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Title Page

A systematic review of decision-making impairments in Parkinson's Disease: Dopaminergic medication and methodological variability

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A systematic review of decision-making in PD

Abstract

Cognitive impairments in Parkinson's disease have been studied with great interest, and decision-making abilities in particular have received attention over the past decade. The degree of decision-making impairments in Parkinson's disease has been debated in relation to different types of decision-making tasks and the possible effect of dopaminergic medication, among others. The present review presents a systematic overview of literature investigating decision-making in patients with Parkinson's Disease treated with dopaminergic medication. The aim of the review is to discuss decision-making impairments displayed by patients considering effects of dopaminergic medication. Patients with Parkinson's Disease on dopaminergic medication were found to be impaired in decision making tasks. Dopaminergic medication has a complex, but often significant, relationship with decision making impairments. Finally, the influence of methodological differences in the assessment of decision-making will be considered offering important implications for future research.

Keywords: Parkinson's disease, decision-making, dopaminergic medication, Iowa Gambling Task, Game of Dice task

Introduction

Parkinson's Disease (PD)¹ is a neurodegenerative disorder characterized by bradykinesia, rigidity, tremor, and postural instability [1]. Beyond these cardinal motor symptoms, cognitive functions undergo critical alterations as the disease progresses [2] ranging from relatively minor cognitive deficits in the early stages of the disease, to dementia in later stages [2–4]. In addition, sudden cognitive alterations have been associated with acute adverse effects of dopaminergic medication [4] including levodopa (L-dopa) and dopamine agonists (DA).

Executive functions, and decision-making in particular, have received substantial attention in PD research [3,5,6]. Decision-making is a complex executive function, based on functions such as selection, inhibition, working memory, feedback, and estimation and involves choosing between two or more options, considering available opportunities and potential outcomes [4,7].

¹ Abbreviations: PD = Parkinson's disease. DA = dopamine agonists. DBS = deep brain stimulation. DND = Deal no deal task. GDT = Game of dice task. HC = healthy controls. IGT = Iowa gambling task. L-dopa = Levodopa. LEDD = Levodopa equivalent daily dose. STN = subthalamic nucleus.

PD is associated with progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta in the basal ganglia [5,8] leading to the characteristic motor symptoms of PD [5]. Besides motor functioning, the basal ganglia have been shown to affect executive functions including reward processing, evaluation of outcomes, and decision-making [5]. The neuroanatomical and functional underpinnings of decision-making has been identified as the lateral, medial and orbitofrontal cortex, and additionally the striatum, amygdala, the anterior cingulate cortex, and the prefrontal cortex [8–10]. Dopaminergic medication aims to counteract the dopamine depletion related to PD through administration of L-Dopa or dopamine agonists [11]. However, dopaminergic medication has shown varying effects on cognition in PD, alleviating some cognitive deficits while worsening others [12,13]. The overdose hypothesis has been proposed to explain these asymmetrical effects. Studies show that the loss of dopaminergic neurons in PD is unequally distributed across the striatum [14,15]. In early stages of the disease the putamen and the dorsal part of the caudate nucleus is more severely affected, while the ventral striatum is less affected [14,16]. Thus, according to the dopamine overdose hypothesis, dopaminergic medication causes the ventral striatum to be overstimulated or overdosed [4,14]. When assessing PD patients on dopaminergic medication, the medication normalizes performance on tests that depend on the putamen and dorsal part of the caudate nucleus, while it impairs performance on tasks dependent on the ventral striatum [14]. This was supported by Cools et al. [15] who found withdrawal of dopaminergic medication to have a positive effect on probabilistic reversal learning, associated with the ventral striatum, whilst having negative effects on task-set switching, associated with the caudate nucleus. In this way, dopaminergic treatment can be expected to alter decision-making performance differently, depending on the decision-making task.

Additionally, inclusion of feedback in decision-making tasks seems to be relevant to consider when evaluating effects of dopaminergic medication, as the dopaminergic system has been suggested to play an important role in learning from feedback [5,17]. Dopaminergic medication has been suggested to impair learning from feedback in PD patients [17,18]. According to the overdose hypothesis, inability to utilize feedback might be a consequence of striatal overdosing with dopaminergic medication, which prevents dips in dopamine, thereby hindering learning from negative feedback [17,19]. The present review aims to provide an overview of findings from empirical studies on decision-making abilities in PD patients treated with dopaminergic medication. Thus, the present review will systematically expand on the knowledge from previous meta-analysis

and reviews [5,20,21], through inclusion of all decision-making tasks and exploring impairments in patients treated with dopaminergic medication.

Decision-making is typically divided into two categories: 1) decision making under *risk*, which involves situations where probabilities are known or can be known [5]; 2) decision making under *uncertainty*, also called *ambiguous* decision-making, wherein probabilities in the situation are not known and cannot be deduced [5]. This distinction is not clearly defined, and although most studies define the Iowa Gambling Task (IGT) as a task of decision-making under uncertainty [5,22,23] other studies label the task as risky decision-making [24], or a combination of both [25]. Evidence has associated decision-making under risk with greater activation of the ventral striatum, while decision-making under uncertainty to a greater extent involved the orbitofrontal cortex [26,27]. Generally, decision-making under risk seems to be more dependent on executive functions than decision-making under uncertainty [8,21]. Therefore, the distinction between decision-making under risk and uncertainty seems reasonable and useful for the purpose of the present review.

Materials and methods

As argued above, the aim of the present study is to systematically review empirical findings on decision-making in PD patients treated with dopaminergic medication to clarify if they are impaired and to discuss how dopaminergic therapy impact decision-making in PD. Studies included in the review were identified through PubMed and MEDLINE entering the following search words: Parkinson AND (decision making OR choice making) AND (medication OR dopamine). The final search was conducted on 11th of May 2018 and excluded animal studies and articles in other languages than English. A total of 281 studies were identified and were screened according to the following criteria: A) Inclusion criteria: Empirical studies examining decision-making in PD patients treated with dopaminergic medication; B) Exclusion criteria: Reviews or theoretical papers; studies exclusively focusing on other diseases than PD or focusing on non-medicated patients; studies focusing on other tasks than decision-making, e.g. learning; studies exclusively focusing on patients with impulse control disorders. In total, 29 studies fulfilled inclusion and exclusion criteria and were included in the review. All included studies are presented in **table 1** and the inclusion process is presented in **figure 1**.

Fig. 1: Overview of the identification process of relevant studies

Summary and discussion of findings

All PD patients participating in the reviewed studies received dopaminergic medication and the majority were treated with a combination of L-dopa and DA. Some patients received either L-dopa- or DA monotherapy, while a minority of patients received other forms of medication, such as COMT inhibitors or MAO inhibitors. Finally, some patients were treated with deep brain stimulation (DBS) predominantly in the subthalamic nucleus (STN).

For an overview of findings on decision-making impairments, see **figure 2**. Overall, findings suggest that PD patients on dopaminergic medication are impaired in decision-making, either indicated by significantly reduced decision-making scores on various paradigms, compared to HCs, or by applying disadvantageous strategies, or making more impulsive or risky decisions during task performance. As shown in **fig. 2** most studies found PD patients, both on and off medication, to be significantly impaired compared to HCs. Few studies focused specifically on the role of dopaminergic medication, but the possible impact hereof on decision-making was emphasized by several authors [23,28,29]. Furthermore, multiple studies suggested that impairments in decision-making may be related to deficits in feedback processing [22,27,29].

Based on the included studies, it is evident that while PD patients on dopaminergic medication show impaired performance on decision-making tasks, results are blurred by varying methodological approaches including different paradigms requiring different functions, sample variation, and heterogeneity in PD symptomatology, progression, and treatment. Some studies used a repeated measures approach when testing patients on/off medication [22,24,30], while others tested different subjects for the on and off medication condition [31,32]. Moreover, in some studies patients were tested several times, while HCs were only tested once [23,24]. This could potentially be problematic and result in test-retest effects confounding the results. In addition, not all studies included HCs [33–36] and thirteen studies [23,27–29,33,35,37–43] did not test patients off medication, which contributes to the uncertainty about effects of medication. Thus, it remains unclear to what extent decision-making is impaired in PD and to what degree dopaminergic medication impacts decision-making processes.

Decision-making tasks

A variety of decision-making tasks are included in this review and used to assess decision-making abilities. Included tasks will be briefly described and summarized below.

Decision-making under uncertainty

The **Iowa Gambling Task** (IGT) is commonly used as a measure of decision-making under uncertainty and is designed to simulate real-life decision-making [44]. The IGT presents participants with four decks of cards (A, B, C, or D) from which they are instructed to select one card at a time for a total of 100 trials [44]. The goal of the task is to maximize the amount of imaginary money through card selections [44].

Decision-making under risk

Game of Dice task is a gambling task designed to assess the influence of executive functions on decision-making [45]. The task involves 18 throws of a die, in which participants must try to maximize their fictive starting capital by betting on one or multiple numbers [45]. Other betting tasks include the **Investment task** [46] and the **Cambridge Gamble Task** [47].

In the **Deal no Deal task** [48] participants initially selects one of 26 briefcases which is removed and is their briefcase. When presented with the content of the other cases they can choose to keep their case or accept a price offered. The **Vancouver Gamble task** [26] involves participants deciding

between options to maximize monetary gains while the **Framing paradigm** [23] entails deciding between a sure win or gambling to win more. Finally, the **Balloon Analog Risk task** [49] involves deciding between potential rewards or losses.

Uncategorized decision-making tasks

Uncategorized decision-making tasks in this review includes a range of tasks, neither defined as decision-making under risk nor uncertainty. The **Dynamometer task** [34] and the **Choice task** [50] are tasks in which participants decide if they want to put in the effort for a given reward. In the **Pixel task** [43] participants are shown circles with red and blue pixels and are asked to estimate which color there are more of. **Binary choice task, choice titration task, and intertemporal choice task** [31,51] are all based on the principle that participants select between smaller rewards given sooner or larger rewards later, while in the **Valuation rating task** [31] participants rate the attractiveness of monetary rewards. In the **Moving dots task** [52] participants are either instructed to complete each trial fast or accurately. **Beads task** [38] participants are required to select from which one of two cups a bead is being drawn. In the **Rogers Decision-Making task** [53] participants are similarly told to guess the location of a token and bet on their own guess. Others include **Dynamic decision-making** [32] in which participants continually decide and receive feedback, the **Moral decision-making** [39] participants had to decide if they would act altruistically or egoistically in moral issues scenarios. **Probabilistic selection task** [18] and the **Face decision task** [54] involves selecting between options and learning through feedback.

In the following, selected studies will be compared and discussed distinguishing between decision-making under uncertainty, under risk, and uncategorized tasks. For an overview of the included studies and their findings see **table 1**.

Fig. 2: Number of studies reporting significant results in decision-making abilities compared to a HC group. For studies with multiple decision-making assessments, impairments are reported if there is significant impairments in any tasks.

Table 1. Overview of included studies

Reference	PD group, N	Control group, N	Treatment: N	Mean LEDD, mg/day (<i>SD</i>)	Mean age PD years (<i>SD</i>)	Mean disease duration (<i>SD</i>)	Age of onset	Decision-making task	Feed-back	Additional measures	Tested off medication	Main findings
Decision making under risk												
Boller et al. (2014) [22]	18	(HC from previous study)	L-dopa+DA+ STN-DBS: 18	519.61 (382.47)	64.3 (10.2)	13.61 (7.11)	-	GDT	Yes	-	Yes (DBS on/off)	* -GDT performance of PD patients vs. HC.
Brandt et al. (2014) [23]	30	15	L-dopa+DA: 12 STN-DBS: 15 Other: 3	MED: 1262.98 (829.83) DBS: 1351.02 (868.61)	MED: 64.78 (8.09) DBS: 67.15 (6.28)	-	-	GDT, DND, Framing Paradigm	Yes	-	No (DBS on/off)	PD patients + risky decisions in GDT. DBS on patients were risk-averse in DND.
Euteneuer et al. (2009) [27]	21	23	L-dopa+DA: 21	487.69 (317.18)	67.60 (7.31)	85.7 (72.70) months	-	GDT, IGT	Yes	EDA	No	- IGT score, - use of negative feedback, * - GDT in patients.
Labudda et al. (2010) [29]	10	12	L-dopa+DA: 10	-	57.60 (7.83)	84.75 (44.49) months	-	GDT	Yes	fMRI	No	PD patients * - in GDT, - use of feedback, and + risky choices.
Rossi et al. (2010) [33]	20	-	L-dopa+DA: 20	+PG: 935.9 -PG: 698.2	+PG: 61.4 (6.9) -PG: 65.1 (3.8)	-	+PG: 52.0 (5.6) -PG: 58.3 (6.9)	IGT, GDT, Investment Task	Yes	-	No	- IGT score for PD patients with PG vs. PD patients without PG.
Sharp et al. (2013) [26]	18	18	L-dopa: 11 L-dopa+DA: 7	631.15 (294.73)	65.47 (9.17)	-	Time since diagnosis: 5.59 (4.04)	Vancouver Gambling Task	Yes	-	Yes	MED off showed * risk aversion for large losses vs. MED on and HC.
Simioni et al. (2012) [49]	23	20	L-dopa/carbidopa: 17 DA: 10 Other: 12	541.6 (357.3)	65 (8.6)	6.3 (6.1)	-	Balloon Analog Risk Task	Yes	-	Yes	PD patients MED on took * more risks across trials vs. controls

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Torta et al. (2009) [47]	15	13	L-dopa+DA: 15	1048.83 (313)	58.4 (6.9)	13.2 (3.2)	-	Cambridge Gamble Task	Yes	N-back task	Yes	PD patients lacked strategy and + in impulsivity. Higher MED doses = - decision-making and + impulsivity.
Decision making under uncertainty												
Benussi et al. (2017) [35]	60	-	-	Cathodal tDCS: 392 (280) Anodal tDCS: 384 (275) Sham tDCS: 506 (367)	Cathodal tDCS: 62.9 (10.5) Anodal tDCS: 63.2 (9.2) Sham tDCS: 63.5 (8.6)	-	-	IGT	Yes	-	No	* + scores for PD patients with cathodal transcranial direct current stimulation vs. sham stimulation.
Castrioto et al. (2015) [24]	20	24	L-dopa+DA+STN-DBS: 20	1459 (657)	53.2 (6.6)	10.3 (3.8)	-	IGT	Yes	-	Yes (DBS pre- and post operation)	* + scores for PD patients after DBS surgery vs. before surgery.
Euteneuer et al. (2009) [27]	21	23	L-dopa+DA: 21	487.69 (317.18)	67.60 (7.31)	85.7 (72.70) months	-	GDT, IGT	Yes	EDA	No	- IGT score, - use of negative feedback, * - GDT in patients.
Evens et al. (2015) [41]	33 + 33 (DBS)	34	L-dopa+DA: 33 L-dopa+DA+STN-DBS: 33	882.71 (386.63) DBS: 938.54 (367.16)	65.18 (8.13) DBS: 65.88 (6.40)	7.37 (4.26) DBS: 15.27 (5.37)	-	IGT	Yes	Delay discounting, incentive value of everyday objects	No	PD DBS patients made * disadvantageous choices vs. PD
Gescheidt et al. (2012) [40]	19	20	L-dopa+DA: 18 L-dopa+other: 1	1259 (690.6)	50.32 (8.74)	11.32 (6.42)	-	IGT	Yes	-	No	PD patients - effective strategy and preferred deck B.
Gescheidt et al. (2013) [28]	18	18	L-dopa+DA: 18	1155.8 (862.5)	52.67 (7.45)	6.33 (2.87)	-	IGT	Yes	fMRI	No	- IGT score for PD patients. * - activation of left putamen after loss.
Kobayakawa et al. (2017) [42]	20	37	L-dopa+DA: 20	383.4 (216.3)	70.1 (8.7)	6.3 (3.4)	-	IGT	Yes	MRI (VBM)	No	PD patients had * - IGT scores in the latter half of the task vs. HC.

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Rossi et al. (2010) [33]	20	-	L-dopa+DA: 20	+PG: 935.9 -PG: 698.2	+PG: 61.4 (6.9) -PG: 65.1 (3.8)	-	+PG: 52.0 (5.6) -PG: 58.3 (6.9)	IGT, GDT, Investment Task	Yes	-	No	- IGT score for PD patients with PG vs. PD patients without PG.
Uncategorized decision-making tasks												
Chong et al. (2015) [30]	26	26	L-dopa+DA: 11 L-dopa: 10 DA: 5	538 (275)	66.6 (6.8)	5.1 (3.1)	-	Dynamometer task	Yes	-	Yes	MED on patients invested * more effort vs. MED off.
Cools et al. 2003 [53]	12	12	L-dopa: 12 L-dopa+DA/selegiline: 4	552 (60)	64.6 (1.5)	-	-	Rogers Decision Making Task	Yes	Task-switching	Yes	PD patients MED on made quicker bets vs. MED off.
Djamshidian, O'Sullivan, Lawrence et al. (2014) [43]	29 + 15 (ICD)	17	L-dopa+DA: 17 L-dopa: 12 DA (ICD): 15	L-dopa+DA: 671.6 (82) L-dopa: 627.0 (97) DA (ICD): 935.0 (87)	L-dopa+DA: 62.6 (8.0) L-dopa: 66.1 (7.9) DA (ICD): 58.1 (9.7)	L-dopa+DA: 9.9 (4.4) L-dopa: 9.1 (6.7) DA (ICD): 11.1 (5.4)	L-dopa+DA: 52.1 (8.1) L-dopa: 57 (6.6) DA (ICD): 47.1 (8.6)	Pixel task	Yes	RT task	No	+errors in patients. Patients treated with L-dopa were * slower vs. patients treated with L-dopa and DA.
Djamshidian, O'Sullivan, Lees et al. (2012) [54]	27 + 26 (ICD)	16	L-dopa: 27 L-dopa (ICD): 26	740.1 (369) ICD: 934.2 (407)	65.3 (5.3) ICD: 58.0 (9.3)	10.0 (6.6) ICD: 11.0 (4.2)	55.3 (7.4) ICD: 47.7 (9.5)	Face decision task	Yes	-	Yes	* decrease in emotion bias in MED on vs. MED off in PD.
Djamshidian, O'Sullivan, Tomassini et al. (2014) [37]	27	17	STN-DBS+L-dopa+DA: 14 STN-DBS+L-dopa: 13	DBS+L-dopa+DA: 794.3 (292.2) DBS+L-dopa: 613.3 (379.0)	DBS+L-dopa+DA: 55.9 (10.0) DBS+L-dopa: 60.0 (7.2)	DBS+L-dopa+DA: 15.0 (4.9) DBS+L-dopa: 13.3 (4.8)	DBS+L-dopa+DA: 40.1 (8.1) DBS+L-dopa: 46.1 (7.5)	Pixel task	Yes	-	No	+ errors for PD group. Patients treated with DBS, L-dopa, DA made * faster decisions vs. patients not treated with DA.
Foerde et al. (2016) [31]	33	18	L-dopa+DA: 26 DA: 2 Other: 3	On MED: 499.7 (371.0) Off MED: 658.7 (362.3)	On MED: 70.8 (8.0) Off MED: 61.9 (7.8)	On MED: 7.6 (6.9) Off MED: 7.2 (5.1)	-	Binary choice task, valuation rating task, choice titration task	No	-	Yes (different groups)	MED on PD patients showed + farsightedness vs. MED off and HC.
Frank et al. (2007) [18]	15 + 17 (DBS)	27	L-dopa+DA: 32	-	67.8 (2.1) DBS: 64.5 (2.8)	8.8 (0.8) DBS: 14.4 (1.5)	-	Probabilistic selection task	Yes	-	Yes	PD patients had * slower responses in high-conflict vs. low-conflict situations.
Huang et al. (2015) [52]	13	14	L-dopa+DA: 13	793.64 (359.74)	61.62 (13.96)	7.27 (.64)	-	Moving Dots Task	Yes	-	Yes	MED on PD patients made * + errors vs. HC and MED off.

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Le Bouc et al. 2016 [50]	24	25	L-dopa+DA: 24	1148 (86)	60.2 (1.6)	11.4 (1.3)	-	Choice task	No	Force task	Yes	MED off PD patients were willing to invest * - less force for high incentives vs. MED on and HC.
Lees et al. (2013) [38]	61	18	L-dopa+DA: 20 L-dopa: 14 STN-DBS+L-dopa+DA: 16 STN-DBS+L-dopa: 11	L-dopa+DA: 854.2 (356) L-dopa: 511 (321) DBS+L-dopa+DA: 771.4 (337) DBS+L-dopa: 739.2 (409)	L-dopa+DA: 64.3 (5.2) L-dopa: 67.2 (7.5) DBS+L-dopa+DA: 59.1 (11.6) DBS+L-dopa: 57.0 (7.0)	L-dopa+DA: 11.1 (7.0) L-dopa: 6.2 (3.8) DBS+L-dopa+DA: 15.6 (6.0) DBS+L-dopa: 14.4 (5.0)	L-dopa+DA: 53.2 (1.8) L-dopa: 61.1 (2.2) DBS+L-dopa+DA: 43.7 (2.2) DBS+L-dopa: 42.5 (2.3)	Beads task	Yes	-	No	PD patients treated with L-dopa and DA made * + irrational choices vs. to patients only treated with L-dopa.
Milenkova et al. (2011) [51]	17	17	DA: 17	342.1 (309.4)	60.6 (7.6)	4.4 (3.4)	-	Intertemporal Choice Task	No	-	Yes	PD patients had * + discount rates vs. HC.
Osman et al. (2014) [32]	35	19	L-dopa+DA: 20 MED off: 15	MED on: 699.35 (263.42) MED off: 584.62 (199.31)	MED on: 68.07 (7.06) MED off: 69.85 (5.56)	MED on: 11.61 (7.87) MED off: 10.57 (8.13)	-	Dynamic decision-making	Yes	-	Yes (different groups)	MED on PD patients showed - performance vs. MED off patients and HC.
Rosen et al. (2015) [39]	20	23	L-dopa+DA: 20	999.42 (756.87)	67.45 (6.84)	8.40 (6.92)	-	Moral decision-making	No	SCR	No	PD patients made * more egoistic decisions vs. HC.
Seinstra et al. (2016) [36]	14 + 18 (DBS)	-	L-dopa: 32 DA: 10	MED+DBS: 594 (209.4) MED: 671 (118.0) DBS: 623 (120.3) MED off, DBS off: 642 (125.0)	MED+DBS: 66.5 (1.4) MED: 57.1 (1.4) DBS: 63.5 (2.6) MED off, DBS off: 64.7 (2.9)	MED+DBS: MED: DBS: MED off, DBS off:	-	Intertemporal Choice Task	No	Holt-Laury Task	Yes (different groups)	No effect of DBS or MED on delay discounting.
Zénon et al. (2016) [34]	12	-	L-dopa+ STN-DBS: 12	993.75 (258.51)	63.8 (6.8)	9.4 (2.5)	-	Dynamometer task	Yes	Local field potential response (LFP)	Yes	LFP responses in the STN reflected subjective value of reward.

N: Number of participants; Treatment N: Number of participants receiving certain treatments; LEDD: Levodopa equivalent daily dose; L-dopa: Levodopa; DA:

*Dopamine agonist; L-dopa+DA: Patients receiving a combination of L-dopa and DA; GDT: Game of Dice Task; IGT: Iowa Gambling Task; STN-DBS: Deep brain stimulation in the subthalamic nucleus; MED on/off: Medication treated group on/off medication; +/-PG: patients with/without pathological gambling; Other medication includes COMT inhibitors, MAOIs, other PD medication (eg. Amantadine); ICD: Impulse control disorder; HC: Healthy controls; tDCS: Transcranial direct current stimulation; * the finding was significant; -/+ reduced/increased; LEDD in Zénon et al. 2016 was calculated using the doses noted for each patient in the study*

Decision-making under uncertainty

The IGT was applied in eight of the included studies. Two studies [33,35] did not include a HC group and were thereby unable to unravel whether patients displayed impairments relative to HCs. The remaining studies showed impaired IGT performance in PD patients, either expressed as a significantly poorer, or trend towards poorer, performance in patients compared to HCs, or as employment of disadvantageous strategies in PD patients [24,27,28,40,42]. However, as seen in **fig. 2** only three of these studies found PD patients to be significantly impaired, while the remaining three did not detect significant differences compared to the HC group.

Only a single study using the IGT tested patients both on and off dopaminergic medication [24] suggesting that PD patients off medication showed impaired IGT performance. Yet, after receiving STN-DBS, patients no longer displayed impairments [24]. Unfortunately, as STN-DBS was followed by a drastic reduction in dopaminergic medication, the potential effect of medication on IGT performance remains unclear, and it cannot be determined whether STN-DBS or reduction in medication, or perhaps the combination, resulted in the normalization of performance.

Another behavioral paradigm measuring decision-making under uncertainty is the Deal No Deal task (DND), which has indicated a tendency for PD patients to be risk-averse compared to HCs [23]. This finding, however, contradicts findings from the IGT, suggesting an increased tendency towards risky decision-making in PD. This inconsistency in findings may relate to structural differences in task design. While the IGT continuously provides feedback following each choice, the DND does not provide any information on choice quality or success. Furthermore, the IGT requires participants to decide which decks to draw from, whereas in the DND participants are instructed to either refuse or accept a given offer. This difference between tasks in form of feedback and decision might explain the contrasting findings regarding risk-aversion or risk-willingness.

Overall, findings based on paradigms examining decision-making under uncertainty, indicate impaired performance in PD patients relative to HCs, which is reflected in the lack of efficient strategies for problem-solving and based on inadequate use of feedback and learning during task performance. Potential effects of medication cannot be estimated.

Decision-making under risk

Decision-making under risk is commonly examined using the Game of Dice Task (GDT), which was applied in five of the included studies. As seen in **fig. 2** six studies showed that patients on medication make significantly riskier decisions than HCs [22,23,26,27,29,49]. One study did not include a HC group [33]. Though the study of Boller et al. [22] failed to reach statistical significance the results showed a trend towards an increase in risky decision-making in patients on medication relative to untreated patients (medication off and DBS off). The authors of the study do however point out that patients receiving STN-DBS get a reduced medication dose, and the results may therefore not apply to patients not treated with DBS. Considering the possible role of dopaminergic medication this implies, that medication effects might be dose-dependent. We will return to this point later in the discussion.

Torta et al. [47] assessed risky decision-making in PD patients using the Cambridge Gambling Task and found patients to make more impulsive choices and to lack an optimal strategy for efficient task performance compared to HCs. In comparison, Sharp et al. [26] found that while pre-medicated patients were risk-averse in relation to big losses, patients on dopaminergic medication had a normal perception of loss in the Vancouver Gambling Task. Since the effect was only present for losses, an alternative interpretation of the findings could be considered. Rather than having a normal perception of losses on dopaminergic medication, it is possible that PD patients are reluctant or unable to use negative feedback to guide decision-making and thus make more impulsive choices. If so, patients on medication will appear less risk-averse in contrast to patients off medication. This explanation is supported by the abovementioned studies highlighting impulsivity and impaired use of feedback in medicated PD patients [26,47]. However, to test the hypothesis it is necessary to test PD patients on and off medication using a task assessing perception of both gains and losses, as well as a task providing trial by trial feedback.

Overall, findings suggest that dopaminergic medication is associated with increased risky decision-making in PD, which may further link to impaired use of feedback.

Uncategorized tasks

A number of decision-making tasks are neither categorized as decision-making under uncertainty nor under risk. As shown in **fig. 2** the majority of uncategorized tasks found PD patients to be significantly impaired compared to HC groups, both on and off dopaminergic medication. One such task is the

Dynamometer Task on which, Chong et al. [30] found patients with PD to be willing to invest less effort (i.e. patient were less willing to squeeze the dynamometer to get a reward) than HCs, regardless of medication status. In addition, patients on medication were willing to invest more effort than patients off medication. In line with this, Le Bouc et al. [50] found PD patients off dopaminergic medication to be willing to invest less effort for rewards than patients on medication or HCs. In a similar tasks Zénon et al. [34] found dopaminergic medication to increase acceptance for efforts associated with low rewards, but did not compare findings to an HC group. The finding that patients generally invest less effort than HCs, could be related to the tendency of risk-aversion in patients performing the DND. Both tasks require participants to refuse or accept, rather than decide between multiple options, and both tasks have been associated with increased refusal and risk avoidance in patients. Additionally, the tendency to show risk-aversion seems to be alleviated when patients receive dopaminergic medication. This could indicate that dopaminergic medication normalizes decision-making in PD, or conversely that effects of medication cause patients to be more impulsive and increase willingness to take risks.

Cools et al. [53] found that PD patients placed their bets in the task significantly faster and had an abnormal betting strategy when on dopaminergic medication relative to off medication. This could indicate that dopaminergic medication may lead to impulsive decisions. Studies demonstrated a higher occurrence of irrational choices and a tendency to gather less information before making decisions and make faster decisions (i.e. jumping to conclusions) in patients on medication compared to patients off medication [32,52] as well as in patients receiving polytherapy (L-dopa and DA) relative to L-dopa monotherapy [37,38,43]. Seinstra et al. [36] found no effects of DBS or dopaminergic medication when measuring delay-discounting behavior, used to evaluate impulsive choice. However, since all patients in the study had STN-DBS implanted this could potentially be different in comparison to patients only on medication. Frank et al. [18] found STN-DBS to induce faster and more impulsive responses in PD patients during high-conflict decisions in a probabilistic selection task. For patients treated with dopaminergic medication they found impaired learning from feedback [18]. This suggests that different types and combinations of dopaminergic medication are associated with different effects on decision-making and the matter is complex. Moreover, findings could reflect variation in disease progression associated with different PD-related decision-making difficulties, varying needs for treatment, and accordingly different treatment-induced alterations to decision-making processes. However, systematic studies are needed to clarify these issues.

Taken together, findings based on paradigms assessing decision-making under risk, uncertainty, and uncategorized tasks confirm the presence of decision-making deficits in PD patients. These impairments appear to vary depending on task architecture, but generally findings indicate that impaired or limited use of feedback is central to decision-making deficits in PD. Overall, dopaminergic medication appear to impact decision-making and risk taking, though magnitude and directionality of effects remain unclear.

Feedback processing

In the present review, impaired or limited use of feedback, perhaps negative feedback in particular, has been proposed to constitute a general impairment in PD compromising performance across decision-making tasks. Several studies have shown an impaired use of negative feedback in medicated patients compared to HCs [27,29], which seems to be unrelated to task structure and category. Similarly, measurements of brain activity reveal altered feedback processing in PD patients on both the IGT and GDT [28,29], supporting the hypothesis that impaired use of feedback plays a role in decision-making deficits in PD. However, whether PD patients are impaired in general feedback processing, or show deficits in use of negative feedback alone, remains unanswered. Relevantly, the two explanations are not mutually exclusive and could depend on different decision-making tasks or other executive or motor functions (e.g. mental or motor flexibility) mediating decision-making processes. If PD patients show general deficits in feedback processing, the impaired use of negative feedback could explain the lack of development and employment of effective strategies for problem-solving. Following the same line of arguments, impaired use of positive feedback might cause PD patients to repeat actions leading to positive feedback, even when these decisions are risky. This offers an explanation for risky decision-making observed in PD.

Medication effects

Moreover, the link between dopaminergic medication and impaired feedback processing remains unresolved, as most studies only assessed patients on medication. Yet, medication has been associated with a range of adverse cognitive effects in PD [4], and thus it seems plausible that medication also impacts the ability to use feedback to guide and adapt decision-making. However, mixed findings underscore the notion that this relationship is very complex and likely mediated by various factors including individual differences, disease progression, variation in task structure and context, type and dose of medication etc. [5]. These mixed findings are also displayed in **fig. 2**, which shows that despite that PD patients on medication often show impairment compared to healthy control participants, there are also cases of impairment off medication and cases of no significant impairment on and off medication.

Torta et al. [47] found a dose-dependent effect of dopaminergic medication suggesting that patients receiving higher doses are more impulsive and show increased deficits in probabilistic decision-making [47]. The contradictory findings may be associated with the different types of decision-making tasks applied, but could also relate to differences in medication doses. Patients in the study by Torta et al. [47] had a mean levodopa equivalent daily dose (LEDD) of 1048.83mg ($SD=313$ mg). Perhaps, a high dose of medication is necessary in order to identify clear dose-dependent effects, which may not be present or be unobservable in low-dose groups. Again, the great variability in medication doses could mirror variation in disease progression and thus variation in general cognitive decline including decision-making deficits.

In addition, high-dose studies, with a few exceptions [26,28,40], generally found patients on medication to be more severely or more extensively impaired in decision-making performance. As previously discussed, these findings could reflect a positive association between impulsivity and medication, as impaired performance in patients receiving high doses of medication appears to be related to impaired feedback processing, i.e. limited use of feedback in guiding decision-making.

The low-dose studies on the other hand, present more mixed results. Three studies found positive effects of medication on performance, however only two hereof reached statistical significance [22,30,31]. Some studies [27,42] found impaired performance in patients compared to HCs, but did not compare results to patients off medication, which prevents any firm claims regarding effects of medication and dose variation. Finally, Milenkova et al. [51] demonstrated that patients both on and

off medication had a steeper discounting function, indicating the presence of medication related as well as dose related effects. Furthermore, the contradictory low-dose findings contribute to the hypothesis that dopaminergic medication might alleviate task-specific difficulties in some patients, while inducing impairments in others.

Methodological differences

Following the presented reasoning, an additional factor to consider with regards to the inconclusive findings presented is methodological variabilities across studies. As summarized in **table 1**, great variability exists within and across studies on various parameters e.g. LEDDs. Consequently, some patients received low doses of dopaminergic medication, while other patients received high doses. In the study of Torta et al. [47] the patient receiving the lowest dose received 300mg L-dopa, while the patient receiving the highest dose received 1350mg. Moreover, there is a great variance in the average medication dose when comparing the included studies. In the study reporting the lowest medication dose patients received an average LEDD of 342.1mg [51], while patients in the highest dose study received an average LEDD of 1459mg [24]. As there is still ongoing debate about the role and effect of dopaminergic medication on cognition, it is unclear if these patients and studies are at all comparable.

In addition to medication dose, there is a great variance within and between several studies regarding age and disease duration. Only few studies present age of onset, but variance in this measure is of importance. Since PD is a progressive disorder, patients are less impaired in early stages of the disease, confirmed by Poletti et al. [3] who found de novo patients to perform similar to HCs. This highlights the potential differences between PD patients in different stages of the disease and emphasizes that a great variance in disease duration and age might make patients less comparable.

Finally, numerous of the included studies did not test patients both in an *on* and *off* medication state. It should be prioritized to test in both states, to the extent it is possible for the patients to be tested off their usual medication, to estimate potential effects of dopaminergic medication.

A central limitation to the current review needs to be addressed. While the review has focused on dopaminergic medication, there has been no clear distinction of different kinds of medication or any separation of L-dopa compared to DA or other kinds of medication. This distinction could potentially

have further unraveled the cause of impairments in decision-making in PD patients, as DA have been suggested to have a distinct role.

Conclusion

The present systematic review aimed to determine if PD patients on dopaminergic medication are impaired in decision-making tasks, and created an overview of the influences of dopaminergic medication on decision-making abilities. Generally, PD patients treated with dopaminergic medication are impaired in decision-making tasks, both regarding decision-making under risk and decision-making under uncertainty. Overall, impaired use of negative feedback seems to be a critical factor in these decision-making deficits. Impaired use of negative feedback was found to be present across decision-making paradigms, and was supported by a lack of strategy presented by PD patients. Studies indicated that dopaminergic medication influenced use of feedback, but further research is needed. There is a need for longitudinal research to uncover potential differences in decision-making impairments in different stages of PD and effects of duration of medical treatment. Importantly, there is a need for awareness on methodological problems regarding the great variance in assessment of medication, and reporting of age and disease duration. To get a clearer view of effects of dopaminergic medication, studies should test patients both on and off medication, to the extent it is possible, and the need for a standardized distinction between high and low doses should be addressed.

Conflicts of interest

The authors have no conflicts of interest to declare.

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