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Editor's comment: Pathologic gambling in Parkinson's disease recently has become more widely recognized as a possible complication of dopamine agonist therapy. It is a class specific effect and not necessarily related to any particular dopamine agonist. It usually occurs in younger males, but it also may develop in patients with earlier symptomatic disease onset, in those with a prior history of alcohol and/or substance abuse, or in those who possess personality traits characterized by impulsivity. The first line of therapy usually is a dose reduction or discontinuation of the dopamine agonist. Pathologic gambling also may occur in patients on levodopa monotherapy, but this is less frequent. In this review article, Gabriella Santangelo and her colleagues provide a comprehensive analysis of the prevalence of pathologic gambling and the associated clinical, behavioral, and cognitive features of this complication. Genetic susceptibility and possible therapeutic management also are addressed, as are the potential neuro-anatomical and functional correlates of pathological gambling.

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Review

Pathological gambling in Parkinson's disease. A comprehensive review

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ABSTRACT

Pathological gambling (PG) and other Impulse Control Disorders (ICDs), such as hypersexuality, compulsive eating and buying, are often reported in Parkinson's disease (PD). The prevalence of PG is 2.2%–7% in treated PD patients, which is higher than the background population rate. As other non motor symptoms in PD, PG is frequently under-reported by patients and caregivers and may be under-recognized by the treating physicians.

Factors associated with PG include male sex, younger age or younger age at PD onset, personal or family history of substance abuse or ICD, a personality profile characterized by impulsiveness, and treatment with dopamine agonists (DA) more than with levodopa (L-dopa). The DA effect seems to be a class effect and not specific for any DA.

Neurofunctional studies suggest that medication-induced downregulation of frontostriatal connections and upregulation of striatum might combine to induce impulsive behavior. A dysfunction of fronto-subcortical circuits in PD patients with PG is also supported by neuropsychological findings of impaired executive control and monitoring abilities.

Management of ICDs in PD is complex, and until now only discontinuation and/or tapering of DA treatment seem to be an effective management strategy for ICDs in PD. There is no empirical evidence supporting the use of psychiatric drugs for PG such as antipsychotics and antidepressants. Data regarding the effect of deep brain stimulation (DBS), particularly of subthalamic nucleus, on PG and ICDs in PD are still limited and sometimes conflicting since improvement of PG or new onset of PG after surgery have been reported.
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1. Introduction

Pathological gambling (PG) is a behavioral disorder characterized by persistent and recurrent maladaptive gambling that can have devastating psychosocial consequences for the person involved and her/his family [1]. Point and lifetime prevalence rates

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of PG in general population are reported to be as high as 1.4% and 5.1%, respectively, but they seem to increase progressively with the spread of legalized gambling [2].

PG is considered as an impulse control disorder (ICD) that combines impulsive and compulsive features, namely repetitive gambling and impaired inhibition of this negative behavior [3]. Neuroimaging and neuropsychological studies found an association between PG and abnormalities in the prefrontal cortex and subcortico-cortical networks projecting to the frontal cortex [4–6]. Current neurobiological research highlighted both an abnormal functioning of mesolimbic structures and an altered neurotransmitter regulation of the 'reward pathways' in the brain of pathological gamblers [4], particularly of the neurotransmitter dopamine.

As it will be described below, PG is largely more frequent in patients affected by Parkinson's disease (PD) than in the general population. Alteration of dopaminergic transmission in both PG and PD might support common pathophysiologic mechanisms and some clinical overlap of the two conditions. Traditionally, PG has been considered as a side effect of dopamine agonists (DA) treatment in PD [7–9]. However, since only a small proportion of patients treated with DA develop PG and/or other ICDs, we will argue that DA medication can trigger these non motor symptoms in PD patients with specific individual predisposing factors.

In the present paper we will offer an overview of the most recent advances in the study of clinical, neuropsychological, behavioral, neurofunctional and genetic correlates of PG in PD. Finally, the management of PG in PD will also be reviewed.

2. Prevalence of PG in PD

The prospective PG prevalence (either current or anytime during PD) in a tertiary PD clinic has been reported to vary from 2.2% to 7% (Table 1); such percentages are higher than those reported in general population (see above) and become also higher if one considers "problem gambling" (not clinically relevant gambling behavior). As evident in Table 1, prevalence rates in Caucasian samples [7–13] tend to be higher than those reported in Asian countries [14–17]. This divergence might depend on cultural and ethnic differences [14] (e.g., reluctance to admit presence of PG, availability of legalized gambling, lower DA usage in Asian countries than in Caucasian populations), methodological differences (e.g., different diagnostic criteria or assessment methods), or genetic differences (e.g., variable occurrence of genetic polymorphisms among Caucasians and Asians). However, significant discrepancies in prevalence rates of problem/pathological gambling can be found even between two Caucasians populations (i.e., US and Canadian patients; [7]), thus highlighting that differences among PD populations have not been fully elucidated.

Apart from ethnic and cultural factors, one source for variability in prevalence rates of PG in PD seems to be related to measures used for screening. As shown in Table 1, prevalence rates tend to be lower when diagnosis rests on self-administered questionnaires [8] than on informant-based interviews [9,10,12,13,18], as many patients have reduced insight into the social consequences of their behavior or conceal it from their families because of shame or denial [19]. Use of specifically devised and validated diagnostic tools administered to both patients and caregivers can likely reduce possible underestimation of PG, and of other ICDs in PD. Two such questionnaires have been developed in recent years: the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) [20] and the Parkinson's disease Dopamine Dysregulation Syndrome-Patient and Caregiver (DDS-PC) inventory [21]. Both screening tools have good clinometric properties. The QUIP has been proved to be a sensitive instrument for detection of ICD whether completed by a patient or informant [22]. Agreement between patient- and informant-reporting of any ICD behaviors on the QUIP was moderate to fair for individual ICDs, but was high for PG [23].

It is important to underline here that the assessment of prevalence rates during the disease course will likely provide valuable cues for comprehending the genesis of PG and other ICDs in PD. Two recent studies reported low prevalence of PG among newly diagnosed PD patients with rates (0.9% [24] and 1.2% [25]) similar to those reported in general population, whereas prevalence of at least one ICD was quite high (17.5% [24] and 20% [25]). Such findings would suggest that several factors contribute to development of ICDs in PD.

3. Clinical and behavioral features associated with PG in PD

In general population, older age, poor socioeconomic status, mental disorders (e.g. manic and depressive disorders) [26] and alcohol or substance use seem to be factors associated with development of disordered gambling (for a recent review, see Ref. [27]). Moreover, two personality traits seem to be associated with PG: high impulsivity (the tendency to react to internal or external stimuli with diminished regard to negative consequences of these reactions [28]) and high novelty seeking (an individual's tendency toward excitement in response to new stimuli or cues for potential rewards, leading to frequent exploratory activity in pursuit of such experiences), which appears to be modulated by dopaminergic transmission in the ventral striatum [29,30]. Finally, pathological

Table 1
Results of prevalence studies in PD patients with PG.

Authors	N. patients	Population	Prevalence (%)	Tools
Lu et al., 2006 [12]	200	Tertiary PD clinics	7 (PG alone)	Face-to-face interviews
Grosset et al., 2006 [13]	388	Tertiary PD clinics	4.4 (PG alone)	Semi-structured interview based on DSM-IV criteria
Voon et al., 2006 [8]	297	Tertiary PD clinics	3.4 (PG alone)	Modified SOGS
Avanzi et al., 2006 [10]	98	Tertiary PD clinics	6.1 (PG alone)	Interview based on DSMIV-TR; SOGS
Weintraub et al., 2006 [9]	272	Tertiary PD clinics	2.2 (active cases of PG)	Modified MIDI
Crockford et al., 2008 [11]	140	Tertiary PD clinics	9.8 (problem gambling: 3.6; PG: 5.7)	CPGI
Weintraub et al., 2010 [7]	3090	Tertiary PD clinics	5 (problem and pathological gambling)	Massachusetts gambling screen
Antonini et al., 2011 [24]	103	Tertiary PD clinics	0.9 (problem/pathological PG)	SOGS
Weintraub et al., 2013 [25]	168	Tertiary PD clinics	1.2 (problem/pathological PG)	QUIP
Asian countries				
Fan et al., 2009 [15]	400	Tertiary PD clinics	0.32 (PG alone)	Modified south oaks gambling screen (SOGS), interview based on DSM-IV-TR criteria for PG
Lee et al., 2010 [17]	1167	Tertiary PD clinics	1.3 (PG alone)	Minnesota impulsive disorders interview
Chiang et al., 2012 [14]	278	Tertiary PD clinics	1.49 (PG alone)	Interview based on DSM-IV-TR criteria for PG
Auyeung et al., 2011 [16]	213	Tertiary PD clinics	6.1 (PG alone)	Structured screening questionnaire

SOGS = South Oaks Gambling Screen; MIDI = Minnesota Impulsive Disorders Interview; CPGI = Canadian Problem Gambling Index; QUIP = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease.

gamblers show high rates of other ICDs, particularly compulsive buying, compulsive sexual behavior and intermittent explosive disorder [31–33].

In PD patients, PG occurs in relation to DA and L-dopa treatment (see below the "PD therapy and management of PG" section), but some of the abovementioned factors seem to be associated to development of PG. In particular, male gender, young age at onset of PD, previous personal or family history of gambling problems, alcohol and/or substance abuse have been found to increase risk for developing PG [28,34–40]. In a recent prospective study, patient-specific risk factors for ICDs including greater usage of caffeine and cigarettes, motor complications, and higher peak dopamine agonist dosage have been identified [41].

Moreover in PD patients (see Table 2), as in the general population, novelty seeking and high impulsivity were associated with PG [36,38,39,42,43]. In particular, Voon et al. [43] reported that PG patients had greater impulsive choice with higher reward magnitudes reflecting the tendency toward immediate over delayed gratification.

Some studies tend to show higher aggressiveness, anxiety, irritability, disinhibition, obsessive compulsive features, medication-induced hypomania or mania in PD pathological gamblers than in non-gamblers [42–44], but these findings have not been confirmed by other studies [45,46]. As in general population, in PD patients too (Table 2) PG often co-occurs with hypersexuality (HS), compulsive shopping (CS), compulsive eating (CE), and Internet addiction [44,46,47]. Since PG and CS share more severe psychological aspects (greater anxiety, compulsive features, and novelty seeking) than other ICDs (CE and HS), it has been suggested that differences between these subtypes of ICDs (PG and CS versus CE and HS) may reflect differences between intrinsic (e.g., food, sex) and learned (e.g., money) rewards [36,43], with likely different neural correlates, yet to be explored in neuroimaging studies.

In summary, results from recent studies evidenced that development of PG in PD patients under DA treatment is frequently associated with individual features similar to those reported in the general population, including specific personality traits (mainly novelty seeking and impulsivity). Also comorbidity of PG and other ICDs seems to be similar in PD patients and general population, but the relationships among clinical and behavioral aspects associated with PG in PD seem to require further studies.

4. Cognitive impairments associated with PG in PD

In pathological gamblers not affected by PD some recent studies have documented presence of frontal/executive dysfunctions [33,48–53], and, in particular, impairments in decision-making processes [54]. Decision-making connotes both the process of choosing under ambiguous or risky situations and the optimal selection in terms of rewarding or punishing outcomes among several alternative courses of action [55]. Decision-making impairments, independently from PG, have also been found in patients with focal lesions in the prefrontal cortex, amygdala, striatum, insula and parietal cortex [56,57].

Until now, few studies explored cognitive correlates of PG in PD (Table 3). Santangelo et al. [45] found more severe frontal lobe dysfunction, including alteration of cognitive flexibility and set-shifting, in non-demented PD patients with PG as compared with PD patients without PG. A further neuropsychological study comparing the cognitive profiles of PD patients affected by PG, HS, or CE alone or in combination [47] revealed that PG patients are generally less impaired on some frontal and memory tests than patients with other single or combined ICDs. The presence of frontal dysfunction in PD patients with PG has not been confirmed in two studies [42,44], in which however, demented patients were not excluded and gamblers were significantly younger than non-gamblers.

The possible association between deficits in decision making and PG has been recently investigated in a small PD sample [46], showing that PD patients with PG might have poorer decision-making abilities than non gambler PD patients. When challenged for ambiguous situations, PD gamblers selected disadvantageous alternatives and had difficulties to shift to the more advantageous ones, suggesting a dysfunction of both ventral medial pre-frontal cortex (VMPFC) and amygdala-ventral striatum circuit. When decision-making was required in conditions where outcome probabilities were known or calculable, PD gamblers showed normal decision-making [46]. These interesting observations merit to be replicated in larger PD samples.

In summary, the studies on cognitive impairments associated to PG suggest that, in both general population and PD patients, compulsive and perseverative behaviors might reflect an impairment in monitoring, controlling, and modifying negative behavior.

Table 2
Results of behavioral studies in PD patients with PG.

Authors	N. Patients	Behavioral aspects	Results
Voon et al., 2007 [42]	21 PD + PG; 42 PD−PG; 286 PD−PG	BIS-11, TCI, SCID-I, BDI, AS, SCID-I	PD + PG > PD−PG on total score and planning subscore of BIS-11, novelty seeking score of TCI; SCID-I for personal or family history alcohol use disorder and mania. No difference on BDI, AS and SCID-I for anxiety disorder
Santangelo et al., 2009 [45]	15 PD + PG; 15 PD−PG	HAM-D, SCID-I for mania	No difference on all tools
Siri et al., 2010 [44]	21 PD + PG; 42 PD−PG;	NPI; GDS	PD + PG > PD−PG on disinhibition, irritability, eating disorders subscales of NPI. No difference on GDS and hallucinations, delusions, depression, euphoria, sleep disorders, anxiety, apathy, aberrant motor behavior subscales of NPI
Rossi et al., 2009 [46]	7 PD + PG; 13 PD−PG	NPI, MADRS, Zuckerman−Kuhlman Questionnaire	No difference on all tools
Voon et al., 2011 [43]	54 PD + PG; 282 PD−PG	STAI-state, STAI-trait, GDS, BIS, novelty seeking, novelty seeking exploratory, extravagant, impulsive, disorganized, impulsive choice (DDT) K and large reward	PD + PG > PD−PG on STAI-state, novelty seeking total score, impulsive, disorganized, Impulsive choice (DDT) K and large reward. No difference on GDS, STAI-trait, novelty seeking exploratory, extravagant, BIS total

BIS = Barratt Impulsiveness Scale; TCI: Temperament and Character Inventory; SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders; BDI = Beck Depression Inventory; HAM-D = Hamilton Depression Rating Scale; NPI = Neuropsychiatric Inventory; GDS = Geriatric Depression Scale; MADRS = Montgomery-Asberg Depression Rating Scale; DDT = Delay Discounting Task; *K* = slope; PD + PG = PD patients with PG; PD−PG = PD patients without PG.

Table 3
Results of cognitive studies in PD patients with PG.

Authors	N. Patients	Cognitive tasks	Results
Voon et al., 2007 [42]	21 PD + PG; 42 PD−PG; 286 PD−PG	FAB	No difference
Santangelo et al., 2009 [45]	15 PD + PG; 15 PD−PG	FAB, Phon-Fluency, TMT: B-A, WCST; Sem-Fluency, Corsi's Test, Verbal span, RCPM, ROCF-copy; Memory: immediate and delayed recall, ROCF-delayed recall	PD + PG < PD−PG on FAB, Phon-Fluency; TMT: B-A. No difference on WCST, Sem-Fluency, Corsi's Test, Verbal span, RCPM, ROCF-copy, immediate and delayed recall and ROCF-delayed recall
Siri et al., 2010 [44]	21 PD + PG; 42 PD−PG;	Phon-Fluency, Sem-Fluency, Attentive Matrices, Digit Span, Corsi's Test, FAB, RCPM; Denomination, Memory: immediate and delayed recall	PD + PG > PD−PG on Phon-Fluency and Sem-Fluency. No difference on Attentive Matrices, Digit Span, Corsi's Test, FAB, RCPM, Denomination and Memory: immediate recall and delayed recall
Rossi et al., 2009 [46]	7 PD + PG; 13 PD−PG	Addenbrooke's Cognitive Examination, FAB, WCST, Stroop Test, Go/No-Go task, SRL-RET	No difference on all tools
Vitale et al., 2011 [47]	14 PD + PG; 14 PD-ICDs; 13 PD + HS; 12 PD + CE; 10 PD + mICDs	TMT, ROCF-copy, WCST, Attentive Matrices, Stroop Test, verbal long-term memory	PD + PG < PD-ICDs on TMT, ROCF-copy. No difference on WCST, Attentive Matrices, Stroop Test, verbal long-term memory. PD + PG > PD + HS, PD + PG > PD + CE, PD + PG > PD + mICDs on verbal long-term memory. PD + PG > PD + HS, PD + PG > PD + mICDs on Stroop Test. No difference on TMT, ROCF-copy, WCST, Attentive Matrices

FAB = Frontal Assessment Battery; Phon-Fluency = Phonological Fluency Task; TMT: B-A = Trail Making Test: B-A; WCST = Wisconsin Card Sorting Test; Sem-Fluency: Semantic Fluency; RCPM = Raven's colored progressive matrices; ROCF = Rey-Osterrieth complex figure test; SRL-RET = Stimulus reward learning, reversal and extinction task; PD + PG = PD patients with Pathological GamblingG; PD−PG = PD patients without PG; PD + HS = PD patients with Hypersexuality; PD + CE = PD patients with Compulsive Eating; PD + mICDs = PD patients with multiple ICDs.

Alterations of frontostriatal and limbic circuits might contribute to the onset and maintenance of PG [58].

5. Genetic susceptibility

The involvement of brain's reward system in addictions made the dopamine system genes the primary targets of candidate genes for association studies on PG, but the possible role of other neurotransmitter systems has been also explored [59].

In general population, early studies focused on the dopamine receptor D2 (DRD2). The A1 allele of DRD2 Taq 1A is associated with decreased receptor density in the striatum and with cocaine addiction and PG [60–62]. Moreover, associations between dopamine receptor D1 (DRD1) polymorphism with PG [63] and with comorbid PG and alcohol dependence have been reported [64]. The dopamine receptor D3 (DRD3), mainly distributed in the limbic areas of the brain, displays a number of single nucleotide polymorphisms (SNPs), the most frequently studied of which is Ser9Gly SNP [65,66]. This polymorphism has not found to be associated with PG [67]. As for the dopamine receptor D4 (DRD4), a polymorphism in exon III has been reported to encode a receptor with lower affinity for dopamine [68], and to be associated with impulsive personality traits [69,70] and PG [71]. Moreover, in general population genetic polymorphisms of DAT and COMT seem to contribute to ICDs: COMT Val158Met and a 40 base pairs variable number of tandem repeat (VNTR) DAT polymorphism have been found to be associated with alcohol dependence and drug abuse [72].

Dysfunctions of other neurotransmitter systems, such as the serotoninergic system, may contribute to deficient impulse control and impulsive personality features [73]. The serotonin transporter gene (5-HTTLPR) "S" allele has less transcriptional activity and has been associated to both PG [74] and impulsivity [75] in general population. Finally, also glutamate seems to participate in transition from reward learning to repetitive behaviors in drug addiction [76]; glutamate levels within the nucleus accumbens seem to mediate reward-seeking behavior [77].

In PD patients, only a few studies investigated the role of genetic polymorphisms of the dopaminergic system in PG and other ICDs (Table 4). Some relevant polymorphisms investigated in general population have not been assessed in PD patients (i.e., DRD1 and DRD4), whereas other polymorphisms have been assessed in PD patients with PG or other ICDs without finding any significant association (i.e., DRD2 Taq 1A variants [78,79], genetic polymorphisms of DAT and COMT [77]). Notably, the homozygous variant Ser9Gly (AA genotype) of DRD3 is possibly associated with lower binding affinity to dopamine and seemed to be associated with two-fold increase in the risk of PG and ICDs in PD patients [78], but not in general population.

Table 4
Results of molecular genetic association studies in PD patients with PG.

Authors	Sample		Polymorphism	Results
	Subjects diagnosis	Controls		
Lee et al., 2009 [78]	404 PD patients (58 ICD+; 346 ICD−)	559 healthy subjects	DRD2 Taq 1A	No association
			5-HTTLPR	No association
			DRD3 Ser9Gly	Association with AA genotype
			GRIN2B	Association with CC genotype
Vallelunga et al., 2012 [79]	41 PD-ICD+ patients	49 PD-ICD− patients	DRD2 Taq 1A	No association
			COMT Val158Met	No association
			DAT1 (30 UTR 40 bp VNTR)	No association
Lee et al., 2012 [80]	404 PD patients (58 ICD+; 346 ICD−)	409 healthy subjects	HTR2A 102T > C	Association with CT and TT genotype

PD: Parkinson's disease; ICD+: Impulse Control Disorders positive (PG and other ICDs); ICD−: Impulse Control Disorders negative; DRD2: Dopamine D2 Receptor; 5HTTLPR: Serotonin Transporter Gene; DRD3: Dopamine D3 Receptor; GRIN2B: glutamate N-methyl-D-aspartate (NMDA) receptor, 2B subunit; COMT: catechol-O-methyltransferase; DAT: Dopamine transporter Gene; HTR2A: serotonin 2A receptor gene.

As regards serotoninergic systems, the serotonin transporter gene (5-HTTLPR) "S" allele has been shown to be more frequent in PD patients with PG and ICDs, although neither dominant nor recessive model revealed any associations [78]. More recently, a genetic variant affecting serotonin 2A receptor (HTR2A) pathway has been found to be associated with ICDs in PD patients receiving dopamine replacement therapy, mainly under low-dopaminergic-dose conditions [80].

Last, the CC genotype of the 2B subunit (GRIN2B) of the glutamate N-methyl-D-aspartate (NMDA) receptor, mainly expressed in the striatum [81], has been found to be more frequent in PD patients with PG and ICDs than in non-affected patients [78].

In synthesis, studies on genetic susceptibility for PG and ICDs in PD patients are quite limited and often included a relatively small number of patients (for a recent review, see Ref. [82]). Available data seem to suggest an association of PG with DRD3 and not with DRD2, differently from what reported in non-PD population, and with polymorphisms of serotoninergic and glutamatergic pathways, but these results await to be confirmed in further independent studies on larger samples of PD patients.

6. Neuro-anatomical and functional correlates in PG

Frontal lobes are involved in processing, integrating and inhibiting impulses received from the limbic system, striatum, temporal lobes, and neocortical sensory regions [83–88]. In general terms, prefrontal cortex can be considered as a cortical region mediating 'top down' regulation of subcortical ('bottom up') mechanisms of reward and incentive [88]. Therefore, patients with frontal-striatal pathways dysfunctions may have difficulties to inhibit unwanted movements or thoughts, and may develop perseverative, compulsive and impulsive behaviors [89], such as PG [45]. Accordingly, neuroimaging studies in pathological gamblers not affected by PD revealed structural and functional abnormalities of frontal-striatal pathways, in particular in the ventromedial prefrontal cortex and cortico-basal-ganglionic-thalamic circuits [90–100].

In recent years, neuro-anatomical and functional correlates of PG in PD patients have been explored by several studies [101–105] (Table 5). Reported findings are not easy to summarize, also because of the different methodological approaches employed, but there is substantial convergence in highlighting that dysfunction of orbitofrontal cortex, anterior cingulate cortex (ACC), amygdala, insula and ventral striatum are often found in pathological gamblers. These cortical and subcortical structures are considered to be part of a brain network implicated in decision making, risk processing, and response inhibition; dysfunction of this network has been found to be correlated with gambling severity in PD patients [103]. The evidence of a lack of "connectivity" within this functional network, specifically a lack of correlation between activity in the anterior ACC and the striatum, is consistent with previous neuropsychological findings [45,47] and with the idea that PG can arise from a specific impairment of shifting behaviors after negative outcomes and perseverative risk-taking habits despite self-destructive consequences.

Recent neurofunctional studies with different radiotracers provided new information about possible neural correlates of PG in PD patients. The novel findings from these studies mainly relate to the possibility that some cortical regions involved in the control of behavior, such as medial orbitofrontal cortex [104] or anterior cingulate cortex [105], may show dysfunctional activation, thus suggesting that alteration of DA homeostasis might impact individuals' vulnerability for impulsivity and modulate risk for development of PG in PD.

Taken together, available findings seem to be consistent with the hypothesis that PG occurs in PD patients as a result of abnormal reward-based learning processes and reduced inhibition of impulsive drives combined with dopamine overstimulation of mesocorticolimbic pathways. Further prospective controlled studies in larger cohorts are needed to investigate the predisposing factors for development of PG in PD patients undergoing dopamine replacement therapy.

7. PD therapy and PG management

Numerous studies evidenced a strong association between DA therapy and PG. This association has been ascribed to excessive activation of the mesocorticolimbic dopaminergic system, which under physiological conditions mediates the response to natural rewards [28]. In PD patients, dopamine neurons projecting to the dorsal striatum (putamen and dorsal caudate) are less severely affected than those projecting to the ventral striatum (ventral caudate and nucleus accumbens) [106]. This raises the possibility that pharmacological restoration of dopamine neurotransmission in the motor striatum leads to overstimulation of the limbic striatum thus eliciting abnormal behaviors [107]. This difference in dopamine levels between the dorsal and ventral striatum can also

Table 5
Results of neuroimaging studies in PD patients with PG.

Authors	Methods	Sample	Results
Cilia et al., 2008 [101]	TC99m SPECT	11 PD + PG patients; 40 matched PD controls	Abnormal resting state overactivity in orbitofrontal cortex, hippocampus, amigdala, insula and ventral pallidum in PD patients with PG
Steeves et al., 2009 [102]	[^{11}C]Raclopride PET	7 PD + PG patients; 7 matched PD patients	Increased striatal dopamine release in PD + PG patients
Cilia et al., 2011 [103]	SPECT	15 PD + PG patients; 15 PD–PG patients; 15 matched healthy controls	Decreased prefrontal cortex, cingulate, insula, parahippocampal gyrus, and striatal resting perfusion in PD + PG patients; Anterior Cingulate Cortex-Striatal disconnection in PD + PG patients
Jotsua et al., 2012 [104]	[^{18}F]F-Dopa PET	10 PD + PG patients; 10 PD–PG patients	Increased monoaminergic activity in the medial orbitofrontal cortex in PD + PG patients under dopaminergic treatment
Ray et al., 2012 [105]	[^{11}C]FLB-457 PET	7 PD + PG patients; 7 PD–PG patients	Reduced [^{11}C]FLB-457 midbrain binding potential (BP) in PD with PG patients; increased [^{11}C]FLB-457 BP in the anterior cingulate cortex in PD patients with PG

fMRI, functional Magnetic Resonance Imaging; PET, Positron Emission Tomography; SPECT, Single Photon Emission Computerized Tomography; PD, Parkinson's Disease; SPECT, Single Photon Emission Tomography; PG, Pathological gambling.

account for the finding that L-Dopa, by its phasic stimulation of dopamine receptors, improves performance on cognitive tasks involving the dorsal striatum (e.g., working memory and task-set switching), but worsens performance on test which depend on the ventral striatum (e.g., reversal learning and Cambridge Gambling Task) [108–110]. By contrast, tonic stimulation of dopamine receptors with DA specifically desensitizes the reward mesocorticolimbic system by preventing decreases in dopaminergic transmission that occurs with negative feedback [111]. These observations fit well with the increased risk to develop PG specifically related to DA treatment in PD patients [7,8,112].

Another neurobiological factor that may contribute to mesocorticolimbic overdosing is sensitization, which refers to an increased effect of stimulant drugs with repeated administration [113]. The dopamine D3 receptor may play a role in sensitization and in the development of addictive syndromes in PD. DRD3 is primarily expressed in the limbic system, and is upregulated in response to levodopa treatment in animal models of PD [114]. Moreover, DRD3 appears to control the phasic, but not tonic, activity of dopaminergic neurons which may be induced by novelty or presentation of drug-conditioned cues in rodents [115–117]. Since non ergot DA such as pramipexole and ropinirole have a high affinity for both D2 and D3 receptors and the stimulation of D3 receptors mediates activation of mesocorticolimbic reward system, it is possible that abnormal expression of D3 receptors in ventral striatum is associated with ICDs occurrence. These data seem to converge on an important role for the D3 receptor in modulating the physiologic and emotional experience of novelty, reward, and risk assessment and likely explain the relatively higher rates of pathological behaviors among patients taking DA.

An important review showed that PG in PD is associated with DA therapy, as a class, in 98% of cases [40], although this finding may be confounded by factors such as higher rates of DA use in younger patients [9,28]. Most authors reported a dose-dependent onset of PG in PD patients treated with DA, with improvement or resolution following DA tapering. Other reports referred to an "all-or-none" phenomenon with complete resolution of PG after DA withdrawal [37,118–120]. Although ICDs have been reported during treatment with all DA, an analysis of the Food and Drug Administration Adverse Event Reporting system database showed that 58% of 67 gambling reports are associated with pramipexole [121], likely because of its high relative selectivity for DRD3.

While DA use is strongly associated with development of ICDs in PD patients, levodopa in monotherapy is not [9,112], although it has been suggested that L-dopa might play a role in priming these behaviors [122–125]. There are few reports implicating monoamine oxidase-B inhibitors in PG, although these patients were already taking other antiparkinsonian medication [29,126].

Data regarding the effect of deep brain stimulation (DBS) on PG and ICDs in PD are still limited. Variable and sometimes conflicting reports about PG in PD patients with DBS on subthalamic nucleus (STN) have been published to date. A recent retrospective study evidenced that only in a few (2 out of 7) PD patients ICDs resolved after unilateral or bilateral STN DBS; therefore, the authors suggested that clinicians should not consider unilateral or bilateral DBS to be a solution to ICDs in PD [127]. In fact, the few reports of positive outcome after STN DBS [128,129] might be likely related to discontinuation of dopaminergic treatment after surgery, whereas in other patients ICD were observed as a new onset phenomenon after surgery [130,131]. Selective stimulation of the associative and limbic region of the STN, and of surrounding related structures, has also been reported to trigger or worsen non-motor side effects [132–136].

Little is known about optimal management strategies of PD patients with PG, as available evidence mainly came from open label studies and case reports [9,40,124,137]. Two long-term follow-up studies [119,138] and further recent case reports [139–142], however, suggested that discontinuation of DA treatment can represent the first line management strategy of ICDs, with full remission or clinically significant reduction of symptomatology. Tapering DA treatment can be useful too, and only in patients who do not tolerate tapering, replacement with other drugs (including L-dopa, anticholinergics, catechol-O-methyltransferase inhibitors, and monoamine-oxidase-B inhibitors) can be considered [36,38,143]. Notably, a recent study [144] reported that 19% of patients who tapered DA treatment (one-third because of ICDs), particularly those with higher peak DA doses and greater cumulative DA exposure, developed a withdrawal syndrome. The Dopamine Agonist Withdrawal Syndrome (DAWS) is characterized by prominent psychiatric (e.g., anxiety, dysphoria, depression, agitation) and autonomic (orthostatic hypotension, diaphoresis) manifestations, similarly to withdrawal syndromes observed with other drugs (such as cocaine and amphetamines) stimulating mesocorticolimbic dopaminergic pathways. Since DAWS can cause severe, long-term psychosocial consequences, some authors suggested to monitor patients with ICDs whenever DA are withdrawn, and to taper DA as soon as ICDs develop [144].

Atypical antipsychotics [145–149] have been reported to reduce PG in PD patients, but with variable degree of motor function worsening. Antidepressants, mood stabilizers, and several psychosocial interventions may also be beneficial [145,146,149]. All these strategies might be considered as secondary management strategies for ICDs, but this issue should be further explored. Recent preliminary studies with zonisamide and topiramate have shown promising results in reducing gambling urges in PD [150,151]. Conflicting data have been reported regarding use of amantadine: it proved to be beneficial in 17 PD patients with PG, reducing or abolishing gambling urges and hours spent gambling [152], but two further studies and a case report have shown that amantadine is associated with PG and other treatment-related behavioral disorders [35,153,154]. Moreover, according to the recently published MDS-EBM (Movement Disorders Society, Evidence Based Medicine) review update for treatment of non motor symptoms in PD, there is insufficient evidence for the efficacy of amantadine for treatment of PG in PD patients [155]. More recently, treatment of PG with opioid antagonist naltrexone resulted in full remission of disorder in three parkinsonians [156]. It has been proposed that the efficacy of opioid antagonists in the treatment of addictive disorders involves opioidergic modulation of mesolimbic dopamine circuitry [157]. Further work to define if opioid antagonists have beneficial effects for PG and also other ICDs could enhance treatment strategies.

8. Conclusions and future perspectives

PG can impair activities of daily living and have a strong negative impact on quality of life of patients and their families. The largest prospective study on PD patients demonstrated that point prevalence of PG can be as high as 5% [7], and nonetheless PG is still frequently under-reported as many patients have reduced insight into social consequences of their behavior. These data show how much important is to screen PG using specifically devised and validated diagnostic tools and to consider both patients' and caregivers' reports. It is also important to take into account that, as in general population, some risk factors can help to identify PD patients who are susceptible to develop PG during DA therapy. Clinical factors associated with development of PG include young age at disease onset, personal or family history of alcoholism, impulsive or novelty-seeking personality, and prior history of ICDs.

The cognitive correlates of PG in PD have been poorly investigated. As pathological gamblers without PD, non-demented PD

patients with PG showed more severe frontal lobe dysfunction, including alteration of decision making, cognitive flexibility and set-shifting as compared with PD patients without PG. Also neuroimaging studies revealed some similarities in non-PD gamblers and in PD patients with PG, pointing to abnormalities in the ventromedial prefrontal cortex and in cortico-basal-ganglionic-thalamic circuits. The alterations in the reward centers of the brain suggest possible drug-induced overstimulation of less affected mesolimbic dopamine system than the nigrostriatal systems in PD patients with PG.

The genetic of PG awaits for further independent studies. A few studies investigated the role of genetic polymorphisms of the dopaminergic system in PD with ICDs: DRD3 was found associated with PG in PD, differently from what observed in general population. The next step would be to promote larger molecular genetic studies addressing the issue of population stratification, sample size, multiple testing and selection of genetic polymorphism. Actually, stimulation of mesolimbic DRD3 receptors by DA is thought to underlie the development of PG and possibly of other ICDs. The DA effect seems to be a class effect and not specific for any particular DA.

The management of ICDs in PD is complex. Emerging data suggest that reducing DA dose can improve PG symptoms over time in PD patients. Other possible approaches include discontinuing or switching DA therapy, reducing levodopa dose, and considering alternative therapies such as atypical antipsychotics or DBS.

In conclusion, the present review supported the idea that PG can be a side effect of DA therapy but also that a constellation of several factors can contribute to develop this neuropsychiatric disturbance in PD, as well as in general population. The association of PG with behavioral disorders, cognitive impairments, and functional abnormalities in cortical and subcortical regions involved in 'top-down' cognitive monitoring and inhibition of inappropriate behaviors are compatible with the idea that DA treatment can trigger PG in susceptible PD patients with an imbalance of prefrontal-subcortical limbic circuitries. In this perspective, it seems necessary to identify different sub-phenotypes of PD to shed light on the biological mechanisms that could render some PD patients vulnerable to the development of PG secondary to the use of DA.

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