Delay discounting in Parkinson's disease: A systematic review and meta-analysis

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# Delay discounting in Parkinson's disease: A systematic review and meta-analysis

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**Abstract.** Delay discounting refers to the depreciation of the value of a reward as a function of the time it takes to obtain it. Growing evidence shows altered delay discounting in several pathological conditions, including neurological disorders. Here, we conducted a systematic review and meta-analysis of the published literature on delay discounting (DD) in Parkinson's Disease (PD). We found steeper DD in patients with PD, compared to healthy controls, both in "on" and "off" dopaminergic medication. These results confirm altered DD in PD and suggest an independent influence of the dopaminergic medication and the clinical condition itself on it. Also the effect of impulse control disorder and of pharmacological treatments are analysed.

**Keywords:** Steeper delay discounting, Parkinson's disease, Dopaminergic medication, Impulsivity

## 1. Introduction

Most decisions have delayed consequences; therefore, people must frequently make tradeoffs between outcomes occurring at different points in time. Interestingly, humans, as well as no human species, tend to "discount" gains as a function of time such that the equivalent value is apparently worth less in the future than it is in the present ([2]; Loewenstein, 1988; Green & Myerson, 2004). Delay discounting (DD) is well captured by the expression of the Italian playwright Carlo Goldoni who in is masterpiece "La Locandiera" (1752) wrote that it is "better an egg today, than a hen tomorrow", which afterwards became a popular proverb. For example, most people would choose to gain €110 in 13 months instead of €100 in 12 months and choose €100 now instead of €110 1 month from now, even though both choices involve a gain of €10 in 1 month. The standard explanation for DD is that subjective value (relative to objective value) is discounted over time, typically following a hyperbolic function ([66]), although the specific choice models are still debated (e.g., [112]).

DD is commonly assessed through intertemporal choice tasks involving choices between immediate and delayed rewards (e.g., money) to estimate a person's discounting rate (k) or other quantitative indices (e.g., area under the curve, impulsive choice ratio). Steeper delay discounting and, subsequently, smaller area under the discounting curve is frequently interpreted as reflecting an impulsive preference for immediate rewards over delayed gratification.

Although a tendency to discount the value of a reinforcement over time is well documented both in humans and non-human species [55], numerous variables can have an influence on this process, leading to considerable variability in the magnitude of DD across individuals (Tesch & Sanfey, 2008; [64]).

Several studies have shown that specific personality traits and medical conditions can contribute to such variability (Keidel et al., 2021). In the last ten years there has been a growing interest in the field of neuropsychology and psychiatry, and abnormal DD has been documented in a number of disorders including, for example, Parkinson's disease (PD) [3], [77], [84], Alzheimer's disease [124], autism spectrum disorders [25], attention deficit hyperactivity disorders (ADHD), Tourette syndrome [113], [129].

Interestingly, a recent meta-analysis reported that altered DD is a stable feature of most of psychiatric disorders, with steeper DD in people with major depressive disorder, schizophrenia, borderline personality disorder, bipolar disorder, bulimia nervosa, and binge-eating disorder and shallower DD in people with anorexia nervosa [5]. Steeper DD was also reported in meta-analyses on individuals with narcissistic personality disorders [32], substance related disorders and addictive behaviors [4], [70], [77], [78]), including Internet and gaming addiction ([27], [29]), and individuals with ADHD [35], [82] relative to healthy controls. Scholars have suggested that abnormal DD in psychopathology may be related to dysfunction of two competing neural systems involved in decision-making: a frontal cortical system involved in executive control and a limbic-subcortical system that drives immediate reward seeking [5]. Interestingly, these neural systems are affected in several neurological conditions as well. Yet, to date quantitative meta-analysis has been conducted in this area of research.

Here, we aimed to evaluate DD in patients with Parkinson Disease (PD) by performing a quantitative meta-analysis of the available literature. Our main scope is to evaluate DD in PD, but we will also include other extrapyramidal and

movement disorders because extrapyramidal symptoms are the most common adverse drug effects patients experience from dopamine-receptor blocking agents [36]. Moreover, in recent years there have been numerous studies that have found anomalies in DD in movement disorders (i.e., [122], [52]); however, there is still no clear perspective on what are the different factors that influence DD in these patients.

PD is a neurodegenerative disorder characterized by motor symptoms as tremor, rigidity and hypokinesis, and is associated with progressive neuronal loss of the nigrostriatal pathway and a concomitant reduction in the striatal concentration of dopamine [125], [103]. PD patients often show a variety of non-motor deficits, that include sensory, cognitive, affective, autonomic and sleep disorders [101], [102], [26], part of which are thought to be related to dysfunctions of basal ganglia, limbic and frontal areas [95], [26]. In recent years, studies have reported DD abnormalities in PD patients with and without impulse control disorder (ICD) (e.g., [134], [84], [77]) – a non-motor disorder observed following dopaminergic medication [133].

Separate lines of research on healthy individuals and animal models have also shown that DD can be influenced both by ICD and dopaminergic treatments (e.g., [19], [89]). For example, the study by Mobini et al. [85] found that DD rates were positively correlated with both functional and dysfunctional impulsivity measures, non-planning-impulsiveness and total scores of the Barratt Impulsiveness Scale [11]. A similar pattern has been reported also in more recent investigations (e.g., Wainwright et al. [135]). With regard to the influence of dopaminergic activity of DD the results are mixed. A recent systematic review and meta-analysis [24] on rats documented a reduced DD following the exposure to dopamine transporter-modulating drugs, while the exposure to D1-like and D2-like receptors antagonist increased discounting. This is in contrast with the study by Arrondo et al. [8] on healthy humans, showing that the administration of metoclopramide, a D2-like receptor antagonist, reduces DD making them more prone to postpone a reward to increase its value. Finally, the literature documents that D2/like (D2/D3) dopaminergic agonists, such as pramipexole and ropinirole, increase DD in rats, non-human primates, and humans (e.g., [79], [81]).

In view of the literature mentioned above, to disentangle the effects of the PD syndrome on DD from those played by impulsivity and dopaminergic pharmacological treatment we also compared any DD difference between patients in “on” and “off” dopaminergic medication and between patients in “on-medication” condition without ICD and healthy controls.

## 2. Methods

A systematic literature research was performed using Scopus, Science Direct, PubMed and ISI Web with the last search conducted on 13.07.2022. The search terms were organized in string A and string B. String A: “delay discounting”, “temporal discounting”; “intertemporal choice”, “time discounting”, “time preference”, “intertemporal decision”; “delay of gratification”. While our primary focus was on PD, we initially extended search criteria, to check whether comparisons could be made between different types of extrapyramidal movement disorders. Therefore for string B we included: “Parkinson”, “hemi-parkinsonism”, “Paralysis Agitans”, “Parkinsonism”, “Malignant Neuroleptic Syndrome”, “Secondary Parkinsonism”, “Hallevorden-Spatz”, “Degenerative Diseases of Basal Ganglia”, “Progressive Supranuclear

Ophthalmoplegia", "Steele-Richardson-Olszewski", "Multiple System Atrophy", "Dystonia", "Spasmodic Torticollis", "Blepharospasm", "Essential tremor", "Tremor", "Myoclonus", "Chorea", "Tics", "Akathisia", "Restless Legs Syndrome", "Stiff-Person Syndrome", "Extrapyramidal Disorders", "Movement Disorders". The operator that regulated the relationship between the words within each string was OR; the operator that linked the two strings was AND. The list of extrapyramidal and movement disorders was taken from the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10; VI, G20-G26). The research was extended to all fields (title, abstract, keywords, full text, and bibliography).

Through database searching, we identified 4664 studies. These were reduced to 3452 after duplicates were removed. Included and excluded studies were collected following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; [86]). See flow diagram (Fig. 1).

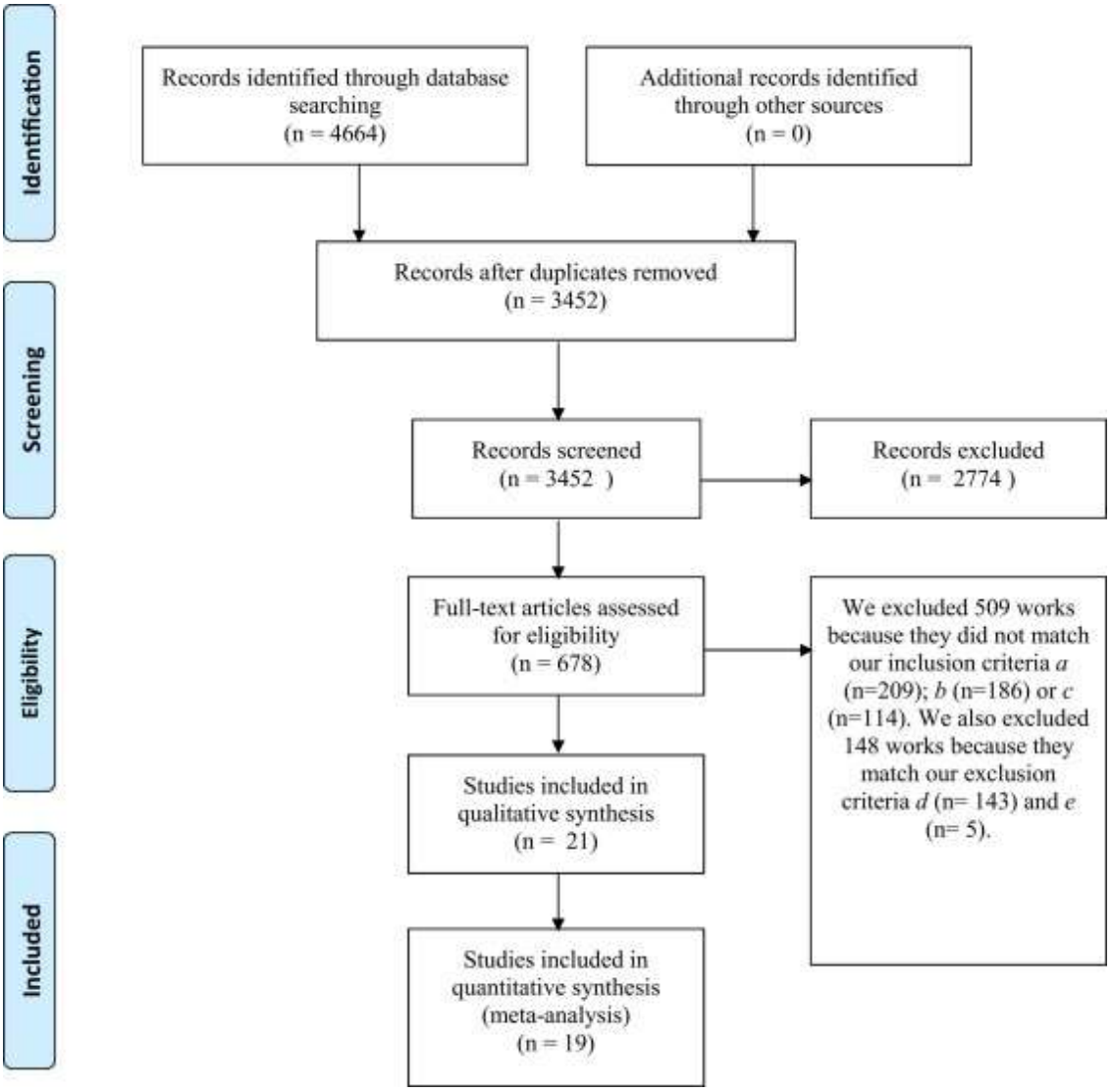


**Fig. 1.** Prisma flow diagram.

### 2.1. Screening and eligibility criteria

The fourth author initially screened all titles and abstracts. The aim was to exclude studies that were not centered on DD or on extrapyramidal and movement disorders. The first screening led to the exclusion of 2774 results. After the screening, we assessed 678 results for eligibility. The following is the full list of inclusion and exclusion criteria for assessing eligibility.

#### 2.1.1. Inclusion criteria

a) The study had to be experimental. We excluded studies that had no original experimental perspective, such as surveys, and research that was not associated to any scientific experiment.

b) The study had to be focused entirely or partially on temporal discounting in neurological disorders

c) The study had to include at least one group of participants with a diagnosis of extrapyramidal and/or movement disorders and at least a control group

#### 2.1.2. Exclusion criteria

a) Studies with non-human animals as experimental subjects

b) Case studies

### 2.2. Final sample

In this phase, the third and fourth author individually evaluated whether to exclude or include every single work. There was disagreement on one work (n = 1). The decision to include or exclude it was discussed collectively, and its inclusion was finally decided unanimously. Before discussion, the % of inter-rater agreement was 99 % (Cohen's k = 0.97). During the eligibility assessment, we excluded 509 results because they did not fulfil the inclusion criteria (a= 209; b= 186; c= 114) and 148 results because they fell within our exclusion criteria (d=143; e=5). The eligibility assessment led to exclusion of a total of 657 results. Our final sample consisted of 21 articles; but in two of them (Joutsa et al., 2015; [88]) there were not data useful for our questions, so the final sample for the meta-analyses consisted of 19 articles.

### 2.3. Risk of bias

Risk of bias assessment was performed using the Egger's linear regression method [40] and the Duval and Tweedie's trim and fill procedure [39]. The Egger's linear regression method evaluates whether the funnel plot of publication bias is asymmetrical and is usually considered more reliable than the Begg and Mazumdar's rank correlation [16] in the evaluation of funnel plot asymmetry [60].

However, because the assessment of the funnel plot's asymmetry does not necessarily depend on publication bias but should also be linked to the small-study effect (ivi), we also used the Trim and Fill method [39], which is more reliable when primary studies have small samples [38]. Funnel plots are presented in Fig. 3, Fig. 4, Fig. 5.

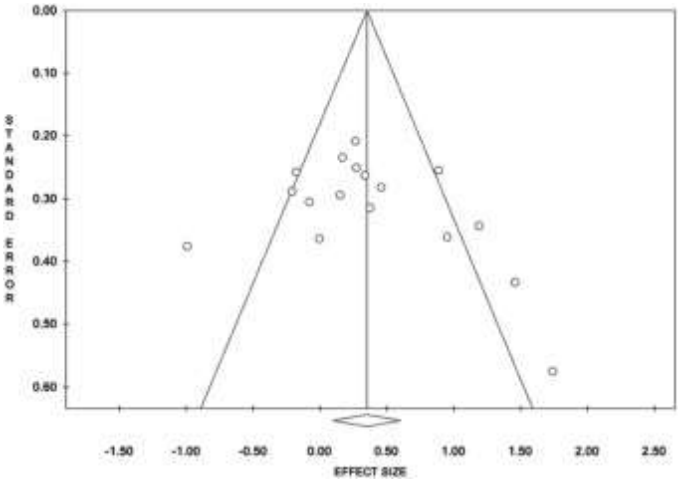


**Fig. 3.** Funnel plot H1. Trim and fill analysis reported 0 trimmed studies.

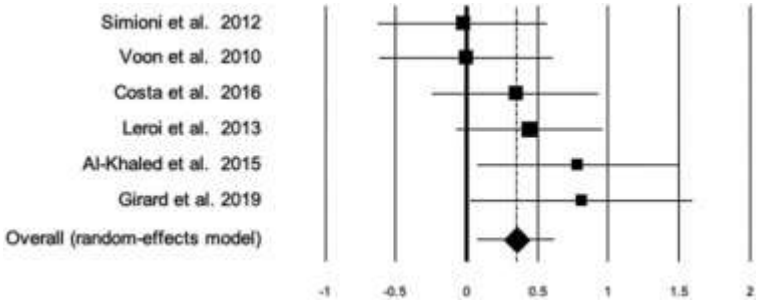


**Fig. 4.** Plot H2.

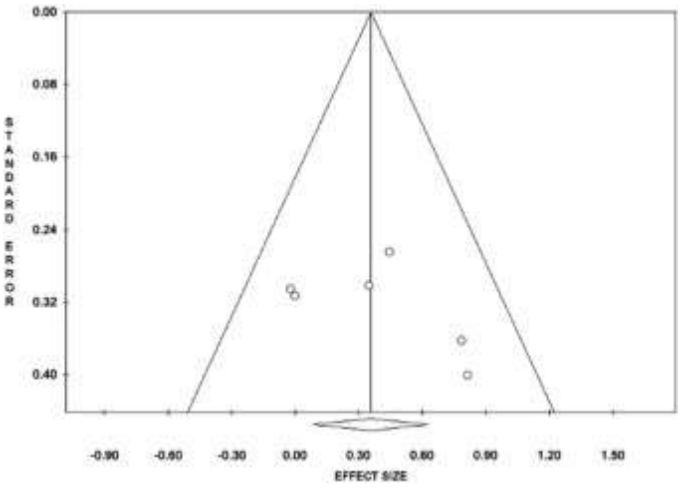


**Fig. 5.** Funnel plot H2. Trim and fill analysis reported 0 trimmed studies.

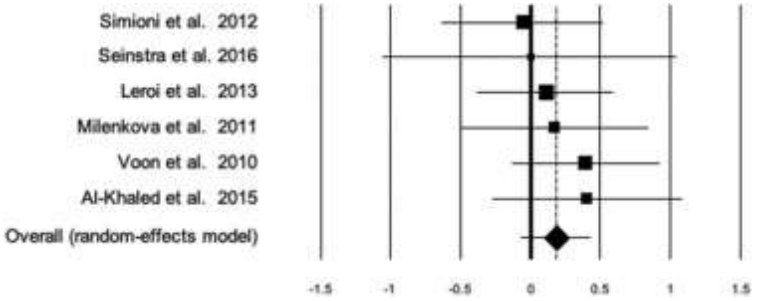


**Fig. 6.** Plot H3.

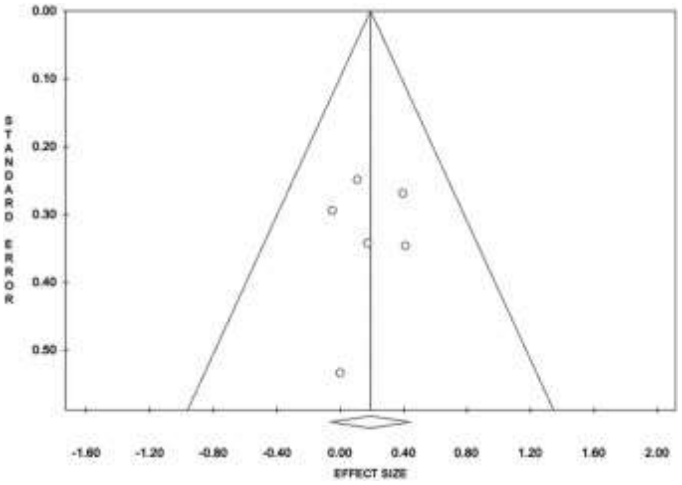


**Fig. 7.** Funnel plot H3. Trim and fill analysis reported 0 trimmed studies.

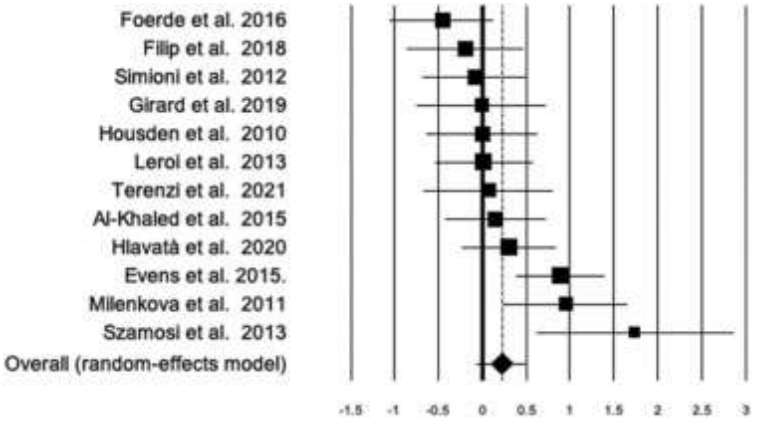


**Fig. 8.** Plot H4.

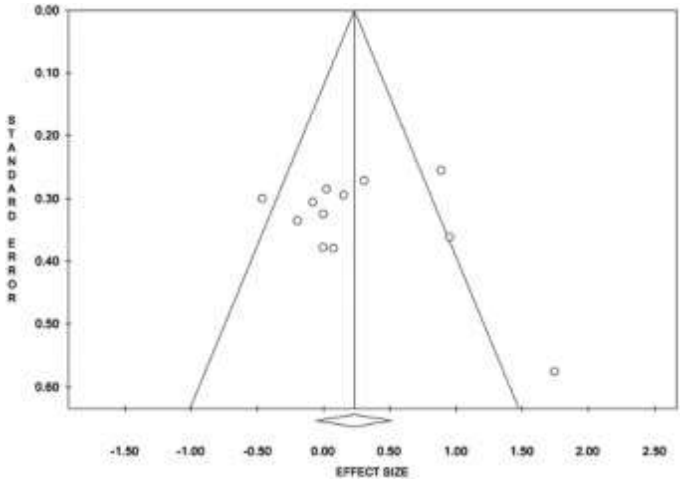


**Fig. 9.** Funnel plot H4.

## 2.4. Statistical analysis

In harmony with meta-analytic recommendations, we (a) collected data from each single study; (b) calculated standardized mean difference effect sizes for each comparison (Cohen's d) [31]; (c) determined the overall effect sizes for each comparison with a random effect model; (d) identified potential moderator variables; (e) measured heterogeneity through I2 (Higgins and Green 2006; Rosenthal [110]); and (f) used the Egger's linear regression method [40] and the Duval and Tweedie's trim and fill procedure [39] in order to evaluate publication bias.

The sample revealed that carrying out quantitative analyses would be possible on one disorder only among those on our list: PD. Three hypotheses were then formulated: (H1) patients with PD in "on medication condition" show steeper DD than healthy controls (HC); (H2) patients in "off-medication" condition show steeper DD than HC; (H3) patients in "on-medication" condition show steeper DD than those in "off-medication" condition. The latter hypothesis was formulated based on the literature linking dopaminergic manipulation with steeper DD (e.g., [134]). Because H1 showed a moderate level of heterogeneity, we additionally tested another hypothesis: H4 patients with PD in "on medication" without ICD show steeper DD than healthy controls.

To evaluate the significance of the results, we used Cohen's [31] parameters: where d = 0.00 is a null effect; d = 0.20 is a small effect; d= 0.50 is a medium effect; d= 0.80 is a big effect. In this way, if d has a positive value, the first group mentioned in the null hypotheses show higher levels of DD (made more impulsive choices) than the second group, if d has a negative value the second group has higher levels of DD than the first one. To interpret heterogeneity, we used Higgins and Green's (2006) parameters. Therefore, we considered I2 = 0–24 as null; I2 = 25–49 as low; I2 = 50–74 as moderate; and I2 = 75–100 as high.

For statistical analysis we used Prometa3 software.

## 3. Results

Our final sample for the systematic review consisted of 21 studies. The main methodological features of all studies are reported in Table 1. The different ways in which DD was measured in each study are reported in Table 2.

In all the studies of our sample there was at least one group of participants with PD. Al-Khaled et al. [3] included a group of patients with restless leg syndrome; Joutsa et al. (2015) included a group of pathological gamblers, but no other diseases were included in the remaining studies in our sample; so quantitative analysis was focused on PD. The greater part of the studies in our sample compared "on" and "off" pharmacological medication condition ([3], [52]; Joutsa et al., 2015; [72], [84]; Seinstra et al., 2016; [115], [134]). Aiello et al. [1] and Evens et al. [42] compared PD patients treated with deep brain stimulation with patients treated with dopaminergic treatments and healthy controls. Some studies compared participants with and participants without impulse control disorders but always in "on" medication condition ([47], [56], [58], [59]). Some others simply considered participants with PD in "on medication" condition and compared them with healthy controls [88], [93]. De Rezende Costa et al. [33] compared patients who had never been treated with dopaminergic drugs with healthy controls.

**Table 1.** A synthesis of main characteristics of all paper of the sample.

| Study | Participants | Matched by | Tested by | Main results |
|---|---|---|---|---|
| [1] | A. 15 patients with PD treated with STN-DBS<br>B. 15 patients with PD without DBS under dopaminergic replacement therapy<br>C. 15 healthy subjects<br>ICD not declared | Age (m= 62,8; sd= 7,2)<br>Education years (m= 12,5; sd= 4,7)<br>Mini-Mental State Examination (m= 29,13; sd= 0,91) | FAB[6]<br>DigitSpan Task[96]<br>Phonological and Semantic Verbal Fluency tests[94]<br>Corsi Span Task[96]<br>Rey's 15-word test-immediate recall and delayed recall[22]<br>Temporal discounting task (3 kinds of reward: food, money, discount voucher) | For group A, the shorter the time from surgery, the higher the preference for immediate monetary rewards.<br>Authors compared in group A differences in delay discounting between patients who developed weight gain after surgery and the ones who did not experience weight gain; no differences were found between these two subgroups.<br>The three groups did not differ in delay discounting, regardless of the type of reward.<br>According to these data STN-DBS did not affect temporal discounting. |
| [3] | A. 13 unmedicated patients with PD<br>B. 24 medicated patients with PD<br>C. 24 patients with Restless Leg Syndrome medicated with L-DOPA and/or DAs<br><br>A. 22 healthy subjects<br>No ICD | Age range (m=69,9) | Alertness test with and without warning tone to test attention<br>Farb-Wort-Interferenz Test to test executive functions<br>RegensburgerWortflüssigkeitstest to test verbal fluency<br>LPS 3 and LPS 4 to test deductive reasoning California Verbal Learning test to test memory PANDA test[63] to test cognitive abilities Intertemporal choice task | The discounting of delay was similar between group A and group B; in group A it was significantly lower than in group C and group D.<br>The authors concluded that impulsive decision making in PD patients is probably not a collateral effect of medications, but a trait marker of PD. |
| [33] | A. 25 patients with PD who have never been treated with dopaminergic drugs<br>B. 20 healthy controls<br><br>A. ICD not declared | Age (m=54,2; sd=10,5)<br>Education yrs (m=14; sd= 3,7)<br>Mini Mental State Examination (m=29,1; sd= 0,8)<br>FAB(m=15,5; sd= 2,8)<br>FAB Go-No Go (m=2,53; sd= 0,92)<br>RT (ms) (m=5535; sd= 2898) | Beads task[34]<br>Kirby temporal discounting questionnaire[68] | Group A made significantly more irrational choices at the Beads task, but had analogous performances to group B at the Kirby temporal discounting questionnaire. |

| | | | | |
|---|---|---|---|---|
| Evens et al. [42] | A. 33 patients with PD who have been treated with deep brain stimulation of the subthalamic nucleus (DBS-STN)<br>B. 33 patients with PD that did not receive DBS-STN but that received pharmacological treatments<br><br>A. 34 healthy controls<br>No ICD | Age (m=65,88; sd= 6,4)<br>Education yrs (m= 10,79; sd= 1,85) | Delay discounting<br>Incentive Value of Everyday Objects<br>Iowa Gambling Task (Bechara et al. 1994) | At the delay discounting task, an increased devaluation of delayed rewards was observed in group A in relation to both groups. The effect was significant for the comparison of all groups. No effect of stimulation was observed comparing DBS-on/-off conditions.<br>At the Incentive Value of Everyday Objects a significant group effect was observed with group A and group B giving higher value to objects than group C. No significant effect of the DBS -on/-off conditions was found.<br>At the Iowa Gambling task no significant group differences were found. There was a significant group effect for the difference between advantageous and disadvantageous choices, with group A making more disadvantageous choices than group B. Patients of group A made more disadvantageous choices in DBS-on than in DBS-off conditions.<br>The authors concluded that DBS-STN affect specific aspects of reward processing. |
| [47] | A. 13 non-impulsive patients with PD<br>B. 8 patients with PD and with impulse control disorder (ICD)<br>28 healthy controls | | Go/No Go task<br>Delay discounting<br>MRI data Acquisition<br>Groups A and B performed all tasks in "on medication" condition. Participants were treated with L-dopa. | Performances in behavioral tests did not differ among groups.<br>The fMRI investigations found in group B decreased activation in the striatum and vast connectivity changes in various other cerebral areas. |
| [48] | A. 14 patients with PD with high dose of medication<br>B. 17 patients with PD with low dose of medication<br><br>A. 18 healthy controls | Age (m= 70,8; sd= 8)<br>Education (m=17,7; sd= 2,3) | Binary Choice Task<br>Valuation Rating Task<br>Choice Titration Task | In comparison to groups B and C, group A preferred larger but later rewards to immediate but smaller.<br>Group B showed a reduced valuation of single outcomes, but its choices did not differ significantly from group C. |

| Study | Participants | Matched by | Tested by | Main results |
|---|---|---|---|---|
| | A. No ICD | | | The authors concluded that dopamine seems to be implicated in intertemporal choice preferences. |
| [52] | A. 13 Patients with PD and hypersexual<br>B. 14 Patients with PD who are not hypersexual<br>14 healthy controls | Age (m=58,5; sd=8,3)<br>Hamilton Anxiety Depression Scale$_{Depression}$(m= 6,3; sd=2,7)<br>Hamilton Anxiety Depression Scale$_{Anxiety}$(m=8,5; sd= 3,2)<br>FAB (m=15,9; sd= 1,6)<br>Mattis Dementia Rating Scale (m=134,2; sd= 5,8) | Delay discounting task<br>fMRI scanning<br>Participants were tested both in "on medication" and "off medication" condition | Patients in group A discounted less delayed erotic stimuli than the other two groups; this means that patients in group A accepted to wait longer to view erotic images for a longer period of time.<br>An abnormal reinforcing effect of levodopa in group A was found. Patients in group A differed from those in group B in the activity of medial prefrontal cortex and ventral striatum during the decision. |
| [56] | A. 15 patients with PD and with ICD<br>B. 22 patients without ICD<br>A. 36 healthy controls | Age (m=59,27; sd= 8,88)<br>Gender (M=11; F=4)<br>Education<br>Laterality<br>Socioeconomic status | BIS[98]<br>UPPS-P[139]<br>Montgomery-Asberg Depression Rating Scale [87]<br>Zung Self-Rating Anxiety Scale[141]<br>Go/No-Go task<br>Stop Signal Task<br>Delay Discounting Task<br>Iowa Gambling Task<br>MRI data acquisition<br>All participants were tested in "on medication" condition | Group A showed significantly higher levels of impulsivity than the other two groups.<br>At the Iowa Gambling Task group A made significantly less risky decisions than the other two groups.<br>No differences were found among groups at the delay discounting task.<br>Group A and B were more anxious and depressive than group C.<br>Patients of group B showed lower volumes and cortical thickness of bilateral inferior frontal gyrus.<br>Patients of group A showed higher volumes of right caudal anterior cingulate and rostral middle frontal cortex. |
| [58] | A. 18 patients with PD with impulsive compulsive spectrum behaviors<br>B. 18 patients without impulsive compulsive spectrum behaviors<br>A. 20 healthy controls | Gender (M=11; F=7) | Kirby delayed discounting questionnaire[68]<br>Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)[83]<br>State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1970)<br>Beck Depression Inventory (BDI)[15]<br>Salience Attribution Test[109]<br>Mini Mental-State Examination[49]<br>Wechsler Test of Adult Reading[137]<br>Digit-span test[136]<br>All participants were tested in "on medication" condition | No differences were found in BDI and STAI between clinical groups, but these scores were higher in clinical groups than in controls.<br>Schizotypy, measured by the O-LIFE, was higher in clinical groups than in control groups. Group A scored higher than group B.<br>Group A scored higher than others at the Kirby delayed discounting questionnaire. Group B and C did not differ.<br>Participants of all groups were able to learn the discrimination between the reward probability levels.<br>The authors concluded that the excessive dopaminergic transmission frequent in patients with PD and impulsive compulsive behaviors induces a strong preference for immediate over future rewards. |
| [59] | A. 51 patients with PD; 10 of whom had ICD<br>A. 42 healthy controls; 9 of whom had ICD | • Age (m=70,34; sd= 7,15)<br>• Gender (M=28; F=19)<br>• Occupational status (13 working; 38 retired)<br>FAB (m=15,08; sd= 2,96) | BIS-11 (Barratt et al. 1995)<br>Cognitive Reflection Test[50]<br>Kirby Delay Discounting Questionnaire[68]<br>All participants were tested in "on medication" condition | The aim of the study was to find a test to prevent the occurrence of ICD.<br>ICD was predicted by different aspects of impulsivity in the two groups. Specifically, it was predicted by a strong preference for immediate rewards at the Kirby Delay Discounting Questionnaire in patients with PD and by giving all wrong answers on the Cognitive Reflection Test in healthy control participants.<br>Groups did not differ significantly on the Kirby Delay Discounting Questionnaire. |
| Joutsa et al. 2015 | A. 9 patients with PD with dopamine medication-induced behavioral addiction<br>B. 8 patients with PD without dopamine medication-induced behavioral addiction<br>C. 12 pathological gamblers<br>A. 12 healthy controls | Gender (all participants were males) | Temporal discounting task<br>[11 C]raclopride PET<br>[18 F]fluorodopa PET | In group C greater temporal discounting correlates with decreased ventral striatal binding potential. In groups A and B temporal discounting correlates with greater left caudate dopaminergic terminal function. In group B, delay discounting is further correlated with greater dopaminergic terminal function in the anterior |

| Study | Participants | Matched by | Tested by | Main results |
|---|---|---|---|---|
| | | | | putamen.<br>The authors concluded that these data support a U-shaped relationship between striatal dopaminergic function and delay discounting. |
| [72] | A. 35 patients with PD and ICD<br>B. 55 patients with PD without ICD<br><br>A. 20 healthy controls | | Unified Parkinson's Disease Rating Scale[43] Levodopa equivalent daily dose[126]<br>BIS (Patton 1995)<br>Apathy Evaluation Scale[80]<br>The South Oaks Gambling Screen[73]<br>5-min word recall test<br>FAS task[118]<br>Computerized version of the Wisconsin Card Sorting Task[75]<br>Trail Making Test A and B[105]<br>Serial 7′s<br>Digit n-back[69]<br>National Adult Reading Test[18]<br>Stop task[20]<br>Delay Discounting Task[104]<br>An allelic TaqMan discrimination assay was used to decipher COMT *val met* genotypes<br>Participants were tested in both "on medication" and "off medication" condition | The main aim of the study was to investigate the interaction of medications and genotype on dopaminergic state. Groups were tested at the DD task in different pharmacologic conditions (ON and OFF) and patients were also divided into different allelic variants of COMT (*val/val*vs. *met/met*).<br>At the DD task, group A made more impulsive choices than group B in the ON condition, but not in the OFF condition.<br>The *met* homozygous group performed differently to the *val* homozygous group in executive functioning.<br>The authors concluded that both pharmacologic and genotypic factors influence impulsive-compulsive behaviours. |
| [84] | A. 17 participants with PD without ICD<br>B. 17 healthy controls | • Age (m=60,6; sd= 7,6)<br>• Gender (m=12; f=5)<br>• Education (years=14) | Temporal discounting task in "on" medication condition and in "off" medication condition PANDA[63] to assess cognitive functions<br>Digit Ordering Test[138] to assess executive functions RegensburgerWortflüssigkeits Test[9] to assess verbal fluency<br>A variant of the Stroop Test[13]<br>California Verbal Learning Test[92] to assess verbal learning and memory<br>Subtests 3 and 4 from the Leistungs-Prüf system[120] and a go/no-go computerized test (Zimmerman and Fimm 2002) to assess attention functions Participants were tested in both "on medication" and "off medication" condition | Participants of group A made more impulsive decisions than participants of group B.<br>No significant differences were found between the "on" medication and the "off" medication conditions. |
| [88] | A. 33 participants with PD<br>35 healthy controls | | Temporal discounting test[97]<br>Mini-mental state examination (MMSE score,[91]) and Montreal Cognitive Assessment[90] to check for cognitive deficit<br>Stroop color and word test[53]<br>Brief multidimensional measure of religiousness/spirituality[46] fMRI<br>Participants were tested in "on medication" condition | The study tested the hypothesis that religious primes influence temporal discounting in healthy controls, but not in patients with PD.<br>In both groups the more religious an individual, the higher their discounting rate: higher levels of religiosity and spirituality significantly predicted higher discounting rates.<br>No significant effect of religious semantic primes was found on discounting rates for both groups.<br>Religious semantic priming reduced reaction times on discounting decisions in healthy controls who are religious, but not in PD patients.<br>Differences in response time were significantly associated with functional connectivity between the nucleus accumbens and various regions. |
| [93] | A. 30 patients with PD<br><br>A. 30 healthy controls | • Age (m= 66,4; sd= 10,5)<br>• Gender (14:16)<br>• Education (y = 12,8; sd= 1,7)<br><br>• MMSE (m=28,3; sd= 1,8) | The study empirically describes the complexity of the phenomenon of impulsivity by assessing three kinds of test.<br>• Test Type 1 - tests based on questionnaires or interview and self-reporting: Kirby Temporal Dis- counting[67]; BIS[11]; Behavioral Inhibitory Sys- tem Behavioral Approach System [23]; South Oaks Gambling Screening[73]; Modified-Minnesota Impulsive Disorders Interview[54]<br>• Test Type 2 - tests are behavioral response measures for manual tasks: Motor Go-No Go task; Temporal Interval estimation; FAB[37]; Stop-signal Task (Cambridge Neuropsychological Test Automated Battery, CANTAB); Cambridge Gambling Task (CANTAB); Hayling Sentence Completion Test [21]; Stroop test [119] | Groups showed significant differences at the Kirby Temporal Discounting<br>Impulsivity is common in PD also in absence of ICD<br>Impulsivity is a heterogenous phenomenon |

| Study | Participants | Matched by | Tested by | Main results |
|---|---|---|---|---|
| | | | • Test Type 3 – saccadometric decision task: Saccade No Go[99]<br>Participants were tested in "on medication" condition. | |
| Seinstra et al. 2016 | A. 8 patients with PD on pharmacological treatment and on DBS<br>B. 7 patients with PD on pharmacological treatment and off DBS<br>C. 10 patients with PD off pharmacological treatment and on DBS<br><br>A. 7 patients off pharmacological treatment and off DBS | Age (m=66,5; sd=1,4) | DDT[67]<br>Holt-Laury task[57], a measure of risk attitude | Nor DBS neither medication seem to not have impact on DDT or on Holt-Laury task |
| [115] | A. 23 patients with PD<br><br>A. 20 healthy controls | Age (m=65; sd= 8,6) | Balloon Analog Risk Task (to evaluate risk taking)<br>Computerized delay discounting task[44] Patients were tested in both "on-medication" and "off-medication" condition. Moreover a subset of participants was tested 1,5–3 years later in order to evaluate the effects of disease progression. | Participants of group A tended to take increasing risk decisions across time; however, neither the progression of the disease, nor the use of medication affected the delay discounting. |
| [117] | A. 32 patients with PD<br><br>A. 32 healthy controls | • Age (m=66,06; sd=5)<br>• Education (y = 15,13; sd=2,62) | Charity selection[116] Dictator game[62]<br>Altruistic Intertemporal Choice task[116] All these tests were made in "on condition". | The main aim of the study was to investigate how PD affect altruism. In the Altruistic Intertemporal Choice task, the two groups showed analogous performances. |
| [122] | A. 7 participants with presymptomatic α-Synuclein (SNCA) duplication carriers who later developed PD (follow- up after 5.6 years)<br><br>A. 10 non carrier controls. | • Age (m=47,7; sd= 8,6)<br>• Education (m=13; sd=3,5)<br>• Gender ratio (5/2)<br>• No ICD. | Kirby discounting questionnaire<br>Measurement of the volume of the caudate nucleus and cerebral cortex using structural MRI.<br>All these tests were made in "on condition". Both tests were proposed to participants at baseline and at the follow-up. | At baseline both groups showed analogous performances at the Kirby discounting questionnaire and analogous caudate volume. At the follow-up, group A showed higher delay discounting and smaller caudate volume than group B. |
| Terenzi et al. 2022 | A. 15 patients with PD and ICD<br>B. 13 patients with PD without ICD<br><br>A. 15 healthy controls | • Age (m= 70,8; sd= 6,5)<br>• Education (m=10,9; sd=4,1)<br>Gender ratio (4/11) | To test the hypothesis that a single session of anodal tDCS over left dorsolateral prefrontal cortex may have an effect on temporal discounting, participants performed all tests during three different stimulations with tDCS:<br>- active anodal tDCS of the left dorsolateral prefrontal -cortex,<br>- anodal tDCS of the primary motor cortex<br>- sham tDCS (placebo)<br>During each of these conditions, participants performed: a reward-craving test<br>two temporal discounting tasks<br>All these tests were made in "on condition". | Group A showed a steeper temporal discounting than other groups Group B and C did not differ in discounting rates<br>A single session of anodal tDCS aver left dorsolateral prefrontal cortex did not affect temporal discounting in all groups (no differences were found among tDCS conditions) |
| [134] | A. 14 participants with PD with ICDs<br>B. 14 participants with without ICDs<br><br>A. 16 healthy participants | Age (m=51,52; sd= 8,33)<br>• Gender (10 males in the first two groups, 11 males in group C) | Experimental Discounting Task[107]<br>Spatial Working Memory task from CANTAB<br>Attentional set shifting from CANTAB<br>Participants of groups A and B were tested "on" and "off" dopamine antagonists. | The "on" condition was associated with more impulsive choices in delay discounting task in participants of group A, but not in participants of group B.<br>In both conditions participants of group A had shorter reaction times than participants of group B.<br>The "on" condition was associated with shorter reaction times in group A but not in group B.<br>The "on" condition was associated with worse performances in the spatial working memory task in group A but not in group B. |

[1]When not otherwise specified, data reported in parentheses refer to group A PD= Parkinson Disease
STN-DBS= Deep Brain Stimulation of the Subthalamic Nucleus M= males
F= females
m= means
sd= standard deviation
FAB= frontal assessment battery
RT= reaction times
ICD= impulse control disorder BDI= Beck Depression Inventory STAI= State-Trait Anxiety Inventory
O-LIFE=Oxford-Liverpool Inventory of Feelings and Experiences

BIS= Barratt Impulsiveness Scale
MMSE= Mini-Mental State Examination score
CANTAB= Cambridge Neuropsychological Test Automated Battery

### 3.1. Quantitative analysis

We tested the hypotheses. Numerical moderator analyses were conducted for: age of participants, dopamine agonists-L-Dopa-equivalent daily dosage (DA LEDD), L-Dopa LEDD, Total LEDD, disease duration, publication year. Categorical moderator analyses were made for: presence of impulse control disorders in participants (yes, no, not declared or mixed); kind of treatment (drugs or Deep Brain Stimulation - DBS); object of reward. When not otherwise specified, these analyses were not significant. Analyses for publication biases were made for all hypotheses.

### 3.2. H1. Patients with PD in "on medication" condition show steeper DD than HC

The hypothesis was significant (Sig.=0.007) with a small effect size (d= 0.35; group a= 462 – group b= 389) (see Fig. 2). Heterogeneity was moderate (I2 =68.2). The Egger's linear regression test was not significant (p = 0.2) and the trim and fill analysis reported 0 trimmed study (see plot in Fig. 3). The age of participants, DA LEDD, L-Dopa LEDD, total LEDD and disease duration were examined as numerical moderators, but the weighted regression (random-effects model) was not significant for all of them (p > 0.05).

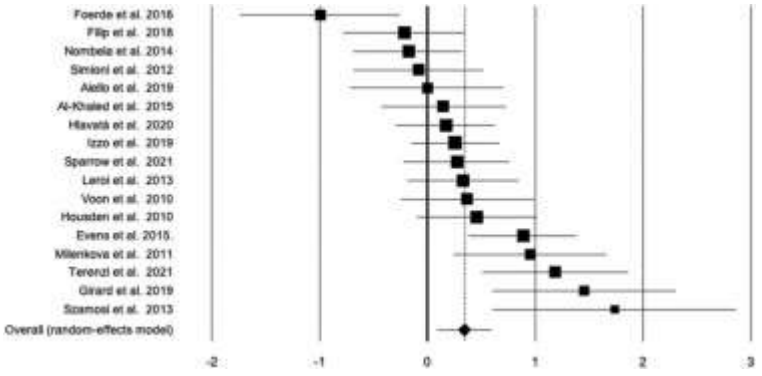


**Fig. 2.** Plot H1.

We also considered a possible categorical moderator: the presence of impulse control disorders (ICD). The test of difference (ANOVA Q-Test random effect) was not significant (p > 0.05). Therefore, the hypothesis is accepted with a small effect (complete data are reported in Table 3).

Although the analysis of the categorical moderator (ICD) did not provide significant results, the presence of ICD is not reported/examined in all primary studies. Moreover, in some studies it was not possible to distinguish DD data in patients with or without ICD. To make sure that ICD is not the cause of the moderate level of heterogeneity we conducted a further meta-analysis in which we compared DD between patients with PD in "on-medication" without ICD and HC (see §3.5).

### 3.3. H2. Patients in "off-medication" condition show steeper DD than HC

The analysis revealed a positive small effect size (d=0.35; group a=155 – group b=112) across studies that was statistically significant (p = 0.01) (see Fig. 4). Heterogeneity was null (I2 =11.92). The Egger's linear regression test was not significant (p = 0.3), the trim and fill analysis reported 1 trimmed study (see plot in Fig. 5). However, the difference between the estimated effect size (0.30) and the observed effect size (0.35) is minimum (so the effect size remains significant with a small effect). All moderator analyses were not significant. Therefore, the hypothesis is accepted with a small effect (complete data are reported in Table 3). This means that patients in off-medication show higher discounting rates than healthy subjects.

### 3.4. H3. Patients in "on-medication" condition show steeper DD than patients in "off-medication" condition

The analysis revealed a positive nearly small effect size (d=0.19; group a=155 – group b=112) across studies that did not reach significance (p = 0.1) (see Fig. 6). Heterogeneity was null (I2 =11,92). The age of participants, DA LEDD, L-Dopa LEDD, total LEDD and disease duration were examined as numerical moderators, but the weighted regression (random-effects model) was not significant for all of them (p > 0.05). The trim and fill analysis reported 0 trimmed studies so there is no publication bias (see plot in Fig. 7).

### 3.5. H4. Patients in "on-medication" condition without ICD show steeper DD than healthy controls

The analysis revealed a positive small effect size (d=0.23; group a=247 – group b=254) across studies that was not significant (p = 0.1) (see Fig. 8). Heterogeneity was moderate (I2 =59.39). Among moderators, only the weighted regression for DA-LEDD was significant (p = 0.03). This means that DA-LEDD has a significative effect on DD. The trim and fill analysis reported 0 trimmed studies so there is no publication bias (see plot in Fig. 9).

## 4. Discussion

In the current study we investigated DD in PD, by taking into consideration the presence of dopaminergic medication and ICD. In this regard, several hypotheses were tested. The main result is the steeper DD in PD compared to HC. As shown by H1 and H2, this result was found in "on medication" and "off medication" patients, respectively. We also found steeper DD in "on medication" compared with "off medication" patients (H3). The effect appeared of small size, but it did not reach statistical significance. It should be noted that, except for the study by Simioni et al. [115] that showed a negative effect size (d = -0.05), all other studies reported steeper DD in "on medication" compared to "off medication" patients. Thus, in this case, lack of significance is probably due to the low number of studies involved in the analysis. Altogether, these results suggest an independent influence of both the dopaminergic medication and the clinical condition on DD. In order to test whether presence of ICD is critical for observing steeper DD in patients with PD (H4),

we compared PD patients without ICD with HC. Our results indicate a small effect size, although the analysis did not reach statistical significance. Taken together these results suggest a cumulative/synergic effect of the clinical condition and dopaminergic medication on DD, although more studies are needed to reach firm conclusions

Due to the limited number of studies, it was not possible to quantitatively evaluate the impact of other kinds of treatments (such as DBS). However, according to current evidence (e.g., Seinstra et al.,2016; Aliello et al., 2019; [42]) it could be suggested that DBS does not affect DD. This hypothesis is confirmed also by another study [127] that we excluded from our analysis because it used a DD task (i.e., the Quick Delay Questionnaire by [30]), that was not compatible with the criterion adopted to perform the current meta-analysis.

The evidence of a selective effect of DA-LEDD on DD is in contrast with the results of a recent meta-analysis on healthy animal models, where an effect of L-DOPA instead of DA- on DD [24] was reported. However, our work refers to clinical populations which, probably, have a different response to dopaminergic medications, compared to that of healthy models. Moreover, recent insights from a study on healthy humans suggest a non-linear effect of dopaminergic medication on DD [100]. In individuals with optimal dopamine signalling DD would become steeper when receiving dopamine-enhancing drugs (L-DOPA), whereas those with suboptimal dopaminergic signalling would exhibit reduced DD, following L-DOPA treatment. This suggests that dopaminergic signalling represents a further variable to consider when predicting respective effects of dopaminergic medication on DD.

With regard to the influence of clinical status on DD, we are aware that PD patients can be affected by impulse control disorders, which can lead to several abnormal behaviours such us pathological gambling, binge eating, hypersexual disorder, compulsive buying (See [51], for a review), which are known to be related to a steeper DD [111]. As impulse control refers to the prefrontal neural network [14] one might link the steeper DD of PD (in the “off medication” condition) to their prefrontal lobe disfunction [123], [7]. However, this does not mean to exclude the role of the limbic-subcortical system, which is known to play a role in DD by driving immediate reward seeking [17], which is abnormal in PD [106].

In keeping with the evidence of prefrontal-mesolimbic alterations in PD, further insights to explain the steep DD in PD could originate from the extensive literature linking this neural network with time-keeping skills [10], [74], [131], which are known to predict DD. Evidence documents a tendency to time-overestimate in the context of steeper DD [12], [65], or in individuals with addictions [130], [140], who are known to be affected with steep DD [4]. Moreover, reduced DD was found in individuals who tended to underestimate durations [121], [128], while temporal overestimation [130] is reported in individual with steep DD such as in obesity [108]. Finally, the steeper DD pattern in PD is compatible with the evidence of temporal overestimation of short intervals in PD [61], [71]. On the other hand, we would exclude the hypothesis that the reported DD pattern in PD may be linked to an intolerance of uncertainty, another variable related to a steeper DD [76], as no evidence of abnormal “intolerance of uncertainty” was found in PD [45].

**Table 2.** How has delay discounting been tested in literature?

| Study | Name of test | Structure of test | What does exactly the test measure? |
|---|---|---|---|
| [1] | Temporal discounting task with three kinds of rewards | Participants were asked to choose their favourite rewards among six different kinds of food and six different kinds of discount voucher. Then participants performed three computerized tasks in which they had to choose between an immediate small reward or a delayed greater reward. There were three kinds of reward: food, money, discount voucher. The delayed options included six possible delays: 2 days, 2 weeks, 1 month, 3 months, 6 months, 1 year. | This test measures if participants tend to delay a reward and in what measure. |
| [3] | Temporal discounting task | Participants had to choose between two alternatives, one with a smaller but immediate reward; the second with a larger but delayed reward. Participants made 54 virtual choices via computer. At the end, they received a reward from one of the choices they actually made. | This test measures if participants tend to delay a reward or not. |
| [33] | Kirby temporal discounting questionnaire | Participants had to make 27 choices between a smaller, immediate monetary reward or larger but delayed monetary reward. Questions were similar to the following "would you prefer 300 $ today or 450 $ in 30 days"? Participants were not really paid at the end of the study. | This questionnaire measures if participants tend to delay a reward or not. |
| [42] | Delay discounting | This version was computer- administered. Participants had to choose between receiving soon (i.e. today) a small amount of money (i.e. 10 €) or later (i.e. in 30 days) larger amounts of money (i.e. 12€). The participants were told that they would receive the amount of one randomly selected choice. All participants in the end received 25 € in one month. | This test measures if participants tend to delay a reward or not. |
| [47] | Delay discounting | Two options were shown to participants: one with immediate reward and the other with delayed reward. | This test measures if participants tend to delay a reward or not. |
| [48] | A. Binary Choice Task<br>Choice Titration Task | The task included three kinds of questions: difficult questions (with similar rewards); easy questions (with very different values of rewards) and control questions (with objective advantage, i. e. naught vs some reward later).<br>A. Binary choices between a smaller reward that comes soon or a larger delayed reward were submitted to participants. Across trials, many factors varied: the relative difference between rewards (i.e. the delayed one will be 0,5%, 1%, 30%, 75% larger than the smaller); the time difference between rewards; if the small reward is immediate or not; etc… Participants had to choose between an earlier small reward which remained constant and a larger later reward which changed | A. This test measures whether participants tend to delay a reward or not. This test evaluates the participants' indifferent point between the low and the high reward, both as a function of reward magnitude, and as a function of time of delivery |
| [52] | A. Delay discounting task | A. Participants looked at a fuzzy erotic picture. The experimenter asked participants to choose if they wanted to see the picture clearly and immediately for a smaller amount of time (1 s), or if they wanted to see the picture clearly for a longer time (3 s) but after having waited a delay period of time between 3 and 9 s | A. This test measures whether participants tend to delay the sexual reward or not. |
| [56] | Delay discounting task | Participants had to choose between a smaller immediate amount of money or a bigger but delayed amount of money. There were five possible delays and two possible reward levels. | This test measures whether participants tend to delay a reward or not. |
| [58] | Kirby temporal discounting questionnaire | See de Rezende Costa et al. [33] | This questionnaire measures whether participants tend to delay a reward or not. This questionnaire measures whether |
| [59] | Kirby temporal discounting questionnaire | See de Rezende Costa et al. [33] | |

(*continued on next page*)

**Table 2** (*continued*)

| Study | Name of test | Structure of test | What does exactly the test measure? |
|---|---|---|---|
| | | | participants tend to delay a reward or not. |
| Joutsa et al. (2015) | Kirby temporal discounting questionnaire | See de Rezende Costa et al. [33] | This questionnaire measures whether participants tend to delay a reward or not. |
| [72] | Delay-discounting task | Modified computer version of the task designed by Rachlin et al.[104]. The rewards were hypothetical but realistic. | This test measures whether participants tend to delay a reward or not. |
| [84] | Intertemporal choice task | Participants had to choose between a smaller immediate reward and a larger delayed reward. Rewards were monetary; 27 choices were presented to participants. There were three classes of larger delayed reward (small 25–35 euro; medium 50–60 euro; large 75–85 euro) to assess magnitude effect. Before starting the test, participants were informed that randomly some of them would receive one or more rewards of their choices. At the end of the test some of participants randomly received one of rewards they chose during the test (in cash in case of smaller delay; via bank transfer in case of larger delay). | This test measures whether participants tend to delay a reward or not. |
| [88] | Intertemporal discounting task | 48 temporal discounting choices. The monetary rewards range was $15 - $85 and the longest delay was 200 days. | This test measures whether participants tend to delay a reward or not. |
| [93] | Kirby temporal discounting questionnaire | See de Rezende Costa et al. [33] | This questionnaire measures whether participants tend to delay a reward or not. |
| Seinstra et al. 2016 | Kirby temporal discounting questionnaire | See de Rezende Costa et al. [33] | This questionnaire measures whether participants tend to delay a reward or not. |
| [115] | Computerized temporal discounting task | Participants had to make 27 choices. The delay was between 7 and 180 days. | This test measures whether participants tend to delay a reward or not. |
| [117] | Altruistic Intertemporal Choice task | Participants had to choose between a smaller immediate or a larger delayed reward. There are three reward type conditions: gain, loss or donate. Participants had to make 84 choices. The smaller amount was 5 $; the highest 7.50 $. The smaller delay was 7 days, the larger 180. The classical gain and loss condition were similar to the other versions of this task; in the donation condition the participant had to choose if the experimenter had made a smaller donation at the end of the test or a larger donation after some days of delay. Money were real. | This test measures whether participants tend to delay a reward or not and it also evaluates charitable behaviours in intertemporal choice tasks. |
| [122] | Kirby temporal discounting questionnaire | See de Rezende Costa et al. [33] | This questionnaire measures whether participants tend to delay a reward or not. |
| Terenzi et al. 2021 | Temporal discounting tasks | Participants performed two different delay discounting tasks. Both provided hypothetical rewards. One of them used food as reward, the other used money. The smaller delay of rewards was 2 days, the larger was 1 year. | These tasks measures whether participants tend to delay a reward or not. |
| [134] | Experimental discounting task | Computerized real-time task | This test measures whether participants tend to delay a reward or no |

## 5. Limitations

Limitations need to be outlined. First, based on the search strategy adopted, the study identified enough studies for PD only. Therefore, the original goal of this review to provide a meta-analysis on DD in extrapyramidal and movement disorders was not reached. Hence, future research in the field is needed to verify current discoveries in other neurological disorders belonging to the same category.

Second, no clear information was available on the potential use or abuse of substances and their respective influence on DD. Third, the literature examined included different types of dopaminergic medications, which makes it difficult to establish the extent to which each medication can affect DD.

**Table 3.** Main results of each meta-analysis.

| Hypothesis | *K* | $n_{groupA}$-$n_{groupB}$ | ES (95%CI) | Sig. | SE | Cohen's *d* interpretation | $I^2$ | Egger's linear regression test | Trim and fill analysis |
|---|---|---|---|---|---|---|---|---|---|
| **H1** | 17 | 462–389 | 0.35 | 0.007 | 0,13 | Small effect | 68.2 | 0.2 | Trimmed studies= 0 |
| **H2** | 6 | 155 - 112 | 0.35 | 0.01 | 0,14 | Small effect | 11.92 | 0.03 | Trimmed studies= 1 |
| **H3** | 6 | 131 - 120 | 0.19 | 0.1 | 0,12 | Null effect | 0.00 | 0.8 | Trimmed studies= 0 |
| **H4** | 12 | 247 - 254 | 0.23 | 0.1 | 0.16 | Small effect | 59.39 | 0.4 | Trimmed studies= 0 |

## 6. Conclusions

To the best of our knowledge, this is the first meta-analysis of DD on PD. In a recent meta-analysis, Amlung et al. [5] reported altered DD across multiple psychiatric disorders (see also [4], [27], [29], [32], [35], [82] and based on this, proposed DD as a transdiagnostic process for psychiatric disorders. Indeed, DD may provide insights into the common underlying features of those disorders, which include alterations of frontal and limbic brain networks supporting decision-making – that are affected also in PD patients [114]. Additional mechanisms that could contribute to steeper DD in people with psychiatric disorders [5] are also often affected in PD and include altered future-oriented cognitive processes, such as episodic future thinking [132], [41] which is important for considering larger delayed rewards in the context of DD and intolerance of uncertainty [28] (which would lead to preference for immediate rewards as delayed rewards can be interpreted as uncertain). All in all, our meta-analysis provides evidence that extends the suggestion of DD as a transdiagnostic process in psychiatric disorders [5] to neurological populations, and furthermore corroborates the suggestion to include DD in the Research Domain Criteria (RDoC) framework of the US National Institute of Mental Health, proposing this index as a relevant marker of mental (psychiatric and neurological) illness. Future works might wish to test this transdiagnostic process hypothesis to other neurological disorders, once a sufficient number of articles in the field are available by the literature.


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## Declaration of interest

None.

## Data Availability

Data are published in the papers of the final sample.

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