IMPULSE CONTROL DISORDERS, IMPULSIVITY AND RELATED BEHAVIORS IN PARKINSON'S DISEASE

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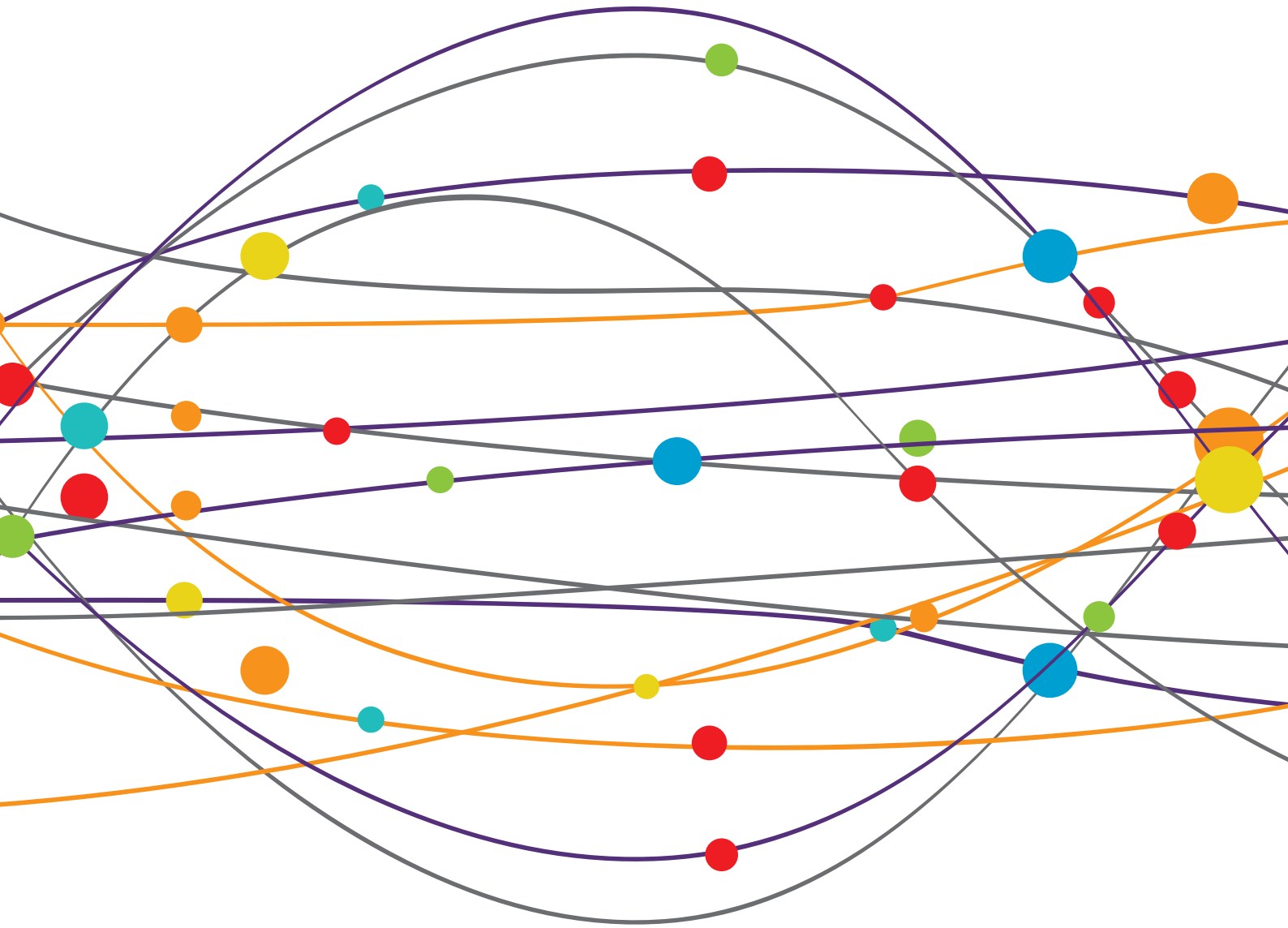

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IMPULSE CONTROL DISORDERS, IMPULSIVITY AND RELATED BEHAVIORS IN PARKINSON'S DISEASE

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EDITORIAL
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Editorial: Impulse Control Disorders, Impulsivity and Related Behaviors in Parkinson's Disease

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Keywords: impulse control and compulsive behaviors, impulsivity, impulse control (pathology) disorders, related behavior, Parkinson's disease

Editorial on the Research Topic

Impulse Control Disorders, Impulsivity and Related Behaviors in Parkinson's Disease

Impulse control disorders (ICDs) are defined as a failure to resist a temptation, urge, or impulse leading to pursue certain reward-based activities or make poorly informed decisions without insight to the consequences of these repeated activities (1). First reports of ICDs in people with Parkinson's disease (PD) on dopaminergic replacement treatment began to appear in the early 2000s (2, 3). The first large study, the DOMINION Study, was published in 2010 establishing the relation of ICDs not only with dopaminergic treatment but with other demographic and clinical variables (4). Since then over 500 papers on ICD ranging from clinical features to neuroimaging and genetic risk factors have been published.

As editors of this special edition on Impulse Control Disorders, Impulsivity, and Related Behaviors in Parkinson's disease, we are pleased to present the collection of papers featured in this Research Topic.

The final collection is comprised of 11 high-quality papers including two minireviews, one review, and one perspective. In addition, three systematic reviews and four original research manuscripts complete this Research Topic.

In the review papers, Gatto and Aldinio shares a brief review on the definition and classification of ICD and their related behaviors, their prevalence, risk factors, clinical tools, neuroimaging, as well as their treatment. Garcia-Ruiz provides a comprehensive overview of ICD as a side effect of dopaminergic treatment but considering the possibility of an individual susceptibility mainly due to genetic factors. Finally, the author highlights another possible consequence of ICD manifested as enhanced creativity in persons with Parkinson without previous artistic abilities. De Micco et al. address the fact that not all persons with PD develop and ICD despite receiving dopaminergic treatment. They based their review on data derived for neuroimaging studies assessing dopaminergic signaling or reward processing. The authors conclude that there is evidence suggesting an increased dopaminergic firing in response to reward and that prospective multimodal imaging studies are still needed. Lastly, Eisinger et al. provide insight into some additional factors such as the role of country of residence, comorbidities, non-dopaminergic medications, and deep brain stimulation surgery. Overall, these set of paper give the reader a broad but comprehensive look at the current state of knowledge on ICDs and PD.

The systematic reviews include a meta-analysis of case-control studies by Molde et al. Along with confirmation of ICDs being s significantly associated with PD, being medically treated for PD and disease duration were the two variables associated with an increased risk of ICD. A meta-analysis from Martini et al. assessed PET or SPECT studies on dopaminergic neurotransmission in persons with PD and ICD. They conclude that persons with PD and ICD show lower

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dopaminergic transporter levels in the dorsal striatum and increased dopamine release in the ventral striatum when engaged in reward-related tasks. Another meta-analysis by Martini et al. evaluated measures of cognitive, affective, and motivational domains between PD subjects with and without ICDs. They found that ICD in PD is associated with poor reward-related decision-making, and neuropsychiatric symptoms such as depression, anxiety, and anhedonia.

Two original articles provide information derived from neuroimaging studies. Ruitenberg et al. assessed impulsivity by analyzing resting-state functional connectivity and structural MRI in subjects with and without ICDs. Their findings include reduced frontal-striatal connectivity and GPe volume were associated with more impulsivity. A different approach was taken by Zadeh et al. by shifting focus to alterations of white matter tract in drug-naïve subjects with PD and with ICDs using diffusion MRI connectometry. The authors report disrupted connectivity in the complex network of dynamic connections between cerebellum, basal ganglia, cortex, and its spinal projections.

Next, Erga et al. report some novel genetic data using whole-exome sequencing data from the Norwegian ParkWest study. Eleven SNPs were found to be associated with ICDs, with rs5326 in *DRD1* being the strongest risk factor, and rs702764 in *OPRK1* being associated with a decreased risk. Lastly, Martini et al. presents a cross sectional study comparing ICDs and related behaviors across people with PD with normal cognition, mild cognitive impairment and PD-related dementia. While frequency and severity of ICDs did not differ between groups, subjects with ICD showed more deficits within the attentive and executive domains in the mild cognitive impairment group.

We wish to thank all authors, and peer reviewers in the research featured. We hope that this collection of papers shed new light to the still expanding body of knowledge on ICDs in PD.

AUTHOR CONTRIBUTIONS

MR-V: conception, drafting the work, revising it and final approval of the version to be published. AA: conception, revising the work critically for important intellectual content and final approval of the version to be published.

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ORIGINAL RESEARCH
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Dopaminergic and Opioid Pathways Associated with Impulse Control Disorders in Parkinson's Disease

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Introduction: Impulse control disorders (ICDs) are frequent non-motor symptoms in Parkinson's disease (PD), with potential negative effects on the quality of life and social functioning. ICDs are closely associated with dopaminergic therapy, and genetic polymorphisms in several neurotransmitter pathways may increase the risk of addictive behaviors in PD. However, clinical differentiation between patients at risk and patients without risk of ICDs is still troublesome. The aim of this study was to investigate if genetic polymorphisms across several neurotransmitter pathways were associated with ICD status in patients with PD.

Methods: Whole-exome sequencing data were available for 119 eligible PD patients from the Norwegian ParkWest study. All participants underwent comprehensive neurological, neuropsychiatric, and neuropsychological assessments. ICDs were assessed using the self-report short form version of the Questionnaire for Impulsive-Compulsive Disorders in PD. Single-nucleotide polymorphisms (SNPs) from 17 genes were subjected to regression with elastic net penalization to identify candidate variants associated with ICDs. The area under the curve of receiver-operating characteristic curves was used to evaluate the level of ICD prediction.

Results: Among the 119 patients with PD included in the analysis, 29% met the criteria for ICD and 63% were using dopamine agonists (DAs). Eleven SNPs were associated with ICDs, and the four SNPs with the most robust performance significantly increased ICD predictability (AUC = 0.81, 95% CI 0.73–0.90) compared to clinical data alone (DA use and age; AUC = 0.65, 95% CI 0.59–0.78). The strongest predictive factors were rs5326 in *DRD1*, which was associated with increased odds of ICDs, and rs702764 in *OPRK1*, which was associated with decreased odds of ICDs.

Conclusion: Using an advanced statistical approach, we identified SNPs in nine genes, including a novel polymorphism in *DRD1*, with potential application for the identification of PD patients at risk for ICDs.

Keywords: Parkinson's disease, impulse control disorders, addiction, elastic net, OPRK1, DRD1

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INTRODUCTION

Patients with Parkinson's disease (PD) have a threefold increased odd for developing impulse control disorders (ICDs) and related compulsive behaviors when compared to controls (1, 2). These behaviors are characterized by lacking control of rewarding behaviors, such as gambling, sexual activity, eating, and buying. In addition, patients may also develop a preoccupation with hobbies, punding behaviors, and an addiction-like pattern of dopaminergic medication use. Although common in PD, ICDs are not merely a result of PD pathology (3), but are closely associated with the use of dopaminergic replacement therapy (DRT), such as dopamine agonists (DAs) (1, 2, 4). Still, not all patients develop ICDs when exposed to dopaminergic medications, arguing that some individuals are more susceptible to DRT than others. Previously identified demographic-risk factors, such as familial history of addiction, increased impulsivity, and novelty-seeking traits (1, 5), argue that the individual vulnerability may be of genetic origin.

To date, the evaluation of ICD susceptibility in PD has primarily focused on independent associations of single genetic variants. Several studies have reported an association between ICD development in PD patients and genetic polymorphisms in dopamine receptor (*DRD1–3*) and glutamate receptor (*GRIN2B*) genes (6–9), while individual studies also point toward a potential association with genetic polymorphisms in serotonin receptor (*HTR2A*), dopamine transporter (*DAT1*), and tryptophan hydroxylase 2 (*TPH2*) genes (10, 11). Recently, the spectrum of monoaminergic ICD candidate genes was expanded through the identification of a polymorphism in *OPRK1*, which encodes an opioid receptor, as the strongest genetic predictive factor in a clinical–genetic model designed to predict the occurrence of ICDs in early PD in the Parkinson's Progression Markers Initiative (PPMI) cohort (12). The authors further reported that the inclusion of a panel of candidate-genetic variants improved the prediction of incident ICDs (identifying up to 76% of incident ICD cases in early-stage PD patients) compared to prediction based on clinical variables alone (12), arguing for the potential clinical utility of genetic testing. The authors estimated that common genetic variants accounted for 57% of the variance of ICD incidence among PD patients in the PPMI study. This heritability estimate is comparable to estimates from the general population, but current knowledge about individual risk genes is limited. We suggest that several neurotransmitter systems may contribute to ICD pathogenesis, and multiple genes within one system may play a crucial role in the pathogenesis of these behaviors.

To date, the identification of patients at risk of ICDs remains a primary aim in clinical research. Although several genetic polymorphisms have been suggested to aid clinical identification of ICD risk, most published studies utilize a candidate-gene approach based on previously published findings. In this study, we aimed to determine the association of genetic polymorphisms across several neurotransmitter pathways using an advanced statistical approach. A secondary aim was to investigate the clinical utility of a genetic panel in the prediction of ICD status in patients with PD.

Abbreviations: PD, Parkinson's disease; ICD, impulse control disorder; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; SNP, single-nucleotide polymorphism; ROC, receiver-operating characteristics; AUC, area under the curve; DRT, dopaminergic replacement therapy; DA, dopamine agonist; PPMI, Parkinson's progression markers initiative; UPDRS, Unified Parkinson's Disease Rating Scale; LED, levodopa equivalent dose; MAF, minor allele frequency; EN, elastic net; LD, linkage disequilibrium.

MATERIALS AND METHODS

Study Design

This cross-sectional study is based on participants from the Norwegian ParkWest study, a population-based longitudinal study of incident PD. The ParkWest cohort is composed of patients with newly diagnosed PD and normal control subjects recruited from four counties in Norway between 2004 and 2006, who were prospectively followed up by movement disorder neurologists. A detailed presentation of the diagnostic procedures and case ascertainment has previously been published (13). Screening for ICDs was first introduced at 5-year follow-up, and this study included 155 patients with PD who still remained in the study after 5 years of follow-up. Of these, 28 patients were excluded due to dementia and two due to missing data on Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), leaving 125 patients eligible for this study. Patients with missing information on relevant genetic variants ($n = 6$) were removed from this study.

Clinical Measures

A standardized examination program was administered by trained members of the ParkWest study group. Information regarding demographic variables, lifestyle factors, clinical history, and medication was obtained using semi-structured interviews. Severity of motor symptoms was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III (14). Self-evaluated functioning on activities of daily life and complications of dopaminergic therapy were assessed using UPDRS parts II and IV. Hoehn and Yahr (H&Y) was used to assess disease stage (15). Levodopa equivalent doses (LEDs) were calculated according to published recommendations (16). Mini-Mental State Examination (MMSE) was used to assess global cognitive functioning (17). The Montgomery and Aasberg Depression Rating Scale (MADRS) was used to assess depressive symptoms (18). Lastly, ICDs were assessed using the self-report short form version of the QUIP (19). Participants with a positive response to one or more screening questions of the QUIP were classified to have ICD (20).

Candidate Gene and Variant Selection

Of the 125 patients eligible for this study, 119 had previously been characterized by whole-exome sequencing (WES) (unpublished material). We selected 16 genes (*ADRA2C*, *DRD1–5, SLC6A3/DAT1*, *DDC, COMT, SLC6A4/5HTTLPR, TPH2,* HTR2A, OPRM1, OPRK1, *GRIN2B*, and *BDNF)* based on established roles in candidate neurotransmitter pathways, or a published involvement in ICD and related behaviors in either patients with PD or in non-PD

populations. This was achieved by performing a literature search, and the genes identified were involved in four neurotransmitter pathways (dopaminergic, serotonergic, glutamatergic and opioid) (6–12). All variants (n = 185) present in the candidate-gene regions were extracted using ingenuity variant analysis (Qiagen, CA, USA) and filtered to retain only those with minor allele frequency (MAF) >0.5 in the ParkWest and the 1,000 genomes project (n = 71). A further 12 single-nucleotide polymorphisms (SNPs) were removed based on a high linkage disequilibrium (LD) measured using the Broad Institute SNP Annotation and Proxy Search (SNAP) (21). In addition, two SNPs that have frequently been studied in ICDs in PD, but which were not in the original data extraction, were also included: rs1800497 in *ANKK1* was extracted from the WES data and rs6280 in *DRD3* was genotyped using a custom-made TaqMan SNP-genotyping assay (Thermo Fisher Scientific), as described (22). For further analysis, the genotypes were converted to carrier status, and five variants removed due to a carrier frequency >95% in the study population.

Statistical Analyses

Statistical procedures were performed using IBM SPSS Statistics version 24.0.0.1, R 3.4.0 and STATA IC 14.2. Group differences were analyzed using *t*-tests, Mann–Whitney tests, χ^2–tests, and Fisher exact tests as appropriate.

Performing an extensive investigation of genetic variants associated with ICDs is inherently difficult due to the large number of possible variants identified in a single neurotransmitter pathway. The number of variants (p) will often exceed the number of participants (n) in the study. In these cases ($p >> n$), the traditional strategies for multivariable regression modeling will fail. An option here is to assume a sparse solution, i.e., that only a small subset of variants are involved in a single neurotransmitter pathway. Recent advances in statistical modeling, such as elastic net (EN) regularized generalized linear regression, reduce the number of predictors by penalizing those that do not have enough prediction power. This allows one to reduce the risk of overfitted models and increase the generalizability to other cohorts (23, 24). In this study, regularized logistic regression with EN penalization was used to identify SNPs associated with ICDs. Regularized regression with EN is well suited for model selection of high-dimensional data, as is often the case in analyses of genetic polymorphisms in clinical cohorts (23, 25). In addition, EN handles variants with high LD and multiple SNPs from one neurotransmitter pathways well (26).

Elastic net analyses were performed in *R*, using the *glmnet*-package (27). The level of regularization parameter λ was chosen as the minimal λ that yielded prediction error estimated by cross-validation within one standard error from its minimal value. In the *glmnet*, the parameter α decides the balance between l_1 and l_2 regularizations, of which the former is the regularization used in Lasso regression ($\alpha = 1$) and the latter is used in Ridge regression ($\alpha = 0$). In our analyses, the EN was repeated for all α from 0 to 1, with 0.01 increments. Non-zero estimated coefficients consistent throughout the entire range of α support the evidence of associations between relevant SNPs and ICD status.

The discriminative ability of the biomarkers with regard to ICD diagnosis was assessed from receiver-operating characteristic (ROC) curve analysis. The test variable was the predicted probability from logistic regression with ICD diagnosis (yes/no) as outcome. In order to not overfit the model, the four SNPs with a most robust performance in EN analysis were selected as candidate SNPs. Robustness of candidate SNPs was defined by the consistency of the estimated *B*-values in EN analyses (which are visually represented by color in **Figure 1**). The ROC curve was plotted with preselected clinical variables alone (age and either DA use), for the genetic variables alone (genetic model), and with the clinical and candidate SNP data combined (clinical–genetic model). Area-under-the-curve (AUC) values were compared using DeLong test.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics are presented in **Table 1**. Of 119 patients in the study, 29.4% (35/119) reported at least one ICD. Patients with ICD did not differ from patients without ICD in terms of sex, education, duration of PD, MMSE scores, or scores on UPDRS II, III, or IV, but patients with ICDs tended to be younger ($p = 0.050$) and scored significantly higher on MADRS ($p = 0.010$). Patients with ICDs also used DA more frequently ($p = 0.001$) and had a higher total LED ($p = 0.017$). DA dosage was not different when comparing DA users with ICDs with those without ICDs ($p = 0.958$).

Variant Selection

The complete results from EN analyses are presented in **Figure 1**. Fifty-six SNPs were identified across the genes selected for analysis (Table S1 in Supplementary Material), and 11 SNPs from four neurotransmitter pathways were robustly associated with ICDs across all levels of α in the EN analysis (**Figure 1**; **Table 2**). Specifically, carriers of the minor alleles of the *DRD1* rs5326, *DRD2* rs6277, COMT rs4646315, and DDC rs4490786 SNPs were associated with an increased risk of ICDs. Carriers of the minor allele of the *OPRM1* rs677830, *OPRK1* rs702764, *GRIN2B* rs1105581 and rs7301328, *COMT* rs4646318, TPH2 rs4290270, DRD5 rs6283 SNPs were associated with a decreased risk of ICDs. Of these, the *DRD1* rs5326, *OPRK1* rs702764, *OPRM1* rs677830, and *COMT* rs4646318 were most robustly associated with ICD status and thus considered candidate variants.

Prediction of ICDs

The prediction of ICDs was estimated by using ROC curves with AUC (**Figure 2**). In the clinical model, ROC curves plotted with the clinical variables age and DA use yielded an estimated AUC of 0.68 (95% CI 0.59–0.78). In this analysis, DA use [odds ratio (OR) 4.5; 95% CI 1.5–13.5; $p = 0.006$] was associated with the presence of ICDs. The genetic model, consisting of the SNPs *DRD1* rs5326, *OPRK1* rs702764, *OPRM1* rs677830, and *COMT* rs4646318, yielded an estimated AUC of 0.70 (95% CI: 0.61–0.79). Of these, one variant, the *DRD1* SNP rs5326, was significantly associated with ICDs (OR 2.9; 95% CI 1.1–7.6; $p = 0.026$).

In the clinical–genetic model, we included four candidate SNPs identified in the EN analyses, resulting in an estimated

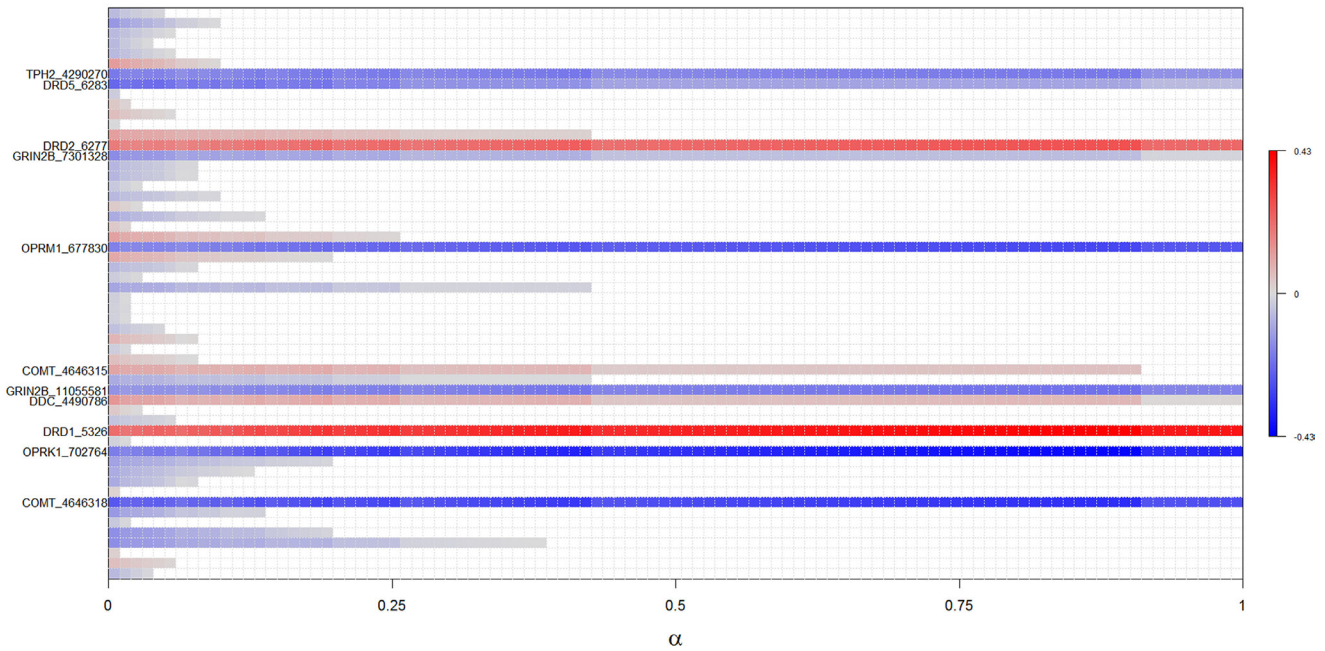

FIGURE 1 | Results of regularized regression with elastic net penalization for α-values between 0 and 1. Polymorphisms positively associated with ICDs (i.e., increases risk) are highlighted with red, while polymorphisms negatively associated with ICDs (i.e., decreases risk) are highlighted in blue, with the intensity of color reflecting the strength of association. Polymorphisms not associated with ICDs are white. Identified polymorphisms demonstrate significant association across all levels of α.

TABLE 1 | Demographic and clinical characteristics.

Characteristics	Total ($n = 119$)	ICD ($n = 35$)	No ICD ($n = 84$)	p-Value[a]
Age	70.5 (9.3)	67.9 (7.7)	71.6 (9.7)	**0.050**
Male, *n* (%)	74 (62.2)	25 (71.4)	49 (58.3)	0.180
Education	11.6 (3.2)	11.49 (3.0)	11.7 (3.3)	0.803
Duration of PD	7.4 (1.8)	7.3 (1.4)	7.4 (1.9)	0.658
Mini-Mental State Examination	27.8 (2.6)	28.5 (1.7)	27.5 (2.8)	0.063
Montgomery and Aasberg Depression Rating Scale	3.9 (4.4)	5.5 (5.1)	3.2 (4.0)	**0.010**
UPDRS II	10.7 (5.4)	12.0 (6.0)	10.1 (5.0)	0.126
UPDRS III	22.7 (10.8)	23.8 (10.7)	22.3 (10.9)	0.422
UPDRS IV	1.8 (1.7)	2.0 (1.8)	1.7 (1.7)	0.369
Hoehn and Yahr stage	2.2 (0.6)	2.2 (0.6)	2.2 (0.6)	0.920
DA users, *n* (%)	75 (63.0)	30 (85.7)	45 (53.6)	**0.001**
Total LED	619.0 (350.2)	740.7 (354.9)	568.2 (333.7)	**0.017**

PD, Parkinson's disease; UPDRS, Unified PD Rating Scale; DA, Dopamine agonist; LED, Levodopa equivalent dosage; ICD, Impulse control disorder.
[a]*Group differences between patients with and without ICDs.*
Significant p-values are highlighted in bold.

AUC of 0.81 (95% CI 0.73–0.90). This 13% point increase in AUC between the clinical and the clinical–genetic model was statistically significant ($p = 0.003$). Similarly, the 11% point increase in AUC between the genetic and the clinical–genetic model was also significant ($p = 0.008$). In the clinical–genetic model, DA use (OR 7.4; 95% CI 2.1–26.2; $p = 0.002$) was again associated with increased odds of ICDs, and the significant genetic predictors *DRD1* SNP rs5326 (OR 6.1; 95% CI 1.9–19.6; $p = 0.003$) and *OPRK1* SNP rs702764 (OR 0.2; 95% CI 0.1–0.8; $p = 0.040$) were associated with an increased and a decreased risk of ICDs, respectively. Full details of the clinical and the clinical–genetic models are presented in **Table 3**.

DISCUSSION

In this study, we identified an association between ICDs and SNPs in the dopaminergic, glutamatergic, serotonergic, and opioid neurotransmitter system using an advanced statistical procedure. Using four polymorphisms from this panel significantly increased the level of prediction of ICD status beyond known clinical risk factors. These results confirm and expand existing knowledge about the genetic architecture of ICDs in PD. To date, this is the most extensive investigation of polymorphisms in relation to ICDs in PD.

Guiding Clinical Practice Using Genetic Markers

Despite new insights into the pathophysiology of ICDs in PD, a consistent model for clinical differentiation between patients with high and low risk of ICDs has still not been developed. Although younger age has been associated with ICDs in several cohorts, DA is more often prescribed to younger patients than that to older. As evident in the clinical model of ICD risk, age is not significantly associated with ICDs when controlling for

TABLE 2 | Characteristics of identified SNPs in elastic net analysis.

Gene	SNP	Location[a]	Transcript[b]	Protein	MAF[c]		Association with impulse control disorders in ParkWest[d]
					ParkWest	1,000 genomes	
DRD1	rs5326	5:175443193	c.-94G > A		0.14	0.17	+
DRD2	rs6277	11:113412737	c.957C > T	p.Pro319Pro	0.50	0.24	+
OPRM1	rs677830	6:154107531	c.1231C > T	p.Gln411Ter	0.29	0.15	–
OPRK1	rs702764	8:53229597	c.843A > G	p.Ala281Ala	0.11	0.24	–
GRIN2B	rs11055581	12:13675725	c.1125 + 20A > G		0.18	0.10	–
COMT	rs4646318	22:19967324	c.466 – 1212G > A		0.07	0.07	–
TPH2	rs4290270	12:72022455	c.1125A > T	p.Ala375Ala	0.64	0.49	–
DRD5	rs6283	4:9783007	c.978C > T	p.Pro326Pro	0.60	0.39	–
GRIN2B	rs7301328	12:13865843	c.366C > G	p.Pro122Pro	0.46	0.44	–
DDC	rs4490786	7:50476616	c.1041 + 8G > A		0.18	0.20	+
COMT	rs4646315	22:19964374	c.615 + 75G > C		0.19	0.17	+

SNPs, single-nucleotide polymorphisms; MAF, minor allele frequency.

[a]*Genome location in GRCh38 assembly.*

[b]*Transcript position of most severe consequence according to the Human Genome Variation Society guidelines (28).*

[c]*MAF in the patients of the ParkWest cohort or 1,000 genomes project.*

[d]*"+" indicated a positive association with ICDs in the ParkWest cohort and "–" indicates a negative association with ICDs in the Park cohort.*

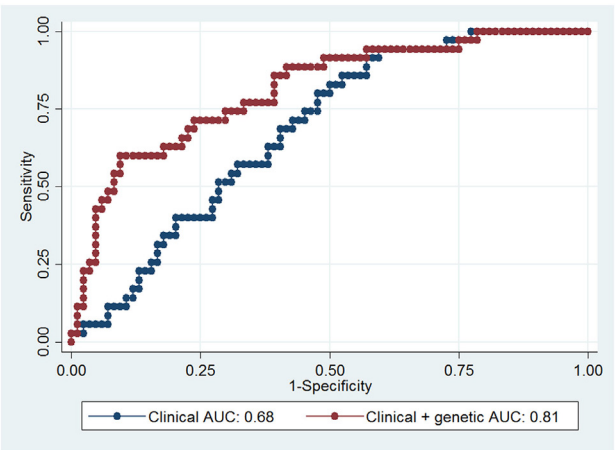

FIGURE 2 | Receiver-operating characteristic (ROC) curves for prediction of impulse control disorders (ICDs). The blue curve was plotted with clinical variables (age and dopamine agonist use), while the red curve was plotted with clinical and the four candidate single-nucleotide polymorphisms. Area under the curve (AUC) for each model is indicated in the figure.

DA use (**Table 3**). Even though DA use is the predominant risk factor for ICDs in patients with PD, DA is still a preferred drug in the early stages of PD due to the diminishing effects of levodopa over time. Therefore, the identification of risk factors that predict ICDs *before exposure* to DA is important to guide clinical practice. Genetic panels have been advocated to be a clinically useful predictor of disease and may be especially important when investigating common polymorphisms, which may have a small effect size and be contingent upon gene-by-environment interactions. Recently, a predictive genetic panel for ICDs in PD has been proposed. Kraemmer and colleagues utilized a panel of 13 candidate polymorphisms, which in concert with clinical variables resulted in an AUC of 76% (95% CI 70–83%) for prediction of ICDs. Our findings support the use of a genetic and clinical model in the prediction of ICDs in PD and also advocate for an approach in which genetic variants are selected based on not only the previously published literature but also using a statistical approach that can handle a gamut of variants. Using such an approach, we have replicated the finding that OPRK1 rs702764 is associated with ICDs when controlling for DA use and identified a novel association between an SNP in *DRD1* and ICDs. In addition, we also identified a sparse clinical–genetic model with a high degree of prediction [AUC of 81% (95% CI 73–90%)] of ICD status, using only four candidate SNPs.

Dopaminergic Pathways

When controlling for DA use and age, we identified two genes with polymorphisms that were independently associated with ICDs (**Table 3**). rs5326 is positioned in the 5' untranslated region (UTR) of the *DRD1* gene, which encodes the dopamine receptor D1, and was associated with an increased risk of ICDs. The D1 receptor is the most abundant dopamine receptor in the central nervous system, particularly expressed in the prefrontal areas, and is considered a modulator of dopaminergic activity (29). Stimulation of D1 receptors by agonists or illicit drugs (like cocaine and amphetamine) has been suggested to trigger punding and hobbyism behaviors in both patients with PD and patients with addiction (30). Previously, polymorphisms in the noncoding regions of *DRD1* (rs4867798 in the 3'-UTR and rs4532 in the 5'-UTR) have been associated with ICDs in a Malaysian PD cohort (8). Furthermore, polymorphisms in *DRD1* have been linked to ICDs, neuropsychiatric disease, problem gambling, addiction, and cognitive functioning in non-PD populations (31, 32). Risk variants of rs5326 have been associated with a decreased *DRD1* expression, a reduced cognitive functioning in both healthy males and bipolar patients, and an increased risk of neuropsychiatric disorders, such as schizophrenia and heroin addiction (33–36).

TABLE 3 | Association between ICD status and a clinical, genetic, and clinical + genetic model.

	Clinical model		Genetic model		Clinical + genetic model	
Factor	**OR (95% CI)**	***p*-Value[a]**	**OR (95% CI)**	***p*-Value[a]**	**OR (95% CI)**	***p*-Value[a]**
(Intercept)	0.6	0.756	0.1	0.099	1.1	0.948
Age	1.0 (0.9–1.0)	0.434	–	–	1.0 (0.9–1.0)	0.234
DA use	4.5 (1.5–13.5)	**0.006**	–	–	7.4 (2.1–26.2)	**0.002**
DRD1 rs5326	–	–	2.9 (1.1–7.6)	**0.026**	6.1 (1.9–19.6)	**0.003**
OPRK1 rs702764	–	–	0.3 (0.1–1.1)	0.072	0.2 (0.1–0.9)	**0.040**
OPRM1 rs677830	–	–	0.5 (0.2–1.2)	0.105	0.5 (0.2–1.3)	0.153
COMT rs4646318	–	–	0.3 (0.1–1.5)	0.140	0.2 (0.1–1.5)	0.117

OR, odds ratio; 95% CI, 95% confidence interval; DA, dopamine agonist; ICD, impulse control disorder.

[a]*Single factor association from stepwise logistic regression with ICD status as dependent variable.*

Significant p-values are highlighted in bold.

Few studies have investigated the *DRD1* gene with regard to ICDs in PD, while considerable effort has been made in identifying polymorphisms in *DRD2* and *DRD3*, mostly due to the established importance of these genes in ICDs in the general population and the high affinity of DAs to these receptors (37, 38). In our data, the rs6277 SNP in *DRD2* was robustly associated with ICDs in the EN analysis, but was not a strong individual predictor of ICD in regression analysis. rs6277 has previously been associated with individual differences in cognitive functioning, reward processing, and impulsivity (39–45). Although the association between ICDs and the rs6277 is novel, it should be noted that this SNP has not been included in previous studies of ICDs in PD. Several other genetic variants in *DRD2*, including rs6277 neighboring SNP rs1800497 (Taq1A), have been studied in PD and found to be associated with ICDs, although not in all studies (6–8, 12).

The D1 and D2 receptors have been suggested to have opposing roles in reward processing, modulating reward and avoidance-based learning, respectively (46). However, the precise interplay between polymorphisms in *DRD1* and *DRD2* and the presentation of ICDs is largely unknown. One theory suggests that polymorphisms in the promoter region of *DRD1* can affect mRNA stability and result in a lower expression of the D1 receptor itself (8, 32). Given the modulating role of the *DRD1* gene in dopaminergic signaling and reward processing, patients with polymorphisms may be prone to a hyperdopaminergic state when exposed to DRT. Similarly, some authors have speculated that polymorphisms in *DRD2*, like the Taq1A polymorphism, may result in modifications in the protein structure of the receptor and ultimately lead to a reduced expression of the D2 receptor (8). This theory is supported by neuroimaging studies that have identified low D2/D3 receptor availability in ventral striatum in patients with ICDs [see (47) for a review]. However, it is still unknown if polymorphisms in these SNPs can result in a reduced expression of D1 and D2 receptors and, if so, if these polymorphisms result in functional dysfunctions, like aberrant reward processing. In order to test these theories, studies at the cellular and molecular levels are needed.

Opioid Pathways

The second polymorphism having an independent association with ICDs was rs702764, located in the kappa-opioid receptor (*OPRK1*) gene. This polymorphism was negatively associated with ICDs in the clinical–genetic model. *OPRK1* encodes the kappa-opioid receptor 1 (KOR1), which is one of four-related opioid receptors in the brain. KOR1 is involved in processes such as feeding behavior, pain management, and addiction. In rodent models, the *OPRK1* gene has been shown to modulate dopaminergic tone, suggesting that *OPRK1* is involved in reward processing (48, 49). Previously, the TC genotype of the *OPRK1* SNP rs702764 has been associated with incident ICDs (12). The neurophysiology between KOR1 and dopamine signaling is not fully understood, but some authors have suggested that the opioid receptors mu1 (MOR1) and KOR1 have opposing roles in the modulation of basal dopaminergic tone in the nucleus accumbens (50–52). Thus, the involvement of the *OPRK1* in modifying the risk of ICDs may be of special interest due to the potential for pharmacological interventions with opioid antagonists. The opioid antagonist naltrexone, which has high affinity to the MOR1 and KOR1, has been deemed efficacious in reducing the severity of other ICDs, such as hoarding and compulsive disorders in the general population. To date, only one trial with PD patients has been published (53). Although naltrexone was not associated with change on the Clinical Global Impression scale, naltrexone was associated with significant changes in QUIP score, arguing that further studies are warranted.

The possible association between polymorphisms in dopamine and opioid receptors and ICDs is interesting, as they are also considered candidate genes for what has been termed "reward deficiency syndrome," a hypothesized neuropsychological state characterized by decreased feelings of satisfaction caused by gene-by-environment interactions (37, 54, 55). This theory, composed of evidence from ICD patients without PD, suggests that polygenic variability, given the right environmental factors, could result in a hypodopaminergic state that causes insensitivity to reward and results in an atypical reward-seeking behavior, as often seen in patients with behavioral or chemical addictions. However, the current models of ICDs in PD suggest that ICDs in PD are a result of a hyperdopaminergic state, caused by exogenous dopamine and possibly exacerbated by frontal cognitive dysfunctions (56, 57). Based on these observations, one might argue that although ICDs in patients with PD and patients without PD are similar in terms of phenotype and share genetic risk profiles, the gene-by-environment profiles and pathophysiology might differ in the two populations.

Strengths and Limitations

There are several limitations that should be considered. First, we have not validated our findings in an external cohort, making generalization or clinical utility of these findings impossible before replication. Despite this, our approach positively identifies variants previously associated with ICDs in the PPMI study (12) and provides new insights into the genetic architecture of ICDs in PD. A second limitation is the use of QUIP as a definition of ICDs. This measure has high sensitivity, but lacks specificity and may inflate the frequency estimates of ICDs. Third, causative relations between the identified genetic polymorphisms and ICDs are difficult to infer based on the current research design. Due to the involvement of DA in ICD development, one might argue that the identified SNPs could increase the risk of DA use, rather than ICDs. We have attempted to meet this challenge by adopting a clinical–genetic model that controls for DA use. Strengths of this study include the use of patients with and without ICDs that are matched in terms of motor impairment and H&Y stage. As argued by Cormier and colleagues, investigations into the genetic architecture of ICDs in PD should include matched groups in terms of motor impairment, H&Y stage, and DA LED (58). Although patients differed in terms of total LED, patients with ICDs were not significantly different than patients without ICDs in terms of DA LED. Lastly, we argue that using an advanced statistical approach that yields robust findings when analyzing a large amount of variants is a major strength of this study.

CONCLUSION

Our findings demonstrate that a genetic panel (DRD1, OPRK1, OPRM1, and COMT) can provide valuable information with regard to the clinical differentiation between PD patients at risk of ICDs and PD patients without risk. Using an advanced statistical approach, we also identified one novel polymorphism associated with ICDs in PD. Although promising, our results need replication in other, larger cohorts.

ETHICS STATEMENT

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway.

AUTHOR CONTRIBUTIONS

AE was involved in the conception, design, statistical analysis, interpretation of data, and writing of the first draft. JG and KP were involved in the conception, design, interpretation of data, and supervision of the study. ID and AU were involved in statistical analysis and interpretation of data. JG, CT, and JC were involved in the analysis of genetic data. GA and OT were involved in the conception and study supervision. All authors made critical contributions and approved this manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fneur.2018.00109/full#supplementary-material.

TABLE S1 | Included genes in regularized regression with elastic net penalization.

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White Matter Tract Alterations in Drug-Naïve Parkinson's Disease Patients With Impulse Control Disorders

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Impulse control disorders (ICDs) are relatively frequent in patients with Parkinson's disease (PD), although it is still unclear whether an underlying pathological process plays a significant role in the development of ICD in PD apart from dopaminergic replacement therapy. In this study, we have investigated alterations of white matter tract in drug-naïve PD patients with ICDs *via* diffusion MRI connectometry. Our results showed that disrupted connectivity in the complex network of dynamic connections between cerebellum, basal ganglia, cortex, and its spinal projections serves as the underlying neuropathology of ICD in PD not interfered with the contribution of dopaminergic replacement therapy. These findings provide the first evidence on involved white matter tracts in the neuropathogenesis of ICD in drug-naïve PD population, supporting the hypothesis that neural disturbances intrinsic to PD may confer an increased risk for ICDs. Future studies are needed to validate the attribution of the impaired corticocerebellar network to impulsivity in PD.

Keywords: impulse control disorders, Parkinson's disease, diffusion MRI, connectometry, drug-naïve

INTRODUCTION

Impulse control disorders (ICDs) are repetitive, excessive, and compulsive behaviors, disrupting a person's function in major areas of life (1). Prevalence of ICDs is higher among patients with Parkinson's disease (PD) compared to normal population affecting 6–15.5% of PD patients while hitting 1.1–1.6% of the general adult population (2). Major ICDs distressing PD patients, include pathological gambling, hypersexuality, compulsive buying, and binge eating (3). In addition, other disorders have been reported in the impulsive–compulsive spectrum in PD patients, such as dopamine dysregulation syndrome, dopamine dependency syndrome, dopamine deficiency syndrome (4), punding (stereotyped, repetitive, aimless behaviors), hobbyism (e.g., artistic endeavors, excessive writing) (5), and excessive hoarding (6).

It is now well established that ICDs can be triggered by dopaminergic drugs (7). Therefore, previous studies have mainly attributed the emergence of ICDs in PD patients to the side effect of dopaminergic replacement therapy. Preliminary comparison studies have shown that ICDs are more common in PD patients on dopamine agonists than healthy controls (HC) (8–11), and untreated *de novo* PD patients manifest these behavioral phenotypes not more than general population (12, 13). However, not all PD patients on dopaminergic drugs suffer ICD. Besides other possible contributing variables, such as younger age, being unmarried, cigarette smoking, male sex, and positive family history (10, 14),

it is not yet clear whether neural disturbances intrinsic to PD may confer an increased risk for ICDs. Although prevalence studies have not reached to this notion, there exist some supportive evidence. Milenkova et al. showed that PD patients without ICD perform more impulsively irrelevant of on/off treatment status (15). In addition, disinhibition failure in treated PD was revealed to be related to cortical atrophy in fronto-striatal areas (16), the key regions of the hallmark mesocorticolimbic network responsible of impulsive–compulsive behaviors (17). Similar phenotypic manifestations and neural underpinnings of ICD in PD and non-PD population are apparent in subsequent studies. Different neuroimaging studies in treated PD patients with ICD have shown various dysfunctions in the brain networks involved in decision making and risk processing, such as disconnection between anterior cingulate cortex and the striatum, increased monoaminergic activity in the medial orbitofrontal cortex, an abnormal resting-state dysfunction of the mesocorticolimbic network, etc (18–23). Consequently, it is suggested that ICD should be considered as a distinct endophenotype in PD, resulting from neuroanatomical abnormalities in impulse control regions of the brain, which would be provoked mainly by dopaminergic replacement therapy (24). However, all these studies have been conducted on PD patients already on dopaminergic treatment, so it is impossible to distinguish these findings as a reflection of treatment (25) or potential biomarkers of ICD in PD. A recent functional MRI study was designed to explore neural markers of upcoming ICD in drug-naïve early PD patients after initiation of the dopaminergic therapy. The results demonstrate that altered connectivity in salience, executive, and default-mode networks in baseline visits predict the development of ICD triggered by dopaminergic treatment (26).

In order to examine whether an underlying neuropathological process apart from medication-related effects plays a remarkable role in the establishment of ICD in PD, we investigated alterations of white matter tract in drug-naïve early PD patients with ICDs (PD-ICD) compared to PD patients without ICD (PD-nICD) and healthy controls (HC) *via* diffusion MRI connectometry.

MATERIALS AND METHODS

Participants

Participants involved in this research were recruited from Parkinson's Progression Markers Initiative (PPMI, http://www.ppmi-info.org/) (27). The study was approved by the institutional review board of all participating sites. Written informed consent was obtained from all participants before study enrollment. The study was performed in accordance with relevant guidelines and regulations. The participants' PD status was confirmed by Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the loss of dopaminergic neurons was observed on DAT scans. Patients were tested and confirmed negative for any neurological disorders apart from PD. Subjects were only excluded if imaging failed specific quality control criteria. 113 cases divided into three groups, (21 PD-ICD, 68 PD-nICD, and 23 HC) were recruited from baseline available diffusion imaging data from PPMI project. ICD was assessed using the Questionnaire for Impulsive–Compulsive Disorders (QUIP), which is a validated screening tool in PD patients (28). Participants in each category were matched for age, sex, and years of education. PD patients of two groups did not differ in terms of disease duration, motor severity (total UPDRS and Hoehn and Yahr stage), motor subtype (tremor versus postural instability gait difficulty), cognitive status (Montreal Cognitive Assessment), and other non-motor symptoms (REM sleep behavior disorder, excessive daytime sleepiness, and olfaction dysfunction). Although neither group showed depressive symptoms based on geriatric depression scale (29), nICD group showed significantly higher scores than ICD group. However, in the following connectometry analysis, PD-nICD did not show lower connectivity in any white matter pathways compared to PD-ICD. PD patients differed from HC in motor impairment and also only in olfactory dysfunction and depressive symptoms among all non-motor symptoms surveyed. Demographic and clinical data are represented in **Table 1**.

Data Acquisition

Data used in the preparation of this article were obtained from the PPMI database (www.ppmi-info.org/data) (27). This dataset was acquired on a 3 T Siemens scanner, producing 64 diffusion MRI (repetition time = 7,748 MS, echo time = 86 ms; voxel size: 2.0 mm × 2.0 mm × 2.0 mm; field of view = 224 mm × 224 mm) at $b = 1{,}000$ s/mm^2 and one b0 image along with a 3D T1-weighted structural scan (repetition time = 8.2 ms, echo time = 3.7 ms; flip angle = 8°, voxel size: 1.0 mm × 1.0 mm × 1.0 mm; field of view = 240 mm, acquisition matrix = 240 × 240).

Diffusion MRI Processing

The diffusion MRI data were corrected for subject motion and eddy current distortions using Explore DTI toolbox, which reorients the B-matrix in the stage of realigning the images to preserve the orientational information correctly (30). Orienting B-matrix is a simple, but indeed essential step in avoiding bias in diffusion measures especially in PD patients who are susceptible to move during the scans (31). We also performed quality control analysis on the subject's signals based on the goodness-of-fit value given in q-space diffeomorphic reconstruction (QSDR) of fibers (32). Each QSDR reconstruction file has a goodness-of-fit value quantified by R2. For example, an R82 indicates a goodness-of-fit between of the subject and template of total 0.82. We excluded cases in which the R2 value did not reach a threshold of 0.6 otherwise.

Between Groups Analysis

The diffusion data were reconstructed in the MNI space using QSDR to obtain the spin distribution function (SDF), to detect the differences between groups (PD-ICD, PD-nICD, and HC).

Connectometry (33) is a novel approach in the analysis of diffusion MRI signals that simply tracks the difference of white matter tracts between groups, or correlation of white matter fibers with a variable of interest. Connectometry approach extracts the SDF in a given fiber orientation, as a measure of water density along that direction. There is a multitude of diffusion indices derived from spin density, i.e., SDF, quantitative anisotropy (QA) being one of them. QA of each fiber orientation gives the peak value of water

TABLE 1 | Demographic information and comparison of clinical outcomes between HC and patients with PD.

Characteristic	HC (n = 23)	PD-ICD (n = 21)	PD-nICD (n = 68)	*P* Value	*Post hoc P* value (PD groups)
Age, mean (SD) [95% CI], years	58.3 (10.5) [53.7–62.8]	57.7 (9.8) [53.3–62.2]	59.1 (9.5) [56.9–61.5]	0.801[a]	0.829
Female/male, No. (% male)	11/12 (52.2)	7/14 (66.6)	24/44 (64.7)	0.511[b]	0.869
Left-handed/right-handed, No. (% right-handed)[x]	3/19 (82.6)	1/19 (90.5)	7/58 (85.3)	0.925[b]	0.741
Education, mean (SD) [95% CI], years	14.6 (2.8) [13.4–15.8]	14.6 (2.7) [13.4–15.8]	15.4 (2.9) [14.6–16.0]	0.374[c]	0.307
Disease duration, mean (SD) [95% CI], years	…	10.4 (10.5) [5.6–15.1]	5.8 (5.3) [4.6–7.1]	0.272[d]	…
Hoehn and Yahr stage, mean (SD)	…	1.6 (0.5)	1.6 (0.5)	0.891[b]	…
Tremor score, mean (SD)	0.063 (0.84)	0.446 (0.300)	0.458 (0.282)	<0.001[c,e]	0.631
PIGD score, mean (SD)	0.052 (0.108)	0.229 (0.192)	0232 (0.164)	<0.001[c,e]	0.702
MDS-UPDRS part I score, mean (SD)	2.8 (1.6)	6.2 (3.1)	4.4 (3.2)	<0.001[c,e]	0.007
MDS-UPDRS part II score, mean (SD)	2.2 (2.7)	5.1 (4.5)	5.2 (5.0)	0.008[c,e]	0.880
MDS-UPDRS part III score, mean (SD)	0.6 (1.2)	21.1 (8.5)	21.4 (8.8)	<0.001[c,e]	0.973
MDS-UPDRS total score, mean (SD)	5.6 (3.6)	32.4 (10.7)	31.0 (11.2)	<0.001[c,e]	0.492
MoCA score, mean (SD)	28.4 (1.1)	27.2 (2.0)	27.6 (2.0)	0.196[c]	0.450
GDS score, mean (SD)	4.7 (1.1)	3.8 (1.4)	4.6 (1.2)	0.046[c]	0.033
UPSIT score, mean (SD)	33.5 (4.6)	22.1 (8.1)	23.2 (8.4)	<0.001[c,e]	0.474
RBD score, mean (SD)	3.2 (2.3)	4.7 (3.2)	3.8 (2.4)	0.357	0.342
ESS score, mean (SD)	6.2 (4.3)	6.8 (3.3)	6.1 (3.3)	0.739	0.478
Type of ICD					
Hypersexuality		1 (4.5%)			
Compulsive buying		1 (4.5%)			
Compulsive eating		8 (36%)			
Hobbies		2 (9%)			
Punding		5 (23.5%)			
Walking or Driving + hobbies		2 (9%)			
Compulsive eating + punding		1 (4.5%)			
Compulsive buying + hobbies		1 (4.5%)			
Compulsive buying + eating + punding		1 (4.5%)			

HC, healthy controls; PD, Parkinson disease; PIGD, postural instability and gait difficulty; MDS-UPDRS, movement disorder society-sponsored revision of the unified Parkinson's disease rating scale; MoCA, montreal cognitive assessment; GDS, geriatric depression scale; UPSIT, University of Pennsylvania smell identification test; ESS, epworth sleepiness scale; RBD, REM sleep behavior disorder.

[a]*Based on one-way ANOVA.*

[b]*Based on χ^2 test.*

[c]*Based on Kruskal–Wallis test.*

[d]*Based on Mann–Whitney U test.*

[e]*Post hoc analysis showed significant differences between HC and two PD groups.*

[x]*Others were mixed-handed.*

density in that direction. We used diffusion MRI connectometry to identify white matter tracts in which QA was significantly different between three groups. Resulting uncorrected output was corrected for multiple comparisons by false discovery rate (FDR). A deterministic fiber tracking algorithm (34) was conducted along the core pathway of the fiber bundle to connect the selected local connectomes. Tracts with QA > 0.1, angle threshold lesser than 40°, and tract length greater than 40 mm were included. To estimate the FDR, a total of 2,000 randomized permutation was applied to the group label to obtain the null distribution of the track length. Permutation testing allows for estimating and correcting the FDR of type-I error inflation due to multiple comparisons. The analysis was conducted using publicly available software DSI Studio (http://dsi-studio.labsolver.org).

Statistical Analysis

Demographic and clinical data were analysed using SPSS version 22 (IBM Corp., Armonk, NY, USA). *P* values less than 0.05 were considered to be statistically significant. Pearson's chi-square was used to assess nominal variables across groups. Mann–Whitney *U* test was used to assess differences between two groups, and Kruskal–Wallis test or one-way ANOVA was used for multiple comparisons for three groups.

RESULTS

PD-ICD Patients Versus PD-nICD Patients

The group differences between PD-ICD patients and PD-nICD are shown in **Figure 1**. Compared with PD-nICD patients, PD-ICD patients showed decreased connectivity in the left and right cortico-thalamic tract, the left and right cortico-pontine tract, the left and right corticospinal tract (CST), the left and right superior cerebellar peduncle (SCP), and the left and right middle cerebellar peduncle (MCP) (FDR = 0.008).

PD-nICD Versus HC

The group differences between PD-nICD patients and HC are shown in **Figure 2**. The differences were that connectivity in HC was higher than that in PD-nICD in the left inferior longitudinal fasciculus (ILF), the left and right CST, and the left and right cingulum (FDR = 0.001).

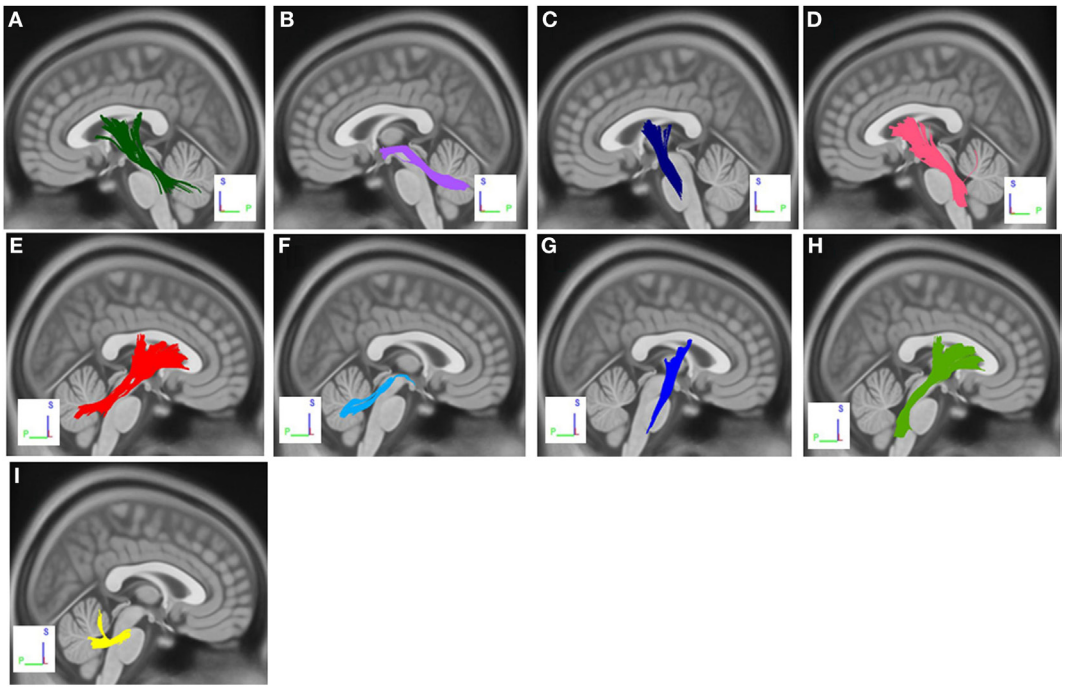

FIGURE 1 | White matter pathways with significantly reduced anisotropy in PD-ICD patients compared to Parkinson's disease-nICD [false discovery rate = 0.008]. **(A)** Left cortico-thalamic tract, **(B)** left superior cerebellar peduncle (SCP), **(C)** left corticospinal tract (CST), **(D)** left cortico-pontine tract, **(E)** right cortico-thalamic tract, **(F)** right SCP, **(G)** right CST, **(H)** right cortico-pontine tract, and **(I)** middle cerebellar peduncle. The results are overlaid on ICBM152 (mni_icbm152_t1) from the McConnell Brain Imaging Centre using DSI-STUDIO software.

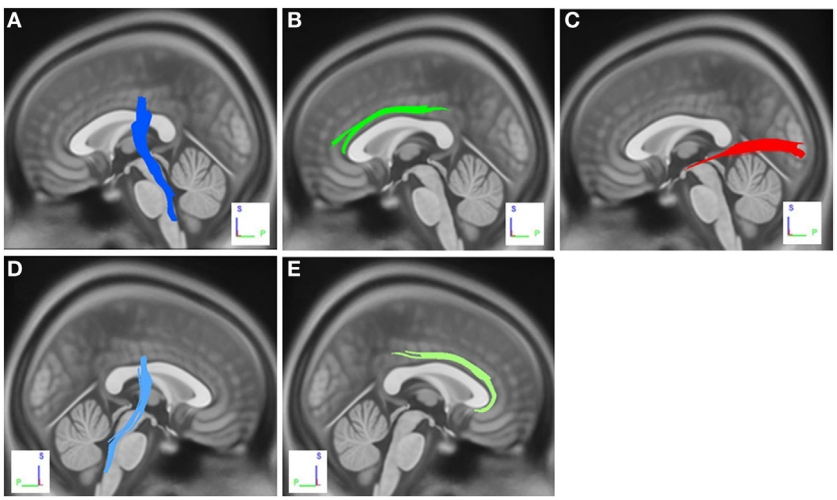

FIGURE 2 | White matter pathways with significantly reduced anisotropy in Parkinson's disease-nICD compared to healthy controls (false discovery rate = 0.001). **(A)** Left corticospinal tract, **(B)** left cingulum, **(C)** left inferior longitudinal fasciculus, **(D)** right corticospinal tract, and **(E)** right cingulum. The results are overlaid on ICBM152 (mni_icbm152_t1) from the McConnell Brain Imaging Centre using DSI-STUDIO software.

PD-ICD Patients Versus HC

The differences were that connectivity in HC was higher than that in PD-ICD patients in the left and right ILF, genu and body of the corpus callosum (CC), the left and right CST, the left SCP, and the left and right cingulum (FDR = 0.002).

DISCUSSION

This study revealed that compared to HC, drug-naïve PD patients have microstructural changes in the CST, ILF, and cingulum. PD-ICD patients also showed additional pathways, i.e., genu and

body of CC and SCP compared to HC. These tracts are commonly presented in the literature in relation to various motor and non-motor symptoms of PD, such as olfaction dysfunction, mood and sleep dysregulations, and cognitive decline [reviewed in Hall et al. (35)].

Neural contributions of impulsivity in PD have recently grabbed attention, and some studies have investigated white tract alterations in PD patients with ICDs. In a DTI study, Canu et al. compared white matter microstructure of PD patients with and without punding, at the time when they were on dopaminergic medication. They showed that punding in PD patients is associated with the disconnection between midbrain, limbic, and white matter tracts projecting to the frontal cortex (36). Yoo et al. also indicated some structural alterations in PD-ICD patients, especially in the CC (22). Another study using DTI and resting-state fMRI showed that PD-ICD patients had more severe involvement of frontal, mesolimbic, and motor circuits (23). These results suggest that ICD might be the result of a disconnection between sensorimotor, associative, and cognitive networks in PD patients (23).

fMRI studies showed that ventral striatum and anterior cingulate might be associated with risk and reward-related behaviors and decision making (37, 38). In a risk-taking task, PD-ICD patients showed decreased anterior cingulate and orbitofrontal cortex activity in comparison to PD-nICD. Moreover, pharmacological manipulation (using dopamine agonists) resulted in decreased ventral striatal activity in PD-ICD group, compared with PD-nICD group (38). An experiment with gambling-related visual cue showed that in PD patients with pathological gambling, there is altered activity in the ventral striatum, anterior cingulate cortex, and frontal gyri (39). Resting-state fMRI studies also indicated a functional disconnection between a striatal associative area (the left putamen) and cortical associative (inferior temporal) and limbic regions (anterior cingulate) in PD patients with ICD compared to PD-nICD group (40).

Regarding gray matter (GM), studies are not consistent. Some studies showed that PD patients with ICD had a reduction in cortical thickness of fronto-striatal regions when compared to other PD patients (41). Moreover, Biundo et al. indicated that the level of GM alterations is associated with the severity of ICDs in PD patients (42). Interestingly, Tessitore et al. had completely different results. They indicated that PD-ICD patients have thicker orbitofrontal and anterior cingulate cortices, in comparison to PD-nICD. They also showed that these abnormalities were positively correlated with ICD severity (26). Finally, another study showed relatively preserved GM in PD patients with ICD when compared to PD patients without such disorder (43).

Most studies have compared brain alterations of PD patients with and without ICD at the time they were on dopaminergic medication (44). However, evidence from our study on white matter microstructural alterations in drug-naïve PD patients supports the hypothesis that these abnormalities may be due to neurodegenerative processes intrinsic to PD. These changes might be an independent risk factor for developing ICDs in PD patients and may interact with chronic treatment with dopamine agonists. Other studies have shown that decreased dopamine transporter availability might predict the risk of future ICD behaviors in drug-naïve PD patients who are going to take dopamine replacement therapy in the future (45). Variend et al. also showed that lower level of dopamine transporters in striatal regions might predate the incidence of ICDs in PD patients after the beginning of dopaminergic treatment and may be an independent risk factor for punding behaviors (46). These results highlight the fact that PD itself may play a significant role in developing ICDs in parkinsonian patients.

Cerebellum participates in higher order functions of cognition and emotion by means of bidirectional communications to limbic and paralimbic regions and neocortex, especially prefrontal and posterior parietal areas (47–50). Several behavioral disorders such as impulsive actions are reported following cerebro-cerebellar circuitry damage (51, 52). Disruption of the parieto-ponto-cerebellar loop through lower connectivity in MCP and cerebello-basal ganglia-thalamo-cortical loop *via* lower connectivity in SCP was demonstrated in relation to ICD in our cohort of PD patients. These loops process information in cognitive, emotional, and behavioral domains. In this complicated network, cerebellum, cortex, and basal ganglia have integrated roles in reinforcement learning anchored to reward predictions of dopamine signals in the striatum (53). The interplay between these structures underlies the complex motor and cognitive functions. Evidence regarding disruption of this system is multitude with respect to motor and cognitive features of PD (53). In particular, the cerebellum is strongly connected to the striatum *via* output projections of SCP to the thalamus (54). Since striatum as a part of mesocorticolimbic network plays the central role in the pathology of misbehaviors such as addiction and impulsion–compulsion linked to reward learning (17), it seems that cerebellar corroboration in this scenario is often neglected. Although the vast network of cerebro-cerebellar communications is often assumed to be confined to multi-synaptic pathways by means of pontine and thalamic nuclei, simultaneous activation of corticospinal fibers plays a definitive role in relaying feedbacks to the learning processes (53). The contribution of the multi-synaptic cortico-cerebellar network as underlying neuropathology of ICD in early PD without the interference of dopaminergic drugs is a novel and promising result that should be more addressed in future studies.

Some methodological limitations should be considered when interpreting our results, such as small sample size of participants, no-follow up assessments, and not to take into account other risk factors attributed to ICD such as previous histories of addiction and family histories of ICD. Although PD-ICD and PD-nICD patients did not differ in terms of motor and non-motor symptoms, PD patients showed worse scores in screening tests of olfaction function and depressive symptoms compared to healthy controls. This may account for observed alterations in neural connectivity comparing PD-ICD with HC. Future studies are needed to validate if the presented white matter tracts by this preliminary study serve as possible neural markers of ICD in PD.

Measurement of the correlation of severity of ICD symptoms with MRI parameters will add valuable information.

In conclusion, this is the first study that investigates the alteration of white matter tracts relative to impulsive–compulsive behaviors in drug-naïve PD patients. Our results showed that disrupted connectivity in the complex network of dynamic connections between cerebellum, basal ganglia, cortex, and its spinal projections serves as the underlying neuropathology of ICD in PD not interfered with the contribution of dopaminergic replacement therapy. Association of these novel pathways provides a potential explanation of why dopamine agonists can lead to an unconscious bias toward risk in some individuals suffering PD. Further studies can evaluate this hypothesis and bring about more evidence, to diagnose ICDs in early stages of PD.

ETHICS STATEMENT

All procedures performed here, including human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. *Informed consent:* informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

MZ, AA-G, FS and MA contributed to the conception and design of the study. MZ, MH, FS, and MA contributed to data collection and analysis. MZ, AA-G, FS, and MA contributed to writing the manuscript.

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Impulsivity in Parkinson's Disease Is Associated With Alterations in Affective and Sensorimotor Striatal Networks

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A subset of patients with Parkinson's disease (PD) experiences problems with impulse control, characterized by a loss of voluntary control over impulses, drives, or temptations regarding excessive hedonic behavior. The present study aimed to better understand the neural basis of such impulse control disorders (ICDs) in PD. We collected resting-state functional connectivity and structural MRI data from 21 PD patients with ICDs and 30 patients without such disorders. To assess impulsivity, all patients completed the Barratt Impulsiveness Scale and performed an information-gathering task. MRI results demonstrated substantial differences in neural characteristics between PD patients with and without ICDs. Results showed that impulsivity was linked to alterations in affective basal ganglia circuitries. Specifically, reduced frontal–striatal connectivity and GPe volume were associated with more impulsivity. We suggest that these changes affect decision making and result in a preference for risky or inappropriate actions. Results further showed that impulsivity was linked to alterations in sensorimotor striatal networks. Enhanced connectivity within this network and larger putamen volume were associated with more impulsivity. We propose that these changes affect sensorimotor processing such that patients have a greater propensity to act. Our findings suggest that the two mechanisms jointly contribute to impulsive behaviors in PD.

Keywords: Parkinson's disease, impulsivity, basal ganglia, affective striatum, sensorimotor striatum

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INTRODUCTION

Approximately 6–15.5% of Parkinson's disease (PD) patients experience problems with impulse control (1–3). Impulse control disorders (ICDs) are characterized by a loss of voluntary control over impulses, drives, or temptations to engage in excessive hedonic behavior that interferes with daily functioning and is harmful to the patient and/or others. The most common ICDs in PD are pathological gambling, hypersexual behavior, compulsive buying, and compulsive eating [e.g., Ref. (2, 3)]. There are indications that dopamine agonists are linked to ICDs in PD [e.g., Ref. (2, 4–6)], although not all studies support this claim (7). Understanding the neural bases of ICDs in PD could provide biomarkers for tracking ICD risk and recovery.

PD patients with ICDs compared to those without have a reduced reward circuitry functional connectivity between the striatum and anterior cingulate cortex (ACC) (8, 9). Atypical

functioning within this circuitry has also been associated with addictive behaviors and impaired inhibitory control [for a review, see Ref. (10)]. While some studies found no structural gray matter (GM) differences between PD patients with and without ICDs (11, 12), another observed a reduced GM volume in orbitofrontal cortex (OFC) of PD patients with pathological gambling compared to those without (13). Also, compared to healthy participants, PD patients with pathological gambling showed a smaller GM volume in the OFC and ACC, among other structures. The OFC is also part of the reward circuitry and involved in detecting, encoding, and updating the reward value of events, thereby influencing future decision making (14). Interestingly, the studies reporting no GM differences did find cortical thickness increases in the ACC and OFC in PD patients with ICDs compared to those without (11, 12), which were positively correlated with ICD severity (12). These discrepancies between GM volume and cortical thickness measures are difficult to interpret [cf Ref. (15)]. This difference aside, the literature indicates that ICDs in PD are associated with neurostructural and functional reward circuitry changes.

At the behavioral level, PD patients with ICDs gather less information before making decisions than patients without ICDs (16). Previous studies demonstrated that healthy participants who gathered more information before decision making engaged a parietal–frontal network more strongly (17) and had larger GM volumes in areas within this network (18) than participants who gathered less information. The overlap between anomalies in functional connectivity and structural brain properties in PD patients with ICDs on the one hand, and networks and structures involved in information gathering and decision making in healthy participants on the other hand suggests that differences in functional connectivity and structural properties between PD patients with and without ICDs may be associated with behavioral differences in impulsivity. To date, investigations of the neural correlates of impulsivity in PD have primarily focused on reward and decision-making circuitries, with less focus on sensorimotor striatal pathways. However, alterations in sensorimotor pathways likely contribute to impulsivity too, as cerebellar volume has been linked to impulsive tendencies in psychiatric patients (19) and abnormal premotor cortical connectivity to impulsivity in juveniles (20). Therefore, the present study aimed to investigate differences in both affective and sensorimotor striatal circuitries between PD patients with and without ICDS and their association with impulsive behaviors. We had two groups of PD patients (with vs. without ICDs) perform an information-gathering task in which they chose between evidence-seeking actions and actions leading to potential rewards or losses (16, 17). Using such a well-characterized task to study the neural bases of ICDs in PD is a novel approach, as previous studies have compared only brain indices of PD patients with and without ICDs and did not include behavioral assessments (other than scores on impulsivity questionnaires). We collected resting-state functional connectivity MRI (rs-fcMRI) and structural MRI data to (1) investigate structural and resting-state functional connectivity differences between PD patients with and without ICDs, and (II) evaluate whether individual differences in these neural measures were associated with behavioral impulsivity (i.e., information-gathering task performance and impulsiveness questionnaire score; see Materials and Methods). In line with previous studies, we expected PD patients with ICD to exhibit a reduced corticostriatal connectivity (especially between striatum and ACC). Moreover, we hypothesized that less information gathering and higher impulsivity scores would be associated with reduced network connectivity strength and smaller GM volume in affective striatum but increases in sensorimotor striatum.

MATERIALS AND METHODS

Participants

Fifty-one mild to moderate-stage PD patients [aged 40–74 years, Hoehn and Yahr stages 1–3 (21)] participated in the study. Using the Questionnaire for Impulsive–Compulsive Disorders in PD [QUIP (22)], we classified 21 patients as having ICD (ICD+ group) and 30 as not (ICD− group). The ICD+ group indicated pathologic gambling ($n = 1$), compulsive sexual behaviors ($n = 9$), compulsive buying ($n = 7$), compulsive eating ($n = 11$), or other compulsive behaviors ($n = 6$; nine patients indicated a combination of two or more behaviors). All patients provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the medical institutional review board of the University of Michigan.

Experimental Task and Procedure

Patients were tested while their symptoms were being well controlled by dopamine replacement medication. The Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale was used to assess motor symptoms. Patients completed the Barratt Impulsiveness Scale (BIS) questionnaire, for which we determined a total score as well as separate scores for the three factors: attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness (23, 24). We also used the Montreal Cognitive Assessment (MoCA) (25) and the National Adult Reading Test-Revised (NART-R) (26) to assess patients' global cognitive abilities and verbal intelligence, respectively. After completing these assessments, patients performed the "beads task," which has been used in previous investigations on evidence-seeking and impulsivity in both healthy and clinical populations [e.g., Ref. (16–18, 27)]. Participants were instructed to imagine two urns filled with blue and green beads, with one (the "blue urn") containing mostly blue beads and the other (the "green urn") containing mostly green beads. They were informed that in each trial, they would view a sequence of beads drawn from one of the urns and that they had to infer from which "hidden urn" each sequence of bead colors was drawn. They were allowed to practice the task before they performed it in the scanner.

As illustrated in **Figure 1**, each sequence began with an instruction screen (2.5 s) showing the proportion of bead colors in the two urns (either 80/20 or 60/40 color split) and the cost for an incorrect urn choice (either \$10 or \$0). Participants then viewed a bead color (2.5 s) followed by a response prompt (3 s), at which point they decided either to choose an urn or to draw another bead (maximum of nine draw choices per sequence).

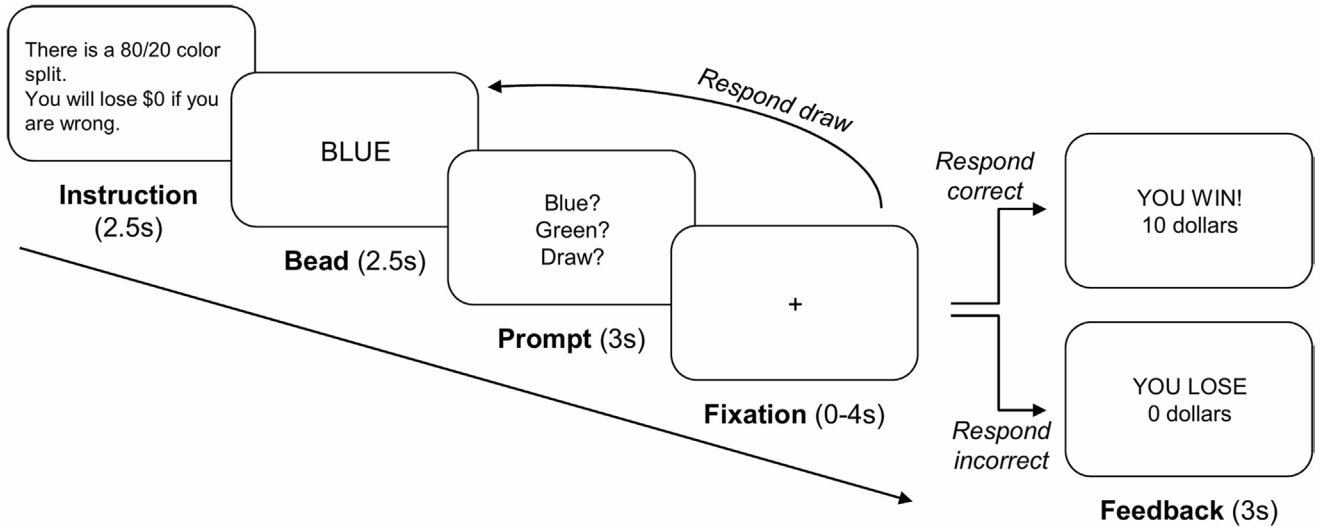

FIGURE 1 | Overview of the beads task. Each sequence started with an instruction screen showing the proportion of bead colors in the two urns (80/20 or 60/40 color split) and the cost for an incorrect urn choice ($10 or $0). Participants then viewed a bead color and indicated that they either chose to draw another bead ($0.25 cost) or chose an urn. Upon a draw choice, another bead of the sequence was presented. Upon an urn choice, a feedback screen was presented, which displayed whether the participant chose the correct or incorrect urn and how much money they won or lost during that sequence.

To reduce working memory demands, we displayed the previously drawn beads' color as dots on the screen. After a 0- to 4-s randomly jittered fixation period, the next stimulus was either a new bead color or a feedback screen (3 s), depending on the participant's response. The feedback screen informed participants whether they were correct or incorrect and how much money they won or lost during that sequence. Participants completed six runs of 16 bead sequences, with four sequences in each cell of a 2 × 2 factorial design with bead probability (80/20 or 60/40) and loss ($10 or $0) as repeated measure factors. Participants were informed that they would accumulate wins and losses throughout the task. They always incurred a $0.25 cost for each draw choice and won $10 for each correct urn choice. After the experiment, participants were paid 5% of the total amount that they won (M = $29.03, SE = $0.79).

Stimulus presentation, timing, and behavioral data registration were controlled by Cogent software (http://www.vislab.ucl.ac.uk/cogent.php) running in the Matlab environment. Patients responded *via* an MRI-compatible claw, with separate buttons designated for choosing the blue urn, the green urn, or drawing another bead. For each patient, structural and rs-fcMRI scans were obtained prior to completion of the task in the scanner; task-based fMRI results will be presented elsewhere. All patients performed the experimental task and other assessments in a single test session which lasted about 90–120 min.

MRI Acquisition

Resting-state functional connectivity images were acquired on a 3-T GE Signa MRI scanner using a gradient-echo T2*-weighted gradient-echo pulse sequence. The field of view (FOV) was 220 mm × 220 mm with a 64 × 64 × 43 matrix resulting in an in-plane voxel resolution of 3.44 mm × 3.44 mm × 3.00 mm (for two subjects, the matrix was 64 × 64 × 35 and the voxel size was 3.44 mm × 3.44 mm × 3.50 mm.). The repeat time to accomplish a full volume (TR) was 2,000 ms, the echo time (TE) was 30 ms, and the flip angle was 90°. The slices were collected in an interleaved multi-slice mode (no slice gap), covering the whole brain (scan duration of ~8 min). Structural images were acquired using a T1-weighted spin-echo pulse sequence (TR = 540 ms, TE = 2.32 ms, flip angle = 15°) with an FOV of 220 mm × 220 mm and with a 256 × 256 × 124 matrix, resulting in an in-plane voxel resolution of 1.0156 mm × 1.0156 mm × 1.20 mm (scan duration of ~10 min).

MRI Data Processing

We used Statistical Parametric Mapping software version 12 (SPM12; Wellcome Trust Center for Neuroimaging) running in the Matlab R2015b environment (Mathworks, Sherborn, MA, USA) for slice timing and motion correction. Slice timing correction to the first slice was performed using SPM's sinc interpolation. Head motion correction was performed by co-registering each image to the mean EPI image. To examine outliers due to spiking and motion, and additionally to estimate Euclidian motion, we used the Artifact Detection Tool software package [ART (web.mit.edu/swg/software.htm)]. None of the patients showed head motion (translation and rotation about each of the axes) greater than 3 mm during the experiment.

Functional connectivity MRI data were normalized using Advanced Normalization Tools v2.1.0 rc3 [ANTs (28)], following a multistep approach in which we (1) preprocessed the T1-weighted image, (2) calculated the warp parameters from the T1-weighted image to an MNI152 template, and (3) applied these warp parameters to the fcMRI data. First, for preprocessing image intensity, non-uniformity correction was estimated and applied to all T1 images within a subject-specific brain mask using N4ITK (29). The brain masks were created using FSL's

Brain Extraction Tool (30) with robust brain center estimation and a fractional intensity threshold of 0.2. For each patient, we co-registered the structural preprocessed T1-weighted image to the mean functional image. Because the side of the body that was predominantly affected by the disease differed among patients, we flipped the images of subjects with left-sided motor symptom dominance along the *x*-axis (i.e., left–right direction) prior to normalization (10 patients in the ICD+ and 11 patients in the ICD− group). This ensured that in our analyses, the left hemisphere in all images reflects the patients' most disease-affected hemisphere. Next, we spatially normalized the co-registered skull-stripped T1 images to the MNI152 template (31). The warp from the single subject T1 to the MNI152 template was calculated using ANTs with cross-correlation as the similarity metric and symmetric normalization as the transformation model (28). Finally, the resulting normalization parameters were applied to the patient's functional images, which were then spatially smoothed with a Gaussian kernel with a sigma of 3.4 mm (i.e., 8-mm FWHM) using FMRIB Software Library (32).

Behavioral Analyses

We used the number of draw choices and the proportion of correct urn choices as performance measures for the beads task [cf Ref. (16, 17)]. We performed a mixed ANOVA on each measure with Group (2; ICD+ vs. ICD−) as a between-subject variable and probability (2; 80/20 vs. 60/40) and loss (2; $10 vs. $0) as within-subject variables. Shapiro–Wilk tests confirmed that the data of both measures were normally distributed in each group (p's > 0.11).

Functional Connectivity Analyses

We used the CONN toolbox [version 16.a (33)] with default settings (34) to perform our rs-fcMRI analyses. Residual head motion realignment parameters and motion outliers as determined during preprocessing by the ART toolbox and signals from the white matter and cerebrospinal fluid were regressed out during the calculation of functional connectivity maps. For the first-level analysis, we used six regions of interest (ROIs) to examine differences in functional connectivity between the ICD+ and ICD− groups. We identified five basal ganglia ROIs from the Basal Ganglia Human Area Template [BGHAT (35)]: the left putamen, caudate, external and internal portions of the globus pallidus, and subthalamic nucleus. Because a previous study reported that activation in parietal cortex during making of an urn choice is associated with individual differences in the average number of draws (17), we also included a parietal ROI of 4-mm radius around the peak coordinates (40, −40, 40). The CONN toolbox determined the mean time series of each ROI. Next, the software calculated Pearson's correlation coefficients between this mean time series of each ROI and the time series of each remaining voxel.

For the second-level analysis, performed in SPM12, a two-sample *t*-test was applied to evaluate group differences. We used a one-sample *t*-test to examine associations between behavioral performance and connectivity between the ROIs and the rest of the brain. We entered the average number of draw choices and the BIS score (total score as well as scores on each of the three factors) as predictors and included age as a covariate of no interest. All effects were evaluated using a statistical threshold of $p < 0.0005$ (uncorrected for multiple comparisons) and a minimum cluster size of 10 voxels; a few effects were significant at a family-wise error (FWE) corrected $p < 0.05$, as indicated in the tables and text. We used the Harvard-Oxford Cortical and Subcortical Structural Atlases (36) and the probabilistic cerebellar atlas (37) for anatomical localization.

Structural Analyses

We used voxel-based morphometry (toolbox in SPM5) to evaluate group differences in structural properties and associations with behavior. Each subject's SPGR scan was segmented into GM, WM, CSF, and other nonbrain partitions and warped to MNI space. Warped images were modulated to allow for tests of GM volumes and were then smoothed using a 10-mm FWHM Gaussian kernel. To evaluate differences in striatal GM volume between the ICD+ and ICD− groups, we performed a two-sample *t*-test within the volumes of the bilateral summed BGHAT ROIs. In addition, we examined associations between GM volume and the average number of draw choices and the BIS score; age was included as a covariate of no interest. Tests were evaluated using a cluster size threshold of 10 voxels and $p < 0.005$ (uncorrected); again, a few effects were significant at FWE-corrected $p < 0.05$ as reported in the text and tables.

RESULTS

Table 1 shows the group demographic and clinical characteristics. The groups did not differ significantly on age, gender, age of PD onset, disease duration, UPDRS motor subscale scores, or

TABLE 1 | Overview of the demographic and clinical characteristics of the impulse control disorder (ICD)+ and ICD− groups (mean ± SD).

Measure	PD ICD+	PD ICD−	Group difference
# subjects	21	30	
Age (years)	60 ± 5	62 ± 8	$t(49) = -3.92$, $p = 0.69$
Gender	7 F/14 M	11 F/19 M	$\chi^2(1) = 0.06$, $p = 0.80$
Handedness	3 L/18 R	4 L/26 R	$\chi^2(1) = 0.01$, $p = 0.92$
Age of PD onset (years)[a]	55.9 ± 6.2	58.1 ± 8.4	$t(47) = -0.99$, $p = 0.32$
Disease duration (months)[a]	57.3 ± 30.7	44.2 ± 37.7	$t(47) = 1.31$, $p = 0.19$
LED (mg)	561 ± 322	486 ± 332	$t(49) = 0.80$, $p = 0.42$
UPDRS motor	25.95 ± 9.92	25.33 ± 9.49	$t(49) = 0.22$, $p = 0.82$
BIS total score	61.90 ± 15.16	54.10 ± 8.85	$t(49) = 2.32$, $p = 0.025$
Attentional impulsiveness	16.33 ± 5.25	14.00 ± 3.47	$t(49) = 1.91$, $p = 0.062$
Motor impulsiveness	21.90 ± 4.93	19.10 ± 2.99	$t(49) = 2.53$, $p = 0.015$
Non-planning impulsiveness	23.67 ± 6.39	21.00 ± 4.55	$t(49) = 1.74$, $p = 0.088$
MoCA	27.95 ± 1.59	27.33 ± 1.54	$t(49) = 1.39$, $p = 0.17$
NART-R (FSIQ score)	112.49 ± 7.58	112.25 ± 5.56	$t(49) = 0.13$, $p = 0.89$

[a]*Data from two patients in the ICD− group were missing.*

PD, Parkinson's disease; BIS, Barratt Impulsiveness Scale; MoCA, Montreal Cognitive Assessment; NART-R, National Adult Reading Test-Revised; FSIQ, Full Scale IQ; LED, Levodopa Equivalent Dose; UPDRS, Unified Parkinson's Disease Rating Scale.

levodopa equivalent dose ($ps > 0.19$). The ICD+ group scored significantly higher on the BIS questionnaire than the ICD− group, $t(49) = 2.32$, $p = 0.025$. The BIS scores are consistent with those previously reported for PD patients with and without impulsivity (38), and scores of the ICD− group fall within the normal limits (24). When differentiating between the different BIS factors, we observed that the ICD groups mainly differed on motor impulsiveness and less so on attentional and non-planning impulsiveness (see **Table 1**). MoCA scores ranged from 24 to 30 and did not differ significantly between the two patient groups ($p = 0.17$). NART-R scores indicated that IQ estimates were within the normal range and did not differ significantly between groups ($p = 0.89$).

Behavioral Results

Participants drew more beads during sequences with 60/40 compared to 80/20 probability (2.65 vs. 1.59 draws), $F(1,49) = 99.48$, $p < 0.001$, $\eta_p^2 = 0.67$. They also drew more beads during $10 loss than $0 loss trials (2.33 vs. 1.90 draws), $F(1,49) = 29.79$, $p < 0.001$, $\eta_p^2 = 0.38$. Results showed no significant effects of group (ps > 0.17). Participants more often chose the correct urn during sequences with 80/20 than with 60/40 probability (0.89 vs. 0.72), $F(1,49) = 121.51$, $p < 0.001$, $\eta_p^2 = 0.71$. Again, we observed no significant group effects ($ps > 0.33$).

Functional Connectivity Results

Results revealed an increased connectivity between the left STN and the left parietal operculum in the ICD+ group that was significant at an FWE-corrected threshold. Furthermore, patients with higher BIS scores (i.e., more impulsivity) exhibited a weaker connectivity between the left putamen and the right inferior temporal gyrus. At the conservative uncorrected threshold, connectivity differed significantly between the ICD+ and ICD− groups for all ROIs (see **Figure 2**; **Table 2**). The left putamen showed a stronger connectivity with the central operculum in the ICD+ compared to that in the ICD− group. The left caudate showed a stronger connectivity with the occipital fusiform gyrus and various cerebellar regions in the ICD+ compared to that in the ICD− group, but a weaker connectivity with the right frontal pole, superior parietal lobule, and parahippocampal gyrus. Functional connectivity between the left GPe and various frontal cortical areas was weaker in the ICD+ group compared to ICD−. For the left GPi, the ICD+ group showed a stronger connectivity with the left superior temporal gyrus, but a weaker connectivity with various frontal and parietal areas. The ICD+ group further showed a stronger connectivity between the left STN ROI and the left caudate, and some cerebellar regions. However, the ICD+ group showed a weaker connectivity between the left STN and various frontal areas. Finally, results showed a stronger connectivity between the parietal ROI and various temporal areas in the ICD+ group, but a weaker connectivity between this ROI and the paracingulate gyrus, middle frontal gyrus, and several subcortical areas.

All ROIs showed significant associations between connectivity strength and BIS scores across all patients (see **Figure 3**; **Table 3**). There were a few networks in which connectivity strength was

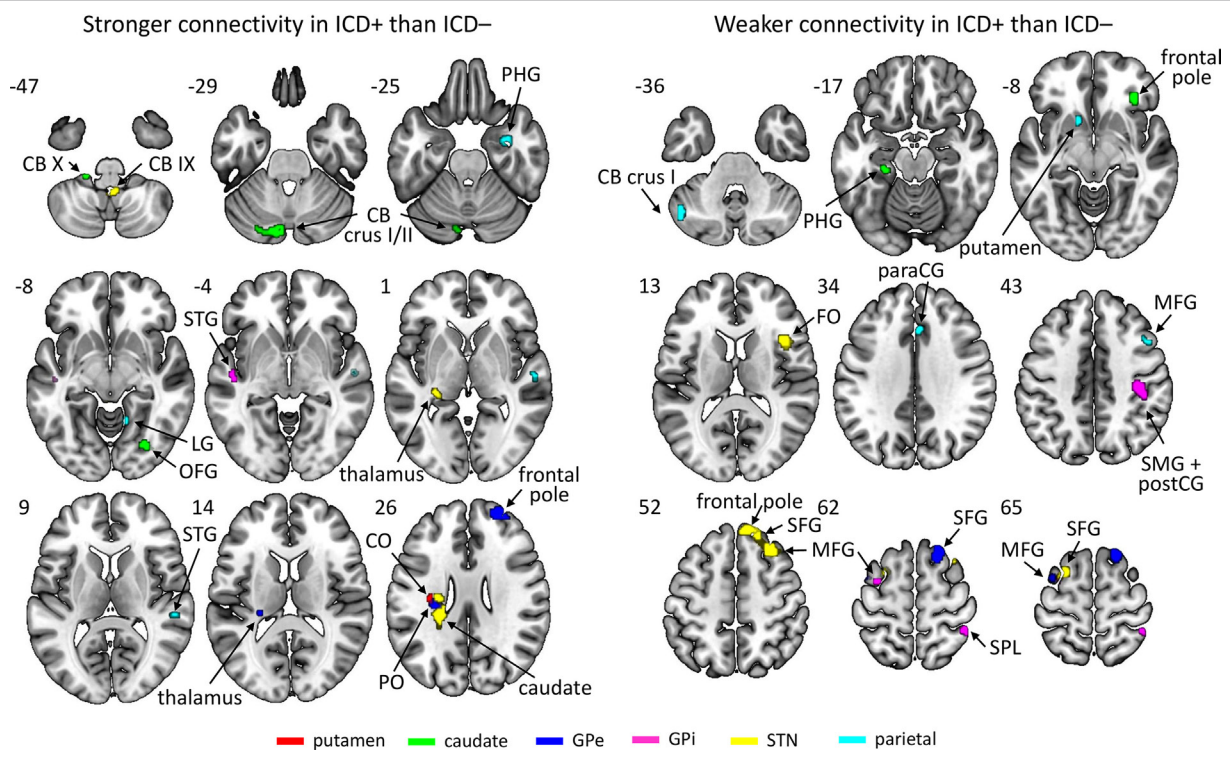

FIGURE 2 | Regions showing stronger (left) or weaker (right) connectivity with their respective region of interest in the impulse control disorder (ICD)+ group than in the ICD− group. The key for the abbreviations can be found in the notes of **Table 2**.

TABLE 2 | Regions that showed differences in connectivity to the region of interest (ROI) between the impulse control disorder (ICD)+ group and the ICD− group.

ROI	ICD+ > ICD−				ICD+ < ICD−			
	Anatomic location	Coordinates of peak	Cluster size	*Z*-score	Anatomic location	Coordinates of peak	Cluster size	*Z*-score
L putamen	L CO (S1)	−34, −18, 26	10	3.43	–	–	–	–
L caudate	L CB lob X	−20, −34, −46	51	4.30	R frontal pole	34, 34, −8	49	4.03
	R OFG	30, −74, −8	26	3.82	L SPL	−18, −50, 78	11	3.62
	L CB crus II	−10, −82, −30	93	3.80	L PHG	−26, −28, −18	15	3.54
	LCB crus I	−24, −82, −32	(93)	3.77				
L GPe	R frontal pole	26, 56, 26	98	4.21	R SFG	20, 22, 62	96	4.12
	L thalamus	−24, −30, 16	57	3.56	R SFG	6, 40, 62	11	3.51
	L PO	−30, −22, 26	(57)	3.48	L MFG	−34, 0, 68	15	3.49
L GPi	L STG	−48, −18, −4	14	3.71	R postCG	38, −24, 42	79	3.80
					R SMG	44, −32, 44	(79)	3.54
					R SPL	42, −42, 64	29	3.74
					L MFG	−32, −2, 62	13	3.62
L STN	L PO[a]	−22, −30, 22	189	4.86	R MFG	30, 26, 54	286	4.24
	L caudate	−26, −16, 26	(189)	3.62	R frontal pole	8, 42, 52	(286)	3.90
	R CB lob IX	4, −48, −46	27	3.93	R SFG	20, 32, 56	(286)	3.77
	L thalamus	−28, −30, 2	18	3.89	R FO	44, 12, 10	70	4.06
	L CB lob I-IV	−4, −42, −6	15	3.73	L SFG	−24, 8, 66	47	4.04
					L OFC	−16, 14, −30	11	3.55
R parietal	R PHG	32, −6, −22	47	4.29	Brain stem	−2, −40, −52	27	4.06
	R LG	14, −54, −8	11	3.73	L CB crus I	−46, −62, −34	29	3.70
	R STG	56, −32, 8	11	3.56	L putamen	−14, 12, −8	12	3.60
	R STG	56, −14, −2	18	3.47	R paraCG	4, 24, 34	13	3.55
					R MFG	46, 14, 44	15	3.44

Cluster sizes between parentheses denote additional peaks within the same cluster as listed in the row immediately preceding.

GPe/GPi, external/internal portion of the globus pallidus; STN, subthalamic nucleus; CO, central operculum; S1, primary sensory cortex; CB, cerebellum; OFG, occipital fusiform gyrus; SPL, superior parietal lobule; PHG, parahippocampal gyrus; PO, parietal operculum; SFG, superior frontal gyrus; MFG, middle frontal gyrus; STG, superior temporal gyrus; postCG, postcentral gyrus; SMG, supramarginal gyrus; FO, frontal operculum; OFC, orbitofrontal cortex; LG, lingual gyrus; paraCG, paracingulate gyrus.

[a]*Remained significant at FWE-corrected $p < 0.05$.*

positively associated with BIS scores, but the results mainly revealed negative associations demonstrating that higher BIS scores (i.e., more impulsivity) were related to a reduced connectivity. For example, patients with higher BIS scores exhibited a weaker connectivity between the left putamen and various frontal, temporal, and cerebellar areas, between the left caudate and temporal areas, as well as between the left STN and frontal areas. We also ran separate analyses on each of the three BIS factors to evaluate associations between connectivity strength and factor scores across all patients and observed a similar pattern of results. An overview of the significant associations is presented in Tables S1–S3 in Supplementary Material.

The basal ganglia ROIs (but not the parietal ROI; see **Figure 4**; **Table 3**) showed significant associations between resting-state network strength and behavioral performance on the beads task. The putamen, GPe, and GPi showed a stronger connectivity with frontal areas when more draw choices were made (i.e., less impulsivity).

Structural Results

Results revealed a significant negative association that survived FWE correction between the average number of draw choices in the beads task and GM volume in the bilateral putamen, indicating that patients who made more draw choices (i.e., less impulsivity) exhibited a smaller putamen GM volume than those who made fewer draw choices and thus collected less evidence. When evaluating results at the uncorrected threshold, we further observed that patients in the ICD+ group showed a reduced GM volume in the right GPe compared to patients in the ICD− group (see **Figure 5**; **Table 4**). There were no regions in which GM volume was significantly increased in the ICD+ group compared to that in the ICD− group. Results also showed a significantly positive association between BIS scores and GM volume in the right putamen, such that higher BIS scores (i.e., more impulsivity) were associated with a larger GM volume. We also evaluated associations between GM volume and scores on each of the three BIS factors. Only scores on the motor impulsiveness factor were associated with GM volume (see Table S4 in Supplementary Material). Specifically, results showed that higher scores on this factor were associated with a larger GM volume in the right putamen.

DISCUSSION

We examined differences in affective and sensorimotor corticostriatal functional connectivity and structural brain properties between PD patients with and without ICDs. We found that compared to patients without ICDs, the connectivity between various basal ganglia nuclei (caudate, GPe, GPi, STN) and frontal cortical areas was reduced in PD patients with ICDs.

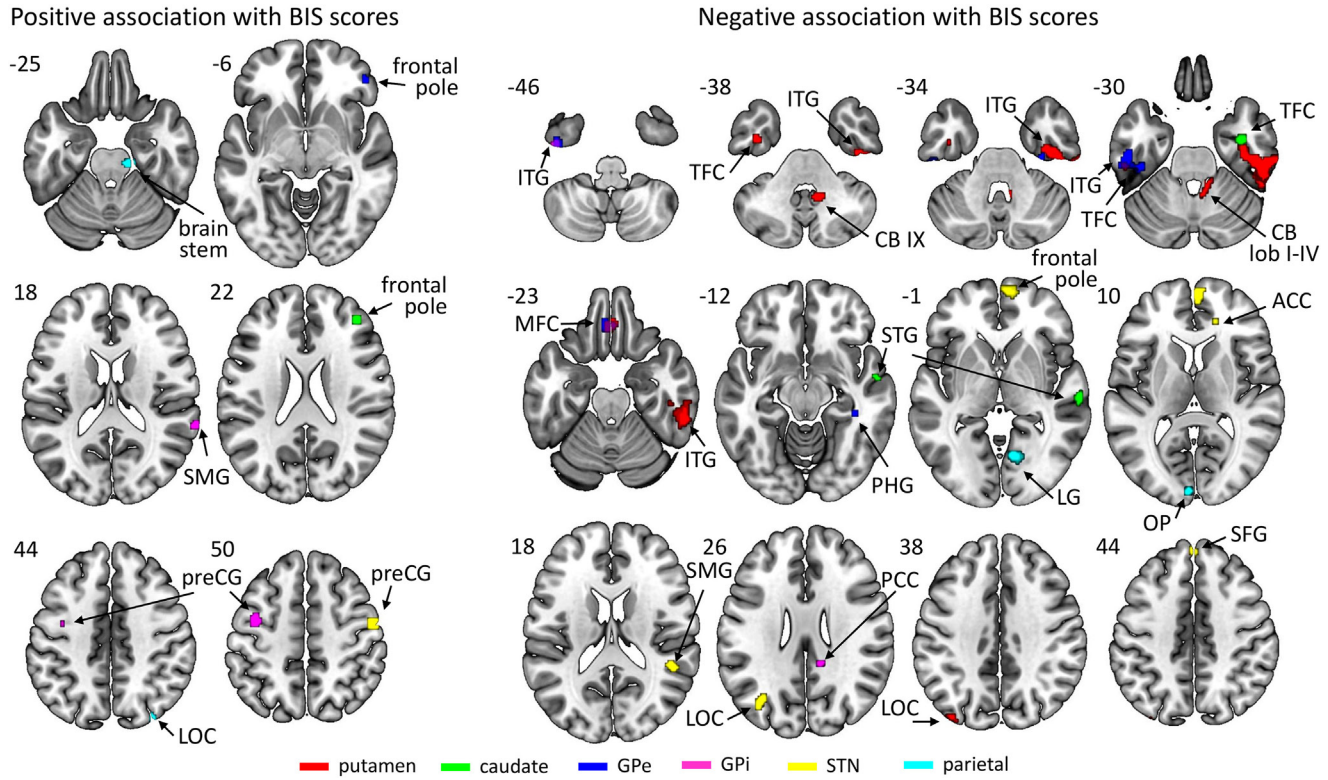

FIGURE 3 | Regions of which the connectivity strength with their respective region of interest was associated positively (left) or negatively (right) with Barratt Impulsiveness Scale (BIS) scores across participants. The key for the abbreviations can be found in the notes of **Table 3**.

In addition, patients with ICDs showed a reduced GPe GM volume. Extending previous work, we also used behavioral assessments to examine whether individual differences in brain properties were associated with behavioral impulsivity in PD. Across all patients, we observed that *reduced* frontal–basal ganglia connectivity and *stronger* motor cortical- and cerebellar–basal ganglia connectivity were associated with more impulsivity as reflected in higher BIS scores and fewer draw choices before selecting an urn. In addition, a greater putamen volume was associated with higher BIS scores and fewer draw choices.

Our findings in combination with the literature suggest that there may be two mechanisms underlying impulsivity in PD patients. First, weaker connectivity in a frontal–striatal network may lead to impaired assessment of the reward value of actions and more risk-taking. This is in line with previous findings that ICDs in PD were associated with a reduced connectivity in cognitive and affective corticostriatal pathways (8). Dysregulation of the reward pathway may cause patients to overestimate the expected outcomes of actions and thus increase risk-taking. Second, stronger connectivity between the basal ganglia and motor areas (motor cortex and cerebellum) may result in a greater propensity to act. Besides being linked to the motor cortex, the basal ganglia are reciprocally connected with the cerebellum and involved in motor behavior [(39, 40); for a review, see Ref (41)]. Our neurostructural findings provide further support for the idea that sensorimotor basal ganglia networks contribute to impulsivity. We observed that greater GM volume of the putamen [i.e., the sensorimotor striatum; e.g., Ref. (42)] and smaller GM volume of the GPe were associated with more impulsivity. These basal ganglia regions are linked, in the sense that the putamen is known to inhibit the GPe [e.g., Ref. (43)]. As such, it is likely that greater putamen volume could be related to stronger inhibition of the GPe. The GPe in turn is part of a motor-suppressing pathway [indirect "no-go" pathway (43)], and smaller volume of this structure in PD patients with ICDs could be related to reduced inhibition of actions. Combining these notions, we speculate that greater putamen volume may more strongly inhibit the (already-smaller) GPe, resulting in less motor pathway suppression by the GPe, in turn making patients more likely to act and thus more impulsive. Together, our findings suggest that impulsivity in PD could be associated with problems in both valuation and inhibition of inappropriate behavior, although a recent review suggests that decisional rather than motor impulsivity may contribute more strongly to ICDs (44).

We further observed that ICD+ patients showed stronger striatal–cerebellar connectivity but reduced parietal–cerebellar connectivity. The cerebellum has traditionally been associated with motor functions, but cerebellar involvement in non-motor functions mediated by (among others) parietal areas has also been recognized (45). For example, cerebellar and parietal cortices are involved in response inhibition and suppression of inappropriate

TABLE 3 | Regions of interest (ROIs) and their connected regions of which the connectivity strength was associated across all participants with Barratt Impulsiveness Scale (BIS) scores and with the number of draw choices, respectively.

	ROI	Positive association				Negative association			
		Anatomic location	Coordinates of peak	Cluster size	*Z*-score	Anatomic location	Coordinates of peak	Cluster size	*Z*-score
BIS scores	L putamen	–	–	–	–	R ITG[a]	56, −38, −26	515	4.70
						L MFC	−2, 34, −22	63	4.41
						R CB lob IX	12, −52, −40	64	3.82
						R CB lob I-IV	10, −42, −28	(64)	3.64
						L LOC	−38, −84, 38	15	3.75
						L TFC	−38, −6, −38	20	3.68
						L ITG	−54, −28, −32	18	3.54
	L caudate	R frontal pole	40, 42, 22	21	3.62	R TFC	36, −8, −28	27	3.90
						R STG ant	56, −2, −10	18	3.64
						R STG post	62, −20, 0	19	3.54
	L GPe	R frontal pole	46, 42, −6	12	3.50	L MFC	−4, 36, −24	63	4.16
						L ITG ant	−42, −8, −44	51	3.75
						R PHG	38, −32, −12	10	3.72
						L ITG post	−54, −26, −30	119	3.65
						L TFC	−40, −28, −28	(119)	3.63
						R TFC	30, −24, −36	15	3.57
	L GPi	L preCG	−40, −4, 50	55	4.04	R PCC	12, −40, 26	14	3.98
		R SMG	66, −40, 18	20	3.67	L ITG post	−44, −12, −48	27	3.70
	L STN	R preCG	52, −6, 50	42	3.83	R frontal pole	12, 62, 2	193	4.36
						R SMG	46, −42, 16	45	4.00
						L LOC	−36, −72, 28	46	3.95
						R ACC	18, 38, 12	11	3.87
						L SFG	0, 46, 44	20	3.67
	R parietal	Brain stem	14, −24, −26	31	4.42	R LG	16, −68, −4	147	4.44
		R LOC	34, −82, 44	20	3.63	L OP (V1)	−4, −94, 6	39	3.76
Number of draw choices	L putamen	R SFG	16, 18, 58	163	4.27	R MFC	2, 54, −32	15	4.10
		R paraCG	10, 40, 20	70	3.83	R SMG	46, −34, 52	13	3.72
		R SFG	20, 56, 16	23	3.77				
		L MTG	−56, −22, −10	22	3.61				
		R AG	46, −56, 42	20	3.51				
	L caudate	L PHG	−18, 2, −32	31	3.80	R PCC	18, −42, 24	12	3.98
		R CB lob I-IV	12, −40, −24	11	3.70				
		Brain stem	−8, −38, −38	14	3.56				
	L GPe	R SFG	8, 12, 58	12	3.60	L CALC	−28, −64, 6	26	3.86
		R paraCG	2, 50, −6	12	3.48				
	L GPi	R frontal pole	16, 56, 8	257	4.40	L CB lob VIII	−14, −62, −38	33	4.10
		R paraCG	12, 46, 12	(257)	4.27	R precuneus	14, −52, 44	10	3.53
		L SFG	−8, 32, 42	26	3.82				
		L ITG	−58, −52, −24	14	3.51				
		L MFG	−30, 16, 46	21	3.50				
		R ACC	4, 34, 18	13	3.46				
	L STN	R CB lob V	6, −56, −28	11	3.74	R SFG	20, −4, 62	108	4.38
		R CO	32, −8, 20	16	3.60	L ITG	−44, −52, −12	17	3.62
		L MCC	−10, −14, 30	18	3.54	L preCG	−12, −14, 64	15	3.51
						L preCG	−22, −10, 62	10	3.37

Cluster sizes between parentheses denote a second peak within the same cluster as listed in the row immediately preceding.

GPe/GPi, external/internal portion of the globus pallidus; STN, subthalamic nucleus; ITG, inferior temporal gyrus; MFC, medial frontal cortex; CB, cerebellum; LOC, lateral occipital cortex; TFC, temporal fusiform cortex; STG ant/post, superior temporal gyrus, anterior/posterior division; ITG ant/post, inferior temporal gyrus, anterior/posterior division; PHG, parahippocampal gyrus; preCG, precentral gyrus; SMG, supramarginal gyrus; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; SFG, superior frontal gyrus; LG, lingual gyrus; OP, occipital pole; V1, primary visual area; paraCG, paracingulate gyrus; MTG, middle temporal gyrus; AG, angular gyrus; CALC, calcarine cortex; MFG, middle frontal gyrus; CO, central operculum; MCC, middle cingulate cortex.

[a]*Remained significant at FWE-corrected $p < 0.05$.*

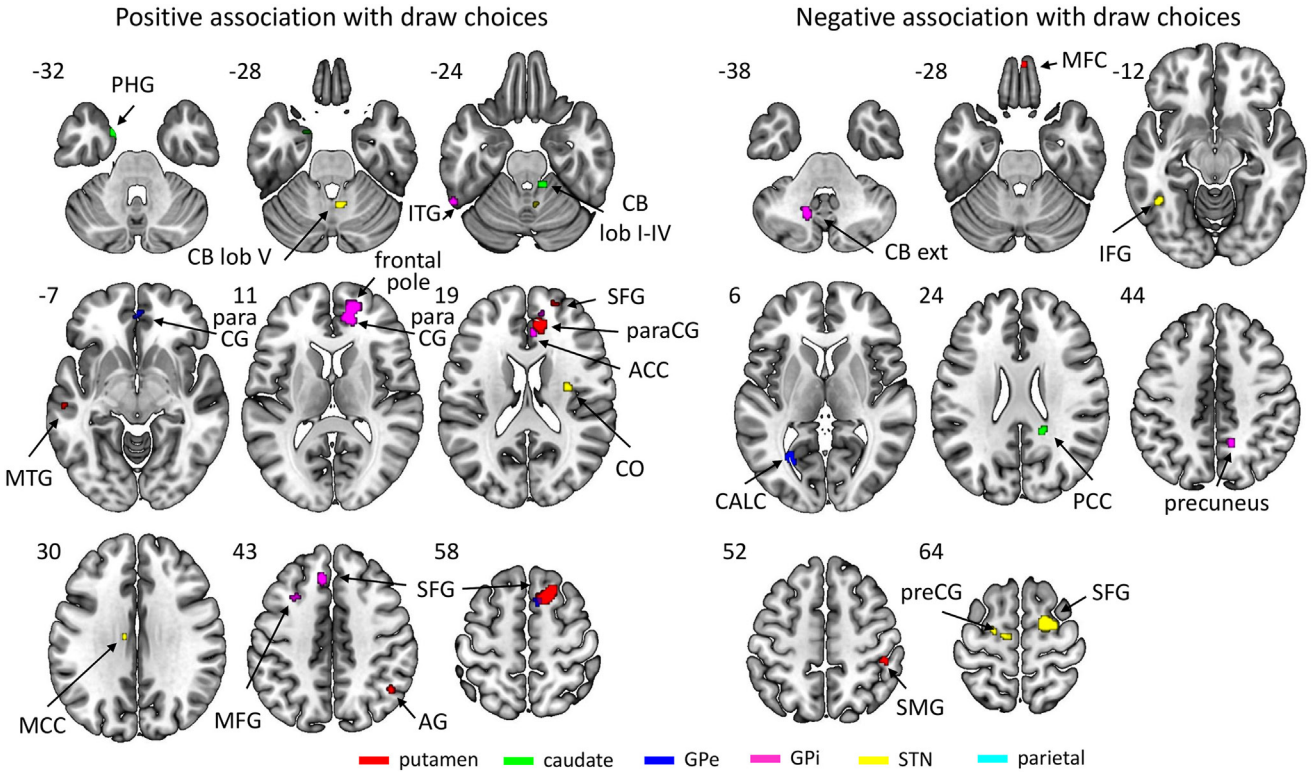

FIGURE 4 | Regions of which the connectivity strength with their respective region of interest was associated positively (left) or negatively (right) with the number of draw choices across participants. The key for the abbreviations can be found in the notes of **Table 3**.

behavior, and changes in parietal–cerebellar connectivity are associated with poorer inhibitory control in cannabis users (46). The enhanced striatal–cerebellar connectivity we observed may subsequently cause patients to be more likely to act upon their impulses. Our findings regarding cerebellar connectivity differences between PD patients with and without ICDs fit the notion of a dual mechanism of impulsivity, with aberrant connectivity within affective parietal–cerebellar and sensorimotor striatal–cerebellar networks underlying problems in cognitive and motor control, respectively.

Our results showed no behavioral group differences in beads task performance, which contrasts with earlier findings that PD patients with ICDs drew fewer beads than patients without ICDs (16). Compared to that study, our beads task protocol was slightly modified and optimized for imaging purposes [cf Ref. (17)]. While both studies involved the same probabilities and loss amounts, subjects in the current study completed 24 trials per condition while subjects in the Djamshidian et al. (16) study completed only three trials. We repeated our behavioral analyses on just the first three trials of each condition but this did not reveal significant group differences. The demographic makeup of the patients also differed between the studies. PD patients with ICDs in Djamshidian et al. (16) study were on higher doses of medication, were younger, had an earlier age of disease onset, and a longer disease duration than the patients in the current study. In addition, the previous study showed group differences in age at PD onset, whereas the current study found no differences in clinical or demographic characteristics between groups. Importantly, patients with ICDs did show significantly higher BIS scores compared to those without ICDs, thus corroborating our classification based on the QUIP. As medication dosage affects impulsivity (6), this may explain the discrepancy in behavioral results on the beads task. Future studies should systematically examine how current age and age of disease onset might contribute to information gathering and decision making.

While two connectivity and two structural effects were significant following FWE correction, most results reported here were detected using uncorrected statistical thresholds ($p < 0.0005$ and $p < 0.005$ for the connectivity and structural analyses, respectively). As we compared two groups of PD patients, it seems reasonable that group differences are not as strong as those found when comparing patients to control subjects—especially since the two patient groups did not differ significantly in terms of current age, age of PD onset, disease duration, medication dose, and scores on the MoCA, NART-R, and UPDRS motor subscale. In addition, relative to previous studies, we used a large sample size [i.e., ≥21 patients per group, compared to ~12–20 patients per group in Ref. (8, 9, 11–13)].

A limitation of the current study is the lack of a healthy control group. However, we were interested in the effect of impulsivity on brain structural and functional connectivity changes in PD,

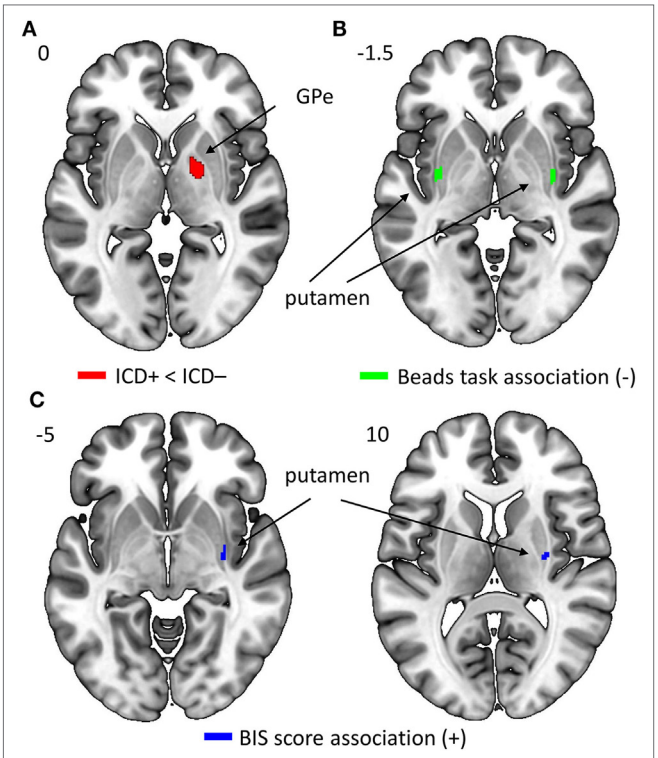

FIGURE 5 | Regions in which gray matter (GM) volume was reduced in impulse control disorder (ICD)+ compared to that in ICD– patients [right GPe; panel **(A)**], in which GM volume was negatively correlated with the average number of draw choices in the beads task [bilateral putamen; panel **(B)**], or in which GM volume was positively correlated with Barratt Impulsiveness Scale (BIS) scores [right putamen; panel **(C)**].

TABLE 4 | Regions of interest (ROIs) that show differences in GM volume between the impulse control disorder (ICD)+ and ICD– groups, and ROIs showing associations between GM volume and behavioral measures [i.e., number of draw choices in the beads task and scores on the Barratt Impulsiveness Scale (BIS) questionnaire].

Contrast	Anatomic location	Coordinates of peak	Cluster size	*Z*-score
Group difference	R GPe	21, –3, 0	32	2.79
Association of GM volume and draw choices (–)	R putamen[a]	33, 2, –3	69	3.79
	L putamen[a]	–35, –4, 0	46	3.73
Association of GM volume and BIS score (+)	R putamen	29, –12, 10	18	2.88
	R putamen	33, –12, –5	23	2.85

Note that the association with the number of draw choices was negative, whereas the association with BIS scores was positive.
GM, gray matter; GPe, external portion of the globus pallidus.
[a]*Remained significant at FWE-corrected p < 0.0.5.*

rather than the pathophysiology of PD in general. Several prior studies have already evaluated differences in brain structure and function between PD patients and healthy control subjects. Reviews evaluating structural differences indicate that PD is typically associated with GM loss in frontal areas and basal ganglia regions (47, 48). With respect to resting-state functional connectivity, a systematic review concluded that PD patients assessed off-medication and *de novo* patients typically show a reduced corticostriatal connectivity compared to controls (49). Still, there are also indications for an increased corticostriatal connectivity in PD patients (50), as well as indications that the direction of the connectivity change may be network-specific (51). Another limitation is that all patients were tested while they were on dopamine replacement medication. Previous work has shown that medication status can modulate resting-state connectivity in PD patients [e.g., Ref. (50, 52); for a review, see Ref. (49)]. However, as medication doses did not differ between the patient groups in the present study, it is unlikely that this impacted ICD-related group differences. In addition, our approach of assessing patients on medication is in line with that of other studies investigating differences between PD patients with and without ICDs (8, 9, 11, 12, 16). Patients in the off-medication state often experience difficulties related to motor responses (and sometimes even cognitive processing), which may confound behavioral performance and thus interpretation of the task results. Finally, a technical benefit of testing patients while they were on dopamine replacement medication is that medication reduces tremor in PD patients and thus also reduces potential movement-related artifacts during scanning.

Our findings demonstrate that impulsivity in PD is associated with brain structural and functional connectivity alterations. However, they leave open the question of whether these associations reflect predispositions (i.e., neural differences existing prior to the emergence of ICDs) or whether they are related to impulsiveness-induced plasticity. Longitudinal designs may help to adjudicate these possibilities. In addition, future studies could take into account recent advances in the domain of genotyping and impulse control (53) to evaluate whether the neural characteristics observed here could potentially be associated with specific dopaminergic gene profiles that are predictive of impulsivity.

Overall, the current results corroborate that alterations in affective basal ganglia circuitries are linked to impulse control problems in PD patients [cf Ref. (8)]. Our findings show that reduced frontal–striatal connectivity and GPe volume were associated with more impulsivity. Additionally, we report the novel finding that impulsivity in PD is also linked to changes in sensorimotor striatal networks, with enhanced connectivity within this network and larger putamen volume being associated with more impulsivity. We suggest that two mechanisms may underlie impulsive behaviors in PD: one affecting decision making such that patients are more likely to select risky or inappropriate actions and one affecting sensorimotor processing such that patients are more likely to subsequently perform these actions.

ETHICS STATEMENT

All patients provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the medical institutional review board of the University of Michigan.

AUTHOR CONTRIBUTIONS

BA, KC, and RS designed the study. TW organized and performed the study. MR, VK, and RS performed the data analyses.

MR and RS wrote the first draft of the manuscript. All authors reviewed and edited the manuscript, and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at https://www.frontiersin.org/articles/10.3389/fneur.2018.00279/full#supplementary-material.

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Impulse-Control Disorders in Parkinson's Disease: A Meta-Analysis and Review of Case–Control Studies

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Background: Although several case–control studies on the prevalence of Impulse-Control Disorders (ICDs) in Parkinson's Disease (PD) have been conducted, no meta-analytic study on this topic has previously been published. Thus, knowledge about the overall prevalence rate of ICD in PD and factors that might moderate this relationship is lacking.

Method: Prevalence studies of ICDs in PD were identified by computer searches in the MEDLINE, PsycINFO, and Web of Science databases, covering the period from January 2000 to February 2017. Data for $N = 4,539$, consisting of 2,371 PD patients and 2,168 healthy controls, representing 14 case–control studies were included. Estimation of the odds ratio (*OR*) of ICDs in PD compared to healthy controls was conducted using random-effects models. Mixed-effects models were applied in the moderator analysis of heterogeneity. Publication bias was estimated using a contour-enhanced funnel plot, the Rüker's test, and fail-safe *N* test for estimating the number of potential missing studies.

Results: Overall, the results showed significantly higher ratios for several ICDs in PD compared to healthy controls with the estimated overall *OR*s ranging between 2.07, 95% CI [1.26, 3.48], for having any ICDs, and 4.26, 95% CI [2.17, 8.36], for hypersexuality. However, the random-effects results for shopping were non-significant, though the fixed-effects model was significant ($OR = 1.66$, 95%CI [1.21, 2.27]). The testing of potential moderator variables of heterogeneity identified the following two variables that were both associated with increased risk: being medically treated for PD and disease duration. The results must be interpreted with some caution due to possible small-studies effect or publication bias.

Conclusion: Individuals with PD seem to have a significantly greater risk of suffering from ICDs compared to healthy controls. Gambling, hypersexuality, eating, punding, and hobbying are all ICDs significantly associated with PDs being medically treated for PD.

Keywords: Impulse-control disorders, Parkinson's disease, case–control, meta-analysis, dopamine agonists

INTRODUCTION

Impulse control disorders (ICDs) are a collective term for non-motor symptoms that include pathological gambling, compulsive shopping, hypersexuality, and binge eating (1). In addition, behavioral disorders such as hobbyism (including pathological internet use), punding, and walkabout have been reported in patients with Parkinson's disease (PD) (2–4). ICDs are behavioral addictions marked by an uncontrollable and irresistible drive or temptation to perform an action, even though this may be adverse to oneself or others. Such behaviors are often performed without the patient experiencing distress (5). ICDs are more frequently reported in PD patients compared to healthy control subjects, or the general population (6). ICDs in PD were first presented in a case report from 2000 (7).

Impulse control disorders have different levels of severity. Pathology is defined by its interference with financial, personal, family, and/or professional life. The addictive behavior is often time-consuming, and can cause significant distress and impinge on the quality of life (6, 8). ICDs are also associated with depression and low activity level (9, 10). Additionally, PD patients with ICDs experience more motor complications, although this may be due to medication (11).

Although ICDs are considered a common non-motor complication of PD, frequency estimates range from approximately 14–60% in PD (12, 13). Early investigations into ICDs in PD typically used screening tools and diagnostic criteria validated for the four most common ICDs (gambling, eating, hypersexuality, and shopping) in PD (13). With the introduction of the PD Impulsive-Compulsive Disorders Questionnaire (QUIP) (14), evaluation of the full range of impulsive and compulsive behaviors became more common and led to an increase in frequency estimates in later studies (15, 16). However, the estimated frequency of ICDs in PD still varies between cohorts, possibly due to differences in recruitment strategies between studies (15, 17, 18). Finally, the use of self-assessment of ICDs may serve as a possible bias in many studies, especially when estimating the frequency of hypersexuality, punding, and compulsive medication use (19).

Impulse control disorders in PD seem to be linked to certain risk factors: young age, male gender, being unmarried, higher education, novelty-seeking personality traits, personal or family history of addictions prior to PD diagnosis, and comorbid psychiatric disorders (11, 13, 18, 20–23). Hypersexuality and gambling seem to be more prevalent among males, while a female preponderance has been shown for compulsive shopping and binge eating (11, 13, 24). Type of ICD is further likely to be influenced by cultural or ethnic differences, genes, and access (e.g., to casinos) (11, 13, 25).

Dopaminergic medication, especially dopamine agonists (DAs) are associated with higher frequencies of ICDs (26–32). Although PD patients report ICDs more frequently than controls, this difference is not observed among unmedicated PD patients, arguing for a potential relation between ICDs and pharmacotherapy (33). Indeed, ICDs have consistently been associated with dopamine replacement therapy, such as DA. Hence, DA treatment seems to be a risk factor in the development of ICDs among Parkinson patients, although patients, family members, and physicians may disregard medication side effects and misinterpret them as changed behavior, or a psychiatric disorder (34).

Although several narrative reviews on ICDs related to PD have been published (1, 35, 36), a quantitative meta-analysis that summarizes the existing research could extend earlier reviews by providing overall prevalence estimates (precision estimates) as well as identifying significant moderator variables. Against this backdrop, we conducted a meta-analysis of ICDs in PD aiming to determine the overall prevalence of different ICDs in PD patients in comparison with healthy controls across case–control studies. The second aim was to model how different moderators, e.g., the severity of Parkinsonism (H–Y stage) (37) in a study, are related to ICD prevalence rates. The main research questions are: are ICDs significantly associated with PDs in case–control studies? If so, what moderates the level of association?

METHOD

Search Strategy, Inclusion and Exclusion Criteria

We conducted a systematic search and literature review following the PRISMA guidelines (38) in MEDLINE, Web of Science and PsycINFO for articles published between the year 2000 and January 19, 2017. The following keywords: Parkinson* AND "impulse control disorder*" OR impulsiv* OR gambl* OR shop* OR binge* OR "eating" OR "punding" OR "sex" OR hypersex* OR "hobbying" OR "buying" OR "gaming" OR "internet addiction*" OR "kleptomania" OR "skin picking" OR "trichotillomania" OR "intermittent explosive disorder" OR "pyromania" OR "walkabout" OR "medication" OR "dopamine dysregulation syndrome" OR "compulsive medication use" OR "repetitive behavior*" OR "stereotypical movement disorder*" OR "behavioral addiction" AND prevalen* OR inciden* OR frequen* were used for the search.

The studies were included if they fulfilled the following criteria: (a) the full article was published in English, (b) the article was published between the year 2000 and January 19, 2017, (c) the article had to contain original data on prevalence rates for ICDs and/or impulse-control disorders and related behaviors, and (d) the article had to be a case–control study or a case–control poster.

Together the search generated a total of 3,359 articles. References for 391 articles were further screened by their abstracts, as well as their method and results sections for inclusion eligibility.

From this pool, 17 articles were retained for further evaluation of relevance. Of these, four articles were excluded due to: (1) measuring only outcomes for obsessive–compulsive disorders (39); (2) using a population estimate as a control condition (40); (3) a published poster (41) later published as an article (42); and (4) a published poster (43) later published as an article with an updated *N* (33). In addition, data from one article included was provided by one of the coauthors (Aleksander Hagen Erga) and published online first in February 2017 (15). Thus, a total of 14 case–control studies met the inclusion criteria (15, 16, 33, 42, 44–54). See **Figure 1** for details.

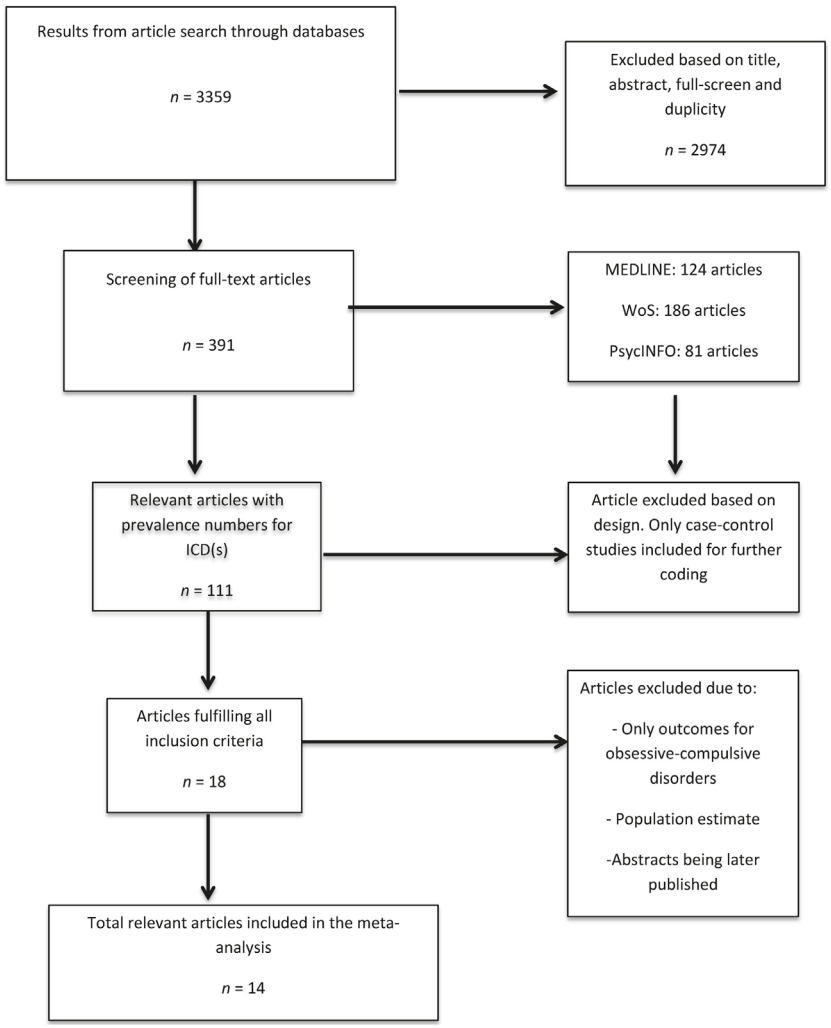

FIGURE 1 | Flow diagram of literature search.

The total participant population was $N = 4{,}538$, consisting of 2,371 PD patients and 2,168 healthy controls. For further details regarding the specific studies' characteristics of response rate, the severity of Parkinsonism or H–Y stage, mean age, sample size, duration of illness, number of patients on DAs, as well as the proportion of Parkinson patients versus healthy controls, see **Table 1**.

Coding Procedures

A coding scheme was developed and used by two of the authors (Yasaman Moussavi and Stine Therese Kopperud) who coded the studies and were trained to ensure a common understanding of the coding scheme. Potential disagreements were resolved by discussing the topic with a third author (Helge Molde) in order to reach an agreement. The coding scheme comprised a number of descriptive codes such as study ID (numeric), coder (1 or 2), journal of publication, publication year, country and continent, ethical approval, and conflicts of interest (yes/no). Furthermore, the coding scheme consisted of information regarding the specific data and findings; total sample size for PD patients, sample size for healthy controls, measurement instrument for the ICD (self-report, interview, objective measure of a diagnosis, clinical testing, local medical registry, local administrative registry, national registry/database), mean Parkinson stage (Hoehn–Yahr), mean age, sex, duration of PD and whether patients with dementia were included or not. Finally, the coding scheme covered information about medical treatment of PD: *n* participants on levodopa as well as *n* participants on DAs. In addition, we also included the mean UPDRSIII motor score, being medically treated versus "*de novo*" PDs (treated = 1) and mean onset of PD (calculated as "age minus duration of PD") as potentially moderators. The last section of the coding scheme included the prevalence of the total and individual ICDs. These were reported as numerals, as well as percentages. The last section was identical to that of the healthy control group.

The ICDs that were listed in the coding scheme were: Gambling, shopping, binge eating, punding, hypersexuality, hobbying, gaming, internet addiction, kleptomania, skin picking, trichotillomania, intermittent explosive disorder, pyromania, walkabout, compulsive medication use, repetitive behavior,

TABLE 1 | Characteristics of case–control studies on the prevalence of ICD(s) in Parkinson patients and healthy controls.

Reference	Country	Sample type	*N* (PP)	Response rate%	Hoehn–Yahr	Age mean	Sample size (male)	Duration of Parkinson	*n* DA	*n* Levodopa	ICD + PP%	*N* (HC)	ICD +HC%
Antonini et al. (44)	Italy	Patients/clinic	103	100	1.5	60.5	67	15.4	0	0	16.5	100	20
Avanzi et al. (45)	Italy	Patients/Clinic	98	100	2.26	69.9	49	7.6	13	44	6.12	392	0.25
de Chazeron et al. (46)	France	Patients/Clinic	115	72.3	–	66.9	60	7.4	65	101	14.4	115	17
Erga et al. (15)	Norway	NRR/MR	155	80.7	2.2	70.4	60	7.4	78	103	30.4	159	11.9
Gescheidt et al. (47)	Czech Republic	Patients/Clinic	49	100	2.29	47	69.4	11	38	40	26.5	38	10.5
Giladi et al. (48)	Israel	Patients/Clinic	203	95	2.7	67.5	63.2	9.6	115	157	14	190	0
Isaias et al. (49)	Italy	Patients/Clinic	50	100	–	65	62	9	50	48	28	100	20
Perez-Lloret et al. (42)	France	Patients/Clinic	203	100	8.95	67	62	9	161	178	25	52	0
Rodríguez-Violante et al. (16)	Mexico	Patients/Clinic	300	100	2.27	61.7	54.3	–	172	220	25.6	150	16.6
Sarathchandran et al. (50)	India	Patients/Clinic	305	100	2.5	58	71.1	7.6	149	244	31.6	234	15.4
Vela et al. (53)	Spain	Patients/Clinic	87	96.6	2	47	60.7	5	68	54	58.3	85	32.2
Valença et al. (52)	Brazil	Patients/Clinic	152	100	2.5	67.3	56.6	7.2	39	138	18.4	212	4.2
Weintraub et al. (33)	USA/Multinational	Patients/Clinic	168	90.3	2	61.5	71.4	[a]	0	0	18.5	143	20.3
Weintraub et al. (54)	USA/Multinational	Patients/Clinic	423	100	1.97	61.7	65	6.65	0	0	21	196	18

Data that were not reported are presented with a dash. PP, Parkinson's disease patients; DA, dopamine agonist; ICD+, Impulse-control disorder positive; HC, healthy control participants.

[a]*Within 2 years.*

stereotypical movement disorder, and dopamine dysregulation syndrome.

Description of Studies

Two studies were multinational and included a number of European and US sites. Eight studies were from Europe, one was from South America, three from North America, one from the Middle East, and one from the southwest part of Asia (India). See **Table 1** for details. Different ICDs were studied with different frequency. For gambling there were 14 relevant articles, eating 10 articles, hypersexuality 13 articles, shopping 12 articles, punding 8 articles, and finally hobbyism 6 articles.

Statistical Analysis

We conducted a meta-analysis for each ICD separately, in addition to an analysis with an estimate of any/composite ICDs using random-effect models. For all models and outcomes, a first step in the analysis was to fit a random-effects model. See **Table 2** for an overview of the results. This model assumes variance or heterogeneity between studies, in addition to within-study measurement error (55). This is a null-model without predictors. Tau2 is a measure of between-study variance, and a Tau2 = 0 would imply that there is no variance between the studies. A significant *Q*-statistics implies significant between-study variance, or that there are significant differences between the studies in the overall estimate of the mean effect. The I^2 statistics $[100\% \times (Q - df./Q)]$ is a measure of percentage of variability in effect sizes that is a result of true differences between the studies. Hence, I^2 is an index of percentage of unexplained between-study variance of the mean estimate. A rough guide to interpret I^2 is that percentages of around 25, 50, and 75% imply low, medium, and high heterogeneity, respectively. Also, the I^2 index and the Tau2 are directly related, as the higher the between-study variance (Tau2), the higher the I^2 index (56).

After assessing heterogeneity, potential moderators were regressed using mixed multivariate models. All moderators, except being medically treated for PD, were mean-centered in order to easily interpret the intercept (57). All results in the text and tables are reported as odds ratio (*OR*). The *OR* was calculated in such a way that an *OR* above 1 indicates higher odds for the Parkinson group having an ICD, in comparison to the odds for the healthy control group.

Some moderator variables had missing data. Data for these variables was imputed using "multivariate imputation by chained equations" through the mice package in R (58).

Small-study effects (or "publication bias") were estimated using a *contour-enhanced funnel plot*. A funnel plot is a plot of each trial's *OR* against the standard error. The plot should be shaped like a funnel if no publication bias is present (59). The contour-enhanced plot may help in differentiating between asymmetry due to publication bias and/or other reasons. Different gray areas correspond to different levels of significance, and studies missing in the white region are due to publication bias (e.g., no significant studies). Studies missing in the gray areas are missing due to other reasons (60). Furthermore, evaluating funnel plot asymmetry for binary data, Sterne et al. recommended the parametric Harbord's test, the Peter's tests and/or the Rüker's test when Tau2 < 0.1, and

TABLE 2 | Random-effects model.

	Total ICD	95% CI	Gambl.	95% CI	Hypers.[a]	95% CI	Shopping	95% CI	Eating	95% CI	Punding	95% CI	Hobbying	95% CI
Intercept (β0)[b]	2.10	[1.26, 3.48]	2.70	[1.56, 5.67]	4.26	[2.17, 8.36]	1.80	[0.99, 3.27]	2.32	[1.15, 4.68]	3.02	[2.31, 3.96]	1.72	[0.48, 6.18]
Heterogeneity														
Tau2	0.27		0.02		0.51		0.41		0.58		0.00		0.78	
I^2 (%)	70.7	[47.1, 83.7]	1.70	[0.00, 55.8]	42.4	[0.00, 70.0]	50.8	[4.70, 74.6]	66.8	[35.2, 82.9]	0.00	[0.00, 21.3]	81.1	[59.5, 91.2]
H	1.85	[1.37, 2.48]	1.01	[1.00, 1.50]	1.32	[1.00, 1.83]	1.43	[1.02, 1.98]	1.73	[1.24, 2.42]	1.00	[1.00, 1.13]	2.30	[1.57, 3.37]

CI, confidence interval; ICD, impulse-control disorder.

[a]*Hypers. = hypersexuality.*

[b]*Odds ratio estimate.*

only use of the Rüker's test when Tau2 > 0.1 (61). Hence, we used the Rüker's test, evaluating missing studies due to small-studies effects.

In addition, the Rosenthal's fail-safe *N* test was applied, estimating how many non-significant studies are needed in order to have a non-significant overall result (62).

The residuals of the fitted models were inspected for normality using QQ-plots. Statistical analyses were conducted using the R packages *meta* (63) and *metafor* (64). Estimating the random-effects models, the Manzel–Haenszel estimator was used as estimator for the *OR* estimate, with Hartung-Knapp adjustment for small-studies effects. In addition, the DerSimonian–Laird estimator was used for estimating Tau2. All moderator analyses were conducted using a restricted maximum-likelihood estimator (REML), which is the default in the *metafor* package (64) in R (65).

RESULTS

Of all studies identified, 14 finally met all inclusion criteria and were included for further analysis. Eleven studies reported which DAs and mean dose were given to the patients, and nine studies reported levodopa usage and mean dose. Of all the patients having PD disease in this meta-analysis, 948 patients were on DA treatment, and 1,327 patients were on levodopa.

Any ICDs

Random-Effects Model

The results from the random-effects model on *any ICDs* showed a significant *OR* estimate of point 2.10, 95% CI [1.26, 3.48]. The *Q*-statistics were significant ($Q = 37.5$, $p < 0.0001$), indicating significant heterogeneity between the studies. The between-study variance, Tau2, was 0.27, and the percentage of unexplained between-study variance $I^2 = 70.7$, 95% CI [47.1, 83.7]. This indicated high unexplained between-study variance with respect to the total number of ICDs. See **Figure 2** for a forest plot of the results.

We conducted a contour-enhanced funnel plot estimating publication bias. As seen from **Figure 3**, there seems to be a greater number of studies with low standard error lacking in the upper gray area, as compared to the number of studies (2) with large standard errors lacking in the lower white area, in order to create more balance in the figure. Thus, the former may indicate a small-study effect for other reasons than publication bias, while the latter indicate missing studies due to publication bias. As such, the Rüker's test was non-significant ($t = 0.69$, $p > 0.05$), indicating no publication bias.

The Rosenthal's fail-safe *N* test was significant ($p < 0.0001$), indicating that 226 non-significant studies would be needed in order for the random-effects model to be non-significant.

The univariate testing of possible moderators of heterogeneity resulted in two significant univariate models: treated PDs and disease duration. Hence, these parameters were included in a mixed multivariate model.

Mixed-Effects Model

The final model included only medically treated PDs as a moderator. The results from the meta-regression analysis showed a

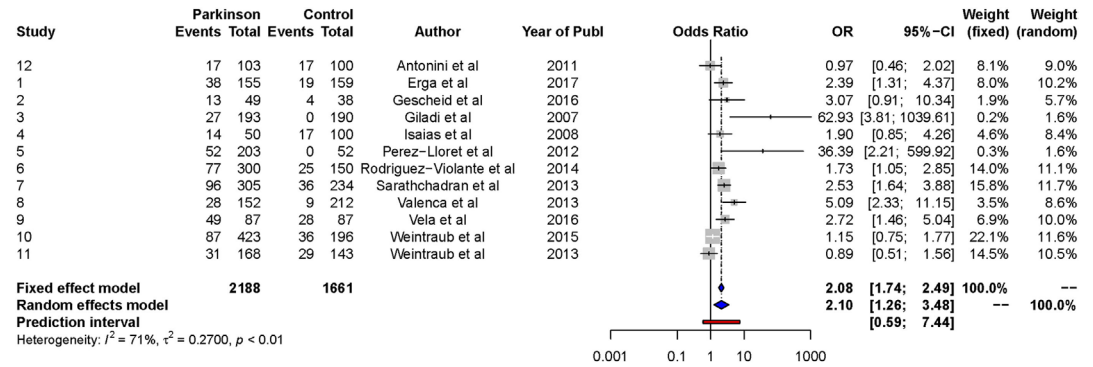

FIGURE 2 | Forest plot of any ICDs.

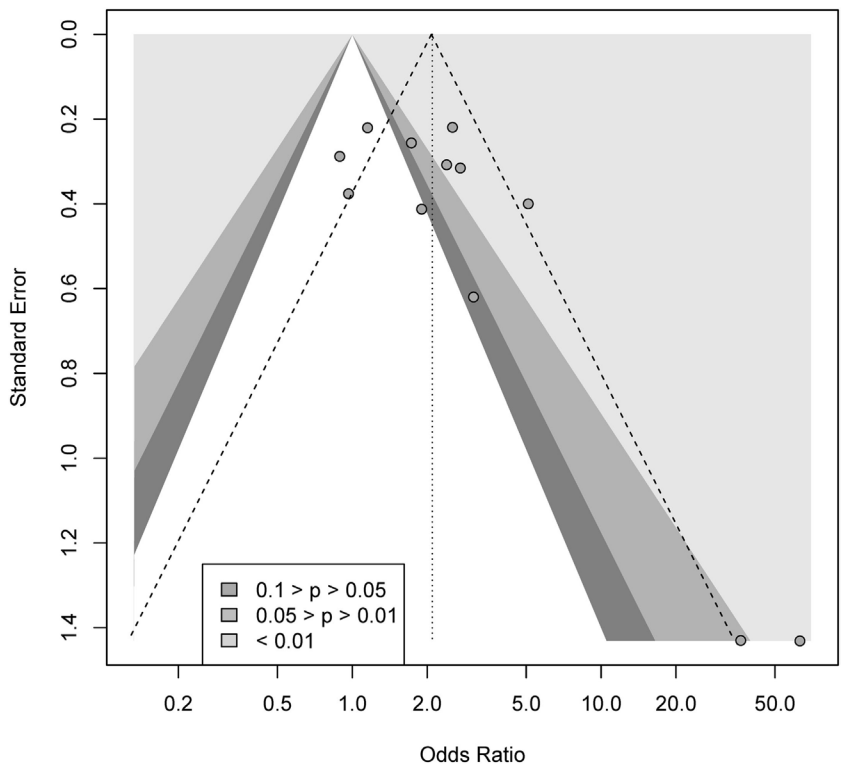

FIGURE 3 | Contour-enhanced funnel plot for gambling.

non-significant log-*OR* point estimate of β0 = 0.03 (*OR* = 1.03, 95% CI [0.67, 1.59]). The intercept β0 refers in this model to *de novo* patients, or non-medically treated patients. The test for residual heterogeneity indicated non-significance, QE = 15.0, $p = 0.13$. The overall moderator model was significant, QM = 13.90 ($p = 0.004$). Being medically treated for PD was significant at the 0.01 level, *OR* = 2.46, 95% CI [1.44, 4.22].

The model accounted for 100% (R^2) of the heterogeneity, and the percentage of residual heterogeneity, I^2, was 0%. Tau2, or residual heterogeneity, was 0.00 ($SE = 0.04$). The QQ-normal plot indicated a normal distribution of the residuals.

Gambling

Random-Effects Model

The results from the random-effects model on *gambling* showed a significant *OR* estimate of point 2.70, 95% CI [1.56, 4.67]. The *Q*-statistics were non-significant ($Q = 13.3$, $p > 0.05$), indicating non-significant heterogeneity between the studies. The between-study variance, Tau2, was 0.02, and the percentage of unexplained between-study variance $I^2 = 1.70\%$, 95% CI = [0.00, 55.8]. This indicates almost no unexplained between-study variance with respect to gambling. See **Figure 4** for a forest plot of the results.

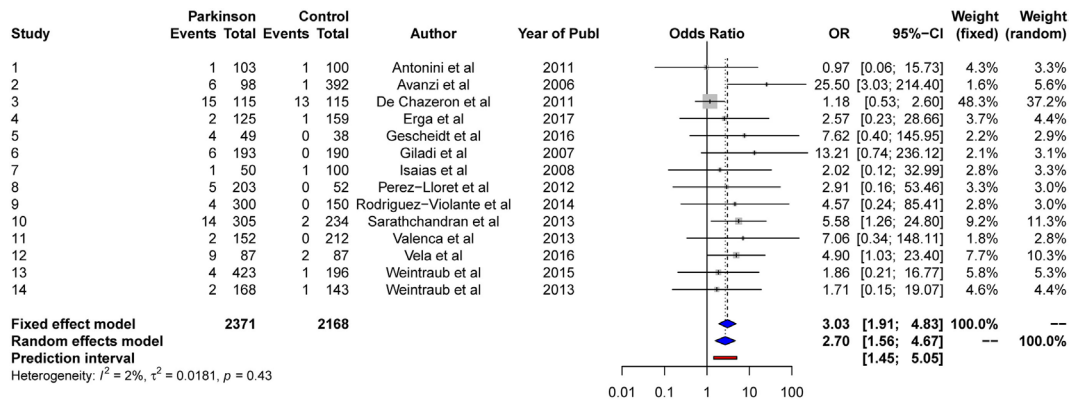

FIGURE 4 | Forest plot of gambling.

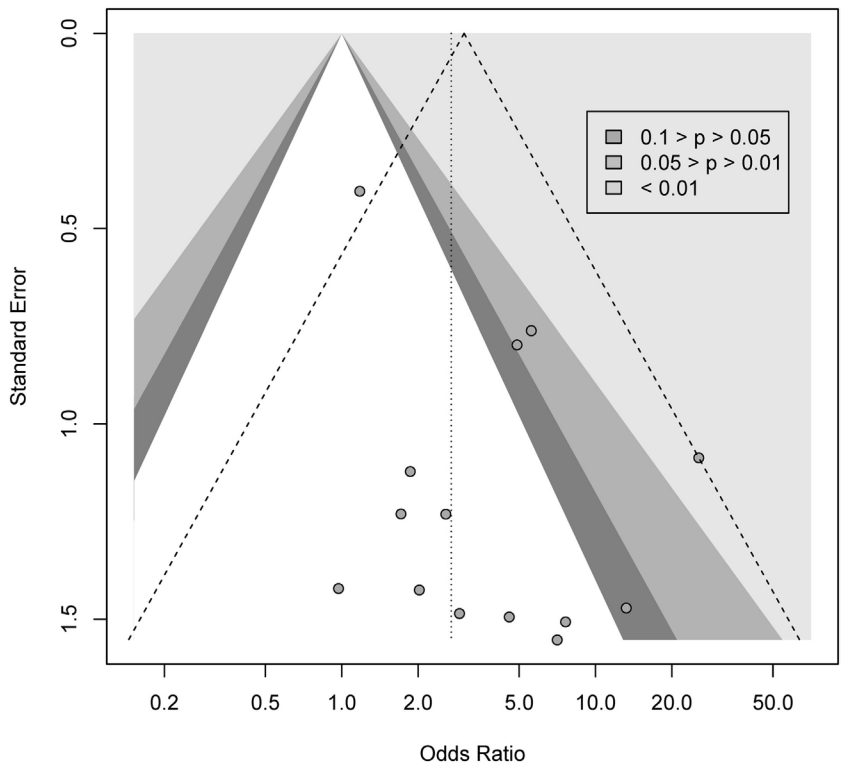

FIGURE 5 | Contour-enhanced funnel plot for gambling.

We conducted a contour-enhanced funnel plot estimating publication bias. As seen from **Figure 5**, there seem to be lot more studies lacking in the lower white area, in comparison to the gray area, in order to create more balance in the figure. Thus, this may indicate a possible publication bias for gambling. However, the Rüker's test was non-significant ($t = 1.01$, $p > 0.05$).

Rosenthal's fail-safe N test was significant ($p < 0.0001$), indicating that 81 non-significant studies would be needed for the random-effects model to be non-significant.

As there was no significant between-study variance or heterogeneity, no further analyses were conducted for gambling.

Hypersexuality

Random-Effects Model

The results from the random-effects model on *hypersexuality* showed a significant *OR* estimate of point 4.26, 95% CI [2.17, 8.36]. The Q-statistics were non-significant ($Q = 20.8$, $p > 0.05$), indicating non-significant heterogeneity between the studies.

The between-study variance, Tau2, was 0.51, and the percentage of unexplained between-study variance $I^2 = 42.4\%$, 95% CI [0.00, 70.0]. This indicated moderate unexplained between-study variance with respect to hypersexuality. See **Figure 6** for a forest plot of the results.

We conducted a contour-enhanced funnel plot estimating publication bias. As seen from **Figure 7**, there seem to be several studies with large standard error lacking in the lower white area, as in comparison to studies with low standard errors lacking in the gray area, in order to create more balance in the figure. Thus, this may indicate both a small-study effect and a publication bias. However, the Rüker's test was non-significant ($t = 1.4$, $p > 0.05$), indicating no publication bias.

The Rosenthal's fail-safe N test was significant ($p < 0.0001$), indicating that 165 non-significant studies would be needed for the random-effects model to be non-significant. The univariate testing of possible moderators of heterogeneity resulted in two significant bivariate models: disease duration and medically treated PDs.

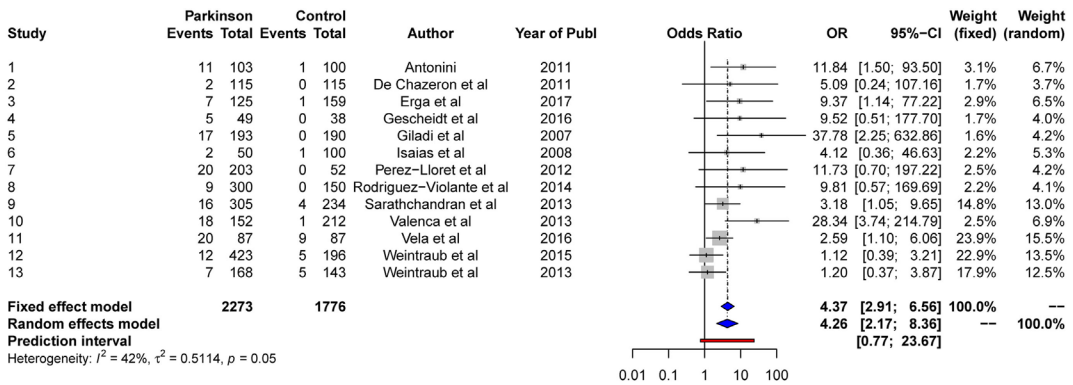

FIGURE 6 | Forest plot for hypersexuality.

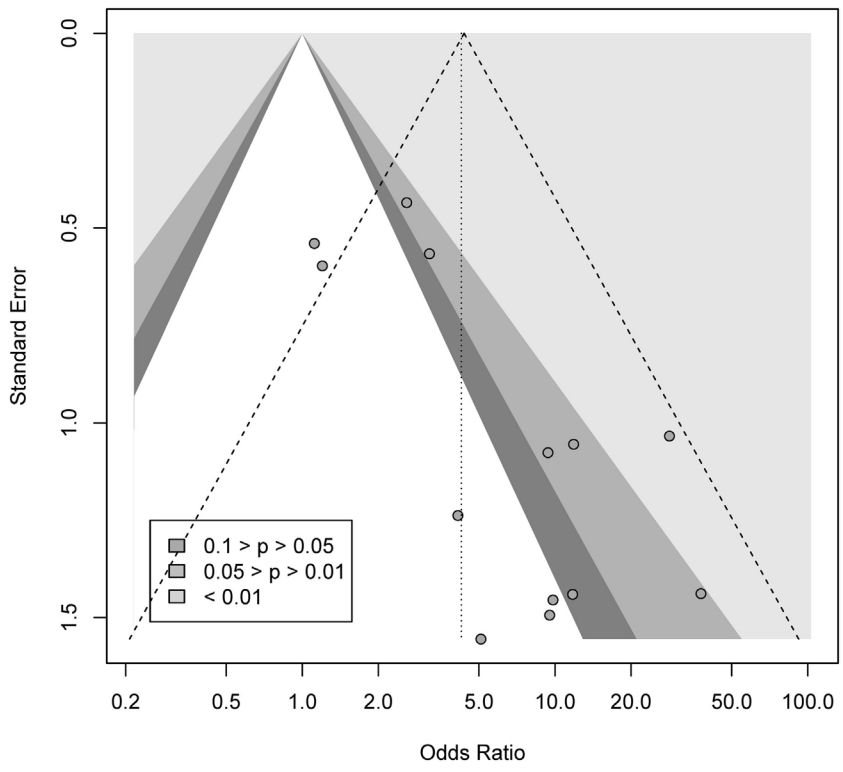

FIGURE 7 | Contour-enhanced funnel plot for hypersexuality.

Mixed-Effects Model

The results from the meta-regression analysis showed a significant log-*OR* point estimate of β0 = 0.81 (*OR* = 2.48, 95% CI [1.02, 5.00]). The overall moderator model was significant, QM = 7.36 ($p = 0.011$). Both of the moderators included were significant. Disease duration was significant at the 0.05 level, *OR* = 1.20, 95% CI [1.02, 1.40]. Treated PDs was also significant at the 0.05 level, *OR* = 2.63, 95% CI [1.04, 6.61]. The test for residual heterogeneity was non-significant, QE = 7.60, $p = 0.68$.

The model accounted for 96.5% (R^2) of the heterogeneity, and the percentage of residual heterogeneity, I^2, was 2.39%. Tau2, or residual heterogeneity, was 0.02 (SE = 0.28). The QQ-normal plot indicated a normal distribution of the residuals.

Shopping

Random-Effects Model

The results from the random-effects model on *shopping* showed a non-significant *OR* estimate of point 1.80, 95% CI [0.99, 3.27]. The *Q*-statistics were non-significant ($Q = 22.3$, $p > 0.05$), indicating no significant heterogeneity between the studies. The between-study variance, Tau2, was 0.40, and the percentage of unexplained between-study variance $I^2 = 50.8$, 95% CI [4.7, 74.6]. This indicates a moderate level of between-study variance with respect to shopping. See **Figure 8** for a forest plot of the results.

Due to the non-significant intercept, no further analyses were conducted for shopping.

Eating

Random-Effects Model

The results from the random-effects model on *eating* showed a significant *OR* estimate of 2.32, 95% CI [1.15, 4.68]. The *Q*-statistics were significant ($Q = 27.1$, $p < 0.001$), indicating significant heterogeneity between the studies. The between-study variance, Tau2, was 0.58, and the percentage of unexplained between-study variance $I^2 = 66.8$, 95% CI [35.2, 82.9]. This indicates high unexplained between-study variance with respect to eating. See **Figure 9** for a forest plot of the results.

We conducted a contour-enhanced funnel plot estimating publication bias. As seen from **Figure 10**, there seems to be about an equal number of studies lacking in the upper white area, as compared with studies with low standard error lacking in the upper gray area, in order to create more balance in the figure. Thus, this may indicate a small-study effect, but perhaps not due to publication bias. Also, the Rüker's test was non-significant ($t = 0.14$, $p > 0.05$), indicating no publication bias.

The Rosenthal's fail-safe *N* test was significant ($p < 0.0001$), indicating that 64 non-significant studies would be needed in order for the random-effects model to be non-significant.

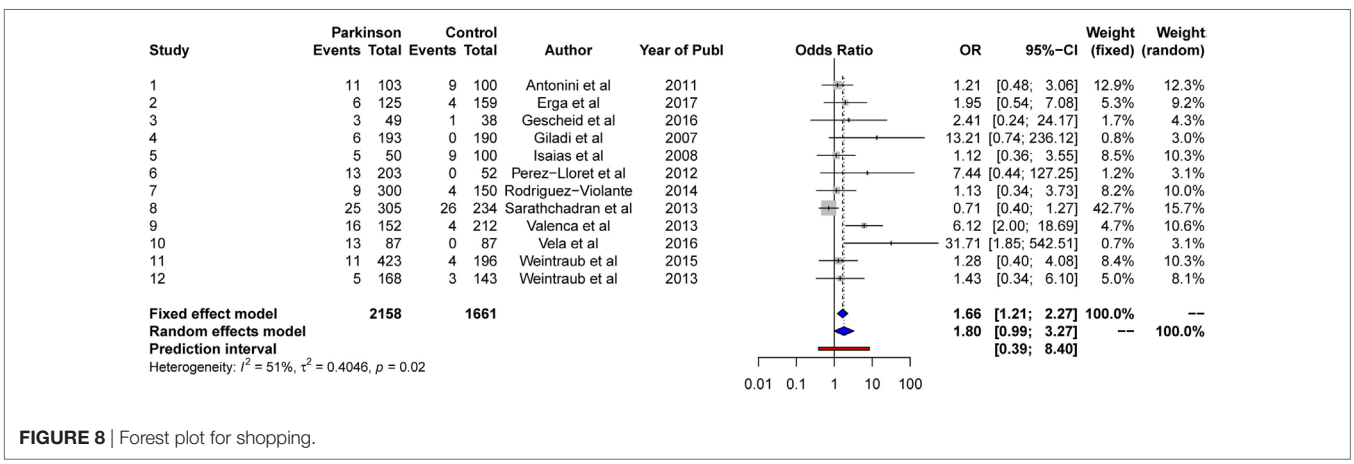

FIGURE 8 | Forest plot for shopping.

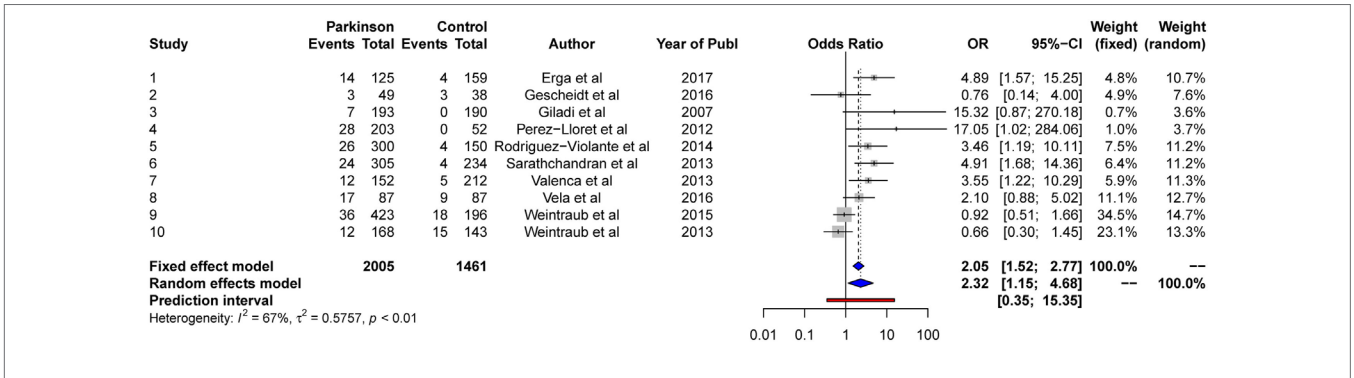

FIGURE 9 | Forest plot for eating.

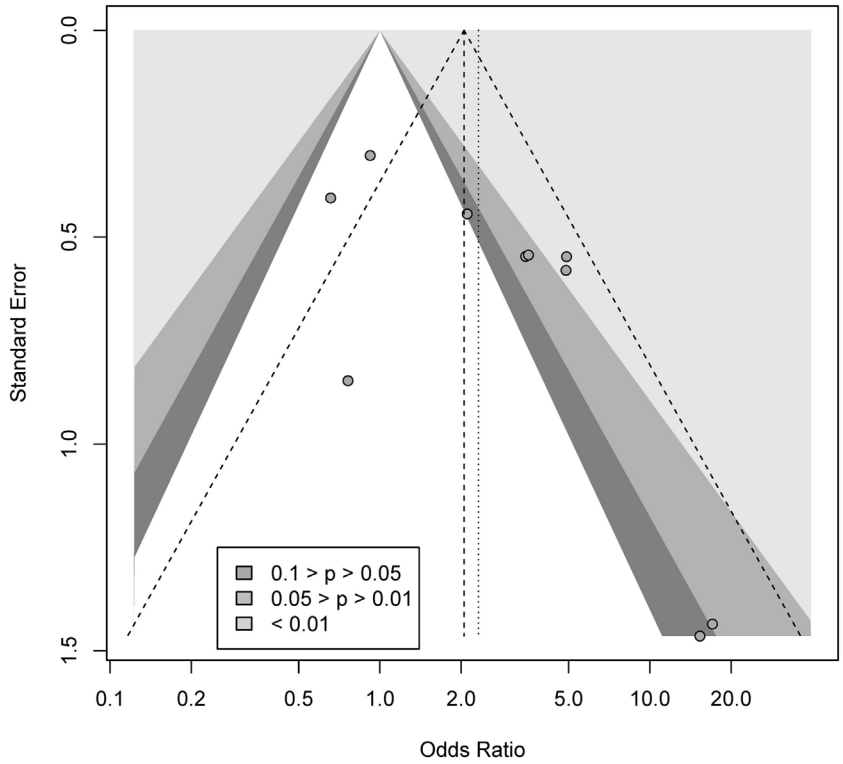

FIGURE 10 | Contour-enhanced funnel plot for eating.

The univariate testing of possible moderators of heterogeneity resulted in three significant univariate models: number of patients using DAs, number of patients using L-dopa and being medically treated for PD. The correlation between the two former moderators was 0.91, thus we only included being medically treated for PD in the mixed model.

Mixed-Effects Model

The results from the meta-regression analysis showed a non-significant log-*OR* point estimate of $\beta 0 = -0.20$ (*OR* = 0.82, 95% CI [0.47, 1.42]). The intercept β0 refers in this model to *de novo* patients or non-medically treated patients. The results indicate that *de novo* PD patients do not differ in comparison with normal controls with respect to eating problems. The overall moderator model was significant, QM = 18.5 ($p = 0.002$), and as stated above, being medically treated for PD (*OR* = 4.06, 95% CI [1.92, 8.58]) was significant. The test for residual heterogeneity was non-significant, QE = 7.89, $p = 0.44$. The model accounted for 100% (R^2) of the heterogeneity, and the percentage of residual heterogeneity, I^2, was 0.0%. Tau2, or residual heterogeneity, was 0.00 (*SE* = 0.13). The QQ-normal plot indicated a normal distribution of the residuals.

Punding

Random-Effects Model

The results from the random-effects model on *punding* showed a significant *OR* of point 3.02, 95% CI [2.31, 3.96]. The *Q*-statistics was non-significant ($Q = 2.88$, $p > 0.05$), indicating no significant heterogeneity between the studies. The between-study variance, Tau2, was 0.0, and the percentage of unexplained between-study variance was: $I^2 = 0.0\%$, 95% CI [0.00, 21.3]. See **Figure 11** for a forest plot of the results.

We conducted a contour-enhanced funnel plot estimating publication bias. As seen from **Figure 12**, the plot indicated a larger number of studies with standard error lacking in the gray area, as in comparison to studies with standard errors lacking in the white area, in order to create more balance in the figure. Thus, this does not indicate a small-study effect or publication bias. Due to the low number of studies (<10), no Rüker's test was conducted.

Due to the I^2 estimate, no mixed-effects model was conducted. Hence, no further testing was applied for punding.

Hobbying

Random-Effects Model

The results from the random-effects model on *hobbying* showed a non-significant *OR* at point 1.73, 95% CI [0.48, 6.18]. The *Q*-statistics were significant ($Q = 26.5$, $p < 0.0001$), indicating significant heterogeneity between the studies. The between-study variance, Tau2, was 0.78, and the percentage of unexplained between-study variance $I^2 = 81.1$, 95% CI [59.5, 91.2]. This indicates large unexplained between-study variance with respect to hobbying. See **Figure 13** for a forest plot of the results.

As two of the six *hobbying* studies included are using *de novo* PDs, we decided to use patients being medically treated for PD as a moderator.

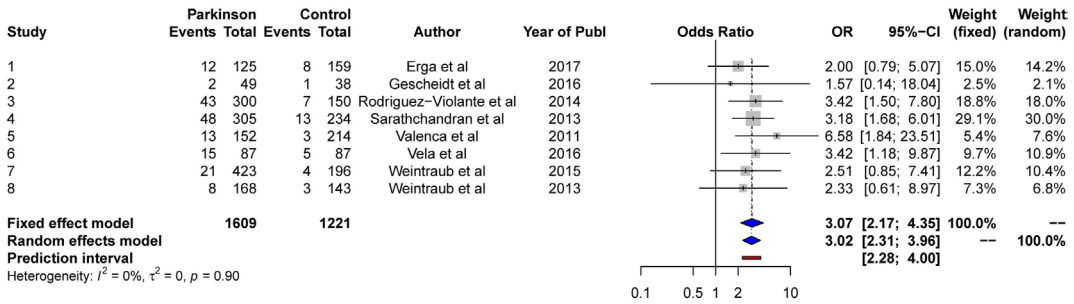

FIGURE 11 | Forest plot for punding.

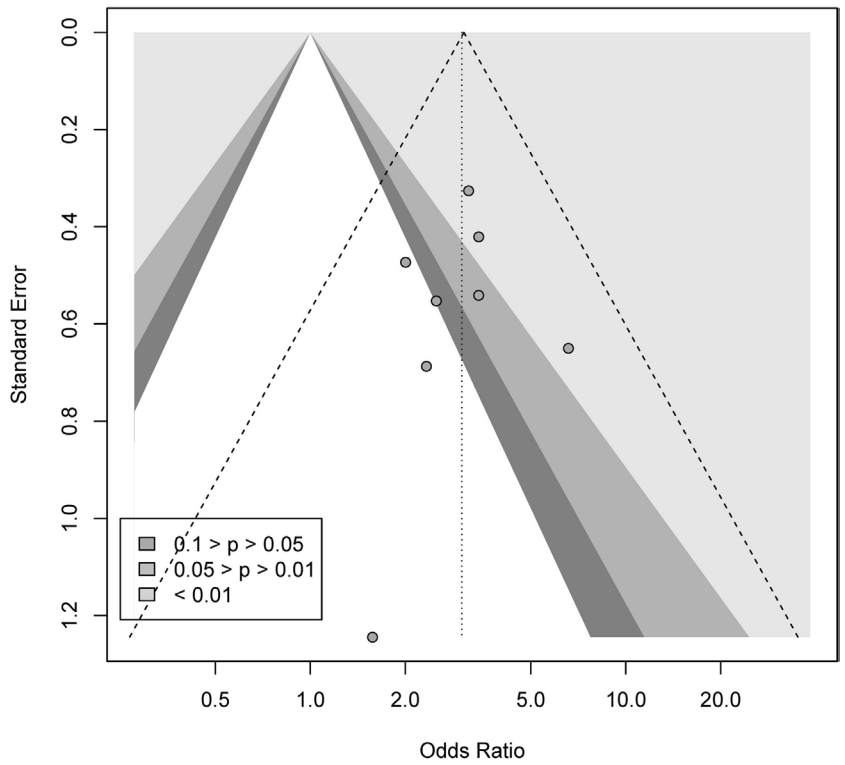

FIGURE 12 | Contour-enhanced funnel plot for punding.

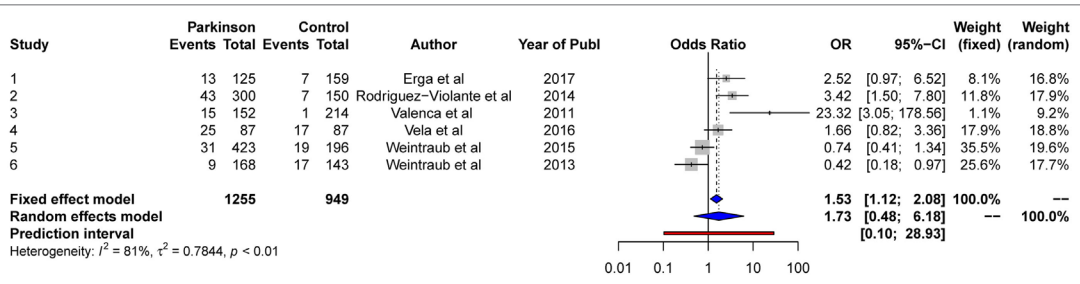

FIGURE 13 | Forest plot for hobbying.

Mixed-Effects Model

The results from the meta-regression analysis showed a non-significant log-*OR* point estimate of $\beta 0 = -0.53$ (*OR* = 0.59, 95% CI [0.20, 1.79]). The intercept β0 refers in this model to *de novo* patients, or non-medically treated patients. The results indicate that *de novo* PD patients do not differ in comparison with normal controls with respect to hobbying.

The overall moderator model was significant, QM = 8.53 ($p = 0.04$), and being medically treated for PD (*OR* = 4.66, 95% CI [1.08, 20.0]) was significant. The test for residual heterogeneity was non-significant, QE = 7.59, $p = 0.11$. The model accounted for 92.6% (R^2) of the heterogeneity, and the percentage of residual heterogeneity, I^2, was 27.60%. Tau2, or residual heterogeneity, was 0.00 (SE = 0.28).

The QQ-normal plot indicated a normal distribution of the residuals.

DISCUSSION

This is, as far as we know, the first meta-analysis to examine ICDs in PD using case–control studies. With this quantitative synthesis we wanted to summarize the existing research and extend earlier reviews in order to better understand, and quantify the association between ICDs in PD. The estimated *OR*s ranged between 2.07 for having any ICD, and 4.26 for hypersexuality. These results demonstrate that ICDs are significantly associated with PD, which is in line with previous narrative reviews (17, 23, 26).

In several of the random-effects models, there was significant heterogeneity, with high between-study variations, as shown with index I^2. This implies that there are important between-study characteristics that moderate the between-study estimates of the true effect. Using meta-regression models, we identified sources of between-study variations by modeling moderators of heterogeneity. This is vital for the development of new hypotheses because moderators can identify factors that may be of significance and thus, effectively target treatment and prevention strategies (66).

The results suggest that impulsive behavior is not an invariant feature of PD, but varies by a number of important explanatory variables including; being medically treated for PD and disease duration. Still, it should be noted that the associations are not at the individual level, but at the study level, or as a moderation of between-study estimates. This distinction is important. That said, DA treatment has been suggested as a risk factor for ICDs (67), and our results seem to support this notion. Number of patients using Levodopa, however, was only significant in a bivariate model for eating. Still, previous studies have identified levodopa as a possible risk factor for ICDs (17, 23). However, and notably, the moderator: being medically treated for PD covers all types of medication, L-dopa included. Thus, the likely explanation for the lack of significance is the lack of power, or the relatively low number of studies included in the present meta-analysis. Thus, for *shopping* the random-effects estimate was almost significant, with the 95% CI ranging from 0.99 to 3.27. Notably, the fixed-effects model for *shopping* was significant (*OR* = 1.66, 95% CI [1.2147, 2.2742]), meaning there is an effect for the studies included, but that the effect cannot be generalized to the wider population of studies. However, overall, it should also be noted that our mixed-effects models explained a significant amount of heterogeneity in the different models, to the point where there was no heterogeneity left to explain.

Still, and as mentioned in Section "Introduction," ICDs in PD do have a multifactorial nature to be considered. Several variables regarded as risk factors were not included in our data, e.g. novelty-seeking personality traits, personal or family history of addictions prior to PD diagnosis, comorbid psychiatric disorders, and cognitive dysfunctions (e.g., decision making, set-shifting, etc.) (68). It is important to stress the multifactorial nature of ICDs in PDs, as not all patients developing ICDs are exposed to dopaminergic medications (69). Thus, other explanations and mechanisms should be identified, especially related to individual genetically vulnerability. Genetically, studies have shown that dopaminergic, opioid, and serotonergic genotypes are related to ICDs in PDs. In addition, environmental and cultural factors may also contribute (70).

Publication Bias

As the presented results show, two of the models (hypersexuality and having any ICD) had some possibility of publication bias according to the contour-enhanced plots. For the other models, the plots indicated very little publication bias. Notably also, the Rüker's test was not significant for any model, supporting an interpretation of lack of publication bias within the models/results. Regarding the Rosenthal's fail-safe *N* from 64 (*eating*) to 165 (*hypersexuality*) to 226 (any ICD) non-significant studies would needed to be included to make the overall results non-significant. Overall, this suggest stability of results.

Strengths and Limitations

The inclusion of observational studies in meta-analyses has led to questions about validity of results. Observational studies are in general criticized as susceptible to subjective interpretations, unidentified confounding variables, and risk modification. The analysis of the data from the meta-analysis itself is accordingly also vulnerable to subjective bias (66, 71).

We made use of random-effects models, which are generally more vulnerable to publication bias than fixed-effects estimates. On the other side, using a fixed-effects model would assume only within-study errors, or no between-study variation, which is an assumption that is seldom met (55).

We did not conduct a subgroup sensitivity analysis due to the low number of studies included. However, with a larger sample of studies, this would enable researchers to evaluate the impact of heterogeneity versus the impact of publication bias in the estimates (72).

When evaluating the methods used, we depended on data reported in the included studies. We did not contact the authors if methods were poorly reported. Unclear reporting does not necessarily mean insufficient study administration, but can limit the understanding of the study (17).

Although it can be challenging, one of the intents of a meta-analysis is to find and assess all studies meeting a set of inclusion criteria. Many studies may not have been published and can systematically differ from the published ones. Significant, positive findings are shown to be more likely to be published compared

to small, negative studies, hence this may lead to publication bias (66, 72, 73). Still, attempts to retrospectively gather information from unpublished studies does not seem to address publication bias sufficiently (74).

A potential bias can arise due to excluding studies reported in languages other than English. However, language bias is reported to only have modest or no effect (75).

It should also be noted that direct comparisons of ICD prevalence in various studies are complicated by different assessment methods, with emphasis put on different time frames (76).

Implications

The results of the present meta-analysis show that there is a significant chance of developing ICDs in PD patients compared to healthy controls. The investigation of possible moderators of heterogeneity resulted in two variables (being medically treated for PD and disease duration) which are significant in mixed models. This is supported by previous studies looking into risk factors for development of ICDs in PD (13, 26, 28). The present results can as such have implications for how PD patients should be met and treated. Thus, practitioners should routinely ask about behavioral changes during assessment, and relevant countermeasures such as down-titration of DA and cognitive behavioral therapy should be considered. Warning patients about behavioral side-effects of DA should be implemented, as least for vulnerable PD patients (77–79).

CONCLUSION

The present results show a significant relationship between ICDs and PD. Duration of PD and being medically treated for PD are moderators positively associated with ICDs in PD patients. Proper assessment during physician consultations is critical as ICDs can significantly harm the overall social functioning and personal relationships of this patient group. The use of DAs seems to pose an especially high-risk factor for ICD development, thus pharmacological treatment needs to be carefully monitored. Caretakers and relatives should be involved, as patients may lack insight, or find their behavior embarrassing.

Finally, conducting a precise meta-analysis is dependent on the quality of the included research articles. As there always will be a risk of publication bias, results must be interpreted with caution.

AUTHOR NOTES

Ref. (15, 16, 33, 42, 44–55) are studies included in the meta-analysis.

AUTHOR CONTRIBUTIONS

HM, YM, and SK did the literature research and study coding. HM did the statistical analysis. All authors have significantly contributed ideas, commenting on the manuscript and reviewing the paper during the writing process.

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SYSTEMATIC REVIEW
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Impulse Control Disorder in Parkinson's Disease: A Meta-Analysis of Cognitive, Affective, and Motivational Correlates

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Background: In Parkinson's disease (PD), impulse control disorders (ICDs) develop as side-effect of dopaminergic replacement therapy (DRT). Cognitive, affective, and motivational correlates of ICD in medicated PD patients are debated. Here, we systematically reviewed and meta-analyzed the evidence for an association between ICD in PD and cognitive, affective, and motivational abnormalities.

Methods: A systematic review and meta-analysis was performed on PubMed, Science Direct, ISI Web of Science, Cochrane, EBSCO for studies published between 1-1-2000 and 8-3-2017 comparing cognitive, affective, and motivational measures in PD patients with ICD (ICD+) vs. those without ICD (ICD–). Exclusion criteria were conditions other than PD, substance and/or alcohol abuse, dementia, drug naïve patients, cognition assessed by self-report tools. Standardized mean difference (SMD) was used, and random-effect model applied.

Results: 10,200 studies were screened (title, abstract), 79 full-texts were assessed, and 25 were included (ICD+: 625 patients; ICD–: 938). Compared to ICD–, ICD+ showed worse performance reward-related decision-making (0.42 [0.02, 0.82], $p = 0.04$) and set-shifting tasks (SMD = −0.49 [95% CI −0.78, −0.21], $p = 0.0008$). ICD in PD was also related to higher self-reported rate of depression (0.35 [0.16, 0.54], $p = 0.0004$), anxiety (0.43 [0.18, 0.68], $p = 0.0007$), anhedonia (0.26 [0.01, 0.50], $p = 0.04$), and impulsivity (0.79 [0.50, 1.09], $p < 0.00001$). Heterogeneity was low to moderate, except for depression ($I^2 = 61\%$) and anxiety ($I^2 = 58\%$).

Conclusions: ICD in PD is associated with worse set-shifting and reward-related decision-making, and increased depression, anxiety, anhedonia, and impulsivity. This is an important area for further studies as ICDs have negative impact on the quality of life of patients and their caregivers.

Keywords: Parkinson's disease, impulse control disorder, cognition, affective factors, motivation, impulsivity, meta-analysis, depression

INTRODUCTION

Impulse control disorders (ICDs), such as pathological gambling, hypersexuality, binge-eating, and compulsive shopping, can occur in over 13% of medicated Parkinson's disease (PD) patients (1). Although ICDs are recognized as side-effect of dopamine replacement therapy (DRT), mainly D2 dopamine agonists and levodopa, their pathophysiology is unclear.

It has been hypothesized that, in vulnerable individuals, DRT used to restore dopamine levels in nigrostriatal circuitry may overstimulate the less severely affected mesocorticolimbic circuitry (2). Mesocorticolimbic overstimulation may disrupt prefrontal-dependent executive function, affect and motivation and thus increase vulnerability to ICD. According to this view, in medicated PD patients, we should expect a correlation between ICD and cognitive, affective and motivational factors. However, data in the literature are inconclusive.

Studies on cognition, affective processing and motivation conducted in small cohorts of PD patients with and without ICD (i.e., n: 17–155 patients) yielded inconsistent findings with respect to frontal cognitive abilities in PD patients with ICD. Some studies reported worse performance in executive function, including set-shifting (3–7), working memory (8), concept formation and reasoning (5, 7), and reward-related decision-making (9–15) in PD with ICD (ICD+) compared to PD without ICD (ICD-). Conversely, other studies found similar performances for inhibition (9, 16–18), set-shifting (19, 20), working memory (3, 11, 17, 21, 22), and reward-related decision-making (16, 17, 20, 23). Finally, a single study reported better executive functions in ICD+ (24). Reports on affective factors are also inconclusive, as self-reported depression and anxiety were sometimes found to be associated with ICD (18, 20, 21, 25–28), and sometimes not (3–6, 17, 19, 22, 29–31). However, motivational factors such as self-reported apathy (11, 21, 27, 28), anhedonia (27, 32), and impulsivity (17, 20–22, 32) appeared to be elevated in ICD+ vs. ICD–.

A recent meta-analysis identified several cognitive subdomains (i.e., concept formation, set-shifting, reward-related decision-making, and visuospatial abilities) to be worse in ICD+ vs. ICD– (33), but it included a mixed sample of medicated and drug naïve patients that did not allow to explore the relationship between cognitive disturbances, DRT and ICD.

Moreover, it included patients with comorbidities for substance abuse and/or dementia, two factors that could be independently associated with cognitive changes. Finally, the relationship between cognition-emotion and cognition-motivation, critical to understanding the broader context in which ICDs develop, was not explored in the previous meta-analysis (34).

To reconcile discordant findings in the literature about cognitive, affective and motivational correlates of ICD in medicated PD patients, a systematic review and meta-analysis was conducted. Moreover, this work is meant to address the issues of a previous meta-analysis and to offer new information on this topic. To this aim, we applied stricter inclusion and exclusion criteria, by including only studies on PD patients under DRT at the time of assessment and free from co-morbid substance abuse and/or dementia. Moreover, we included studies with affective and motivational measures, so that any cognitive change could be interpreted within the broader context of cognition-emotion and cognition-motivation relationships (34). A clear understanding of cognitive, affective and motivational changes in ICD may indirectly increase our understanding of ICD pathophysiology and in turn its management.

Abbreviations: DBS, deep brain stimulation; DRT, dopamine replacement treatment; H and Y, Hoehn and Yahr scale; ICD, impulse control disorder; LEDD, levodopa equivalent daily dose; PD, Parkinson's disease; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; SDM, standardized mean difference; STN-DBS, sub thalamic nucleus deep brain stimulation; UPRDS, Unified Parkinson's Disease Rating Scale.

METHODS

Study Design, Participants, and Comparators

A systematic review and meta-analysis were performed to identify cognitive, affective and motivational factors associated with ICD in PD under DRT (ICD+). The comparator group was patients with PD but no ICD (ICD–).

Search Strategy and Selection Criteria

On June 26th 2016, PubMed, Science Direct, ISI Web of Science, Cochrane, EBSCO were searched for peer-reviewed papers in English, Italian and Spanish published since January 2000, when the first report of ICD development after dopaminergic medication initiation was reported (35). The systematic review was further updated on March 8th 2017.

Studies were identified using the following string (36) in PubMed: "(Parkinson's disease) AND (impulse control disorders OR impulsivity OR cognition OR decision-making)." The search strategy for the other databases included (Parkinson's disease) AND (impulse control disorders), then (Parkinson's disease) AND (impulsivity), then (Parkinson's disease) AND (cognition), and (Parkinson's disease) AND (decision-making). A total of 40,672 papers were identified. After exclusion of duplicates, 10,200 papers were title and abstract screened.

Studies were included if: (a) PD patients were under DRT; (b) ICD assessment was performed in a reliable manner with the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), the QUIP rating scale (QUIP-rs), the Minnesota Impulse Disorders Interview, clinical interview based on diagnostic criteria, or a combination of these; (c) performances of PD patients with ICD (ICD+) were compared with those with PD but no history of ICD (ICD–); (d) cognitive, affective, and/or motivational measures were reported. A further inclusion criterion was independence of samples. Only baseline data for prospective studies and the study with the largest sample for multiple studies published by the same author(s) were included.

We excluded reviews, case studies, commentaries, letters, abstracts and dissertations, and postal surveys. Studies including drug naïve PD patients were also excluded since we were interested in ICD developed as a DRT side-effect. Studies in which PD patients underwent non-pharmacological treatments

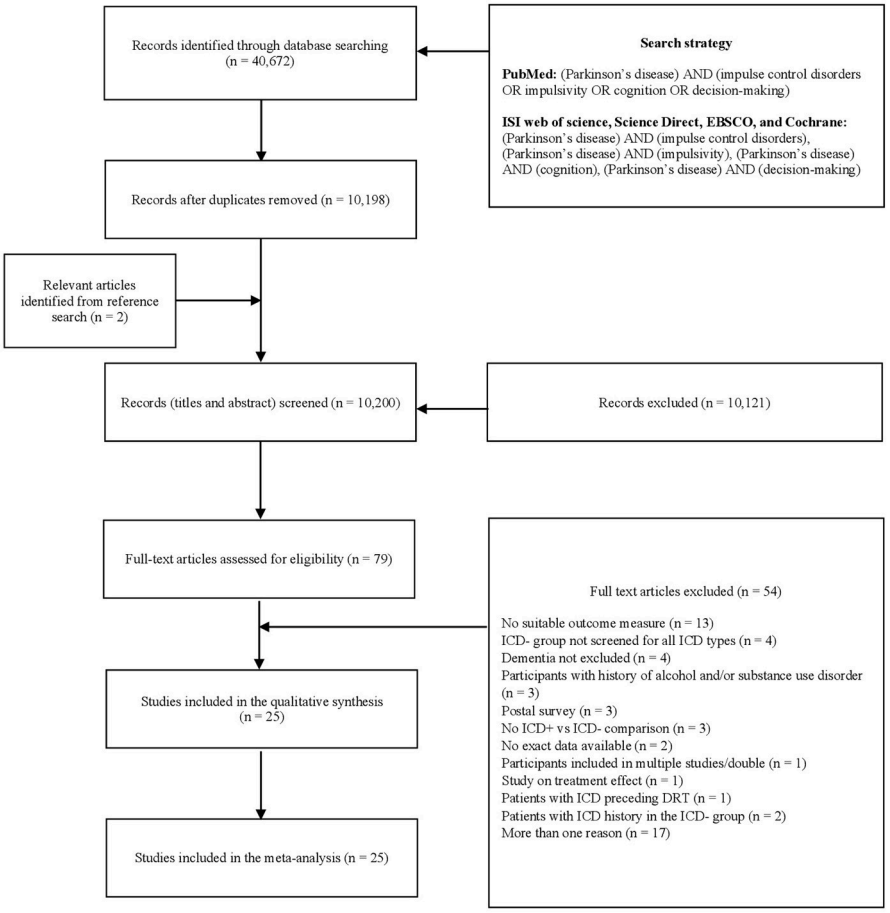

FIGURE 1 | PRISMA diagram of the study (www.prisma-statement.org). DRT, dopaminergic replacement treatment; ICD, impulse control disorder; ICD+, PD patients with ICD; ICD–, PD patients without ICD; PD, Parkinson's disease.

such as deep brain stimulation (DBS) were excluded. This criterion was based on controversial reports of either ICD amelioration or ICD appearance after DBS (37), and the notion that DBS may worsen some cognitive outcomes (38). Studies including participants with dementia and drug/alcohol abuse were excluded, as these conditions might be independently associated with cognitive and neuropsychiatric changes. Other exclusion criteria were: cognition assessed by self-report measures or by general screening tools (e.g., Mini-Mental State Examination) because of their limited specificity and sensitivity (39). Studies focusing on dopamine dysregulation syndrome and/or punding only were not included since these conditions are considered different from ICD, as they are more common in patients with advanced PD, cognitive impairment and dementia (40). However, screening questionnaires (e.g., QUIP, QUIP-rs) include dopamine dysregulation syndrome and punding, and some ICD+ patients we included may have had these conditions too, in addition to ICD. Finally, to ensure that the ICD- group included patients without any type of ICD, studies not assessing all ICD types (e.g., using only the South Oaks Gambling Screen) were excluded.

Data Extraction

Following exclusion of duplicate and irrelevant articles through title and abstract screening, 79 papers were included for full-text evaluation. Reference lists of these studies were manually searched to identify additional relevant articles, and two papers were included at this stage.

Two reviewers (AM, DDL) independently screened titles and abstracts using Rayyan software (41), and three reviewers (AM, DDL, ST) independently evaluated papers selected for full-text examination. Disagreements were resolved through discussions. Disagreement concerned one paper (42) over the 75 selected for full-text examination (inter-rater agreement: 98.67%). Twenty-five articles were included for quantitative analysis (**Figure 1**).

Corresponding authors of five studies were contacted for exact data. Means and standard deviations were obtained for two studies, which reported median and interquartile ranges (20, 25), according to a proposed formula (43). Two reviewers (AM, DDL) independently extracted the following data: sample size, age at evaluation, age at PD onset, PD duration, education (years), Hoehn and Yahr (H and Y) stage, Unified

TABLE 1 | Characteristics of the studies included in the meta-analysis.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	Education (y)*	H and Y	UPDRS-III (ON)*	Depression†	Antidepressant (N)
Bentivoglio et al. (17)	ICD+: 17 (14) ICD–: 17 (11)	ICD+: 62.0 (10.1) ICD–: 63.9 (9.2)	NR	ICD+: 6.9 (3.8) ICD–: 7.3 (4.4)	ICD+: 8.7 (3.7) ICD–: 10.2 (4.4)	ICD+: 2.0 (0.8) ICD–: 2.3 (0.5)	ICD+: 23.8 (11.0) ICD–: 22.5 (6.9)	NO	ICD+: 2 ICD–: 4
Biundo et al. (3)	ICD+: 33 (18) ICD–: 24 (17)	ICD+: 61.3 (10.2) ICD–: 70.4 (6.8)	ICD+: 53.2 (10.6) ICD–: 60.5 (10.0)	ICD+: 8.8 (4.8) ICD–: 8.9 (5.4)	ICD+: 11.8 (3.9) ICD–: 10.4 (4.8)	NR	ICD+: 30.2 (13.2) ICD–: 32.3 (12.8)	NO	NR
Biundo et al. (4)	ICD+:58 (38) ICD–:52 (32)	ICD+: 60.3 (9.3) ICD–: 63.1 (10.2)	ICD+: 50.1 (12.1) ICD–: 54.7 (11.6)	ICD+: 9.0 (5.5) ICD–: 8.0 (5.7)	ICD+: 10.9 (4.3) ICD–: 11.3 (4.7)	ICD+: 2.4 (0.7) ICD–: 2.3 (0.7)	ICD+: 26.7 (16.5) ICD–: 28.5 (12.3)	NO	NR
Cera et al. (16)	ICD+:9 (6) PG:10 (7) ICD–:14 (7)	ICD+: 59.3 (6.8) PG: 60.6 (6.8) ICD–: 59.0 (9.5)	NR	ICD+: 29.0 (8.5)‡ PG: 28.2 (12.3) ICD–: 27.2 (8.4)	ICD+: 10.3 (3.2) PG: 11.7 (2.6) ICD–: 11.7(1.9)	ICD+: 1.7 (0.3) PG: 1.9 (0.2) ICD–: 1.7 (0.0)	ICD+: 21.4 (4.2) PG: 20.5 (6.8) ICD–: 21.6 (6.9)	NO	NR
Cilia et al. (30)	ICD+: 11 (10) ICD–: 40 (27)	ICD+: 57.4 (5.8) ICD–: 55 (7)	ICD+: 49.5 (4.7) ICD–: 46.4 (7.2)	ICD+: 8.4 (3.4) ICD–: 8.4 (5.1)	NR NR	ICD+: 2.1 (0.6) ICD–: 2.3 (0.8)	ICD+: 18.0 (11.0) ICD–: 19.1 (8.5)	YES	NO
Claassen et al. (31)	ICD+: 12 (8) ICD–:12 (6)	ICD+: 59.4 (5.5) ICD–: 60.8 (7.2)	NR	ICD+: 6.5 (4.7) ICD–: 6.1 (3.8)	ICD+: 17.1 (2.7) ICD–: 16.3 (2.8)	NR	ICD+: 15.9 (6.6) ICD–: 15.7 (8.3)	YES	NO
Djamshidian et al. (8)	ICD+:18 (13) ICD–:12 (9)	ICD+: 55 (2.1) ICD–: 63.6 (2.2)	ICD+: 43.9 (2.1) ICD–: 50.9 (2.2)	ICD+: 10.9 (1.2) ICD–: 12.7 (2.1)	ICD+: 12.2 (0.9) ICD–: 14.2 (1.3)	NR	ICD+: 18.0 (2.2)§ ICD–: 13.0 (1.4)	NO	NR
Djamshidian et al. (9)	ICD+: 28 (21) ICD–:24 (21)	ICD+: 54.6 (9.2) ICD–: 64.2 (10.1)	ICD+: 44.5 (8.7) ICD–: 52.5 (9.6)	ICD+: 10.1 (5.5) ICD–: 11.7 (7.2)	ICD+: 13.4 (3.0) ICD–: 14.7 (3.6)	NR	ICD+: 15.5 (8.3) ICD–: 14.4 (5.8)	NO	ICD+: 4 ICD–: 2
Erga et al. (18)	ICD+: 38 (26) ICD–:87 (49)	ICD+: 67.9 (7.7) ICD–: 71.4 (9.8)	NR	ICD+: 7.4 (1.6) ICD–: 7.4 (1.9)	NR	ICD+: 2.2 (0.5) ICD–: 2.2 (0.6)	ICD+: 23.8 (10.5) ICD–: 22.2 (10.7)	NO	ICD+: 5 ICD–:11
Housden et al. (11)	ICD+: 18 (11) ICD–:18 (12)	ICD+: 62.3 (7.6) ICD–: 67.7 (5.5)	NR	ICD+: 13.9 (9.0) ICD–: 12.9 (8.3)	NR	ICD+: 2.5 (0.6) ICD–: 2.5 (0.7)	ICD+: 20.0 (6.6) ICD–: 21.3 (10.4)	YES	NR
Joutsa et al. (23)	ICD+:9 (9) ICD–:8 (8)	ICD+: 59.3 (8.4) ICD–: 60.1 (5.9)	ICD+: 53.1 (8.7) ICD–: 55.3 (5.1)	ICD+: 6.1 (1.8) ICD–: 5.1 (2.0)	NR	NR	ICD+: 31.7 (4.9) ICD–: 30.1 (10.7)	YES	NR
Leroi et al. (21)	ICD+: 35 ICD–:38	NR	NR	NR	NR	NR	ICD+: 26.9 (10.0) ICD–: 24.1 (10.4)	NO	NR
Mack et al. (19)	ICD+: 17 (11) ICD–:17 (8)	ICD+: 61.1 (7.5) ICD–: 63.8 (8.5)	ICD+: 48.1 (5.2) ICD–: 53.7 (10.0)	ICD+: 13.1 (6.9) ICD–: 10.2 (5.6)	NR	ICD+: 2.8 (1.0) ICD–: 2.4 (1.3)	ICD+: 36.7 (16.1) ICD–: 28.5 (15.2)	NO	YES
Merola et al. (42)	ICD+: 8 (8) ICD–: 113 (60)	NR	ICD+: 48.2 (9.4) ICD–: 46.6 (7.3)	ICD+: 13.4 (7.8) ICD–: 13.1 (4.4)	NR	NR	ICD+: 14.3 (6.7) ICD–: 15.5 (7.8)	NO	NR
O'Sullivan et al. (29)	ICD+:39 (31) ICD–:61 (44)	ICD+: 59.3 (9.1) ICD–: 66.6 (9.5)	ICD+: 45.8 (10.3) ICD–: 55.9 (11.7)	ICD+: 12.0 (6.0) ICD–: 9.6 (7.1)	NR	ICD+: 2.6 (0.5) ICD–: 2.2 (0.5)	ICD+: 16.3 (7.5) ICD–: 18.5 (8.8)	NO	NR
O'Sullivan et al. (28)	ICD+: 30 (26) ICD–: 62 (46)	ICD+: 58.9 (8.5) ICD–: 66.4 (9.7)	ICD+: 46.2 (10.1) ICD–: 55.8 (12.0)	ICD+: 11.5 (5.9) ICD–: 9.5 (7.0)	NR	ICD+: 3 (2–3)¶ ICD–: 2 (2–3)	NR	NO	YES
Pettorruso et al. (32)	PG: 11 (8) ICD+: 23 (18) ICD–: 120 (60)	PG: 64.9 (10.9) ICD+: 62.0 (9.1) ICD–: 67.7 (9.4)	PG: 56.6 (10.6) ICD+: 53.2 (9) ICD–: 60.6 (9.2)	PG: 8.3 (3.2) ICD+: 8.8 (6) ICD–: 7.0 (5.4)	PG: 10 (4.2) ICD+: 11.3 (4.4) ICD–: 11 (5.2)	NR	PG: 20.4 (12.3) ICD+: 18.4 (8.5) ICD–: 20.4 (8.4)	NO	NR
Pineau et al. (20)	ICD+: 17 (14) ICD–: 20 (13)	ICD+: 55 (37–69)‖ ICD–: 55 (40–62)	ICD+: 48 (32–65)‖ ICD–: 48 (35–55)	ICD+: 7 (2–10)‖ ICD–: 5.5 (4–12)	ICD+: 7 (3–7)‖ ICD–: 7 (3–7)	NR	ICD+: 7 (0–23)‖ ICD–: 8.5 (0–34)	NO	NR
Piray et al. (22)	ICD+: 16 (14) ICD–: 15 (12)	ICD+: 64.4 (3.3) ICD–: 63.3 (4.0)	NR	ICD+: 9.6 (2.5) ICD–: 8.9 (3.1)	NR	ICD+: 2.5 (0.5) ICD–: 2.4 (0.6)	ICD+: 19.0 (5.3) ICD–: 19.6 (6.4)	NO	NR

(Continued)

TABLE 1 | Continued

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	Education (y)*	H and Y	UPDRS-III (ON)*	Depression†	Antidepressant (N)
Pontieri et al. (27)	PG: 21 ICD+: 36 ICD–: 98	PG: 58 (9) ICD+: 64 (8) ICD–: 66 (9)	PG: 51 (8) ICD+: 57 (10) ICD–: 61 (9)	PG: 8 (5) ICD+: 7 (4) ICD–: 5 (3)	PG: 10 (4) ICD+: 11 (4) ICD–: 10 (4)	PG: 2.0 (0.5) ICD+: 1.9 (0.8) ICD–: 1.8 (0.5)	PG: 21.5 (11.6) ICD+: 19.1 (12.7) ICD–: 19.0 (11.9)	NO	PG: 4 ICD+: 7 ICD–: 26
Rossi et al. (10)	ICD+: 7 (6) ICD–: 13 (10)	ICD+: 61.4 (6.9) ICD–: 65.1 (3.8)	ICD+: 52.0 (5.6) ICD–: 58.3 (6.9)	NR	ICD+: 13.8 (4.1) ICD–: 11.9 (5.5)	ICD+: 2.2 (0.7) ICD–: 2.0 (0.7)	ICD+: 17.0 (9.1) ICD–: 14.7 (6.7)	NO	NR
Tessitore et al. (5)	ICD+: 15 (13) ICD–: 15 (12)	ICD+: 62.9 (8.6) ICD–: 63.1 (8.0)	NR	ICD+: 5.3 (2.9) ICD–: 6.6 (3.9)	ICD+: 9.8 (5) ICD–: 12.9 (8)	ICD+: 1.3 (0.5) ICD–: 1.4 (0.6)	ICD+: 10.9 (4.5) ICD–: 12.1 (4.4)	NO	NO
Vela et al. (25)	ICD+: 49 (28) ICD–: 35 (23)	ICD+: 48 (44–52)¶ ICD–: 46 (42–52)	NR	ICD+: 7 (3–11)¶ ICD–: 3 (1–10)	NR	ICD+: 2 (2–2)¶ ICD–: 2 (1–2)	ICD+: 16(10–22)¶ ICD–: 17 (11–24)	NO	NO
Vitale et al. (6)	HS: 13 (13) M-ICD: 10 (9) ICD–: 14	HS: 68.7 (5.4) M-ICD: 62.2 (7.5) ICD–: 61.3 (8.2)	HS: 59.5 (5.6) M-ICD: 55.5 (5.3) ICD–: 53.2 (9.1)	HS: 8.5 (3.9) M-ICD: 8.1 (4.5) ICD–: 7.6 (4.4)	HS: 9.5 (5) M-ICD: 8.2 (2.8) ICD–: 13 (4)	HS: 1.8 (0.5) M-ICD: 1.5 (0.7) ICD–: 1.8 (0.8)	HS: 15.1 (6.5) M-ICD: 13 (7.1) ICD–: 11.7 (6)	NO	HS: 1 M-ICD: 2 ICD–: 0
Wu et al. (26)	S-ICD: 7 M-ICD: 10 ICD–: 9	S-ICD: 62.3 (3.9) M-ICD: 58.1 (2.8) ICD–: 60.2 (3.2)	S-ICD: 51.7 (4.0) M-ICD: 43.8 (3.4) ICD–: 50.3 (3.4)	S-ICD: 10.6 (2.0) M-ICD: 14.3 (11.2) ICD–: 9.9 (2.1)	NR	NR	NR	NO	NR

Ref	Antipsychotic: N	LEDD (mg)			Outcomes	ICD	
		Total LEDD*	LD-LEDD*	DA-LEDD*		Diagnosis**	Type: N
Bentivoglio et al. (17)	ICD+: 3	ICD+: 606.1 (319.2) ICD–: 616.2 (367.8)	ICD+: 539 (264.3) ICD–: 455.7 (299.0)	ICD+: 172.9 (112.2) ICD–: 192.5 (88.5)	Digit span forward; CBTT; Immediate visual memory; RAVLT; Digit span backward; Double barrage; FAB; MWCST; RCPM; Stroop; Fluency (semantic, phonological); IGT; Apraxia (ideomotor, orofacial, constructional); Oral confrontation naming (nouns, verbs); HAM-D; HAM-A; BIS-11	Clinical interview (DSM-IV)	HS: 8; CS: 2; PG: 10; BE: 6; M-ICD: 7
Biundo et al. (3)	NR	ICD+: 556.8 (304.6) ICD–: 497.4 (341.2)	NR	ICD+: 186.5 (149.3) ICD–: 165.8 (108.8)	Digit span forward; CBTT; RAVLT; ROCF (copy, delayed); Digit span backward; TMT A; FAB; TMT B; RCPM; Similarities for abstract verbal reasoning; Stroop; Fluency (semantic, phonological); BDI	MIDI; DSM-IV-TR; interview (caregivers); additional clinical interview	HS: 11; CS: 9; PG: 1; punding: 2; M-ICD: 12
Biundo et al. (4)	NR	ICD+: 923.1 (474.1) ICD–: 722.6 (498.5)	NR	ICD+: 163.7 (111.3) ICD–: 148.9 (105.0)	Digit span forward; CBTT; Prose (immediate, delayed); ROCF; Digit ordering test; TMT-A; TMT B; Stroop; Fluency (semantic, phonological); Naming; VOSP; Clock drawing test; BDI	QUIP-RS; MIDI; clinical interview (patient and carergiver)	HS: 6; CS: 7; PG: 2; hoarding: 2; impulsive aggression: 1; M-ICD: 40
Cera et al. (16)	NO	ICD+: 283.3 (132.9) PG: 294.5 (123.1) ICD–: 307 (96.3)	NR	NR	Stroop test; Emotional Stroop test; Monetary risk tasking task	DSM-IV, QUIP-RS, SOGS	PG:10; M-ICD: 9

(Continued)

TABLE 1 | Continued

Ref	Antipsychotic: N	LEDD (mg)			Outcomes	ICD	
		Total LEDD*	LD-LEDD*	DA-LEDD*		Diagnosis**	Type: N
Cilia et al. (30)	NO	ICD+: 811.8 (229.0) ICD–: 877.3 (289.3)	NR	ICD+: 289.1 (57.5) ICD–: 340.1 (157.2)	FAB; RPM; GDS	Diagnostic criteria; SOGS	PG:1; PG+HS: 5; PG+BE: 2; PG+CS: 2; PG+IA: 1
Claassen et al. (31)	NO	ICD+: 618.7 (361.9) ICD–: 520.3 (314.9)	ICD+: 408.2 (349.6) ICD–: 319.7 (318.9)	ICD+: 293.8 (167.4) ICD–: 200.6 (116.8)	Stop signal task; CESD	QUIP; clinical interview	HS: 5; CS: 5; BE: 6; hobbyism: 9
Djamshidian et al. (8)	NR	ICD+: 971 (183)§ ICD–: 732 (203)	ICD+: 752 (109)§ ICD–: 604 (73)	NR	Digit span backward; Risk Task; Learning task.	Diagnostic criteria	PG: 10; HS:9; CS: 5; BE: 7; DDS: 6; punding: 2; kleptomania: 1
Djamshidian et al. (9)	NR	ICD+: 832 (425) ICD–: 821 (400)	NR	NR	Stroop	Diagnostic criteria	PG: 11; HS: 13; CS: 8; punding:4; kleptomania:1
Erga et al. (18)	NR	ICD+: 730.6 (343.3) ICD–: 658.4 (275.9)	ICD+: 505.2 (279.1) ICD–: 408.7 (266.7)	ICD+: 293.7 (132.4) ICD–: 289.5 (150.0)	CLVT-II; Stroop; Fluency (phonological); VOSP; MADRS	QUIP	M-ICD: 36 (PG: 2; HS: 7; CS:6; BE:14; punding:12; hobbyism:13; DDS: 3)
Housden et al. (11)	NR	ICD+: 891.5 (432.1) ICD–: 804.8 (358.5)	ICD+: 643.5 (254.1) ICD–: 634.2 (301.7)	ICD+: 248 (301.3) ICD–: 170.5 (159.3)	Digit span forward; Digit span backward; KDDT; WTAR; SAT; BDI; STAI-state	Structured interview (diagnostic criteria)	PG:9; BE: 9; HS: 7; CS: 6; DDS: 4; punding: 8
Joutsa et al. (23)	NR	ICD+: 628 (186) ICD–: 762 (269)	NR	ICD+: 173 (80) ICD–: 216 (67)	KDDT	Diagnostic criteria	PG: 5; HS: 4; BE: 1
Leroi et al. (21)	NR	NR	NR	NR	n-back; Fluency (phonological); HADS-D; HADS-A; AES-C; BIS-11	Diagnostic criteria; SOGS	PG: 12; HS: 9; CS: 5; BE: 3; DDS: 3; punding: 3
Mack et al. (19)	NR	ICD+: 1,677.9 (893.0) ICD–: 1,269.3 (560.7)	NR	NR	Digit span; HVLT-R; TMT-A; TMT-B; Fluency (semantic, phonological); NART; BDI	Semistructured interview (diagnostic criteria)	NR
Merola et al. (42)	NR	ICD+: 1576.4 (397.6) ICD–: 1216.2 (403.0)	NR	ICD+: 344.4 (314.5) ICD–: 297.2 (235.3)	Digit span forward; Bi-syllabic words repetition test; CBTT; Paired associate learning; TMT-A; Digit cancelation test; FAB; TMT-B; MWCST; RCPM; Fluency (semantic, phonological); BDI; STAI-state; AES-C	Clinical interview (diagnostic criteria)	PG, HS, CS, punding, DDS
O'Sullivan et al. (29)	NR	ICD+: 927 (658) ICD–: 742 (477)	ICD+: 684 (512) ICD–: 588 (418)	ICD+: 259 (472) ICD–: 139 (200)	HADS-D; HADS-A; BSCS; Impulse buying tendency;	Semistructured interview (diagnostic criteria)	Punding: 20; BE: 14; HS: 12; PG: 11; CS: 11; DDS: 11

(Continued)

TABLE 1 | Continued

Ref	Antipsychotic: N	LEDD (mg)			Outcomes	ICD	
		Total LEDD*	LD-LEDD*	DA-LEDD*		Diagnosis**	Type: N
O'Sullivan et al. (28)	NR	ICD+: 981 (651) ICD–: 645 (443)	ICD+: 701 (508) ICD–: 543 (399)	ICD+: 201 (0–284)¶ ICD–: 0 (0–201)	HADS-D; HADS-A	Semistructured interview (diagnostic criteria)	HS: 12; PG: 11; CS: 8; BE: 8; punding: 15
Pettorruso et al. (32)	NR	PG: 712 (373) ICD+: 654 (380) ICD–: 575 (420)	PG: 592 (404) ICD+: 458 (376) ICD–: 445 (386)	PG: 120 (99) ICD+: 196 (113) ICD–: 130 (112)	FAB; HAM-D; HAM-A; SHAPS; BIS-11	Interview (diagnostic criteria)	S-ICD: 24; M-ICD: 10 (PG: 11; HS: 20; BE: 9; CS: 5)
Pineau et al. (20)	NR	ICD+: 897.5 (299.9–1247.3)‖ ICD–: 1049.9 (527.1–1549.8)	NR	ICD+: 299.9 (77–718.0)‖ ICD–: 340.2 (66.7–700.0)	Conner's performance test; TMT B-A; MWCST; Fluency (phonological); IGT; MADRS; Starkstein apathy scale; BIS-11	Semistructured interview; ASBPD	PG: 6; HS: 1; CS: 2; CE: 2; M-ICD: 6
Piray et al. (22)	NR	NR	NR	NR	Digit span forward; Digit span backward; Probabilistic reward learning task; NAART; BDI; BIS-11	Interview	S-ICD: 4; M-ICD: 12 (CS: 10; HS: 9; PG: 6; BE: 4)
Pontieri et al. (27)	PG: 2 ICD+: 3 ICD–:4	PG: 794 (603) ICD+: 704 (509) ICD–: 416 (304)	PG: 487 (625) ICD+: 388 (278) ICD–: 251 (279)	PG: 307 (275) ICD+: 316 (374) ICD–: 166 (197)	RAVLT (immediate, delayed); ROCF (immediate, delayed); MWCST; Stroop; Fluency (semantic, phonological); HAM-D; HAM-A; SHAPS; Starkstein apathy scale	Diagnostic criteria; QUIP	PG: 21 (PG only:10; PG and other ICD:11); HS:16; CS:3; BE:10;M-ICD: 7
Rossi et al. (10)	NR	ICD+: 935.9 (548.6) ICD–: 698.2 (474.6)	NR	ICD+: 201.9 (78.0) ICD–: 223.9 (136.8)	FAB; MWCST; Go/No-Go; Stroop; IGT; Game of dice; Investment task; Social cognition; Reversal and extinction learning; MADRS	Interview (diagnostic criteria); MIDI; SOGS;	PG: 7; HS: 2; CS: 2; DDS:2
Tessitore et al. (5)	NO	ICD+: 477.3 (222.9) ICD–: 532.1 (207.2)	NR	ICD+: 243.3 (82.1) ICD–: 243.3 (90.2)	CBTT; RAVLT (immediate, delayed); Attentional matrices; TMT-B; WCST; RCPM; Stroop; Fluency (semantic, phonological); ROCF; HAM-D; HADS	MIDI	HS:13; BE:8; PG: 1
Vela et al. (25)	NO	ICD+: 543 (248–1039)¶ ICD–: 460 (133–700)	ICD+: 300 (0–675)¶ ICD–: 300 (0–600)	ICD+: 210 (168–308)¶ ICD–: 180 (0–300)	BDI	QUIP	PG: 9; HS: 20; CS: 13; BE: 17; hobbyism: 25; punding: 15; walkabout: 4
Vitale et al. (6)	HS: 2 M-ICD: 0 ICD–: 0	HS: 727.3 (254.3) M-ICD: 808.3 (292.2) ICD–: 630.3 (311.8)	NR	HS: 200 (130.4) M-ICD: 207.1 (159.2) ICD–: 267.1 (201.3)	WCST; ROCF copy; TMT B-A; Attentional matrices; Stroop; RAVLT (immediate, delayed); HAM-D; HADS-A; HADS-D	MIDI; clinical interview	HS: 13; M-ICD: 10

(Continued)

TABLE 1 | Continued

Ref	Antipsychotic: N	LEDD (mg)			Outcomes	ICD	
		Total LEDD*	LD-LEDD*	DA-LEDD*		Diagnosis**	Type: N
Wu et al. (26)	NR	S-ICD: 782.3 (83.5) M-ICD: 724.0 (99.0) ICD-: 831.9 (119.2)	S-ICD: 538.0 (83.4) M-ICD: 268.5 (84.9) ICD-: 666.3 (129.0)	S-ICD: 244.3 (51.4) M-ICD: 244.0 (55.4) ICD-: 165.6 (48.9)	BDI	Semistructured interview	HS: 4; PG: 3; M-ICD: 10

*AES-C, Apathy evaluation scale by a clinician; ASBPD, Ardouin scale of behavior in Parkinson's disease; BDI, Beck depression inventory; BE, binge eating; BIS-11, Barrat impulsiveness scale-11; BSCS, Brief self-control scale CBTT, Corsi's block-tapping test; CESD, Center for Epidemiological Studies-Depression scale; CLVT-II, California verbal learning test II; CS, compulsive shopping; DA, dopamine agonist; DDS, Dopamine dysregulation syndrome; DSM-IV, diagnostic and statistical manual of mental disorders, fourth edition; DSM-IV-TR, diagnostic and statistical manual of mental disorders, fourth edition, text revision; FAB, frontal assessment battery; GDS, Geriatric depression scale; HADS-A, Hospital anxiety and depression scale—anxiety subscale; HADS-D, Hospital anxiety and depression scale—depression subscale; HAM-A, Hamilton rating scale for anxiety; HAM-D, Hamilton rating scale for depression; H and Y, Hoehn and Yahr score; HS: hypersexuality; HVLT-R, Hopkins verbal learning test revised; IA: internet addiction; ICD, impulse control disorder; ICD+, PD patients with ICD; ICD–, PD patients without ICD; IGT, Iowa gambling task; KDDT, Kirby delayed discounting questionnaire; LEDD, levodopa equivalent daily dosage (mg); LD, levodopa; MADRS, Montgomery-Asberg depression rating scale; M-ICD, multiple ICD; MIDI, Minnesota impulsive disorder interview; MWCST, Modified Wisconsin card sorting test; N, number of patients; NAART, North American adult reading test; NART, The National adult reading test; NR, not reported. PD, Parkinson's disease; PG, pathological gambling; Pts, patients; QUIP questionnaire for impulsive-compulsive disorders in Parkinson's disease; QUIP-RS, questionnaire for impulsive-compulsive disorders in Parkinson's disease rating scale; RAVLT, Rey's auditory verbal learning test; RCPM, Raven's colored progressive matrices; Ref, reference number; ROCF, Rey-Osterrieth complex figure test; RPM, Raven's progressive matrices; SAT, salience attribution test; SHAPS, Snaith-Hamilton pleasure scale; S-ICD, single ICD; SOGS, South oaks gambling screen; STAI-state, state-trait anxiety inventory; TMT-A, trail making test part A; TMT-B, trail making test part B; UPDRS-III, unified Parkinson's disease rating scale part III (motor subscale) score; VOSP, visual object and space perception battery; WCST, Wisconsin card sorting test; WTAR, Wechsler test of adult reading; y, years. *Mean (SD) unless otherwise stated. †Depression as an exclusion factor. ‡Data reported in months. §Mean (SEM). ¶Median (interquartile range). ||Median (lower–upper quartile). **Questionnaire or method used to screen and/or diagnose ICD.*

Parkinson's Disease Rating Scale motor section (UPDRS-III) ON-medication, depression, antidepressants use, antipsychotics use, total levodopa equivalent daily dose (LEDD, mg), levodopa LEDD, dopamine agonist LEDD, outcomes, ICD screening tool, ICD type, and statistics.

Primary outcomes were cognitive, affective, and motivational scores. Cognitive tests were categorized on the basis of the main cognitive process involved (44). The categories were "memory"(short-term verbal and visuospatial memory, long-term verbal and visuospatial memory); "working memory"; "attention"; "executive function" (concept formation and reasoning, concept formation sort and shift, set-shifting, inhibition, cognitive flexibility, reward-related decision-making); "visuospatial abilities"; "language"; "apraxia"; "novelty seeking"; "incentive salience" and "data gathering." Concept formation and reasoning relates to the development of ideas based on the common properties of objects, events, or qualities using abstraction and generalization processes whilst concept formation sort and shift requires to form a sorting principles and apply it (sort), and then abandon it and switch to a different principle (shift) (44).

Affective and motivational measures were categorized as depression, anxiety, anhedonia, apathy, and impulsivity.

Cognitive processes assessed in a single study (i.e., novelty seeking, incentive salience, data gathering, apraxia) were not included in the meta-analysis. When a study reported multiple measures for the same outcome, the most relevant one was chosen by two reviewers with expertise on neuropsychological assessment (AM, DDL).

Data Analysis

Data were analyzed using ReviewManager v5.3 (45). Effect size was estimated as standardized mean difference (SMD), which is comparable to Hedges' adjusted g value. Effect sizes of 0.2, 0.5, and 0.8 or more are considered as small, moderate and large, respectively (46). Cochran's Q (χ^2) was used to test heterogeneity between studies. The degree of heterogeneity was quantified by I^2, which values range between 0 and 100%. I^2 percentages of 25, 50, 75 are considered as low, moderate and high, respectively (47). Random-effect model was applied, as patients differ in clinical (e.g., UPDRS-III ON medication range: 10.9–36.7) and demographic characteristics (e.g., age range: 54.6–71.4), therefore the true effect may vary from study to study. In contrast to fixed-effect models, random-effect models consider both within and between study variances. As heterogeneity was moderate to high for some outcomes (i.e., working memory, depression, anxiety, and apathy), the consequences of applying a fixed-effect model, which does not consider between studies variance, may result in type I error rate inflation (48). Conversely, if random-effect models are applied with effect sizes that vary only due to sampling error as when heterogeneity is low (i.e., short-term visuospatial memory, attention, concept formation reasoning, anhedonia), the consequences are less dramatic (e.g., using Hedges' method, the additional between-study effect size variance used in the random effect method becomes zero when sample effect sizes are homogeneous, yielding the same

TABLE 2 | Cognitive subdomains and tasks used in the studies included in the meta-analysis.

Cognitive subdomain	Cognitive tasks	References
Short-term verbal memory	CVLT-II immediate	Erga et al. (18)
	Digit Span Forward	Biundo et al. (3, 4); Housden et al. (11); Bentivoglio et al. (17); Piray et al. (22); Merola et al. (42)
	RAVLT—immediate	Tessitore et al. (5); Vitale et al. (6); Pontieri et al. (27)
Short-term visuospatial memory	CBTT	Biundo et al. (3, 4); Tessitore et al. (5); Bentivoglio et al. (17); Merola et al. (42)
Long-term verbal memory	CVLT-II delayed	Erga et al. (18)
	HVLT-R delayed	Mack et al. (19)
	Paired associate learning	Merola et al. (42)
	Prose Memory	Biundo et al. (4)
	RAVLT- delayed	Biundo et al. (3); Tessitore et al. (5); Vitale et al. (6); Bentivoglio et al. (17); Pontieri et al. (27)
Long-term visuospatial memory	ROCF—delayed	Biundo et al. (3, 4); Pontieri et al. (27)
Working memory	Digit Ordering Test	Biundo et al. (4)
	Digit Span Backward	Biundo et al. (3); Djamshidian et al. (8); Housden et al. (11); Bentivoglio et al. (17); Piray et al. (22)
	n-Back	Leroi et al. (21)
Attention	Attentive Matrices	Tessitore et al. (5); Vitale et al. (6)
	Conner's Performance Test	**Pineau et al. (20)**
	Double barrage—accuracy	Bentivoglio et al. (17)
	TMT-A	**Biundo et al. (3, 4); Mack et al. (19); Merola et al. (42)**
Set-shifting	TMT-B	**Biundo et al. (3, 4); Tessitore et al. (5); Mack et al. (19); Merola et al. (42)**
	TMT- B-A	**Vitale et al. (6); Pineau et al. (20)**
Concept formation (sort and shift)	MWCST—categories	Rossi et al. (10); Bentivoglio et al. (17); Pineau et al. (20); Pontieri et al. (27); Merola et al. (42)
	WCST—global score	**Vitale et al. (6); Tessitore et al. (5)**
Concept formation (reasoning)	RCPM	Biundo et al. (3); Tessitore et al. (5); Bentivoglio et al. (17); Merola et al. (42)
	RPM	Cilia et al. (30)
Inhibition	Go/no-Go—errors	**Rossi et al. (10)**
	Stop Signal Task	Claassen et al. (31)
	Stroop errors	**Biundo et al. (3, 4);** Vitale et al. (6)**;Djamshidian et al. (9); Bentivoglio et al. (17)**
	Stroop time	**Tessitore et al. (5); Cera et al. (16); Erga et al. (18); Pontieri et al. (27)**
Cognitive flexibility	Phonological Fluency	Biundo et al. (3, 4); Tessitore et al. (5); Bentivoglio et al. (17); Erga et al. (18); Mack et al. (19); Leroi et al. (21); Pineau et al. (20); Pontieri et al. (27); Merola et al. (42)
Reward-related decision-making	IGT	**Rossi et al. (10); Bentivoglio et al. (17);** Pineau et al. (20)
	KDDQ	Housden et al. (11); Joutsa et al. (23)
	Monetary risk taking	Cera et al. (16)
	Probabilistic Reward	Piray et al. (22)
	Risk Task	Djamshidian et al. (8)
Visuospatial abilities	Constructional apraxia	Bentivoglio et al. (17)
	ROCF—copy	Biundo et al. (3, 4); Tessitore et al. (5); Vitale et al. (6); Pontieri et al. (27)
	VOSP—silhuette	Erga et al. (18)
Language	Naming	Biundo et al. (4)
	Oral Verbal Naming	Bentivoglio et al. (17)

(Continued)

TABLE 2 | Continued

Affective and Motivational	Self-report measures	References
Depression	BDI	Biundo et al. (3, 4); Housden et al. (11); Mack et al. (19); Piray et al. (22); Vela et al. (25); Wu et al. (26); Merola et al. (42)
	CESD	Claassen et al. (31)
	GDS	Cilia et al. (30)
	HADS-D	Vitale et al. (6); Leroi et al. (21); O'Sullivan et al. (28, 29)
	HAM-D	Tessitore et al. (5); Bentivoglio et al. (17); Pontieri et al. (27); Pettorruso et al. (32)
	MADRS	Rossi et al. (10); Erga et al. (18); Pineau et al. (20)
Anxiety	HADS-A	Tessitore et al. (5); Vitale et al. (6); Leroi et al. (21); O'Sullivan et al. (28, 29)
	HAM-A	Bentivoglio et al. (17); Pontieri et al. (27); Pettorruso et al. (32)
	STAI-state	Housden et al. (11); Merola et al. (42)
Anhedonia	SHAPS	Pontieri et al. (27); Pettorruso et al. (32)
Apathy	AES-C	Leroi et al. (21); Merola et al. (42)
	Starkstein Apathy Scale	Pineau et al. (20); Pontieri et al. (27)
Impulsivity	BIS-11	Bentivoglio et al. (17); Pineau et al. (20); Leroi et al. (21); Piray et al. (22); Pettorruso et al. (32)
	BSCS	O'Sullivan et al. (29)

AES-C, Apathy evaluation scale by a clinician; BDI, Beck depression inventory; BIS-11, Barrat impulsiveness scale-11; BSCS, brief self-control scale; CBTT, Corsi's block-tapping test; CVLT-II, California verbal learning test II; CESD, Centre for Epidemiological Studies-Depression scale; GDS, Geriatric depression scale; HADS-A, Hospital anxiety and depression scale-anxiety subscale; HADS-D, Hospital anxiety and depression scale-depression subscale; HAM-A, Hamilton rating scale for anxiety; HAM-D, Hamilton rating scale for depression; HVLT-R, Hopkins verbal learning test revised; IGT, Iowa gambling task; KDDQ, Kirby delayed discounting questionnaire; MADRS, Montgomery-Asberg depression rating scale; MWCST, modified Wisconsin card sorting test; RAVLT, Rey's auditory verbal learning test; RCPM, Raven's colored progressive matrices; ROCF, Rey-Osterrieth complex figure test; RPM, Raven's progressive matrices; SHAPS, Snaith-Hamilton pleasure scale; STAI-state, state-trait anxiety inventory; TMT-A, trail making test part A; TMT-B, trail making test part B; VOSP, visual object and space perception battery; WCST, Wisconsin card sorting test. In bold scores that have been reversed in order to obtain scores with the same meaning (e.g., higher scores better performances).

result as the fixed effect method) (48). Moreover, following this approach, studies were not excluded because of their small sample size, because in random-effect models effect sizes are weighed by their variance, which is higher in smaller studies.

Two authors independently explored funnel plots for publication bias (AM, DDL), and incongruences were resolved by discussion with two other authors (ST, JAG). Funnel plots of outcomes with less than ten studies were not inspected since the power is too low to discriminate publication bias's asymmetry from chance (49). Blinding of assessors (performance bias) and incomplete data outcome (attrition bias) were independently assessed for each study as "low risk," "high risk," or "unclear" by two reviewers (AM, DDL) following Cochrane Collaboration recommendations. Sensitivity analysis was performed by excluding one study at time and verifying its impact on the overall effect size. Sensitivity analysis was not performed for outcomes with two studies. Moderator analysis via meta-regression was performed using SPSS version 21.0 (50). We tested the hypothesis that variation among studies in effect size was associated with differences in age, years of education, disease duration, UPDRS-III score, H and Y score, total LEDD, levodopa LEDD, and dopamine agonist LEDD. As suggested by Borenstein (51), moderator analysis was conducted only for outcomes in which there were at least 10 studies to one covariate.

RESULTS

After removal of duplicates, 10,200 records were screened by title and abstract, 79 full-text articles were assessed for eligibility, and 54 were excluded (**Figure 1**). Twenty-five studies were included in the meta-analysis (**Table 1**).

Four studies investigated cognitive performance without affective and motivational outcomes (8, 9, 16, 23), 17 studies included both cognitive, affective and motivational outcomes (3–6); (10, 11, 17–22); (27, 30–32, 50), and four studies included affective and motivational data only (25, 26, 28, 29). Three studies divided ICD+ in two groups: PD patients with pathological gambling and those with ICD other than pathological gambling (16, 27, 32), and one study divided the ICD+ in multiple and single ICD groups (26). As the comparison between ICD subtypes was not relevant in our meta-analysis, sub-groups were merged by calculating the pooled means and standard deviations. In one study (6) ICD+ group was divided in pathological gambling, binge-eating, hypersexuality and multiple ICD sub-groups. Since seven PD patients belonging to either the pathological gambling or the binge-eating sub-groups developed ICD before DRT initiation, only data from hypersexuality and multiple ICD sub-groups were extracted and merged as described above. Six studies focused on neuroimaging outcomes but also provided affective (26) and cognitive measures (3–5); (23, 30). One study retrospectively investigated persistent, remitting, and new-onset

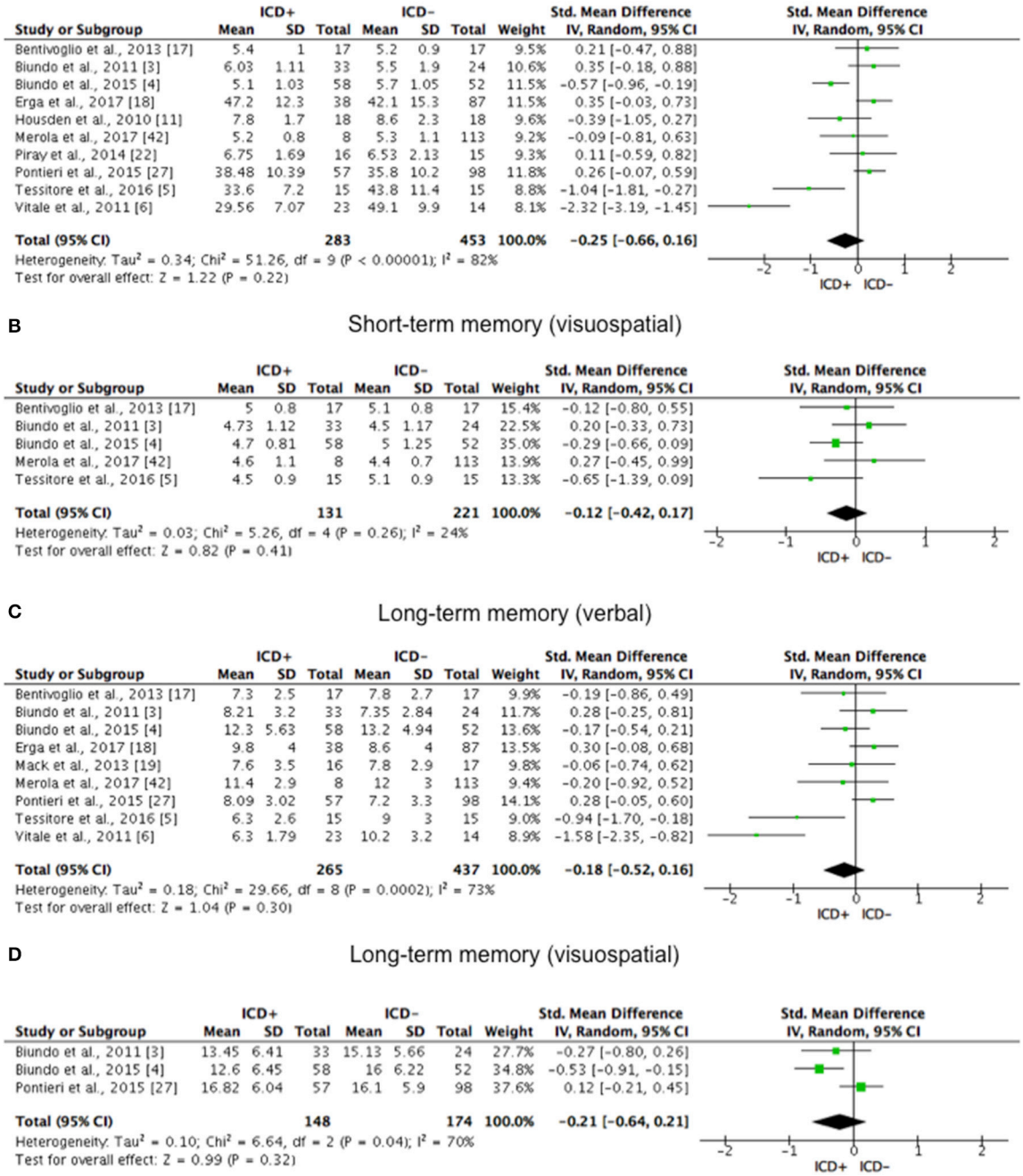

FIGURE 2 | Forest plots for memory. Here are reported forest plots for short-term (verbal, **(A)** visuospatial, **(B)** and long-term (verbal, **(C)**; visuospatial, **(D)** memory outcomes. Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate worse performance in PD patients with ICD (ICD+) in comparison to those without ICD (ICD–). ICD, impulse control disorder; PD, Parkinson's disease.

ICD before and after subthalamic nucleus DBS (STN-DBS) (42). For this study, only pre-STN-DBS data of persistent and never experienced ICD were included in the meta-analysis. Despite the fact that dementia was not explicitly excluded (42), data were included because STN-DBS is performed in non-demented patients only.

The meta-analysis includes 1,563 subjects. The ICD+ group was composed of 625 patients (mean age range: 54.6–68.7

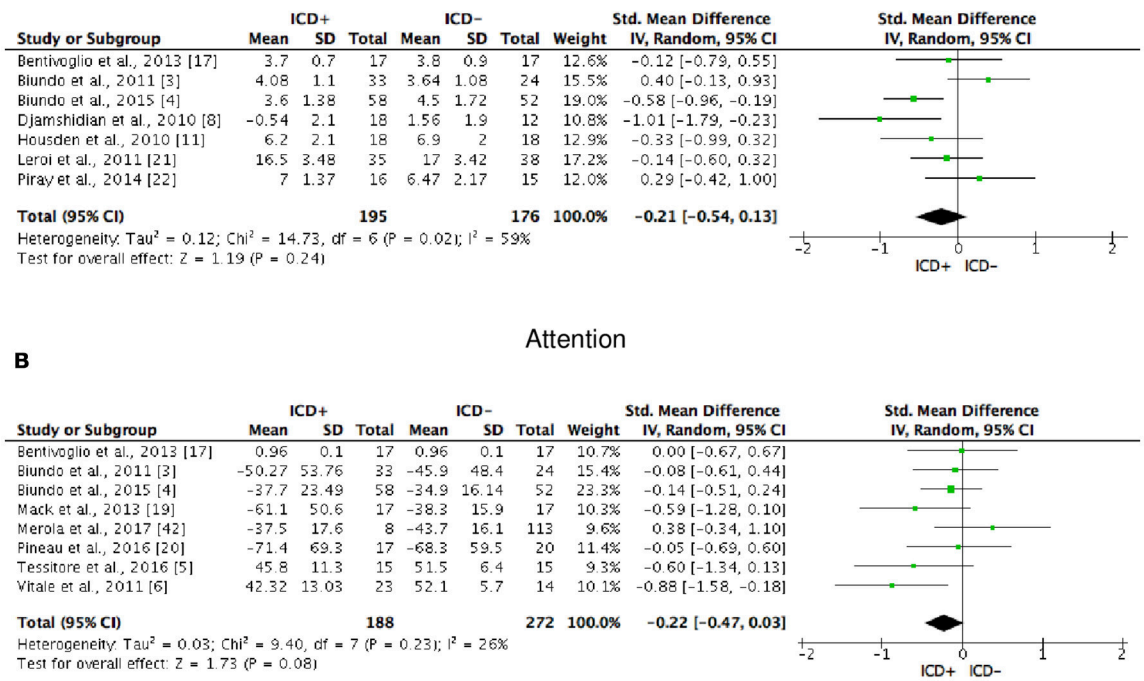

FIGURE 3 | Forest plots for working memory and attention. Here are reported forest plots for working memory **(A)** and attention **(B)**. Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate worse performance in PD patients with ICD (ICD+) in comparison to those without ICD (ICD−). ICD, impulse control disorder; PD, Parkinson's disease.

years; mean PD duration: 2.4–14.3 years; mean H and Y: 1.3–2.8; mean UPDRS-III score ON medication: 10.9–36.7). The ICD− group included 938 patients (mean age: 55–71.4 years; mean PD duration: 2.3–13.1 years; mean H and Y stage: 1.4–2.5; mean UPDRS-III score ON medication: 11.7–32.3).

Fourteen meta-analyses were performed to compare cognitive outcomes and five to compare affective and motivational measures in ICD+ compared to ICD− groups.

The following cognitive outcomes were explored: short-term verbal and visuospatial memory, long-term verbal and visuospatial memory, working memory, attention, set-shifting, concept formation (reasoning, sort and shift), inhibition, cognitive flexibility, reward-related decision-making, visuospatial abilities, and language (**Table 2**).

ICD+ showed worse performance in set-shifting (SMD = −0.49; 95% CI: −0.78, −0.21; Z = 3.37; $p = 0.0008$) and reward-related decision-making (SMD = 0.42; 95% CI: 0.02, 0.82; Z = 2.05; $p = 0.04$). The heterogeneity was low-to-moderate for set-shifting ($\chi^2 = 9.32$, $p = 0.16$, $I^2 = 36\%$) and moderate for reward-related decision-making ($\chi^2 = 15.50$, $p = 0.03$, $I^2 = 55\%$). Effect sizes for the other cognitive outcomes did not differ significantly between groups. Heterogeneity was low for short-term visuospatial memory, attention, concept formation (reasoning), moderate for cognitive flexibility, concept formation (sort and shift), and language, high for short-term verbal memory, long-term verbal memory, long-term visuospatial memory, visuospatial abilities, and inhibition, moderate-to-high for working memory (**Figures 2–6**).

The following self-reported affective and behavior outcomes were explored: depression, anxiety, anhedonia, apathy, and impulsivity. ICD+ showed increased depression (SMD = 0.35; 95% CI: 0.16, 0.54; Z = 3.54; $p = 0.0004$), anxiety (SMD = 0.43; 95% CI: 0.18, 0.68; Z = 3.39; $p = 0.0007$), anhedonia (SMD = 0.26; 95% CI: 0.01, 0.50; Z = 2.01; $p = 0.04$), and impulsivity (SMD = 0.79; 95% CI: 0.50, 1.09; Z = 5.26; $p < 0.00001$), but comparable apathy symptoms (**Figure 7**). Heterogeneity was low for anhedonia ($\chi^2 = 0.01$, $p = 0.94$, $I^2 = 0\%$), moderate for impulsivity ($\chi^2 = 8.89$, $p = 0.11$, $I^2 = 44\%$), and moderate-to-high for depression ($\chi^2 = 51.42$, $p = 0.0001$, $I^2 = 61\%$), anxiety ($\chi^2 = 21.27$, $p = 0.01$, $I^2 = 58\%$), and apathy ($\chi^2 = 9.09$, $p = 0.03$, $I^2 = 67\%$; **Figure 7**). Results of the meta-analyses are summarized in **Table 3**.

Risk of Bias

Visual exploration of funnel plots did not suggest possible publication bias for short-term verbal memory, inhibition, cognitive flexibility, depression, and anxiety that were the only outcomes with at least 10 studies (**Figure 8**).

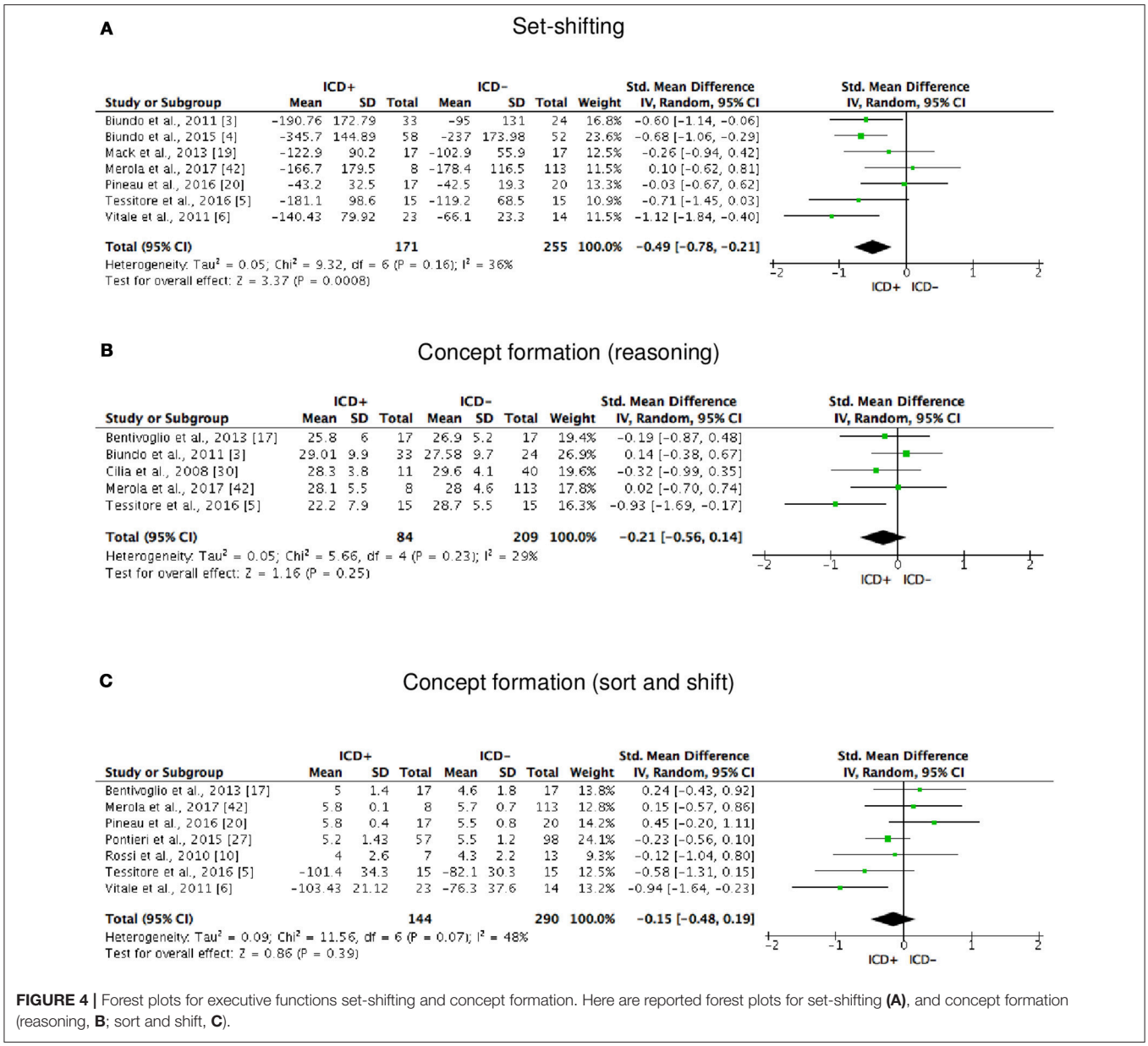

FIGURE 4 | Forest plots for executive functions set-shifting and concept formation. Here are reported forest plots for set-shifting **(A)**, and concept formation (reasoning, **B**; sort and shift, **C**).

Risk of performance bias was unclear with only 2/25 studies indicating assessors blinding procedures.

Attrition bias was low, with 4/25 studies with missing data.

Sensitivity Analysis and Moderator Analysis

Sensitivity analysis showed that after removing Pontieri et al. (27), the overall effect size of long-term visuospatial memory became significant (SMD = −0.44; 95% CI: −0.75, −0.13; Z = 2.81; p = 0.005) and the heterogeneity changed from high (χ^2 = 6.64, p = 0.04, I^2 = 70%) to low (χ^2 = 0.62, p = 0.43, I^2 = 0%). After removing Biundo et al. (3), the overall effect size of working memory became significant (SMD = −0.32; 95% CI: −0.63, −0.01; Z = 2.05; p = 0.04) and the heterogeneity changed from high (χ^2 = 14.73, p = 0.02, I^2 = 59%) to moderate (χ^2 = 8.41, p = 0.13, I^2 = 41%). The overall effect size of attention became significant after removing Merola et al. (42) (SMD = −0.27; 95% CI: −0.50, −0.04; Z = 2.29; p = 0.02), but heterogeneity remained low. The overall effect size of inhibition became significant after removing Biundo et al. (4) (SMD = −0.34; 95% CI: −0.65, −0.03; Z = 2.18; p = 0.03) and heterogeneity changed from high to moderate-to-high (χ^2 = 24.18, p = 0.004, I^2 = 63%). The overall effect size of reward-related decision-making lost significance after removing Bentivoglio et al. (17) (SMD = 0.42; 95% CI: −0.05, 0.89; Z = 1.75; p = 0.08), Housden et al. (11) (SMD = 0.36; 95% CI: −0.08, 0.81; Z = 1.59; p = 0.11), Piray et al. (22) (SMD = 0.35; 95% CI: −0.08, 0.78; Z = 1.58; p = 0.11), and

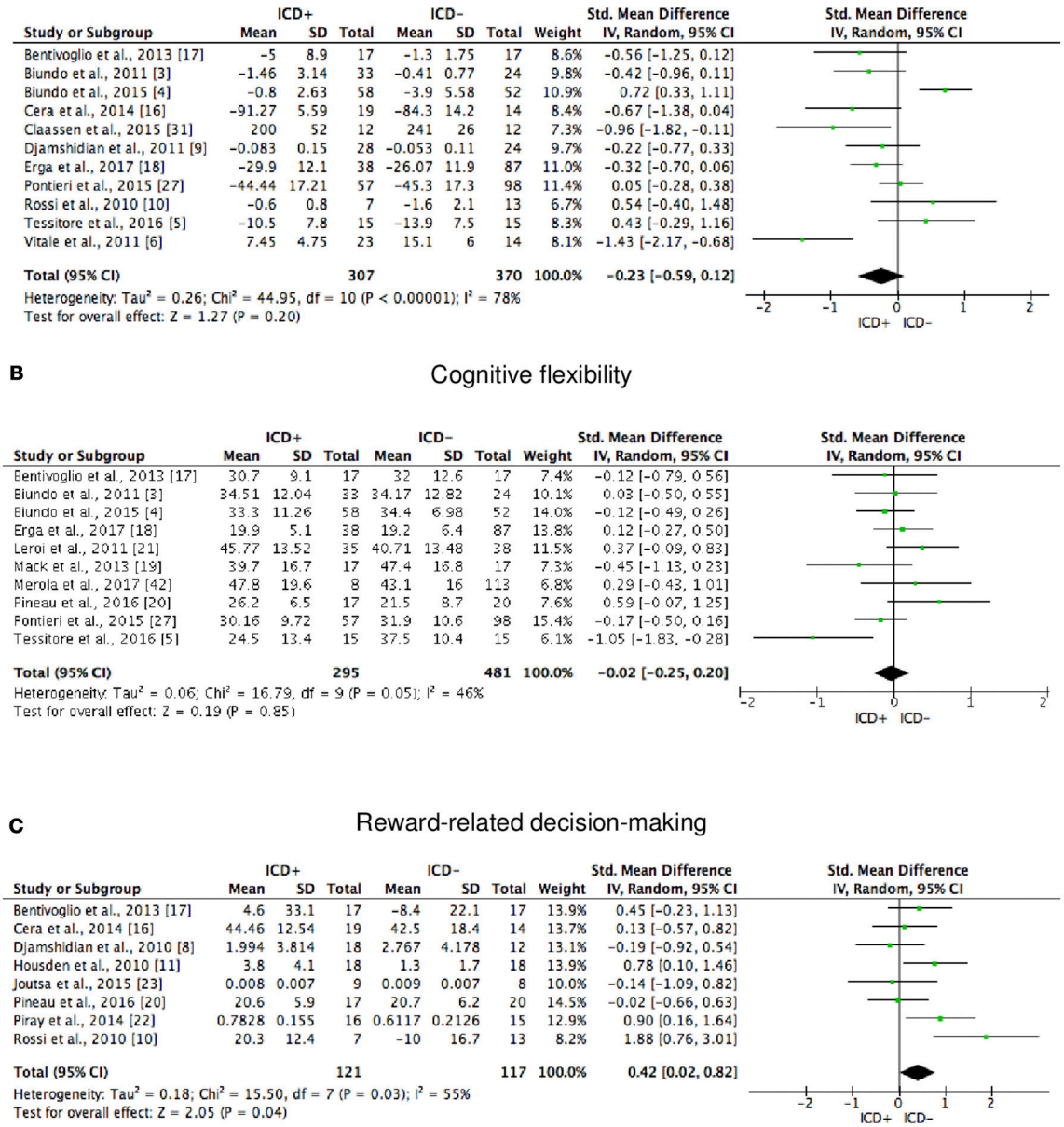

FIGURE 5 | Forest plots for executive functions inhibition, cognitive flexibility, and reward-related decision-making. Here are reported forest plots for inhibition **(A)**, cognitive flexibility **(B)**, and reward-related decision-making **(C)**. Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate worse performance in PD patients with ICD (ICD+) in comparison to those without ICD (ICD–). ICD, impulse control disorder; PD, Parkinson's disease.

Rossi et al. (10) (SMD = 0.29; 95% CI: −0.03, 0.61; Z = 1.78; $p = 0.07$). After removing Rossi et al. (10), heterogeneity changed from moderate ($\chi^2 = 15.50$, $p = 0.03$, $I^2 = 55\%$) to low ($\chi^2 = 8.27$, $p = 0.22$, $I^2 = 27\%$). Including or excluding the other studies did not change heterogeneity. The overall effect size of apathy became significant after removing Pontieri et al. (27) (SMD = 0.60; 95% CI: 0.25, 0.95; Z = 3.38; $p = 0.0007$) and heterogeneity changed from high ($\chi^2 = 9.09$, $p = 0.03$, $I^2 = 67\%$) to low ($\chi^2 = 2.07$, $p = 0.35$, $I^2 = 4\%$). Moderator analysis was performed for short-term verbal memory, inhibition, cognitive flexibility, and depression, which were the only outcomes that included at least 10 studies each (51). Anxiety did not undergo moderator analysis, because none of the covariates of interest were assessed in at least 10 studies. Moderator analysis showed no effect of age, education, PD duration, H and Y, UPDRS-III, and total LEDD, levodopa LEDD, dopamine agonist LEDD on

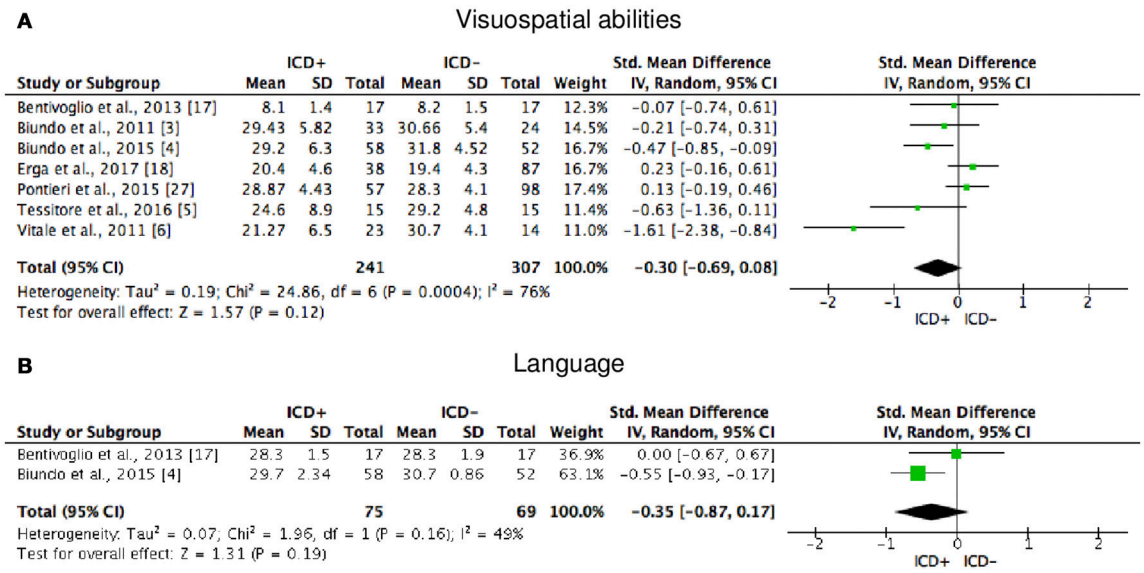

FIGURE 6 | Forest plots for visuospatial abilities and language. Here are reported forest plots for visuospatial abilities **(A)** and language **(B)**. Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate worse performance in PD patients with ICD (ICD+) in comparison to those without ICD (ICD−). ICD, impulse control disorder; PD, Parkinson's disease.

short-term verbal memory, inhibition, cognitive flexibility, and depression (**Table 4**).

DISCUSSION

The primary aim of this meta-analysis of 25 studies was to describe the pattern of cognitive function in DRT-medicated ICD+ compared to ICD–. A stricter set of inclusion criteria was applied than used previously (33), to achieve a more homogenous ICD+ group, and a better understanding of the relationship between ICD and cognition in medicated PD. A secondary aim was to examine affective and motivational correlates of ICD, as emotion-cognition and motivation-cognition relationships are receiving increasing attention to understand psychopathology and improve pharmacological and psychological treatments (34).

Our findings suggest ICD to be associated with worse performance on a set of executive function measures assessing set-shifting (Trail Making Test part B, and B-A) and reward-related decision-making (Iowa Gambling Task, Monetary Risk Task, Kirby Delay Discounting Questionnaire), with relative sparing of other executive tasks that assess concept formation and reasoning (Raven's progressive matrices standard and colored versions), concept formation sort and shift (Wisconsin card sorting test standard and modified versions), inhibition (Stroop, Stop Signal Task, Go/no-Go), and cognitive flexibility (phonological fluency), as well as memory, working memory, attention, visuospatial abilities, and language.

Set-shifting and reward-related decision-making abilities are important determinants of advantageous behavior, serving to translate goals into action planning, as well as monitoring response and errors (52).

Structural and functional neuroimaging outcomes were not included in this meta-analysis, but neuroanatomical findings in patients with abnormalities in set-shifting and reward-related decision-making may help speculate on brain areas that may undergo DRT overdose in PD. Lesion-symptom mapping studies suggest reward-related decision-making to rely upon an anatomical network composed of the ventromedial, orbitofrontal and frontopolar cortices. Set-shifting, which is one of the processes underlying cognitive control, depends on rostral anterior cingulate cortex functioning (52). These brain areas form part of the mesocorticolimbic system that, in the early stages of PD, undergo less dopaminergic damage than the dorsal striatal pathways.

According to the "overdose hypothesis," the DRT amount required to control motor symptoms in PD has the potential to move the same patient away from the optimum for certain cognitive functions (53). The relationship between the efficiency of neuronal activity and the state of dopaminergic modulation is represented by a Yerkes-Dodson inverted U-shaped curve with cognitive functions declining with deviation away from optimum dopamine levels, indicated by the center of the curve (2). Extrapolating this model to set-shifting and reward-related decision-making implies that DRT has the capacity to both improve and impair these executive functions depending on baseline dopamine levels in the underlying neural circuitry. For patients with low baseline dopamine levels in the mesocorticolimbic system, DRT may optimize activity as supported by improved set-shifting and reward-related decision-making when assessed in an optimally medicated state compared to the same patients assessed following DRT withdrawal (54, 55). By the same token, if patients start out with higher

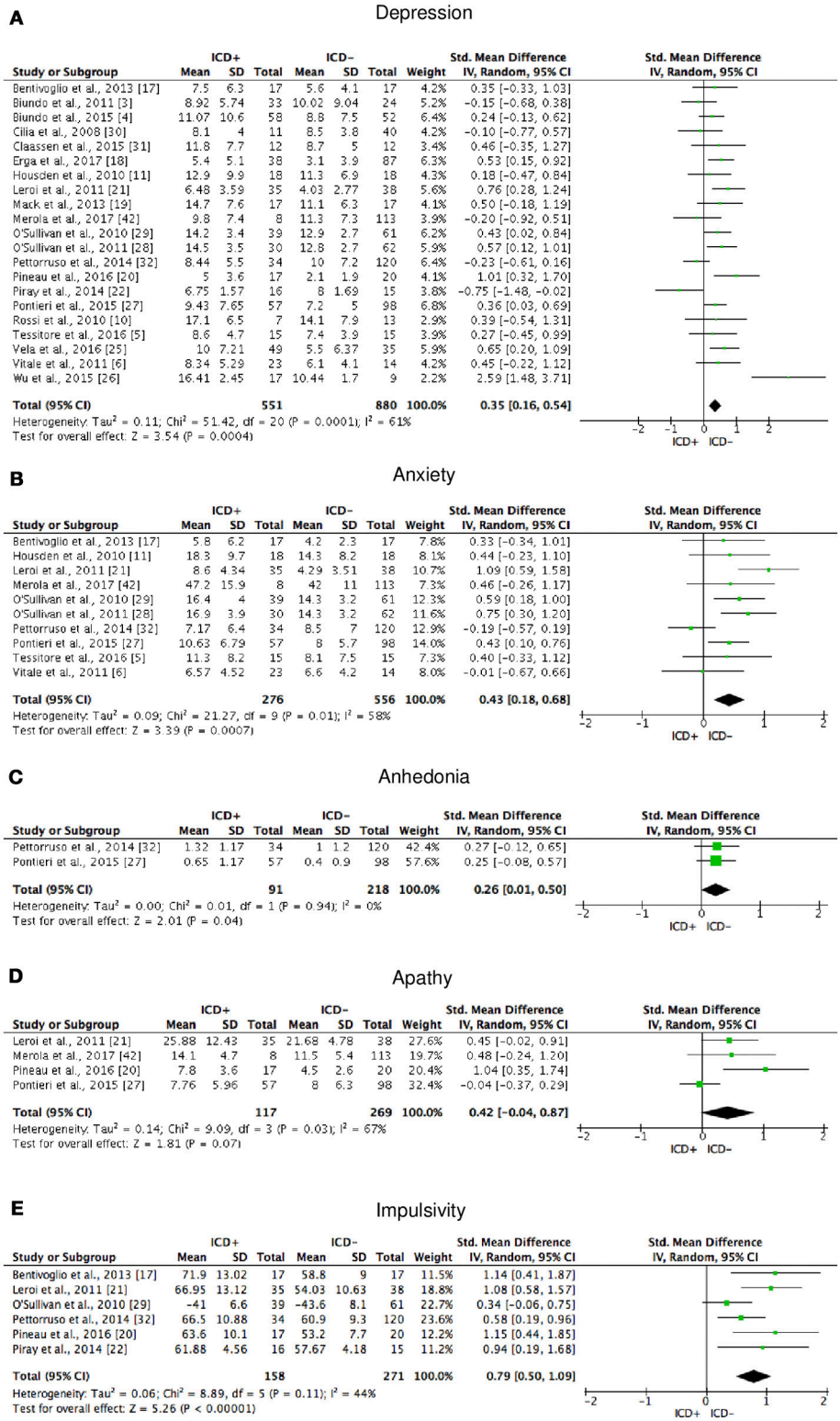

FIGURE 7 | Forest plots for affective and motivational outcomes. Here are reported forest plots for depression **(A)**, anxiety **(B)**, anhedonia **(C)**, apathy **(D)**, and impulsivity **(E)**. Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate worse performance in PD patients with ICD (ICD+) in comparison to those without ICD (ICD−). ICD, impulse control disorder; PD, Parkinson's disease.

TABLE 3 | Results of the meta-analyses.

			Random-effect model results				Heterogeneity		
Outcome	**K**	**N**	**SMD**	**[95% CI]**	**Z**	***p***	X^2	***p***	I^2(%)
Short-term verbal memory	10	736	−0.25	[−0.66, 0.16]	1.22	0.22	51.26	*<0.00001*	82
Short-term visuospatial memory	5	352	−0.12	[−0.42, 0.17]	0.82	0.41	5.26	0.26	24
Long-term verbal memory	9	702	−0.18	[−0.52, 0.16]	1.04	0.30	29.66	*0.0002*	73
Long-term visuospatial memory	3	322	−0.21	[−0.64, 0.21]	0.99	0.32	6.64	*0.04*	70
Working memory	7	371	−0.21	[−0.54, 0.13]	1.19	0.24	14.73	*0.02*	59
Attention	8	460	−0.22	[−0.47, 0.03]	1.73	0.08	9.40	0.23	26
Set-shifting	7	426	−0.49	[−0.78, −0.21]	3.37	*0.0008*	9.32	0.16	36
Concept formation (sort and shift)	7	434	−0.15	[−0.48, 0.19]	0.86	0.39	11.56	0.07	48
Concept formation (reasoning)	5	293	−0.21	[−0.56, 0.14]	1.16	0.25	5.66	0.23	29
Inhibition	11	677	−0.23	[−0.59, 0.12]	1.27	0.20	44.95	*<0.00001*	78
Cognitive flexibility	10	776	−0.02	[−0.25, 0.20]	0.19	0.85	16.79	*0.05*	46
Reward-related decision-making	8	238	0.42	[0.02, 0.82]	2.05	*0.04*	15.50	*0.03*	55
Visuospatial abilities	7	548	−0.30	[−0.69, 0.08]	1.57	0.12	24.86	*0.0004*	76
Language	2	144	−0.35	[−0.87, 0.17]	1.31	0.19	1.96	0.16	49
Depression	21	1431	0.35	[0.16, 0.54]	3.54	*0.0004*	51.42	*0.0001*	61
Anxiety	10	832	0.43	[0.18, 0.68]	3.39	*0.0007*	21.27	*0.01*	58
Anhedonia	2	309	0.26	[0.01, 0.50]	2.01	*0.04*	0.01	0.94	0
Apathy	4	386	0.42	[−0.04, 0.87]	1.81	0.07	9.09	*0.03*	67
Impulsivity	6	429	0.79	[0.50, 1.09]	5.26	*<0.00001*	8.89	0.11	44

K, number of studies; N, number of participants; SMD, standardized mean difference; CI, confidence interval. P values below the significance level ($p < 0.05$) are reported in italics.

mesocorticolimbic baseline levels of dopamine, DRT causes dopamine over-activity in the mesocorticolimbic system. This view is consistent with evidence that dopamine agonists increase frontal cortex blood flow (56), and enhance reward-related risk-taking behavior in ICD+ compared to ICD– (57).

A recent meta-analysis of case-control studies on the prevalence of ICD in PD provides indirect evidence of dopaminergic over-activity, as being medicated for PD and disease duration were both factors that increased the risk of ICD (58). As disease duration advances, the dopaminergic degeneration spread to brain areas that were spared in the early stages of the disease, such as prefrontal cortex (59). The progressive involvement of brain areas during PD progression may have two consequences. The first is a dysregulation of brain regions involved in the top-down mechanisms of cognitive control of behavior (60). The second is the need to increase DRT dosage to compensate motor symptoms and the consequent overstimulation of less damaged brain areas. However, the relationship between ICD and DRT dosage is not well-established; some studies report no difference between DRT doses and ICD (18, 25, 61, 62), with others reporting an association between ICD and dopamine agonists doses (63–68). In this meta-analysis we lacked the power for conducting moderator analysis for disease duration, total LEDD, LD LEDD, and DA LEDD in reward-related decision-making and set-shifting leaving this question unanswered.

Our data may help reconcile the debate whether ICD in PD is associated with frontal lobe dysfunction (69–72). The discrepancy between previous reports is likely due to differences in the tasks and the underlying executive function subdomains investigated. Our data indicate that some frontal tasks and related subdomains may not be affected by ICD. Therefore, neuropsychological evaluation of ICD+ patients should include a broad range of executive function tasks, encompassing both reward-related decision-making and set-shifting, and not be limited to a general frontal screening test, such as the Frontal Assessment Battery, which does not include those subdomains.

The profile of executive dysfunction we found confirms the conclusions of a previous meta-analysis (33) that also reported reduced abstraction/concept formation and visuospatial abilities in ICD+. The discrepancy between the two meta-analyses can be ascribed to our inclusion of two reports (18, 50) not available at the time of the former one, and by our stricter exclusion criteria. We excluded four studies included by Santangelo et al. (7, 14, 58, 59), because of (a) patients with hypersexuality and compulsive shopping included the ICD– group (7), (b) dementia not excluded (14), and (c) patients screened for pathological gambling (73) or punding (74) only, thereby the presence of other ICDs in the ICD– group could not be ruled out.

Our secondary aim was to explore affective and motivational outcomes associated with ICD, as evidence indicates a role for dopamine dysregulation in the pathophysiology of impulsivity, apathy, and anhedonia in pathological gambling, drug addiction, and ICD+ (75–77). We found increased rates of self-reported depression, anxiety, anhedonia, and impulsivity, but not apathy in ICD+ compared to ICD–.

Impulsivity and apathy have been suggested to represent opposite ends of a dopaminergic continuum, where the former

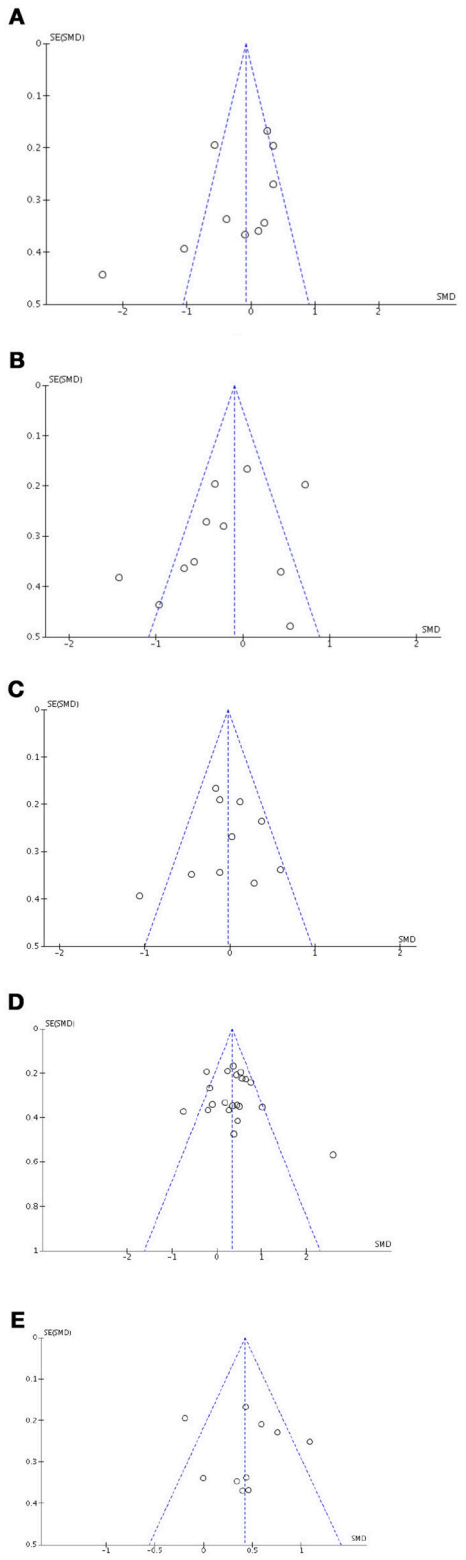

FIGURE 8 | Funnel plots for cognitive, affective and motivational outcomes. Here are reported funnel plots for short-term verbal memory **(A)**, inhibition **(B)**, phonological fluency **(C)**, depression **(D)**, and anxiety **(E)**. There is no evidence to suggest publication bias.

and the latter are associated with hyper and hypodopaminergic state, respectively (75). According to this view, DRT mesocorticolimbic overstimulation increases impulsivity that, in turn, may enhance reward-related behavior that, over time, may become addictive in nature (78). The association between ICD+ and impulsivity but not apathy in our meta-analysis is consistent with this model and the evidence that the D2 dopamine agonist pramipexole improves apathy in PD patients without ICD (79) but also increases impulsivity (1).

Anhedonia is defined as the decreased ability to experience pleasure from positive stimuli (80). Pramipexole may reduce anhedonia in ICD–, suggesting its hypodopaminergic nature (81).

The co-occurrence of hypodopaminergic anhedonia with hyperdopaminergic ICD is surprising. One possible explanation is that ICD+ patients may have decreased ability to experience pleasure when not engaged in ICD. This hypothesis is supported by the evidence that people addicted to alcohol or drugs experience anhedonia during withdrawal syndrome, a feature that may facilitate relapse (82). However, the relationship between anhedonia and dopaminergic states is not so straightforward and anhedonia is also recognized as one of the overlapping symptoms between apathy and depression (83). The association with anhedonia may be confounded by the presence of depression, which in some cases might be serotoninergically mediated (84). However, there are only two studies and further investigation is needed.

The pathophysiology of depression and anxiety in PD is likely to be multifactorial including reaction to disease diagnosis and anxiety about its future course. Depression and anxiety are present in the premorbid PD stage (85), therefore suggesting they may represent a core feature of PD. In our meta-analysis depression and anxiety levels were higher in ICD+ compared to ICD–. ICD may have a negative impact on the quality of life (21, 25), and in turn increase depression and anxiety levels. Also, as the mesocorticolimbic pathways dysfunction may be involved in depression, anxiety and ICD, they might co-occur as epiphenomena of shared neural correlates (40).

The main limitation of this meta-analysis is the small number of studies, most of which with small samples that might have contributed to high heterogeneity for some of the outcomes explored. This consideration could be reflected in the sensitivity analysis data for long-term visuospatial memory, working memory, attention, inhibition, reward-related decision-making, apathy, and it suggests caution in the interpretation of the results for these outcomes. Moreover, the inclusion in the same domains of tasks that might involve different cognitive processes could have contributed to the high heterogeneity and the low stability of some results. However, considering the single cognitive task would have resulted in a reduction of the power, because of the low number of studies using the same tasks. Unfortunately, we were not able to perform separate analyses for dopamine agonists and levodopa, as the majority of the studies included patients who were under both types of DRT. Due to the small number of studies, moderator analysis for levodopa and dopamine agonist LEDD was performed for depression only,

TABLE 4 | Results of the moderator analysis.

	Short-term verbal memory			Inhibition			Cognitive flexibility			Depression			Anxiety		
Moderators	K	β	*p*	K	β	*p*	K	β	*p*	K	β	*p*	K	β	*p*
Age	9[a]	–	–	11	−0.003	0.970	8[a]	–	–	19	−0.029	0.183	8[a]	–	–
Education	8[a]	–	–	10	−0.050	0.669	6[a]	–	–	10	−0.055	0.332	6[a]	–	–
PD Duration	8[a]	–	–	10	0.045	0.645	9[a]	–	–	19	−.012	0.810	8[a]	–	–
H and Y	8[a]	–	–	8[a]	–	–	6[a]	–	–	14	−0.153	0.570	7[a]	–	–
UPDRS–III	10	0.073	0.081	11	0.018	0.578	10	−0.005	0.799	19	−0.009	0.557	9[a]	–	–
Total LEDD	9[a]	–	–	10	0.002	0.200	9[a]	–	–	19	0.000	0.992	9[a]	–	–
DA LEDD	9[a]	–	–	9[a]	–	–	8[a]	–	–	18	0.001	0.435	9[a]	–	–
LD LEDD	4[a]	–	–	5[a]	–	–	3[a]	–	–	10	0.000	0.749	6[a]	–	–

PD, Parkinson's disease; H and Y, Hoehn and Yahr score; UPDRS–III, unified Parkinson's disease rating scale part III (motor subscale) score; LEDD, levodopa equivalent daily dosage (mg); DA, dopamine agonist; LD, levodopa; K, number of studies. [a]not included in the moderator analysis because k<10.

which showed no effect. This is not surprising, as in the larger study published so far, ICDs were found to be associated either with dopamine agonists or, to a lesser extent, with levodopa (1). These data are in keeping with the notion that both levodopa and dopamine agonists can interfere with the phasic and tonic activity of dopaminergic neurons (86) that, by facilitating neuroadaptive changes in dopaminergic system functioning, may predispose to ICD.

Another limitation is the inclusion of cross-sectional studies that impede the exploration of the direction of the cause-effect relationship between cognitive, affective and motivational outcomes and ICD; therefore multi-center and longitudinal studies are needed. Moreover, even if we excluded studies focusing on punding and dopamine dysregulation syndrome only, these conditions were present in many studies, and probably contributed to high heterogeneity for some outcomes. Furthermore, 23/25 studies did not mention assessors to be blind to the ICD status and this might have affected tools administration and scoring. Future studies should be conducted following blinding procedures. Finally, QUIP, a validated screening instrument with high sensitivity (94%) but low specificity (72%) to ICD in PD (87) was used in two studies (18, 25), possibly leading to false positive and/or subclinical ICD inclusion. Still unanswered questions include whether set-shifting and reward-related decision-making abnormalities in PD patients with ICD reflect structural and functional mesocorticolimbic changes due to acute or chronic DRT effects, or whether they can revert following ICD treatment and remission. Future studies should address these points, since better understanding ICD pathophysiology may help tailoring treatment of ICD+.

AUTHOR CONTRIBUTIONS

The study has been designed by AM, DD, NE, and ST. Data have been gathered and analyzed by AM and DD under the supervision of JG. The manuscript has been drafted by AM, NE, and ST. AM, DD, NE, JG, and ST revised the manuscript.

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Impulse Control Behaviors in Parkinson's Disease: Drugs or Disease? Contribution From Imaging Studies

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Impulse control behaviors (ICB) are recognized as non-motor complications of dopaminergic medications in patients with Parkinson's disease (PD). Compelling evidence suggests that ICB are not merely due to the PD-related pathology itself. Several risk factors have been identified, either demographic, clinical, genetic or neuropsychological. Neuroimaging studies have yielded controversial results regarding ICB correlates in PD and still it is not clear whether they can be triggered by the PD biology or the dopaminergic treatment stimulation. We provided an overview of the imaging studies that offered the most relevant insights into the debate about the role of drugs and disease in ICB pathophysiology. Understanding neural correlates and potential predisposing factors of these severe neuropsychiatric symptoms will be crucial to guide clinical practice and to foster preventive strategies.

Keywords: Parkinson's disease, impulse control behaviors, MRI, PET, reward system

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INTRODUCTION

Impulse control behaviors (ICB) are neuropsychiatric symptoms characterized by impulsive acts, which are performed compulsively and are potentially detrimental to the person itself or others, severely affecting subjects' quality of life (1). ICB are mainly recognized as side-effects of treatment with dopaminergic medications in patients with Parkinson's disease (PD) (2). Compelling evidence suggests that ICB are not merely due to the disease-related pathology itself (3). The lifetime prevalence of ICB in PD patients ranges between 6–9% and increases to 14% in patients taking dopamine-replacement therapy such as dopamine agonists (DAA) or levodopa (2, 3). The risk to develop ICB increases of 2- to 3.5-fold when patients are exposed DAA (2). The prevalence did not differ between the two commonly prescribed oral short-acting DAA, pramipexole and ropinirole (17.7 vs. 15.5%) with a relatively low rate of ICB with long-acting and transdermal DAA (6.6% pramipexole prolonged release and 4.9% for rotigotine) (2, 4). However, not all PD patients develop ICB under dopaminergic treatment. Several risk factors have been proposed, either clinical (i.e., younger age at PD onset, male sex, depression) (3) or genetic (i.e., polymorphisms in dopaminergic, glutamatergic and serotoninergic and opioid receptors) (5, 6).

Interestingly, ICB also occur in patients with restless legs syndrome (7, 8) or prolactinoma (9) under DAA, and this may support the role of the drugs in triggering these neuropsychiatric symptoms.

Modern neuroimaging techniques have been widely tested to support PD diagnosis (i.e., positron emission tomography, PET and single-photon emission computed tomography, SPECT) as well as to provide further insights into motor and non-motor symptoms pathophysiology, complications and treatment-related effects (i.e., PET and magnetic resonance imaging, MRI) (10).

PET and SPECT studies have been extensively applied to analyze neural correlates underpinning ICB in PD (11–14). By means of pre- and post-synaptic tracers, these studies provided crucial insights about the nigrostriatal functioning characterizing ICB patients. Recently, highly selective D2/D3 tracers have been also implemented, allowing to detect the presence of widespread extra-striatal changes related to ICB.

Structural MRI changes have been also observed in PD patients with ICB. Gray matter atrophy as well as corticometric changes across several brain areas involved in behavioral modulation (i.e., orbitofrontal and anterior cingulate cortices) are the most frequent findings related to the ICB presence and severity in PD (15, 16). However, there is also evidence of no morphometric changes (17).

Functional MRI studies (18–21) were performed in resting condition as well as during reward tasks in ICB patients, and were used to shed light on specific reward processing abnormalities. Overall, these studies have consistently demonstrated a dysfunction within and between dopaminergic neural circuitries involving crucial subcortical hubs (i.e., ventral striatum, VS, amygdala) and limbic-cognitive cortical areas (i.e., anterior cingulate and frontal cortices). Interestingly, the most relevant brain areas in the pathogenesis of ICB are involved in the so-called neurocognitive networks, namely the default-mode (DMN), the salience (SN) and the central-executive (CEN) networks.

The DMN encompasses mainly precuneus and posterior cingulate, bilateral inferior-lateral-parietal and ventromedial frontal cortices. It is involved in cognitive processing and mind-wandering and becomes deactivated during specific goal-directed behaviors. The CEN is involved in executive control and decision-making and operates through medio-frontal areas, including anterior cingulate and para-cingulate cortices. The SN is a limbic-paralimbic network that plays an important role in orienting attention toward salient stimuli and facilitating goal-directed behaviors, reward processing and interoceptive awareness (22). It encompasses manly the dorsal anterior cingulate cortex and the bilateral VS. The dynamic interplay between these networks is critical to allow an individual to be behaviorally and cognitively efficient (23), and this highlights their potential relevance in ICB pathophysiology.

Overall, most imaging studies applied cross-sectional designs, yielding controversial results. Thus, it is not possible to rule out whether these findings reflect the effect of chronic dopaminergic treatment or represent a neural pattern predisposing to ICB (24).

Here, we aim to review the most relevant imaging studies that provide a contribution to the debate about the role of drugs and disease in the pathogenesis of ICB in PD.

SEARCH STRATEGY

Articles published on PubMed until June 2018 were checked for the purpose of this review. "Parkinson's disease" were cross-referenced with "impulse control disorders" and synonymies and "magnetic resonance imaging," "positron emission tomography," "impulsive compulsive disorders," "reward system," "dopamine agonists," "levodopa." Two independent observers (RDM and AR) evaluated the results ($n = 984$), excluding duplicates and articles judged irrelevant by title and abstract screening. The same raters performed the quality check of selected studies and the most relevant ones for the topic were finally included in the review (**Table 1**).

NEUROIMAGING STUDIES TO ANALYZE DOPAMINERGIC SIGNALING IN PD PATIENTS WITH ICB

The role of dopaminergic signaling in ICB development is suggested by both PD pathophysiology and DAA targeting. The most prescribed DAA are highly selective on D3 receptors, which are mainly located in the mesolimbic circuit and are thought to be involved in the reward processing (32). Interestingly, animal studies showed that nigrostriatal degeneration itself may result in increasing rewarding properties of D2 and D3 agonists in the mesolimbic pathway (33). Polymorphisms in D2 as well as D1-like receptors genes, potentially leading to abnormal neurotransmitters functioning, have been linked to increased ICB susceptibility in PD (6). On the other hand, chronic dopaminergic treatment may induce long-term abnormalities in the phasic and tonic activity of dopaminergic neurons, potentially leading to changes in post and pre-synaptic receptors density and properties (34, 35). In preclinical studies, these changes have been linked to reward anticipation and risk-taking behaviors [see for a review (24)]. Taken together these findings suggest that both disease and drugs seem to be synergistically involved in triggering ICB symptoms.

Neuroimaging studies are in line with this evidence. Indeed, in a small PET study using [11C]FLB-457, a radiotracer with high affinity for extra-striatal receptors, decreased midbrain D2 and D3 autoreceptor sensitivity have been shown during a gambling task in patients with PD and gambling compared with those without (25). This may reflect enhanced striatal dopamine release in PD patients with ICB when exposed to reward stimuli. Two PET studies (11, 26) found that PD-ICB patients present decreased [11C]raclopride binding potential in the VS during reward cues exposure compared to PD patients without ICB. As [11C]raclopride is highly selective for post-synaptic D2 receptors, a reduced binding may suggest again the presence of a "hyperdopaminergic state" in the VS of patients with PD-ICB. This effect was observed in "off" condition, as well as after a levodopa challenge (26). Interestingly, no binding change was determined by levodopa intake upon neutral cues (26). Recently, more selective tracers have been implemented, such as [18F]fallypride, which is a high affinity D2-like receptors ligand that can measure D2/D3 binding potential throughout

TABLE 1 | Summary of the methods and results from the studies included in the review.

References	Imaging methods	Subjects	ICB screening	Main findings
Ray et al. (25)	[11C]FLB-457 PET	7 PD patients with PG vs. 7 PD patients without PG	G-SAS	Decreased midbrain D2 and D3 autoreceptor sensitivity during a gambling task in patients with PD and PG compared with those without
Steeves et al. (11)	[11C]raclopride PET during gambling task	7 PD patients with PG vs. 7 PD patients without PG	Clinical interview, DSM-IV-TR	Decreased binding potential in the VS in PG patients than control patients at rest and during gambling task
O'Sullivan et al. (26)	[11C]raclopride PET during gambling task, before and after a levodopa challenge	11 PD patients with ICB vs. 7 PD patients without ICB	Semi-structured interview	Decreased binding potential in the VS in PD-ICB patients compared to control patients following reward-related cue exposure
Stark et al. (27)	[18F]fallypride PET	17 PD patients with ICB vs. 18 PD patients without ICB	Clinical interview and QUIP-RS	Lower binding potential within the VS and putamen in ICB patients compared with those without ICB
Cilia et al. (28)	[123I]FP-CIT SPECT	8 PD patients with PG vs. 21 PD patients without PG vs. 14 healthy controls	Clinical interview, DSM-IV-TR	Lower DAT binding in PD patients with PG compared to PD patients without PG
Voon et al. (13)	[123I]FP-CIT SPECT	15 PD patients with ICB vs. 15 PD patients without ICB	Clinical interview, DSM-IV-TR	Lower DAT binding in PD patients with ICB compared to PD patients without ICB
Politis et al. (19)	fMRI during sexual-cues exposure before and after levodopa challenge	12 PD patients with HS vs. 12 PD patients without HS	Clinical interview, DSM-IV-TR	Higher activity within the salience network in PD patients with HS compared to PD patients without HS during sexual cues, enhanced by levodopa administration
Tessitore et al. (20)	Resting-state fMRI	15 PD patients with ICB vs. 15 PD patients without ICB and 24 healthy controls	Clinical interview, MIDI	Increased connectivity within the salience and default-mode networks, and decreased connectivity within the central executive network in ICB-PD patients compared to those without
Tessitore et al. (21)	Resting-state fMRI	15 drug-naïve PD patients which developed ICB after treatment initiation vs. 15 drug-naïve PD patients who did not	Clinical interview, QUIP-RS	Baseline decreased connectivity in the default-mode and central executive networks and increased connectivity in the salience network in PD patients with ICB at follow-up compared with those without
Vriend et al. (14)	[123I]FP-CIT SPECT	11 drug-naïve PD patients which developed ICB after treatment initiation vs. 20 drug-naïve PD patients who did not	Clinical interview	Baseline lower DAT binding in PD patients with ICB at follow-up compared with those without
Voon et al. (18)	fMRI during reward task before and after DAA intake	14 PD patients with ICB vs. 14 PD patients without ICB	Clinical interview, DSM-IV-TR	After DAA treatment, PD-ICB patients present enhanced sensitivity to risk compared to PD patients without ICB
van Eimeren et al. (29)	[H152O] PET before and after DAA intake	7 PD patients with PG vs. 7 PD patients without PG	Clinical interview	DAA intake reduces cerebral blood flow in cortical areas involved in impulse control and behavioral inhibition
van der Vegt et al. (30)	fMRI during reward task	13 drug-naive PD patients vs. 12 healthy controls	Not applicable	Decreased neural response to reward outcomes within mesolimbic and mesocortical regions in drug-naïve PD patients compared to healthy controls
Thaler et al. (31)	fMRI during reward task	36 non-manifesting carriers of LRRK2 mutation vs. 32 non-manifesting non-carriers	Not applicable	Reduced activations upon risky anticipation and punishment in the VS and insula and higher activation upon safe anticipation in the insula in non-manifesting carriers

ICB, impulse control behaviors; fMRI, functional MRI; PET, positron emission tomography; SPECT, single-photon emission computed tomography; PG, pathological gambling; HS, hypersexuality; VS, ventral striatum; G-SAS, gambling symptom assessment scale; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders Text Revision criteria; MIDI, Minnesota Impulsive Disorders Interview; DAA, dopamine-agonist.

the meso-cortico-limbic network. This tracer was used in a cohort of PD patients with ICB compared with those without, confirming that the presence of a reduced binding potential within the VS and putamen may be a marker of increased dopaminergic levels (27). Moreover, this study showed that the integrity of the dopaminergic projections emerging from the

midbrain differentiates PD patients with ICB from those without, and increases along with severity of symptoms (27). This finding is in line with the hypothesis that ICB may result from the imbalanced involvement of the more affected dorsal and the less affected VS in the early stages of PD. Thus, while dopaminergic treatment partially restores the normal functioning within the dorsal striatum (improving motor symptoms), the dopaminergic treatment may "overdose" the VS, potentially triggering affective disturbances and ICB (36, 37).

Other neuroimaging approaches have confirmed the presence of dopaminergic signaling abnormalities in patients with PD and ICB. Indeed, reduced striatal dopamine transporter (DAT) density has been reliably reported in PD-ICB patients compared to PD patients without ICB (13, 28). This is of interest, as the DAT binding may decrease following either mesolimbic projections neurodegeneration or increased dopaminergic synaptic firing.

In a functional MRI (fMRI) study, patients with PD and hypersexuality exposed to sexual cues had higher activity within the SN compared to patients with PD without ICB (19). Moreover, this study showed that subjective sexual desire was enhanced by levodopa administration (19). A similar pattern of increased SN connectivity has been also shown at rest in PD patients with ICB compared to those without (20). Functional connectivity abnormalities were also found to be correlated to ICB severity (20).

In summary, different neuroimaging techniques have been used to analyze the integrity of striatal and extra-striatal dopaminergic pathways in PD patients with and without ICB. The presence of a specific "hyperdopaminergic" state in the brain of patients experiencing ICB have been consistently highlighted. An important limitation is that these studies have mainly enrolled PD patients with a long history of PD as well as ICB, which may both influence the reward and impulse-control pathways themselves. Indeed, after ICB emergence, progressive neuroplasticity processes involving mainly dopaminergic circuitries may occur, eventually leading to consolidation of pathological habits (38). Thus, even though with caution, these studies corroborate the idea that PD-related pathology and dopaminergic treatment may synergistically act on the risk to develop ICB in PD patients.

NEUROIMAGING STUDIES TO ANALYZE REWARD PROCESSING IN PD PATIENTS WITH ICB

Dopaminergic medications can influence rewarding processing, by enhancing learning from positive feedback and impairing learning from negative feedback (39, 40). Moreover, these drugs has been link to increased impulsivity (24).

Reward processing changes after dopaminergic drugs administration has been studied in healthy subjects as well as in patients with restless legs syndrome in order to describe pharmacological effects not biased from neurodegenerative pathology. Pessiglione et al. (41) performed a fMRI study to assess the effects of either levodopa (100 mg) or an antagonist of dopamine receptors (1 mg of haloperidol) on both brain activity and behavioral choice in healthy subjects. They found that during instrumental learning, levodopa increases while haloperidol reduces dopaminergic functioning in the VS along with the magnitude of reward prediction error. Accordingly, compared to subjects treated with haloperidol, subjects treated with levodopa showed greater propensity to choose the most rewarding action, supporting the hypothesis that dopamine-dependent modulation of striatal activity can account for how the healthy brain uses prediction errors to modulate future decisions (41). Another crucial component of the reward processing is the temporal impulsivity, which is the preference for smaller but sooner over larger but later rewards (42). This phenomenon is related to an excessive discounting of future rewards and has been observed in patients with drugs addiction (43). This function was tested in a cohort of young healthy subjects by means of a task-related and pharmacological fMRI paradigm (44). The study revealed that levodopa increases preference for more immediate rewards, likely increasing impulsivity in healthy brains. This result parallels with a corresponding increased neural representation in the striatum, further supporting the idea that a hyperfunctioning in the dopamine system is related to abnormal decision-making.

Along with levodopa, the effect of DAA treatment on the reward processing was tested in both healthy and non-healthy subjects as well. A double-blind study compared results from a probabilistic reward task performed after either a single low dose of pramipexole (0.5 mg) or placebo (45), revealing that DAA may affect the acquisition of reward-related behaviors (45). A similar effect was found also in a cohort of subjects with restless legs syndrome without any history of pathological gambling (46). In this study, fMRI scans were obtained during a gambling game task, once whilst subjects were taking their regular medication (i.e., low dose DAA) and after a washout period. Upon expectation of rewards, significant VS activation was detected only when subjects were taking DAA, but not when they were in the washout period. Contrariwise, upon omission of rewards, the observed VS signal under DAA were significantly different from what revealed during the washout (46).

These results parallel with several evidence coming from PD patients with ICB. A task-related and pharmacological fMRI study performed before and after DAA treatment, showed that PD-ICB patients under DAA present enhanced sensitivity to risk compared to PD patients without ICB in the same experimental condition (18). DAA intake has been also shown to reduce cerebral blood flow in cortical areas involved in impulse control and behavioral inhibition (29).

However, it should be noted that PD results from the degeneration of dopaminergic projections involved in the reward processing itself. By contrast, dysfunctions within the reward system are difficult to study in PD as most patients are treated with dopaminergic drugs. In this context, a fMRI task-related paradigm was used in a small group of drug-naïve PD patients performing a simple two-choice gambling task (30). In this study, PD patients compared to

healthy controls showed decreased neural response to reward outcomes within several mesolimbic and mesocortical nodes, such as the ventral putamen, ventral tegmental area, thalamus and hippocampus. In this framework, reward processing abnormalities were also found in subjects at high risk for future development of PD, such as a cohort of non-manifesting carriers of the G2019S mutation in the LRRK2 gene (31). Indeed, this event-related fMRI study showed differences between non-manifesting carriers and non-carriers when comparing activations in key reward brain areas upon safe and risky anticipation and punishing outcomes. Thus, several nodes of the meso-cortico-limbic reward system are already compromised in the early (and also preclinical) stages of the disease as they are also direct targets of PD-related neurodegeneration.

In summary, even in the absence of manifest ICB symptoms as well as PD pathology, chronic dopaminergic medication was shown to severely impair the reward processing. Although limited, neuroimaging evidence of altered reward-processing in PD patients even in the absence of DAA treatment have been provided.

NEUROIMAGING STUDIES TO PREDATE ICB DEVELOPMENT IN PD PATIENTS

To date, only a few studies have been designed to find potential neuroimaging biomarkers able to predict future development of ICB in PD. This is crucial, as previous studies did not allow to disentangle the complex interplay between drugs and disease in ICB pathophysiology. Vriend et al. (14) performed a retrospective analysis of DAT imaging data acquired in a cohort of drug-naïve PD patients that developed ICB symptoms after dopaminergic treatment initiation. They found that the presence of reduced DAT availability in the VS at baseline is able to predate ICB development after treatment initiation. Dopamine reuptake via striatal DAT is the most important mechanism acting to remove dopamine from the synapse. Thus, PD patients with lower DAT availability could have increased striatal dopamine levels (14, 28) even at the time of the diagnosis. This important finding corroborates the hypothesis that PD patients with higher risk to develop ICB may present at baseline a relatively preserved striato-cortical functioning. As we mentioned above, increased dopaminergic signaling in the VS can interfere with the processing of negative feedback during reward-based learning. Neurobehavioral studies (47, 48) have shown that the high dopaminergic firing occurring upon reward cues is able to reinforce hippocampal inputs and inhibits prefrontal connections on the VS. In the absence of feedback top-down processes, this divergent effect may impair the ability to shift behavioral focus when cues salience change, potentially looping the reward system. A similar condition may occur in PD patients with a "hyperdopaminergic" state in the VS (i.e., patients at higher risk to develop ICB) and then exposed to the dopamine-mimetic treatment (49), leading to impulsive-compulsive behaviors. However, further investigations are warranted to clarify which predisposing factors, potentially genetic (5, 6), may determine this trend toward increased dopaminergic response. In this framework, different polymorphisms in several neurotransmitters receptors genes, potentially leading to high dopaminergic striatal levels, have been linked to increased ICB susceptibility in PD (6).

More recently, resting-state fMRI was used to analyze the intrinsic functional connectivity within and between the major neurocognitive networks in a cohort of drug-naïve PD patients that developed ICB (ICB+) after treatment initiation compared with PD patients who did not (ICB–) (21). In physiological condition, the SN modulates the inter-network connectivity between the CEN and the DMN, resulting in a functional anti-correlation between these two networks (23, 50). This dynamic balance is crucial, as it is thought to drive an efficient behavioral and cognitive outcome (23). When comparing ICB+ and ICB- patients before treatment initiation, an increased resting-state connectivity within the SN was found in ICB+ patients (21). This is of interest, as the SN encompasses cortical and subcortical nodes that are affected by PD-related pathology itself, such as the VS (51, 52). The presence of an increased connectivity within this network may again rely on pre-existing abnormal dopaminergic signaling even at the disease onset, and may also explain the development of such behavioral complications when patients are exposed to dopaminergic medication. Interestingly, the study also revealed that the anti-correlation between DMN and CEN is lost at the time of diagnosis in ICB+ patients and this inverse pattern showed a positive correlation with the time to ICB onset (i.e., the less the anti-correlation between DMN and CEN the earlier is the emergence of ICB). Notably, no differences have been shown between ICB+ and ICB- patients in terms of total levodopa equivalent daily dose (including DAA) at the time of ICB development (21). Thus, these connectivity changes may represent a potential biomarker to predict emergence of ICB symptoms before starting any dopaminergic drugs.

In summary, longitudinal neuroimaging studies on premorbid ICB population are limited. However, they support the hypothesis that a pre-existing vulnerability to ICB development may be present in a specific subset of PD patients, likely related to PD-pathology, involving both dopaminergic signaling and reward processing, which are in turn affected by dopaminergic medications.

CONCLUSIONS

The relationship between PD pathology, DAA treatment and ICB development is complex. Neuroimaging studies have provided crucial insights to support the presence of increased dopaminergic firing in response to reward stimuli in the cortico-striato-cortical pathway in PD patients more prone to develop ICB. Dopaminergic treatment exposure may overdrive this pathway and also induce further dopamine receptors changes, leading to the development of such behavioral disturbances. Future multimodal imaging studies able to look at several aspects of the dopaminergic cortical and

subcortical signaling, as well as prospective longitudinal designs, will allow to disentangle how drugs and disease may interplay to trigger these relevant neuropsychiatric symptoms. Understanding neural correlates and potential predisposing factors of these severe behavioral symptoms will be crucial to guide clinical practice and to foster preventive strategies.

AUTHOR CONTRIBUTIONS

RD study concept and design, acquisition of data, drafting the article. AT drafting the article and revising it critically for intellectual content. AR critically revision of manuscript for intellectual content. GT critically revision of manuscript for intellectual content.

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Dopaminergic Neurotransmission in Patients With Parkinson's Disease and Impulse Control Disorders: A Systematic Review and Meta-Analysis of PET and SPECT Studies

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Background: Around 30% Parkinson's disease (PD) patients develop impulse control disorders (ICDs) to $D_{2/3}$ dopamine agonists and, to a lesser extent, levodopa. We aim to investigate striatal dopaminergic function in PD patients with and without ICD.

Methods: PubMed, Science Direct, EBSCO, and ISI Web of Science databases were searched (from inception to March 7, 2018) to identify PET or SPECT studies reporting striatal dopaminergic function in PD patients with ICD (ICD+) compared to those without ICD (ICD–). Studies which included drug naïve patients, explored non-pharmacological procedures (e.g., deep brain stimulation), and those using brain blood perfusion or non-dopaminergic markers were excluded. Standardized mean difference (SDM) was used and random-effect models were applied. Separate meta-analyses were performed for dopamine transporter level, dopamine release, and dopamine receptors availability in the putamen, caudate, dorsal, and ventral striatum.

Results: A total of 238 studies were title and abstract screened, of which 19 full-texts were assessed. Nine studies (ICD+: $N = 117$; ICD–: $N = 175$ patients) were included in the analysis. ICD+ showed a significant reduction of dopamine transporter binding in the putamen (SDM = −0.46; 95% CI: −0.80, −0.11; $Z = 2.61$; $p = 0.009$), caudate (SDM = −0.38; 95% CI: −0.73, −0.04; $Z = 2.18$; $p = 0.03$) and dorsal striatum (SDM = −0.45; 95% CI: −0.77, −0.13; $Z = 2.76$; $p = 0.006$), and increased dopamine release to reward-related stimuli/gambling tasks in the ventral striatum (SDM = −1.04; 95% CI: −1.73, −0.35; $Z = 2.95$; $p = 0.003$). Dopamine receptors availability did not differ between groups. Heterogeneity was low for dopamine transporter in the dorsal striatum ($I^2 = 0\%$), putamen ($I^2 = 0\%$) and caudate ($I^2 = 0\%$), and pre-synaptic dopamine release in the dorsal ($I^2 = 0\%$) and ventral striatum ($I^2 = 0\%$); heterogeneity was high for dopamine transporter levels in the ventral striatum ($I^2 = 80\%$), and for dopamine receptors availability in the ventral ($I^2 = 89\%$) and dorsal ($I^2 = 86\%$) striatum, putamen ($I^2 = 93\%$), and caudate ($I^2 = 71\%$).

Conclusions: ICD+ patients show lower dopaminergic transporter levels in the dorsal striatum and increased dopamine release in the ventral striatum when engaged in reward-related stimuli/gambling tasks. This dopaminergic imbalance might represent a biological substrate for ICD in PD. Adequately powered longitudinal studies with drug naïve patients are needed to understand whether these changes may represent biomarkers of premorbid vulnerability to ICD.

Keywords: Parkinson's disease, impulse control disorder, dopamine, PET, SPECT, transporter, receptors, meta-analysis

INTRODUCTION

Impulse control disorders (ICD), such as pathological gambling, hypersexuality, binge-eating, and compulsive shopping are diagnosed in around 30% of patients with Parkinson's disease (PD) (1–4).

ICDs are considered a complication of $D_{2/3}$ dopamine agonist treatment and, to a lesser extent, levodopa (5). This is evident from studies showing higher ICD rates in medicated PD patients compared to healthy controls (2, 3, 6, 7). Although ICD rates have not been directly compared between medicated and drug naïve PD patients, other studies have shown that rates in drug naïve PD patients do not differ from healthy controls (8, 9). There are also retrospective case reports (10–12) and prospective studies (13–15) showing that in some cases ICDs onset (10–12, 14, 15) and their reduction or resolution (10, 13, 16) covary with dopaminergic treatment.

Preclinical animal studies provide further evidence of a modulatory effect of dopamine agonists on impulsivity using delay discounting paradigms. In these paradigms, impulsivity results in a behavioral preference for an immediate (smaller) reward over a delayed (larger) reward. However, the direction of the effect of dopamine on the reward system is inconsistent. For example, some studies showed lower levels of impulsivity on 1 and 2 mg/kg doses of *d*-amphetamine (17, 18) whereas others report increased impulsivity in rats treated with similar or higher doses (e.g., 0.8, 1, 1.20, 3.2 mg/kg) (19–21) or no effects (21, 22).

Studies in healthy volunteers show a modulatory effect of dopamine agonists on impulsivity; however, like rodent studies previously mentioned, the direction of the effect is unclear, in that some studies report increased impulsivity while other ones show decreased impulsivity to dopamine agonists. For example, *d*-amphetamine decreases impulsive behavior on the Stop task and in the Go/no Go task (measured as Stop reaction time and number of false alarms), and decreases delay discounting (23). However, other dopaminergic agents such as levodopa and pramipexole increase impulsivity on delay discounting and gambling tasks (24, 25).

In summary, evidence from preclinical rodent studies and healthy volunteers indicate that dopamine agonists modulate the reward system and impulsivity, but the direction of the effect is not clear. This implies that impulsivity is modulated by a complex interplay of dopamine activity across a network of systems, and dopamine agonists disrupt the balance between brain areas modulating impulsivity.

In the first stages of PD, the function of ventral striatum is relatively more preserved than the dorsal striatum (26). Therefore, the dopaminergic treatment dose required to restore motor dorsal striatal dopaminergic levels may overstimulate the relatively intact ventral striatum (27). This hyperdopaminergic state may promote an abnormal activity in the connected cortico-striatal cognitive and limbic pathways that mediate reward-related behavior (28). As a consequence, the control of goal-directed behavior is impaired, facilitating ICD development.

If ICDs in PD are linked to the disruption of the equilibrium in dopamine activity across ventral and dorsal striatum, then brain positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can provide a direct measurement of putative dopaminergic differences between PD with and without ICDs. These nuclear medicine techniques use molecular imaging to assess biochemical, neurochemical, or pharmacological processes in the brain. For example, changes in neurotransmission can be detected using radiotracers with high affinity for dopamine receptors.

When a radiotracer is injected, it competes with dopamine for binding to free dopamine receptors. Thus, if dopamine is released endogenously, radiotracer binding can therefore be used as a marker for dopamine release (29). According to the binding affinity and the type of radiotracer, it is possible to investigate the nature of the dopaminergic dysfunction, whether linked to dopamine release, dopaminergic re-uptake in the presynaptic terminals, and $D_{2/3}$ post-synaptic receptors availability. The spatial resolution of current PET and SPECT machines allow separate assessment of the dorsal and ventral striatal regions, and their components (i.e., putamen, caudate).

A limitation of the PET and SPECT studies of ICD in PD published so far is the small sample size, with the largest study including 21 PD patients with ICD and 68 without ICD (30) and the smallest including 7 PD patients with ICD and 7 without ICD (31). Small sample sizes are not surprising, given the high cost of PET and SPECT exams. Moreover, variability in clinical and demographic characteristics, types of tracer, protocols of analysis, and scanners makes the comparison between studies difficult.

A meta-analytic approach can overcome these limitations. Low powered studies can be combined and differences in striatal dopaminergic function between PD patients with and without ICD estimated with a higher reliability. To the best of our knowledge, no previous meta-analysis has been published on this topic.

Therefore, the objective of this study was to investigate differences in dopaminergic function in the striatum in PD patients with and without ICD. To this aim, we systematically reviewed and meta-analyzed PET and SPECT based reports on dopamine transporter level, presynaptic dopamine release, and post-synaptic $D_{2/3}$ receptors availability in the ventral and dorsal striatum.

MATERIALS AND METHODS

Search Strategy

The PubMed, Science Direct, EBSCO, and ISI Web of Science databases were searched for peer-reviewed studies on PET or SPECT striatal dopaminergic function in PD-related ICD and published from database inception until the 7th of March 2018.

The following search string was used: "[(Parkinson's disease OR Parkinson) AND (impulse control disorders OR impulse control disorder OR impulsive compulsive behaviors OR impulsive compulsive behaviors OR impulsive compulsive behavior OR impulsive compulsive behavior OR ICD OR ICB OR hypersexuality OR gambling OR buying OR shopping OR eating)] AND (Positron emission tomography OR PET OR Single Photon Emission Computed Tomography OR SPECT OR SPET OR DaTSCAN)." A total of 384 papers were identified. After the exclusion of duplicates, 238 papers went through title and abstract screening. Two authors (AM, DDL) independently screened titles and abstracts using Rayyan software (32) and 17 papers were included in the full-text screening. The reference lists of these papers were manually searched for additional studies missed in the databases search, and two relevant papers were included at this stage. Two authors (AM, DDL) independently evaluated the 19 papers selected for full-text examination and disagreements were planned to be resolved via discussion with a third author (ST). However, there was 100% agreement between the two authors. Nine studies were included for quantitative analysis (**Figure 1**).

Selection Criteria

Studies were included if they met the following inclusion criteria: (i) PET or SPECT study; (ii) PD patients without ICD (ICD–) compared with PD patients with ICD (ICD+); (iii) data reported for at least one striatal region; (iv) independence of the sample. Therefore, if a study sample was reported in multiple publications, only the study with the largest sample was included.

We excluded reviews, case studies, commentaries, letters, abstracts and dissertations, conference papers, and postal surveys. Studies including drug naïve PD patients were excluded, as we were interested on ICD developed after dopamine replacement treatment (DRT) initiation. Moreover, drug naïve PD patients represent a different sample than those treated with DRT, as the former have shorter PD duration, and are not chronically exposed to DRT. Therefore, dopaminergic systems may be affected and stimulated differently in medicated and non-medicated PD patients.

Studies in which PD patients underwent deep brain stimulation (DBS) were also excluded, as ICDs may either improve or develop after DBS (33). Finally, studies using measures of brain blood perfusion were excluded, as they do not explore striatal dopaminergic functioning. Similarly, we excluded studies with non-dopaminergic markers.

Data Extraction

Corresponding authors of four studies (30, 34–36) were contacted for exact data. Data reported as median and range (37) were converted to mean and SD, as proposed by Hozo et al. (38). When standard error was reported, it was converted to SD (31, 39). Two authors (AM, DDL) independently extracted the following demographic and clinical data: sample size, sex, age at evaluation, age at PD onset, PD duration, education (years), Hoehn and Yahr (H&Y) stage, Unified PD Rating Scale motor section (UPDRS-III) ON-medication, depression, antidepressant use, antipsychotic use, number of patients under dopamine agonist treatment, dopamine agonist levodopa equivalent daily dose (LEDD, mg), levodopa LEDD, total LEDD, ICD screening tool, and ICD type. Methodological characteristics of the included studies were also extracted: imaging technique (i.e., PET or SPECT), type of tracer, reference region, imaging approach, radiotracer delivery method, drug delivered prior to scan, outcome measure, and striatal division and subdivision that was examined (i.e., ventral striatum, dorsal striatum, putamen, caudate).

The outcomes measures were the differences in the dopaminergic imaging parameters (e.g., binding potentials) between PD patients with and without ICD in striatal areas (i.e., ventral striatum, dorsal striatum, putamen, caudate).

Data Analysis

Separate meta-analyses were performed for studies focusing on dopamine transporter level, dopamine release (presynaptic), and dopamine receptors availability (postsynaptic) in the ventral striatum, dorsal striatum, putamen, and caudate. Data were analyzed using ReviewManager v5.3 (40). Standardized mean difference (SMD) was used as effect size measure, with values around 0.2, 0.5, and 0.8 considered as small, moderate, and large, respectively (41). Heterogeneity between studies was calculated by the I^2 value with percentages around 25, 50, and 75 considered as low, moderate, and high, respectively (42). As PD samples may vary in their clinical (e.g., H&Y stage, UPDRS scores) and demographic characteristics (e.g., age, sex), a random-effect model was applied.

Sensitivity analysis was performed by excluding studies clearly stating current antipsychotic or antidepressant use, as these drugs may affect dopamine receptor binding potential (43) or DAT uptake (44). As the number of studies was low, we lacked the power for conducting moderator analysis (45), or visual inspections of funnel plots for publication bias (46). A $p < 0.05$ was used as statistical significance threshold for all the analyses.

RESULTS

Demographic, clinical and methodological characteristics of the 117 ICD+ and 175 ICD– PD patients reported in the nine studies included in the meta-analysis are reported in **Tables 1**, **2**.

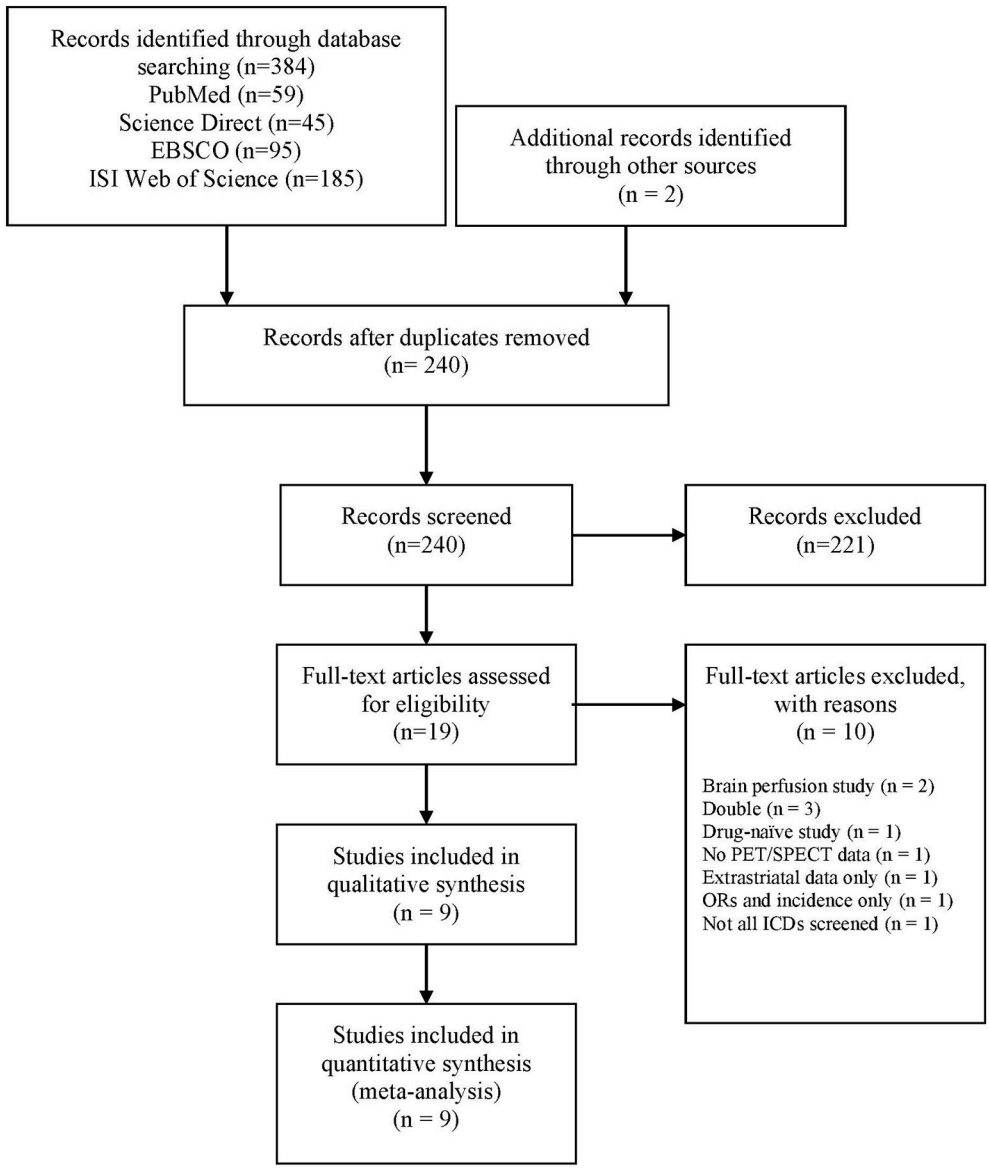

FIGURE 1 | PRISMA diagram of the study (www.prisma-statement.org). ICD, impulse control disorder; ORs, odds ratios; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

There was heterogeneity on the procedure to assess ICD across studies. ICDs were diagnosed either with a clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders fourth edition text revision (DSM-IV-TR) (34–37, 44, 48), the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM 5) (39) criteria or with the Questionnaire for Impulsive-Compulsive Disorders in PD—Rating Scale (QUIP-rs) (30). In four studies, the clinical interview followed the South Oaks gambling screen (SOGS) (34, 35), Gambling Symptom Assessment Scale (G-SAS) (31), QUIP-rs (36), and Sexual Addiction Screening test (35). In the paper of Steeves et al. (31), no specific information was provided on criteria for diagnosing ICDs apart from the use of SOGS for pathological gambling.

All patients were under DRT. In seven studies there were no between-group differences in total or dopamine agonist LEDD (31, 34, 36, 37, 39, 44, 48). One study reported a higher number of patients under dopamine agonist, however total LEDD and dopamine agonist doses were comparable between ICD+ and ICD– groups (30). In one study ICD+ had higher levodopa LEDD than ICD– (35).

One study divided the ICD+ group in single and multiple ICD subgroups (39). As the comparison between single and multiple ICD was not relevant for our meta-analysis, means and SDs of the subgroups were merged by calculating the pooled means and SDs.

Six studies provided results in the left/right (30, 34, 37, 39, 44, 48) and/or anterior/posterior striatal sub-regions (37); data from

TABLE 1 | Demographic and clinical characteristics of the studies included in the meta-analysis.

References	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	Education (y)*	H&Y*	UPDRS-III (ON)*	Depression as exclusion criteria?	Antidepressant use (N)
Cilia et al. (34)	ICD+: 8 (7) ICD–: 21 (11)	ICD+: 60.7 (7.5) ICD–: 60.1 (9.4)	NR	ICD+: 6.25 (2) ICD–: 6.1 (2.4)	NR	ICD+: 2.1 (0.74) ICD–: 2 (0.53)	ICD+: 18.1 (9.3) ICD–: 20.2 (5.6)	NO (GDS available)	NO
Joutsa et al. (37)	ICD+: 10 ICD–: 10	ICD+: 61.5 (45-7)¶ ICD–: 61.5 (53-7)¶	ICD+: 53 (40-64)¶ ICD–: 57 (47-63)¶	ICD+: 7 (3-9)¶ ICD–: 5 (1-8)¶	NR	All patients were in stages 2 to 3	ICD+: 31 (24-41)¶ ICD–: 32 (19-49)¶	NO	NR
Lee et al. (47)	ICD+: 11 (8) ICD–: 11 (6)	ICD+: 56.6 (8.7) ICD–: 58.5 (7.3)	ICD+: 46.4 (8.7) ICD–: 49.2 (7.3)	ICD+: 10.1 (6.9) ICD–: 9.4 (2.3)	NR	ICD+: 2.3 (0.4) ICD–: 2.1 (0.5)	ICD+: 14.2 (11.0) ICD–: 15.3 (7.6)	YES	NO
Payer et al. (35)	ICD+: 11(9) ICD–: 21 (11)	ICD+: 58.9 (7.8) ICD–: 63.3 (8.7)	NR	ICD+: 12.1 (3.7) ICD–: 7.4 (4.5)	ICD+: 15.5 (2.7) ICD–: 15.1 (1.8)	NR	ICD+: 33.1 (10.2) ICD–: 28.1 (10.6)	YES	YES: ICD+: 1 ICD–: 0
Premi et al. (30)	ICD+: 21 (16) ICD–: 63 (38)	ICD+: 65.8 (8.4) ICD–: 68.5 (11.0)	NR	ICD+: 1.9 (2.2) ICD–: 1.7 (2.4)	NR	ICD+: stage 1 ($N = 4$); stage 1.5 ($N = 3$); stage 2 ($N = 5$); stage 2.5 ($N = 5$); stage 3 ($N = 4$) ICD–: stage 1 ($N = 8$); stage 1.5 ($N = 13$); stage 2 ($N = 18$); stage 2.5 ($N = 17$); stage 3 ($N = 7$)	ICD+: 16.5 (7.2) ICD–: 14.6 (7.7)	NO	YES: ICD+: 2 ICD–: 10
Stark et al. (36)	ICD+: 17 (11) ICD–: 18 (13)	ICD+: 60.9 (6.6) ICD–: 62.7 (10.1)	NR	ICD+: 5.7 (3.2) ICD–: 6.1 (4.5)	NR	NR	NR	YES	NR (unlikely considering the exclusion criteria)
Steeves et al. (31)	ICD+: 7 (5) ICD–: 7 (6)	ICD+: 47-72§ ICD–: 51-74§	NR	ICD+: 7.4 (3.2) ICD–: 5.6 (2.5)	NR	ICD+: 2 (0.6) ICD–: 1.9 (0.7)	OFF medication: ICD+: 25.2 (4.5) ICD–: 20.2 (5.4)	NO	NR
Voon et al. (44)	ICD+: 15 (9) ICD–: 15 (9)	ICD+: 55.1 (8.9) ICD–: 60.1 (8)	NR	ICD+: 7.5 (5.4) ICD–: 5.5 (5.2)	NR	ICD+: 3† ICD–: 3†	NR	NR	NR
Wu et al. (39)	ICD+: 17 ICD–: 9	S-ICD: 62.3 (3.9)‖ M-ICD: 58.1 (2.8)‖ ICD–: 60.2 (3.2)‖	S-ICD: 51.7 (4)‖ M-ICD: 43.8 (3.4)‖ ICD–: 50.3 (3.4)‖	S-ICD: 10.6 (2)‖ M-ICD: 14.3 (11.2)‖ ICD–: 9.9 (2.1)‖	NR	NR	OFF medication: S-ICD: 42.1 (3.8)‖ M-ICD: 41 (3.5)‖ ICD–: 32.8 (3)‖	NO (but BDI scores available)	NR

References	Antipsychotic use (N)	Drugs that may affect PET binding exclusion criterion	Patients under DA treatment (N/Total)	LEDD (mg)			Dementia excluded	ICD	
				Total LEDD*	LD-LEDD*	DA-LEDD*		Diagnosis**	Type: N
Cilia et al. (34)	NO	YES	NR	ICD+: 831.2(293.6) ICD–: 852.3 (301.1)	NR	ICD+: 240.6 (118) ICD–: 251.6 (121)	YES (MMSE<24)	Clinical interview (DSM-IV-TR criteria); SOGS	2 PG; 5 PG+HS; 3 PG+BE; 2 PG+CS

(Continued)

TABLE 1 | Continued

References	Antipsychotic use (N)	Drugs that may affect PET binding exclusion criterion	Patients under DA treatment (N/Total)	LEDD (mg)			Dementia excluded	ICD	
				Total LEDD*	LD-LEDD*	DA-LEDD*		Diagnosis**	Type: N
Joutsa et al. (37)	NR	NO but none used nicotine or had current substance-use disorder	ICD+: 9/10 ICD–:9/10	ICD+: 635 (250–876)¶ ICD–: 826 (210-1127)¶	NR	ICD+: 171.5 (0–280)¶ ICD–: 200 (0-320)¶	NO	Structured Clinical Interview for DSM-IV Axis I Disorders	4 PG;1 PG+subclinical HS; 1 HS; 2 HS+subclinical BE; 1 HS+subclinical CS; 1 BE
Lee et al. (48)	NO	YES	NR	ICD+: 914.4 (338.7) ICD–: 925.2 (458.4)	NR	ICD+: 217.9 (175.3) ICD–: 153.2 (110.7)	YES (MMSE<24)	Clinical interview (DSM-IV-TR criteria); modified MIDI	1 HS; 2 PG; 3 CS+BE; 1 CS+HS+BE; 1 CS+HS+BE+PG; 2 CS+BE+punding; 1 HS+BE+PG
Payer et al. (35)	NR (unlikely considering the exclusion criteria)	YES. Current treatment with DA was exclusionary as it may interfere with ligand binding.	ICD+: 0/11 ICD–: 0/21	NR	ICD+: 813.6 (318.5) ICD–: 426.2 (144.6)	NR	YES (MMSE<26)	clinical interview according to proposed criteria; SOGS; DSM-IV-based gambling questionnaire; sexual addiction screening test	10 PG; 3 HS; 1 CS. Only 5 patients meeting ICD criteria at the time of the study
Premi et al. (30)	NR	Antidepressant therapy, if present, was suspended 3 weeks before the assessment	ICD+: 19/21 ICD–: 30/63	ICD+: 594.2 (388.6) ICD–: 359.1 (280.1)	NR	ICD+: 282.1 (227.9) ICD–: 174.4 (97.2)	NO but MMSE scores reported	QUIP-rs	12 BE; 7 PG; 6 HS; 2 punding; 33 DDS + other ICDs; 1 DDS
Stark et al. (36)	NR (unlikely considering the exclusion criteria)	Patients excluded if they were prescribed psychoactive drugs that could alter dopamine receptor availability	ICD+: 17/17 ICD–: 18/18	ICD+: 673.8 (440) ICD–: 693.9 (406.3)	NR	ICD+: 103.9 (65.1) ICD–: 135.4 (76.4)	YES (MoCA<22)	Clinical interview (DSM-IV-TR criteria); QUIP-rs;	11 HS; 11 BE; 4 CS; 12 hobbyism
Steeves et al. (31)	NR	NR	ICD+: 7/7 ICD–: 7/7	ICD+: 856 (407) ICD–: 756 (400)	NR	ICD+: 138 (172) ICD–: 167 (113)	YES	G-SAS	7 PG

(Continued)

TABLE 1 | Continued

References	Antipsychotic use (N)	Drugs that may affect PET binding exclusion criterion	Patients under DA treatment (N/Total)	LEDD (mg)			Dementia excluded	ICD	
				Total LEDD*	LD-LEDD*	DA-LEDD*		Diagnosis**	Type: N
Voon et al. (44)	NR	Patients were required to stop any drug that would bind to the DAT seven days prior to the scan	ICD+: 13/15 ICD−: 10/15	ICD+: 785.8 (402.7) ICD−: 852.1 (520.4)	NR	ICD+: 325.8 (156.1) ICD−: 384.3 (212.8)	NR	clinical interview	4 HS; 5 CS; 3 PG; 6 punding
Wu et al. (39)	NR	NR	NR	S-ICD: 782.3 (83.4)‖ M-ICD: 724 (99)‖ ICD−: 831.9 (119.2)‖	S-ICD: 538 (83.4)‖ M-ICD: 268.5 (84.9)‖ ICD−: 666.3 (129)‖	S-ICD: 244.3 (51.4)‖ M-ICD: 244 (55.4)‖ ICD−: 165.6 (48.8)‖	YES (MMSE<24)	semi-structured interview	4 HS; 3 PG; 1 CS+three ICDs; 2 CS+two ICDs; 7 CS +one ICD;

*BDI, Beck depression inventory; BE, binge eating; CS, compulsive shopping; DA, dopamine agonist; DAT, dopamine transporter; DDS, Dopamine dysregulation syndrome; DSM-IV, diagnostic and statistical manual of mental disorders, fourth edition; DSM-IV-TR, diagnostic and statistical manual of mental disorders, fourth edition, text revision; G-SAS, Gambling symptom assessment scale; GDS, Geriatric depression scale; H&Y, Hoehn & Yahr score; HS, hypersexuality; ICD, impulse control disorder; ICD+, PD patients with ICD; ICD−, PD patients without ICD; LEDD, levodopa equivalent daily dosage (mg); LD, levodopa; M-ICD, multiple ICD; MIDI, Minnesota impulsive disorder interview; MMSE, mini mental state examination; MoCA, Montreal cognitive assessment; N, number of patients; NR, not reported. PD, Parkinson's disease; PET, positron emission tomography; PG, pathological gambling; Pts, patients; QUIP-rs, questionnaire for impulsive-compulsive disorders in Parkinson's disease rating scale; Ref, reference number; S-ICD, single ICD; SOGS, South Oaks gambling screen; UPDRS-III, unified Parkinson's disease rating scale part III (motor subscale) score; y: years. *Mean (SD) unless otherwise stated. ‖Median (range). §Range. †Median. ‖Mean (SEM). **Questionnaire or method use to screen and/or diagnose ICD.*

these studies were merged by calculating the pooled means and SDs.

Seven studies provided means and SDs for putamen and caudate separately (30, 35–37, 39, 44, 48). For these studies, putamen and caudate measures were merged to generate a measure of the whole dorsal striatum, according to Howes et al. (43). To this aim, the means of the dopaminergic index in the putamen and caudate were weighed by their volumes to reflect the larger contribution of the putamen compared to the caudate, and averaged (43). Since none of the studies reported the putamen and caudate anatomical volumes, we used those used by Howes et al. (43) and derived from healthy adults ($n = 34$, mean age = 32.5 years, $SD = 8.8$ years; mean, SD mm^3 volume: putamen = 8805, 994; caudate = 5562, 865). SD was calculated accounting for the dependency of measures, by assuming a between-measures correlation of $r = 0.5$ in the striatal sub-regions. To test whether the whole dorsal striatum measure might have concealed differences in its sub-regions, analyses were repeated considering the putamen and caudate separately.

According to the radiotracer and the imaging approach used, studies were categorized as investigating (i) dopamine transporter level (30, 34, 37, 44, 48), (ii) dopamine release (31, 39), and (iii) dopamine receptors availability (31, 35, 36, 39). Information about radiotracers used in the studies included in the meta-analysis is reported in **Table 3**.

In the dopamine transporter level subgroup, three studies (30, 34, 44) used [123I]FP-CIT, a SPECT radiotracer with high affinity for DAT and modest affinity for the serotonin transporter (47); one study (48) used the [18F]FP-CIT radiotracer, which has also cross-affinity to serotonin transporter but a better contrast than [123I]FP-CIT (56); and one study (37) used [18F]fluorodopa, which is a marker of both dopaminergic re-uptake and dopamine synthesis (57).

The pre-synaptic dopamine release subgroup included two studies (31, 39) using [11C]raclopride, which is a competitive $D_{2/3}$ antagonist sensitive to changes in endogenous dopamine levels (53). Both studies (31, 39) used a two PET sessions design, with one baseline scan [i.e., control task (31), neutral cues visual exposure (39)] and one scan during the experimental condition [i.e., gambling task (31), reward cues visual exposure (39)]. The binding potential in baseline condition is a measure of basal level of receptor availability. Conversely, the change in binding potential between baseline and experimental conditions is an indirect measure of alteration in striatal dopamine concentration due to pre-synaptic dopaminergic release. A decrease in binding potential in comparison to baseline is associated with increase in dopamine, while an increase in binding potential in comparison to baseline is associated with a dopamine decrease (53). Therefore, for the pre-synaptic dopamine release studies (31, 39), the outcome was the percentage [11C]raclopride binding potential reduction when comparing the experimental and baseline conditions.

Finally, the post-synaptic dopamine receptors availability subgroup included one study (35) with [11C]-(+)-PHNO, a D_3-preferring $D_{2/3}$ receptor ligand, and one study (36) with [18F]fallypride, which is one of the high affinity $D_{2/3}$ receptor ligands that allow quantification of both striatal and extrastriatal

TABLE 2 | Methodological characteristics of the studies included in the meta-analysis.

References	Imaging technique	Type of tracer	Reference region	Imaging approach	Radiotracer delivery method	Drug delivered prior scan	ON/OFF	Withdrawal period
Cilia et al. (34)	SPECT	[123I]FP-CIT	Occipital cortex	Single scan	Intravenous injection	Thyroid blockade (oral Lugol solution 10–15 mg) 30-40 min before the injection	OFF	Overnight withdrawal of dopaminergic medications
Joutsa et al. (37)	PET	[18F]fluorodopa	Occipital cortex	Single scan	Bolus injection	Carbidopa 150 mg 1h before the scan	OFF	At least 12 h drug discontinuation (>24 h for slow-release medications)
Lee et al. (48)	PET	[18F]FP-CIT	Cerebellum	Single scan	Bolus injection	NO	OFF	At least 12 h withdrawal of all PD medications
Payer et al. (35)	PET	[11C]-(+)-PHNO	Cerebellum	Single scan	Bolus injection	NO	OFF	At least 8 h withdrawal of levodopa (current DA use was an exclusion criteria)
Premi et al. (30)	SPECT	[123I]FP-CIT	Occipital lobe	Single scan	Intravenous injection	$KClO_4$ 800 mg 30 min before the injection	NR	NR
Stark et al. (36)	PET	[18F]fallypride	Cerebellum	Three emissions scans	Bolus injection	NO	OFF	Washout was at least 40 h for DA and 16 h for levodopa
Steeves et al. (31)	PET	[11C]raclopride	Cerebellum	Two scans in two separate days within 2 weeks, in randomized order: baseline; gambling task	Ten mCi injections	NO	OFF	12–18 h overnight withdrawal of PD medications
Voon et al. (44)	SPECT	[123I]FP-CIT	Occipital lobe	Single scan	Slow intravenous injection	Thyroid blockade (oral potassium iodate) 24h prior to the study	ON	NO
Wu et al. (39)	PET	[11C]raclopride	Cerebellum	Two scans in 2 separate weekdays mornings: neutral stimuli; reward-related stimuli	Bolus injection	NO	OFF	12 h withdrawal of PD medications

DA, dopamine agonist; mCi, millicurie; PD, Parkinson's disease; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

binding. Two studies (31, 39) with [11C]raclopride were also included in the post-synaptic dopamine receptors availability analysis; for these studies the outcome was the value reported for the baseline conditions.

A total of 292 subjects were included in the meta-analysis, 117 were PD patients with ICD (age range: 45–72 years; PD duration: 1.9–14.3 years; H&Y: 2–3; UPDRS-III score ON medication: 14.2–41) and 175 were PD patients without ICD (age: 51–74 years; PD duration: 1–9.9 years; H&Y stage: 1.9–3; UPDRS-III score ON medication: 14.6–49) (**Table 1**).

Four meta-analyses were performed for the dopamine transporter levels in the ventral striatum, dorsal striatum, putamen, and caudate. Two meta-analyses were performed for the pre-synaptic dopamine release in the ventral and dorsal striatum; the putamen and caudate were not explored for this outcome, because only one study provided separate values for these two structures (39). Four meta-analyses were performed for the post-synaptic dopamine receptors availability in the ventral striatum, dorsal striatum, putamen, and caudate. Results of the meta-analyses are provided in **Table 4**.

Dopamine Transporter Levels

Compared to the ICD– group, tracer binding in the ICD+ group was significantly reduced in the dorsal striatum (SDM = −0.45; 95% CI: −0.77, −0.13; $Z = 2.76$; $p = 0.006$) but not in the ventral striatum (SDM = −0.91; 95% CI: −2.10, 0.27; $Z = 1.51$; $p = 0.13$). When dorsal striatum sub-regions were analyzed separately, both putamen (SDM = −0.46; 95% CI: −0.80, −0.11; $Z = 2.61$; $p = 0.009$) and caudate (SDM = −0.38; 95% CI: −0.73, −0.04; $Z = 2.18$; $p = 0.03$) tracer bindings were significantly reduced in the ICD+ vs. ICD– (**Figure 2**, **Table 4**).

Heterogeneity was low for the dorsal striatum ($\chi^2 = 1.99$, $p = 0.74$, $I^2 = 0\%$), putamen ($\chi^2 = 1.43$, $p = 0.70$, $I^2 = 0\%$), and caudate ($\chi^2 = 1.79$, $p = 0.62$, $I^2 = 0\%$). However,

TABLE 3 | Radiotracers used in studies included in the meta-analysis.

Type of tracer	Study	Function and characteristics
[123I]FP-CIT	Cilia et al. (34); Premi et al. (30); Voon et al. (44)	SPECT radiotracer with high affinity for DAT (49) and serotonin transporter (50)
[18F]FP-CIT	Lee et al. (48)	SPECT radiotracer with high affinity for DAT with high signal-to-noise ratio and kinetics (51)
[18F]fluorodopa	Joutsa et al. (37)	PET radiotracer for both presynaptic dopamine metabolism (synthesis) (52) and striatal dopamine uptake
[11C]raclopride	Steeves et al. (31); Wu et al. (39)	PET selective D2/D3 antagonist sensitive to changes in endogenous dopamine levels; it can be used to assess both basal levels of receptor availability and changes in availability caused by alterations in striatal dopamine concentration (53)
[11C]-(+)-PHNO	Payer et al. (35)	PET ligand with high affinity and selectivity for D_3 receptors (54)
[18F]fallypride	Stark et al. (36)	PET ligand with high affinity to $D_{2/3}$ receptors in striatal and extrastriatal regions (55)

DAT, dopamine transporter; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

heterogeneity in the ventral striatum was high ($\chi^2 = 10.14$, $p = 0.006$, $I^2 = 80\%$; **Figure 2**). Sensitivity analysis was performed by excluding Premi et al. (30), which enrolled 12 patients under anti-depressant treatment that was suspended 3 weeks before assessment. Exclusion of Premi et al. (30) did not change overall effect size for dorsal striatum (SDM = −0.58; 95% CI: −0.99, −0.16; $Z = 2.73$; $p = 0.006$), putamen (SDM = −0.54; 95% CI: −1.02, −0.06; $Z = 2.23$; $p = 0.03$), and caudate (SDM = −0.54; 95% CI: −1.02, −0.07; $Z = 2.24$; $p = 0.03$), and heterogeneity (dorsal striatum: $\chi^2 = 1.07$, $p = 0.78$, $I^2 = 0\%$; putamen: $\chi^2 = 1.19$, $p = 0.55$, $I^2 = 0\%$; caudate: $\chi^2 = 0.87$, $p = 0.65$, $I^2 = 0\%$).

Pre-synaptic Dopamine Release

ICD+ group, compared to the ICD− group, showed reduced binding in the ventral striatum in response to reward-related stimuli/gambling task (SDM = −1.04; 95% CI: −1.73, −0.35; $Z = 2.95$; $p = 0.003$), but not in the dorsal striatum (SDM = −0.36; 95% CI: −1.01, 0.28; $Z = 1.10$; $p = 0.27$; **Figure 3**, **Table 4**).

Heterogeneity was low for both ventral ($\chi^2 = 0.22$, $p = 0.64$, $I^2 = 0\%$) and dorsal ($\chi^2 = 0.42$, $p = 0.52$, $I^2 = 0\%$) striatal regions (**Figure 3**).

Post-synaptic Dopamine Receptors Availability

Post-synaptic dopamine receptor bindings potentials did not differ between ICD+ and ICD− groups in the ventral striatum (SDM = −1.29; 95% CI: −2.68, 0.10; $Z = 1.82$; $p = 0.07$), dorsal striatum (SDM = −0.69; 95% CI: −1.86, 0.48; $Z = 1.16$; $p = 0.25$), putamen (SDM = −1.06; 95% CI: −2.94, 0.81; $Z = 1.11$; $p = 0.26$), and caudate (SDM = −0.59; 95% CI: −1.40, 0.23; $Z = 1.41$; $p = 0.16$; **Figure 4**, **Table 4**).

Heterogeneity was high in the ventral striatum ($\chi^2 = 26.71$, $p < 0.00001$, $I^2 = 89\%$), dorsal striatum ($\chi^2 = 21.90$, $p < 0.0001$, $I^2 = 86\%$), putamen ($\chi^2 = 28.99$, $p < 0.00001$, $I^2 = 93\%$), and caudate ($\chi^2 = 6.86$, $p = 0.03$, $I^2 = 71\%$; **Figure 4**).

Sensitivity analysis was performed by excluding Payer et al. (35), which enrolled one patient taking antidepressant. Exclusion of Payer et al. (13) did not change the overall effect size for the ventral striatum (SDM = −1.42; 95% CI: −3.54, 0.69; $Z = 1.32$; $p = 0.19$), dorsal striatum (SDM = −0.84; 95% CI: −2.55, 0.86; $Z = 0.97$; $p = 0.33$), putamen (SDM = −1.54; 95% CI: −4.87, 1.80; $Z = 0.90$; $p = 0.37$), and caudate (SDM = −0.56; 95% CI: −1.99, 0.87; $Z = 0.77$; $p = 0.44$), and heterogeneity (ventral striatum: $\chi^2 = 26.58$, $p < 0.00001$, $I^2 = 92\%$; dorsal striatum: $\chi^2 = 20.53$, $p < 0.0001$, $I^2 = 90\%$; putamen: $\chi^2 = 25.42$, $p < 0.00001$, $I^2 = 96\%$; caudate: $\chi^2 = 6.86$, $p = 0.009$, $I^2 = 85\%$).

DISCUSSION

This is the first systematic review and meta-analysis on PET/SPECT dopaminergic striatal correlates of ICD in PD. Our aim was to investigate if striatal dopaminergic function differs in PD patients with and without ICD. To this aim, we reviewed and analyzed studies on dopamine transporter levels, presynaptic dopamine release, and post-synaptic $D_{2/3}$ receptors availability in the ventral and dorsal striatum. We found ICD+ to be associated with (i) lower DAT levels in the dorsal striatum and in its subdivisions (i.e., putamen, caudate) and (ii) reduced binding (i.e., increased dopamine release) in the ventral striatum in response to reward-related stimuli or gambling task, but (iii) no relationship between ICD+ and striatal post-synaptic receptors availability in either the dorsal or ventral striatum.

Dopamine Transporter Levels

ICD+ group showed lower dorsal striatum DAT binding than the ICD− one.

In the striatum, DAT is localized in axon varicosities and terminals that contain synaptic vesicles, as well as in non-synaptic region where it regulates and terminates extracellular dopamine activity (44). Therefore, reduced DAT might reflect more pronounced dorsal striatal dopaminergic terminal loss, functional DAT downregulation, or genetically determined lower membrane expression on otherwise normal neurons (34).

The hypothesis of more severe degeneration of nigrostriatal projections in ICD+ patients is supported by a recent meta-analysis of case-control studies showing that the risk of ICD in PD increases with disease duration and being medicated for PD (58), two factors that are directly correlated with the amount of

TABLE 4 | Results of the meta-analysis.

Outcome	K	*N*	Random-effect model results				Heterogeneity		
			SMD	[95% CI]	Z	*p*	X^2	*p*	I^2(%)
Dopamine transporter level–ventral striatum	3	71	−0.91	[−2.10, 0.27]	1.51	0.13	10.14	*0.006*	80
Dopamine transporter level–dorsal striatum	5	184	−0.45	[−0.77, −0.13]	2.76	*0.006*	1.99	0.74	0
Dopamine transporter level–putamen	4	155	−0.46	[−0.80, −0.11]	2.61	*0.009*	1.43	0.70	0
Dopamine transporter level–caudate	4	155	−0.38	[−0.73, −0.04]	2.18	*0.03*	1.79	0.62	0
Dopamine release–ventral striatum	2	40	−1.04	[−1.73, −0.35]	2.95	*0.003*	0.22	0.64	0
Dopamine release–dorsal striatum	2	40	−0.36	[−1.01, 0.28]	1.10	0.27	0.42	0.52	0
Receptors availability–ventral striatum	4	107	−1.29	[−2.68, 0.10]	1.82	0.07	26.71	*<0.00001*	89
Receptors availability–dorsal striatum	4	107	−0.69	[−1.86, 0.48]	1.16	0.25	21.90	*<0.00001*	86
Receptors availability–putamen	3	93	−1.06	[−2.94, 0.81]	1.11	0.26	28.99	*<0.00001*	93
Receptors availability–caudate	3	93	−0.59	[−1.40, 0.23]	1.41	0.16	6.86	*0.03*	71

K, number of studies; N, number of participants; SMD, standardized mean difference; CI, confidence interval. P values below the significance level ($p < 0.05$) are reported in italics.

nigrostriatal loss. Moderator analysis for these two factors was not possible, because of the small number of studies included in the meta-analysis.

The lower DAT binding in ICD+ may also reflect medication-related DAT downregulation, but DAT regulation by DRT was found to be modest (44, 59). It is unlikely that lower DAT binding is a compensatory effect of medication, as longitudinal studies on drug naïve PD patients show that dorsal striatal DAT downregulation precedes DRT initiation (15, 60). SPECT findings are further supported by a genetic study showing an association between ICD in PD and a variant of the dopamine transporter gene, i.e., 9-repeat allele of the SLC6A3 (61); this variant results in lower presynaptic DAT expression, reduced synaptic clearance, and increased DA availability in the synaptic space (62).

Pre-synaptic Dopamine Release

ICD+ group showed reduced binding potential in ventral but not dorsal striatum when exposed to reward-related cues or when engaged in a gambling task.

Participants to a gambling task are required to actively choose options associated either with reward or penalty and process related feedback. Conversely, in reward-related cues paradigms, participants passively view neutral or reward-related stimuli (e.g., food, erotic pictures, gambling, or shopping related activities) without any active choice. Albeit being different, these tasks share neurobiological underpinnings. In pathological gamblers, reductions of ventral striatal and ventromedial prefrontal cortex activity have been documented in a gambling task (63) and reward-related reactivity has been shown to involve the dorsal lateral prefrontal cortex network (64) that is functionally connected to the ventral striatum.

[11C]raclopride is sensitive to competition from endogenously released dopamine to a stimulus, therefore decreased binding potential found in ICD+ vs. ICD− groups in response to gambling tasks or rewarding stimuli reflects increased dopamine release. These findings are in keeping with functional imaging studies of behavioral and pharmacological addiction in the general population, whereby monetary and sexual stimuli elicit the same patterns of striatal activation as recreational drugs (31, 65). Increased dopamine release during a gambling task has been reported in pathological gamblers (66, 67) and it correlates both with gambling severity (68) and increased excitement levels despite lower performances (66). This may be the consequence of conditioned response to the reward-related or gambling cues, although increased dopaminergic release has been observed also for unconditioned stimuli (39).Whether the increased dopamine release in the ventral striatum exists in the premorbid phase therefore representing a vulnerability factor or it is the consequence of repeated exposure to gambling or rewarding-related stimulus (69, 70), to DRT (71), or a combination of these factors (31) is unknown. Only preclinical models and prospective studies can address this point.

These findings have important implications, since the exposure to any reward-related cue (e.g., through advertisement) may have the potential to increase abnormal dopamine release in vulnerable PD patients (72), as supported by a study showing increased dopamine release in single ICD PD patients to reward-cues not related to their ICD (e.g., gamblers to food-related cues) (39).

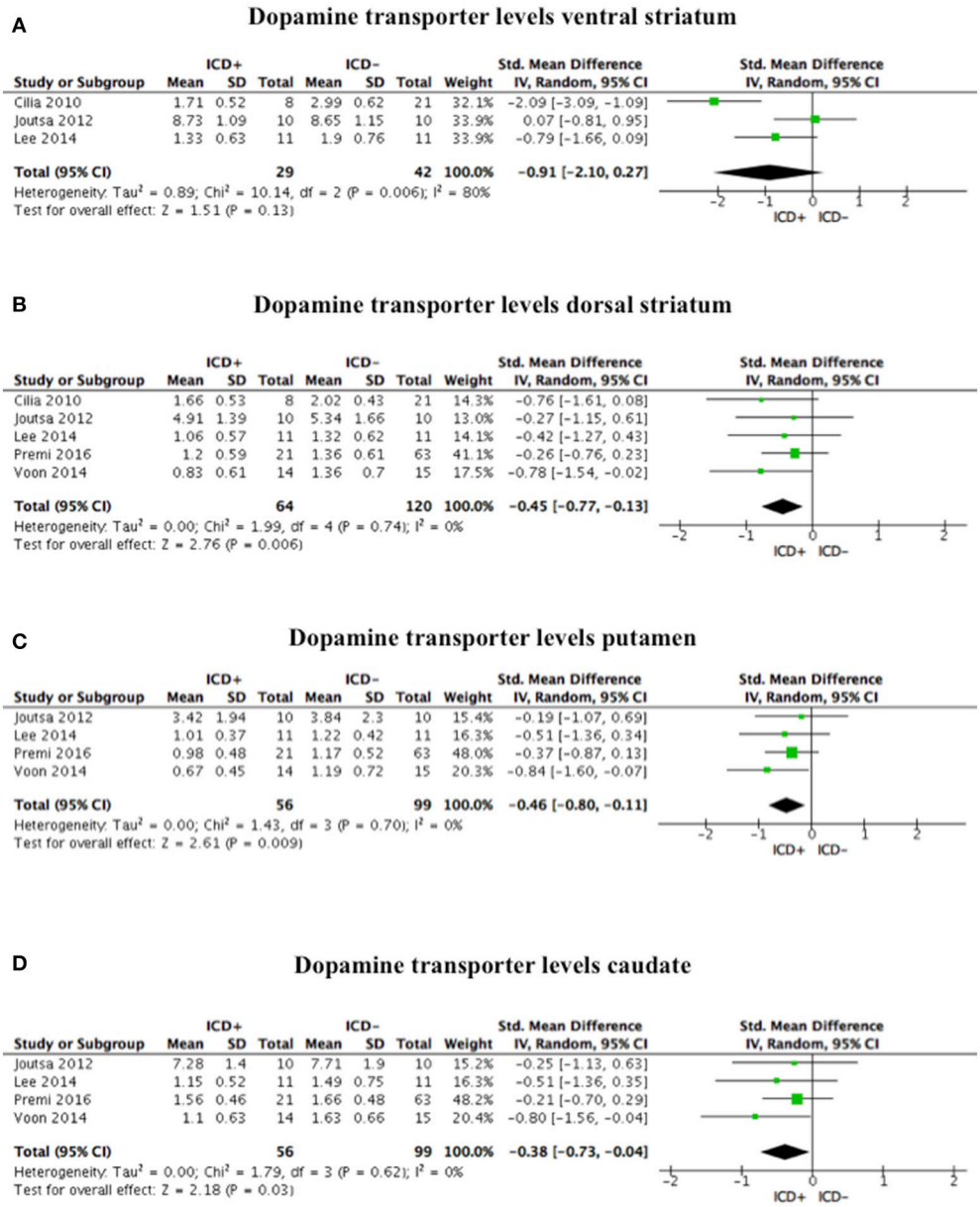

FIGURE 2 | Forest plots for dopamine transporter levels. Here are reported forest plots for dopamine transporter levels in the ventral striatum **(A)**, dorsal striatum **(B)**, putamen **(C)**, and caudate **(D)**. Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate lower dopamine transporter levels in PD patients with ICD (ICD+) in comparison to those without ICD (ICD–). ICD, impulse control disorder; PD, Parkinson's disease.

There are two other neuropharmacological mechanisms that should be considered. First, in patients treated with dopamine agonists the activation of presynaptic D_2-like presynaptic autoreceptors in the mesolimbic system reduces phasic dopamine release in the nucleus accumbens (25, 73, 74). Therefore, reward responsiveness is blunted and risk propensity enhanced in order to normalize mesolimbic efflux (73). Second, reward detection capacity depends on phasic dopaminergic cell firing. Phasic dopamine dips encode prediction errors therefore providing outcome-related feedback which signal the need of behavioral adjustments as reward contingencies change (75). In rats, a low dose of monoamine-depleting agent reserpine administered together with pramipexole, exacerbated its effects on disadvantageous decision-making without changing pramipexole-induced decrease in the phasic dopamine release. This suggests that the effect of dopamine agonist on ICD may not be caused by changes in phasic dopamine release in the nucleus accumbens (73). Moreover, dopamine agonists tonically

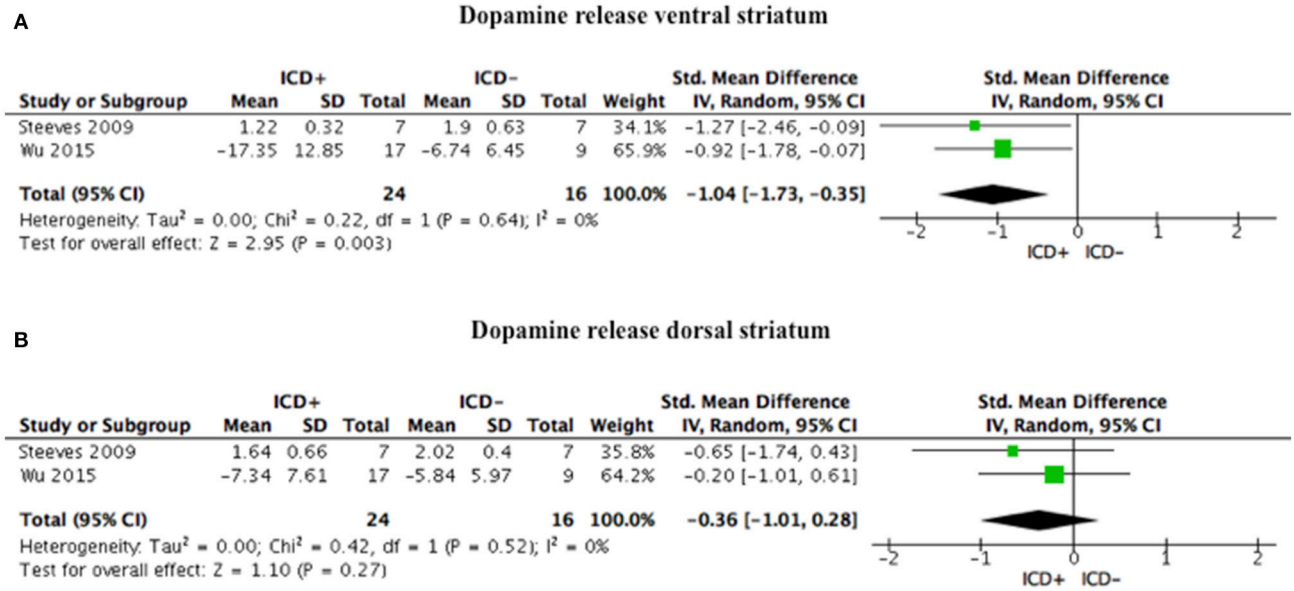

FIGURE 3 | Forest plots for dopamine release. Here are reported forest plots for dopamine release in the ventral striatum **(A)**, and in dorsal striatum **(B)**. Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate lower dopamine release in PD patients with ICD (ICD+) in comparison to those without ICD (ICD–). ICD, impulse control disorder; PD, Parkinson's disease.

bind to D_2 receptors irrespective of phasic changes in firing (76).

Post-synaptic Dopamine Receptors Availability

We did not find changes in $D_{2/3}$ receptors availability between ICD+ and ICD– PD patients. This finding is, to some extent, surprising for a number of considerations. Animal PD models showed increased D_3 expression after repeated administration of DRT (35). A PET study found relationships between higher D_3 levels, dopamine release in the ventral striatum, and ICD severity in people without PD (77). Preclinical rats models of PD shows that ICD–like behaviors can be triggered by pramipexole (78, 79) and ropinirole (80, 81), which mainly target $D_{2/3}$ receptors. Polymorphisms of $D_{2/3}$ receptors genes are associated with addictive behaviors in PD (82), and in the general population (83). D_3 receptor antagonists may block reward seeking in animal models (84–86).

Different lines of reasoning may explain this apparently paradoxical finding. Heterogeneity was high for this outcome in our meta-analysis, and this may reflect differences in the radiotracers used by the studies we included. However, random effect model does not assume homogeneity of the effect and findings should have been robust to heterogeneity. $D_{2/3}$ receptors localize both to pre-synaptic mesolimbic terminal auto-receptors and post-synaptic indirect-pathway medium spiny neurons (36). Therefore, binding of radiotracers may reflect a mix of pre- and post-synaptic changes (35). Moreover, $D_{2/3}$ receptors changes have not been universally observed across the spectrum of maladaptive reward-seeking behavior, where reductions are notably absent in primary gambling addiction (36, 87). In individuals with substance dependence there is lower $D_{2/3}$ receptors availability than healthy controls (88), but no differences have been reported in pathological gamblers (66, 67).

Limitations and Future Directions

The main limitation of the present meta-analysis is the small number of studies included, and consequently the low statistical power, which impede any definite conclusions on the mechanisms underlying ICD in PD. The small number of studies hampered a moderator analysis, which would have added information on the variables potentially contributing to our results. Our data suggest that more studies with large numbers of patients are needed. They should have a longitudinal design with drug naïve patients, to clarify the causative relations between striatal dopaminergic changes and ICD, and whether they are pre-morbid vulnerability traits, or a consequence of DRT. Current cross-sectional studies may only document associative links. Future studies should incorporate a healthy control group (34, 35, 48), as some dopaminergic changes might be age-related and not directly linked to PD or ICD (89).

PET/SPECT studies on extrastriatal regions, which interact with the striatum in the control of motivated and addictive behavior (37, 48), are still scarce, and focus on a range of different structures, impeding a meta-analysis. The role of extrastriatal dopaminergic changes should be assessed. At the time of our literature search, five studies reported data on extrastriatal regions, including the orbitofrontal (37), medial orbitofrontal (35), ventromedial prefrontal (48), and left

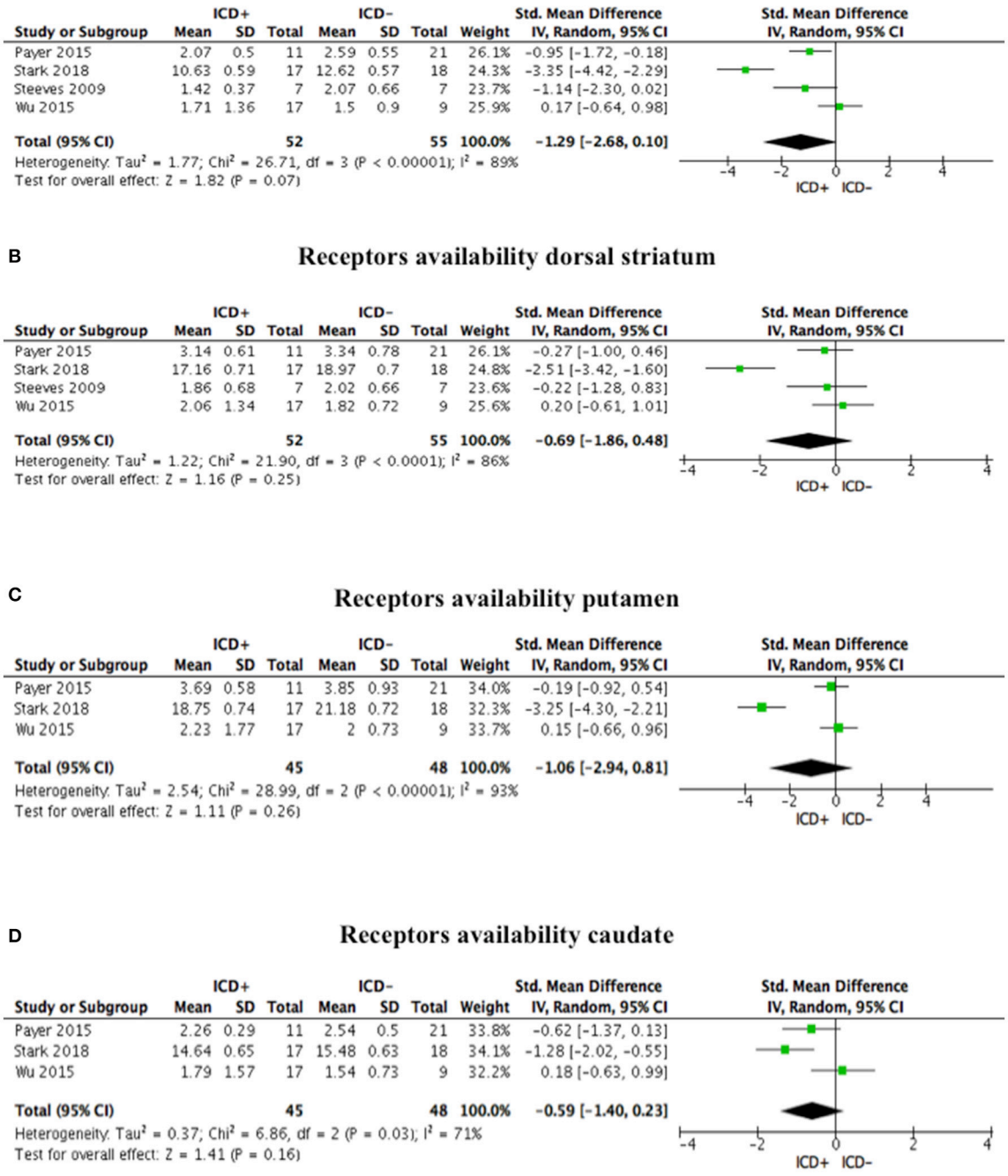

FIGURE 4 | Forest plots for post-synaptic receptors availability. Here are reported forest plots for post-synaptic receptors availability in the ventral striatum **(A)**, dorsal striatum **(B)**, putamen **(C)**, and caudate **(D)**. Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate lower receptors availability in PD patients with ICD (ICD+) in comparison to those without ICD (ICD–). ICD, impulse control disorder; PD, Parkinson's disease.

anterior cingulate cortex (90), the amygdala (48), substantia nigra (35), globus pallidus (35, 36), ventral pallidus (35), thalamus (36), and the midbrain (36, 90). Exploring these areas would be important, since, e.g., abnormal functioning of $D_{2/3}$ midbrain receptors might results in increased dopamine release (91).

Since the dopamine system may not be the only player in ICD development, multi-modal imaging studies should explore the contribution of serotoninergic systems to ICD in PD (30, 61, 92).

Finally, ICD in PD was found to be associated with cognitive (worse set-shifting and reward-related decision-making), and neuropsychiatric features (increased depression, anxiety, anhedonia, and impulsivity) (93). The potential confounding role of these clinical variables should be considered in future PET/SPECT studies.

CONCLUSIONS

Our meta-analysis showed specific patterns of dopaminergic dysfunction in the dorsal and ventral striatum in PD patients with ICD. These changes, which, to some extent, differ from those in people with ICD but no PD, may reflect either a preexisting neural trait vulnerability for impulsivity or the expression of a maladaptive synaptic plasticity under non-physiological dopaminergic stimulation (30).

AUTHOR CONTRIBUTIONS

The study has been designed by AM, NE, and ST. Data have been gathered by AM and DDL, under the supervision of MS and ST. Data have been analyzed by AM. The manuscript has been drafted by AM, NE, and ST. AM, DDL, FL, MS, NE, and ST revised the manuscript.

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Impulse Control Disorders and Dopamine-Related Creativity: Pathogenesis and Mechanism, Short Review, and Hypothesis

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Impulse control disorder (ICD), including pathological gambling, hypersexuality, and compulsive shopping has been linked to antiparkinsonian medication, especially dopamine agonists. The mechanism of ICD is not completely clear, but it seems that ICD is the result of an activation of dopamine receptors, mostly D3 in the ventral striatum. Patients treated with dopamine agonists that have preferential affinity for D3 (including ropinirole and pramipexole) are much more prone to develop ICD. In addition, a genetic component is probably present, especially in young patients. Finally, environment and lifestyle may also play a role: those patients engaged in physical, social, and artistic activities are probably less likely to develop ICD compared to those patients with poor physical activity living in isolated environments.

Keywords: impulse control disorder, dopamine agonists, genetics, environment, enhanced creativity

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INTRODUCTION

Impulse control disorder (ICD) is currently one of the most frequent and devastating side effects of antiparkinsonian medication. J.A. Molina was the first author to describe gambling as a peculiar and typical manifestation of ICD (1). He found several gamblers among his patients by chance (1); over time, it became clear that ICD was very frequent in Parkinson disease (PD), that this disorder was very complex (2–5); and included several abnormal behaviors such as gambling, hypersexuality, compulsive shopping, kleptomania, and eating disorders (4, 5). It was also clear that ICD was associated with antiparkinsonian drugs, mainly dopamine agonists (6, 7). The relationship of dopamine agonists and ICD has been confirmed in several studies (6–10), most especially in young individuals (11). This review discusses several aspects concerning the pathogenesis and mechanisms of this common and devastating condition.

IMPULSE CONTROL DISORDER AS A DOPAMINERGIC SIDE EFFECT

The mechanisms of ICD are not completely clear, but several clues have emerged over time. PD itself does not seem to confer an increased risk for development of ICD (12), thus making ICD mainly a drug-related side effect.

Dopaminergic medication—primarily dopamine agonists (4–11), occasionally MAO-inhibitors (7, 13), and, only rarely, levodopa (14)—has been associated with ICD. Dopamine agonists are clearly related to ICD, not only in PD, but also in restless legs syndrome (10, 15), and occasionally hyperprolactinemia (10, 16).

Although its mechanism is still partially unknown, Castrioto et al. (17) suggested an interesting framework to explain ICD in opposition to apathy in PD. Apathy and ICD (like akinesia and dyskinesia) lie at the opposite ends of a spectrum of dopaminergic tone. Pulsatile dopaminergic medication induces sensitization of the limbic ventral striatum and the motor dorsal striatum. This sensitization may lead to a shift from apathy to ICD (and, from a motor point of view, from bradykinesia to dyskinesia). In this regard, Jimenez-Urbieta et al. suggested that levodopa-related dyskinesias and ICD could be defined as a maladaptation to dopaminergic therapy (18). These elegant and plausible hypotheses certainly explain ICD in the context of PD, but they do not explain the occurrence of ICD in other non-parkinsonian conditions such as restless legs syndrome, in which no dopaminergic neurodegeneration is present. In any case, the contribution of the dopaminergic system to the pathophysiology of ICD is solid (17, 18). In addition, Palermo et al. (19) suggested an interesting neurocognitive approach to ICD; these authors suggest that a fronto-striatal and cingulo-frontal dysfunction may reflect impairment in metacognitive-executive abilities (such as response-inhibition, action monitoring, and error awareness) and promote compulsive repetition of behavior. In this regard ICD could be partly defined as a response-inhibition disability (19).

Dopamine agonists are by far the most frequent drugs associated with ICD (4–11), but there is still an ongoing debate; for some authors, ICD could be defined as a dopamine agonist class effect, with all dopamine agonists sharing this side effect (7). Recently, however, several studies have suggested that some dopamine agonists (including ropinirole and pramipexole) are much more strongly associated with ICD than rotigotine (9, 10) or apomorphine (10). Although the figures vary, in general terms the relative risk of ICD is as follows: pramipexole > ropinirole > rotigotine > apomorphine (9, 10, 20). The reason for this difference is unknown, but according to Seeman (20) those dopamine agonists with preferential affinity for the D3 receptor are much more likely to be associated with ICD compared to other less selective agonists, and in general terms, the relative risk of ICD is proportional to D3 affinity (20). And even so, rotigotine and apomorphine are also associated with ICD (9, 10); in fact, the most severe case of ICD we have ever seen was related to apomorphine, and it seems that there is no dopamine agonist that is entirely free from ICD. Treatment of ICD is a challenge. Reduction and/or suppression of dopamine agonists is usually recommended (18), but ICD is not easily reversible. The substitution of a high affinity dopamine D3 agonist for another less selective dopamine agonists is not always successful. Levy and Lang suggested that previous remote exposure to a dopamine agonist may prime patients to develop ICD with further dopaminergic medication (13). In this regard, dopamine agonists may predispose the striatum to develop ICD and medication-related dyskinesias as well (13, 17, 18). Besides the reduction/withdrawal of dopamine agonists, a plethora of therapeutic measures has been suggested, including atypical neuroleptics such as clozapine and quetiapine (21, 22), anticonvulsants (23), amantadine (24), selective serotonin reuptake inhibitors, and opioid antagonists (25) to mention just a few. There is no solid evidence for the effectiveness of these drugs (25). Recently it has been suggested that intraduodenal infusion of levodopa–carbidopa might help (26), though this measure is probably valid in the presence of an important reduction of dopamine agonist, and in any case, there are also anecdotal reports of ICD after the introduction of levodopa–carbidopa infusion (14). Some other authors suggest that deep brain stimulation (DBS) might be useful for patients with ICD (27); similarly, however, this measure is probably effective only if an important reduction of dopamine agonist is carried out (25, 28). It is important to keep in mind that there are reports of cases of ICD occurring after DBS (25, 28). We have had experience with some parkinsonian patients with ICD submitted for DBS; surgical intervention did not improve their ICD despite a profound reduction of dopamine medication and excellent motor control.

GENETIC ASPECTS OF IMPULSE CONTROL DISORDERS

Since not all individuals with PD taking dopamine agonists develop ICD, a genetic component is also likely. In addition,

TABLE 1 | Creativity related to dopaminergic drugs.

Subject	Age/Sex	Years	Motor Compl.	LD	Dopamine agonist	Artistic activity
1	69/M	10	F,GF,D	+ (+R)	ROP	Painting, scale models, woodwork
2	70/M	8	GF	+ (+R)	PRM	SCALE models (SHIPS)
3	74/M	10	F,GF	+	PRM	Gardening
4	75/M	8	F	+ (+R)	PRM	Painting
5	67/F	3	–	+ (+R)	PRM	Painting/dance/theater
6	53/F	5	D	+ (+E)	–	Painting
7	71/M	5	F, D	+ (+R)	ROT	Gardening
8	80/M	12	–	+	PRM	Carving, engraving
9	60/M	12	F	+ (+R)	PRM	Scale models (TRAIN)
10	80/F	8	F,GF	+ (+R)	PRM	Painting (>100)

Motor Comp., Complications; F, Fluctuations; GF, Gait freezing; D, Dyskinesias; LD, Levodopa; ROP, Ropinirole; PRA, Pramipexole; ROT, Rotigotine; R, Rasagiline; E, Entecapone.

there are similarities between the phenotypic presentation of ICD and that of other reward-based behavioral disorders, including binge-eating disorder, pathological gambling, and substance-use disorder (19, 29).

In the general population, genetic factors might contribute up to 60% of the variance in the risk for substance-use disorders and pathological gambling (30); hence, a genetic component of ICD has been pursued as a viable explanation.

First, although newly diagnosed but still untreated patients with PD do not have an increased risk of developing an ICD when compared to controls (12), certain subpopulations such as younger patients (11) and Parkin mutation carriers (31) do have increased risk.

To date, several polymorphisms of dopaminergic genes have been associated with ICD in PD patients (32–36). However, some findings have challenged this relation, probably due to differences in study design, method of ICD behavior assessment, cohort characteristics, and ethnic background (32–36). The most promising candidate at present is probably the DRD3 single nucleotide variation (SNV) rs6280 (35, 36), which has been associated with ICD in early onset PD in European and Asian patients (35, 36).

FIGURE 1 | This patient combines realistic portraits and modeling.

In any case, it is evident that multiple factors influence the presence of ICD. Several recent papers found that ICD was mainly associated with an early onset of the disease, dopamine agonist treatment, and the presence of the rs6280 DRD3 SNV (35, 36).

FIGURE 2 | Detailed depiction of a palace (Madrid).

FIGURE 3 | Ship modeling (Schooner), another classic from our patients.

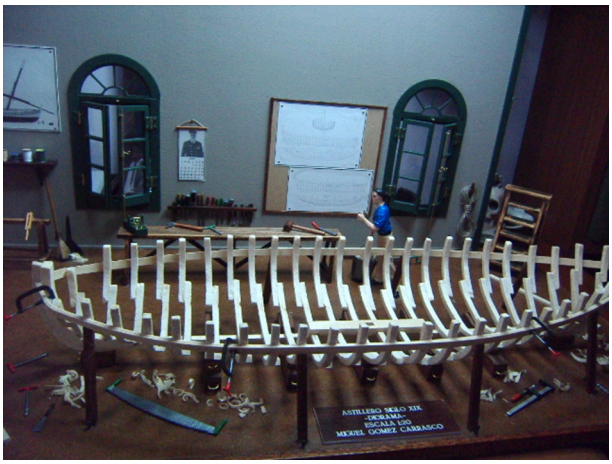

FIGURE 4 | Highly detailed boatyard model.

TABLE 2 | Impulse control disorders and dopaminergic creativity short review and hypothesis.

- Impulse control disorder (ICD) has been linked to antiparkinsonian medication especially dopamine agonists
- The mechanism of ICD is not completely clear, but activation of dopamine D3 receptor is likely; those patients treated with dopamine agonists with higher affinity to D3 (including ropinirole and pramipexole) are much more prone to develop ICD
- A genetic component is probably present, especially in young patients
- The management of ICD includes reduction/suppression of dopamine agonists
- Occasionally, dopamine agonists enhance creativity and the patients engage in artistic, non-disruptive behavior described as positive by patients and families
- Probably, the environment influences the apparition of enhanced creativity, our hypothesis is that fostering a rich and stimulating environment for patients with PD may contribute to the appearance of the enhanced creativity phenomenon instead of ICD.

IMPULSE CONTROL DISORDERS, ENHANCED CREATIVITY, AND ENVIRONMENT

Epidemiological studies revealed that ICD figures vary depending on the country as well as social and economic factors (7–9, 11, 37). Even the characteristics of ICD vary depending on the study (hypersexuality, gambling, compulsive eating, etc., depending on the country) (7–11, 37), hence several environmental factors clearly play a role in the development of the disorder (7, 9, 11, 37).

Another related and interesting aspect is that occasionally, dopamine agonists give rise to enhanced creativity in PD patients, many without previous artistic abilities (38–43); this non-disruptive behavior is described as positive by patients and families. Canesi et al. suggested that artistic-like production might represent the emerging of innate skills in a subset of predisposed patients with PD on dopaminergic therapy (39).

At our center, we have had the chance to follow 10 PD patients with this "newfound talent" and the impact on their lives has been positive, in contrast with the much more frequent ICD. All these patients began their artistic activity after dopaminergic medication (**Table 1**), most had motor complications including motor fluctuations (7/10), gait freezing (3/10), or dyskinesias (3/10). All but one patient were treated with dopamine agonists including pramipexole (7/9), ropinirole (1/9), or rotigotine (1/9).

Most patients with this new artistic activity preferred painting as their main medium, but many were engaged in several activities, usually in combination (**Figures 1–4** show some of the art produced by these patients). Some patients began their artistic endeavor after meeting with other subjects already engaged in artistic activities (personal observation). Our hypothesis is that fostering a rich and stimulating environment for patients with PD may contribute to the appearance of this dopamine agonist-related positive phenomenon instead of ICD.

CONCLUSION

In summary, ICD is a complex antiparkinsonian medication-related situation most commonly associated with dopamine agonists. Since not all parkinsonian patients suffer from ICD, a genetic component has been pursued. Young patients, including parkin carriers, have increased risk. In addition, environmental factors may also play a role. In any case, early detection of IDC is of paramount importance, as patients must be warned of the onset of this rather frequent side effect.

Recently, a positive, non-disruptive, dopamine agonist-related effect has been noted. Some parkinsonian patients develop enhanced creativity after being treated with dopamine agonists. Facilitating a positive environment (including artistic and cultural activities) for parkinsonian patients may contribute to enhanced creativity instead of ICD. **Table 2** summarizes the most relevant points of ICD.

AUTHOR CONTRIBUTIONS

PG-R: conception and design, interpretation of data, drafting the submitted material, and critical review.

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Art examples from some patients were presented at the 20th Congress on Parkinson's disease and Movement Disorders. Berlin. June 19–23, 2016. The local ethics committee approved this work and the patients consented to have their artwork appear as part of this study. We appreciate the editorial assistance of Dr. Oliver Shaw.

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REVIEW
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Medications, Deep Brain Stimulation, and Other Factors Influencing Impulse Control Disorders in Parkinson's Disease

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Impulse control disorders (ICDs) in Parkinson's disease (PD) have a high cumulative incidence and negatively impact quality of life. ICDs are influenced by a complex interaction of multiple factors. Although it is now well-recognized that dopaminergic treatments and especially dopamine agonists underpin many ICDs, medications alone are not the sole cause. Susceptibility to ICD is increased in the setting of PD. While causality can be challenging to ascertain, a wide range of modifiable and non-modifiable risk factors have been linked to ICDs. Common characteristics of PD patients with ICDs have been consistently identified across many studies; for example, males with an early age of PD onset and dopamine agonist use have a higher risk of ICD. However, not all cases of ICDs in PD can be directly attributable to dopamine, and studies have concluded that additional factors such as genetics, smoking, and/or depression may be more predictive. Beyond dopamine, other ICD associations have been described but remain difficult to explain, including deep brain stimulation surgery, especially in the setting of a reduction in dopaminergic medication use. In this review, we will summarize the demographic, genetic, behavioral, and clinical contributions potentially influencing ICD onset in PD. These associations may inspire future preventative or therapeutic strategies.

Keywords: impulse control disorder, Parkinson's disease, impulsivity, dopaminergic medications, deep brain stimulation

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder of dopamine-producing neurons in the substantia nigra and also includes widespread dysfunction throughout motor and non-motor brain circuits (1). PD motor symptoms such as tremor, bradykinesia, and rigidity are well-recognized (2), however PD is strongly associated with several non-motor symptoms as well. In contrast to the motor symptoms, non-motor symptoms are understudied and encompass cognitive, autonomic, and neuropsychiatric abnormalities (3). Among these problems, PD patients may experience changes in affective or goal-directed behaviors that can manifest as impulsivity. Impulse control disorders (ICDs) are commonly characterized by four major subtypes: pathological gambling, hypersexuality, compulsive shopping, and binge eating, but can also include punding, hobbyism, and dopamine dysregulation syndrome (DDS), which may be separated into ICD-related behaviors

(ICD-RB) in some classifications (**Figure 1**) (4, 5). These behaviors as a whole may also be referred to as impulsive-compulsive behaviors (ICBs), but in this paper we refer to all subtypes collectively as ICDs.

Those with ICDs have an inability to resist inappropriate internal drives, and these may result in repetitive behaviors with harmful consequences that can impact quality of life for both patients and caregivers (6). A recent, large multicenter study of ICDs found a 5-year cumulative incidence of 46.1% (7). It has been estimated that ICDs affect 13.6% of PD patients, although this number varies widely across samples (8). Nonetheless, the true prevalence may be higher, especially since PD patients tend to underreport embarrassing and in many cases pleasurable behaviors, (9) and may lack insight into their problematic behaviors (10). In one study, only one quarter of PD patients experiencing ICDs were clinically identified (11). Patients may also experience sub-clinical impulsivities (9, 12).

ICDs in PD have classically been attributed to long-term exposure to dopaminergic medications such as levodopa and dopamine agonists. These drugs alter the pathophysiology of reward-based neural networks (13). However, other pertinent risk factors have been identified and include gender, country of residence, age of PD onset, disease duration, alcohol/tobacco use, family history of impulsivity, genetic factors, non-dopaminergic medications, deep brain stimulation, personality traits, and more (**Figure 2**) (5, 8). Several recent studies have even observed these non-dopaminergic factors as significantly contributing most to the variance in impulse control disorder risk. Recognizing the multiple associations that have been reported in the literature is crucial in order to identify areas for further investigation of the etiology and management of ICDs.

In this review, we provide a summary of the known ICD risk factors and associations with a focus on five main areas: demographics; medical and surgical associations; premorbidities and comorbidities; family history and genetics; and personality traits. We also include a brief section on neural correlates and cognitive changes associated with ICDs as observed through behavioral studies, human imaging, and electrophysiology. We conclude by highlighting that dopamine alone cannot account for all ICDs, and we point out limitations of present studies which may help to motivate future investigations.

DEMOGRAPHICS

Gender

In general, proportionally more male than female PD patients screen positive for ICDs (5, 8, 14–20). One large PD study of 32 sites in Italy found that 223 (32.5%) of 686 males and 83 (21.7%) of 383 females screened ICD-positive (5). Such gender effects have been widely reported (21–23). For instance, the DOMINION study of 3090 PD patients found that males comprised 64% of both ICD+ and ICD- patients, although the prevalence of specific ICD subtypes differed by gender (8). It is difficult to determine if gender is decisively a risk factor for ICDs in PD, or if the higher prevalence in males with ICDs is largely observed due to the overall demographics of the PD population, which is predominantly male (24). Additionally, differences in the expression of ICD behaviors could contribute to under-reporting.

Gender differences can also arise when examining specific subtypes of ICDs. For instance, patients with compulsive sexual behavior are predominantly male (8, 25–28). On the other hand, patients with compulsive shopping and binge eating are predominantly female, indicating that biological and social factors may influence the expression of ICD behaviors (8, 25–27). These gender patterns for compulsive sexual behavior and binge eating also hold true in non-PD ICD populations (27). A limited number of studies suggest that pathological gambling occurs more in males with PD (29) and in the general population (27). Finally, although few studies have examined gender differences across PD patients with other ICBs, there seems to be a male predominance for punding and hobbyism (30–32) and a lack of gender difference for rates of DDS (33).

Age, Age at Diagnosis, and Disease Duration

Most studies are in agreement that younger PD patients have an increased risk of ICDs (5, 8, 14–16, 19, 21, 23, 26, 31, 34–39). Patients with ICDs are also usually younger at PD onset and at the time of diagnosis (5, 14, 16, 21, 26). Therefore, early-onset PD and those with longer disease duration tend to have a higher risk of ICDs (5, 20, 39, 40). It is possible that those who have been diagnosed at younger ages and have longer disease duration consequentially have more exposure to dopaminergic medications, potentially increasing their risk for developing an ICD. However, despite robust associations between ICDs and dopaminergic medication use, other studies have failed to identify a relationship between ICDs and age or disease duration (8, 16, 21, 22, 27), and so the effect of dopamine treatment cannot not fully explain this association. To investigate such factors simultaneously, multivariate analysis must be used to measure independent effects across multiple variables. For example, a dearth of studies have collectively shown persistent age-dependent effects even when controlling for DA use (8). Interestingly, in non-PD populations, ICDs represent a category of diseases with a younger age of onset relative to other DSM-V disorders (41), further highlighting the independent effect of age on ICDs.

Country of Residence

Cultural and other environmental differences may affect both the incidence and presentation of ICD behaviors (25, 42). When evaluating PD-associated ICDs across different regions in the world, ICD prevalence varies widely as seen in **Table 1** and depicted in **Figure 3**. For example, in one large multicenter study, ICDs were more common in the United States (US) vs. Canadian PD populations, with pathological gambling, and compulsive buying reported more commonly in US patients (8). Asian countries such as China, Taiwan, and South Korea tend to show a lower prevalence of PD ICDs (22, 42, 43). However, India was noted to have a particularly high prevalence of ICDs at 31.6% (45). Interestingly, most of the European

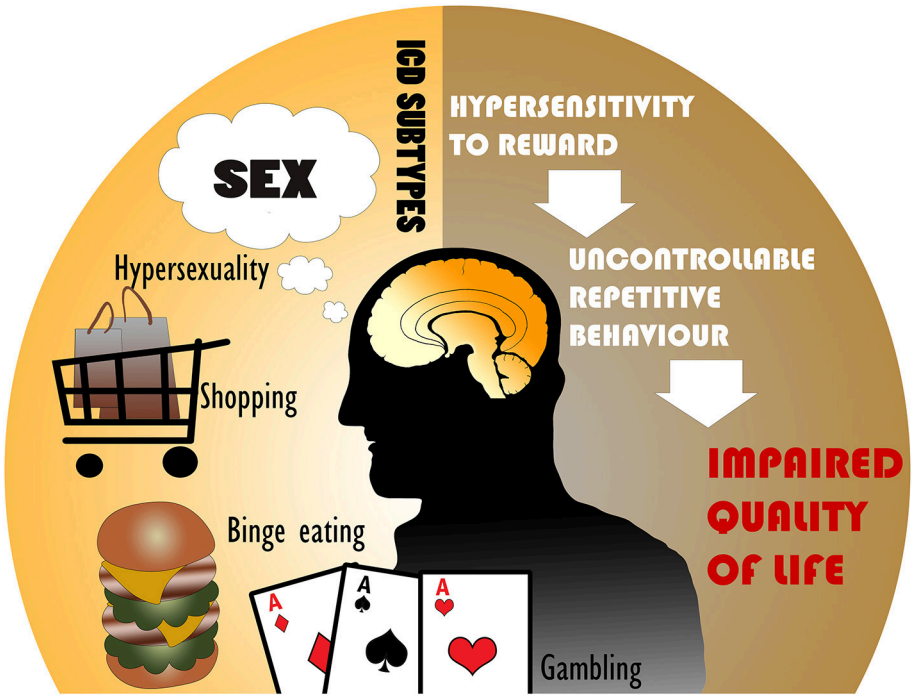

FIGURE 1 | The most common impulse control disorders (ICDs) in Parkinson's disease include hypersexuality, compulsive shopping, binge eating, and pathological gambling. ICDs are associated with hypersensitivity to reward and uncontrollable repetitive behaviors, leading to an impaired quality of life.

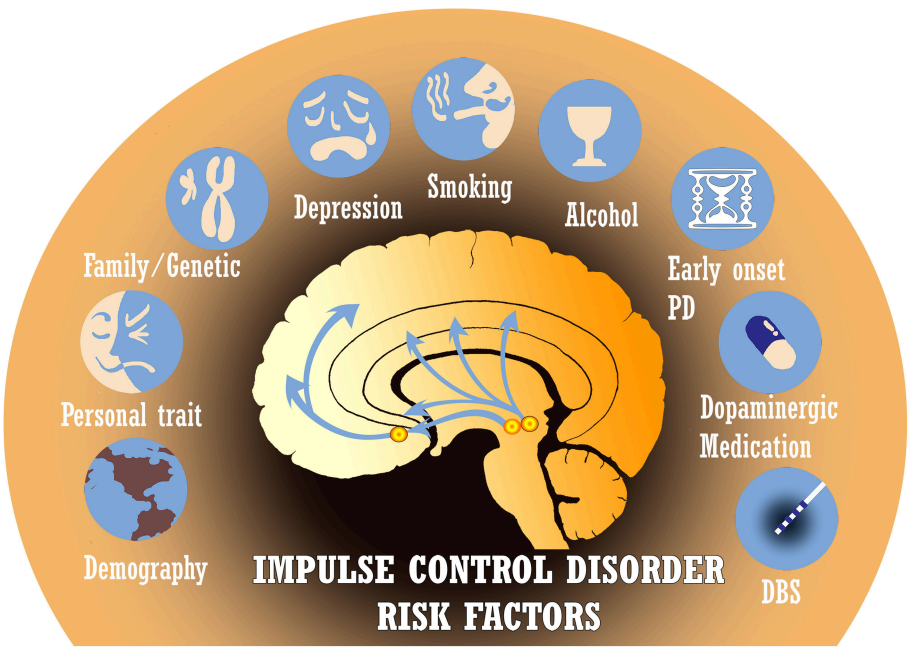

FIGURE 2 | There are many established risk factors for impulse control disorders (ICDs) in Parkinson's disease (PD), including demographics, personality traits, genetic predisposition, depression, tobacco/alcohol use, age of disease onset, dopaminergic medications, and deep brain stimulation (DBS). Several other risk factors under investigation are not depicted.

nations evaluated had a PD ICD prevalence greater than that of the US(5, 18, 35, 37, 49). A study of Finnish PD patients found a prevalence of pathological gambling seven times higher than in the general Finnish population (36). Central and South American nations have revealed a prevalence near equivalent or moderately higher than that of the US (15, 46). Interestingly,

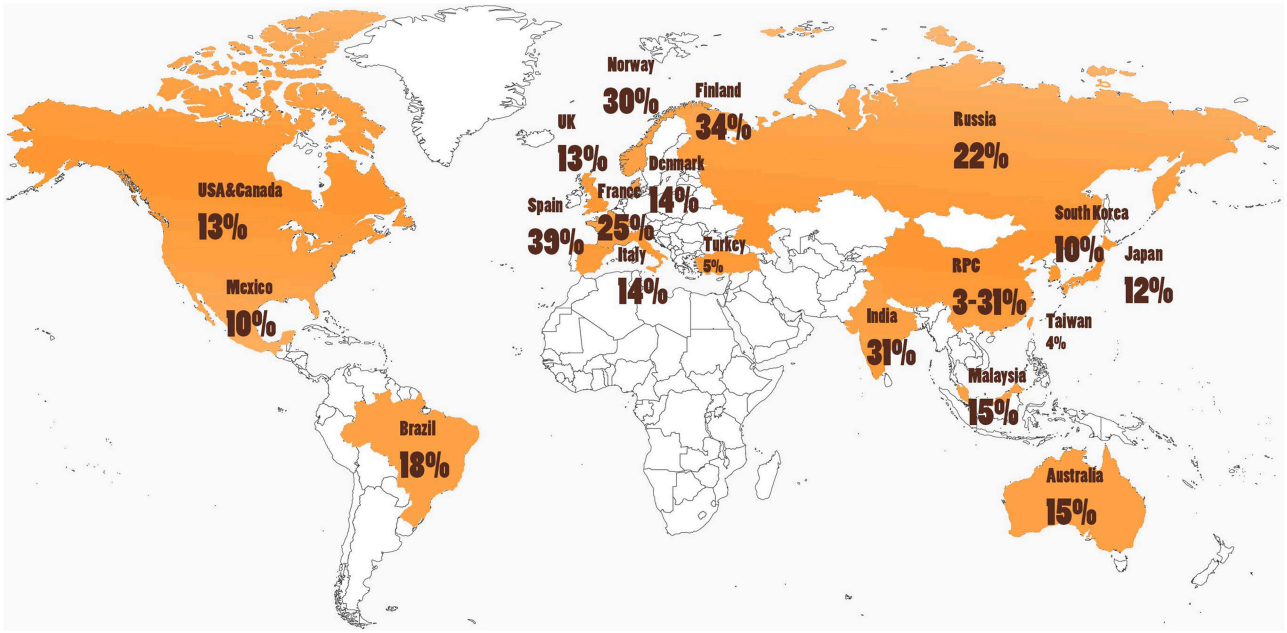

FIGURE 3 | Cultural and environmental factors may influence ICD risk, as rates of impulse control disorders (ICDs) in people with Parkinson's disease (PD) around the world are highly variable (see **Table 1** and text). Further studies are needed that investigate ICD rates in South America, Africa, and areas in Europe and Asia.

punding is the most common of the ICDs reported in Turkey (44).

Comparison across studies assessing the prevalence of ICDs has been severely limited by differences in study design, clinical criteria, and ICD screening tools. Self-report questionnaires may lead to a sampling bias (22). Despite such limitations, potential cultural, and geographic differences bring into question the role of environmental factors on ICDs. Several studies have noted such differences and attribute them to cultural factors generally without offering more specific ideas or explanations (52). One study of a sample of early-onset PD patients from Spain suggested that the use of technologies in younger populations contributed to higher rates of hobbyism, as this was also the highest impulse control behavior identified in a non-PD age-matched control cohort (25). In the US, casinos and shopping malls are more accessible than in Canada, which might explain the higher prevalence of gambling and compulsive buying. Yet, it is hard to draw conclusions on the directionality of this relationship, since the availability of casinos and shopping malls may be related to intrinsic cultural differences between the populations.

It is important to consider that most studies characterize ICD prevalence rates in PD patients without comparison to rates in a non-PD sample. It is also important to note that PD and ICD management strategies may differ throughout the world. For instance, the dopaminergic medication pramipexole has only been available in China since 2007 (22). Nonetheless, differences can be seen across many countries and ICD subtypes, but explanations that capture these differences are mostly speculative, and non-empirical. Using standardized methodologies, future work could be directed to study a region with a relatively low rate of ICDs and one with a relatively high rate of ICDs as a method to uncover potential preventative strategies.

MEDICATION AND SURGICAL ASSOCIATIONS

Dopaminergic Medications

The association between dopaminergic medications and ICDs is the most documented of all associations. Many well-designed studies have collectively observed that higher dopamine use through either dopamine agonists or levodopa increases the risk of developing ICDs (5, 8, 14, 15, 21, 22, 25, 26, 34). In the DOMINION study, dopamine treatment was the risk factor with the highest odds ratio for ICD risk in a multivariable analysis with a value of 2.72 (8). When extending the analysis to ICD subtypes the odds ranged from 2.15 (pathological gambling) to 3.34 (binge eating). Dopamine treatment was associated with a seven-fold increased risk of ICBs in one study of early-onset PD patients (25). Other dopaminergic medications, such as monoamine oxidase-B inhibitors (MAOB-Is), have not demonstrated such clear results. While some studies have found evidence of an association between MAOB-Is and ICDs (37), others have reported no relationship (15, 25). A few case studies have shown MAOB-I-induced hypersexuality and pathological gambling (53, 54). The role of MAOBIs in ICDs is attributed to its effect on behavioral plasticity and personality traits such as impulsivity and aggression (55).

The physiological connection between dopaminergic medications and ICDs has been published extensively (56, 57). Briefly, dopamine differentially modulates impulsivity and

TABLE 1 | Prevalence rates of ICDs across the world.

Country	Percentage of PD patients exhibiting ICD
China	3.53% of 400 (22), 7.0% of 213 (19), 31% of 142 (38)
Taiwan	4.5% of 268 (42)
South Korea	10.1% of 1167 (43)
Japan	12.9% of 118 (23)
Malaysia	15.4% of 195 (20)
Turkey	5.9% of 554 (44)
India	31.6% of 305 (45)
United States & Canada*	13.6% of 3090 (8)
United States	6.6% of 272 (11), 12.8% of 250 (39)
Australia	15% of 100 (6)
Brazil	18.4% of 152 (15)
Mexico	10.6% of 300 (46)
UK	17.8 of 500 (47), 13.7% of 297 (48)
Russia	22.4% of 246 (49)
Finland	34.8% of 575 (36)
Norway	30.4% of 125 (50)
Denmark	14.9% of 490 (31)
Spain	39% of 233 (37)
Italy	28% of 1069 (5), 7.6% of 1063 (28), 8.1% of 805 (14),
France	25% of 203 (51)

**Higher in the US. PD: Parkinson's disease; ICD: Impulse control disorder.*

behavioral addictions, likely through its involvement in neural pathways of reward and punishment (13). Many of the commonly prescribed dopamine agonists such as pramipexole and ropinirole have a higher affinity for D3 than D1/D2 receptors, leading to significant binding outside of the targeted nigrostriatal projections (57). The association between ICDs and dopaminergic drugs suggests an overactivation of the mesolimbic dopaminergic system that underlies pathological responses to natural rewards. Dopamine replacement therapies restore normal dopamine levels in motor pathways but may adversely stimulate the relatively preserved mesocorticolimbic system, particularly in genetically-predisposed or otherwise-vulnerable patients. This may result in patients experiencing hypersensitivity to rewards. Additionally, there has been compelling evidence suggesting that other brain structures and neurotransmitters may be critical to the development of these disorders in PD (58–60).

Despite the vast body of evidence supporting the neurobiological plausibility of dopaminergic overdosing of non-motor pathways and subsequent behavioral abnormalities, a direct causality has been challenged by numerous studies that hint at more complex dopamine-ICD relationships. First, several studies have not found the simple association between impulsivity or ICDs and dopamine agonist or levodopa use (6, 18, 23, 38, 61). Secondly, there may be differential effects across the various dopaminergic medications and their routes of delivery. For instance, some studies find a graded relationship between ICDs and levodopa dose but not between ICDs and dopamine agonist dose (8, 23, 62). Others find the opposite, concluding a graded relationship between dopamine agonists and ICDs but not between levodopa and ICDs (25, 35). Still other studies show that dopamine-ICD associations are statistically present only when considering a combination of dopamine agonists and levodopa using a total levodopa equivalent daily dose (LEDD), but not with a dopamine agonist LEDD alone (27, 31). Numerous reports have shown differences in oral vs. transdermal or short-acting vs. long-acting routes of dopaminergic medication delivery (37, 63–65), suggesting some importance for pharmacokinetics of non-continuous vs. continuous dopamine receptor stimulation (45). Third, individuals with restless leg syndrome (RLS) treated with dopaminergic agonists show lower rates of ICDs than PD patients (35), implying that in PD patients certain susceptibility factors are likely at play. For instance, a history of ICDs prior to PD diagnosis is a contributing risk factor for the development of ICDs after dopamine agonist use for PD treatment (11). Fourth, withdrawal or reduction of dopaminergic agents after ICD onset does not always predictably reverse an ICD (66, 67), suggesting some persistent dopaminergic effect [e.g., PD patients with pathological gambling still show elevated presynaptic ventral striatal dopamine release off-medication (68)] or that ICD pathophysiology critically implicates factors beyond dopamine. In one large study, more than half of ICDs persisted even 1 year after discontinuation of dopamine agonists (7). This situation can be compared to the fact that in multiple regression models, dopaminergic medications do not explain the bulk of variability in impulsiveness. For example, a Danish model including sex, age, age at PD onset, motor symptomology, total dopaminergic medication use, dopamine agonist use, smoking, depression, and personality traits only explained at most 31.2% of ICD variance (31). Fifth, many studies have demonstrated equivalent risk for dopaminergic medication use and the various ICD subtypes (40, 63, 69, 70), solidifying the necessity of susceptibility or other factors that, for instance, predispose to pathological gambling vs. hypersexuality. Sixth, there is a lack of evidence that dopaminergic blockade improves impulsive behaviors (64). In fact, in one account aripiprazole worsened pathological gambling in a PD patient (71). Finally, not all patients using dopaminergic medications report ICDs (72), and conversely, ICDs have been reported in PD patients prior to starting dopaminergic treatments (7, 52, 73). These are all important observations that motivate exploration of ICD associations beyond dopaminergic medications.

Although considering the impact of dopaminergic treatment on impulsive behaviors in PD is supported by many large studies, other studies have concluded that there are greater roles for non-dopaminergic factors. For example, a study of PD patients found that smoking was a stronger predictor for the presence of ICD than was dopamine agonist use, with smoking leading to a three-fold increase in the risk for ICD (31). In another study of 575 patients, depression played a larger role than sex, age, age of disease onset, alcohol use, or medication in explaining the variance in ICDs (36). These types of analyses are only permitted through multiple variable models, which are commonly missing

in numerous papers of ICD associations as a result of low sample size (23, 42, 66, 74). Results from multiple variable models may significantly differ from those in univariate models (15, 17). For instance, younger patients tend to use dopamine agonists more and so these variables may not be independent contributors to ICD risk.

Moving forward, ascertaining the role of dopaminergic agents in ICD-onset requires more robust investigation. To develop a model of causality classically requires satisfying several criteria, especially association, time order, and biological gradient (75). While the association between dopamine and ICDs has been realized extensively, rigorous statistical approaches controlling for other associated interrelated factors should be used. Although difficult to tease apart, the temporal sequence of dopamine use and ICDs must also be clearly established using longitudinal, prospective studies. Currently, whether or not a biological gradient truly exists—that is, whether dopaminergic doses independently contribute to ICD onset—remains an open question for future investigation. Controlled studies are therefore needed, particularly because the link between dopamine agonists and ICDs has been more firmly established. Hence, PD individuals at higher risk of ICDs included in recent studies may not have been prescribed dopamine agonists, leading to an important selection bias (5, 36). Similarly, controlled studies are needed because heterogeneity in ICD subtypes is not negligible. For example, dopamine agonists may be more associated with specific subtypes in select PD populations (43). Future work could address these current shortcomings and considerations.

Nondopaminergic Medications

Non-motor symptoms in PD involve more than just dopamine (76), but the influence of non-dopaminergic medications specifically on ICDs is unclear. A large percentage of studies that evaluate ICDs are retrospective cohort studies and since some non-dopaminergic medications are used as treatments for ICDs (e.g., antidepressants and antipsychotics) it is difficult to determine the directionality of reported associations. Long-term treatment with some of these medications, such as antidepressants, has been associated with overactivity of dopaminergic neuropathways (77). One study found that after accounting for possible confounding variables including motor score, age, gender, and disease duration, antidepressants were significantly associated with total impulsivity score, and sleep inducers were significantly associated with a binge eating impulsivity subscore (78). Few case reports have reported non-dopaminergic medications inducing ICDs in PD (79). Other studies have found no association between ICDs and commonly used non-dopaminergic medications such as benzodiazapines and antidepressants (14, 21, 22). The results are variable and a specific drug effect is difficult to determine as patients may be using different combinations of these drugs. Similarly, studies have suggested that GABAergic neurotransmission is associated with impulsivity, which is the target of common medications such as benzodiazepines (80). Given the scarcity of studies, it is hard to conclude if non-dopaminergic medications have any major association with ICDs; however, it is important to recognize the overlap of medication targets with brain pathways important to impulsivity.

Deep Brain Stimulation (DBS)

The relationship between DBS and ICDs is complex with conflicting reports. The mechanisms behind the motor and non-motor effects of subthalamic nucleus (STN) DBS are under investigation and remain of great interest, especially since they can reveal further insight into functional networks including those involved in impulsivity, reward, and inhibition (81). With regards to ICDs after DBS, studies have found contrasting results ranging from observable benefit, worsening, or no change (82, 83). STN DBS may improve ICDs indirectly because of marked reductions in dopaminergic medication from the positive effect of DBS on reducing motor symptoms (84–89). For instance, one large, longitudinal prospective study of 110 PD patients showed a decrease in DDS behaviors 1 year after STN-DBS (90). Another large, longitudinal study found a significant decrease in rates of hypersexuality, pathological gambling, and DDS after STN-DBS, with ICDs remitting in 69% of patients but persisting in 31% (91).

Nonetheless, binge eating, impulsive aggressive behavior, pathological gambling, hypersexuality, and dopaminergic medication addictions after STN stimulation have been previously reported (92–98), and 67% of Parkinson Study Group (PSG) centers reported the occurrence of *de novo* ICDs after DBS surgery, despite only 13% utilizing consistent and formal ICD assessment tools (99). Animal work and preclinical models tend to corroborate and support the possibility of increased impulsivity after STN lesions (100). One study demonstrated postoperative persistence or worsening in 71% of patients with preoperative ICDs (101), and a systematic review found that across a total of 19 studies, the mean prevalence of new ICDs after DBS was around 15% (102). *De novo* ICDs after surgery may be associated with specific independent risk factors such as younger age, lower dyskinesia improvement, and schizoid personality traits (91). Long-term follow-up is mostly lacking, but one small study found groups of patients with new ICD-onset shortly after STN-DBS as well as several years after surgery (103). In other cases, worsening of impulsivity symptoms occurred after surgery but with eventual resolution, such as in one study of pathological gambling and STN DBS (85). The globus pallidus internus (GPi) is becoming another popular anatomical target for PD DBS, and although there are fewer DBS studies of the GPi in general, it should be noted that there are also reports of new-onset ICDs after GPi DBS (82, 104, 105).

It remains unclear why STN stimulation can affect ICDs, but it may be related to decision-making impairment and adverse influences on the reward processing function of the STN, particularly in situations of high conflict [for review, see Eisinger et al. (81)]. In this manner, the STN regulates behavior by providing a stopping mechanism within the cortico-striato-thalamo-cortical circuit (106). Beyond basic motor control, the STN is notably involved in numerous non-motor functions and lesions impact decision-making and inhibition (107–110). Both motor impulsivity and impulsive decision-making can contribute

to ICDs (106, 107, 111). Ultimately, ICDs are complex and relate to elements beyond impulsivity including novelty seeking, depression, anxiety, and the many other factors discussed in this paper; thus, isolating the effect of stimulation can be difficult. For example, one study reported that a patient repeatedly experienced "morphine-like" effects while switching between off and on STN DBS (112), and cases of suicide have also been reported after DBS (96), some of which are thought to be directly related to impulsivity (113, 114). Another interesting study reported a case of trichotillomania that was right-dominant preoperatively but left-dominant postoperatively (115). Postoperative behavioral changes can be widespread and complex, and therefore the underlying pathophysiology of ICDs in the setting of DBS is wide open to continued investigation.

Interestingly, several reports have described a higher frequency of impulsive behaviors in DBS patients despite a reduction of dopaminergic medications (116, 117). In the setting of increasing dopaminergic medications and DBS together, it may be difficult to determine which factor, if any, more so accounts for new-onset ICD (93). In one large study, a prior history of DBS did not seem to confer an additional risk for ICD overall (8). Yet this may differ with specific ICD subtypes, as one paper, for instance, found that DBS—but not dopamine use—predicted postoperative binge eating (92). Nonetheless, other authors have concluded that dopamine agonist use and DBS carry a similar risk for ICD (116, 117). If dopaminergic-induced ICDs are related to dysfunction of reward pathways, it is possible that stimulation-induced ICDs have a similar underlying mechanism (102). In addition, research shows that STN DBS impairs impulse suppression when patients are either on or off dopaminergic medications (118, 119). Not all STN surgeries are comparable, as lead position and active contact configurations may vary considerably across subjects (120–122). This may in part account for the unpredictable effect of DBS on ICDs, and further studies are warranted.

PREMORBIDITIES AND COMORBIDITIES

Alcohol and Smoking

Similar to other risk factors, studies of the effect of alcohol on ICDs have presented mixed results. While some studies have found that PD patients with ICDs are more likely to regularly consume alcohol (22), the DOMINION study and others found no such difference (5, 8, 27, 38). Another study found no difference in alcohol consumption between early-onset PD patients with or without ICDs (25). The effect of alcohol has also been examined for specific subtypes of ICDs. In non-PD populations, a large study by the National Epidemiologic Survey on Alcohol and Related Conditions stated that around 73% percent of pathological gamblers have an alcohol use disorder (123). This relationship holds true for PD populations as well, with PD pathological gambling patients being 6.9 times more likely to have a personal or immediate family history of alcohol use disorders (124). The trend for smoking as a risk factor for ICDs seems to be more consistent, showing that PD patients with ICDs are more likely to be current, regular, or past smokers (5, 8, 15, 27, 31, 36, 38). Few studies have found no effect of cigarette use (22). Although the reason for this association is not clear, it has been hypothesized that it could be related to a decrease in both D2 receptors and dopaminergic cell activity similar to what is observed in patients with addictions (15).

Family History and Genetics

It has been shown that patients with a family history of impulsivity are at greater risk of developing addictions (41). It is difficult to determine if this is due to genetic factors that affect impulsivity-related neural pathways, or because of the home environment. Family history has been commonly regarded as a risk factor for ICDs in PD populations, yet only a few studies have been conducted on this issue. The largest study to date was Weintraub et al. which observed that PD patients with a family history of gambling and alcohol use have higher rates of ICDs (8). The odds ratio for having a family history of gambling was considerably high (2.08), scoring above levodopa treatment (1.51) and smoking (1.70) (8). Another study that investigated a sub-population of PD patients with restless leg syndrome also found that a family history of gambling was associated with developing an ICD (125). Although the association between ICDs and family history has been examined, additional studies are needed to draw parallels to PD populations. Understanding a patient's family history might offer a more clear picture of susceptibility and thus likelihood to develop an ICD.

Genetics has also been proposed as a risk factor for ICDs. Several non-PD twin and adoption studies predicted the hereditability of pathological gambling and substance abuse to be around 60% (126, 127). A large longitudinal cohort of *de novo* PD patients obtained a similar value of 57% (128). In recent years, polymorphisms in dopamine receptors (DR) have been studied as possible explanations for ICDs. DRD1 and DRD2 are both associated with the motor effects of dopamine, DRD3 with behavioral effects and addictions, and DRD4 and DRD5 with attention deficit disorders (129). A common DR polymorphism studied is the DRD2 Taq1a, which substitutes glutamic acid for lysine in a serine/threonine kinase, possibly decreasing substrate binding in the DRD2 receptor (130), however some studies have not found this association (129–132). Other polymorphisms associated with ICDs include: DRD1 rs4867798, DRD1 rs4532, GRIN2B rs7301328, DRD3 p.S9G, and HTR2Ac.102T > C (129, 132, 133). Recently, a study by Kraemmer et al. suggested expanding the investigation of PD polymorphisms in DR genes to also include other genes such as DDC, which has also been linked to impulsivity (128). Parkin-associated PD patients also appear to be at a higher risk specifically for compulsive shopping, binge eating, and punding/hobbyism (134). Overall more gene-environment studies are needed to reach more firm conclusions and ideally develop models to identify at-risk patients.

Personality Traits

Not surprisingly, impulsivity is the most commonly-studied personality trait in PD patients with ICDs. In this manner, impulsivity is defined as "actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes" (135) and can be assessed using questionnaires or behavioral paradigms.

Many studies have found a positive association with impulsivity and ICDs (27, 136). Levels of impulsivity are related to severity of impulse control disorders (137). Similarly, novelty seeking has also been discussed in previous reports given its interrelatedness to impulsivity (16, 27) and its emergence after dopamine therapies (138). As expected, PD patients with ICDs are more likely to choose novel options and are more attracted to novel stimuli compared to PD patients without ICDs (16). Poor social behavior and obsessive-compulsive features have also been linked to ICDs (27), although the results have been mixed (42).

The greatest differences in personality traits and ICDs arise when studying specific subtypes of ICDs. A literature review in non-PD patients that evaluated seven empirically-validated studies on pathological gambling found that coping styles, impulsivity, sensation seeking, and engaging in maladaptive delinquent/illegal activities are all risk factors for pathological gambling (139). Similar results have been observed in PD populations, in which pathological gambling has been linked to bizarre ideation, cynicism, and a tendency to lie (124, 140). A small case series identified a preliminary association between hypersexuality and delusional jealousy (28). Patients with ICDs also tend to show higher neuroticism, lower agreeableness, less conscientiousness, more paranoid ideation, and more negative emotionality, as well as more borderline, schizoid, and/or schizotypal traits (21, 31, 91, 141). Some studies have drawn parallels between the personalities of PD patients with ICDs and individuals with substance abuse (141). Future work should explore independent contributions of genetics and personality traits for the development of ICDs.

Comorbidities and Other Clinical Associations

PD patients with ICDs have reduced quality of life and are more likely to exhibit prior or ongoing anxiety and depression (5, 6, 17, 19, 27, 34, 36, 47). The same is true for ICD patients with early onset PD (25). The directionality of the association is unclear, since it is often difficult to predict whether these comorbidities are a risk factor for the development of ICDs or results from ICD behavior (18, 25). Although a general link between PD and depression has been established, the interpretation of these results is complicated by the fact that rates of depression are similar between drug-naïve PD patients and non-PD individuals (18, 52, 142). Nonetheless, as mentioned above, depression levels may explain ICDs more so than other common associations such as dopaminergic medications (36).

Sleep disorders have also been investigated, with some studies finding more sleep impairment and daytime sleepiness in PD patients with ICDs (5, 65). Although some studies that defined sleep disorders through questionnaires found an association with ICDs, more recent studies—including those that have screened sleep disorders through polysomnography exams—have revealed inconsistent results (15, 78, 143, 144). Patients with ICDs may also have more restless leg syndrome (65). The association between sleep disorders and ICDs continues to be debated and thus larger, prospective studies are needed to clarify this relationship.

Other comorbidities that have been evaluated include diabetes mellitus, hypertension, coronary heart disease, and constipation, yet no consistent associations with PD ICD have been found (15). Whether or not PD patients with ICDs exhibit greater motor symptom severity is also controversial with reports of positive, negative, and null results (5, 15, 19, 27, 31, 145). One study found specifically that freezing of gait is associated with higher rates of ICD (38), although another study examined motor subtypes and found no significant difference in ICD rates between postural instability and gait disorder dominant (PIGD) and non-PIGD PD patients (47). Other, less common and less consistent associations have been described, including autonomic function (73), sexual function (5), apathy (5, 146), motivation (27), delusions (14), dementia (14), hallucinations (21), and illusions (21)—contrasting other studies that did not find such associations with hallucination (19, 23) or apathy (23), for example. However, these associations are important to recognize, as they may directly impact prevalence rates. For instance, some studies specifically exclude PD patients with dementia (21), which could thus lead to a higher ICD prevalence because patients with dementia tend to have lower rates of ICD. Therefore, risk factors for ICDs in PD may differ across studies depending on inclusion and exclusion criteria.

NEURAL SUBSTRATE

Imaging and Electrophysiological Alterations

Numerous imaging studies have been conducted with non-PD populations, however fewer studies have examined PD populations. Patients with PD in general and ICDs in particular have prefrontal and basal ganglia circuit alterations revealed by functional magnetic resonance imaging particularly implicating reward substrate (147–152). These changes may predispose patients to further dysexecutive or cognitive dysfunction important for progression to ICDs (146). Patients with pathological gambling show reduced frontal lobe activity during the Iowa Gambling Task (153). These patients also exhibit dysfunction of the mesocorticolimbic network (i.e., abnormal activity and blood flow in a network including the orbitofrontal cortex, cingulate cortex, hippocampus, amygdala, insula, and ventral pallidum) (154, 155). In one PD patient with hypersexuality, single-photon emission computed tomography (SPECT) imaging revealed increased medial temporal blood flow (156). Functional magnetic resonance imaging studies show increased ventral striatal activation in dopamine-medicated PD patients with pathological gambling and buying exhibited during rewarding outcomes (150). Imaging studies also demonstrate that with acute dopaminergic therapy, dopamine release in the ventral striatum is abnormal in patients with ICDs compared to non-ICD patients during reward wanting (68, 150, 157). Patients most susceptible to ICDs appear to have relatively preserved limbic-paralimbic neural architecture, suggesting a predisposition to dopaminergic overdosing of the reward system (158). With continued efforts, imaging will continue to define network-level

alterations to potentially assist with the assessment, diagnosis, and treatment of ICDs in PD.

Aside from imaging, a vast literature has characterized the electrophysiology of the basal ganglia during action control and reward processing, both highly relevant processes for impulse control (108). Few studies have examined the electrophysiology of PD patients with ICDs. PD patients with ICDs have proportionally more reward-responsive neurons and less loss-responsive neurons in the STN (159). In a stop signal task with a small sample of 10 PD patients, STN high frequency (35–75 Hz) oscillatory activity decreased during inhibition (160). However, in the four patients with ICDs included in the study, this observation was not seen. It is unclear what the physiological meaning of this high frequency activity is, but it demonstrates the possibility of measuring meaningful electrophysiological pathology in the basal ganglia. In a separate study, relative to PD patients without ICD, PD patients with ICDs exhibited stronger differences in low frequency (2–12 Hz) power between risky and non-risky gambling decisions (161). Lastly, a study of nine PD patients with ICDs and without dopamine-induced dyskinesias found more STN theta (4–7.5 Hz) activity that was associated with similar theta activity in the premotor and frontal cortex (162). This signal may reflect the prominent role of the STN as a hub of response inhibition in the basal ganglia, perhaps through the hyperdirect pathway with the neocortex, which has been implicated in impulsivity (106). Together with imaging work, electrophysiological characterization of impulsivity will continue to remain as a valuable endeavor for pathophysiological insight and for motivating innovative neuromodulatory treatment modalities.

Cognitive and Neuropsychological Factors

Studies of cognition in PD patients with ICDs have been extensively reviewed elsewhere (163) but generally implicate brain regions found to be dysfunctional through imaging studies. Importantly, PD patients with dementia exhibit lower rates of ICDs, suggesting that they likely do not exhibit global cognitive impairment (14). However, studies have also associated low MMSE or MOCA scores to ICDs even after controlling for numerous other variables such as age at onset and motor severity (38, 73). Other studies have examined targeted cognitive domains, such as the Iowa Gambling Task, in which PD patients with ICDs show poor decision making compared to age, sex, education, and disease severity matched PD controls (17). Across the four main subtypes, ICD patients have impaired spatial planning and set shifting (63). Patients with hypersexuality in particular are selectively impaired on the Stroop test, a behavioral paradigm testing attention and inhibition (63). Another study found Stroop deficits in a PD ICD cohort relative to non-ICD PD patients but did not include ICD subtype analyses (164). However, not all studies are in agreement about Stroop deficits (17). With the exception of PD individuals with pathological gambling, PD patients with ICDs have lower performance on verbal learning and memory tasks (63). PD patients with pathological gambling and shopping show faster gain learning during a probabilistic reward task (150). These differences across subtypes may reflect abnormal cortical regions specific to certain ICD subtypes. For instance, given these neuropsychological profiles, hypersexuality may implicate the temporal and frontal lobes, whereas pathological gambling may be more frontal-specific.

CONCLUSION

In this review we have provided an overview of the numerous associations and risk factors for ICD-onset in individuals with PD. The review reveals that these factors vary considerably across samples and cultures, however some of the most consistent associations include dopaminergic medications, male gender, young age, early PD onset, longer disease duration, smoking, and increased impulsivity or novelty seeking personality traits. These characteristics may raise flags for clinicians as they consider patients at risk for impulsivity. Other risk factors discussed above, such as deep brain stimulation and non-dopaminergic medication use, have been less consistently established and will require further studies before definitive conclusions can be drawn. Although we have chosen to focus on the most common associations, there are several others that were not discussed here but may gain more research attention in the coming years, including socioeconomic status (21, 46), education (8, 74), and marriage status (8).

It is important to consider the many limitations in the studies presented in this review. In the overwhelming majority of cases, the studies are retrospective, observational, and utilize small sample sizes, although several large studies do exist (8, 28, 43). Across the various methodologies utilized, there are considerable differences in data collection. Numerous screening tools exist and may influence selection bias due to false positive or false negative ICD cases. For instance, compared to the modified Minnesota Impulsive Disorders Interview, the Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease Rating may overestimate ICD rates (5, 142), although some head to head comparisons have revealed similar rates (35). Some studies rely on private screening whereas others use self-administered assessments (5, 165). Another major limitation may be the time scale of a study. Although many studies consider cumulative incidence, cross-sectional prevalence and its connection to certain risk factors is difficult to accurately assess. For example, there can be a substantial time lag between dopamine agonist use and ICD onset (166). In addition, inclusion and exclusion criteria differ across studies and therefore results must not be hastily generalized to populations until external validity has been clearly established.

Remarkably, whether PD confers additional risk for ICD remains debated. Despite the strong associations between ICDs and PD characteristics like impulsivity traits, male gender, and increased depression, some studies conclude that PD patients in general are not at a particularly higher risk of ICDs (25, 142). A dearth of studies have compared unmedicated PD patients to non-PD controls and found no difference in ICD prevalence (142), however unmedicated PD patients differ greatly from those with more advanced disease. Another solution is to study other samples of non-PD patients that are treated with dopaminergic

agents, although this does not account for cases of ICDs in PD that are unrelated to dopamine treatment (167). Nonetheless, it is useful to study ICDs in PD-specific cohorts with hopes of tailoring treatment strategies specific to this complex disease.

In conclusion, with few exceptions the literature surrounding ICDs in PD is vastly mixed and further research is greatly needed in many areas. We believe the literature presently supports that PD patients are uniquely susceptible to ICDs through numerous potential risk factors discussed in this review. For instance, one profound example of susceptibility with respect to impulsive behaviors comes from a hallmark animal experiment in which preference for alcohol after an STN lesion depended critically on preference for alcohol prior to surgery (100). There exists a complex relationship between susceptibility and impulsivity outcomes, and parallels may be drawn to DBS where after surgery patients can experience improvement, worsening, or no change in preoperative impulsivities. It is necessary to appreciate that analyses at the group level can mask this type of important individual variability. In addition to the numerous environmental and non-environmental risks discussed throughout this review, ICDs are likely related to susceptibility factors involving specific cognitive dysfunctions or neural circuitries (63, 150). Additionally, susceptibilities may differ across the heterogeneity of ICD subtypes. Specific ICDs can result from intrinsic reward hypersensitivities (e.g., sexuality) or learned ones (e.g., gambling) (146) dependent on cultural factors, genetics, and neuropsychiatric profiles (21, 46, 59, 128, 146). Clinicians should bear in mind the potential influences of prior history, current behaviors, and treatment modalities as they may relate to ICD behaviors in PD patients.

AUTHOR CONTRIBUTIONS

RE designed and wrote the paper with contributions from AR-Z, SC, and BP. RE and ZP-C designed the figures and ZP-C created the figures. All authors provided critical input and edits.

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ORIGINAL RESEARCH
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Impact of Cognitive Profile on Impulse Control Disorders Presence and Severity in Parkinson's Disease

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Background: Impulse control disorders (ICDs) and related behaviors are frequent in Parkinson's disease (PD). Mild cognitive impairment (PD-MCI) and dementia (PDD), both characterized by heterogeneous cognitive phenotypes, are also commonly reported in PD. However, the frequency and severity of ICD within PD cognitive states is unknown.

Methods: Three hundred and twenty-six PD patients completed a comprehensive neuropsychological assessment and were classified as PD-MCI, PDD, or without cognitive alterations (PD-NC). The Minnesota impulsive disorders interview was used to ascertain the presence (ICD+) or absence (ICD–) of ICD. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale was used to assess ICD severity. A subsample of 286 patients evaluated with the same cognitive tasks was selected in order to investigate the characteristics of ICD in PD cognitive phenotypes.

Results: ICDs were present in 55% of PD-NC, in 50% of PD-MCI, and in 42% of PDD patients. Frequencies of ICD+ with attentive (ICD+: 20% vs. ICD–: 4%; $p = 0.031$) and executive impairments (ICD+: 44% vs. ICD–: 30%; $p = 0.027$) were higher in the PD-MCI and PDD subgroups, respectively. As expected, no differences were observed in the PD-NC. PD-MCI with attentive impairments presented higher percentage of ICD+ with deficits in the Trail Making Test B-A but not in the Digit Span Sequencing task. In PDD, executive failures concerned Similarities task (ICD+: 67%; ICD–: 29%; $p = 0.035$), with no differences between ICD+ and ICD– in the Stroop task.

Conclusions: Prevalence and severity of ICDs and related behaviors do not differ in PD with different cognitive states. However, ICD+ are more likely to show deficits, respectively in attentive and in executive domains, specifically in the Trail Making Test B-A task for the attention and working memory domain in PD-MCI and in the Similarities task for the executive function domain in PDD. Prospective studies should evaluate if these tests can be used as screening tool for ICDs in PD.

Keywords: Parkinson's disease, mild cognitive impairment, dementia, impulse control disorder, cognitive profile, cognition, cognitive states, cognitive phenotypes

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INTRODUCTION

In Parkinson's disease (PD), impulse control disorders (ICDs) are reported in around 30% of medicated patients (1, 2). They include pathological gambling (PG), hypersexuality (HS), compulsive shopping (CS), and binge-eating (BE). Either alone or in co-occurrence with the major ICDs, other repetitive and compulsive behaviors have been observed (3, 4). These are referred as impulsive-compulsive behaviors (ICBs) and include punding (repetitive simple non goal-oriented behaviors), hobbyism (repetitive complex behavior), and dopamine dysregulation syndrome (DDS), which is a pattern of compulsive dopaminergic medication use.

Prevalence rates of ICDs are similar in drug naïve PD patients and in the general population (5, 6), but higher in medicated PD patients (1, 2). The association between dopaminergic medications and ICDs is now well-recognized (7), with an increased risk for PD patients taking dopamine agonists alone or together with levodopa (1, 8).

In addition to dopaminergic therapy, other demographic and clinical variables may interact with exogenous and endogenous dopaminergic levels, therefore increasing the susceptibility to ICDs (8–10). Moreover, patients with ICDs report higher rates of anhedonia (11), depression and anxiety (2, 12, 13), and cognitive impairments (14, 15).

Cognitive deficits are common in PD and a significant proportion is at risk to develop dementia (PDD) (16). Evidence suggests that mild cognitive impairment in PD (PD-MCI) is a frequent condition (17) and refers to a state of cognitive alterations but preserved daily living autonomy, therefore representing an intermediate stage between normal cognition and dementia (18, 19). PD-MCI is characterized by heterogeneous cognitive profile (20, 21) and cognitive phenotypes may be differently associated with the presence and severity of specific non-motor symptoms, possibly underlying pathophysiological variability (22).

Both PD-MCI and PDD as well as ICD are well-recognized cognitive and behavior conditions in PD. Since patients with PD normal cognition (PD-NC), PD-MCI, and PDD differ for demographic and clinical features, we might expect ICD prevalence and characteristics to differ between these cognitive categories. For example, in PDD the use of dopamine agonists is discouraged due to the likelihood to develop psychosis (23, 24) which in turn might result in reduced risk of ICD. Younger age is one of the risk factors for ICD in PD (8), possibly related to preserved ventral striatal responsiveness and dopaminergic overstimulation (25). By contrast, PDD, who are older than PD-NC and PD-MCI, might be less susceptible to ICD. This concept would be also supported by a previous study showing lower prevalence rates of dementia in patients with vs. without ICD (26).

A recent meta-analysis showed worse performance of PD patients with ICD in set-shifting and reward-related decision-making tasks (15). To our knowledge, there are no studies on ICDs prevalence across cognitive states and specific domains. This is an important issue as recognizing factors associated with ICD in PD across cognitive states and domains may improve clinical diagnosis and pave the way for future studies on therapeutic management. Considering the heterogeneous cognitive profile disclosed by PD patients, we might expect that ICD rates would change according to the cognitive domains affected.

Here, for the first time, ICDs and related behaviors will be described across PD patients with normal cognition (PD-NC), PD-MCI, and PPD, and within specific cognitive phenotypes. The study aims to investigate whether PD cognitive states and phenotypes are associated with changes in prevalence and severity of ICDs.

MATERIALS AND METHODS

Patients and Clinical Assessment

We recruited 600 consecutive patients with PD at the Parkinson's disease and Movement Disorders Unit, Neurology Clinic in Padua, Italy, and IRCCS San Camillo Hospital in Venice, between May 2010 and August 2018. All patients met the clinical diagnostic criteria of the UK Parkinson's Disease Society Brain Bank (27). Exclusion criteria were diagnosis of atypical Parkinsonism as well as clinically significant or unstable medical conditions including cardiovascular, metabolic, psychiatric diseases and neurosurgical procedures (including deep brain stimulation). Among this large cohort, we included only PD patients who underwent a comprehensive neuropsychological evaluation according to Level II criteria (28, 29), and ICD assessment with Minnesota Impulsive Disorder Interview (MIDI) and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) (30), resulting in a sample of 326 PD patients (see **Figure 1**). Of note, diagnosis of ICDs and ICBs were based on the MIDI, which was administered by an experienced neuropsychologist. ICDs and ICBs that were not included in the MIDI but were already well-known to occur in the PD population were also investigated, namely BE, punding, and DDS. All patients diagnosed with ICDs answered affirmatively one gateway question plus an affirmative answer to one or more of the remaining questions. In order to evaluate ICDs severity, the QUIP-RS was also administered. Finally, single and multiple ICDs and ICBs prevalence rates were also investigated using published QUIP-RS cutoffs (30), following a previous study of PD patients with ICDs in Italian cohorts (31).

Demographic information including sex, age, education, age at symptoms onset, disease duration, and dopaminergic medication were also collected. We calculated dopamine agonist equivalent daily dose (DAED) and total L-dopa-equivalent daily dose (LEDD) for each patient according to Tomlinson et al. (32); further, DAED and LEDD were adjusted by body weight (DAED/kg and LEDD/kg). Disease severity was assessed with the motor part of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) (33).

All subjects underwent a comprehensive assessment including functional autonomy (by instrumental- and activity of daily living, ADL/IADL) (34), subjective cognitive complaints and their impact on daily functioning (by the Parkinson's Disease—Cognitive Functional Rating Scale, PD-CFRS) (35) and presence

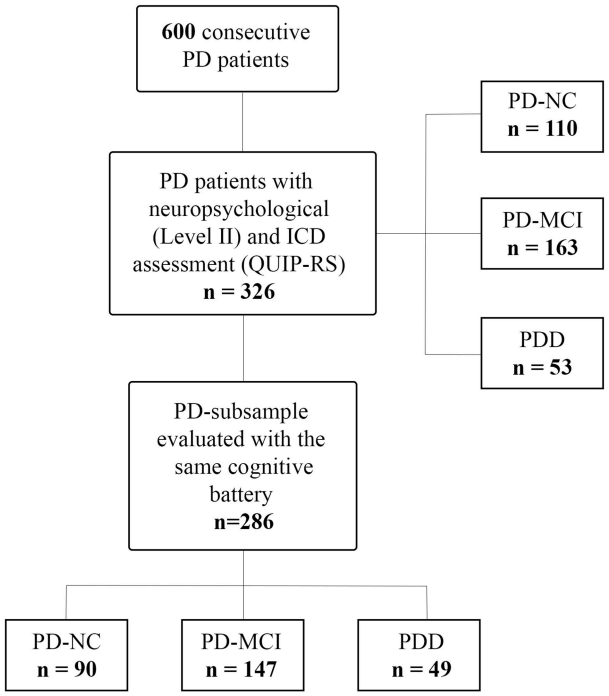

FIGURE 1 | Study flowchart. PD, Parkinson's disease; PD-NC, PD with normal cognition; PD-MCI, PD with mild cognitive impairment; PDD, PD with dementia; ICD, impulse control disorder; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale.

of depression, anxiety and the quality of life using the Beck Depression Inventory (BDI-*II*), State-Trait Anxiety Inventory forms (STAI-Y1 and Y2), and an 8-item version of the Parkinson's Disease Questionnaire for quality of life (PDQ-8), respectively (36).

Patients underwent a comprehensive neuropsychological battery as previously described (17), specifically designed to target cognitive deficits in Parkinson's disease with at least two tests for each cognitive domain (e.g., attention and working memory, executive, memory, language, and visuospatial abilities) (28, 29).

We calculated z-scores for each test and participant, based on standardized published Italian norms that are adjusted for age and education, then PD patients were classified as PD-MCI if z-score was at least 1.5 SD below appropriate norms on at least two tests (i.e., within a single cognitive domain or at least one test in two or more cognitive domains) (28). Presence of PDD was assessed based on the Movement Disorders Society Task force recommendations (29), which included cognitive, daily functioning, and behavioral assessment. Patients without cognitive alterations were defined as PD-NC. Neuropsychological tests were performed on two separate occasions within 5–7 days and administered in the morning ON medication.

Finally, to investigate the association between presence of ICDs and cognitive phenotypes, we selected a PD-subsample, which was evaluated with the same cognitive battery, leaving a final sample of 286 PD (see **Figure 1**).

Specifically, attention and working memory domain was tested with the Trail Making Test part B-A (TMT B-A) (37) and Digit Span Sequencing (DSS) of Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV) (38). Executive functions were evaluated with the Stroop Color and Word test (39), and the WAIS-IV similarities (38). Memory was assessed with the delayed recall of Rey-Osterrieth complex figure test (ROCF) (40), and prose memory tests (41). Language was tested with the semantic fluency task, and Novelli's naming test (42). Visuospatial and visuoperceptive functions were assessed by Benton's Judgment of Line Orientation Test (43), and the Visual Object and Space Perception incomplete letters recognition subtask (44).

Patients gave written informed consent, according to the Declaration of Helsinki, before study enrolment, and ethical approval was obtained from the Venice Research Ethics Committee, Venice, Italy.

Statistical Analysis

Statistical analyses were performed using SPSS version 22 (IBM SPSS, Chicago, IL) (45). Demographic and clinical continuous variables were analyzed using Kruskal-Wallis test, with Mann–Whitney-*U post-hoc* test ($p < 0.05$) for between-groups comparisons. Pearson's Chi-square test was applied to categorical variables. Frequencies of ICDs and related behaviors across cognitive states were investigated using Pearson's Chi-square test. Linear trend of increase/decrease in frequency by cognitive decline status was investigated using Chi-square test for trend. ICDs severity and related behaviors across cognitive states were compared between groups via ANCOVA model including the continuous QUIP-RS score as dependent variable and as covariate those demographic and clinical variables differing between cognitive states, which has a significant effect on the QUIP-RS continuous score in a multiple regression model. Distribution normality was checked with Kolmogorov–Smirnov tests and homogeneity of variance with Levene's test.

Within each cognitive state, the frequencies of PD failing two tests of the same cognitive domain were compared between patients with (ICD+) and without (ICD–) ICDs/ICBs, using Pearson's Chi-square test. For all analyses, the significance threshold was set at $p < 0.05$.

RESULTS

PD Demographic and Clinical Characteristics Among Cognitive States

Out of 326 PD patients, 110 were cognitive normal (PD-NC), 163 had MCI (PD-MCI) and 53 dementia (PDD).

Mean age was different across subgroups (PDD>PD-MCI>PD-NC, $p < 0.0001$) while gender distribution was similar. PD-NC had lower age at symptoms onset, and higher years of education than both PD-MCI and PDD groups ($p < 0.0001$ for both variables). PDD had longer disease duration compared to PD-NC and PD-MCI groups ($p = 0.006$).

The three PD cognitive subgroups did not differ for LEDD and LEDD/kg. However, the DAED, the DAED/kg, and the

percentage of patients under DA were lower in the PDD group compared to PD-NC and PD-MCI groups ($p = 0.0002$, $p = 0.0001$, $p = 0.0005$, respectively).

UPDRS-I and UPDRS-II scores were higher in the PDD, but comparable in the PD-NC and PD-MCI ($p = 0.0002$ and $p < 0.0001$, respectively). The UPDRS-III scores were different across the three subgroups, with the lowest scores in PD-NC, and the highest in PDD ($p < 0.0001$). Global cognitive status (measured by mean of MMSE and MoCA scales) was different across the three subgroups, with best cognitive performances observed in PD-NC and worst in PDD ($p < 0.0001$ for both variables). BDI-*II* scores differed across the three subgroups, with the lowest value in PD-NC and the highest in the PPD ($p < 0.0001$). However, the percentage of patients with BDI-*II* score above the cutoff (>14) was higher in PDD ($p = 0.0027$), but comparable in the PD-NC and PD-MCI. State (STAI-Y1), but not trait (STAI-Y2) anxiety score, was higher in PDD compared to PD-NC and PD-MCI ($p = 0.0076$). PDD had greater disability on ADL/IADL compared to PD-NC and PD-MCI groups ($p < 0.0001$ and $p < 0.0002$, respectively). Finally, functional disability due to mainly cognitive impairments (PD-CFRS) was significantly different across PD cognitive subgroups (PDD>PD-MCI>PD-NC) ($p < 0.0001$). Demographic and clinical data are reported in **Supplementary Table 1**.

Demographic and Clinical Characteristics Associated With ICD Among Cognitive States

Out of 326 PD patients, 60 PD-NC patients, 81 PD-MCI patients, and 22 PDD patients were diagnosed with presence of at least one ICD or ICB.

In PD-NC, ICD+, and ICD– did not differ for mean age, gender distribution, education level, and age at symptoms onset, although ICD+ had longer disease duration ($p = 0.0017$). LEDD and LEDD/Kg were higher in the ICD+ ($p = 0.0002$ and $p = 0.0001$, respectively), but there were no differences in the DAED, DAED/Kg, and in the percentage of patients under DA.

In PD-MCI, ICD+ had lower mean age and age at symptoms onset, and longer disease duration than ICD– ($p = 0.0142$, $p < 0.0001$, and $p = 0.0003$, respectively). LEDD, LEDD/Kg, DAED, DAED/Kg, and the percentage of patients under DA were higher in the ICD+ compared to ICD– ($p = 0.0028$, $p = 0.0156$, $p = 0.0305$, $p = 0.0469$, and $p = 0.0013$, respectively).

In both PD-NC and PD-MCI, the quality of life of ICD+ patients was worse ($p = 0.0009$ and $p = 0.0052$, respectively). Conversely, UPDRS-I, UPDRS-II, and UPDRS-III scores, global cognitive status (measured by MMSE and MoCA scales), BDI-*II* score and percentage of patients with BDI-*II* score above the cutoff, state and trait anxiety (STAI-Y1 and STAI-Y2 scores), disability on the ADL, IADL, and PD-CFRS scales did not differ between ICD+ and ICD–.

In the PDD, there were no difference between ICD+ and ICD– in any demographic and clinical characteristic investigated. Demographic and clinical data of ICD+ and ICD– among cognitive states are reported in **Table 1**.

ICDs Presence and Severity Across Cognitive States

According to the MIDI, ICDs, and/or ICBs were present in 55% (60 patients) of PD-NC, in 50% (81 patients) of PD-MCI, and in 42% (22 patients) of PDD. Results are reported in details in **Table 2** and **Figure 2**.

Frequencies decrease across cognitive states, but trend toward a decrease of frequencies with cognitive decline do not reach statistical significance ($p = 0.34$).

According to the QUIP-RS, either ICDs or ICBs above the cutoff were present in the 24% of PD-NC, in the 24% of PD-MCI, and in the 23% of PDD. The 20% of PD-NC, the 20% of PD-MCI, and the 21% of PDD, presented both ICDs and ICBs.

Considering QUIP-RS scores above 0, either ICDs or ICBs were present in the 54% of PD-NC, in the 49% of PD-MCI, and in 42% of PDD.

Severity of ICD+ did not differ across cognitive states ($p = 0.877$). No differences were also observed considering ICDs and ICBs separately ($p = 0.769$ and $p = 0.329$, respectively) (see **Table 2**).

ICDs and Cognitive Phenotypes

In the PD-NC group, there were no differences between the percentages of ICD+ and ICD– failing two tests of the same cognitive domain.

In PD-MCI, there was higher number of ICD+ patients failing two tests of attention (ICD+: 20% vs. ICD–: 4%; $p = 0.031$) (see **Table 3**). Percentage of patients with TMT B-A z-scores below 1.5 SD was significantly higher in the ICD+ than in the ICD– subgroup (ICD+: 41%; ICD–: 24%; $p = 0.035$), with no differences in the DSS performances (see **Table 4**).

In PDD, there were higher rates of ICD+ patients failing two tests of executive function (ICD+: 44% vs. ICD–: 30%; $p = 0.027$), with no differences in the other domains (see **Table 3**). Data seems to be driven by the Similarities task as the percentage of patients with z-scores below 1.5 SD was significantly higher in the ICD+ than in the ICD– subgroup (ICD+: 67%; ICD–: 29%; $p = 0.035$), with no differences in the Stroop task (see **Table 4**).

Detailed demographic characteristics of PD-MCI group based on performances at TMT B-A test and PDD based on performance at Similarities task are provided in the **Supplementary Tables 2**, **3**.

DISCUSSION

This is the first study describing prevalence and characteristics of ICDs and related behaviors in PD cognitive states including both PD with dementia and PD-MCI. We found that their prevalence tends to decrease from PD-NC to PDD, although differences in rates were not significant while severity was similar across cognitive states.

These findings are different from other studies reporting an association with cognitive performance (14, 15) and particularly with one prevalence study in which ICDs were less frequent in PDD compared to PD-NC (26). Discrepancies with the latter study, may reflect differences in PDD diagnostic procedures

TABLE 1 | Demographic and clinical characteristics of ICD+ and ICD– across PD cognitive states.

	PD-NC ($n = 110$)		PD-MCI ($n = 163$)		PDD ($n = 53$)		ICD+ vs. ICD-		
	ICD+ $n = 60$	ICD– $n = 50$	ICD+ $n = 81$	ICD– $n = 82$	ICD+ $n = 22$	ICD– $n = 31$	PD-NC	PD-MCI	PDD
Age (yr)	60.58 (9.36)	61.48 (10.49)	67.24 (8.61)	70.27 (8.93)	71.50 (9.39)	74.10 (7.53)	0.5991	**0.0142**	0.3199
Sex (%, male)	49%	59%	68%	55%	67%	71%	0.4007	0.1356	0.9812
Education (yr)	12.80 (3.82)	12.70 (4.35)	9.45 (4.45)	9.85 (4.46)	9.91 (4.85)	8.55 (4.65)	0.8657	0.4991	0.1901
Age of onset symptoms (yr)	51.45 (10.36)	54.56 (10.32)	55.55 (10.20)	62.67 (10.48)	59.22 (10.40)	63.17 (9.67)	0.1604	**<0.0001**	0.2032
Disease duration (yr)	9.12 (4.54)	6.08 (5.45)	10.85 (6.55)	7.10 (5.09)	11.50 (5.19)	11.00 (5.15)	**0.0017**	**0.0003**	0.8432
LEDD	963.06 (476)	589.40 (507.28)	973.90 (492.03)	750.54 (526.12)	814.06 (416.35)	655.86 (380.37)	**0.0002**	**0.0028**	0.1405
LEDD/kg	14.00 (7.91)	8.10 (6.75)	13.45 (7.04)	11.00 (8.19)	10.98 (5.78)	8.76 (4.73)	**0.0001**	**0.0156**	0.1711
DA (%)	80%	73%	90%	67%	57%	52%	0.5684	**0.0013**	0.9418
DAED	157.37 (110.42)	132.16 (117.06)	141.46 (95.05)	110.30 (113.62)	79.95 (96.07)	78.15 (87.52)	0.2786	**0.0305**	0.8610
DAED/kg	2.29 (1.77)	1.86 (1.65)	1.97 (1.41)	1.65 (1.85)	1.06 (1.24)	1.03 (1.16)	0.3143	**0.0469**	0.8015
MDS-UPDRS-I	10.57 (5.41)	9.24 (5.51)	11.19 (4.89)	9.29 (4.44)	13.88 (7.47)	16.73 (7.57)	0.3944	0.0748	0.5597
MDS-UPDRS-II	11.67 (6.43)	9.43 (6.47)	14.29 (6.94)	11.62 (6.37)	19.50 (4.31)	19.47 (8.93)	0.1137	0.0972	0.7465
MDS-UPDRS-III	20.75 (12.64)	18.00 (12.76)	28.52 (11.72)	24.67 (12.84)	37.46 (10.38)	33.69 (13.06)	0.2177	0.0894	0.3347
ADL	5.74 (0.60)	5.83 (0.81)	5.43 (1.01)	5.35 (0.96)	4.39 (1.33)	3.52 (1.91)	0.1045	0.4780	0.1441
IADL	5.96 (1.44)	5.95 (1.66)	5.45 (1.66)	5.64 (1.64)	3.39 (1.58)	2.85 (1.81)	0.8489	0.3608	0.3357
PD-CFRS	2.24 (2.23)	1.42 (1.75)	4.61 (4.16)	3.40 (3.35)	10.88 (5.28)	13.87 (6.97)	0.1025	0.1495	0.2153
PDQ-8	9.60 (5.29)	5.80 (4.23)	10.93 (5.30)	8.47 (5.33)	12.56 (6.44)	14.18 (5.53)	**0.0009**	**0.0052**	0.3974
STAI-Y1	37.82 (11.47)	37.97 (8.58)	38.86 (10.58)	39.62 (10.09)	42.25 (11.05)	44.05 (8.98)	0.4616	0.6162	0.4636
STAI-Y2	41.79 (10.80)	41.00 (9.49)	41.25 (10.40)	41.58 (10.63)	44.94 (11.80)	45.45 (10.54)	0.7461	0.9260	0.7499
BDI-*II*	9.10 (8.02)	8.35 (6.60)	10.62 (7.05)	10.77 (8.26)	12.80 (7.06)	15.54 (7.40)	0.9235	0.7234	0.2616
BDI-*II* (%, cutoff > 14)	18%	16%	28%	28%	40%	54%	0.9775	0.8829	0.5263
MoCA	27.52 (2.06)	27.55 (1.86)	25.98 (2.82)	25.62 (2.18)	21.37 (4.30)	21.10 (4.36)	0.7254	0.2793	0.6006
MMSE	25.89 (2.39)	25.04 (2.65)	22.30 (3.52)	22.00 (2.95)	15.68 (4.85)	17.17 (3.66)	0.1248	0.5933	0.3682

Significant differences ($p < 0.05$) are reported in bold type. SD, standard deviation; PD, Parkinson's disease; PD-NC, PD with normal cognition; PD-MCI, PD with mild cognitive impairment; PDD, PD with dementia; ICD+, patients with impulse control disorders and related behaviors according to MIDI; ICD-, patients without impulse control disorders and related behaviors according to MIDI; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose; DAED, dopamine agonist equivalent dose; LEDD/kg, LEDD adjusted by body weight; DAED/kg, DAED adjusted by body weight; ADL, Activity of daily living; IADL, Instrumental activities of daily living; PD-CFRS, Parkinson's Disease—Cognitive Functional Rating Scale; PDQ-8, Parkinson's Disease Questionnaire; STAI (Y-1, Y-2), State-Trait Anxiety Inventory; BDI-II, Beck Depression Inventory-II; MoCA, Montreal Cognitive Assessment; MMSE, Mini Mental State Examination.

(46). In our cohort all patients underwent level II cognitive, daily functioning and behavioral assessments, and cognitive states diagnosis included PD-MCI as well as PD-NC and PDD, following proposed criteria for PD (28, 29).

Indeed clinical and demographic characteristics in our cohort of PD-NC, PD-MCI, and PDD are in line with literature, and this was indirectly confirmed by the observation of older age, longer disease duration, worse motor symptomatology, cognitive decline, and depression levels in our PDD (16, 47, 48).

In our study, diagnosis of ICDs or ICBs was based on the MIDI and behaviors that were not included in the MIDI but commonly occur in PD were also investigated. The QUIP-RS, since it has not been validated in the Italian population, was used only for assessing severity. In order to characterize the type of ICDs and ICBs of our sample, data were also presented according to published US sample cutoff score (30) further validated in the German population (49). According to published cutoff scores (30), pure single ICDs were not present in any patient in our cohort. This may imply either that QUIP-RS cutoff scores are too conservative for Italian population, or that ICDs infrequently occur as single entity. In any case, future studies are needed to further explore this point.

Exploring ICDs frequency based on scores of QUIP-RS>0, we found similar results. Of note, frequencies of HS and BE were similar in PDD and in PD-NC regardless of lower DAED levels and lower number of patients on dopamine agonists (8, 23, 24, 50, 51). We speculate that similar rates might be either due to (i) shared underlying mechanisms (i.e., dementia-like neurodegenerations vs. ICDs-related) or (ii) the characteristics of QUIP-RS, which may capture features of disinhibitions related to impulsivity without ruling out dementia-like behavioral disinhibition (50, 52).

Our study confirms, in PD-NC and PD-MCI, previously reported risk factors for ICD. In the PD-NC group, ICD was associated with higher disease duration and LEDD. In the PD-MCI, ICD was associated with lower age and age at symptoms onset, and higher disease duration, LEDD, DAED, and percentage of patients under DA. Conversely, ICD+ and ICD– PDD patients did not differ in any demographic and clinical variable investigated. For a clinical point of view, these finding

TABLE 2 | Severity and frequencies of ICDs and ICBs across cognitive states.

	PD-NC ($n = 110$)			PD-MCI ($n = 163$)			PDD ($n = 53$)			ANCOVA
	QUIP-RS score Mean (SD)[a]	**% QUIP-RS>0[b]**	**% QUIP-RS above cutoff[b]**	**QUIP-RS score Mean (SD)[a]**	**% QUIP-RS>0[b]**	**% QUIP-RS above cutoff[b]**	**QUIP-RS score Mean (SD)[a]**	**% QUIP-RS>0[b]**	**% QUIP-RS above cutoff[b]**	***P*-value**
ICD+ (MIDI)	10.56 (8.90)	55		10.19 (7.74)	50		10.41 (8.48)	42		0.877
ICD[c]	4.00 (1.65)	22	0	4.85 (3.02)	20	2	3.66 (2.25)	21	2	0.769
PG only		1	0		2	0		0	0	
HS only		5	0		4	0		8	0	
CS only		8	0		3	0		2	0	
BE only		5	0		4	0		6	0	
Multiple ICD		3	0		7	2		5	2	
ICB[c]	4.73 (3.17)	10	4	5.64 (4.14)	9	2	/	0	0	0.329
Hobbyism only		7	3		4	1		0	0	
Punding only		3	1		0	0		0	0	
DDS only		0	0		3	1		0	0	
Multiple ICB		0	0		1	0		0	0	
ICD & ICB[c]	17.33 (8.40)	22	20	16.49 (6.96)	20	20	14.09 (8.38)	21	21	0.976

ICD+, impulse control disorders and related behaviors according to MIDI; ICD, patients with ICD but not ICB; ICB, patients with ICB but not ICD; Multiple ICD, patients with multiple ICDs but no ICB; Multiple ICB, patients with multiple ICBs but no ICD; ICD&ICB, patients with at least an ICD and an ICB; PG, pathological gambling; HS, hypersexuality; CS, compulsive shopping; BE, binge-eating; DDS, dopamine dysregulation syndrome; PD, Parkinson's disease; PD-NC, PD with normal cognition; PD-MCI, PD with mild cognitive impairment; PDD, PD with dementia; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; % QUIP-RS>0, percentage of patients with QUIP-RS score above 0; % QUIP-RS above cutoff, percentage of patients with QUIP-RS score above the cutoffs.

[a] *No significant differences were found on severity (QUIP-RS mean scores) between PD subgroups after ANCOVA including disease duration, DAED, UPDRS-I, ADL, PDQ-8, BDI-II and MoCA scores as covariates.*

[b] *No significant differences or linear trends were found within and between PD subgroups.*

[c] *Percentages of patients with single ICDs, single ICBs, multiple ICDs, multiple ICBs, or at least an ICD and an ICB (ICD&ICB), according to previously published cutoff values (PG: QUIP-RS ≥ 6; HS: QUIP-RS ≥ 8; CS: QUIP-RS ≥ 8; BE: QUIP-RS ≥ 7; hobbyism: QUIP-RS ≥ 7; punding: QUIP-RS ≥ 7; DDS: QUIP-RS ≥ 7; multiple ICDs: QUIP-RS combined ICDs score ≥ 10; multiple ICBs: QUIP-RS combined ICBs score ≥ 7) (30).*

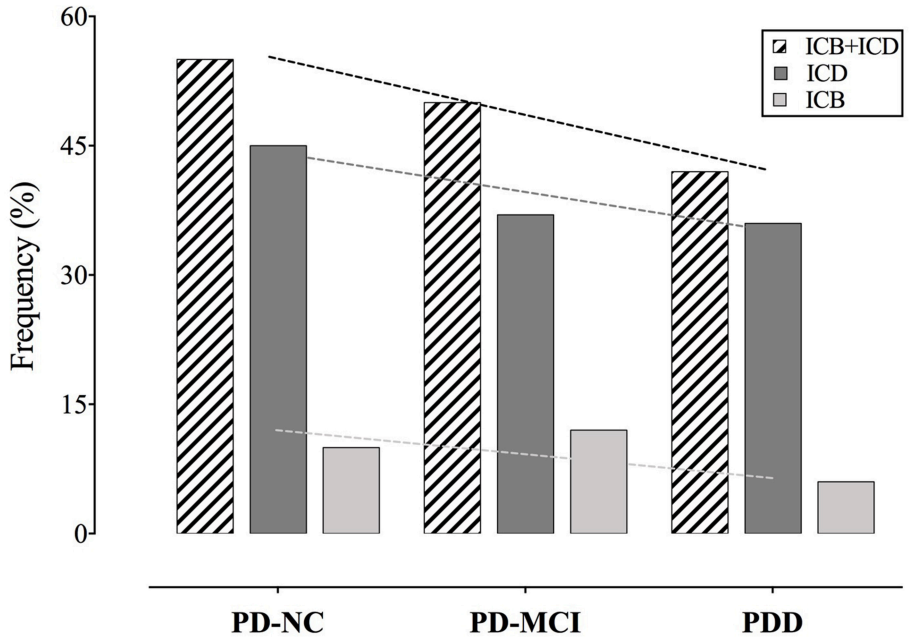

FIGURE 2 | Frequency of ICDs and ICBs among cognitive states. Slopes of the trend lines are reported. PD, Parkinson's disease; PD-NC, PD with normal cognition; PD-MCI, PD with mild cognitive impairment; PDD, PD with dementia; ICD, impulse control disorder; ICB, impulsive compulsive behavior.

TABLE 3 | Frequencies of patients with a failure in at least two tests within a cognitive domain across cognitive states and ICD-subgroups.

Cognitive domains	PD-MCI ($n = 147$)		PDD ($n = 49$)		PD-MCI	PDD
	ICD– ($n = 75$) (%)	ICD+ ($n = 72$) (%)	ICD– ($n = 29$) (%)	ICD+ ($n = 20$) (%)	*P*-value ICD+ vs. ICD-	
Attention/working memory	4	20	76	73	**0.0315**	0.8453
Executive	5	4	30	44	0.8550	**0.0279**
Language	3	0	26	36	0.4970	0.8687
Memory	2	9	48	47	0.2246	0.7930
Visuospatial	22	27	80	81	0.7241	0.7138

Significant differences ($p < 0.05$) are reported in bold type. PD, Parkinson's disease; PD-NC, PD with normal cognition; PD-MCI, PD with mild cognitive impairment; PDD, PD with dementia; ICD+, patients with impulse control disorders and related behaviors according to MIDI; ICD-, patients without impulse control disorders and related behaviors according to MIDI.

suggest that i) ICD are equally common in PDD as PD-NC and PD-MCI, and that ii) the recognized risk factors for ICD in PD may not apply to PDD, further encouraging physician awareness.

Furthermore, quality of life, as assessed by PDQ-8, differs between ICD+ and ICD- in PD-NC and PD-MCI as previously reported (13). Interestingly, we do not find any difference in PDQ-8 score of PDD patients with and without ICDs maybe because other motor and/or non-motor symptoms are likely to impact more than ICDs on QoL.

Despite frequencies and severities of ICDs were similar across PD-NC, PD-MCI and PDD, patterns of cognitive alterations (i.e., failure in two tests of the same domain), associated with presence/absence of ICDs, differed within each cognitive state. Presence of ICDs in PD-MCI is associated with attention impairments, whilst in PDD with ICDs cognitive decline involved the executive domain. In PD-NC, there were no patterns of cognitive alterations and this reflects the MDS guidelines, with failure in two tests of the same cognitive domain indicative of PD-MCI (28). Taken together these findings support frontal-striatal (i.e., executive and attentive) instead of posterior impairments (i.e., language and visuospatial abilities) in ICD+ (53–55) and the involvement of altered mesocorticolimbic activity (56–58). Moreover, this study further extends previous results showing that the patterns of frontal dysfunctions of ICD+ differ within each cognitive state. Clinically, these results have important implications as attentive impairments in PD-MCI and executive dysfunctions in PDD measured by level II neuropsychological assessment may suggest co-presence of ICDs and related behaviors.

When performances were analyzed considering the single neuropsychological test, the TMT B-A but not the DSS was associated with higher rates of ICD+ in PD-MCI.

TABLE 4 | Percentage of ICD+ and ICD– across cognitive states with a cognitive performance below 1.5 SD, in the attentive and executive domains.

	PD-MCI		PDD		PD-MCI	PDD
	ICD– (%)	ICD+ (%)	ICD– (%)	ICD+ (%)	*P*-value	
ATTENTION AND WORKING MEMORY DOMAIN						
TMT B-A	24	41	79	60	**0.0350**	0.2500
DSS (WAIS-IV)	13	15	58	75	0.9190	0.3790
EXECUTIVE DOMAIN						
Stroop test	46	49	75	89	0.9141	0.4609
Similarities	15	18	29	67	0.8948	**0.0355**

Significant differences ($p < 0.05$) are reported in bold type. PD, Parkinson's disease; PD-NC, PD with normal cognition; PD-MCI, PD with mild cognitive impairment; PDD, PD with dementia; ICD+, patients with impulse control disorders and related behaviors according to MIDI; ICD–, patients without impulse control disorders and related behaviors according to MIDI; TMT B-A, Trail Making Test part B-A; DSS, Digit Span Sequencing subtest of the Wechsler Adult Intelligence Scale–Fourth Edition; SD, standard deviation.

Worse TMT-B-A performances have been reported in non-PD pathological gamblers (59) and in PD patient with ICDs (53, 60, 61), although no specifically investigated within cognitive states. The TMT B-A and the DSS, albeit being categorized within the attentive domain are tasks investigating set-shifting and working memory abilities, respectively. TMT B-A requires cognitive flexibility in order to switch from numerical to alphabetical sequences, which is an important ability for maintaining goal-oriented behaviors when facing environmental changes or task demands in daily life (62). In lesion mapping studies, TMT B-A performances are associated with rostral anterior cingulate cortex (63), which is part of the mesocorticolimbic pathway mediating the control of reward-related behaviors that may be overstimulated by dopaminergic medication. In the early stages of the PD, dopaminergic depletion is relatively circumscribed to the dorsal striatum, whilst the limbic (nucleus accumbens) and cortical (prefrontal cortex) structures are relatively spared and only degenerate in the later stages (64). Medication levels necessary to restore dopaminergic depletion in the dorsal striatum may abnormally stimulate mesocorticolimbic structures. Interestingly, deficits in the TMT B-A task are more common in PD-MCI patients with lower age and lower age at symptoms onset, longer disease duration, higher DEAD and LEDD levels, and higher percentage of dopamine agonists use (see **Supplementary Table 2**) who may be more vulnerable to the overdosing effect of medication. The TMT B-A, albeit being a sensitive test of ICD+ in PD-MCI, may not be indicated for assessing PDD patients. In our sample, high number of PDD patients was not able to perform either the TMT B-A or the DDS.

In PDD patients, performance in the Similarities but not the Stroop tasks was associated with ICD+. Lack of differences between ICD+ and ICD– patients in the Stroop task (2, 53, 54, 65, 66) as well as in the Similarities task (53, 65) have been reported, although in these studies dementia was an exclusion criteria. This may explain why we found that ICD+ was associated with impairments in the Similarities task contrarily the previous results (53, 65). Compared to the Stroop task that evaluates verbal inhibition, the similarities task assesses abstract thinking, concept formation, and verbal reasoning as participants are instructed to describe how two things are similar. Abstract thinking is associated with anterior prefrontal, fronto-parietal cortices, and insula functioning (63). Therefore, we might speculate that, as PD cognitive severity increases, presence of ICDs is associated with wider cortical and subcortical dysfunctions which target limbic and frontal and parietal areas. PDD patients who fail the Similarities task present worse general cognitive performance and higher levels of trait anxiety (see **Supplementary Table 3**).

Although the study was conducted in a large cohort of PD patients following proposed guidelines for PD-MCI and PDD diagnosis, there are some limitations that should be acknowledged.

First, participants were recruited during clinics and this limits the generalizability of the results to the whole PD population. Second, the QUIP-RS has not been validated in the Italian population therefore prevalence rates of ICDs according to QUIP-RS cutoff scores should be considered cautiously as may not apply for our sample. However, patients were categorized as ICD+ by an experiencing neuropsychologist who also administered the MIDI and clinical diagnosis was done according to established diagnostic criteria. Third, in PDD, lack of differences between ICD+ and ICD- in the attentive domain might be biased by the floor effect of the TMT B-A and DSS, with high number of PDD patients not able to perform the tasks. Fourth, the TMT B-A and Similarities tasks are not purely attentive and executive, but they also investigate executive functions and language, respectively (67). However, we might exclude a language involvement in PDD with ICD as performances in semantic fluencies and naming did not differ between ICD+ and ICD–. Further studies should use experimental tasks investigating specific cognitive processes to assess neurological underpinnings of ICDs and medication effects across cognitive states and domains.

In conclusion, our findings provide evidence that cognitive states *per sè* are not associated with (i) the presence and the (ii) severity of ICDs and related behaviors. Conversely, (iii) impairments in ICD+ are circumscribed to attentive and executive domains in PD-MCI and PDD patients, respectively. Finally, (iv) the TMT B-A task for the attention and working memory domain in PD-MCI, and the Similarities task for the executive function domain in the PDD were the tasks more sensitive of ICD and related behavior presence. Taken together these findings may suggest different ICDs

entities according to disease cognitive progression. Namely, a relative early phase dopamine agonist dependent ICDs characterized by mainly attentive problems and a late phase medication independent ICDs characterized by wider cortical and dysexecutive dysfunctions. Future studies should help addressing this hypothesis.

PD patients should be carefully interviewed for the presence of ICDs and related behaviors at any stage of the disease, as being diagnosed either with PD-MCI, PDD, or being PD-NC is not indicative *per sè* of a higher or lower risk of ICD.

DATA AVAILABILITY

The datasets for this study will not be made publicly available because the authors don't have the permission to share the dataset.

AUTHOR CONTRIBUTIONS

The study has been designed by RB, LW, and AA. Data have been collected by RS, VC, and EF and analyzed by LW. The manuscript has been drafted by AM, EF, and RB. AM, LW, EF, RS, VC, AA, and RB revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00266/full#supplementary-material

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Impulse Control Disorders in Parkinson's Disease. A Brief and Comprehensive Review

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Impulse control and related disorders (ICDs-RD) encompasses a heterogeneous group of disorders that involve pleasurable behaviors performed repetitively, excessively, and compulsively. The key common symptom in all these disorders is the failure to resist an impulse or temptation to control an act or specific behavior, which is ultimately harmful to oneself or others and interferes in major areas of life. The major symptoms of ICDs include pathological gambling (PG), hypersexualtiy (HS), compulsive buying/shopping (CB) and binge eating (BE) functioning. ICDs and ICDs-RD have been included in the behavioral spectrum of non-motor symptoms in Parkinson's disease (PD) leading, in some cases, to serious financial, legal and psychosocial devastating consequences. Herein we present the prevalence of ICDs, the risk factors, its pathophysiological mechanisms, the link with agonist dopaminergic therapies and therapeutic managements.

Keywords: impulse control disorders, ICD, pathological gambling, binge eating, hypersexual disorder, compulsive buying, Parkinson disease

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DEFINITION

Impulse control and related disorders (ICDs-RD) encompass a heterogeneous group of disorders that involve pleasurable behaviors performed repetitively, excessively, and compulsively (1–8).

The common key symptom in all of these disorders is the failure to resist an impulse or temptation to control an act or specific behavior (1, 3, 9), which is ultimately harmful to oneself or others and interferes in major areas of life functioning (1, 3, 6, 10, 11).

The American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5) included impulse control disorders (ICDs) in the chapter of "Disruptive, Impulse-Control, and Conduct Disorders" as a dysregulation of self-emotional and behavioral control (8).

ICDs have recently been sub-classified as ICD groups and ICD-related disorder (ICDs-RD) groups (1, 3, 6, 7).

The major symptoms of ICDs include pathological gambling (PG), hypersexuality (HS), compulsive buying/shopping (CB) and binge eating (BE) (1–4, 8, 9, 12–21).

However, PG was moved from the category of ICDs to a new category of "Substance-Related and Addictive Disorders" in the DSM-5 (1–3, 6, 7), taking into account the similarities to drug addiction (risk factors, clinical features, cognitive changes, neurobiological substrates, and treatment approaches) (2, 6). This modification highlights the variability of reward-driven behaviors (2, 6, 16, 22).

The spectrum of ICDs-RD also includes punding, hobbyism, walkabout, hoarding, and compulsive medication use.

ICDs and ICDs-RD have been included in the behavioral spectrum of non-motor symptoms in Parkinson's disease (PD), leading in some cases to serious financial, legal and psychosocially devastating consequences with a greater impact on the quality of life. Moreover, in recent years we have noticed that PD patients are at increased risk of developing more than one of the major ICDs.

Along these lines, although it is not the focus of the present paper, some authors have suggested that the increased drive or motivation to certain behaviors cannot be harmful but rather beneficial (1). Therefore, it remains under discussion whether artistic productivity or hypercreativity should be included in ICDs or in ICDs-RD, or if it might represent an innate–skill that emerges in PD patients on dopaminergic therapy (8, 12, 13, 23, 24).

COMPONENT ASPECTS

Three main aspects that characterize ICDs groups and ICD-related disorders in relation to reward-driven activities are:

1. The presence of impulsive aspects (lack of forethought or consideration of consequences) (1, 3, 9).
2. The presence of compulsive aspects (repetitive behaviors with a lack of self-control) (1, 3, 9).
3. A negative or harmful behavior to oneself or to others (1, 3, 6).

The four major ICDs include:

Pathological Gambling (PG) characterized by an excessive and uncontrollable "preoccupation with gambling and the excitement that gambling with increasing risk provides" despite financial loss and social problems (3, 7, 22, 25–27). PG was one of the earliest recognized ICDs in PD (3). It was recently moved to the category of "Substance-related and addictive disorders" in the DMS-5, since substance abuse and PG activate brain reward areas and this bears similarities to drug addiction (7, 28).

Hypersexual disorder (HS) included in "The Sexual and Gender Identity Disorders Workgroup" of DSM-5 (7). It could be described as an excessive amount of time consumed by sexual fantasies and by planning for engaging in sexual behavior which interferes with important activities and obligations in ordinary life (3, 7). Other behaviors that might often occur are fetishism and voyeurism (7). As in substance abuse, patients with HS pursue a short-term reward and may develop tolerance and withdrawal-like syndromes (7). This condition is more common among adult men, and it may additionally occur with erectile failure (6, 7, 9, 17, 29).

Binge eating has been included in "Feeding and Eating Disorders" in DSM-5 (3, 6, 7). It is "a persistent disturbance of eating or eating-related behavior that results in the altered consumption of food, which significantly impairs physical health or psychosocial functioning" (7). The specific criteria proposed are:

1. Episodes of recurrent binge eating in the absence of any maladaptive compensatory behaviors.
2. Sense of lack of control over eating during the episodes.
3. Intake, in a discrete period of time (within any 2 h period), of an amount of food that is much larger than most people would eat in a similar period of time under normal circumstances.

The difference between binge eating and bulimia is that the former tends to be fluctuating while the latter is permanent (3, 7).

Compulsive buying (CB) is characterized by a constant urge to buy that leads to senseless contraction of debts with continuous delay of payment until a catastrophe clears the situation. As other ICDs, the repetitive loss of control over spending and the negative emotional state that emerges when not buying resemble substance use disorders (3, 7).

A prevalence of 5.8% in the general population at risk of CB is described (1, 3).

ICD-RELATED BEHAVIORS (ICDs-RD)

ICDs-RD are classified as related behaviors that have a contrast clinical presentation with respect to the four major ICDs. However, the biological link between both conditions may be identified in the dysregulation or inappropriate regulation of the reward pathways in the mesocorticolimbic network (22, 30). ICDs-RD is characterized by repetitive perseverative behaviors that appear to be more closely linked to pulsatile drugs, such as levodopa or intermittent apomorphine therapy rather than dopaminergic agonist (DA) *per se*.

ICDs-RD include the following:

1. Dopamine dysregulation syndrome (DDS) is a drug addiction-like state characterized by a compulsive and excessive desire for use of high potency and short-acting dopaminergic medication (L-dopa, subcutaneous apomorphine) (1–4, 6–8, 12, 13, 15, 17–22, 30, 31). DDS is more frequent in early-onset male PD patients with history of mood disorders and family history of psychiatric disorders (26, 31).
2. Punding is characterized by repetitive, purposeless behaviors and excessive preoccupation with specific items or activities, collecting, arranging or taking objects apart (1–4, 6–8, 12, 15, 17–21, 26, 32). It has been reported to occur frequently in conjunction with DDS (32).
3. Hobbyism pertains to higher-level repetitive behaviors (sports, artistic endeavors) (1, 2, 4, 6, 8, 15, 17–21).
4. Walkabout is excessive aimless wandering (1, 2, 4, 7, 8, 12, 15, 17, 19–21, 26).
5. Hoarding is the acquisition of and failure to discard a large number of items with no objective value (1–4, 6, 7, 12), (8, 15, 18, 21).

EPIDEMIOLOGY

ICD in the General Population

The prevalence of ICDs in the general population, which has been underestimated, shows a wide range with variability according to different populations: from 0.2 to 5.3% (1). This enormous variability may be explained not only by different genetic, ethnic and cultural backgrounds, but also by the

TABLE 1 | Shows the estimated prevalence of each of the four major ICDs.

ICDs	General population	Dominion study ICD subgroup	ICARUS study (at baseline, use QUIP) ICD subgroup	The drug interaction with genes in Parkinson's disease DIGPD study (ICD at baseline)
Total	0.2–5.3%	17.10%	28.6%	19.7%
Age (mean SD)	N/A*	60.2 (8.1)	63.6 ± 9.5	58.5 (8.9)
UPDRS III score (mean SD)		N/A	14.1 ± 5.89	18.8 (9.4)
Cognitive scores MMSE adjusted total score			27.9 ± 1.62	28.4 (1.7)
Disease Duration		7.1 (3.8–10.8)	6.9 ± 5.19	3.1 (1.4)
Median dopamine agonist LEDD		300 mg	N/A	211.1 (118.0)
Median levodopa LEDD associated DA		450 mg		N/A
Median levodopa LEDD without a dopamine agonist		621 mg		263.4 (230.7)
Compulsive Buying	5.8% (2–8)	5.7%	6.5%	4.6%
Pathological Gambling	0.4–1.1%	5%	5.30%	3.9%
Binge eating	2%	4.3%	9.9%	10.5%
Hypersexual disorder	3–6%	3.5%	9.7%	8.5%
References	(1)	(29)	(19)	(33)

N/A: non available or Non applicable.*

instruments used to assess these symptoms in the population (3, 18–20) (**Table 1**).

Although the ICDs were initially reported in PD patients on DA therapies, some studies report the occurrence of ICDs in the general population and in novo PD patients (10, 11, 34). It is still under discussion whether PD biology could be a risk factor for ICDs (35).

ICD in *de novo* PD

As mentioned above, it remains under discussion whether or not PD itself confers an increased risk for developing ICDs (35). Identifying the frequency of this disorder in novo PD patients could contribute to resolving these questions (1). A recent study analyzing data from the Parkinson's Progression Markers Initiative failed to demonstrate an increased risk for the development of ICDs or ICDs-RB in PD patients in the absence of treatment. Nevertheless, some symptoms suggestive of ICD have been reported in 20% of newly diagnosed, untreated PD patients with respect to the appropriately matched controls (36). In recent years, imaging studies have offered relevant insight to this debate (35). However, at the moment, results remain controversial over whether PD itself constitutes a risk factor for the development of ICDS or ICDs-RD (1, 3, 6).

ICDs-RD in PD in Different Populations

ICDRs continue to be under-recognized and under-managed in clinical practice. Determining the true frequency of ICDs in the health population, in PD *de novo* patients, and in PD patients with and without DA agonist therapies in different populations represents a significant challenge since a number of variables must be analyzed, including assessment tools, DA dose, DA formulations, years of disease, as well as cultural and other factors. Moreover, in many cases more than one ICD has been identified (29). In **Table 2** we present a summary of various studies conducted to assess the presence of ICD behaviors over different periods of time and evaluate the risk factors and clinical characteristics.

Assessment Tools

Several instruments have been developed to assess and identify ICD symptoms in PD, some of which are summarized in **Table 3**.

Risk Factors

Several studies have been conducted to identify the risk factors for ICD development in PD patients (8). They include:

+ Demographic: young patient, male gender, unmarried (3–8, 14–21, 24, 27, 29, 59, 60).
+ Treatment related: although ICDs have been reported to be associated to different drugs, such as L-dopa, amantadine and rasagiline, DA intake appears as the major risk factor for ICDs (1–5, 7, 8, 13–15, 17–22, 27, 29, 59, 60).
  Prevalence of ICDs was compared among different DA drugs (pramipexole, ropirinole) and between extended releases or immediate formulations (1, 3, 6, 29, 60). However, controversial findings from preliminary reports suggest that long-acting DA and patch or pump formulations may reduce the risk for ICDs (8, 15, 61).
  It remains under discussion whether there is an association between ICDs and DA dose. The same controversial results were reported regarding DA treatment duration, higher daily dose and DA higher peak dose (3, 7, 29, 60).
+ Personal or family history: history of cigarette smoking, drug abuse, depression, apathy, REM behavior disorders (RBD), tea, coffee and mate consumption, positive personal or family history of alcoholism or gambling, and impulsive or novelty-seeking traits increase the risk for ICDs and their predictors (2–8, 14, 16–18, 29, 59, 60).
+ PD onset and related ICDs: prevalence increases over time, while ICDs tend to occur in the first years of

TABLE 2 | Shows different epidemiologic studies.

References	Study		Type of study	*N* participants		Scales			Age (mean/SD) years		Disease duration (mean/SD) years		Motor scores (mean/SD)		Levodopa or Levodopa equivalent LEED Dopamine agonist L-dopa dose equivalent DA-LEDD		Results
	Name of the study	Geographic Distribution		PD	Controls	Motor	ICDs	Others	PD ICDs	PD non ICDs	PD ICDs	PD non ICDs	PD ICDs	PD non ICDs			
Driver-Dunckley et al. (37)	Initial	United States	Retrospective database	1,884	N/A	H&Y, UPDRS	N/A		57.2 (30-72)	N/A	11.6 (4–22)	N/A	mean H&Y stage 2.5	N/A	Mean dose LEDD 883.4 mg/day	Pramipexole 4.3 mg/day Pergolide 4.5 mg/day	PG can occur as the PD progresses, appears with an increase in DA therapy and resolves reduction
Maia et al. (38)	N/A	Brazil	Case/control study	100	100	UPDRS mHYS	Y-BOCS,	SEADLS	62.2 ± 11.9 Total PD		N/A	N/A	Total UPDRS mean 40.28 ± 20.6		N/A		OCD are NOT MORE frequent in PD patients
Weintraub et al. (29)	DOMINION Study	United States and Canada	Cross-sectional, multicenter	3,090	N/A	H&Y	Massachusetts Gambling Screen, MIDI		60.2 (8.1)	64.4 (7.8)	7.1 (3.8–10.8)	6.5 (3.7–10.6)	2.0 (2.0–2.5) H&Y	2.0 (2.0–2.5) H6Y	Pramipéxole 3.1 mg (SD, 1.7 mg) and LEDDs 306.9 mg (SD, 168.2 mg) Ropirinole 11.1 mg (SD, 6.6 mg) and LEDDs 277.9 mg (SD, 164.9 mg) Pergolide 2.9 mg (SD, 1.7 mg) and LEDDs 286.6 mg (SD, 169.3 mg)		DA treatment in PD is associated with 2- to 3.5-fold increased odds of having an ICD
Joutsa et al. (59)		Finland	Cross-sectional.	575	N/A		South Oaks Gambling Screen, QUIP,	BDI.	64 (range 43–90) total PD		6 (<1–29) years Total PD		N/A	N/A	Total L-Dopa was 561 (26–3,230) mg DA LEDD was 160 (105–210) mg		There is a high proportion of patients with PD with ICDS. Prevalence of PG in PD is 7 times higher than general population. Depression associated with all ICDS.
Sarathchandran et al. (39)		India	Case/control study	305	234	H&Y UPDRS	MIDI, DSM IV, BIS, BDI	Eysenck personality inventory; Anxiety and Depression Scale, PDQ-39	54.6 ± 9.9	59.6 ± 9.8	8.2 ± 4.9	7.3 ±4.8	H&Y ON 2.0 ± 0.5 UPDRS-III ON 18.7 ± 9.2	H&Y in ON 1.9 ± 0.5 UPDRS-III ON 18.5 ± 8.8	PD without ICD LEDD: 448 ± 280 mg; L-Dopa:326.2 ± 31.9 mg PD with ICD LEDD: 590 ± 364.8 mg; L-Dopa: 373.4 ± 68.5 mg		Revealed a relatively higher frequency of ICD-RBs	

(Continued)

TABLE 2 | Continued

References	Study		Type of study	*N* participants		Scales			Age (mean/SD) years		Disease duration (mean/SD) years		Motor scores (mean/SD)		Levodopa or Levodopa equivalent LEED Dopamine agonist L-dopa dose equivalent DA-LEDD	Results
	Name of the study	Geographic Distribution		PD	Controls	Motor	ICDs	Others	PD ICDs	PD non ICDs	PD ICDs	PD non ICDs	PD ICDs	PD non ICDs		
Rodríguez-Violante et al. (40)		Mexico.	Case/control study	300	150	MDS-UPDRS H&Y	QUIP-RS		58 ± 14.1	63 ± 12.5	N/A	N/A	MDS-UPDRS part III 31 ± 15.9; H&Y: 2.2 ± 0.6	MDS-UPDRS part III 32.8 ± 17; H&Y 2.3 ± 0.8	PD with ICD group LEDD 638 ± 448.5 mg; DA-LEDD: 147.4 ± 123.3 mg PD without ICD LEDD: 561.3 ± 417.4 mg; DA-LEDD: 97.1 ± 124.9 mg	ICD significantly more frequent in PD than controls subjects. lower overall frequency and distinct pattern of ICDs related with socioeconomic differences
Ramírez Gómez et al. (5)		Argentina, Colombia, Ecuador	Multicenter. Structured Clinical Interview. cross-sectional	255	N/A	UPDRS; H&Y	QUIP, QUIP-RS; CISI-PD		58.6 (SD, 11.11)	N/A	4	10	Mean UPDRS 10	Mean UPDRS 33	N/A	ICD in Latin American PD > Anglosaxon population
Rizos et al. (41)		UK, Spain, Denmark and Romania	Multicenter Retrospective and prospective survey based on medical records and clinical interviews.	425	N/A	H&Y	NMS Questionnaire		62.7 (42–85)		7.0 (0–24)	N/A	H&Y: 3.0 (1.0–5.0)	N/A	N/A	Relatively low rate of ICDs with long-acting or transdermal DAs.
Vela et al. (17)		Spain	Multicenter study, Cross-sectional, case/control study	87	87	UPDRS; H&Y	QUIP	BID, EuroQol, PDQ-39	48 (44–52)	46 (42–52)	7 (3–11)	3 (1–10)	Mean UPDRS III: 16 (10–22); H&Y:2 (2–2)	Mean UPDRS III 17 (11–24); H&Y 2 (1–2)	LEDD 300 (0–600) mg DA LEDD 210 (99–300) mg	ICBs are much more prevalent in early onset PD patients vs. health controls Associated with DA intake, depression and a worse QoL
Erga et al. (20)	Norwegian ParkWest Study	Norway	Multicenter Cross-sectional study, Semistructured Clinical interviews, cases and controls	125	159	UPDRS; H&Y	QUIP	MMSE, Stroop test, Semantic verbal fluency test, CLVT-II, VOSP, NPI, MADRS, Epworth Sleepiness Scale (PDSS-2	67.9 (7.7)	71.4 (9.8)	7.4 (1.6)	7.4 (1.9)	H&Y: 2.2 (0.5); Mean UPDRS III: 23.8 (10.5)	UPDRS motor score 22.7 (10.6). H&Y: 2.2 (0.6)	PD without ICD LEDD: 408.7 ± 266.7 mg; DA LEDD:289.5 ± 150.0 PD with ICD LEDD: 505.2 ± 279.1; DA LEDD: 293.7 ± 132.4	Patients with PD treated with DA, have increased odds of having ICBs compared with age- and gender-matched controls.

(Continued)

TABLE 2 | Continued

References	Study		Type of study	*N* participants		Scales			Age (mean/SD) years		Disease duration (mean/SD) years		Motor scores (mean/SD)		Levodopa or Levodopa equivalent LEED Dopamine agonist L-dopa dose equivalent DA-LEDD	Results
	Name of the study	Geographic Distribution		PD	Controls	Motor	ICDs	Others	PD ICDs	PD non ICDs	PD ICDs	PD non ICDs	PD ICDs	PD non ICDs		
Biundo et al. (42)	ALTHEA study	Italy	Multicenter	251	N/A	H&Y, UPDRS; UDysRS	QUIP-RS; BDI	MoCA; BDI-II	ICD-RBs below cut-off 66.5 6 10.2 ICD-RBs above cut-off 63.5 6 9.9	67.2 ± 9.4	ICD-RBs below cut-off 52.7 ± 61.1 (months); ICD-RBs above cut-off 148.0 ± 64.5 (months)	140.2 ± 68.21 (months)	ICD-RBs below cut-off UPDRS III: 11.9 ± 7.1 ICD-RBs above cut-off UPDRS III: 12.2 ± 7.4	UPDRS III: 11.8 (6.9)	No ICD-RBs LEDD 971.0 6 ± 401.1 mg; DA-LEDD 147.0 6 ± 162.7 mg ICD-RBs above cut-off LEDD 1,016.4 6 ± 418.3 mg; DA-LEDD 133.1 ± 129.0 mg	>50% of PD patients with dyskinesia have ICDs and RBDs. Severity is associated with Dopaminergic therapy total dose
Zhang et al. (4)		China	Xin Hua Hospital	142		H&Y, UPDRS, the scale for freezing of gait	QUIP.	MMSE, NMS, RBDQ-HK, HAMA, HAMD, PDQ- 39	65.55 ± 7.43	69.67 ± 8.16	7.76 ± 5.90	5.22 ± 5.23	Mean UPDRS: 20.18 ± 11.56; H&Y: 2.32 ± 0.99	Mean UPDRS: 18.93 ± 12.82; H&Y: 2.21 ± 0.77	Total LEDD, mg PD without ICD:329.82 ± 340.65 mg PD with ICD: 522.06 ± 412.46 mg	ICD and RBD commonly found in Chinese PD patients. Independent factors associated with ICRDs: Earlier onset, dose of DA, severe cognitive impairment; dyskinesia.
Antonini et al. (19)	ICARUS Study	Italy	Prospective, non-interventional, multicenter	1,069 DA alone L-Dopa alone L-Dopa + DA		H&Y, UPDRS	mMIDI; QUIP	NMSS, PDSS-2, PD-CRS, PDQ-8, BDI-II, FAB and three items of NPI-3: delusions, hallucinations and apathy/ indifference.	63.6 ± 9.5	66.6 ± 9.3	6.9 ± 5.19	5.8 ± 4.92	H&Y: 2.0 ± 0.70; Mean UPDRS III: 14.1 ± 5.89	H&Y:2.0 ± 0.63; Mean UPDRS III: 14.2 ± 7.09	N/A	Prevalence of ICD was relatively stable throughout the 2-years follow-up. No differences between patients receiving DAs and those on L-Dopa. No differences between PD with or without ICD in motor symptoms severity and cognitive function.

(Continued)

TABLE 2 | Continued

References	Study		Type of study	*N* participants		Scales			Age (mean/SD) years		Disease duration (mean/SD) years		Motor scores (mean/SD)		Levodopa or Levodopa equivalent LEED Dopamine agonist L-dopa dose equivalent DA-LEDD	Results
	Name of the study	Geographic Distribution		PD	Controls	Motor	ICDs	Others	PD ICDs	PD non ICDs	PD ICDs	PD non ICDs	PD ICDs	PD non ICDs		
Corvol et al. (33)	DIGPD	France	Multicenter, face to face semistructured interviews.	411	N/A	MDS-UPDRS (parts I-IV) H&Y	MDS-UPDRS part I	Mini-Mental State	58.5 (8.9) at Baseline	63.3 (9.8) at Baseline	3.1 (1.4) at Baseline	2.5 (1.5) at Baseline	Mean UPDRS III: 18.8 (9.4)	Mean UPDRS III: 20.5 (10.5)	Baseline NO ICD LEDD 235.7 ± 181.1; DA-LEDD: 145.0 ± 99.1 ICD LEDD:263.4 ± 230.7; DA-LEDD: 211.1 ± 118.0	5-years cumulative incidence of ICDs ≈46%. ICDs: strongly associated with DA use and dose-effect.

Anxiety and Depression Scale; BDI-II, Beck Depressive Inventory; CISI-PD, Clinical Impression of Severity Index for Parkinson's Disease; CLVT-II, California Verbal Learning Test II; Epworth Sleepiness Scale; Eysenck personality inventory. FAB, Frontal Assessment Battery; H&Y, Hoehn & Yahr stage; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MADRS, Montgomery and Asberg Depression Rating Scale; Massachusetts Gambling Screen; MDS-UPDRS; mH&Y, modified Hoehn & Yahr stage; mMIDI, modified versión of the Minnesota Impulsive Disorders Interview; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NMSS, Non-Motor Symptom Scale; NPI-3, Neuropsychiatric Inventory; PD-CRS, Parkinson's Disease-Cognition Rating Scale; PDQ-39, 39-item Parkinson's Disease Questionnaire; PDQ-8, Parkinson's Disease Questionnaire-8 items; PDSS-2, Parkinson's Disease Sleep Scale-2; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale; RBDQ-HK, REM Sleep Behavior Disorder Questionnaire Hong Kong; SEADLS, Schwab and England Activities of Daily Living Scale; South Oaks Gambling Screen; UDysRS, Scale Unified Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; VOSP, Visual Object and Space Perception Battery; Y-BOCS, Yale Brown Obsessive Compulsive Scale; LEDD, L-dopa-equivalent daily dose; DAED, dopamine agonist-equivalent daily dose; DA, Dopamine Agonist; ICD, impulse control disorders; RBDs, Related Behavior Disorders.

the disease. Early PD onset and the presence of motor complications of PD may predict a higher risk for ICDs (4–8, 13, 14, 16–18, 21, 24, 29, 60).

+ Cultural factors: it remains to be determined if cultural factors may increase the risk for ICDs and ICRDs. Some authors suggest that cultural factors probably contribute not only to the prevalence of ICD but also the type of ICD (7, 17). One classic example in this field was provided by the DOMINIO study that suggests that living in the United States of America may be an independent risk factor for ICD development (1, 6, 29).
+ Deep Brain Stimulation (DBS): the relationship between ICDs and DBS remain under discussion. Initial studies reported improvement in ICDs after DBS, while subsequent studies showed ICD exacerbation (1, 6, 22, 60, 62).

  DBS of the subthalamic nucleus (STN) is an effective, widely used treatment for motor fluctuations or disabling dyskinesias in PD (63).

  STN-DBS has been identified as an independent risk factor for ICRDs; however, the reduction of dopamine agonist dosage after STN-DBS could improve or decrease ICD occurrence (6, 7, 22, 60, 62).

  On the other hand, several studies suggest that DBS may contribute to impulsivity, excessive reward seeking and ICDs. Consistent with this hypothesis, PD patients without ICDs showed impulsive decision making when DBS is turned on (7, 60, 62, 64).

  To explain these controversial findings, it has been hypothesized that STN stimulation plays a role in dynamic aspects of impulse and inhibitory control (22, 60).
+ Personality, Neuropsychiatric symptoms and Cognition in ICDs: a higher level of neuroticism, ineffective coping skills, and lower levels of agreeableness and conscientiousness in PD patients with ICDs has been reported (3). Early onset PD patients constitute a high risk population for ICDs with a self-assertive/antisocial and reserved personality and somatization traits (22).

  A large constellation of comorbid affective symptoms and behavioral traits have been reported in PD with/or at risk for ICDs including depression, anxiety, novelty seeking, impulsivity symptoms and anhedonia (2, 62, 65, 66). Interestingly, in PD patients with ICDs, apathy could be noticed during withdrawal from dopamine replacement therapy (DRT). Impulsivity and apathy are two major comorbid syndromes of PD that may represent two extremes of a dysexecutive and behavioral spectrum involving dopamine-dependent cortico-striato-thalamo-cortical networks (64).
+ Cognition: controversial data have been identified in cognitive battery tests between PD patients with and without ICD (8, 36); the first group presents values lowered in some tests that evaluate the frontal lobe, but did not find significant differences in executive functioning (14, 67). Cognitive flexibility and ability to plan is altered in patients with ICD (8). Visuo-spatial working memory and reward-punishment learning impairments have been reported in different studies; however, many results could not be replicated (6, 17).

TABLE 3 | Assessment tools.

Tools	Objectives	Brief description	Translated into other languages other than English		Self-administered		References
			Yes	No	Yes	No	
Questionnaire for impulsive-compulsive disorders in PD (QUIP)	To screen ICRDs in PD patients.	Most commonly used, validated, self-report screening tool to assess ICDs	+ German, Italian		+		(43)
QUIP rating scale (QUIP-RS)	To screen ICDs in PD patients	Rates severity of the ICDs and provides a measure of change over time	+ German, Italian, Spanish		+		(44), (45, 46)
Minnesota Impulsive Disorders Interview (MIDI)	To assess the degree of impulsivity related to compulsive behavior	A questionnaire to assess the presence of impulsive–compulsive behaviors associated to dopamine replacement therapy in PD.		+		+	(47–49)
Dopamine Dysregulation Syndrome-Patient and Caregiver Inventory (DDS-PC)	To screen ICRDs in PD patients	Questionnaire to assess the presence of several ICD behaviors associated to DDS in PD, for both self-report and caregiver's report, to uncover eventual discrepancies.		+	+		(50)
Movement disorders Society UPDRS, included a single item for DDS	Not valid as an assessment tool for ICDs	The MDS-UPDRS contains questions/evaluations, divided in three domains scoring 18 items of motor, behavior and daily activities		+	+		(51)
Barrat Impulsiveness Scale (BIS)	To assess impulsivity in PD patients.	High reliability and high predictive validity to assess high risk behaviors including symptoms of conduct disorders, attention deficit disorders, substance abuse and suicide attempt.	+ Brazilian Portuguese, Spanish, dialectal Arabic		+		(52–55)
Ardouin scale of behavior in Parkinson's disease	To assess neuropsychiatric features in PD patients	Specifically designed for asses mood and behavior, quantifying changes related to Parkinson's disease, to dopaminergic medication, and to non-motor fluctuations		+		+	(56)
Structured Clinical Interview for Obsessive-Compulsive Spectrum Disorders (SCID-OCSD)	To determine the presence of a range of ICDs.	A structured clinician-administered interview for the diagnosis of putative OCSDs		+		+	(57)
Parkinson's Impulse Control Scale (PICS)	To rate severity of ICD in PD patients.	A brief, clinician-rated screening tool that assess the intensity and impact of a wide range of ICBs common in PD		+		+	(58)

QUIP, Questionnaire for impulsive-compulsive disorders in PD; QUIP-RS, QUIP rating scale; MIDI, Minnesota Impulsive Disorders Interview; DDS-PC, Dopamine Dysregulation Syndrome-Patient and Caregiver Inventory; BIS, Barrat Impulsiveness Scale; SCID-OCSD, Structured Clinical Interview for Obsessive-Compulsive Spectrum Disorders; PICS, Parkinson's Impulse Control Scale.

TABLE 4 | We present the genetic factors reported to be related to ICDs.

Receptor types	Genotype	Associations	References
Dopamine	DRD1rs4867798, rs4532, rs265981	Increased risk of ICDs PD: punding and hobbyism behaviors, ICDs Non-PD: ICDs, neuropsychiatric disease, problem gambling, addiction, and cognitive functioning in non-PD population	(9, 71, 72)
	DRD2 Taq1A Dopamine transporter (DAT1)	No association	(9)
	DRD2/ANKK1 rs1800497	Increased risk of ICDs	(9, 16, 65, 71)
	Dopa decarboxylase (DDC) rs 3837091; rs 1451375	Stronger predictor f ICDs	(16)
	D3Rp.S9G	ICDs and levodopa-induced dyskinesias Stronger predictor of ICDs	(2, 5, 6, 9, 18, 21, 65, 73)
Glutamate	Grin2B rs7301328	Increased risk of ICDs	(2, 5, 6, 9, 16, 71)
Monoamine Transporters	COMT gene Val158 Met	No association	(9, 65)
	COMT rs4646318	No association	(9)
Opioid	OPRK1 rs702764	Stronger predictor f ICDs	(9, 16, 65, 72)
Serotonine	Hydroxytryptamine receptor HTR2A rs6313	Stronger predictor f ICDs	(2, 6, 8, 9, 16, 18)

Interestingly, patients with ICDs showed a more immediate reward response and greater choice impulsivity leading to increased risk behavior (6).

When the cognitive performance was compared according to the type of ICD it was found that patients with HS showed greater general cognitive impairment, including lower performances on learning tests and were more impaired on the Stroop test and memory tasks than were patients with PG (8, 68). However, another study found no differences in the executive functions of patients with PD and PG (69).

+ Genetics: genetic factors have been involved in ICDs in PD. Although heritability was estimated to be 57%, consensus remains a challenge and data need to be replicated in large cohorts from different populations (16). A large number of single nucleotide polymorphisms (SNP) in dopaminergic, glutamatergic, serotonergic, and opioid neurotransmitter systems has been reported as a candidate that improved predictability of ICDs when compared with clinical risk factors (2, 6, 9, 16, 21, 70). Recently, an association of OPRM1 rs1799971 was identified, a gene encoding the mu opioid receptor with ICDs. This gene is central to pain control as well as drug reward and addictive behaviors (70).

In **Table 4** we present the genetic factors reported to be related to ICDs.

Interestingly, the ICARUS study, the largest prospective observational study in an Italian population, contributes to the identification of additional risk factors that include non-motor symptoms (mood and sexual function), mood symptoms (depression), sleep disorders and a low level of quality of life (19).

+Other Risk Factors

Recently, the overexpression of ΔFosB, a transcriptional regulator involved in addiction induced by drugs of abuse and in many types of compulsive behaviors has been reported to be associated with L-dopa induced dyskinesia and to be triggered by pramipexole (60).

The ΔFosB overexpression was identified in the nucleus accumbens (NA) and the striatum (brain regions important for addiction) of healthy and DA-lesioned rats exposed to pramipexole and found to be NMDA receptor dependent. These findings suggest that enhanced ΔFosB expression may represent the strongest predictor of PD patients at risk of ICDs (27, 60).

PATHOPHYSIOLOGY

Although an extensive number of studies have focused on the pathophysiologic mechanisms of ICDs in PD, these remain to be clarified (2, 9). Classically, the appearance of impulsivity in PD has been attributed to neuronal dopaminergic degeneration, facilitating ICD occurrence in dopamine replacement therapies (8).

Nevertheless, in recent years, evidence has suggested a complex multifactorial mechanism beyond the dopaminergic corticostriatal networks, including a complex serotoninergic and noradrenergic interaction. Further investigation is required (9).

DOPAMINERGIC THEORY

Dopaminergic receptors, Dopamine 1 receptor 1 (D1R) (D1 and D5) and Dopamine 2 receptor (D2R) (D2, D3, D4) types possess contrasting roles with inhibitory and excitatory signaling, respectively. These contrasting roles are present not only in the nigro-striatal pathway but also in the mesolimbic and mesocortical circuits. The pathways link cortical and subcortical regions [prefrontal cortex (PFC), ventral striatum, VTA and amygdala]; both circuits are implicated in reward learning and executive decision making or reinforcement behaviors, respectively (6, 22, 74).

TABLE 5A | Structural MRI.

Study objectives	Participants			Results	References
	PD ICD/RBDs	PD No ICD/RBDs	Controls		
To demonstrate morphometric changes	X	X	X	No significant changes PD + ICD vs. PD-ICD	(83)
To measure brain cortical thickness and subcortical volumes, and to assess their relationship with presence and severity of symptoms, in PD patients with and without ICDs.	x	x	x	In ICD+: Significant cortical thinning in right superior orbitofrontal, left rostral middle frontal, bilateral caudal middle frontal region, and corpus callosum and reduced volume in right accumbens and increase in left amygdala in ICD	(84)
To identify Neuroanatomical abnormalities in PD patients with PG	Pathological Gambling (PG)	X	X	Gray matter loss in bilateral Orbitofrontal-cortex in PD-PG vs. PD-CNTR correlated with increase of gambling symptoms in PD-PG	(85)
To assess brain structural and functional alterations in patients PD-ICB vs. controls and PD no-ICB	x	x	x	Cortical thinning in left pre-central and superior frontal cortices, as well as decreased FA of the left uncinate fasciculus and parahippocampal tract; increased mean, radial and axial diffusivity of the left parahippocampal tract and right pedunculopontine tract; increased mean and radial diffusivity of the genu of the cingulate cortex and right uncinate fasciculus.	(86)
To assess whether a functional dysregulation of the habenula and amygdala (modulators of the reward brain circuit), contributes to PD punding.	X Punding	x	x	Cortical thinning of right inferior frontal gyrus compared to controls and PD-without punding	(87)
To investigate structural abnormalities in mesocortical, limbic cortices and subcortical structures in PD ICDs.	x	x	x	Volume loss in the nucleus accumbens of PD patients. PD-ICD showed significant increased cortical thickness in rostral anterior cingulte cortex and frontal pole compared to PD-without ICD. Increased cortical thickness in medial prefrontal regions in PD-ICD	(88)
To determine morphometric changes as predictors of ICB in de novo PD	x	x	x	No significant morphometric changes in PD-ICD and PD-without ICD before and after onset of ICD.	(89)
To better understand the neural basis of ICDs in PD	x	x	x	PD-ICD patients showed a reduced gray mater volume in External Globus Pallidus compared to PD-without ICD	(90)
To investigate gray matter (GM) and cortical thickness (CTh) changes in PD with and without ICDs.	x	x	x	Increased cortical thickness in anterior cingulate cortex, orbitofrontal cortex in PD-ICD.	(91)
Morphometric Changes in PD punding patients	Punding	X	X	Significant cortical thinning in dorsolateral prefrontal cortex in PD-punding. Cortical thinning in PD-punders localized in prefrontal cortex extending into orbitofrontal cortex.	(92)

Modified by: Ramdave et al. (81) and Meyer et al. (82).

Anatomical regions involved in ICDs:

1. Planning and judgment areas: caudal orbitofrontal cortex, ventromedial prefrontal cortex (PFC).
2. Reward system: ventral striatum (VS-nucleus accumbens [NA]).
3. Conditioned responses and emotional processing: amygdala.
4. Medial dorsal and anterior nucleus of the thalamus (6, 75).

In PD with ICDs a marked decrease ventrostriatal D3R-binding has been reported, while experimental PD models have shown an increase in DA levels in the NA associated to bilateral nigrostriatal DA denervation (64, 76). These findings, of a diminished striatal D2/D3 receptor level and an increase in mesolimbic DA tone, lead to an imbalance in the cortico-accumbens network implicated in reward signaling and behavioral changes (64, 77, 78). Moreover, the dopaminergic mesocorticolimbic system provides a role for shift behavior in response to changing stimulus-reward contingencies (64).

In this scenario, the tonic "overdosed" by D2/D3 receptor agonists in the mesocorticolimbic circuit could contribute to suppress, through the impairment of top-down inhibitory control from prefrontal cortical area (PFC) inputs to the

TABLE 5B | Diffusion-tensor images.

Study objectives	Participants			Results	References
	PD ICD/RBDs	PD No ICD/RBDs	Controls		
To assess brain white matter tract alterations in PD+ punding vs. controls and PD ICD, and PD non-ICD	PD + Punding	PD Punding –	X	Greater damage of genu of corpus callosum and left pedunculopontine tract in PD-punding vs. PD-without ICD	(93)
To assess brain structural and functional alterations in patients with PD-ICB vs. with controls and PD no-ICB cases.	x	x	x	Cortical thinning in left pre-central and superior frontal cortices, as well as decreased Fractional anisotropy (FA) of the left uncinate fasciculus and parahippocampal tract; increased mean, radial and axial diffusivity of the left parahippocampal tract and right pedunculopontine tract; increased mean and radial diffusivity of the genu of the cingulate cortex and right uncinate fasciculus.	(86)
To determine the changes in DTI associated with medication-related ICD in PD patients undergoing chronic dopamine-replacement therapy.	x	x	x	PD-ICD showed significantly elevated FA in anterior cingulate cortex (ACC), right internal capsule posterior limbs, right posterior cingulum, and right thalamic radiations compared to PD-without ICD	(92)
To identify alterations of white matter tract in drug-naïve PD-ICDs	x	x	x	Decreased connectivity in left and right cortico-thalamic tract, left and right cortico-pontine tract, left and right corticospinal tract, left and right superior cerebellar peduncle and left and right middle cerebellar peduncle between PD-ICD compared to PD-without ICD. Decreased connectivity in left and right inferior longitudinal fasciculus, genu and body of corpus callosum, left and right corticospinal tract, left superior cerebellar peduncle and left and right cingulum in PD-ICD compared to control.	(94)

Modified by: Ramdave et al. (81) and Meyer et al. (82).

ventral striatum, reward-related learning and induce compulsive, perseverative behavior through the direct D1 receptor pathway (6, 9, 22).

Dopaminergic agonists (DA) show a high D3R affinity in the mesolimbic system (6, 7, 9, 60). In effect, DA therapy, acting on the depleted dorsal striatum (involved in the sensory-motor circuit) and a relatively intact ventral striatum, induces a reduction of inhibitory response and impulse control by the reduction of activity in the lateral orbitofrontal cortex, the rostral cingulated zone, the amygdala, and in the external pallidum (6, 7). Therefore, PD patients on DA are not only at high risk for ICDs but also demonstrate greater choice impulsivity, shorter reaction time and increased risk taking (6, 79).

The D1 receptor family localize in the direct pathway of reward-based behaviors. Stimulation increases the activity of striatal projections to the nucleus accumbens/ventral striatum, while D2 receptors elicit suppression of the cortico-accumbens network (6, 22, 80).

NEUROIMAGING IN PD PATIENTS WITH ICDS

In recent years neuroimaging, particularly that which is focused on the dopaminergic system, has significantly contributed to the knowledge of neurobiological factors for ICDs (2, 7, 8, 81, 82) (see **Tables 5A–D**).

STRUCTURAL AND FUNCTIONAL MAGNETIC RESONANCE IMAGING

1. Structural MRI changes have been reported in PD patients with ICDs with a selective atrophy in the orbitofrontal and anterior cingulate cortices (areas involved in behavioral modulation). Atrophy in the orbitofrontal cortex has been reported in PD patients with ICDs (85, 91).
2. Functional brain resonance (fMRI) studies have reported an abnormal metabolism on the frontostriatal and cingulate cortices, the nucleus accumbens and the amygdala (2, 120).
3. A connectivity dysfunction between the striatal and limbic areas has been proposed. Brain connectivity was impaired in PD patients with ICDs with respect to the PD individuals without ICDs involving the neurocognitive network. A decreased connectivity has been identified in the central executive networks (mediofrontal areas, anterior cingulate and para-cingulate cortices), while an increased connectivity has been identified in the salience network (limbic-paralimbic network) and in the default mode network (pre-cuneus and posterior cingulate, bilateral inferior-lateral-parietal and ventromedial frontal cortices) (95, 97).

Single photon emission computed tomography (SPECT) of the dopamine transporter (DAT).

DAT regulates dopamine turnover. A reduced DAT binding in PD patients with PG and ICDs has been identified in PD patients

TABLE 5C | Resting state and Task-based fMRI.

Study rationale	Participants			Ligand	Results	References
	PD ICD/RBDs	PD No ICD/RBDs	Controls			
RESTING-STATE fMRI						
To identify corticostriatal connectivity (especially between ventral striatum and cortical limbic regions) in PD ICDs	X	X	X	Resting state	Significant functional disconnection between left anterior putamen and both left inferior temporal gyrus and left ACC, in PD-ICD	(95)
To investigate functional alterations in PD ICB+; vs. controls and PD no ICB	X	X	x		Increased functional connectivity of bilateral pre-central and post-central gyrus in PD-without ICDs vs. control and PD-ICD. Increased functional connectivity in left frontoparietal and visual network positively correlated with ICD duration	(86)
To assess whether a functional dysregulation of the habenula and amygdala (modulators of the reward brain circuit), contributes to PD punding	Punding	X	x		Higher functional connectivity of habenula and amygdala with thalamus and striatum bilaterally, and lower connectivity between bilateral habenula and left frontal and pre-central cortices in PD-punding vs. PD-without ICDs and control. Lower functional connectivity between right amygdala and hippocampus in PD-punding vs. PD-without ICD.	(87)
To investigate differences in both affective and sensorimotor striatal circuitries between PD ICD, PD-No ICDS and association with impulsive behavior	X	X	N/A		PD-ICD compared to PD-without ICD: Stronger connectivity between left putamen and central operculum, left caudate and occipital fusiform gyrus and various cerebellar regions, left Globus Pallidus internali and left superior temporal gyrus, left subthalamic nucleus(STN) and left caudate, parietal and temporal areas. Weaker connectivity between left GPe and various frontal cortical areas, left STN and various frontal areas, parietal area and paracingulate, middle frontal gyrus and subcortical areas.	(90)
To investigate brain network connectivity at baseline in a cohort of drug-naive PD patients who successively developed ICDs over a 36-month follow-up period compared with patients who did not.	Drug Naive PD		X		Increased baseline connectivity in subtantia nigra (SN) and decreased baseline connectivity in default mode network and central executive network in PD patients who develop ICD after chronic dopaminergic treatment compared to those who did not	(96)
To investigate intrinsic neural networks connectivity changes in PD with and without ICD.	X	X	x		Increased connectivity in salience network and default mode network and decreased connectivity in central executive network in PD-ICD. Increased connectivity in salience network positively correlated with ICD symptom severity.	(97)
TASK-BASED fMRI						
To identify differences in CBF responses to DA in mesocorticolimbic regions in PD patients with and without ICD	X	X	N/A	On/Off state	Increased CBF in bilateral striatum, SN, periaqueductal gray matter, insular cortex, and ventromedial prefrontal cortex in PD-ICD compared to PD-without ICD. Increased CBF in bilateral VS in PD-ICD in ON state vs. OFF state.	(98)
To identify dysfunctional brain reward networks in PD- Dopamine dysregulation síndrome (DDS)	DDS	X	N/A	ON and OFF medication states. Drug-related visual stimuli. Drug Effects Questionnaire	Exposure to drug-cues increase subjective feeling of being "ON" during both "ON" and "OFF" medication scans, which corresponds to significantly increased activation in ventral striatum (VS) in PD-DDS.	(99)

(Continued)

TABLE 5C | Continued

Study rationale	Participants			Ligand	Results	References
	PD ICD/RBDs	PD No ICD/RBDs	Controls			
To demonstrate that DA treated PD patients with ICDs have increased functional connectivity between the ventral striatum and components of the limbic striato-pallido-thalamocortical loop and additionally to explore amygdala connectivity with reward network components.	X	X	N/A	Incentive learning task with "gain" and "loss" conditions. ON and OFF medication states	Elevated ventral striatal connectivity to anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), insula, putamen, globus pallidus and thalamus in PD-ICD patients compared to PD-without ICD. No difference in connectivity seen between ON and OFF medication scans. Ventral striatum to subgenual ACC connectivity positively correlated with reward learning performance.	(100)
To demonstrate a link between hypersexuality in PD and increased processing in brain regions linked to sexual motivation and cue reactivity	Hypersexuality (PD-HS)	X	N/A	Visual stimuli presented of sexual, other-reward related and neutral cues. ON and OFF medication states	Increased sexual desire correlated with enhanced activation in VS, cingulate and OFC in PD-HS when ON medication.	(101)
To quantify resting cerebral blood flow (CBF) and blood oxygenation level dependent (BOLD) fMRI to measure neural responses to risk taking during performance on the Balloon Analog Risk Task (BART).	X	X	N/A	Balloon Analog Risk Task	Significantly reduced BOLD activity in right ventral striatum during all risk taking trials and significantly reduced resting CBF in right ventral striatum, in PD-ICD	(102)
To demonstrate that DA would be associated with faster learning from gain outcomes along with greater ventral striatal positive δ activity in PD ICDs vs. PD without ICDs	X	X	X	Probabilistic reward learning task. ON and OFF medication states.	Greater left OFC activity in PD-DD patients compared to PD-without ICD. PD patients in the ON state compared to OFF state learn faster from gain outcomes during the task along with greater ventral striatal activity to unexpected rewards.	(103)
To demonstrate that DA would be associated with greater risk taking and lower ventral striatal activity in PD with ICD vs. PD without ICD	X	X	X	Risk task with "Gain" and "Loss" condition. ON and OFF medication states.	ON state associated with lower bilateral ventral striatal activity compared to the OFF state in patients with ICD with the reverse finding in PD control group. Greater correlation between BOLD activity and risk in PD-ICD compared to PD-without ICD in bilateral ACC and caudate, and left OFC.	(104)

Modified by: Ramdave et al. (81) and Meyer et al. (82).

TABLE 5D | PET and SPECT Studies.

Study objectives	Participants			Ligand	Results	References
	PD ICD/RBDs	PD No ICD/RBDs	Controls			
PET						
To evaluate l-dopa induced dopamine neurotransmission in the striatum of patients with DDS compared with PD control patients.	Dopamine dysregulation syndrome (DDS)	x	N/A	[11C] raclopride (D2/D3-affinity)	Greater reduction in ventral striatal binding potential in DDS (14.4%) vs. control (3.6%). Positive correlation with L-DOPA wanting but not liking	(105)
To investigate the effects of reward-related cues and L-dopa challenge in patients with PD ICD; and PD without ICD on striatal levels of synaptic dopamine	x	x	N/A		Greater reduction in ventral striatal binding potential following task in ICD (16.3%) vs. control (5.8%).	(106)
To compare dopaminergic function during gambling in PD patients, with and without pathological gambling (PG), following dopamine agonists.	PD-PG	x	N/A		Greater reduction in ventral striatal binding potential during task in ICD (13.9%) vs. PD control (8.1%)	(107)
(1) To investigate dopamine neurotransmission in PD patients with multiple ICDs, single ICDs and non-ICD controls in response to reward-related visual cues. (2) To compare clinical features of the above three groups.	Single ICD Multiple ICDs	X	N/A		Greater reduction in ventral striatal binding potential in single (17.19%) and multiple ICD (17.51%) vs. control (6.47%). No significant difference between ICD groups	(108)
To investigate whether ICD in PD are associated with greater D3 dopamine receptor availability	x	x	x	[11C]-(+)-PHNO (D3-affinity	Greater reduction (20%) in ventral striatal binding potential in ICD vs. non-ICD.	(109)
To investigate the role of extrastriatal dopaminergic abnormalities in PD patients with PG	Gambling (PD-PG)	X	N/A	[11C] FLB-457 (Extra-striatal D2/D3 affinity)	Greater reduction in midbrain binding potential in PG vs. control during gambling. Increase in binding potential in ACC in PG vs. control in control task	(110)
To investigate the possible involvement of the mesostriatal and mesolimbic monoaminergic function in ICDs associated with PD	x	X	N/A	[18F] F-Dopa	Increased binding potential (35%) in medial orbitofrontal cortex in ICD vs. control PD without ICD.	(111)
To investigate DA-induced changes in brain activity that may differentiate patients with PD with DA-induced PG) from PD without PG	PD-Gambling (PG)	X		H2(15)O [Regional cerebral blood flow (rCBF)]	Significant reduction in rCBF in left lateral orbitofrontal cortex, right rostral cingulate zone, right amygdala, left ventral anterior external pallidum in PG, while controls showed increased rCBF in these areas for ON vs. OFF phase scans.	(112)
To investigate the extrastriatal dopaminergic neural changes in relation to the medication-related ICDs in PD.	X	x	x	[18F]FP-CIT (DAT density/PET)	Increased binding potential in right ventromedial prefrontal cortex, left insular and right posterior cingulate cortex and reduced binding potential at left nucleus accumbens, ventral striatum and ventral pallidum, in ICD vs. non-ICD.	(113)
To describe the metabolic PET substrate and related connectivity changes in PD ICDs.	X	X	N/A	[18F] FDG	Increased glucose metabolism in right middle and inferior temporal regions in PD-ICD compared with PD-CNTR. Higher metabolism in these areas in patients with multiple ICDs vs. single ICD	(114)
SPECT						
To investigate resting state brain perfusion in PD patients with active PG compared with PD controls and healthy controls.	PG X	X	X	[123I]FP-CIT (DAT density/SPECT	Reduced DAT binding in right ventral striatum (nucleus accumbens) of PD-PG compared to PD-CNTR	(115)

(Continued)

TABLE 5D | Continued

Study objectives	Participants			Ligand	Results	References
	PD ICD/RBDs	PD No ICD/RBDs	Controls			
To assess presynaptic dopaminergic function	X	X	x		Reduced tracer binding in the ventral striatum of PD patients with PG compared to PD controls	(116)
To assess striatal dopamine transporter (DAT) density in PD ICD	X	X	N/A		Lower DAT binding in right striatum with trend in ICD.	(117)
To follow-up data from medication-naïve PD patients who underwent dopamine transporter SPECT imaging at baseline and were subsequently treated with DA replacement therapy.	PD-Drug Naïve and subsequently treated with dopaminergic therapy		N/A	[123I]FP-CIT (DAT density/SPECT	11 patients developed ICD symptoms after DRT. PD-ICD patients had lower DAT availability in right ventral striatum, anterior-dorsal striatum and posterior putamen compared to control	(118)
To assess cortico-striatal connectivity in PD ICDs	X	X	N/A		Significant reduction in tracer uptake in left putaminal and left inferior frontal gyrus in PD-ICD vs. PD without ICDI.	(119)
To investigate resting state brain perfusion in PD PG compared with matched PD controls and healthy controls.	X	X	X	99mTc-ECD (rCBF/SPECT)	PD-PG showed a disconnection between the ACC and the striatum, which was not observed in PD patients without PG and HC groups.	(115)

Modified by: Ramdave et al. (81) and Meyer et al. (82).

with ICD compared to PD patients without ICD or healthy controls. This reduced binding of DAT has been suggested as a potential biomarker for risk of developing ICD symptoms (2, 36, 60). The binding reduction was not uniformly reproduced in different studies: some reported a reduction in right ventral striatum (2, 102), while others in the left putamen and left inferior frontal gyrus. These data could reflect a mesolimbic projection and frontostriatal disconnection, suggesting a vulnerability or maladaptive synaptic plasticity under non-physiological DA stimulation (2).

POSITRON EMISSION TOMOGRAPHY (PET) WITH 11C-RACLOPRIDE

Positron emission tomography (PET) neuroimaging with 11C-raclopride explores the DA fluxes within the basal ganglia. The 11C-raclopride is a reversible binding to the post-synaptic D2/3 receptor that competes with endogenous DA (2, 8, 22, 106, 107). Decreased 11C-raclopride binding is an indirect measure of increased endogenous dopamine release or "hyperdopaminergic state."

A significant reduction of 11C-raclopride binding has been reported in ventral striatum, but not in dorsal striatum, in PD with ICDs (single or multiple) as compared to PD individuals without ICDs, following generic reward-related vs. neutral visual stimuli.

A more selective radioligand [18F]fallypride, with high affinity D2-like receptors (D2/D3 receptors) confirmed a reduced binding within the VS and putamen (121).

All of these findings contribute to support a mesocorticolimbic imbalance in PD with ICDs (108).

PD- ICDs TREATMENT

The first approach for ICD is prevention, and a key element is patient and family education concerning potential risks of different dopaminergic therapies. Physicians should be aware of predisposing risk factors and balance cost/benefit before DA prescriptions, excluding genetic factors and taking into consideration clinical findings, such as young age, early PD onset, lengthy disease duration, personal history of addictive behaviors, male gender, short-acting DA drugs, behavior and mood disorders (apathy, depression), DBS and certain cultural factors that require attention before prescription.

When ICDs appear, treatment continues to be a challenge. Individualized treatment must be conducted, identifying potential variables, such as motor status, comorbidities, other non-motor symptoms and quality of life (27, 122, 123).

The relevance of prevention is supported by NICE guidance that includes written information, or verbal information recorded in writing, at DA initiation of treatment. The authors emphasize the relevance of communicating to patients, relatives and carers the risk of ICDs due to the potential impact on their lives and for early detection (124).

The first approach for the treatment of ICD symptoms is the reduction or discontinuation of DAs. However, it should be

considered that neuropsychiatric traits may persist for at least 12 weeks after drug withdrawal (60, 61, 123).

Nonetheless, in certain cases this strategy is not feasible, and some patients are at risk of developing DA withdrawal syndrome and worsening motor symptoms (21, 61, 123).

Although animal PD models have identified serotonin (5HT) depletion as a higher risk for impulsivity and risk behaviors, the serotonin reuptake inhibitors (SSRIs) used to treat ICDs had controversial results (22, 123).

Atypical antipsychotics, such as clozapine and quetiapine have been used to treat ICDs in PD, but no randomized trials have been conducted and evidence is limited (2, 7).

Taking into consideration that specific SNP opioid receptors have been identified as stronger risk factors for ICDs, opioid antagonists employed in the treatment of PG have produced controversial results (naltrexone, nalmefene) (2, 7, 16, 22, 60, 123).

A number of drugs administered to increase Gabaergic inhibition (valproate, topiramate), as well as new drugs to preserve ventral striatal DA system (zonisamide, donepezil, noradrenaline reuptake inhibitor) have been essayed (2).

As previously mentioned, controversial data are available concerning DBS and ICD treatment. A favorable response through reduction in dopaminergic requirements has been noted. It has been suggested that STN stimulation could reduce the risk for ICDs by increased reward-driven behaviors by inhibitor effect in the indirect dopaminergic pathway. However, some patients may develop transient de novo ICDs after STN DBS, and selective patients may develop ICDs a long time after DBS (123, 125).

A non-pharmacologic approach includes cognitive behavioral therapy and patient and caregiver education (7, 60).

CONCLUSIONS

The treatment used for PD, particularly DA, is associated with the development of ICDs and related behaviors. Susceptibility to these disorders depends on the associated risk factors.

ICDs can have serious personal, family, psychosocial, financial, and medical consequences. However, in contrast, artistic activities have been described in patients with PD while undergoing treatment with DA. These patients are compulsive but report a positive influence on quality of life.

These findings highlight the need for a very critical approach at the moment of Dopaminergic Replacement therapy choice.

AUTHOR CONTRIBUTIONS

EG: study concept, design, and editing. VA: study concept and editing of manuscript.

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