To test whether individual differences in the magnitude of medication effects would be associated across both action control processes within the group of PD patients, we first calculated the difference between performance ON and OFF medication. Given the hypothesized beneficial versus adverse effects of medication on PRC and ISPC magnitudes, respectively, we calculated the differences accordingly. We then ran a correlation analysis on these differences PRC and ISPC, which showed that individual differences in medication effects on these indices were not significantly associated ($r = -.429$, $p = .14$; Figure 2a). Finally, we ran correlation analyses between these differences and clinical factors. As illustrated in Figure 2b,c, results showed that medication effects on UPDRS scores (OFF–ON; a larger difference indicates more improvement of motor symptoms with medication) were correlated with those on ISPC magnitudes, $r = -.651$, $p = .016$, but not PRC magnitudes ($r = .073$, $p = .81$). There were no significant correlations with age, disease duration, age at onset, LED, quality of life scores, nor freezing of gait and wearing off severity (*p*s > .18).

DISCUSSION

The current study is the first to investigate the effects of dopaminergic medication on two action control processes—specifically, action selection and initiation through event binding and conflict adaptation—within the same group of people with PD. While we observed reliable ISPC effects in PD patients both ON and OFF their medication as well as control participants, we observed the PRC only in the healthy control group but not in individuals with PD. Our results further showed evidence that action selection and initiation through event binding and conflict adaptation were not modulated by dopaminergic medication status. This contrasts our hypotheses that medication-induced DA changes in brain areas that are involved in action selection and initiation (i.e. dorsal striatal circuitry) would improve this process, whereas DA changes in brain areas involved in conflict adaptation (i.e. ventral striatal circuitry) would hinder the emergence of an ISPC effect. Furthermore, we found no indications that individual differences in the magnitude of medication effects were associated across both action control processes within the group of PD patients. Below, we first discuss the discrepancy between our current and previous findings related to conflict adaptation. We then focus in more detail on our findings regarding the absence of medication effects on action selection and initiation through event binding and within-subject associations. Finally, we address implications for the dopamine overdose hypothesis in relationship to various cognitive processes underlying goal-directed movement and address strengths and limitations of the study.

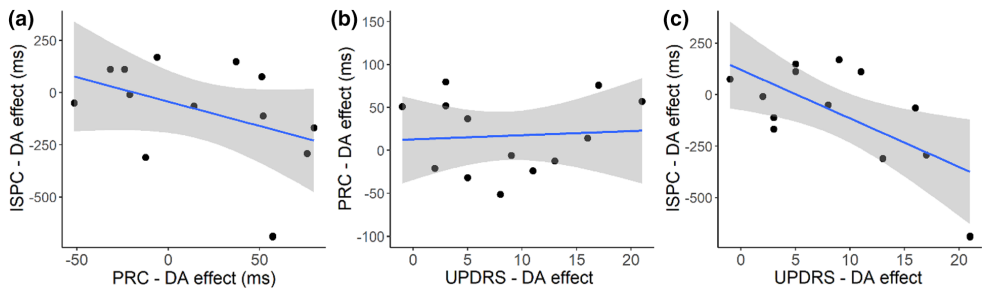

FIGURE 2 Correlations between individual differences in the effects of dopaminergic medication within the group of PD patients on (a) the PRC and the ISPC effect, (b) UPDRS scores and the PRC, and (c) UPDRS scores and the ISPC effect. The blue lines present the fitted linear slope; grey areas represent the 95% confidence interval

Dopaminergic medication and action control

Prior work examining the effects of dopaminergic medication on conflict adaptation in people with PD showed inconsistent results. Specifically, as mentioned in the introduction section, Duthoo et al. (2013) observed that dopaminergic medication impaired transient, trial-by-trial conflict adaptation as reflected in the congruency sequence effect (CSE), whereas Ruitenberg et al. (2016) found evidence that medication did not modulate relatively sustained conflict adaptation as reflected in the proportion congruency (PC) effect. To resolve this discrepancy, we proposed that transient and more sustained cognitive control processes may be differently sensitive to medication effects, which we tested conceptually in the present study via a third type of conflict adaptation, namely the ISPC effect. As both the CSE and ISPC effect are believed to involve reactive, transient (as compared to proactive, sustained) adaptations in attentional settings (Bugg, 2014; Funes et al., 2010; Torres-Quesada et al., 2013) and rely on the ventral striatum and associated areas (e.g. PFC and ACC), we predicted based on the DA overdose hypothesis that dopaminergic medication would reduce the ISPC effect. Contrary to our expectations, however, we observed no effect of medication status on the ISPC effect at the group level. A potential explanation may lie in recent evidence that the CSE and ISPC effect arise from independent mechanisms (Aschenbrenner & Balota, 2019), thus opening up the possibility that dopaminergic medication effects on conflict adaptation are dictated by the underlying mechanism at play. Combining our past and present work, it seems that medication hinders more general response adjustment mechanisms that are not directly tied to trial-by-trial changes in attentional control (CSE) but does not modulate the rapid retrieval or adjustment of control settings that occurs post-stimulus onset (ISPC) nor sustained mechanisms (PC effect). Future studies should systematically manipulate conflict type and behavioural index using within-subject approaches to disentangle the determinants of dopaminergic effects on conflict adaptation in PD. In doing so, we recommend that studies also take into account the role of response modality, given that existing work has used verbal responses (Duthoo et al., 2013), mouse movement responses (Ruitenberg et al., 2016), and key press responses (present study).

With respect to action selection and initiation through event binding, we surprisingly did not observe PRCs at the group level in people with PD—however, reliable PRCs were observed in the healthy control group, thus rendering it unlikely that absence of PRCs in our patient group was due to improperly implementing the experimental protocol. Our results further suggest that action selection and initiation was not modulated by dopaminergic medication in our sample of people with PD. This differs from previous observations that such impaired retrieval and activation of S-R events in PD patients is ameliorated by dopaminergic medication (Colzato et al., 2012), and that this process would be related to the dorsal striatal circuitry. One explanation for this discrepancy could be that participants in our study used two fingers of the same hand to perform the task, whereas participants in the Colzato et al. (2012) study used fingers from both their left and right hands. As medication may differently impact the hand on the most versus least affected side of the body in people with PD, we considered it more meaningful to have participants respond with one hand. However, we acknowledge that this may have introduced noise in terms of dominance and symptoms of the hand used for responding. Specifically, while most of our participants with PD used their dominant hand to perform the tasks, it should be noted that a subset of patients opted to use their non-dominant hand instead. This was likely related to the fact that in each of these individuals, their dominant hand was on the most affected side of the body. While we cannot conclusively rule out that handedness may have impacted the results, we deem the consideration for differential medication effects on the most versus least affected side of the body more essential for our aims. Taken together, the present results on action selection and initiation through event binding suggest that we may need to interpret the prior observations by Colzato et al. (2012) more conservatively than hitherto thought.

We thus did not replicate the modulating effects of dopaminergic medication on cognitive processes underlying action control that were previously reported by Colzato et al. (2012) and Duthoo et al. (2013). The present results imply that we should consider further specifying the DA overdose hypothesis, as it does not seem to hold for the action control processes studied here and thus may only apply to a specific set of cognitive processes. While the present findings suggest that the hypothesis may not hold for that

cognitive processes underlying performance in the motor domain, excluding such processes altogether would be too rigorous, however, as prior work demonstrated dopaminergic modulation of cognitive processes underlying goal-directed behaviour. For example, work has shown that medication differentially modulated the planning versus execution of a trained movement sequence in people with PD (Ruitenberg et al., 2016). Another refinement may pertain to the relative independence of DA effects, given that we observed no associations between individual differences in the size of medication effects on action binding and conflict adaptation.

Strengths and limitations

A strength of the present study is its within-subject design, which allowed us to examine effects of dopaminergic medication on two action control components within the same group of PD patients and evaluate for the first time whether individual differences in the size of medication effects would be associations. However, a limitation of our study is that there are also other action control components that we did not consider here (e.g. task-switching, inhibition; see Ruitenberg et al., 2021). As such, medication effects on other components should be considered as well to examine to what extent effects are generalizable across action control processes before implementing the aforementioned refinement of the DA overdose hypothesis. Another limitation pertains to the sample size of the patient group in the present study, which was relatively small ($n = 13$) and showed relatively large variability in age and clinical characteristics. However, it should be noted that the original effects were observed in relatively small groups of patients as well ($n = 11$ in Colzato et al., 2012; $n = 9$ in Duthoo et al., 2013). This opens up the possibility that the original studies may have been underpowered and consequently that the observed effects may not have been a true positive, or at least unrealistically large (Button et al., 2013). The results could therefore be unlikely to generalize beyond the original samples, which would explain why we were unable to replicate the effects in our patient group.

An additional limitation concerns the class of dopaminergic medication that individuals with PD were taking. While all patients were on levodopa (except for one patient who only took a MAO-B inhibitor), several of the patients in our sample were additionally receiving DA agonists. This latter class is known to have a longer half-life than levodopa, and patients using agonists may therefore have not reached a full off-state. However, as all patients were on agonists also received levodopa, it seems reasonable that overnight withdrawal resulted in at least a partial off-state. Finally, it remains unclear to what extent variations in performance between the two test sessions in the PD group were due to test–retest effects, as controls only completed one test session. While we controlled for such effects by creating two stimulus sets in the Stroop task, this was not the case for the event-file task. As such, test–retest effects may potentially have impacted the present results obtained for this task.

Overall, our findings do not support the notion that dopaminergic medication improves or impairs action control processes depending on the neural circuitry underlying a given task in people with PD. However, the absence of evidence for behavioural effects of dopaminergic medication on action control in PD in line with the DA overdose hypothesis does not refute the possibility that medication modulated neural recruitment during performance (*cf.* Ruitenberg et al., 2021). Future studies should further examine this by combining experimental tasks and neuroimaging methods to be able to meaningfully interpret the lack of expected effects at the behavioural level. Furthermore, future studies on medication effects should distinguish between patients with different motor phenotypes, as recent work by Van Nuland et al. (2020) showed different effects of dopaminergic medication on reinforcement learning depending on whether patients were tremor-dominant or non-tremor-dominant. While the sample size in current study did not allow for a classification into subgroups, future work should consider examining DA effects on action control as a function of phenotype to further elucidate the role of motor symptomatology.

AUTHOR CONTRIBUTIONS

Marit F. L. Ruitenberg: Conceptualization; formal analysis; funding acquisition; investigation; methodology; project administration; software; visualization; writing – original draft. **Elger L.**

Abrahamse: Conceptualization; methodology; writing – review and editing. **Patrick Santens:** Resources; writing – review and editing. **Wim Notebaert:** Conceptualization; methodology; writing – review and editing.

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CONFLICTS OF INTEREST

PS holds a senior clinical research position at the Research Foundation Flanders (FWO). The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The anonymized data that support the findings of this study are available to qualified investigators on request from the corresponding author (MR).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Appendix S1.

Figure S1.

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