Original research

Disrupted reward processing in Parkinson’s disease and its relationship with dopamine state and neuropsychiatric syndromes: a systematic review and meta-analysis

Harry Costello 1,1, Alex J Berry, 2 Suzanne Reeves 2,1, Rimona S Weil 3, Eileen M Joyce 3, Robert Howard 2,1, Jonathan P Roiser 1

ABSTRACT

Background Neuropsychiatric symptoms are common in Parkinson’s disease (PD) and predict poorer outcomes. Reward processing dysfunction is a candidate mechanism for the development of psychiatric symptoms including depression and impulse control disorders (ICDs). We aimed to determine whether reward processing is impaired in PD and its relationship with neuropsychiatric syndromes and dopamine replacement therapy.

Methods The Ovid MEDLINE/PubMed, Embase and PsycInfo databases were searched for articles published up to 5 November 2020. Studies reporting reward processing task performance by patients with PD and healthy controls were included. Summary statistics comparing reward processing between groups were converted to standardised mean difference (SMD) scores and meta-analysed using a random effects model.

Results We identified 55 studies containing 2578 participants (1638 PD and 940 healthy controls). Studies assessing three subcomponent categories of reward processing tasks were included: option valuation (n=12), reinforcement learning (n=37) and reward response vigour (n=6). Across all studies, patients with PD on medication exhibited a small-to-medium impairment versus healthy controls (SMD=0.34, 95% CI 0.14 to 0.53), with greater impairments observed off dopaminergic medication in within-subjects designs (SMD=0.43, 95% CI 0.29 to 0.57). Within-subjects subcomponent analysis revealed impaired processing off medication on option valuation (SMD=0.57, 95% CI 0.39 to 0.75) and reward response vigour (SMD=0.36, 95% CI 0.13 to 0.59) tasks. However, the opposite applied for reinforcement learning, which relative to healthy controls was impaired on-medication (SMD=0.45, 95% CI 0.25 to 0.65) but not off-medication (SMD=0.28, 95% CI −0.03 to 0.59). ICD was the only neuropsychiatric syndrome with sufficient studies (n=13) for meta-analysis, but no significant impairment was identified compared tonon-ICD patients (SMD=−0.02, 95% CI −0.43 to 0.39).

Conclusion Reward processing disruption in PD differs according to subcomponent and dopamine medication state, and warrants further study as a potential treatment target and mechanism underlying associated neuropsychiatric syndromes.

INTRODUCTION

Parkinson’s disease (PD) is the fastest growing neurological disorder globally, with estimated annual societal costs comparable to those of dementia. Traditionally conceptualised as a movement disorder, non-motor symptoms, including dyskinesias to mood, cognition and motivation, are common and have a greater negative impact on health-related quality of life than motor symptoms. Neuropsychiatric syndromes are common in PD (see table 1). One-third of patients experience depression, up to one-half experience apathy and impulse control disorders (ICDs) associated with dopaminergic medication occur in up to one-quarter. Currently, there is a lack of understanding of the mechanisms underpinning psychiatric symptoms in PD and this represents a barrier to the development of more effective treatments.

Reward processing describes how reinforcement-related perceptions guide goal-directed behaviours. Impaired reward processing is a prominent transdiagnostic feature of several mental health disorders such as depression and represents a useful framework for understanding symptoms associated with motivation. The National Institute of Mental Health’s Research Domain Criteria identifies reward processing as one of six major domains underpinning human functioning and psychopathology. Dopamine has a well-established role in both reward and motivational pathways. Evidence from dopamine depletion studies has not supported the hypothesis that dopamine mediates hedonic responses (‘liking’), but has revealed a crucial role in motivated behaviours toward desired goals (‘wanting’).

PD is caused by dopaminergic cell death and consequently is a model of striatal and dopamine dysfunction. The striatum is reciprocally connected with prefrontal areas as well as other parts of the basal ganglia and midbrain, forming frontostriatal circuits involved in the initiation and control of motor, cognitive and emotional function. These pathways also constitute part of the brain’s reward circuit, responsible for modulating reward-related behaviour and learning. Psychiatric syndromes in PD (see table 1) are thought to reflect dysfunction of non-motor frontostriatal circuitry; for example, ICDs are believed to develop through...
aberrant reward processing, due to an interaction between the disrupted reward processing circuitry underlying PD and dopamine agonist treatment. 14

Over the past two decades, studies of reward processing in PD have typically used behavioural tasks assessing three subcomponent processes: (1) option valuation, the process by which individuals evaluate reward-related options when given explicit information about those options (eg, reward, cost and probability); (2) reward response vigour, which reflects the speed or strength with which an individual executes an action to obtain a reward; (3) reinforcement learning, which describes the process by which an individual uses feedback to change their future behaviour. To date, there has been one meta-analysis of Iowa gambling task performance in PD, which reported significantly impaired reward learning.15 However, the degree and pattern of impairments on other reward processing tasks in PD and any relationship with dopaminergic state and psychiatric symptoms remain unclear.

Here we report the first systematic review and meta-analysis of reward processing behaviour in PD and its relationship with dopamine replacement therapy and associated neuropsychiatric syndromes. Our aims were: (1) to clarify the nature and extent of differences across reward processing subcomponents between PD and healthy groups; (2) to test the role of dopamine state (on or off medication) in reward processing in PD; (3) to investigate any differences in reward processing in patients with PD with and without neuropsychiatric syndromes.

METHOD

systematic review

The Ovid MEDLINE/PubMed, Embase, and PsycInfo databases were searched for articles published between 1 January 1946 and 5 November 2020 inclusive, with titles or abstracts containing the terms: Parkinson’s and (reward* or motivat* or incentiv* or effort* or deci*) and (psychiatric or neuropsychiatric or depress* or psychosis or delus* or impuls* or mood or anxiety or apathy or anhedonia or hallucin*). Inclusion criteria were as follows: (1) case-control design; (2) included a group with PD without dementia or deep brain stimulation (DBS) (studies including participants with dementia or DBS within the PD group were excluded); (3) participants were at least 18 years old; (4) participants performed a reward-processing task; (5) task rewards were explicit, that is, money, points, water or food (we did not include studies that used outcomes that could be considered purely informational or social feedback, eg, happy/sad faces or variants of correct/incorrect, to ensure specificity); (6) studies reported data on a behavioural measure of reward processing that could be converted to a case-control standardised mean difference (SMD) score. If this was not reported, data were requested from the authors. Articles were independently assessed by HC and AJB, using a rating tool based on the Newcastle-Ottawa scale for assessing the quality of non-randomised studies (online supplement). Conflicts in quality assessment rating were resolved through in-person discussion.

Meta-analysis

Behavioural measures from each study were categorised as measuring option valuation, reward response vigour or reinforcement learning, and converted to an SMD score and an associated SE (see online supplemental material for equations).17

Within the option valuation and reward response vigour subcategories, a positive SMD represents a greater or faster response to reward by the control than the PD group, respectively. A positive SMD within the reinforcement learning subcategory represents faster use of feedback to maximise reward by the control group than the PD group.

Meta-analysis was conducted if four or more studies were present within a reward processing subcategory for patients with PD compared with healthy controls, PD with and without a psychiatric symptom, or PD on medication compared with off-medication (within-subjects designs only).

Meta-analysis was performed using the R statistical programming language and the packages metafor and metaviz, using random effects models. Heterogeneity was analysed using the approximate proportion of total variability (I²).
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Funnel plot asymmetry was assessed using visual inspection of a contour-enhanced funnel plot and the Egger test.

RESULTS
We initially identified 2122 studies, excluded 1898 of these by title/abstract and retrieved the remaining 224 full papers (figure 1); two studies could not be used in the quantitative analysis due to a lack of reported summary statistics. The median number of patients per study was 24 (IQR 16), median participant age was 63.3 years (IQR 7.5) and median duration of PD was 7.0 years (IQR 4.5).

Meta-analysis across all reward processing subcomponent categories (see online supplemental table 4) identified a small-to-medium reward processing impairment in patients with PD both on-medication (SMD=0.34; 95% CI 0.14 to 0.53) and off-medication (SMD=0.40; 95% CI 0.19 to 0.62), compared with healthy controls (figure 2A, B). Within-subjects comparison of reward processing between on-medication and off-medication states was possible in 14 studies (see online supplemental table 6), revealing relatively impaired reward processing off-medication, with a medium effect size (SMD=0.43, 95% CI 0.29 to 0.57; figure 3A). ICD was the most studied and only neuropsychiatric syndrome with sufficient studies (n=13) for meta-analysis (see online supplemental table 5). No significant impairment (see figure 3B) was identified in reward processing in patients with PD with ICD compared to patients with non-ICD (SMD=−0.02, 95% CI −0.43 to 0.39).

Overall interstudy heterogeneity was substantial ($I^2=57.48\%$), and the median power of included studies and R-index was low (online supplemental figure 1), median power=36%; R-index=28%). Analysis of funnel plot asymmetry using Egger’s regression line did not meet statistical significance (p=0.32) and was likely a consequence of high heterogeneity and small sample size of included studies (see online supplemental figure 1).

Quality assessment and risk of bias analysis using a modified Newcastle-Ottawa scale (see online supplemental table 7) found the majority of included studies used a validated assessment tool for diagnosis of PD (65.5%), and accounted for PD severity (94.5%) and medication status (90.9%). However, almost half of included studies gave no description of how healthy controls were selected (42.2%) or clearly defined controls as having no past psychopathology (42.2%).

Option valuation
We identified 12 studies containing 347 patients with PD and 278 healthy participants that used option valuation tasks (online supplemental table 1). The mean age of participants was 62.9 (±4.6) years, and mean duration of illness was 7.5 (±2.8) years. Effort-based decision-making tasks (three studies) and the game of dice task (three studies) were most commonly used. Four studies reported psychiatric medication use in participants, three of which included participants taking antidepressant medications.

Meta-analysis of studies comparing option valuation in patients with PD compared with healthy controls showed lower reward weighting in PD, which was moderated by dopamine...
medication (figure 4A, B). Patients on-medication did not differ significantly from healthy controls (SMD=0.22, 95% CI −0.04 to 0.49), but off-medication there was a medium-to-large impairment (SMD=0.60, 95% CI 0.30 to 0.89). Within-subjects comparison confirmed lower reward weighting off-medication, with a medium-to-large effect (SMD=0.57, 95% CI 0.39 to 0.75; figure 4C).

Four studies compared option valuation in patients with PD with and without neuropsychiatric syndromes. Three of these studies18–20 compared option valuation in patients with PD with and without ICD, with mixed findings. One study19 using an economic choice task reported lower reward weighting in ICD, while the other two studies18 20 using gambling tasks found no difference18 and increased reward weighting,20 respectively.

One study21 investigating the effect of apathy on option valuation reported lower acceptance of offers of reward obtained through physical exertion. This pattern of impairment in apathy was found to be dissociable from the effects of dopamine. Apathy was characterised by rejection of predominantly low reward offers, while dopamine state increased choices of high effort, high reward offers.

In summary, option valuation impairment in PD is dopamine dependent, with lower reward weighting off dopaminergic medication. Too few studies have investigated option valuation in patients with PD with neuropsychiatric syndromes to draw meaningful conclusions.

**Reinforcement learning**

We identified 37 studies containing 1059 patients with PD and 593 healthy controls that used reinforcement learning tasks (online supplemental table 2). The majority of studies (20/37)
used the Iowa gambling task. Ten studies reported psychiatric medication use, of which three included participants taking antidepressant medication.

Reinforcement learning was slowed in patients with PD on-medication versus healthy controls (figure 5A, B) with a medium effect size (SMD=0.45, 95% CI 0.25 to 0.65). Interestingly, there was no significant group difference off-medication (SMD=0.28, 95% CI −0.03 to 0.59). Comparison of reinforcement learning comparing on-medication and off-medication within-subjects (figure 5Cc) was possible in four studies, which did not detect a significant effect (SMD=0.27, 95% CI −0.08 to 0.62); however, we note that this analysis is likely underpowered due to the small number of included studies.

Sixteen studies investigated reinforcement learning in patients with PD with and without neuropsychiatric symptoms (online supplemental table 2), with the majority (11/16) examining ICD. Meta-analysis of nine studies (online supplemental figure 2) found no significant difference between patients with PD with ICD and non-ICD PD patients (SMD=0.32, 95% CI −0.09 to 0.73).

Two studies22 23 examined reinforcement learning in patients with PD with major depressive disorder. Both22 23 reported impaired reinforcement learning in depressed patients with PD compared with non-depressed patients with PD. One23 also compared reinforcement learning in depressed patients with PD with depressed participants without PD. A similar pattern of impairment in learning from positive feedback was identified in the two groups, suggesting that reinforcement learning impairment may not be specific to depression in PD.23

Two studies24 25 examined the role of apathy in reward learning. Both used the Iowa gambling task but reported conflicting findings: one found significant impairment25 but the other reported better reinforcement learning in patients with PD with apathy,24 compared with those without.

In summary, and in stark contrast to studies of option valuation, reinforcement learning is particularly impaired in PD in the on-medication state. There was no significant impairment in reinforcement learning in patients with PD with ICD compared with those without ICD. Too few studies have investigated reinforcement learning in patients with PD with other neuropsychiatric syndromes to draw meaningful conclusions.

**Reward response vigour**

We identified seven studies containing 232 patients with PD and 69 healthy controls that investigated reward response vigour in PD (online supplemental table 3). Insufficient studies were identified to allow meta-analysis of reward response vigour in PD compared with healthy controls. Of the three studies26–28 that reported reward response vigour in PD and healthy controls, results were mixed, with studies reporting lower,26 greater,27 and no difference28 in patients with PD compared with healthy volunteers.

Meta-analysis of the effect of dopamine state on reward response vigour in four studies (figure 6) identified a small-to-medium increase in reward response vigour on-medication (SMD=0.36, 95% CI 0.13 to 0.59).

Six studies investigated reward response vigour in patients with PD with and without neuropsychiatric syndromes (online supplemental table 3). Two studies27 29 examined apathy, one using a rewarded saccadic eye movement task,27 the other a rewarded spatial search task29; both reported no significant group differences. Similarly, no significant difference in reward response vigour was found in two studies comparing patients with ICD and patients with non-ICD,30 31 and two investigating depression in PD.28

In summary, relatively few studies have investigated reward response vigour in PD, and findings are mixed. Reward response vigour in PD was reduced in the off-medication compared with the on-medication state. Too few studies have investigated reward response vigour in patients with PD with neuropsychiatric syndromes to draw meaningful conclusions.
DISCUSSION
This is the first systematic review and meta-analysis of reward processing in PD, associated neuropsychiatric syndromes and the influence of dopaminergic medication. Across all 55 studies, including different subcomponents of reward processing, we found patients with PD to have small-to-medium reward processing impairments relative to healthy participant groups. The degree of impairment in reward processing is similar to that reported in major depressive disorder, a condition where the reward response vigour subcategory showed a significant small-to-moderate impairment in the off-medication state compared to the on-medication state in PD patients with PD. However, relatively few studies were identified and reaction times may be vulnerable to attentional confounds. Though several studies reported reaction times during tasks, reward-related speeding (ie, the difference between rewarded and non-rewarded conditions) was infrequently measured, without which slower reaction times would likely only reflect bradykinesia associated with PD.

Despite PD being a model for dopamine dysfunction, current treatments of common neuropsychiatric syndromes in PD such as depression do not differ from depression in patients with other long-term conditions and have limited efficacy. Symptoms of anxiety and depression in patients with PD are infrequent, impairments can be more common and severe in the off-dopamine state, suggesting depression in PD may be related to dopaminergic deficit and have a specific aetiology. Our findings suggest PD is characterised by a specific pattern of impairment in reward processing which is dopaminergic dependent and potentially could be a causal mechanism underlying neuropsychiatric symptoms such as depression. Although ICD was not significantly associated with reward processing impairment statistical power was limited, and few studies have investigated reward processing in other PD-associated neuropsychiatric syndromes. Further understanding of how impairment in reward processing is associated with specific neuropsychiatric manifestations of PD is needed to understand the underlying mechanisms of these disabling syndromes and develop more targeted and effective treatments.

LIMITATIONS
We categorised reward processing into three subcomponent categories, however there are several ways to measure function in each category which grouped diverse processes. For example,
the option valuation subcategory included studies measuring risk-taking and decisions to exert effort, resulting in meta-analysis of heterogeneous measures. A minority of studies reported antidepressant medication use in participants. Evidence suggests antidepressant medication may partly exert its effect via modulating reward processing\(^4\) which could have confounded results. Though we measured and compared the effect of dopamine medication state on task performance, the medication regime and proportion of patients on dopamine agonist treatment as opposed to levodopa was reported in less than half of included studies (22/55). Different PD medications are disproportionately opposed to levodopa was reported in less than half of included and proportion of patients on dopamine agonist treatment as associated with dopamine-studies (22/55).

The majority of studies investigating reward processing in PD-associated neuropsychiatric syndromes used patients with PD without the syndrome as a control group. Only one study\(^2\) investigating depression in PD used a control group of patients with depression without PD. In order to establish whether patterns of reward processing impairments are specific to PD-associated neuropsychiatric syndromes and not a common feature of psychiatric symptoms more generally, further studies of this type are needed. Finally, our systematic review and meta-analysis examined the findings of case-control studies which are unable to inform us of the causal relationship between reward processing impairment, PD and its associated neuropsychiatric syndromes. Longitudinal studies are needed to answer these questions and understand how reward processing changes develop as PD advances. Our analyses of the impact of dopamine medication were derived from studies conducted using within-subjects experimental comparisons, and therefore we can be more confident of a causal role. However, the effects of being off-medication in a patient who usually takes dopamine-stimulating drugs, including heightened anxiety and physical discomfort, could plausibly affect task performance. A minority of studies (22/55) measured motor symptom severity in both on and off states, and only four studies measured differences in anxiety symptoms in both states.

CONCLUSIONS
PD is associated with a small-to-medium level of reward processing impairment overall, with variable degrees of impairment across subcomponent reward processing categories. Reward processing is dependent on dopamine state with greater impairment in option valuation and reward response vigour when patients are off dopaminergic medication, but surprisingly faster reinforcement learning. Other than reinforcement learning in ICD, few studies have investigated the relationship between reward processing and PD associated neuropsychiatric syndromes. Further research, including longitudinal studies are needed to conclude whether specific patterns of impairment in reward processing have a causal relationship with neuropsychiatric syndromes in PD.

Correction notice This article has been corrected since it was published online first. The caption of figure 3 has been updated.

Twitter Harry Costello @harry_costello, Suzanne Reeves @Suzannem4823062, Rimona S Weil @rimonaweiwel, Robert Howard @ProfRobHoward and Jonathan P Roiser @jproiser

Contributors HC, JPR and RH contributed to study concept and design. HC and AIB contributed to quality assessment of studies. HC, AIB and JPR contributed to acquisition of data. HC and JPR contributed to analysis and interpretation of data. HC contributed to drafting of manuscript. All authors critically revised successive drafts of the paper and approved the final version. HC accepts responsibility as guarantor for the overall content of the study.

Funding HC is supported by a Wellcome Trust Clinical Training Fellowship (175479).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study is secondary research that synthesised the results of original papers; as such, it is exempt from ethical approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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ORCID iDs
Harry Costello http://orcid.org/0000-0003-4490-9219
Suzanne Reeves http://orcid.org/0000-0001-8053-7024
Rimona S Weil http://orcid.org/0000-0002-5092-6235
Eileen M Joyce http://orcid.org/0000-0003-0469-2844
Robert Howard http://orcid.org/0000-0002-3071-2338
Jonathan P Roiser http://orcid.org/0000-0001-8269-1228

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Supplementary references for Table 1.


Supplement figure 1. Contour-Enhanced Funnel Plot of all studies Parkinson’s versus healthy controls

Supplement figure 2. Forest plot of reinforcement learning (RL) in Parkinson’s patients with and without Impulse Control Disorder (ICD)
Formulae used to convert study measures into Cohen’s ds and associated variances.

The following formulae were used to convert study measures into Cohen’s ds and associated variances **between subjects:**

\[ d = \frac{M_1 - M_2}{SD_{pooled}} \]

**Equation 1.** Cohen’s d from Means and Standard Deviations of 2 samples. \( d \) is Cohen’s d, \( M_1 \) is the mean of one sample \( M_2 \) is the mean of the other sample, \( SD_{pooled} \) is the pooled standard deviation of the two samples (please see below.)

\[ SD_{pooled} = \sqrt{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2} \]

**Equation 2.** Pooled standard deviation of 2 samples. \( SD_{pooled} \) is the pooled standard deviation of the two samples, \( N_1 \) is the size of one sample \( N_2 \) is the size of the other sample, \( SD_1 \) is the standard deviation of one sample, \( SD_2 \) is the standard deviation of the other sample.

\[ d = \frac{t}{\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}} \]

**Equation 3.** Cohen’s d from t-statistic. \( d \) is Cohen’s d, \( N_1 \) is the size of one sample \( N_2 \) is the size of the other sample, \( t \) is the t-statistic

\[ d = \frac{F}{\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}} \]

**Equation 4.** Cohen’s d from F-statistic. \( d \) is Cohen’s d, \( N_1 \) is the size of one sample \( N_2 \) is the size of the other sample, \( F \) is the F-statistic.

\[ Var_d = \frac{N_1 + N_2}{N_1 \times N_2} \left( \frac{d^2}{2(N_1 + N_2)} \right) \]

**Equation 5.** Variance on Cohen’s d for between subjects. \( Var_d \) is the Variance on Cohen’s d, \( N_1 \) is the size of one sample \( N_2 \) is the size of the other sample, \( d \) is Cohen’s d.

The following formulae were used to convert study measures into Cohen’s ds and associated variances **within subjects:**

\[ d = \frac{M_d}{SD_d} \]

**Equation 6.** Cohen’s d from Means and Standard Deviations from within subjects sample. Where \( M_d \) is the mean change and \( SD_d \) is the SD of the change scores (equal to \( SD_d = \sqrt{SD_1^2 + SD_2^2 - 2 \times r \times SD_1SD_2} \)).

\[ d = \frac{t}{\sqrt{N}} \]

**Equation 7.** Cohen’s d from t-statistic for within subjects results. \( d \) is Cohen’s d, \( N \) is the sample size, \( t \) is the t-statistic

\[ d = \frac{F}{\sqrt{N}} \]

**Equation 8.** Cohen’s d from F-statistic. \( d \) is Cohen’s d, \( N \) is the sample size, \( F \) is the F-statistic.

\[ Var[d] = \frac{1}{n} + \frac{d^2}{2n} \]

**Equation 9.** Variance on Cohen’s d for within subjects, \( n \) is the size of the sample.
### Supplemental material

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**Supplement table 1. Option Valuation study characteristics and participant demographics.**

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### Option valuation in Parkinson’s with psychiatric syndrome vs without

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#### Supplement table 2. Reinforcement Learning Study characteristics and participant demographics.

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**PD** = Parkinson's disease, **HC** = healthy controls, **ICD** = Impulse control disorder, **SD** = standard deviation, **IQR** = interquartile range, '-' = not reported, '–' = not applicable, **UPDRS** = Unified Parkinson's Disease Rating Scale, **MMSE** = Mini-mental state examination, **MoCA** = Montreal cognitive assessment, **ACE** = Addenbrooke's cognitive examination, **BDI** = Beck depression inventory, **DASS** = Depression, Anxiety and Stress Scale, **GDS** = Geriatric depression scale, **MADRS** = Montgomery-Asberg Depression Rating Scale.
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**Reinforcement learning in Parkinson's with psychiatric syndrome vs without**

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### Supplemental table 3. Response Vigor and Reward Bias study characteristics and participant demographics.

#### Response vigor in Parkinson’s vs Healthy Controls

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#### Response vigor in Parkinson’s with psychiatric syndrome vs without

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PD = Parkinson’s disease, HC = healthy controls, ICD = Impulse control disorder, SD = standard deviation, IQR = interquartile range, ‘.’ = not reported, ‘-’ = not applicable, UPDRS = Unified Parkinson’s Disease Rating Scale, MMSE = Mini-mental state examination, MoCA = Montreal cognitive assessment, MMPD = Mini-mental Parkinson’s examination BDI = Beck depression inventory, GDS = Geriatric depression scale.
## Supplement table 4. Study summary statistics, tasks and measures included in the Meta-Analysis of Parkinson’s versus healthy controls.

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Supplemental table 5. Study summary statistics, tasks and measures included in the Meta-Analysis of Parkinson’s with & without psychiatric syndrome

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### Supplement table 6. Study summary statistics, tasks and measures included in the Meta-Analysis of Parkinson’s on and off dopaminergic medication

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<th>Task</th>
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Modified version of the Newcastle-Ottawa Scale for Assessing the Quality of Nonrandomized Studies in Meta-Analyses, used to assess potential sources of bias.
Potential sources of bias were assessed using a modified version of the Newcastle-Ottawa Scale for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. The studies are scored on:

1. PD Definition: Is the case definition adequate?
   A) Cases were defined as PD according to a validated assessment tool/criteria or by an experienced clinician
   B) Cases were defined as PD according to a validated assessment tool/criteria but the method for assessing PD status was not stated.
   C) Cases were described as ‘clinically’ but no further description was given.

2. PD Generality: Was a General sample of cases tested?
   A) A General sample of PD was tested.
   B) Recruitment of PD cases was restricted to a specific sub-sample (specific age range, hospitalised only etc.)

3. HC Selection: Selection of Controls
   A) Controls were selected from the same population as cases
   B) Controls were not selected from the same population as cases
   C) No description

4. HC Definition: Definition of Controls
   A) HC were defined clearly defined as having no current or past psychopathology
   B) Controls were not clearly defined as having no current or past psychopathology.

Comparability (Comparability of cases and controls on the basis of the design or analysis)
1. Does the study control for Age: Yes/No/Unclear
2. Does the study control for Gender: Yes/No/Unclear
3. Does the study control for IQ: Yes/No/Unclear
4. Does the study control for Socioeconomic status: Yes/No/Unclear
5. Does the study control for PD severity: Yes/No/Unclear
6. Does the study control for medication status: Yes/No/Unclear

Key: A, B, C
Y = yes, N= no, N/A= Not applicable (such as if no healthy control group in study)
Supplement table 7. Quality rating of included studies

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References


Supplementary references for Table 1.


Supplement figure 1. Contour-Enhanced Funnel Plot of all studies Parkinson’s versus healthy controls

Supplement figure 2. Forest plot of reinforcement learning (RL) in Parkinson’s patients with and without Impulse Control Disorder (ICD)
Formulae used to convert study measures into Cohen’s ds and associated variances.

The following formulae were used to convert study measures into Cohen’s ds and associated variances **between subjects:**

\[ d = \frac{M_1 - M_2}{SD_{pooled}} \]

**Equation 1.** Cohen’s d from Means and Standard Deviations of 2 samples. \(d\) is Cohen’s d, \(M_1\) is the mean of one sample \(M_2\) is the mean of the other sample, \(SD_{pooled}\) is the pooled standard deviation of the two samples (please see below.)

\[ SD_{pooled} = \sqrt{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2} \]

**Equation 2.** Pooled standard deviation of 2 samples. \(SD_{pooled}\) is the pooled standard deviation of the two samples, \(N_1\) is the size of one sample \(N_2\) is the size of the other sample, \(SD_1\) is the standard deviation of one sample, \(SD_2\) is the standard deviation of the other sample.

\[ d = \frac{t}{\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}} \]

**Equation 3.** Cohen’s d from t-statistic. \(d\) is Cohen’s d, \(N_1\) is the size of one sample \(N_2\) is the size of the other sample, \(t\) is the t-statistic

\[ d = \frac{F}{\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}} \]

**Equation 4.** Cohen’s d from F-statistic. \(d\) is Cohen’s d, \(N\) is the sample size, \(F\) is the F-statistic.

\[ Var_d = \frac{N_1 + N_2}{N_1 \times N_2} + \frac{d^2}{2(N_1 + N_2)} \]

**Equation 5.** Variance on Cohen’s d for between subjects. \(Var_d\) is the Variance on Cohen’s d, \(N_1\) is the size of one sample \(N_2\) is the size of the other sample, \(d\) is Cohen’s d.

The following formulae were used to convert study measures into Cohen’s ds and associated variances **within subjects:**

\[ d = \frac{M_d}{SD_d} \]

**Equation 6.** Cohen’s d from Means and Standard Deviations from within subjects sample. Where \(M_d\) is the mean change and \(SD_d\) is the SD of the change scores (equal to \(SD_d = \sqrt{SD_1^2 + SD_2^2 - 2 \times r \times SD_1SD_2}\).)

\[ d = \frac{t}{\sqrt{N}} \]

**Equation 7.** Cohen’s d from t-statistic for within subjects results. \(d\) is Cohen’s d, \(N\) is the sample size, \(t\) is the t-statistic

\[ d = \frac{F}{\sqrt{N}} \]

**Equation 8.** Cohen’s d from F-statistic. \(d\) is Cohen’s d, \(N\) is the sample size, \(F\) is the F-statistic.

\[ Var_d = \frac{1}{n} + \frac{\alpha^2}{2n} \]

**Equation 9.** Variance on Cohen’s d for within subjects, \(n\) is the size of the sample.
Supplement table 1. Option Valuation study characteristics and participant demographics.

### Option valuation in Parkinson’s vs Healthy Controls

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**Reinforcement learning in Parkinson's with psychiatric syndrome vs without**

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### Supplemental table 3. Response Vigor and Reward Bias study characteristics and participant demographics.

#### Response vigor in Parkinson’s vs Healthy Controls

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### Response vigor in Parkinson’s with psychiatric syndrome vs without

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<th>UPDRS</th>
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<th>Depression</th>
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PD = Parkinson’s disease, HC = healthy controls, ICD = Impulse control disorder, SD = standard deviation, IQR = interquartile range, ‘.’ = not reported, ‘-’ = not applicable, UPDRS = Unified Parkinson’s Disease Rating Scale, MMSE = Mini-mental state examination, MoCA = Montreal cognitive assessment, MMSE = Mini-mental Parkinson’s examination, BDI = Beck depression inventory, GDS = Geriatric depression scale.
Supplemental material

Supplement table 4. Study summary statistics, tasks and measures included in the Meta-Analysis of Parkinson’s versus healthy controls.

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Tasks and Measures Included in the Meta-Analysis.

- Game of dice task
- Net score
- Effort based decision making task (apple gathering)
- Effort indifference point (mean effect size across stake levels, fig 4)
- Effort based decision making task (apple gathering)
- Effort indifference point
- Game of dice task
- Net score (fig 1)
- Economic choice task
- Relative risk aversion coefficient (fig 2C, first session)
- Economic choice task
- Relative risk aversion coefficient (fig 2C, first session)
- Effort based decision making task (apple gathering)
- Mean difference in proportion of offers accepted
- Cognitive effort task
- Mean difference in k-value
- Cognitive effort task
- Mean difference in k-value
- Vancouver gambling task
- Gain phase adjust y intercept
- Vancouver gambling task
- Gain phase adjust y intercept
- Cambridge gamble task
- Average bet (across risk levels)
- Cambridge gamble task
- Average bet (across risk levels)
- Incentivised decision making task
- Mean % bets across ascending & descending conditions
- Incentivised decision making task
- Mean % bets across ascending & descending conditions
- Effort based decision making task: Binary choice task
- Choice of effort level at the highest stake level. (fig 4D)
- Effort based decision making task: Binary choice task
- Choice of effort level at the highest stake level. (fig 4D)
- Iowa Gambling Task
- Baseline final round mean score. (fig 1A)
- Iowa Gambling Task
- Baseline final round mean score. (fig 1A)
- Probabilistic rewarded categorisation learning task
- % Optimality during expected reward (fig 3A)
- Probabilistic rewarded categorisation learning task
- % Optimality during expected reward (fig 3A)
- Feedback-based probabilistic classification task
- Final block % optimal decisions (fig 2)
- Feedback-based probabilistic classification task
- Final block % optimal decisions (fig 2)
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<th>Actor’s learning rate (fig 6C)</th>
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<td>1.08</td>
<td>0.11</td>
<td>Instrumental conditioning task</td>
<td>Reward learning index (fig 2B)</td>
<td></td>
</tr>
<tr>
<td>Czernecki et al, 2002 (ON)</td>
<td>RL</td>
<td>ON</td>
<td>28</td>
<td>23</td>
<td>8.32</td>
<td>11.0</td>
<td>2</td>
<td>2.86</td>
<td>16.5</td>
<td>0.40</td>
<td>0.08</td>
<td>Iowa Gambling Task</td>
<td>Final block mean score (fig 1, second session)</td>
</tr>
<tr>
<td>Czernecki et al, 2002 (OFF)</td>
<td>RL</td>
<td>OFF</td>
<td>28</td>
<td>23</td>
<td>8.32</td>
<td>11.0</td>
<td>2</td>
<td>5.36</td>
<td>10.8</td>
<td>0.27</td>
<td>0.08</td>
<td>Iowa Gambling Task</td>
<td>Final block mean score (fig 1, second session)</td>
</tr>
<tr>
<td>Graef et al, 2010 (ON)</td>
<td>RL</td>
<td>ON</td>
<td>15</td>
<td>14</td>
<td>1.8</td>
<td>6.84</td>
<td>9</td>
<td>14.0</td>
<td>60.0</td>
<td>0.67</td>
<td>0.14</td>
<td>Instrumental learning task</td>
<td>% correct choices with constant reward contingencies</td>
</tr>
<tr>
<td>Graef et al, 2010 (OFF)</td>
<td>RL</td>
<td>OFF</td>
<td>15</td>
<td>14</td>
<td>2.1</td>
<td>6.84</td>
<td>9</td>
<td>14.0</td>
<td>59.0</td>
<td>0.86</td>
<td>0.15</td>
<td>Instrumental learning task</td>
<td>% correct choices with constant reward contingencies</td>
</tr>
<tr>
<td>Thiel et al, 2003 (OFF)</td>
<td>RL</td>
<td>OFF</td>
<td>5</td>
<td>5</td>
<td>53.6</td>
<td>15.8</td>
<td>61.2</td>
<td>17.1</td>
<td>0.46</td>
<td>0.41</td>
<td>Iowa Gambling Task</td>
<td>Mean number of advantageous cards selected.</td>
<td></td>
</tr>
<tr>
<td>Perretta et al, 2005 (late PD)</td>
<td>RL</td>
<td>ON late PD</td>
<td>19</td>
<td>16</td>
<td>7.80</td>
<td>1.31</td>
<td>6.80</td>
<td>1.60</td>
<td>0.69</td>
<td>0.12</td>
<td>Iowa Gambling Task</td>
<td>Mean total score</td>
<td></td>
</tr>
<tr>
<td>Perretta et al, 2005 (early PD)</td>
<td>RL</td>
<td>ON early PD</td>
<td>19</td>
<td>16</td>
<td>7.80</td>
<td>1.31</td>
<td>7.60</td>
<td>1.60</td>
<td>0.14</td>
<td>0.12</td>
<td>Iowa Gambling Task</td>
<td>Mean total score</td>
<td></td>
</tr>
<tr>
<td>Kobayakawa et al, 2008 (ON)</td>
<td>RL</td>
<td>ON</td>
<td>22</td>
<td>34</td>
<td>4.8</td>
<td>4.90</td>
<td>12.2</td>
<td>16.0</td>
<td>21.5</td>
<td>0.60</td>
<td>0.08</td>
<td>Iowa Gambling Task</td>
<td>Group difference in choice patterns (advantageous - disadvantageous)</td>
</tr>
<tr>
<td>Kobayakawa et al, 2010 (ON)</td>
<td>RL</td>
<td>ON</td>
<td>22</td>
<td>14</td>
<td>2.9</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Iowa Gambling Task</td>
<td>Group difference in choice patterns (advantageous - disadvantageous)</td>
</tr>
<tr>
<td>Poletti et al, 2010 (OFF)</td>
<td>RL</td>
<td>OFF (de novo)</td>
<td>25</td>
<td>30</td>
<td>6.00</td>
<td>6.82</td>
<td>3.07</td>
<td>12.0</td>
<td>0.29</td>
<td>0.07</td>
<td>Iowa Gambling Task</td>
<td>Mean total score</td>
<td></td>
</tr>
<tr>
<td>Delazer et al, 2009 (ON)</td>
<td>RL</td>
<td>ON</td>
<td>20</td>
<td>20</td>
<td>8.8</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Iowa Gambling Task</td>
<td>Group difference in choice patterns (advantageous - disadvantageous)</td>
</tr>
<tr>
<td>Euteneuer et al, 2009 (ON)</td>
<td>RL</td>
<td>ON</td>
<td>23</td>
<td>21</td>
<td>0.6</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Iowa Gambling Task</td>
<td>Group difference in choice patterns (advantageous - disadvantageous)</td>
</tr>
<tr>
<td>Ibarrutxet-Bilbao et al, 2009 (ON)</td>
<td>RL</td>
<td>ON</td>
<td>24</td>
<td>24</td>
<td>14.56</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Iowa Gambling Task</td>
<td>Group difference in choice patterns (advantageous - disadvantageous)</td>
</tr>
<tr>
<td>Pignatti et al, 2012 (ON)</td>
<td>RL</td>
<td>ON</td>
<td>16</td>
<td>15</td>
<td>12.5</td>
<td>14.8</td>
<td>7</td>
<td>7.47</td>
<td>16.0</td>
<td>0.33</td>
<td>0.13</td>
<td>Iowa Gambling Task</td>
<td>Total score over the last 50 choices</td>
</tr>
<tr>
<td>Evens et al, 2015 (ON)</td>
<td>RL</td>
<td>ON</td>
<td>32</td>
<td>32</td>
<td>7.31</td>
<td>20.7</td>
<td>8</td>
<td>2.09</td>
<td>16.2</td>
<td>0.28</td>
<td>0.06</td>
<td>Iowa Gambling Task</td>
<td>Mean total score</td>
</tr>
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Supplement table 5. Study summary statistics, tasks and measures included in the Meta-Analysis of Parkinson’s with & without psychiatric syndrome

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Category</th>
<th>Psychiatric syndrome</th>
<th>N (PD)</th>
<th>N (PD+PSY CH)</th>
<th>M (PD)</th>
<th>SD (PD)</th>
<th>M (PD +Psych)</th>
<th>SD (PD+Pycn)</th>
<th>d</th>
<th>Vard</th>
<th>Task</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balusubramani et al, 2015 (ON)</td>
<td>RL</td>
<td>ICD</td>
<td>14</td>
<td>16</td>
<td>61.5</td>
<td>4.4</td>
<td>78.6</td>
<td>9.9</td>
<td>78.97</td>
<td>61.56</td>
<td>-0.25</td>
<td>0.13</td>
</tr>
<tr>
<td>Piray et al, 2014 (ON)</td>
<td>RL</td>
<td>ICD</td>
<td>15</td>
<td>16</td>
<td>0.13</td>
<td>0.19</td>
<td>0.067</td>
<td>0.06</td>
<td>0.13</td>
<td>0.47</td>
<td>Probabilistic learning task</td>
<td>Actor’s learning rate (fig 6C)</td>
</tr>
<tr>
<td>Housden et al, 2010 (ON)</td>
<td>RL</td>
<td>ICD</td>
<td>18</td>
<td>18</td>
<td>27</td>
<td>9.1</td>
<td>42.7</td>
<td>19.7</td>
<td>19.7</td>
<td>-0.81</td>
<td>0.12</td>
<td>Salience Attribution Test</td>
</tr>
<tr>
<td>Biars et al, 2019 (ON)</td>
<td>RL</td>
<td>ICD</td>
<td>24</td>
<td>24</td>
<td>3.5</td>
<td>9.7</td>
<td>2.75</td>
<td>8.2</td>
<td>0.08</td>
<td>0.08</td>
<td>Iowa Gambling Task</td>
<td>Final block score (authors provided)</td>
</tr>
<tr>
<td>Balconi et al, 2018 (ON)</td>
<td>RL</td>
<td>PG</td>
<td>20</td>
<td>17</td>
<td>7.6</td>
<td>60</td>
<td>8.2</td>
<td>4.6</td>
<td>33.10</td>
<td>0.46</td>
<td>0.12</td>
<td>Iowa Gambling Task</td>
</tr>
<tr>
<td>Paz-Alonso et al, 2019 (ON)</td>
<td>RL</td>
<td>ICD</td>
<td>17</td>
<td>18</td>
<td>41.8</td>
<td>0</td>
<td>15.3</td>
<td>8</td>
<td>27.00</td>
<td>13.94</td>
<td>1.01</td>
<td>0.13</td>
</tr>
<tr>
<td>Pineau et al, 2016 (ON)</td>
<td>RL</td>
<td>ICD</td>
<td>20</td>
<td>17</td>
<td>15.0</td>
<td>5</td>
<td>15.5</td>
<td>6</td>
<td>14.0</td>
<td>9.63</td>
<td>0.08</td>
<td>0.11</td>
</tr>
<tr>
<td>Bentivoglio et al, 2012 (ON)</td>
<td>RL</td>
<td>ICD</td>
<td>17</td>
<td>17</td>
<td>8.40</td>
<td>22.1</td>
<td>2.40</td>
<td>-4.60</td>
<td>33.10</td>
<td>0.46</td>
<td>0.12</td>
<td>Iowa Gambling Task</td>
</tr>
<tr>
<td>Rossi et al, 2010 (ON)</td>
<td>RL</td>
<td>PG</td>
<td>13</td>
<td>7</td>
<td>2.4</td>
<td>60</td>
<td>12.2</td>
<td>2.60</td>
<td>1.22</td>
<td>0.26</td>
<td>Iowa Gambling Task</td>
<td>Final block mean net score</td>
</tr>
<tr>
<td>Garofalo et al, 2017 (ON)</td>
<td>RL</td>
<td>Psychosis</td>
<td>17</td>
<td>12</td>
<td>15.1</td>
<td>5</td>
<td>6.68</td>
<td>8.67</td>
<td>8.34</td>
<td>0.16</td>
<td>0.88</td>
<td>Instrumental conditioning task</td>
</tr>
<tr>
<td>Sáez-Francés et al, 2014 (ON)</td>
<td>RL</td>
<td>Fatigue</td>
<td>56</td>
<td>33</td>
<td>1.79</td>
<td>0</td>
<td>14.8</td>
<td>0</td>
<td>4.18</td>
<td>11.13</td>
<td>0.44</td>
<td>0.05</td>
</tr>
<tr>
<td>Martínez-Horta et al, 2013 (ON)</td>
<td>RL</td>
<td>Apathy</td>
<td>17</td>
<td>20</td>
<td>1.82</td>
<td>2</td>
<td>5.80</td>
<td>4.10</td>
<td>4.80</td>
<td>-1.12</td>
<td>0.13</td>
<td>Iowa Gambling Task</td>
</tr>
<tr>
<td>Buelow et al, 2014 (ON)</td>
<td>RL</td>
<td>Apathy</td>
<td>14</td>
<td>10</td>
<td>22.1</td>
<td>2</td>
<td>16.8</td>
<td>0</td>
<td>-24.00</td>
<td>14.87</td>
<td>2.88</td>
<td>0.34</td>
</tr>
<tr>
<td>Herzallah et al, 2017 (ON)</td>
<td>RL</td>
<td>MDD</td>
<td>17</td>
<td>13</td>
<td>72.1</td>
<td>0</td>
<td>16.6</td>
<td>2</td>
<td>49.30</td>
<td>22.14</td>
<td>1.19</td>
<td>0.16</td>
</tr>
<tr>
<td>Timmer et al, 2017 (ON)</td>
<td>RL</td>
<td>MDD</td>
<td>22</td>
<td>19</td>
<td>0.10</td>
<td>0.06</td>
<td>0.07</td>
<td>0.06</td>
<td>-0.50</td>
<td>0.10</td>
<td>Deterministic reversal learning paradigm</td>
<td>Error rate for expected reward</td>
</tr>
</tbody>
</table>
**Supplemental table 6. Study summary statistics, tasks and measures included in the Meta-Analysis of Parkinson’s on and off dopaminergic medication**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Category</th>
<th>N</th>
<th>t</th>
<th>F</th>
<th>d</th>
<th>Yard</th>
<th>Task</th>
<th>Tasks and Measures Included in the Meta-Analysis.</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poletti et al, 2011 (OFF)</td>
<td>RL</td>
<td>12</td>
<td>12</td>
<td>4.17</td>
<td>8.37</td>
<td>3.00</td>
<td>Iowa Gambling Task</td>
<td>Number of advantageous minus disadvantageous choices</td>
<td></td>
</tr>
<tr>
<td>Kobayashi et al, 2018 (ON)</td>
<td>OV</td>
<td>15</td>
<td>10</td>
<td>0.30</td>
<td>0.66</td>
<td>-0.19</td>
<td>Relative risk aversion coefficient</td>
<td>Mean difference in proportion of offers accepted</td>
<td></td>
</tr>
<tr>
<td>Le Heron et al, 2018 (ON)</td>
<td>OV</td>
<td>18</td>
<td>21</td>
<td>2.33</td>
<td>0.75</td>
<td>0.11</td>
<td>Effort based decision making task (apple gathering)</td>
<td>Mean difference in proportion of offers accepted</td>
<td></td>
</tr>
<tr>
<td>Voon et al, 2011 (ON)</td>
<td>OV</td>
<td>14</td>
<td>14</td>
<td>0.68</td>
<td>0.14</td>
<td>-0.93</td>
<td>Economic choice task</td>
<td>Mean difference in proportion of offers accepted</td>
<td></td>
</tr>
<tr>
<td>Timmer et al, 2018 (ON)</td>
<td>RV</td>
<td>23</td>
<td>22</td>
<td>14.4</td>
<td>0.40</td>
<td>17.70</td>
<td>Reward related speeding</td>
<td>Reaction time reward benefit (repeat)</td>
<td></td>
</tr>
<tr>
<td>Evans et al, 2010 (ON)</td>
<td>RV</td>
<td>20</td>
<td>20</td>
<td>12.7</td>
<td>-1.13</td>
<td>0.10</td>
<td>Card arranging reward responsiveness objective test</td>
<td>Reward responsivity</td>
<td></td>
</tr>
<tr>
<td>Drew et al, 2020 (ON)</td>
<td>RV</td>
<td>26</td>
<td>23</td>
<td>2.78</td>
<td>-0.48</td>
<td>0.08</td>
<td>Reward speed of gaze shifting task</td>
<td>Residual velocity reward sensitivity</td>
<td></td>
</tr>
<tr>
<td>Lawrence et al, 2011 (ON)</td>
<td>RV</td>
<td>10</td>
<td>10</td>
<td>0.38</td>
<td>0.20</td>
<td>0.28</td>
<td>Reward related speeding</td>
<td>Reward related speeding</td>
<td></td>
</tr>
</tbody>
</table>

**Tasks and Measures Included in the Meta-Analysis.**

- **Reward processing summary statistics for Parkinson’s disease patients ON vs OFF dopaminergic medication**
  - **Author, Year**: The authors and the year of publication.
  - **Category**: The category of task or measure included in the meta-analysis, such as RL (Reward Learning), ICD (Iowa Gambling Task),或其他。
  - **N**: The number of participants.
  - **t**: The parameter used for the analysis, such as the adjusted y intercept or the difference score of bets placed in ascending and descending conditions.
  - **F**: The statistic used in the analysis, such as t-value or F-value.
  - **d**: The effect size measure used in the analysis, such as Cohen's d or Hedge's g.
  - **Yard**: The yardstick for the analysis, such as the number of advantageous minus disadvantageous choices.
  - **Task**: The specific task or measure included in the meta-analysis, such as Iowa Gambling Task, Effort based decision making task,或其他。

- **Tasks and Measures Included in the Meta-Analysis.**
  - **Measure**: The specific measure or outcome used in the analysis, such as the number of advantageous minus disadvantageous choices, the difference score of bets placed in ascending and descending conditions,或其他。
Modified version of the Newcastle-Ottawa Scale for Assessing the Quality of Nonrandomized Studies in Meta-Analyses, used to assess potential sources of bias.

Potential sources of bias were assessed using a modified version of the Newcastle-Ottawa Scale for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. The studies are scored on:

1. PD Definition: Is the case definition adequate?
   A) Cases were defined as PD according to a validated assessment tool/criteria or by an experienced clinician
   B) Cases were defined as PD according to a validated assessment tool/criteria but the method for assessing PD status was not stated.
   C) Cases were described as ‘clinically’ but no further description was given.

2. PD Generality: Was a General sample of cases tested?
   A) A General sample of PD was tested.
   B) Recruitment of PD cases was restricted to a specific sub-sample (specific age range, hospitalised only etc.)

3. HC Selection: Selection of Controls
   A) Controls were selected from the same population as cases
   B) Controls were not selected from the same population as cases
   C) No description

4. HC Definition: Definition of Controls
   A) HC were defined clearly defined as having no current or past psychopathology
   B) Controls were not clearly defined as having no current or past psychopathology.

Comparability (Comparability of cases and controls on the basis of the design or analysis)

1. Does the study control for Age: Yes/No/Unclear
2. Does the study control for Gender: Yes/No/Unclear
3. Does the study control for IQ: Yes/No/Unclear
4. Does the study control for Socioeconomic status: Yes/No/Unclear
5. Does the study control for PD severity: Yes/No/Unclear
6. Does the study control for medication status: Yes/No/Unclear

Key: A, B, C
Y = yes, N= no, N/A= Not applicable (such as if no healthy control group in study)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Category</th>
<th>PD Definition</th>
<th>PD Generality</th>
<th>HC Selection</th>
<th>HC Definition</th>
<th>Age</th>
<th>Gender</th>
<th>IQ</th>
<th>Socioeconomic status</th>
<th>PD severity</th>
<th>PD medication</th>
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</thead>
<tbody>
<tr>
<td>Bayard et al.</td>
<td>2016</td>
<td>OV</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Brandt et al.</td>
<td>2015</td>
<td>OV</td>
<td>A</td>
<td>A</td>
<td>C</td>
<td>B</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Chong et al.</td>
<td>2015</td>
<td>OV</td>
<td>B</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Cools et al.</td>
<td>2003</td>
<td>OV</td>
<td>A</td>
<td>A</td>
<td>C</td>
<td>B</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Haagensen et al.</td>
<td>2020</td>
<td>OV</td>
<td>C</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Kobayash et al.</td>
<td>2019</td>
<td>OV</td>
<td>A</td>
<td>A</td>
<td>C</td>
<td>B</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Le Bouc et al.</td>
<td>2016</td>
<td>OV</td>
<td>C</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Le Heron et al.</td>
<td>2018</td>
<td>OV</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
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