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REVIEW

Neurocognitive correlates of medication-induced addictive behaviours in Parkinson's disease: A systematic review

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Abstract
Dopaminergic medication can induce severe addictive behaviours (e.g., pathological gambling) in susceptible Parkinson's disease (PD) patients. It is still unknown which particular neurocognitive processes become exacerbated or dysfunctional in PD patients with addictive behaviours. We sought to systematically review the relevant literature to identity potential neurocognitive correlates of medication-induced addictive behaviours in PD. We framed our review around neurocognitive processes central to four dominant accounts of substance addiction: 'aberrant learning', 'incentive sensitization', 'impulsivity to compulsivity' and 'impaired response inhibition and salience attribution'. Searches of the PubMed and Scopus databases were completed on June 23, 2017. To be included, studies were required to involve: (a) medicated PD patients, without a history of deep brain stimulation, with and without addictive behaviours; (b) a reward-related or decision-making task; and (c) statistical comparison of addictive and non-addictive groups' 'on' medication performance on the task(s). Studies were summarised

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qualitatively with statistically significant ($p < .05$) group differences and effect sizes (Cohen's d) highlighted. 35 studies were included. Findings showed that the extant literature is highly heterogeneous. The domains of reward and punishment learning, reflection impulsivity and disadvantageous decision-making exemplify this. More homogeneity exists in domains in which (a) neurocognitive dysfunction is not apparent (motor control, cognitive/attentional flexibility and cognitive control) or (b) typical neurocognitive processes appear exacerbated by medication (reward motivation and choice impulsivity). Future large-scale neurocognitive studies are still required to develop our scientific understanding of addictive behaviours in PD and aid their clinical treatment and prediction.

1. Introduction

It is widely recognised that routine administration of dopaminergic medication can cause behavioural changes in susceptible patients with Parkinson's disease (PD) (Weintraub et al., 2015). Behavioral changes can present in subsyndromal forms (e.g., purchasing additional items online), to extremely severe, often-devastating forms (e.g., the case of a hypersexual patient convicted for soliciting sex from a minor; cases of gambling losses over $100,000) (Bartlett et al., 2013; Stenberg, 2016). These more severe instances were initially labelled 'impulse control disorders', following the *DSM-IV* nomenclature (Weintraub et al., 2010), but now are also referred to as 'impulsive-compulsive behaviours', 'behavioural addictions' or 'addictive behaviours' (Averbeck et al., 2014; Witjas et al., 2012).

A study of over 3000 people with PD found 13.6% had an addictive behaviour (Weintraub et al., 2010), the most common being compulsive shopping (5.7%), pathological gambling (5%), binge eating (4.3%) and hypersexuality (3.5%). These addictive behaviours are strongly associated with dopamine agonists (e.g., pramipexole) (Weintraub et al., 2010), although no dose-dependent relationship has been established (Ambermoon et al., 2010). Addiction-like abuse of medication (or 'dopamine dysregulation syndrome' (DDS)) occurs in 2% of patients, while 7% of patients display prolonged, repetitive, stereotyped behaviors (or 'punding') (Averbeck et al., 2014). These dysfunctions are associated more with levodopa use than dopamine agonists (Evans et al., 2005). It is worth noting that these figures are potentially underestimated: there is sometimes lack of clinical screening for addictive behaviours; afflicted patients show impaired insight, guilt and denial (Averbeck et al., 2014; Goerlich-Dobre et al., 2014); there is documented underreporting of addictive behaviours in patients without caregivers (Baumann-Vogel et al., 2015); and there are discrepancies in patient-caregiver addictive behaviour ratings (Ricciardi et al., 2016).

Despite a strong (epidemiologically) causal link between dopaminergic medication administration and addictive behaviours in PD (Ambermoon et al., 2011), it is not clear which neurocognitive processes become exacerbated or dysfunctional in patients with addictive behaviours. Drawing on theories of substance addiction, medication administration could gradually enhance reward learning and impair punishment learning in vulnerable patients (Everitt and Robbins, 2016); enhance the incentive salience of reward cues and motivate their pursuit (Robinson and Berridge, 2008); lead to reduced subjective valuation of long-term rewards and reduced cognitive flexibility (Fineberg et al., 2014); and/or impair impulse inhibition (Goldstein and Volkow, 2011). Numerous individual studies have attempted to assess the impact of medication on a wide range of neurocognitive domains with varying and conflicting results. The neurocognitive correlates of addictive behaviours in PD are thus still unclear (cf. Averbeck et al., 2014).

There has been no attempt to comprehensively review the relevant literature to identity potential neurocognitive correlates of medication-induced addictive behaviours in PD (cf. Santangelo et al., 2017). We reviewed studies assessing neurocognitive processes central to the four following dominant accounts of substance addiction: 'aberrant learning', where over-learned habits come to underpin addictive behaviours (Everitt and Robbins, 2016); 'incentive-sensitization', where excessive incentive salience is attributed to drugs and associated stimuli, driving addictive craving and relapse (Robinson and Berridge, 2008); 'impulsivity to compulsivity', where prolonged, excessive and impulsive substance use eventually leads to compulsive behaviour in vulnerable individuals (Fineberg et al., 2014); and 'impaired response inhibition and salience attribution (iRISA)', where, in addition to drug-induced subcortical neuroadaptations affecting reward processing, drug-induced cortical neuroadaptations impair valuation and control processes (Goldstein and Volkow, 2011). These specific processes and the tasks with which they have been measured in the reviewed literature are outlined in Supplementary materials. We qualitatively summarise findings, before identifying the domains in which further work is required.

2. Experimental procedures

This (unregistered) systematic review followed the PICOS methodology embedded within the PRISMA framework (Liberati et al., 2009). Studies were included if they included: (a) medicated PD patients, without a history of deep brain stimulation (given the significant uncertainty about the role of DBS in independently inducing or ameliorating impulsive behaviour in PD patients), with (*population*) and without (*comparator*) addictive behaviours; (b) reward-related and decision-making tasks that measure the neurocognitive processes outlined in Supplementary materials (*interventions/indices*); and (c) statistical comparison of addictive and non-addictive groups' 'on' medication performance on the tasks (*outcomes*; *study design*). Within-group 'on' and 'off' comparisons were not performed as (a) they are not central to the research question and (b) it is difficult to interpret task performance in the 'off' state due to the potential confounds of medication withdrawal (Evans et al., 2010).

Searches of the PubMed and Scopus databases were completed on June 23, 2017 using the following search terms derived from our *population*, *comparator* and *interventions*: Parkinson* AND (impuls* OR compuls* OR addict* OR gambl* OR hypersex* OR buy* OR eat* OR pund* OR hobby* OR dysreg*) AND (cognit* OR decision OR reward* OR task OR experiment*). No past date limit was set. Journal article and English language filters were applied for both databases.

Data extraction was performed using Excel. As we provide a qualitative summary of the relevant literature by highlighting statistically significant group differences at the $p<.05$ level and effect sizes in terms of Cohen's d, rather conducting than a meta-analysis, extracted variables only included number of participants for each group within the study; the tool(s) used to assess addictive behaviours; and the reward-related and decision-making tasks used.

3. Results

Our search identified 2451 articles in total and 51 relevant (based on title and abstract) articles (see Figure 1) (Moher et al., 2009). These 51 relevant articles were then independently screened by two authors (AD and AC). These authors identified 18 articles in total for exclusion. Where one screening author identified an article for exclusion, but the other did not, the article was thoroughly examined until a consensus was reached. Reasons for excluding these full-text articles included: no reporting of the statistical comparisons of interest (2) (Balasubramani et al., 2015; Biundo et al., 2015); no assessment of a key addiction process according to the four dominant accounts above (13) (Cilia et al., 2014; Djamshidian et al., 2011a, 2011c; Evans et al., 2005; Frosini et al., 2010; Imperiale et al., 2017; Isaias et al., 2008; Leroi et al., 2011; Mack et al., 2013; Pettorruso et al., 2014; Sachdeva et al., 2014; Siri et al., 2010, 2015); use of a gambling task purely as a cue (2) (Ray et al., 2012; Steeves et al., 2009); or use of a within-subjects design (1) (van Eimeren et al., 2009). Scanning reference lists of included articles identified two additional articles (Cerasa et al., 2014; Evans et al., 2006).

3.1. Reward and punishment learning (aberrant learning)

Six studies employed a measure of reward and punishment learning (Table 1). These studies do not provide a clear picture of whether patients with addictive behaviours overvalue rewards (i.e., consistently experience 'better than expected' outcomes) and undervalue punishment (i.e., have reduced sensitivity to 'worse than expected' outcomes) (van Eimeren et al., 2009). Two studies found evidence of significantly increased 'on' medication reward learning in patients with addictive behaviours compared to PD controls (i.e., PD patients without addictive behaviours) (Piray et al., 2014; Voon et al., 2010a). No differences were found between patient groups with and without addictive behaviours in terms of punishment learning in either study. Other groups have not found any evidence of addicted

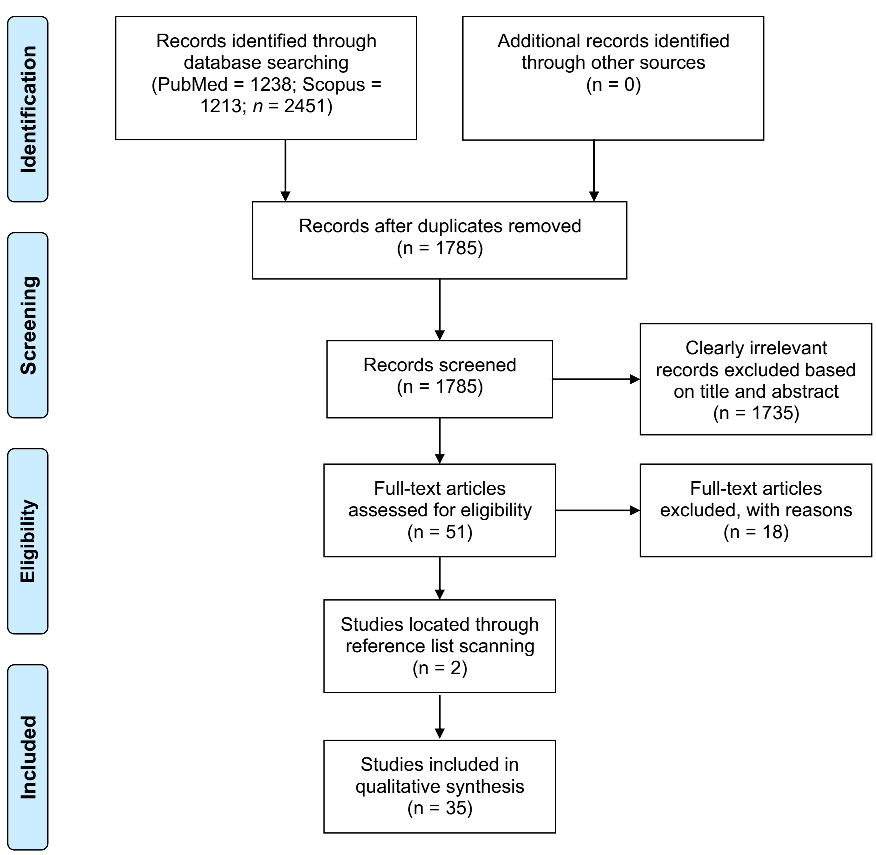

Figure 1 The flow of information through different phases of the systematic review.

Table 1 Findings on 'aberrant learning'.

Study	Groups (total *n*; male *n*)	Assessment tool(s)	Neurocognitive task	Key null findings ($p > .05$)	Key significant findings ($p < .05$)	Effect size(s) (*d*)
Leplow et al. (2016)	PD+ABs (16; 12) PD-ABs (16; 10) HCs (16; 9)	*CSBI*; *FDIQ*; *PDDDS-PCI*; *QUIP*	*Passive Avoidance-Loss of Reward Paradigm*	1. Correct approach: +ABs and -ABs 2. Approach errors: +ABs and -ABs 3. Inhibition errors: +ABs and -Abs	4. Correct inhibition: -ABs ON better than +ABs ON in blocks 5, 8, 10.	1. N/A 2. N/A 3. N/A 4. 0.74 (block 5); 0.74 (block 8); 0.67 (block 10)
Djamshidian et al. (2012a)	PD+ABs (26; 22) PD-ABs (27; 24) HCs (16; 14)	*DSM-IV ICDs*; Evans punding; McElroy CB; Voon ABs	*Probabilistic Face Decision Task*	1. Overall learning: +ABs and -ABs ON and OFF		1. N/A
Djamshidian et al. (2010)	PD+ABs (18; 13) PD-ABs (12; 9) HCs (22; 12)	*DSM-IV ICDs*; McElroy CB; Voon ABs	*Probabilistic Selection Task*	1. Average choices compared to the ideal observer: +ABs and -ABs		1. N/A
Piray et al. (2014)	PD+ABs ON (16; 14) PD-ABs ON (15; 12) PD-ABs OFF (25; 19) HCs (20; 13)	NR	*Probabilistic Selection Task*	1. Punishment learning: +ABs ON compared to -ABs ON *Note simulation analysis replicated this behavioural effect*	2. Reward learning: +ABs ON better than all other groups *Note simulation analysis replicated this behavioural effect*	1. N/A
Voon et al. (2010a)	PD+ABs (14; 10) PD-ABs (14; 10) HCs (16; 11)	*DSM-IV PG*; McElroy CB	*Probabilistic Selection Task*	1. Reward learning rate ON: +ABs v -ABs 2. Punishment learning rate ON: +ABs v -Abs	3. Medication effect on reward learning rate: +ABs faster from OFF to ON but -ABs no change	1. N/A 2. N/A 3. N/A
Housden et al. (2010)	PD+ABs (18; 11) PD-ABs (18; 12) HCs (20; 10)	Evans punding; Giovannoni DDS; Voon PG	*Salience Attribution Test*	1. Rating of highly reinforced stimuli: +ABs ON and HCs 2. Reaction times on high probability trials: +ABs and -Abs	3. Rating of highly reinforced stimuli: +ABs higher than -ABs ON	1. 0.12 2. 0.32 3. 0.74

Abbreviations: '*CSBI*': *Compulsive Sexual Behavior Inventory* (Miner et al., 2007); '*DSM-IV ICDs*': *DSM-IV* criteria for 'Impulse Control Disorders' [American Psychiatric Association, 2000]; '*DSM-IV PG*': *DSM-IV* criteria for 'Pathological Gambling' [American Psychiatric Association, 2000]; 'Evans punding': Evans proposed criteria for punding (Evans et al., 2004); '*FDIQ*': *Functional Dysfunctional Impulsivity Questionnaire* (Dickman, 1990); 'Giovannoni DDS': Giovannoni proposed criteria for DDS (Giovannoni et al., 2000); 'HCs': non-PD controls; 'McElroy CB': McElroy proposed criteria for compulsive buying (McElroy et al., 1994); 'N/A': no exact mean and/or standard deviation values reported; 'NR': not reported; 'OFF': in the 'off' medication state; 'ON': in the 'on' medication state; 'PD+ABs': PD patients with addictive behaviours; 'PD-ABs': PD controls; '*PDDDS-PCI*': *Parkinson's Disease Dopaminergic Dysregulation Syndrome-Patient and Caregiver Inventory* (Cabrini et al., 2009); '*QUIP*': *Questionnaire for Impulsive-Compulsive Disorders* (Weintraub et al., 2009); 'Voon ABs': Voon proposed criteria for addictive behaviours in PD (Voon et al., 2006); 'Voon PG': Voon proposed criteria for pathological gambling (Voon and Fox, 2007).

patients overvaluing rewards 'on' medication (Djamshidian et al., 2010, 2012a; Housden et al., 2010; Leplow et al., 2016).

3.2. Reward motivation (incentive sensitization and iRISA)

Two studies assessed reward motivation (or willingness to work for reward) (Table 2). Both found that, relative to PD controls, PD patients with DDS 'on' medication were faster to perform a physical task (card arrangement) when higher monetary reward was available (Evans et al., 2006, 2010). This effect did not hold in the latter study when all patients were 'off' medication.

3.3. Choice impulsivity

Five studies examined choice impulsivity (which includes delay/temporal and probability discounting) (Table 3). Generally, PD patients with addictive behaviours discount larger, later rewards (both real and hypothetical) to a greater extent than PD controls (Housden et al., 2010; Leroi et al., 2013; Voon et al., 2011a, 2010b; cf. Joutsa et al., 2015). This pattern tends to emerge irrespective of reward magnitude (small (e.g., \$25), medium (e.g., \$50) or large (e.g., \$80)) and whether patients are 'on' or 'off' medication.

3.4. Reflection impulsivity

Two studies investigated reflection impulsivity (Table 3). Whereas PD patients with addictive behaviours 'on' medication sampled less relevant information than PD controls on the *Beads Task* (Djamshidian et al., 2012b), the same group could not replicate this finding on the *Pixel Task* with both groups 'on' medication (Djamshidian et al., 2014a).

3.5. Motor impulsivity (see also iRISA)

Seven studies employed a measure of motor impulsivity (or response inhibition) (Table 3). One study demonstrated better performance, in terms of speed, in PD patients with addictive behaviours, both 'on' and 'off' medication, relative to PD controls (Claassen et al., 2015). All remaining studies found no 'on' medication differences between the groups in terms of speed or errors across standard motor impulsivity tasks (Bentivoglio et al., 2013; Leroi et al., 2013; Pineau et al., 2016; Ricciardi et al., 2017; Rossi et al., 2010; Yoo et al., 2015).

3.6. Disadvantageous decision-making under explicit risk (impulsivity to compulsivity)

Three studies assessed decision-making under explicit risk (Table 4). Findings are mixed. PD patients with addictive behaviours 'on' medication made riskier choices than PD controls when gambling starting at \$0 than when gambling with a pre-existing negative balance (e.g., -\$50) (Voon, et al., 2011a). In contrast, dice and investment decision-making tasks have not revealed 'on' medication group differences in terms of net scores (Rossi et al., 2010). Furthermore, risk preference did not differ between the groups 'on' medication on a gambling task featuring known (i.e., explicit) outcomes (Djamshidian et al., 2010), although a pathological gambling subgroup 'on' medication showed an increased risk preference in this study.

3.7. Disadvantageous decision-making under uncertainty (impulsivity to compulsivity)

Eight studies examined decision-making under uncertainty (Table 4). Irrespective of the particular task used, studies have yielded mixed results. Studies using a well-known 'balloon' paradigm have not generally found that patients with addictive behaviours make more overall balloon inflations in pursuit of higher rewards relative to PD controls, 'on' or 'off' medication (Claassen et al., 2011; Rao et al.,

Table 2 Findings on 'incentive sensitization'.

Study	Groups (total *n*; male *n*)	Assessment tool(s)	Neurocognitive task	Key null findings ($p > .05$)	Key significant findings ($p < .05$)	Effect size(s) (*d*)
Evans et al. (2006)	PD+DDS (8; NR) PD-ABs (8; NR)	NR	*Card Arranging Reward Responsivity Objective Test*		1. Time to complete task: +DDS faster than -ABs ON	1. N/A
Evans et al. (2010)	PD+DDS (20; NR) PD-ABs (20; NR)	Lawrence DDS	*Card Arranging Reward Responsivity Objective Test*	1. Time to complete task: +DDS and -ABs OFF	2. Time to complete task: +DDS faster than -ABs ON	1. 6.1

Abbreviations: Lawrence DDS: Lawrence working criteria for DDS (Lawrence et al., 2003); 'N/A': no exact mean and/or standard deviation values reported; NR: not reported; OFF: in the 'off' medication state; ON: in the 'on' medication state; PD-ABs: PD controls; PD+DDS: PD patients with DDS.

Table 3 Findings on 'impulsivity'.

Specific process	Study	Groups (total *n*; male *n*)	Assessment tool(s)	Neurocognitive task	Key null findings ($p > .05$)	Key significant findings ($p < .05$)	Effect size(s) (*d*)
Choice impulsivity							
	Leroi et al. (2013)	PD+ABs (35; 27) PD-ABs (55; 39) HCs (20; 11)	*DSM-IV* *ICDs*; *MIDI*; *SOGS*	*Delay Discounting Task*		1. Impulsive choices: +ABs higher -ABs ON and OFF	1. 0.48
	Voon et al. (2010b)	PD+ABs (14; 10) PD-ABs (14; 10) HCs (16; 11)	*DSM-IV PG*; McElroy CB	*Experiential Discounting Task*	1. Overall impulsive choices: +ABs and -ABs ON	2. Heightened impulsivity following medication: +ABs but not -ABs	1. N/A 2. N/A
	Housden et al. (2010)	PD+ABs (18; 11) PD-ABs (18; 12) HCs (20; 10)	Evans punding; Giovannoni DDS; Voon PG	*Monetary Choice Questionnaire*		1. Impulsive choices: +ABs higher than -ABs ON for small, medium and large rewards	1. .83 (small); 0.80 (medium); 0.81 (large)
	Joutsa et al. (2015)	PD+ABs (9; 9) PD-ABs (8; 8)	Voon ABs	*Monetary Choice Questionnaire*	1. Impulsive choices: +ABs and -ABs ON		1. N/A
	Voon et al. (2011b)	PD+ABs (282; 191) PD-ABs (282; 191)	*DSM-IV* *BED*; *MGS*; *MIDI*	*Monetary Choice Questionnaire*		1. Impulsive choices: +ABs and -ABs ON	1. 3.0
Reflection impulsivity							
	Djamshidian et al. (2012b)	PD+ABs (26; 22) PD-ABs (27; 24) HCs (36; 33)	*DSM-IV ICDs*; Evans punding; McElroy CB; *QUIP*; Voon ABs	*Beads Task*	1. Irrational opposite colour choices: +ABs and -ABs ON	2. Information sampled: +ABs less than -ABs ON	1. N/A 2. N/A
	Djamshidian et al. (2014a)	PD+ABs (15; 14) PD-ABs (+DA) (17; 15) PD-ABs (12; 10) HCs (17; 14)	*DSM-V GD*; Evans punding; Voon ABs	*Pixel Task*	1. Reaction time: +ABs and -ABs (+DA) for correct decisions ON 2. Total errors: +ABs and -ABs (+DA) and -ABs ON 3. Reaction time on correct trials: -ABs (+DA) and +ABs	4. Reaction time on incorrect trials: +ABs faster than -ABs(+DA)	1. N/A 2. N/A 3. N/A 4. N/A

Motor impulsivity						
Pineau et al. (2016)	PD+ABs (17; 14) PD-ABs (20; 13)	*Ardouin*	*Continuous Performance Test II*	1. Commission errors: +ABs and -ABs ON		1. N/A
Bentivoglio et al. (2013)	PD+ABs (17; 14) PD-ABs (17; 11)	*DSM-IV ICDs*	*Go/No-Go Task*	1. Total errors: +ABs and -ABs ON		1. 1.02
Rossi et al. (2010)	PD+ABs (7; 6) PD-ABs (13; 10)	*DSM-IV PG*; *MIDI*; *SOGS*	*Go/No-Go Task*	1. Commission and omission errors: +ABs and -ABs ON		1. 0.68 (omission); 0.56 (commission)
Yoo et al. (2015)	PD+ABs (10; 6) PD-ABs (43; 25)	Fasano punding; *MIDI*	*Go/No-Go Task*	1. Total errors: +ABs and -ABs ON		1. N/A
Claassen et al. (2015)	PD+ABs (12; 8) PD-ABs (12; 6) HCs (12; 6)	*DSM-IV ICDs*; Grant PG; McElroy CB; *QUIP-RS*; Voon ABs	*Stop-Signal Task*		1. Performance in terms of speed: +ABs better than -ABs ON	1. 1.0
Leroi et al. (2013)	PD+ABs (35; 27) PD-ABs (55; 39) HCs (20; 11)	*DSM-IV ICDs*; *MIDI*; *SOGS*	*Stop-Signal Task*	1. Performance in terms of speed and errors: +ABs and -ABs ON		1. 0.18 (speed) and 0.15 (errors)
Ricciardi et al. (2017)	PD+ABs (19; 12) PD-ABs (19; 11) HCs (19; 8)	*QUIP*; *QUIP-RS*	*Stop-Signal Task*	1. Performance in terms of speed: +ABs and -ABs ON		1. 0.52

Abbreviations: '*Ardouin*': *Ardouin Scale of Behavior in Parkinson's Disease* (Ardouin et al., 2009); '*DSM-IV BED*': *DSM-IV* criteria for 'Binge Eating Disorder' (American Psychiatric Association, 2000); '*DSM-IV ICDs*': *DSM-IV* criteria for 'Impulse Control Disorders' (American Psychiatric Association, 2000); '*DSM-IV PG*': *DSM-IV* criteria for 'Pathological Gambling' (American Psychiatric Association, 2000); '*DSM-V GD*': *DSM-V* criteria for 'Gambling Disorder' (American Psychiatric Association, 2013); 'Evans punding': Evans proposed criteria for punding (Evans et al., 2004); 'Fasano punding': Fasano proposed criteria for punding (Fasano et al., 2008); 'Grant PG': Grant proposed criteria for pathological gambling (Grant et al., 2004); 'HCs': non-PD controls; 'McElroy CB': McElroy proposed criteria for compulsive buying (McElroy et al., 1994); '*MGS*': *Massachusetts Gambling Screen* (Shaffer et al., 1994); '*MIDI*': *Minnesota Impulsive Disorders Interview* (Christenson et al., 1994); 'N/A': no exact mean and/or standard deviation values reported; 'OFF': in the 'off' medication state; 'ON': in the 'on' medication state; 'PD+ABs': PD patients with addictive behaviours; 'PD-ABs (+DA)': PD controls taking dopamine agonists; 'PD-ABs': PD controls; '*QUIP-RS*': Questionnaire *for Impulsive-Compulsive Disorders in Parkinson's disease-Rating Scale* (Weintraub et al., 2012); '*SOGS*': *South Oaks Gambling Screen* (Lesieur and Blume, 1987); 'Voon ABs': Voon proposed criteria for addictive behaviours in PD (Voon et al., 2006).

Table 4 Findings on 'disadvantageous decision-making'.

Specific process	Study	Groups (total *n*; male *n*)	Assessment tool(s)	Neurocognitive task	Key null findings ($p > .05$)	Key significant findings ($p < .05$)	Effect size(s) (*d*)
Disadvantageous decision-making under risk							
	Voon et al. (2011a)	PD+ABs (14; 10) PD-ABs (14; 10) HCs (16; 11)	*DSM-IV PG*; McElroy CB	*Gain and Loss Risk Task*	1. Overall risk-taking: +ABs and -Abs	2. Riskier choices when starting at $0 rather than -$50: +ABs riskier than -ABs ON	1. N/A 2. N/A
	Rossi et al. (2010)	PD+ABs (7; 6) PD-ABs (13; 10)	*DSM-IV PG*; *MIDI*; *SOGS*	*Game of Dice Task* *Investment Task*	1. Net scores: +ABs and -ABs ON		1. N/A
	Djamshidian et al. (2010)	PD+ABs (18; 13) PD-ABs (12; 9) HCs (22; 12)	*DSM-IV ICDs*; McElroy CB; Voon ABs	*Huettal Gambling Task*	1. Increase in risk preference: +ABs and -ABs ON	2. Risk prefer ence when ON: increased in +PG sub group com pared to -ABs	1. N/A 2. N/A
Disadvantageous decision-making under uncertainty							
	Claassen et al. (2011)	PD+ABs (22; 9) PD-ABs (19; 10)	*QUIP*; Voon ABs	*Balloon Analogue Risk Task*	1. Mean number of inflations: +ABs and -ABs ON and OFF 2. Risk-taking following negative outcomes ON and OFF: +ABs and -ABs	3. When ON, +ABs on 'low' doses increased average number of infla tions whereas -ABs on 'low' doses decreased inflations	1. N/A 2. N/A 3. N/A
	Rao et al. (2010)	PD+AB (9; 7) PD-AB (9; 8)	*DSM-IV ICDs;* Giovannoni DDS; *MGS*; *MIDI*	*Balloon Analogue Risk Task*	1. Mean number of inflations: +ABs and -ABs ON		1. 0.21
	Ricciardi et al. (2017)	PD+ABs (19; 12) PD-ABs (19; 11) HCs (19; 8)	*QUIP*; *QUIP-RS*	*Balloon Analogue Risk Task (Modified)*	1. High risk inflations: +ABs and -ABs ON		1. 0.20
	Djamshidian et al. (2010)	See above (as results were not reported to be affected by gamble type - certain, risky or ambiguous).					
	Bentivoglio et al. (2013)	PD+ABs (17; 14) PD-ABs (17; 11)	*DSM-IV ICDs*	*Iowa Gambling Task*	1. Total sum and choice pattern: +ABs and -ABs ON		1. 0.38 (sum); 0.46 (choice pattern)

Pineau et al. (2016)	PD+ABs (17; 14) PD-ABs (20; 13)	*Ardouin*	*Iowa Gambling Task (Adapted)*	1. Number of cards chosen on any deck: +ABs and -ABs ON	2. Mischaracterisation of advantageous Deck B as a disadvantageous deck: +ABs higher than -ABs ON	1. N/A 2. N/A
Rossi et al. (2010)	PD+ABs (7; 6) PD-ABs (13; 10)	*DSM-IV PG*; *MIDI*; *SOGS*	*Iowa Gambling Task*		1. Total sum: +ABs lower than -ABs ON 2. Mean scores on specific blocks: +ABs worse than -ABs on blocks 2, 3, 4, 5 ON	1. 1.97 2. N/A
Cera et al. (2014)	PD+AB (9; 6) PD+PG (10; 7) PD-AB (14; 7)	*DSM-IV ICDs*; *QUIP-RS*; *SOGS*	*Monetary Reward/ Loss Risk-Taking Task*	1. Risky choices: +ABs, +PGs and -ABs ON		1. 0.26 (+ABs vs. -ABs); 0.02 (+PGs v -ABs)

Abbreviations: '*DSM-IV ICDs*': *DSM-IV* criteria for 'Impulse Control Disorders' (American Psychiatric Association, 2000); '*DSM-IV PG*': *DSM-IV* criteria for 'Pathological Gambling' (American Psychiatric Association, 2000); 'Giovannoni DDS': Giovannoni proposed criteria for DDS (Giovannoni et al., 2000); 'HCs': non-PD controls; 'McElroy CB': McElroy proposed criteria for compulsive buying (McElroy et al., 1994); '*MGS*': *Massachusetts Gambling Screen* (Shaffer et al., 1994); '*MIDI*': *Minnesota Impulsive Disorders Interview* (Christenson et al., 1994); 'N/A': no exact mean and/or standard deviation values reported; 'OFF': in the 'off' medication state; 'ON': in the 'on' medication state; 'PD+ABs': PD patients with addictive behaviours; 'PD-ABs': PD controls; 'PD+PG': PD patients with pathological gambling; '*QUIP*': *Questionnaire for Impulsive-Compulsive Disorders* (Weintraub et al., 2009); '*QUIP-RS*': Questionnaire *for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale* (Weintraub et al., 2012); '*SOGS*': *South Oaks Gambling Screen* (Lesieur and Blume, 1987); 'Voon ABs': Voon proposed criteria for addictive behaviours in PD (Voon et al., 2006).

Table 5 Findings on 'compulsivity'.

Specific process	Study	Groups (total *n*; male *n*)	Assessment tool(s)	Neurocognitive task	Key null findings ($p > .05$)	Key significant findings ($p < .05$)	Effect size(s) (*d*)
Cognitive Inflexibility							
	Rossi et al. (2010)	PD+ABs (7; 6) PD-ABs (13; 10)	*DSM-IV PG*; *MIDI*; *SOGS*	*Reversal and Extinction Task* *Wisconsin Card Sorting Test*	1. Total reversal and extinction errors: +ABs and -ABs ON 2. Perseverations and errors: ABs and -ABs ON		1. 0.17 (reversal); .24 (extinction) 2. 0.06 (perseverations); 0.27 (errors)
	Leroi et al. (2013)	PD+ABs (35; 27) PD-ABs (55; 39) HCs (20; 11)	*DSM-IV ICDs*; *MIDI*; *SOGS*	*Wisconsin Card Sorting Test*	1. Perseverative errors: +ABs and -ABs ON		1. 0.40
	Pontieri et al. (2015)	PD+ABs (36; 26) PD+PGs (21; 16) PD-ABs (98; 65)	*DSM-IV ICDs; QUIP*	*Wisconsin Card Sorting Test*	1. Perseverative errors: +ABs, +PGs and -ABs ON		1. 0.10 (+ABs vs. -ABs); 0.32 (+PGs vs. -ABs)
	Santangelo et al. (2009)	PD+ABs (15; 11) PD-ABs (15; 11)	*DSM-IV PG; SOGS*	*Wisconsin Card Sorting Test*		1. Global score: +ABs worse than -ABs ON	1. 0.84
	Tessitore et al. (2016)	PD+ABs (15; 13) PD-ABs (15; 12) HC (24; 17)	*MIDI*	*Wisconsin Card Sorting Test*		1. Global score: +ABs worse than -ABs ON	1. 0.60
	Vitale et al. (2011)	PD+ABs (10; 9) PD+PG (14; 10) PG+BE (12; 6) PD+HS (13; 13) PD-ABs (14; not reported)	*DSM-IV ICDs*; *MIDI*; Voon ABs	*Wisconsin Card Sorting Test*	1. Global score: any group ON		1. 0.63 (+ABs vs. -ABs)
	Bentivoglio et al. (2013)	PD+ABs (17; 14) PD-ABs (17; 11)	*DSM-IV ICDs*	*Wisconsin Card Sorting Test (Modified)*	1. Perseverative errors: +ABs and -ABs ON		1. 0.08
	Cerasa et al. (2014)	PD+PGs (12; 11) PD-ABs (12; 11) HCs (24; 20)	*GSAS*	*Wisconsin Card Sorting Test (Modified)*	1. Perseverative errors: +PGs, -ABs and HCs ON		1. N/A

Merola et al. (2017)	PD+ABs (26; 23) PD-ABs (124; 63)	Voon ABs	*Wisconsin Card Sorting Test (Modified)*	1. Perseveration: +ABs and -ABs ON	1. N/A
Pineau et al. (2016)	PD+ABs (17; 14) PD-ABs (20; 13)	*Ardouin*	*Wisconsin Card Sorting Test (Modified)*	1. Criterions reached: +ABs and -ABs ON	1. N/A
Attentional inflexibility					
Voon et al. (2010b)	PD+ABs (14; 10) PD-ABs (14; 10) HCs (16; 11)	*DSM-IV PG*; McElroy CB	*Intra/Extra Dimensional Set-Shifting Task*	1. Set-shifting errors: +ABs and -ABs ON	1. 0.54

Abbreviations: '*DSM-IV ICDs*': *DSM-IV* criteria for 'Impulse Control Disorders' (American Psychiatric Association, 2000); '*DSM-IV PG*': *DSM-IV* criteria for 'Pathological Gambling' (American Psychiatric Association, 2000); '*GSAS*': *Gambling Symptom Assessment Scale* (Kim et al., 2009); 'HCs': non-PD controls; '*MIDI*': *Minnesota Impulsive Disorders Interview* (Christenson et al., 1994); 'N/A': no exact mean and/or standard deviation values reported; 'OFF': in the 'off' medication state; 'ON': in the 'on' medication state; 'PD+ABs': PD patients with addictive behaviours; 'PD-ABs': PD controls; 'PD+PGs': PD patients with pathological gambling; 'PD+BE': PD patients with binge eating; 'PD+HS': PD patients with hypersexuality; '*QUIP*': *Questionnaire for Impulsive-Compulsive Disorders* (Weintraub et al., 2009); '*SOGS*': *South Oaks Gambling Screen* (Lesieur and Blume, 1987); 'Voon ABs': Voon proposed criteria for addictive behaviours in PD (Voon et al., 2006).

2010; Ricciardi et al., 2017). Other studies using the *Iowa Gambling Task* are more conflicted. In one study, patients with addictive behaviours 'on' medication performed worse due to a preference for a disadvantageous card deck (Rossi et al., 2010), but this effect was not seen in two other studies (Bentivoglio et al., 2013; Pineau et al., 2016). On other gambling tasks used in two separate studies, no 'on' medication group differences emerged (Cera et al., 2014; Djamshidian et al., 2010).

3.8. Cognitive inflexibility (impulsivity to compulsivity)

Ten studies investigated cognitive inflexibility (Table 5), mostly using the *Wisconsin Card Sorting Test*. Eight of ten studies found no difference between patients with addictive behaviours 'on' medication and PD controls in terms of global scores, total errors or perseverative errors (although not every study reported each of these outcomes) (Bentivoglio et al., 2013; Cerasa et al., 2014; Leroi et al., 2013; Merola et al., 2017; Pineau et al., 2016; Pontieri et al., 2015; Rossi et al., 2010; Vitale et al., 2011; cf. Santangelo et al., 2009; Tessitore et al., 2016). This general pattern of results was reflected in the only study that used a cognitive inflexibility task encompassing a reward element (Rossi et al., 2010).

3.9. Attentional inflexibility (impulsivity to compulsivity)

One study employed a measure of attentional inflexibility (Table 5). Patients with addictive behaviours and PD controls 'on' medication showed no differences in their ability to shift their attentional focus (Voon et al., 2010b).

3.10. Cognitive control (iRISA)

Twelve studies assessed cognitive control (Table 6). All but one could not detect 'on' medication group differences in terms of errors, reaction times or overall scores across three different tasks (Bentivoglio et al., 2013; Biundo et al., 2011; Cera et al., 2014; Djamshidian et al., 2011b; Markovic et al., 2017; Pontieri et al., 2015; Rossi et al., 2010; Shotbolt et al., 2012; Tessitore et al., 2016; Wylie et al., 2012; Yoo et al., 2015; cf. Vitale et al., 2011).

4. Discussion

The extant literature on the neurocognitive correlates of medication-induced addictive behaviours in PD is limited and ambiguous. Its ambiguity arguably reflects (a) the methodological variability stemming from the wide array of experimental paradigms deployed (see Supplementary materials); (b) the plausible but seldom considered influence of both positive (e.g., a 'winning' mood) and negative (e.g., fatigue, stress) affective factors that impact performance on, for instance, the *Iowa Gambling Task* (De Vries et al., 2008; Suhr and Tsanadis, 2007); (c) the fact that not all studies involve patients with current addictive behaviours (some desensitisation may have already occurred in

Table 6 Findings on 'cognitive control'.

Study	Groups (total *n*; male *n*)	Assessment tool(s)	Neurocognitive task	Key null findings ($p > .05$)	Key significant findings ($p < .05$)	Effect size(s) (*d*)
Shotbolt et al. (2012)	PD+AB (8; 8) PD-AB (42; 21)	*DSM-IV ICDs;* Giovannoni DDS	*Hayling Sentence Completion Test*	1. Age-adjusted overall score: +ABs and -ABs (ON or OFF not reported)		1. 0.37
Wylie et al. (2012)	PD+AB (19; 10) PD-AB (19; 9)	*QUIP*; Voon AB	*Simon Task*	1. Reaction time and mean accuracy: +ABs and -ABs ON and OFF		1. N/A
Bentivoglio et al. (2013)	PD+ABs (17; 14) PD-ABs (17; 11)	*DSM-IV ICDs*	*Stroop Interference Task*	1. Errors and reaction time: +ABs and -ABs ON		1. 0.58 (errors); 0.09 (time)
Biundo et al. (2011)	PD+AB (33; 18) PD-AB (24; 17)	*DSM-IV ICDs; MIDI*	*Stroop Interference Task*	1. Errors and time interference effect: +ABs and -ABs ON		1. 0.43 (errors) ; 0.35 (time interference)
Cera et al. (2014)	PD+AB (9; 6) PD+PG (10; 7) PD-AB (14; 7)	*DSM-IV ICDs; QUIP-RS; SOGS*	*Stroop Interference Task*	1. Errors: +ABs, +PGs and -ABs ON		1. 0.85 (+ABs vs. -ABs); 0.39 (+PGs vs. -ABs) *(Incongruent trials)*
Djamshidian et al. (2011b)	PD+AB (28; 21) PD-AB (24; 21) HCs (24; 14)	Evans punding; Voon PG	*Stroop Interference Task*	1. Errors and reaction time: +ABs and -ABs ON and OFF		1. N/A
Markovic et al. (2017)	PD+PUND (22; 19) PD-AB (30; 21) HCs (30; 21)	*DSM-IV ICDs;* McElroy CB; Evans punding; Giovannoni DDS; Voon ABs	*Stroop Interference Task*	1. Total correct answers: +PUNDs and -ABs (ON and OFF NR)		1. 0.10
Pontieri et al. (2015)	PD+ABs (36; 26) PD+PGs (21; 16) PD-ABs (98; 65)	*DSM-IV ICDs; QUIP*	*Stroop Interference Task*	1. Interference score: +ABs and -ABs (ON or OFF NR)		1. 0.05 (+ABs vs. -ABs); 0.05 (+PGs vs. -ABs)
Rossi et al. (2010)	PD+ABs (7; 6) PD-ABs (13; 10)	*DSM-IV PG; MIDI; SOGS*	*Stroop Interference Task*	1. Interference score: +ABs and -ABs ON		1. 0.62
Tessitore et al. (2016)	PD+ABs (15; 13) PD-ABs (15; 12) HC (24; 17)	*MIDI*	*Stroop Interference Task*	1. Interference score: +ABs and -ABs ON		1. 0.44
Vitale et al. (2011)	PD+ABs (10; 9) PD+PG (14; 10) PG+BE (12; 6)	*DSM-IV ICDs; MIDI*; Voon ABs	*Stroop Interference Task*		1. Interference score: +ABs and +HSs	1. 1.18 (+ABs vs. -ABs); 1.58 (+HSs vs. -ABs)

	PD+HS (13; 13) PD-ABs (14; not reported).			worse than -ABs ON	
Yoo et al. (2015)	PD+ABs (10; 6) PD-ABs (43; 25)	Fasano punding; *MIDI*	*Stroop Interference Task*	1. Word and color scores: +ABs and -ABs ON (significant colour score difference did not survive correction for multiple comparisons)	1. 0.90 (color); N/A (word)

Abbreviations: '*DSM-IV ICDs*': *DSM-IV* criteria for 'Impulse Control Disorders' (American Psychiatric Association, 2000); 'Evans punding': Evans proposed criteria for punding (Evans et al., 2004); 'Giovannoni DDS': Giovannoni proposed criteria for DDS (Giovannoni et al., 2000); 'HCs': non-PD controls; 'McElroy CB': McElroy proposed criteria for compulsive buying (McElroy et al., 1994); '*MIDI*': *Minnesota Impulsive Disorders Interview* (Christenson et al., 1994); 'N/A': no exact mean and/or standard deviation values reported; 'NR': not reported; 'OFF': in the 'off' medication state; 'ON': in the 'on' medication state; 'PD+ABs': PD patients with addictive behaviours; 'PD-ABs': PD controls; 'PD+PUND': PD patients with punding; '*QUIP*': *Questionnaire for Impulsive-Compulsive Disorders* (Weintraub et al., 2009); 'Voon ABs': Voon proposed criteria for addictive behaviours in PD (Voon et al., 2006); 'Voon PG': Voon proposed criteria for pathological gambling (Voon and Fox, 2007).

patients with past addictive behaviours) and (d) the fact that, despite being an important comorbidity (Sinha et al., 2013), apathy has only been controlled for in a minority of studies. Heterogeneous findings in the domains of reward and punishment learning, reflection impulsivity and disadvantageous decision-making (under both risk and uncertainty) illustrate this ambiguity. We found more homogeneity in other domains in which patients with addictive behaviours do not appear to be neurocognitively dysfunctional (motor control, cognitive and attentional flexibility and cognitive control). Similar homogeneity, albeit from fewer total studies, was observed in domains in which patients with addictive behaviours showed consistently exacerbated response patterns (increased reward motivation and choice impulsivity). We (a) evaluate the strength of the evidence in the homogenous domains showing exacerbated response patterns, before highlighting how the field might proceed with regard to (b) the more heterogeneous domains and (c) the homogenous domains in which there is no demonstrable dysfunction in addicted patients.

Despite converging with findings from animal studies (Salamone et al., 2016), the strength of the relevant evidence for reward motivation is still low. The two relevant studies (Table 4) focussed only on patients with DDS. It is not clear whether the observed group differences and large effect size would arise with patients with a range of addictive behaviours. Further studies are required before strong claims about exacerbated reward motivation in patients with addictive behaviours can be advanced. In any case, a more direct test of incentive sensitization theory would involve examining whether PD patients with addictive behaviours exhibit (unconscious) attentional biases toward relevant appetitive cues (Field et al., 2009). Analogously, addictive behaviours in PD are associated with an unconscious bias toward excessive physical acknowledgement (via button pressing) of medication intake (Evans et al., 2014), while imaging studies show heightened cue reactivity and subjective 'wanting' in patients with addictive behaviours (e.g., Politis et al., 2013).

Despite fairly consistent group differences and moderate-to-large effect sizes, the strength of the relevant evidence for choice impulsivity is moderate. It is unknown whether (a) probability discounting is also exacerbated in patients with addictive behaviours (Rachlin et al., 1991) and (b) whether steeper discounting in patients with addictive behaviours is robust against framing and state effects (Lempert and Phelps, 2016).

As noted, findings on reward and punishment learning, reflection impulsivity and disadvantageous decision-making (under both risk and uncertainty) were mixed. Further studies are required in each of these domains. With regard to reward and punishment learning, Averbeck et al. (2013) provide potentially useful discussion on the subtle influence different reward schedules and modelling approaches have had in past studies. Voon et al. (2009) also make a reasonable case for examining habit learning in this population.

Present findings suggest that a continued focus on motor and cognitive control in this population might not be optimal. Our findings even suggest that some nosological reform may be required. As noted above, the severe behavioural changes we, like others (Witjas et al., 2012), have labelled 'addictive behaviours' are more commonly labelled 'impulse control disorders' (Weintraub et al., 2015). This label seems *prima facie* incompatible with the present findings on motor and cognitive control. A simple 'addictive behaviours' label would be more empirically accurate, reflective of these behaviours' typical transience following medication reduction, and non-stigmatising (cf. 'behavioural addictions'). Consistent with this, leading figures in the field have concluded that, to the extent that patients with addictive behaviours can be usefully thought of as 'impulsive', their impulsivity seems to be of a motivational or affective nature (Claassen et al., 2015), rather than a simple 'brake failure' (Buckholtz, 2015). In any case, gambling disorder is now classified as an addictive disorder rather than an impulse control disorder in the *DSM-V*. The widely-used 'impulsive-compulsive' label could be argued to be similarly incompatible, although this would be premature for two reasons. First, of the ten relevant studies, only Rossi et al. (2010) used an ideal cognitive inflexibility task (i.e., one featuring a reward element; Verdejo-Garcia and Manning, 2015). Future studies utilising probabilistic reversal learning paradigms, or other novel cognitive inflexibility paradigms, are required before the empirical accuracy of the 'impulsive-compulsive' label can be properly assessed. Even if found to be strictly empirically misleading, there are documented ritualistic features of patients' addictive behaviours (e.g., using lucky charms while gambling) (Averbeck et al., 2014) such that this label could maintain some heuristic value (Heather, 2017).

Limitations of this systematic review should be noted. In contrast to a previous systematic review (Santangelo et al., 2017), we did not conduct a meta-analysis. Our intent was to comprehensively review and qualitatively summarise results related to a core group of neurocognitive processes putatively implicated in addictive behaviour, rather than attempt to quantify the influence of a more idiosyncratic spread of processes (e.g., visuospatial abilities) whose *a priori* implication in addictive behaviours in PD is not obvious. We acknowledge the style of our qualitative summary, and assumptions it makes regarding task classification, necessarily affects whether particular domains are labelled heterogeneous or homogenous. For instance, we have classified the *Iowa Gambling Task* as a measure of disadvantageous decision-making under uncertainty, but it could also be classified as a measure of reward and punishment learning (Averbeck et al., 2014). Our particular format, however, resembles that of past eminent reviews (Fineberg et al., 2014; Heather, 2017). In summarising results, we neglected discussion of allostatic dysregulation theory (Koob and Le Moal, 2001) as none of the reviewed studies measured processes central to this account. Learning tasks encompassing punishments do not qualify - allostatic dysregulation theory is a motivational theory that emphasises addicted individuals being driven to remediate an underlying negative affective state. In any case, prospective studies have not found depression and anxiety to be associated with development of addictive behaviours in PD (Smith et al., 2016). In addition, we did not review unpublished literature, which might contain null findings on domains we have labelled relatively homogenous (reward motivation and choice impulsivity) and ambiguous (reward and punishment learning, reflection impulsivity and disadvantageous decision-making under risk and uncertainty). This common reporting bias is partly why we have resisted labelling as 'high' the strength of the evidence in any domain. Finally, we are aware that *Movement Disorders Clinical Practice* is not indexed in PubMed. This journal contains at least two relevant articles we could not include (Codling et al., 2015; Djamshidian et al., 2014b), although results from these studies do not change our conclusions.

In sum, future large-scale studies examining the neurocognitive correlates of medication-induced addictive behaviours in PD are still required. It is critical that such studies take into account positive and negative affective states that can and do influence neurocognitive performance (Ekhtiari et al., 2017); whether included patients suffer from past or present addictive behaviours; and the presence of apathy, an important comorbidity that has been so far overlooked in most studies (Sinha et al., 2013). A better scientific understanding of these correlates could be important for refining delivery of cognitive behavioural therapy (Okai et al., 2013), one of the few promising treatments for addictive behaviours in PD that avoids completely cessing dopaminergic medication (Zhang et al., 2016). This understanding could also inform the kinds of reward-related and decision-making tasks employed in future prospective studies (Smith et al., 2016), which might ultimately aid in clinical prediction and prevention of these often-devastating behaviours.

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Contributors

MY and AC designed the paper. AD conducted all aspects of the literature search and wrote the first draft. AC conducted independent screening of initial search results. ND, AE, GF, DF, PO, AVG, TC, MY and AC provided essential critical feedback on the first draft. All authors have contributed to and approved the final manuscript.

Conflict of interest

AC has provided paid expert evidence to a law firm representing Parkinson's disease patients with addictive behaviours in a class action against the manufacturer of dopamine agonists. No other conflicts are reported.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.euroneuro.2018.03.012.

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