



## Review article

## The role of dopamine in action control: Insights from medication effects in Parkinson's disease

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## ABSTRACT

Parkinson's disease (PD) is a neurological disorder associated primarily with overt motor symptoms. Several studies show that PD is additionally accompanied by impairments in covert cognitive processes underlying goal-directed motor functioning (e.g., action planning, conflict adaptation, inhibition), and that dopaminergic medication may modulate these action control components. In this review we aim to leverage findings from studies in this domain to elucidate the role of dopamine (DA) in action control. A qualitative review of studies that investigated the effects of medication status (on vs. off) on action control in PD suggests a component-specific role for DA in action control, although the expression of medication effects depends on characteristics of both the patients and experimental tasks used to measure action control. We discuss these results in the light of findings from other research lines examining the role of DA in action control (e.g., animal research, pharmacology), and recommend that future studies use multi-method, within-subject approaches to model DA effects on action control across different components as well as underlying striatal pathways (ventral vs. dorsal).

## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder associated with a loss of dopamine-producing neurons in the substantia nigra, resulting in a decrease of dopamine (DA) levels in the striatum. PD is characterized primarily by cardinal motor problems such as resting tremor, bradykinesia, and rigidity, but many patients experience additional non-motor symptoms including (but not limited to) problems with cognition, emotion, sleep, and smell (for reviews see [Dirnberger and Jahanshahi, 2013](#); [Schapira et al., 2017](#)). Although there are currently no treatments that can reverse or stop the progression of PD, the majority of PD patients take dopaminergic medication to manage their motor symptoms and improve quality of life. In the present work, we review findings from studies comparing PD patients' performance on dopaminergic medication to performance after medication withdrawal (off medication) to better understand the role of DA in cognitive processes controlling motor functioning. While PD has also been associated with degeneration of neurotransmitter systems other than DA that may

be implicated with both motor and cognitive functions (e.g., the cholinergic and norepinephrine systems; [Bohnen et al., 2013](#); [Fang et al., 2020](#); [Surmeier et al., 2017](#)), we specifically focus on DA.

Two broad classes of dopaminergic medication are precursors (i.e., levodopa) that increase the production of DA from intact neurons, and agonists that mimic DA at the receptor level. Other classes of medication include Catechol-O-methyl transferase (COMT) inhibitors, monoamine oxidase type B (MAO-B) inhibitors, amantadines, and anticholinergic medication. Levodopa continues to be the gold standard treatment in PD, but because long-term use may cause adverse effects including dyskinesias and response fluctuations ([Fahn, 2018](#)), agonists are used frequently to manage symptoms in patients who do not tolerate levodopa. As agonist use has been linked to a range of side effects, including the development of impulse control problems in PD (e.g., [Djamshidian et al., 2013](#); [Weintraub and Claassen, 2017](#); [Weintraub et al., 2006](#); but see [de Rezende Costa et al., 2016](#)), careful monitoring of medication effects is essential.

While dopaminergic treatment is used primarily to improve motor

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symptoms, studies have also shown it affects non-motor functions. For example, it has been suggested that dopaminergic medication improves some cognitive functions such as working memory and attention switching, but impairs others such as reversal learning and learning from negative feedback (for reviews, see Cools, 2006; MacDonald and Monchi, 2011). Dopaminergic medication may thus produce both beneficial and adverse effects on cognitive performance. This apparent contradiction is sometimes explained by the *DA overdose hypothesis* (Cools et al., 2001a; for a review, see Vaillancourt et al., 2013). The hypothesis was inspired by the asymmetric distribution of dopamine loss in the striatum as the disease progresses, with greater degeneration of dopamine neurons in the dorsal as compared to the ventral striatum in early stages of the disease. Administration of dopaminergic drugs in the early to intermediate stages of PD are expected to benefit dopamine-depleted dorsal striatal circuitries and associated functions, but may “overdose” relatively intact dopamine-dependent circuitries and thus interfere with functions involving the ventral striatum. Overall, the relationship between DA-levels and performance in PD patients is thought to follow an inverted U-shape, in line with animal and human evidence that both DA depletion and DA excess can impair performance (e.g., Aarts et al., 2014b; Cools and D’Esposito, 2011; Williams and Goldman-Rakic, 1995).

A specific way to empirically test the overdose hypothesis is by manipulating the medication status of PD patients and comparing their performance *on* dopaminergic medication to performance after medication withdrawal (*off* medication). As noted, dopaminergic medication typically improves the cardinal motor symptoms associated with PD, since general motor functioning is related to the dorsal striatum and associated motor cortical areas such as the supplementary motor area (SMA) and premotor cortex (PMC). However, successful motor performance is typically not only dependent on the direct, physical control of muscles by the musculoskeletal system to generate movement and stability, but also on cognitive components that allow for goal-directed behavior in the face of uncertain and/or changing contexts (Abrahamse et al., 2013; McDougle et al., 2016; Prinz et al., 2009; Ruitenberg et al., 2015). Core functions of such *action control* include (I) planning through action binding, (II) task-switching, (III) conflict control (i.e., conflict monitoring, conflict suppression, and conflict adaptation), and (IV) action inhibition. Table 1 provides an overview of definitions, dedicated experimental key press paradigms, and key references for each of these components. We will explain these paradigms in more detail in the results section for each specific component. In terms of neural networks underlying these functions, planning and task-switching have been associated with the dorsal striatal circuitry (e.g., Cools et al., 2004; Melcher et al., 2008; Sohn et al., 2000), while conflict monitoring, suppression, and adaptation, as well as action inhibition have been associated with the ventral striatal circuitry (e.g., Botvinick et al., 2001; Grandjean et al., 2013; Jha et al., 2015; Sebastian

et al., 2013). Note that while the implementation of action inhibition has also been linked to the hyperdirect pathway which bypasses the striatum (e.g., Aron et al., 2016), it is not fully independent of the indirect striatal input to the subthalamic nucleus (STN) and therefore still expected to be sensitive to DA.

Previous work has shown that PD is associated with deficits in action control. For example, difficulty in initiating and planning voluntary actions is a key symptom of PD (Rodriguez-Oroz et al., 2009). Prior studies also found indications that PD patients are less proficient at making micro-adjustments in conflict control in response to changing situational demands to maintain goal-directed behavior (Bonnin et al., 2010; Cagigas et al., 2007; Fielding et al., 2005; Rustamov et al., 2013; but see Wylie et al., 2009), or when situations require switching between actions (Cools et al., 2001b; Woodward et al., 2002). In addition, compared to healthy control subjects, PD patients show reduced detection of signals that indicate the need to engage control processes (i.e., performance monitoring; for a review, see Seer et al., 2016). Finally, previous work showed that PD patients have difficulty selectively suppressing conflicting actions or outright inhibiting already initiated actions (Guggel et al., 2004; Nombela et al., 2014; Obeso et al., 2011a). While prior work thus demonstrates that PD clearly impacts multiple mechanisms of action control, the vast majority of these studies involved patients who were on their regular medication regime and did not consider performance in the off medication state. Consequently, the effects of dopaminergic medication on action control remain relatively poorly understood from these studies – preventing deeper insights about the impact of dopaminergic medication on action control in PD and the potential for normalizing or overdosing functional circuitries (i.e., testing the overdose hypothesis).

The present work reviews empirical studies that specifically evaluated the effect of dopaminergic medication on action control in PD, with a special focus on gaining potential insights related to the dopamine overdose hypothesis. As prior studies have mostly evaluated only one of these action control components *in isolation*, reviewing them collectively will provide us with a more coherent and comprehensive understanding of the effects of dopaminergic medication on action control in PD. In the broader sense, the current systematic review aims to further elucidate the role of DA in action control. We identified studies that directly compared performance of PD patients on versus off their dopaminergic medications on tasks that assessed at least one of the aforementioned components of action control. Next, we looked at the consistency across studies of dopaminergic effects on the specific components of action control and evaluated whether the patterns of effects might align with predictions from the overdose hypothesis. Specifically, the latter would predict beneficial effects of dopaminergic medication on action planning and task-switching relying on dorsal striatal circuitries, but adverse effects on conflict control and inhibition relying on ventral striatal circuitries.

**Table 1**

Definitions of the action control components included in the current review, as well as typical experimental paradigms and key references for each component.

Component	Definition	Experimental paradigm(s)	Key references
Action planning through event binding	Activating the code(s) that represent an action and spreading that activation to the motor codes responsible for generating the action (cf. Theory of Event Coding)	Event file task	Hommel (1998, 2004, 2019), Hommel et al. (2001)
Task-switching	Switching attention from an initially important stimulus (feature or dimension) to another in line with environmental demands or goals	Task-switch task	Braem and Egner (2018), Monsell (2003)
Conflict monitoring	Detecting and evaluating errors and subsequently engaging control processes	EEG measures in conflict tasks (e.g., Stroop, Simon, Eriksen flanker)	Holroyd and Coles (2002), Gehring and Knight (2000)
Conflict suppression	Selectively suppressing a (relatively automatic) incorrect action in favor of a more appropriate one	Conflict tasks	Botvinick et al. (2001), Miller and Cohen (2001)
Conflict adaptation	Modulating attentional settings and adjusting ongoing behavior to changing situational demands	Conflict tasks with congruency context manipulation (e.g., congruency sequence effect, proportion congruency effects)	Botvinick et al. (2001, 2004), Braem et al. (2019), Bugg and Crump (2012), Egner (2007)
Action inhibition	Cancelling an already prepared or even initiated action	Go/no-go task Stop-signal task	Aron (2007), Verbruggen and Logan (2008)

## 2. Methods

We performed a systematic literature search using Web of Science to identify studies that evaluated the effect of dopaminergic medication on action control in PD. Specifically, we conducted a search on empirical studies published between 2000 up to and including May 2020 using the following terms: (Parkinson\* AND (medication OR dopamine modulation) AND (Simon OR Stop OR Flanker OR Stroop OR conflict monitoring OR task switching OR motor impulsivity) NOT (animal OR rodent OR rat OR monkey OR cell OR in vivo)). We included studies from 2000 onwards because 1) many studies prior to this date did not compare performance on vs. off medication, but rather only compared performance of PD patients in one of these medication states to performance of healthy control subjects, and 2) critical improvements have been made to experimental action control paradigms to warrant valid measures. Examples of such improvements are the selection of appropriate go and stop trials as well as the inclusion of a staircase procedure to estimate inhibitory abilities in the stop-signal task (e.g., Verbruggen et al., 2008; for a recent consensus guide, see Verbruggen et al., 2019), and controlling for various episodic confounds in conflict adaptation tasks (e.g., Braem et al., 2019; Duthoo et al., 2014). By including studies from 2000 onwards, we achieved a balance between considering a sufficiently large time span on the one hand, and including studies using advanced paradigms on the other hand.

The initial search yielded 254 results and both the title and abstract of each of these articles were screened by the first author (MR). Studies that studied either the effect of dopaminergic medication or action control in PD, but not a combination of both, were excluded from the review. Furthermore, studies that were not written in English or studies that employed an on versus off manipulation based on deep brain stimulation (DBS) condition rather than medication state were excluded. Using these criteria, we identified 26 articles with potential reference to the effect of dopaminergic medication on action control performance in PD patients. An additional 7 relevant articles were identified from the reference lists of the selected articles or from the authors' personal knowledge bases. Three out of the resulting 33 articles were excluded: two studies involving PD patients with active DBS implants, and one study failing to provide patient demographic/clinical characteristics or statistics. Fig. 1 illustrates the selection procedure for the final collection of 30 articles included in this systematic review.

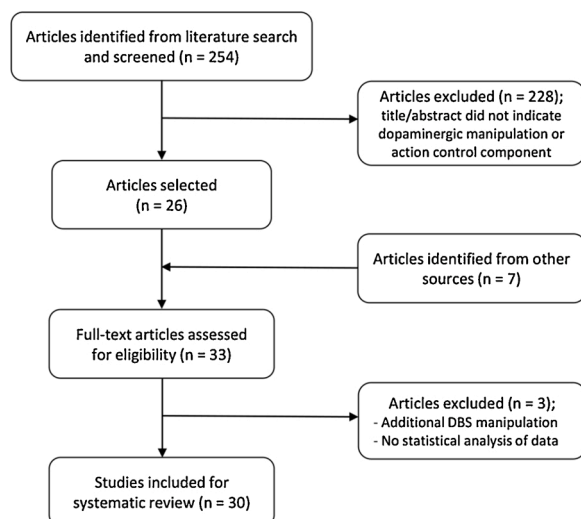


Fig. 1. Flow chart illustrating the selection of studies. DBS = deep brain stimulation.

## 3. Results

Table 2 provides an overview of the patient characteristics and results of the selected studies. The majority of the studies used a within-subject manipulation of dopaminergic medication status in PD patients who take prescribed medications. In 21 of those studies, the order of on vs. off medication testing was counterbalanced. In five studies, patients were always tested in the off medication state first (i.e., Alegre et al., 2013; Cerasa et al., 2015; Farid et al., 2009; Fera et al., 2007; Herz et al., 2014). Finally, for two studies the order of medication status was not explicitly reported (i.e., Shook et al., 2005; Trujillo et al., 2019). A few studies included patients who have been diagnosed with PD, but do not yet take prescribed PD-specific medications (i.e., *de novo* PD patients). Specifically, two studies used a between-subjects design (one study compared groups on and off medication, Cools et al., 2001a,b, another study compared a group on medication to a group of *de novo* patients, Stemmer et al., 2007) and one study involved *de novo* PD patients that were assessed before and after they started using dopaminergic medication (Geffe et al., 2016). Below, we will discuss the findings of the selected studies per action control component in detail. Note that the studies described here mostly involved procedures that had PD patients withdraw from all their dopaminergic medication or specifically withdraw from levodopa; in the isolated cases where effects of DA agonists were studied, this will be explicitly mentioned.

### 3.1. Action planning through event binding

Our literature search yielded only one study that focused on the effect of dopaminergic medication on action planning in PD, namely Colzato et al. (2012). The study is based on the idea that people represent actions in terms of their anticipated effects. Specifically, according to Hommel et al. (Hommel, 2004, 2019; Hommel et al., 2001; Elsner and Hommel, 2001) perceptual and action features of an experienced event (stimulus) become integrated into an *event file* through experience. The planning and intentional selection of an action is subsequently enabled via the retrieval of a stored event file: an action is automatically activated through anticipating the desired effects of that action on the environment and the associated stimulus-response (S-R) features. In healthy adults, performance is typically worse when a stimulus feature repeats while the required action changes, or when the action repeats but the stimulus feature changes (i.e., partial changes), relative to when stimulus and action both repeat or alternate (Hommel, 2004; Ruitenberg and Koppelmans, 2021). Performance is worse in these situations compared to situations where all or none of the stimulus and action events are activated, as the partial activation of both events results in suboptimal planning. Colzato et al. (2012) investigated such feature integration in a group of PD patients, who performed the event-file task once on and once off their medication. In this task, participants respond to two successive stimuli that differ on two features (e.g., shape and color). The first response is cued before presentation of the stimulus and therefore independent of the features of that stimulus, whereas for the second response participants have to follow a predefined decision rule based on a relevant stimulus features. Results showed that the performance decline due to partial changes between the first and second response in either the action or relevant stimulus feature (as compared to full/absent changes) was larger when patients were on their medication than off their medication, suggesting that dopaminergic medication improved the binding between stimuli and associated action events. That is, DA directly benefitted the retrieval and updating of event files among PD patients, which aligns with the proposal that action planning and selection are dependent on the dorsal striatal dopaminergic system (e.g., Howard et al., 2017).

### 3.2. Task-switching

Six studies investigated the effect of dopaminergic medication on

**Table 2**

An overview of the studies included in the present review, organized by action control component. The table presents the characteristic of the patients with Parkinson's disease (PD) and where applicable healthy control participants (HC), as well as the main findings of each study.

Study	PD patients							Controls		Paradigm	Results
	N	Age	H&Y Stage	Duration	LED	UPDRS-III on	UPDRS-III off	N	Age		
<b>Action planning through event binding</b>											
Colzato et al. (2012)	11 (8 M)	68.1	–	10.4	727.4	19.9	–	14 (9 M)	71.1	event-file task	PD off < PD on = HC
<b>Task-switching</b>											
Aarts et al. (2014a)	15 (9 M)	54.1	–	5.5	449.9	20.5	29.3 <sup>a</sup>	n/a		pre-cued task-switching (arrows vs. words)	PD on = PD off
Cools et al. (2001a,b)	14 (6 M) on / 15 (10 M) off	58.2 on / 59.0 off	1–3	5.7 on / 5.0 off	482.1 on / 416.7 off	25.7	36.7 <sup>a</sup>	27 (9 M)	59.4	task-switching (letters vs. numbers)	PD off < PD on < HC
Cools et al. (2003)	12 (5 M)	64.6	1–3	6.5	552	30.9	47.1 <sup>a</sup>	12 (6 M)	62.7	task-switching (letters vs. numbers)	PD off < PD on = HC
Kehagia et al. (2009)	11 (8 M)	61.7	1	–	–	9.4	19.2 <sup>a</sup>	16 (10 M)	63.6	task-switching (letters vs. numbers)	PD off = PD on < /= HC
Rowe et al. (2008)	19 (11 M)	65.1	2–3	7.8	1328.3	19.2	31.9	17 (8 M)	67.4	task-switching (letters vs. spatial positions)	PD off = PD on = HC
Shook et al. (2005)	15 (M <i>nk</i> )	60.3	1–3	10.7	–	<i>M</i> = 24.3		15 (M <i>nk</i> )	60.7	task-switching (color vs. shape)	PD off < PD on = HC
<b>Conflict monitoring</b>											
Seer et al. (2017)	13 (10 M)	64.31	2–4	11.31	1015	17.42	26.33 <sup>a</sup>	13 (10 M)	63.15	flanker EEG	PD on < PD off < HC
Stemmer et al. (2007)	9 (6 M) on / 9 (4 M) <i>de novo</i>	63.4 on / 64.2 <i>de novo</i>	<i>M</i> = 2.6 on / <i>M</i> = 2.1 <i>de novo</i>	6.6 on / 2.2 <i>de novo</i>	–	21.3	22.7 <i>de novo</i>	14 (5 M)	65.6	flanker EEG	PD <i>de novo</i> = PD on < HC
Willemssen et al. (2008)	20 (12 M)	64.5	–	3.2	601	10.8	14.8 <sup>a</sup>	20 (12 M)	64.3	flanker EEG	PD on = PD off < HC
<b>Conflict suppression</b>											
Costa et al. (2014)	20 (9 M)	68.8	–	2.43	336	–	16.6	20 (11 M)	65.5	Stroop	PD off < PD on = HC
Fera et al. (2007)	12 (6 M)	59.9	1–3	3.54	488.6	11.5	18 <sup>a</sup>	10 (5 M)	55.2	Stroop	PD off = PD on = HC
Trujillo et al. (2019)	26 (18 M)	61.2	–	5.4	565	21.2	30.1	n/a		Simon	PD off < PD on
van Wouwe et al. (2016)	55 (36 M)	63.7	1–3	4.4	732	–	26.9	56 (29 M)	62.2	Simon	PD off < PD on < HC
Wylie et al. (2012a,b)	19 (9 M)	63.2	1–3	5.9	218	15.3	–	n/a		Simon	PD off = PD on
<b>Conflict adaptation</b>											
Djamshidian et al. (2011)	24 (21 M)	64.2	–	11.7	821	14.4	26.8	24 (14 M)	57.8	Stroop	PD on > PD off
Duthoo et al. (2013)	9 (6 M)	59.92	–	7	566.7	22.8	32.9 <sup>a</sup>	n/a		Stroop	PD on < PD off
Ruitenberg et al. (2019)	15 (11 M)	63	1–2	7	619.6	15.07	24.64 <sup>a</sup>	n/a		Stroop	PD on = PD off
<b>Action inhibition</b>											
<i>Withholding of prepared action</i>											
Antonelli et al. (2014)	7 (6 M)	58.6	–	6.8	215.3	–	28.6	n/a		go/no-go	PD on = PD off
Farid et al. (2009)	9 (7 M)	61	<i>M</i> = 3	10	1060	11	37 <sup>a</sup>	9 (8 M)	59	go/no-go	PD off = PD on = HC
Geffe et al. (2016)	22 (M <i>nk</i> )	66.4	<i>M</i> = 2.1	2.2	250 mg lev	20.6	29.5 <sup>a</sup>	23 (M <i>nk</i> )	67	go/no-go	PD on < PD off = HC
Herz et al. (2014)	13 (9 M)	67.5	–	6.1	672.3	21.2	32.9	13 (9 M)	68.4	go/no-go	PD off = PD on = HC
Yang et al. (2017)	22 (11 M)	66.77	–	5.23	626.59	17.43	21.82 <sup>a</sup>	n/a		go/no-go	PD off < PD on
<i>Cancellation of initiated action</i>											
Alegre et al. (2013)	10 (6 M)	62.6	–	12.6	1207.4	17	39.9 <sup>a</sup>	n/a		stop-signal	PD on = PD off
Cerasa et al. (2015)	12 (9 M)	67	2–2.5	5.2	380	18.8	25.7	n/a		stop-signal	PD on = PD off

(continued on next page)



Table 2 (continued)

Study	PD patients							Controls		Paradigm	Results
	N	Age	H&Y Stage	Duration	LED	UPDRS-III on	UPDRS-III off	N	Age		
George et al. (2013)	16 (8 M)	62.62	1–3	4.94	–	33.68	41.5 <sup>a</sup>	16 (7 M)	63.5	stop-signal	PD off = PD on < HC
Manza et al. (2018)	17 (11 M)	61.1	1–2.5	2.9	476.5	14.3	20.6	18 (9 M)	65.3	stop-signal	PD off < PD on = HC
Obeso et al. (2011b)	17 (12 M)	69.41	M = 2.12	9.5	915.94	16.25	30.71	16 (7 M)	65.69	stop-signal	PD off = PD on < HC
Picazio et al. (2018)	14 (9 M)	70.4	–	7.7	566.6	13.9	26.1	10 (5 M)	68.3	stop-signal	PD off = PD on = HC
Wylie et al. (2018)	33 (20 M)	63.5	1–3	5	698	12.6 improvement on med		21 (9 M)	61.6	stop-change	PD off < PD on < HC

Values represent means, unless otherwise indicated (i.e., n or range); *nk* = not known.

H&Y Stage = Hoehn and Yahr stage of PD (Hoehn & Yahr, 1967); LED = Levodopa equivalent dose; UPDRS-III = Unified Parkinson's Disease Rating Scale motor subscale III.

<sup>a</sup> In these studies the difference between UPDRS scores on vs. off medication was significant. In Stemmer et al. (2007) the difference was not significant. The other studies either did not report statistics on the UPDRS difference, or only assessed motor symptoms once.

task-switching. Typically, in task-switching paradigms the act of switching between relatively simple tasks leads to slower and less accurate responses; this is referred to as the switch-cost (Monsell, 2003). In the majority of the studies reviewed here that involved a group of healthy controls, patients off their medication showed larger switch-costs than healthy controls. Three of the six studies observed that medication ameliorated this task-switching deficit in PD patients (Cools et al., 2001a,b, 2003; Shook et al., 2005), whereas the other three found no significant effects of dopaminergic medication (Aarts et al., 2014a; Kehagia et al., 2009; Rowe et al., 2008). We propose that these differential results may be related to differences in switch difficulty across the various studies. The studies that observed a beneficial effect of dopaminergic medication involved relatively simple switches. For example, in the Cools et al. (2001a,b, 2003) studies, stimuli consisted of a letter and a digit that were presented centrally on the display. Every two trials, patients had to switch from naming the letter in the display to naming the number. Similarly, in Shook et al. (2005), patients had to switch from identifying the color of a centrally displayed stimulus to identifying its shape. In contrast, the studies that found no significant effect of medication involved relatively complex switches. For example, patients in Kehagia et al. (2009) had to shift between attending the letter or the digit element of the stimulus (cf. patients in the Cools et al. studies) and subsequently classify the relevant element (i.e., vowel/consonant in case of a letter vs. higher/lower than 5 in case of a digit). Aarts et al. (2014a) used a cued version of the word-arrow Stroop conflict paradigm, in which stimuli consisted of the word 'left' or 'right' printed in an arrow pointing right- or leftward, respectively (i.e., always incongruently paired). On each trial, patients had to resolve response conflict generated by the contrast between the meaning of the word and direction of the arrow, such that selecting the correct response required conflict control. In Rowe et al. (2008), stimuli consisted of letters that were presented at one of eight spatial locations on the display. The patients' task was to identify each pair of two successive stimuli as a target or non-target trial, based on two instructed rules (i.e., verbal targets were trials in which the letter 'A' was followed by an 'X'; spatial targets were trials in which a letter at the 6 o'clock position was followed by a letter at the 3 o'clock position). Correct performance thus required remembering both the rules and the first stimulus of the pair, such that the task had a relatively high working memory demand compared to the other studies discussed here.

Taken together, these task-switching studies suggest that relatively simple switches may be sensitive to dopaminergic modulation. For more complex switches, the studies reviewed here showed no significant effect of medication. It is possible that the difficulty of the tasks may confound switching with other processes such as S-R reconfiguration, conflict resolution, or working memory, in a way that masks any

dopaminergic effects on switching. A current debate in the task-switch literature concerns whether this component of action control may be based on associative learning rather than purely cognitive control mechanisms (Braem and Egner, 2018). For example, Braem (2017) demonstrated that voluntary task-switching can be conditioned by rewarding switching behavior in a preceding cued task phase, such that the act of switching is driven by learning rather than control. Of the aforementioned studies on task-switching in PD, those by Aarts et al. (2014a) and Rowe et al. (2008) involved reward as well. As people typically perform better on repeat trials than on switch trials, it could be argued that the former trials are more likely to get rewarded which in turn may affect task-switching behavior through associative learning mechanisms. The presence or absence of reward in task-switching paradigms may thus affect (interpretation of) findings in terms of medication effects on this component of action control in PD and should be examined in future studies.

### 3.3. Conflict control for appropriate action

#### 3.3.1. Conflict monitoring

Three studies investigated the effect of dopaminergic medication on the monitoring of ongoing actions, namely Seer et al. (2017), Stemmer et al. (2007), and Willemssen et al. (2008). In these studies, patients performed a simple conflict task in which relevant and irrelevant stimulus features (i.e., target stimulus flanked by distractor stimuli in the Eriksen flanker task) trigger responses that are either corresponding (i.e., congruent trials) or in competition with each other yielding conflict (i.e., incongruent trials). During performance, their cortical activity was measured via electroencephalography (EEG). The dependent variable of interest was the peak amplitude of the error-related negativity (ERN), an EEG signal that is believed to reflect performance monitoring (Ullsperger et al., 2014) with more negative amplitudes being associated with more effective monitoring. As monitoring refers to the signaling of conflict as a prerequisite for determining the necessity, type, and magnitude of behavioral adjustments (e.g., inhibiting an automatic but incorrect response in favor of a correct one), we here discuss this component of conflict control separately to maintain the conceptual distinction as outlined in the introduction. However, it should be noted that conflict monitoring on the one hand and conflict suppression/adaptation mechanisms on the other hand are hard to fully disentangle empirically, and that monitoring measures may not be entirely deconfounded from behavioral adjustments.

In terms of results reported in the reviewed studies on conflict monitoring, Seer et al. (2017) found that – despite the absence of medication effects on the cost of incongruency reflected in behavioral accuracy rates – the ERN amplitude was smaller (i.e., less negative)

when patients were on compared to off their medication, suggesting that medication impaired performance monitoring. The other two studies did not find a significant effect of dopaminergic medication on the ERN, neither in a within-subject comparison of performance on versus off medication (Willemssen et al., 2008) nor in a between-subject comparison of *de novo* PD patients with a group of PD patients on medication (Stemmer et al., 2007). While the three studies consistently found that across medication states the ERN was attenuated in PD patients compared to healthy control subjects, findings regarding the effect of medication were inconsistent.

One explanation for these differential findings may be related to the duration and/or stage of the disease of the patients included in each study. That is, patients in the Stemmer et al. (2007) study were in the relatively early stages of the disease, with a mean of 2.2 years since initial diagnosis for the *de novo* patients (mean H&Y stage = 2.1) and 6.7 year for the patients that were on medication (mean H&Y stage = 2.6). Similarly, patients in the Willemssen et al. (2008) study had an average disease duration of 3.2 years (H&Y stage not reported). In contrast, patients in the Seer et al. (2017) study – which was the only one reporting effects of medication – were in moderate stages of the disease with a mean disease duration of 11 years (median H&Y stage = 3; range = 2–4). As increasing disease stage across these three studies seems to be associated with smaller (i.e., less negative) ERN amplitudes across medication states ( $M = -6.51$ , Stemmer et al., 2007;  $M = -5.8$ , Willemssen et al., 2008;  $M = -2.79$ , Seer et al., 2017), this may have affected the observed (absence of) effects of dopaminergic medication on error processing. A related explanation, as pointed out by Seer et al. (2017), may be that patients' medication doses differed among the studies. Specifically, the mean dose in Seer et al. (2017; LED = 1015) was relatively high compared to that in Willemssen et al. (2008; LED = 601); the mean dose in Stemmer et al. (2007) was not reported. As medication dose is likely to be related to disease stage, it seems that these explanations are not mutually exclusive.

Another potential explanation may relate to the task parameters – specifically, the proportion of incongruent trials (on which most errors are typically expected) differed among the three studies. Whereas the task in Seer et al. (2017) involved 50 % incongruent trials and 50 % congruent trials, this ratio was unbalanced in the other two studies such that the expectancy of these trial types and thus error probability differed. The task in Stemmer et al. (2007) involved two thirds incongruent trials and one third congruent trials, thus prompting subjects to increase their top-down influence on performance in order to avoid making errors. In contrast, the task in Willemssen et al. (2008) involved 20 % incongruent trials, 60 % congruent trials, as well as 20 % no-go trials, inviting participants to reduce their top-down level of control and rendering the incongruent trials relatively unexpected. Prior work demonstrated that the proportion of incongruent versus congruent trials within a task affects the processing of cognitive conflict (i.e., proportion congruency effect; e.g., Logan and Zbrodoff, 1979; Lowe and Mitterer, 1982) at both the behavioral and the electrophysiological level (Bartholow et al., 2005; Shedden et al., 2013). Specifically, the congruency effect is typically smaller in contexts where there are more incongruent than congruent trials compared to a context with more congruent than incongruent trials. It therefore seems reasonable that these differences regarding the proportion of incongruent trials among the three studies may have affected dopaminergic effects on error monitoring as well.

### 3.3.2. Conflict suppression

Five studies focused on the selective suppression of prepotent, incorrect responses, using either the Stroop task or the Simon task, where relevant and irrelevant stimulus features (e.g., stimulus color and location in the Simon task) signal responses that are either congruent or incongruent. While two of the studies showed no evidence for dopaminergic modulation (Fera et al., 2007; Wylie et al., 2012a,b), three studies showed a beneficial effect of medication on conflict suppression as reflected in the congruency effect (Costa et al., 2014; Trujillo et al., 2019;

van Wouwe et al., 2016). Specifically, Costa et al. (2014) observed that medication enhanced patients' resistance to interference in the Stroop task, but only for patients scoring relatively low on a working memory task and not did for those with relative high working memory capacity. Furthermore, work by Trujillo et al. (2019) and van Wouwe et al. (2016) demonstrates that both DA precursors and agonists improved conflict suppression in the Simon task.<sup>1</sup> Van Wouwe et al. (2016) also examined medication effects on conflict suppression as a function of the response distribution and found that the enhancing effect of medication was especially observed for responses at the slower end of the distribution. This suggests that selective control takes time to build up, and that future studies should consider the response distribution in addition to the more traditional average differences between congruent and incongruent trials. Finally, while Wylie et al. (2012a,b) observed no effect of DA agonist medication withdrawal on conflict suppression in the Simon task at the group level, they found that medication status did modulate conflict suppression when taking baseline performance into account. That is, patients who were relatively good at suppressing incorrect responses while off their medication showed an adverse effect of agonist medication, whereas patients who showed relatively poor conflict suppression off their medication benefited from medication. Importantly, both Costa et al. (2014) and Wylie et al. (2012a,b) used data analysis approaches that accounted for potential regression to the mean effects, allowing them to rule out this alternative explanation and ascertain that effects of dopaminergic medication were driven by individual differences between patients. Taken together, these findings suggest that the presence and/or directionality of DA effects on conflict suppression may depend on individual differences such as working memory capacity, response distributions, and task performance in the off medication state (but see van Wouwe et al., 2016).

### 3.3.3. Conflict adaptation

We identified three studies that evaluated the effect of medication on conflict adaptation. In each of these studies, patients performed a conflict task that included a contextual manipulation aimed at modulating the standard congruency effect where people perform worse on incongruent compared to congruent trials. For example, the congruency effect is typically reduced in contexts with high proportions of incongruent trials (proportion congruency effect; see above) and directly after incongruent as compared to congruent trials (congruency sequence effect or CSE; for a review see Duthoo et al., 2014).

The results showed variable effects of medication across conflict adaptation studies. First, Djamshidian et al. (2011) studied conflict adaptation in terms of the difference in performance between trials that were preceded by a different trial type (i.e., switching from a congruent to an incongruent trial or vice versa) and trials that were preceded by the same trial type. Note that unlike with the typical CSE, the authors did not take current trial type into consideration in this study. They found that PD patients were better at adapting when they were on medication compared to withdrawn from their medication. In contrast, Duthoo et al. (2013) observed that dopaminergic medication negatively affected conflict adaptation as reflected in the CSE. That is, patients showed conflict adaptation when they were tested after withdrawal from their regular medication, but not when they were on their medication. Lastly, Ruitenberg et al. (2019) found no evidence for dopaminergic modulation of conflict adaptation as reflected in the proportion congruency effect – patients showed reliable conflict adaptation both when they were on and off their medication.

With respect to the Djamshidian et al. (2011) study, one may wonder

<sup>1</sup> Note that as most patients in the van Wouwe et al. (2016) study were on levodopa mono- or dual therapy ( $n=45$ ) and only a small subset of patients were on DA agonist monotherapy ( $n=10$ ), it seems that this pattern of effects was largely driven by levodopa. Trujillo et al. (2019) specifically studied the effect of DA agonist medication.

whether comparing performance as a function of whether the previous trial type was the same or different as the current trial type in fact reflects conflict adaptation. As aforementioned, the CSE – a dedicated index of conflict adaptation – additionally takes into account the present trial type. It seems, then, that the measure used by Djamshidian et al. may actually be more indicative of switching abilities than conflict adaptation (note however that the study did not assess task-switching which is discussed below, as the patients' task remained the same throughout the experiment). Another caveat of the study by Djamshidian et al. (2011) is that patients performed only a very small number of trials (i.e., 16 Stroop trials vs. 246 and 360 trials in Duthoo et al. and Ruitenberg et al., respectively), which strongly limits the interpretation of the findings of the study.

The differential impact of medication status between the studies by Duthoo et al. (2014) and Ruitenberg et al. (2019) may pertain to the type of conflict adaptation that was examined in each study. Whereas the CSE as studied by Duthoo et al. (2014) is thought to reflect transient conflict adaptation involving trial-by-trial fluctuations in attentional demand, the proportion congruency effect as studied by Ruitenberg et al. (2019) is thought to reflect more sustained conflict adaptation in which attentional settings were optimized based on the overall congruency context of an entire block (e.g., Funes et al., 2010; Torres-Quesada et al., 2013). The findings related to the former type of conflict adaptation (as in Duthoo et al., 2014) seem to be in line with those for error processing (cf. Seer et al., 2017), suggesting that the use of dopaminergic medication may lead to a reduced ability to efficiently process trial-by-trial fluctuations in errors or conflicting information. In contrast, the latter type of more sustained conflict adaptation may involve more strategic adjustments that do not rely on error processing as much and may not be sensitive to dopaminergic modulation.

### 3.4. Action inhibition

Finally, we identified 12 studies in which the effect of dopaminergic medication on inhibition was examined. Based on the employed paradigms that these studies used to assess inhibition, we distinguish two types of action inhibition: 1) the withholding of a prepared action in go/no-go tasks, where subjects prepare a response (e.g., key press) and are instructed to either execute or withhold this response depending on whether a go stimulus or a no-go stimulus is presented; and 2) the cancellation of already initiated actions or 'stopping ability' in stop-signal tasks, where subjects respond as quickly as possible to a stimulus (i.e., go-signal), but are to terminate their response when a stop-signal is presented after initial stimulus presentation. Note that whereas go/no-go tasks only allow for measuring the success of action inhibition, stop-signal tasks additionally allow for determining the actual timing of the action inhibition process.

We identified five studies that examined PD patients' ability to withhold prepared actions using the go/no-go task. There were two studies showing that dopaminergic medication modulated this ability, with one showing a beneficial effect (Yang et al., 2017) and one showing an adverse effect (Geffe et al., 2016) with medication. However, the other studies found no significant effect of medication status on action inhibition (Antonelli et al., 2014; Farid et al., 2009; Herz et al., 2014). Note that the one study that found a negative effect of medication (Geffe et al., 2016) involved a version of the task that deviated from the more traditional go/no-go tasks used in other studies (Antonelli et al., 2014; Farid et al., 2009; Herz et al., 2014; Picazio et al., 2018; Yang et al., 2017). Whereas go and no-go trials are typically interleaved throughout the task, Geffe et al. presented these trials in a block-wise manner: in some blocks, participants had to respond to a target stimulus and ignore other stimuli (i.e., go blocks), and in other blocks this instruction was reversed (no-go blocks). Moreover, participants were *de novo* PD patients that were assessed before and after they started using medication, whereas patients in the other studies were on stable medication use that they withdrew from for study purposes. This may also contribute to the

differential findings regarding effects of medication. When considering the dependent measures used as an index for performance, it is striking that the only beneficial effect of medication reported by Yang et al. (2017) was observed in terms of the proportion of regular trials on which responses were not given before response deadline. These time-out trials may need to be interpreted differently than other measures, as they may not reflect intentional inhibition but rather slowed processing and/or decision making. Indeed, the go/no-go studies that reported no effects of medication status examined only response times and error rates – notably, Yang et al. (2017) did not observe effects on these measures either. Taken together, these observations suggest that effects of dopaminergic medication on withholding of a prepared response as reflected in go/no-go task performance may be dependent on both design aspects and specific measures used to assess inhibition.

Finally, seven studies examined PD patients' ability to stop already initiated actions using the stop-signal task. While two studies showed that dopaminergic medication enhanced stopping ability (Manza et al., 2018; Wylie et al., 2018), most studies found no significant effect of medication status on action inhibition (Alegre et al., 2013; Cerasa et al., 2015; George et al., 2013; Obeso et al., 2011b; Picazio et al., 2018). For these studies using the stop-signal task, it is notable that the large majority observed that behavior was consistent with horse-race models, where unintended responses on stop-trials are faster than responses on go-trials (with the exception of Obeso et al., 2011b; Picazio et al., 2018). Manza et al. (2018) suggest that previous stop-signal studies in PD did not observe enhancing effects of medication on stopping ability because they included patients that were on mixed medications and in later stages of the disease. As the studies listed here showed a large overlap in terms of task settings, this seems like a reasonable explanation for the significant effect as reported by Manza et al. (2018). While most studies on stopping ability in this review thus used the stop-signal task, a second study reporting a significant effect of medication (Wylie et al., 2018) involved a slightly different task, namely a stop-change paradigm in which participants should either cancel their response or switch to the alternative response upon a 'stop' or 'change'-cue, respectively. Wylie et al. (2018) found that stopping ability was better in patients on as compared to off their medication, but that changing ability was unaffected by medication status. Here, too, this suggests that design aspects of the task at hand should be taken into account, as well as patient characteristics such as disease stage.

## 4. Discussion

To our best knowledge, this is the first systematic review of studies on dopaminergic modulation of action control in PD. In 13 out of the 29 studies that we included in this review, dopaminergic medication status significantly modulated action control – either improving or impairing action control performance (Table 2). Below, we first discuss how neural circuitries underlying different action control components may relate to the directionality of DA effects, and to what extent the discussed studies on PD patients offer support for the DA overdose hypothesis. We then discuss how individual differences in patient characteristics may affect the specific benefits and drawbacks of dopaminergic medication on various action control components in PD. We also address the relationship between the present findings and findings from other fields on the link between DA and action control, including pharmacological and genetic studies on healthy subjects. Finally, we discuss challenges that need to be addressed for a better understanding of the role of DA in action control and suggest directions for future research.

### 4.1. Neural mechanisms and the directionality of DA effects

As outlined in the Introduction, the dopamine overdose hypothesis states that the effect of dopaminergic medication is dependent on the specific cortical-striatal circuitry underlying a function. Due the asymmetrical reduction of DA-levels in the dorsal versus ventral striatum in



the early stages of PD, it is expected that functions relying on circuitries involving the relatively depleted dorsal striatum are enhanced by medication, whereas functions relying on circuitries involving the relatively intact ventral striatum are impaired.

Two of the action control components addressed in the present review, namely planning and task-switching, are thought to rely on dorsal striatal circuitry. Specifically, planning and intentionally selecting an action by activating the anticipated effect of that action has been linked to the dorsolateral striatum (Melcher et al., 2008). In line with the overdose hypothesis, the study on action planning reviewed here showed that medication improved this component in PD patients (Colzato et al., 2012). Prior work has shown that dopaminergic medication also impacts the learning of associations between actions and outcome valence in PD patients (MacDonald and Monchi, 2011; van Wouwe et al., 2017). Together, these lines of research suggest that the retrieval of an event file and the anticipated effect of an action is governed by the dorsal striatum, while learning about the valence of the outcome of that action is governed by the ventral striatum. Task-switching has previously been shown to rely on a dorsolateral fronto-parieto-striatal circuitry (Cools et al., 2004; Sohn et al., 2000), and indeed several of the reviewed studies observed that dopaminergic medication positively affected switching in PD patients. Given indications from prior work that more abstract, higher-order switching seems to increasingly rely on cortical involvement (Cools et al., 2004), we propose that the absence of significant effects of medication status on the other studies was related to the relative difficulty of the used switch paradigms. Overall, the reviewed studies on these two components thus largely align with the overdose hypothesis, by showing beneficial effects of medication on action control functions relying on a dorsal striatal circuitry. This is further corroborated by observations that these functions are impaired in PD patients off their medication relative to healthy control subjects (e.g., Colzato et al., 2012; Cools et al., 2003; Shook et al., 2005).

The other action control components, namely conflict control (i.e., monitoring, suppression, and adaptation), and action inhibition, are thought to rely on a ventral striatal circuitry (e.g., Botvinick et al., 2001; Grandjean et al., 2013; Jha et al., 2015; Sebastian et al., 2013). For monitoring and conflict adaptation, we found some support for the idea that medication would hinder performance. The EEG signal that reflects performance monitoring, namely the ERN, is believed to be generated in the anterior cingulate cortex (ACC; Holroyd and Coles, 2002) which is part of ventral striatal circuitry. Out of the three studies on monitoring included in the present review, the study that observed an effect of dopaminergic medication on monitoring indeed reported that medication negatively affected ERN amplitude (Seer et al., 2017). Conflict adaptation is also thought to be mediated by the ACC (Botvinick et al., 2001, 2004; Grandjean et al., 2013) and thus could be expected to be impaired by dopaminergic medication. This notion was supported by findings of Duthoo et al. (2013) that trial-by-trial conflict adaptation was absent when PD patients were on their medication, but present when they were off their medication. However, Ruitenberg et al. (2019) observed no medication effect on more strategic, sustained conflict adaptation. Combining these findings, it could be argued that the sensitivity of conflict adaptation to dopaminergic modulation may depend on the extent to which adjustments rely on error processing. While conflict suppression and action inhibition are also thought to rely on a ventral striatal circuitry, the studies reviewed here did not generally observe a negative effect of medication on performance. For the suppression of incorrect responses, two studies found no effect and two other studies actually reported an enhancing effect of medication. While such suppression is often related to the ACC, it has also been argued that the prefrontal cortex (PFC) which is linked to the dorsal striatum plays a role (Cohen et al., 2000). It could be speculated that dopaminergic medication benefits the PFC while at the same time hindering the ACC, obscuring specific effects within either circuitry. Stopping ability has also been linked to a ventral striatal circuitry including the ACC and inferior frontal gyrus (Sebastian et al., 2013), yet the majority of the

studies reviewed here found no effect and three studies actually observed a medication-induced improvement. In total, the reviewed studies on ventrally-striatal mediated action control components thus offer little support for the overdose hypothesis, with only three studies showing performance impairment in PD patients on relative to off their medication (i.e., Duthoo et al., 2013; Geffe et al., 2016; Seer et al., 2017).

Taken together, the findings of the studies included in this systematic review converge towards an important role for DA in action control, in the sense that insufficient DA leads to action control impairment. However, evidence for the prediction that too much DA will also lead to action control impairment (cf. overdose effect) is less convincing. We suggest that absence of effects or contrasting findings can in part be explained by task design issues. While some of these issues reflect design differences that may (un)intentionally change the fundamental nature of the task or the strategy the participant engages to perform the task, others pose real limitations that significantly weaken the value of the study results or potentially renders them uninterpretable. Specifically, we believe that the very small number of trials in Djamshidian et al. (2011) and the violation of the key behavioral assumption of the horse-race model for the stop-signal task in Obeso et al. (2011b) and Picazio et al. (2018) call into question the interpretability of the respective study results. We recommend that future studies evaluate and report various performance measures and take into account the distribution of each measure. Moreover, we advocate for more replication studies to examine the role of DA in action control in PD with a specific focus on optimal task designs – that is, clear separation of cognitive processes with a design to avoid difficulty of interpretation and use of standardized quality measures and best practices for each task.

Recently, consensus views have been established on best practices for several of the tasks discussed in this review. For example, Verbruggen et al. (2019) provide straightforward and easy-to-implement guidelines for the design and analysis of the stop-signal task to measure action inhibition – including the recommendation to not estimate the behavioral index for stopping ability when the assumptions of the race model are violated, substantiating our aforementioned concern regarding two of the inhibition studies (Obeso et al., 2011b; Picazio et al., 2018). Conflict task designs should aim to minimize the contribution of other cognitive processes like feature-integration and contingency learning, and analyze a range of dependent measures (e.g., simple congruency effect and conflict adaptation effects) as allowed by the selected paradigm (Braem et al., 2019; see also Erb, 2020). In addition, studies should distinguish different types of conflict (e.g., semantic features causing stimulus-conflict in the Stroop task vs. spatial features causing response-based conflict in the Simon task), to examine whether dopaminergic medication may differently affect the resolution of these types of conflict in PD. Prior work in healthy subjects observed distinct neural bases for each conflict type, with the resolution of stimulus-based conflict relying more on the recruitment of parietal areas and the resolution of response-based conflict more on premotor areas (Egner et al., 2007). This suggests that this latter conflict type may especially be sensitive to medication status. While the studies reviewed in the present work do not directly provide support for this notion, this issue requires further investigation as the number of studies examining each conflict type were limited and stimulus- and response-based conflict were not investigated within the same group of PD patients. Finally, Schmidt and Liefoghe (2016) note that researchers should be wary of feature integration confounds in task-switching paradigms. In addition, Koch et al. (2018) outline various design aspects that could influence the overall size of switch-costs, such as practice amount and instruction type (e.g., cued vs. voluntary switching). Given potential working memory deficits in PD and interactions with DA medication, studies on medication effects in PD would benefit from standardization of these aspects.

Although admittedly speculative, another potential explanation for the differential sensitivity to dopaminergic medication of various action control components with the same underlying neural mechanism may be



that each component may have a distinct optimal DA level. In the domain of executive functioning, Fallon et al. (2015) reported indications that the optimal DA level in PD may be higher for set shifting than for working memory tasks – even though both processes are known to rely on the dorsolateral PFC, thus demonstrating function-specific optimal DA levels in PD. Potentially, in the domain of action control, dopaminergic medication may impair the ability to adapt to conflict in PD by exceeding the optimal DA level for conflict adaptation, whereas it may enhance inhibition of an incorrect response by restoring the optimal DA level for inhibition, and not affect stopping ability even though all three components have been related to the ventral-striatal circuitry. Future studies should further investigate this notion, taking into account baseline performance in the off medication state and other individual differences (see next section).

Another issue to consider is that different experimental approaches for comparing PD patients' performance on vs. off dopaminergic medication may have contributed to the observed results. While most of the reviewed studies used a within-subject design in which the order of medication status across patients was counterbalanced, there may still be potential confounding effects related to time of day as exact measuring moments may vary between patients within a study. In addition, a subset of the studies that employed a within-subject design always tested patients in the off medication state first (i.e., either patients withdrawing from their regular medication or *de novo* PD patients), which may have introduced carry-over practice effects. Furthermore, the use of between-subjects designs comparing performance between a group of PD patients on their medication and either a group of PD patients off their medication (Cools et al., 2001a,b) or a group of *de novo* patients (Stemmer et al., 2007) may have introduced even more sources of between-group variance given the relatively small sample sizes. In particular, the comparison between *de novo* patients and treated patients introduces variance related to disease duration. On a related note, it could be argued that the observed performance differences between the on and off medication states may to some degree be explained by DA-related improvements in motor proficiency (e.g., key press responses). However, with exception of the go/no-go task, the studies reviewed in the present manuscript (partly) control for such potential baseline motor proficiency differences by either evaluating performance indices that are based on within-subject difference scores or using a staircase procedure. Finally, another source of variance may pertain to the fact that the majority of the reviewed studies did not strictly control for the timing of dopaminergic medication intake in relation to the start of task performance. For future work, we recommend employing within-subject designs in which the order of medication status is counterbalanced, time since medication intake is standardized across patients in the on medication state, and performance is measured at the same time of day in both states, in order to minimize bias and confounds.

#### 4.2. Considerations regarding individual differences in patient characteristics

In the previous section we argued that task design issues may affect whether or not DA effects are observed. In addition to such issues, individual differences in patient and medication characteristics should also be taken into consideration when studying the role of DA in action control by manipulating medication status in patients with PD. For example, it is likely that disease stage affects observed outcomes (cf. Manza et al., 2018). Overdose effects are expected to be pronounced relatively early in the disease, as DA levels then are depleted in the dorsal striatum but relatively intact in the ventral striatum. As about one-third of the studies included in this review did not report stages, it is difficult to evaluate how differences in stages across studies may have contributed to contrasting findings. We therefore recommend that future studies specify the mean and range of disease stages of the participating patients, and even use this information in the analyses (e.

g., as a covariate) to evaluate whether stage affects the magnitude of medication effects. While it is clear that dopaminergic medication can affect performance by restoring DA-levels in depleted regions or overdosing intact regions, an open question remains whether the relationship between DA and performance in PD follows an inverted U-curve. For example, ventral striatal-mediated tasks are typically not tested at later stages in the disease; thus it remains uncertain if DA-depletion in this area or associated networks eventually leads to impaired performance with disease progression in PD. Similarly, as medication restores DA-levels in dorsal striatal circuitries, it remains unclear whether excessive DA-levels in such circuitries are associated with impaired performance in PD as has been shown in healthy adults (Aarts et al., 2014b; see below).

Furthermore, there are indications that individual differences in cognitive abilities may modulate the effect of dopaminergic medication on action control. For example, previous studies have observed that the effect of medication was dependent on patients' baseline performance (i.e., performance in the off medication state; Wylie et al., 2012a,b) and their working memory capacity (Costa et al., 2014). Likewise, individual differences in PD symptoms may play a role in modulating effects of DA. That is, medication effects may differ as a function of PD subtypes classified based on, amongst others, motor features (e.g., tremor dominant vs. postural instability and gait dysfunction), non-motor features (e.g., presence vs. absence of depressive symptoms), age at onset, and rate of progression. As prior work has shown behavioral differences between patients from different motor subtypes on the Simon task (Wylie et al., 2012b) and stop-signal task (Tolleson et al., 2017), future studies should examine whether effects of dopaminergic medication on performance in these tasks may also differ among subtypes. A final factor that should be considered concerns the types of dopaminergic medication that patients involved in the study are taking (e.g., DA precursors, DA receptor agonists, or inhibitors of DA metabolism). For example, DA agonists are associated with the development of impulse control disorders (Voon et al., 2017; Weintraub and Claassen, 2017), which in turn were found to be associated with alterations in functional connectivity and structural brain properties (Ruitenberg et al., 2018). It could be argued that such neural alterations may contribute to individual differences in the effect of dopaminergic medication on action control. While there are indications that DA precursors and agonists do not differently affect the inhibition of impulsive actions in PD (van Wouwe et al., 2016), studies systematically examining this issue remain scarce and future work should examine the role of medication types for other action control components in more detail. As we will argue in more detail below, within-subject designs could resolve some of the issues related to individual differences by investigating medication effects on a series of tasks that are associated with dorsal versus ventral striatal functions within the same patient.

#### 4.3. Integration with findings from other fields

To elucidate the role of DA in action control, the present review focused on studies that compared performance of PD patients on versus off dopaminergic medication on tasks that assessed action control. Other lines of research also suggest a role for DA in (at least some components of) action control.

Studies on healthy subjects support the notion that DA can modulate action control. For instance, Aarts et al. (2014b) observed that a reward-induced DA increase resulted in impaired suppression of incorrect responses in the word-arrow Stroop task in healthy subjects with relatively high baseline levels of DA-synthesis capacity in the striatum, which was attributed to a DA overdose. In contrast, the DA increase was found to enhance such suppression in subjects with relatively lower baseline levels. In addition, drug-induced changes in DA levels have been found to affect action control in healthy controls. For example, Van Holstein et al. (2011) showed that administration of a DA receptor agonist improved task-switching performance in healthy subjects with

genetically determined low baseline levels of DA. In another study, [de Bruijn et al. \(2004\)](#) showed that performance monitoring as reflected in the ERN was significantly improved in healthy participants that were administered amphetamine (a dopamine agonist) relative to participants that received a placebo.

Second, studies using an individual differences approach in healthy subjects have provided indications that the effect of DA on cognitive processes depends on baseline levels of striatal DA-synthesis capacity ([Aarts et al., 2014b](#)) and cortical DA release ([Albrecht et al., 2014](#)), personality traits of impulsivity ([Cools et al., 2007](#)), and genetic markers (e.g., [Colzato et al., 2010](#); [Congdon et al., 2008](#); [Fallon et al., 2013](#); [Garcia-Garcia et al., 2010](#); [MacDonald et al., 2016](#)). Given findings of [Costa et al. \(2014\)](#) and [Wylie et al. \(2012a,b\)](#) that medication effects were dependent on individual patient characteristics, it seems likely that individual differences such as the ones listed here for healthy subjects may also modulate the effect of dopaminergic medication in PD patients. We recommend that future studies examining such individual differences should account for potential regression to the mean effects, for example by using working memory capacity rather than baseline action control performance as the predictor of on vs. off medication differences (cf. [Costa et al., 2014](#)). This may mitigate the issue of regression to the mean and rule it out as an alternative explanation, provided that there is no correlation between the predictor and baseline performance.

Finally, animal studies also corroborate the notion that both insufficient and excess DA level can impair cognitive processes ([Williams and Goldman-Rakic, 1995](#)) and that DA is involved in action control ([Eagle et al., 2011](#); [Eagle and Robbins, 2003](#)). Studies in this field have additionally suggested a specific involvement of dopamine D1 versus D2 pathways in action control. For example, D1 antagonists were found to improve stopping ability in rats, while D2 antagonists are associated with decreased performance ([Eagle et al., 2011](#)). In healthy individuals, there are also indications that individual differences in D1 and D2 receptor availability are associated with stopping ability ([Robertson et al., 2015](#)). Future studies should systematically examine the specific involvement of these pathways in relation to action control in PD.

#### 4.4. Limitations and future directions

At the methodological level, a limitation of this systematic review is that we used only one database (i.e., Web of Science) for our literature search and only included articles available in English. Although Web of Science includes major international academic journals, this approach may have potentially biased our search results and the number of studies available. Expanding the scope of the journals included in the literature review by including other databases and articles written in different languages may yield additional results.

At a theoretical level, our discrete categorization of studies on the basis of specific action control components enabled us to manage and accommodate a broad literature. At the same time, this approach may give the false impression that we envisage these components as relating to fully independent mechanisms. We believe that a comprehensive understanding of the role of DA in action control will require further exploration of the interplay between various components and their potentially (partly) shared mechanisms. Indeed, performance modulations evoked by dopaminergic medication in several of the studies included in the current review may not be so clearly attributable to a single component of action control. For example, the lack of *conflict adaptation* effects in PD patients on their medication as reported by [Duthoo et al. \(2014\)](#) may (partly) reflect the impact of dopaminergic medication on *monitoring* processing that steer such conflict adaptation. Future experimental designs and paradigms should aim at elucidating the mechanistic nature of action control components by exposing both shared and unique processes.

Another challenge in interpreting the findings of studies evaluating the effect of dopaminergic (on vs. off) manipulations on behavior in PD patients, is that behavioral measures allow limited inferences regarding

brain mechanisms. Moreover, our understanding of the neural mechanisms involved in ‘normal’ action control in healthy subjects is still in progress. While the studies discussed in this review suggest that dopaminergic medication can modulate DA levels in the dorsal and ventral striatum to either restored or excessive states, respectively, more direct measures of the integrity of the DA system would be required to quantify the changes on and off medication. For example, PET scans could be used to evaluate DA update capacity ([Loane and Politis, 2011](#)). In addition, a somewhat more indirect but well-established measure of dopaminergic function is eye blink rate (for a review, see [Jongkees and Colzato, 2016](#); but see for nuances [Dang et al., 2017](#); [Slagter et al., 2015](#)). For instance, previous work has shown that spontaneous eye blink rate is associated with inhibitory abilities ([Colzato et al., 2009](#); [Zhang et al., 2015](#)). In addition, eye blink rates have been linked to conflict adaptation ([van Bochove et al., 2013](#)). Future studies should quantify (changes in) DA levels in relationship to action control performance.

Vice versa, the absence of a significant effect of dopaminergic medication on cognitive processes or behavioral outcomes does not refute the possibility of effects at another level. For example, it may be that medication status affects brain recruitment during the task, but that compensatory mechanisms that allow for maintained performance obscure such effects to be reflected in behavior. Indeed, [Aarts et al.'s \(2014a\)](#) findings at the neural level supported the overdose hypothesis, even though there was no evidence at the behavioral level. Specifically, individual differences in medication-related increases in switch-related activation in the dorsomedial striatum were associated with improvements in task-switching. Similarly, [Fera et al. \(2007\)](#) found no behavioral effect of medication status on conflict suppression in a Stroop task. However, at the neural level, PD patients on their medication showed greater PFC activation, which was positively correlated with medication-related improvement in Stroop task accuracy. When tested off their medication, PD patients showed underactivity of the PFC (related to dorsal striatal circuitry) as well as more activity of the ACC/pre-SMA (related to ventral striatal circuitry). This could be indicative of a compensatory mechanism involving compensation by a relatively unaffected circuitry. Future studies should further examine neurocognitive mechanisms associated with functions that may be sensitive to DA effects in PD, by complementing experimental tasks with neuroimaging methods to be able to meaningfully interpret potential absent effects at the behavioral level.

Another open question is to what extent performance across the action components addressed in this review relies on DA versus other neuromodulators that could have a compensatory effect. For example, prior work has shown that inhibition of an initiated action in the stop-signal task is linked to serotonin and norepinephrine (e.g., [Ye et al., 2014, 2015](#)), and that norepinephrine can ameliorate inhibition deficits in PD at both the brain and behavioral level ([Rae et al., 2016](#)). Future studies should investigate to what extent the reliance on these neuromodulators and/or compensation by other neurotransmitters could explain the variability of DA effects in studies involving PD patients observed in this review.

Finally, in terms of clinical implications, it remains unclear whether the effects of dopaminergic medication on the various action control components in PD reviewed here are associated or independent. The inconsistent findings on the role of DA both between and within the components reviewed here highlight the need for studies with a more systematic, multi-method approach (i.e., both behavioral and neuroimaging) to model DA effects across action control components within individuals. Future studies should therefore examine the impact of medication status on multiple action control components within the same patients, and evaluate whether individual differences in the magnitude of medication effect are correlated across different action control components. This will also allow comparing DA effects on similar processes across different paradigms (e.g., error monitoring in Simon vs. stop-signal tasks). Furthermore, longitudinal designs may help

in determining whether the trajectory of DA depletion and subsequent effects of medication on action control in PD are associated across components. A better understanding of the (in)dependence and time course of dopaminergic medication effects on various action control components may additionally extend current insights on how cognitive processes underlying movement control are related to debilitating motor symptoms in PD. For example, freezing of gait has been linked to impairments in task-switching (Naismith et al., 2010), conflict suppression (Walton et al., 2015), and action inhibition (Cohen et al., 2014), suggesting that effectively targeting these action control abilities in dopaminergic interventions may promote motor functioning.

## 5. Conclusions

In this review we investigated the role of DA in action control, by evaluating results from empirical work involving a manipulation of medication status in patients with PD. From these studies, we conclude that insufficient DA hinders action control performance whereas excess DA levels may not per definition be problematic. This finding has implications for our general understanding about the role of DA in action control, as it suggests that its specific role may not solely depend on the neural circuitry underlying the action control component at hand. We propose that DA effects may depend on task characteristics, involving both design aspects and specific measures used to assess action control. In addition, DA effects may depend on individual differences in patient characteristics including baseline performance off medication and neurobiological factors. Future studies on the role of DA in action control should systematically evaluate whether optimal DA levels for different action control components are related or independent and examine to what extent effects of specific classes of DA medication in PD are associated across different components. Refining our understanding of DA (overdose) effects in action control may ultimately help clinicians in optimizing medication regimens for PD patients, by adjusting treatments to individual needs based on patients' disease stage and specific symptoms.

## Declaration of Competing Interest

The authors report no declarations of interest.

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