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

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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.

1. Introduction

Parkinson's Disease (PD) 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].

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

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

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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.

2. 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 Fig. 1.

3. 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 Fig. 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.

4. 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.

4.1. 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].

4.2. 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.