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Functional imaging studies of Impulse Control Disorders in Parkinson's disease need a stronger neurocognitive footing

Garance M Meyer ^{1 *}

Charlotte Spay ^{1 *}

Chloé Laurencin ^{2,3}

Bénédicte Ballanger ²

Guillaume Sescousse ⁴

Philippe Boulinguez ^{1 **}

1- *Université de Lyon, Université Claude Bernard Lyon 1, Lyon Neuroscience Research Center, INSERM, U 1028, CNRS, UMR 5292, Action Control and Related Disorders team, F-69000, Lyon, France.*

2- *Université de Lyon, Université Claude Bernard Lyon 1, Lyon Neuroscience Research Center, INSERM, U 1028, CNRS, UMR 5292, Neuroplasticity and Neuropathology of Olfactory Perception team, F-69000, Lyon, France.*

3- *Service de Neurologie C, Centre Expert Parkinson, Hôpital Neurologique Pierre, Wertheimer, Hospices Civils de Lyon, Lyon, France*

4- *Université de Lyon, Université Claude Bernard Lyon 1, Lyon Neuroscience Research Center, INSERM, U 1028, CNRS, UMR 5292, PsyR2 team, F-69000, Lyon, France.*

**** Corresponding author:**

Philippe Boulinguez

Centre de Recherche en Neurosciences de Lyon

95 boulevard Pinel, 69500 Bron, France

Phone: +33 4 72 13 89 78

Email: philippe.boulinguez@univ-lyon1.fr

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* *Co-first author:* C. Spay and G. Meyer contributed equally to this work. Thus, the authors wish to be regarded as joint First Authors.

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1. Introduction

Impulse control disorders (ICDs) include pathological gambling, hypersexuality, compulsive eating and compulsive shopping (Cilia and van Eimeren, 2011; Weintraub et al., 2015). ICDs are common in Parkinson's disease (PD) (Antonini et al., 2017; Weintraub et al., 2010) and affect from 13.6% to 46% of patients (Corvol et al., 2018; Weintraub et al., 2010), with potentially dramatic consequences such as huge financial losses or disintegration of family relationships (Dodd et al., 2005). Recent reviews focusing on the neurochemical and pharmacological underpinnings of ICDs have made it abundantly clear that they are associated with dopaminergic dysfunction and treatment (Aracil-Bolaños and Strafella, 2016; Cilia and van Eimeren, 2011; Corvol et al., 2018; Jiménez-Urbieto et al., 2015; Marques et al., 2018; Probst and van Eimeren, 2013; Voon et al., 2017; Vriend, 2018; Weintraub et al., 2015). As a consequence, the management of ICDs involves mainly discontinuing or decreasing dopamine agonists, with the risk of worsening motor symptoms or developing dopamine agonist withdrawal syndrome (Connolly and Fox, 2014; Samuel et al., 2015). This lack of satisfying therapeutic strategy for handling ICDs calls for a better understanding of the underlying mechanisms (Antonelli et al., 2011; Cilia and van Eimeren, 2011).

1.1 *The major contribution of molecular imaging studies*

ICDs have many similarities with substance abuse and are increasingly being conceptualized as behavioral addictions (Aracil-Bolaños and Strafella, 2016; Leeman and Potenza, 2012; Ray and Strafella, 2013). Notably, in the DSM-V (<http://www.dsm5.org>) gambling disorder has been included in “substance-related and addictive disorders”. This change reflects the similarity in clinical symptoms, as well as the fact that gambling activates similar brain reward-related regions as of drugs of abuse (but see Kardefelt-Winther et al., 2017 for a critical discussion of the conceptualization of behavioral addiction). The evidence underlying this insight on PD-ICDs pathophysiology mostly come from molecular imaging studies (Aracil-Bolaños and Strafella, 2016). The state of the art has been

thoroughly reviewed elsewhere (Aracil-Bolaños and Strafella, 2016; Callesen et al., 2013; Jiménez-Urbieto et al., 2015; Marques et al., 2018; Voon et al., 2017; Vriend, 2018; Vriend et al., 2014b; Weintraub and Claassen, 2017) and is summarized schematically in Figure 1. While dopaminergic treatment allows restoring pathological dopaminergic (DA) activity in the dorsal striatum with subsequent benefits on the motor system, it would lead to uncontrolled activation of the reward system whose pivotal structure is the less damaged ventral striatum. This DA “overdose” of ventral striatal-cortical circuitry would induce increased sensitization to reward cues and abnormal reward seeking (Steeves et al., 2009; Weintraub, 2008). Molecular imaging has been essential to delineate the whole network impacted by this hyper-dopaminergic state, and to understand the interactions between neurotransmitters, transporters and receptors of the dysfunctional DA system (Aracil-Bolaños and Strafella, 2016). It has become clear from PET studies that ICDs are associated with low ventral striatal D2/D3 receptor availability (e.g., Steeves et al., 2009), with low dopamine transporter (DAT) expression in ventral striatum (e.g., Cilia et al., 2010) and with low midbrain dopamine autoreceptor function (Ray et al., 2012). These dopaminergic changes have respectively been associated with altered transmission of reward signals, compensatory downregulation and increased sensitivity to rewards. However, molecular imaging studies have limitations. First, available studies have mostly focused on the dopaminergic system. Yet, there are some clues indicating that non-dopaminergic dysfunctions may contribute to PD-ICDs (Callesen et al., 2013; Napier et al., 2015; Vriend, 2018). Second, available studies have mostly focused on the reward system. Yet, a wealth of research indicates that impulsivity and compulsivity are non-unitary traits mediated by various psychological and neural mechanisms beyond those underlying reward processing (Antonelli et al., 2014; Dalley et al., 2011; Nombela et al., 2014). Third, PET does not allow the identification of the specific neural mechanisms that are potentially dysfunctional in ICDs, since it cannot disentangle the time-course of numerous concurrent activations. Thus, although available molecular imaging studies have provided major theoretical and therapeutic insights by associating clinical symptoms to dysregulation of DA neurotransmission, they

cannot draw a clear and complete picture of the potential neurocognitive dysfunctions leading to PD ICDs.

1.2 The neurocognitive footing of ICDs

Entering the neurocognitive “black box” represents the opportunity to separate different possible sources of dysfunction, to evaluate their respective dependency on the DA system (or on other systems), and their respective contribution to the surfacing behavioral signs and verbal reports of patients on which clinical diagnosis is based. Although challenging to translate into clinical practice (Ekhtiari et al., 2017; Lo et al., 2015), recent developments in the understanding of the distinct psychological, neural and neurochemical mechanisms of decision making and impulsivity have proven useful for the study and treatment of certain neuropsychiatric disorders such as substance use disorders, obsessive-compulsive disorder (OCD) or attention deficit hyperactivity disorder (Bari and Robbins, 2013; Dalley and Robbins, 2017; Fineberg et al., 2014; Robbins et al., 2012; Robbins, 2017; Chamberlain and Robbins, 2013; Cuthbert and Insel, 2013). In PD, it may be useful for instance to evaluate the susceptibility of patients to develop a drug-induced ICD prior to the onset of treatment on the basis of neurocognitive markers (e.g., Nombela et al., 2014; Santangelo et al., 2017). Similarly, identifying the genetic underpinnings of ICDs in PD and the neurocognitive endophenotypes accounting for comorbidities and commonalities across disorders (Napier et al., 2015; Robbins et al., 2012) may help uncover new therapeutic opportunities (e.g., targeting ICDs with noradrenergic agents: Kehagia et al., 2014; Rae et al., 2016).

Recent reviews and modeling studies based on neuropsychological approaches (Dawson et al., 2018; Nombela et al., 2014; Santangelo et al., 2017) have highlighted two important points about the cognitive correlates of PD ICDs. First, the fact that ICDs in PD are multidimensional (e.g., Nombela et al., 2014; see also Napier et al., 2015). Second, the fact that cognitive dysfunctions associated with ICDs are heterogeneous and difficult to identify (e.g., Dawson et al., 2018), especially when cognition

is only measured by means of global neuropsychological batteries (Santangelo et al., 2017). It comes out of these reviews that ICDs reflect dysfunctions in various aspects of decision making and motivation involving the reward system (choice impulsivity), but also possibly in various aspects of motor and executive control (action impulsivity). Dysfunctions in the control of value- or reward-based responding can be due to irrational preference for small, immediate rewards versus larger but delayed rewards –i.e. temporal discounting-, irrational estimation of probabilistic gains –i.e. probabilistic discounting-, or irrational ill-timed decision without adequate accumulation and consideration of available evidence –i.e. reflection impulsivity. Dysfunctions of motor and executive control could rely on clusters of mechanisms related to response conflict/interference processing, time estimation and response inhibition (Nombela et al., 2014). More broadly, the neurocognitive correlates of drug-induced ICDs in PD might also depend on affective states, apathy and depression (Dawson et al., 2018; Vriend et al., 2014b). It is a major issue to identify more precisely the neurocognitive dysfunctions potentially involved in addiction in general (Ekhtiari et al., 2017) and in ICDs in particular (Napier et al., 2015). For instance, as revealed by a meta-analysis from Santangelo and colleagues (2017), persistence of an impulsive and maladaptive behavior in people with PD could depend on executive dysfunction (set-switching) rather than on the rewarding nature of decision-making. This is in line with the broader idea that vulnerability to stimulant addiction may depend on an impulsivity endophenotype (Dalley et al. 2011; Miller et al., 2018; Ray and Strafella, 2013). However, the corresponding ensemble of cognitive processes and discrete deficits in defined neural systems still needs to be precisely identified in PD ICDs.

Here, we provide a critical perspective on the current state of this endeavor, informed by a systematic review of the functional imaging studies examining the brain mechanisms that differentiate PD patients with ICDs from those without ICDs. The hope is that neural-based evidence will reduce the heterogeneity and confounds observed in neuropsychological and behavioral approaches. Indeed, psychological functions are overlapping concepts that integrate, and sometimes share, a variable

number of computational processes. Functional neuroimaging has the potential to provide access to finer-grained mechanisms, and to identify common denominators and discrepancies across psychological functions. This aspect has been only peripherally tackled in most recent reviews (Dawson et al., 2018; Santangelo et al., 2017), and is the central topic of our analysis below.

----- Insert Figure 1 about here -----

2. Neurocognitive bases of ICDs in PD: Current state of knowledge

We performed a systematic review of the functional neuroimaging studies assessing the neural correlates of PD-ICDs. Molecular imaging studies centered on DA neurotransmission and reward (Figure 1) were excluded from the analysis because their scope was considered too narrow with regards to the present goal of surveying all potential neurocognitive mechanisms underlying ICDs (see above).

2.1 Methods

Literature selection

We searched the Web of Science and Pubmed databases on 11/10/2018 using the keywords “impuls* AND Parkinson” combined with “fMRI” OR “PET” OR “imaging” OR “blood flow” (and all variants of these terminologies). Additionally, we used “gambl*” instead of “impuls*” as pathological gambling (PG) is often studied alone. The inclusion criteria for this review were:

- 1) PET regional cerebral blood flow (rCBF) or fMRI studies,
- 2) Including PD patients with current ICDs (ICDs+),
- 3) Including a control group comprised of PD patients without ICDs (ICDs-),
- 4) Reporting at least one of the two contrasts ICDs+ > ICDs- and ICDs- > ICDs+.

The exclusion criteria were:

- 1) Review articles,

- 2) Conference abstracts,
- 3) Animal studies,
- 4) Case reports,
- 5) Metabolism or neurotransmission PET studies.

A flow chart summarizing the literature and search and selection can be found in Figure 2.

Data extraction

Selected papers (n=14) were scrutinized to extract the following information:

- 1) Characteristics of the clinical groups

This includes the number of subjects, the ICD subtypes, the treatment status, as well as the clinical scores on the MIDI (Minnesota Impulsive Disorders Interview), QUIP-RS (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale) or SOGS (South Oaks Gambling Screen).

- 2) Neuroimaging methods

The neuroimaging methods used to characterize dysfunctional neural activity were categorized as a function of:

- The neuroimaging tool used and the nature of the signal captured.
- The data processing method used to infer neural activity (functional connectivity, block design, event-related design).

- 3) Characteristics of the behavioral task and targeted neurocognitive functions

Assessing the neural bases of ICDs consists in associating clinical symptoms with changes in cognitive processes and discrete deficits in specific neural systems. This can rely on different strategies:

- Linking clinical symptoms to global and non-specific brain activity changes in defined neural systems (e.g., identifying the modulations of functional connectivity at rest that account for a clinical score of impulsivity within the reward circuitry).
- Isolating neurocognitive mechanisms of interest through specific behavioral designs, and associate event-related brain activity changes that differ between ICD+ and ICD- patients (e.g., identifying the brain regions showing abnormal gambling cue-induced activation in PD patients with pathological gambling (PG) vs without PG).

In order to characterize the strategies used by the authors, we extracted the following information: the theoretical rationale, the neurocognitive mechanism of interest, the behavioral task used to isolate it, and the brain regions of interest.

4) Results

The clinical, behavioral and neuroimaging main results were extracted for each study.

2.2 Results

Literature selection

298 records were identified through database searching, including 88 duplicates. Among the 210 uniquely identified studies, 196 were excluded based on our inclusion/exclusion criteria. The remaining 14 studies (corresponding to 15 experiments) were included (Figure 2).

----- Insert Figure 2 about here -----

Systematic review of selected studies

Detailed results are presented in Table 1. Studies are referenced with numbers, from #1 to #14.

----- Insert Table 1 about here -----

1) Characteristics of the clinical groups

Seven studies did not select a specific ICD subtype, while four focused on pathological gambling, **two** on pathological gambling and compulsive buying and one on hypersexual patients. Studies included on average 15.0 ± 7.3 ICDs+ and 18.6 ± 12.8 ICDs-. **Three** studies reported QUIP-RS scores (ICDs+= 31.5 ± 8.3 ; ICDs-= 19.0 ± 0.1) and one reported MIDI scores (ICDs+= 6.8 ± 3.2 , ICDs-= 0.4 ± 0.5). **Five** studies (**#6,8,10,11,14**) investigated the interaction between medication (ON vs OFF dopamine **replacement therapy**) and group (ICDs+ vs ICDs-).

2) Neuroimaging methods

Eleven studies used fMRI, two used SPECT imaging, and one used PET. Most experiments (**#1-9a**) recorded resting state data, while **five** of them recorded task-related activity **using** block-designs (**#11-13**) or event-related designs (**#9b-10**). The last study (**#14**) reported activations based on computational modelling.

3) Characteristics of the behavioral tasks and targeted neurocognitive functions:

Nine experiments searched for alterations of intrinsic activity in ICDs+. Among these experiments, four formulated no a priori hypotheses about specific psychological dysfunctions or brain regions (**#1-4**), using for instance SPECT rCBF or ICA to separate independent components corresponding to (dys)functional brain networks. **Four studies** searched for alterations of intrinsic activity specifically in the mesocorticolimbic system of ICDs+, assuming dysfunction in the reward

system, but without probing it directly by means of a behavioral task (#5-6, #8-9a). The last one focused on affective and sensorimotor striatal circuitries based on the rationale that both can contribute to impulsivity (#7).

Six experiments used task-based imaging. Among these experiments, three used block-designs, assessing cue-induced motivation in PD patients with pathological gambling (#13) or hypersexuality (#12), or assessing risk taking by means of a computerized card selection task (#11). Two experiments used event-related designs focusing on risk taking by entering risk level as a linear parametric modulation of the hemodynamic response function (HRF) triggered by the stimuli or the behavioral responses of the subjects (#9b-10). One study used computational modelling to probe incentive value and prediction error signals in a probabilistic gain and loss learning task (#14).

4) Results

Mean clinical scores and main behavioral results are displayed in Table 1. Neuroimaging results are reported in Table 1 and summarized in Figure 3. Abnormal activity or abnormal functional connectivity were found in a widely distributed, poorly replicable network including the limbic system, the sensorimotor network, the visual network, the default mode network, the attentional network, the cerebellum, the striatum and numerous prefrontal areas.

----- Insert Figure 3 about here -----

2.3 Discussion

Three main results emerge from this review. First, and surprisingly given the scale of the problem and the total number of papers on the topic (922 articles in PubMed at the time of writing using the keywords Impuls* AND Parkinson), very few studies (N=14) have examined the functional

brain correlates of PD-ICDs according to our criteria (Figure 2). This, in addition to the heterogeneity of the methods employed, prevents us from performing any quantitative meta-analysis. Second, results are largely inconsistent, as illustrated in Figure 3. Third, among selected studies, only a few have targeted specific neurocognitive mechanisms by combining appropriate behavioral tasks and event-related analyses (Table 1). As a result, it is difficult to extract a clear and coherent picture from this literature.

Even the abnormalities in mesocorticolimbic circuits in PD-ICDs predicted by current neurobiological hypotheses (Aracil-Bolaños and Strafella, 2016; Callesen et al., 2013; Voon et al., 2017; Vriend, 2018; Vriend et al., 2014b) present an overall lack of consensus about their location and direction (Figure 3). Even in comparable studies and brain regions, the comparison of ICDs+ vs. ICDs- reveals inconsistent results showing either decreased or increased activity/functional connectivity. The most striking example is the ventral striatum. Most fMRI resting state studies seem in agreement with molecular imaging studies targeting the DA system, in the sense that they report increased activity/connectivity in the ventral striatum of ICD+ patients (4 hyperactivity pattern against 1 hypoactivity pattern). However, functional studies based on task-related activations report as many decreases (Rao et al., 2010; Voon et al., 2010) as increases (Frosini et al., 2010; Politis et al., 2013) in activity. This might suggest that the hyperactivation pattern of the ventral striatum accounts for motivational aspects guiding sexual and gambling disorders (as specifically tested by Frosini et al., 2010 and Politis et al., 2013), but not for risk-taking or incentive learning (as specifically tested by Rao et al., 2010 and Voon et al., 2010). More generally, this reminds us that the uncontrolled DA activation of the ventral striatum measured at rest in medicated patients developing ICDs+ (as tested in 8 out of the 12 molecular imaging studies identified in Figure 1) does not represent a direct marker of increased functional activation of the ventral striatum for all the neurocognitive mechanisms that this key structure contributes to. Unfortunately, given the small number of available studies, further functional imaging investigations are warranted to disentangle the cognitive mechanisms whose

dysfunction actually 1) accounts for ICDs and 2) is due to, and not just co-occurs with, ventral striatum DA overdose.

Additionally, inconsistent results are observed in numerous spots of the large mesocorticolimbic circuit, and beyond. Abnormal activity or abnormal functional connectivity were found in a widely distributed, poorly replicable network including the limbic system, the sensorimotor network, the visual network, the default mode network, the attentional network, the cerebellum, the striatum and numerous prefrontal areas. In other words, in contrast to our hope to find common denominators between studies, the present analysis did not identify a reliable brain map of ICDs (Figure 3). This further underlines that there are still numerous unanswered questions about ICD-related abnormalities, both within and outside the reward system (Aracil-Bolaños and Strafella, 2016; Napier et al., 2015). It is for instance unlikely that there exists a single common reward system. It is more probable that there are reward type-dependent brain structures (Sescousse et al., 2013) that would explain part of the observed variability. It is even possible that increased sensitivity to rewards or troubles computing the experienced value of rewards are not always the most important triggers of impulsive actions. Incentive salience (cue-triggered ‘wanting’, Lades, 2012) can induce impulsive choices of smaller sooner rewards instead of larger later rewards regardless of the nature or value of these rewards. Furthermore, it is well known from studies outside the field of PD that a variety of action control mechanisms (including in particular different processes of motor response inhibition) are dysfunctional in impulsivity and addiction (Bari and Robbins, 2013; Dalley and Robbins, 2017). Similar dysfunctions could play a direct, substantial role in PD ICDs, as suggested by recent investigations (Antonelli et al., 2011; Kehagia et al., 2014; Nombela et al., 2014; Ye et al., 2015). This could account for some ICD-related brain activity changes in sensorimotor, prefrontal, default mode and basal ganglia networks highlighted in the present analysis. However, knowledge about the neural bases of action impulsivity in PD ICDs is still largely incomplete and requires direct assessment for each single mechanism. Finally, there are also strong comorbidity issues related to cognitive or

affective disorders that are likely to blur the overall picture (Dawson et al., 2018; Ekhtiari et al., 2017; Goerlich-Dobre et al., 2014; Jaakkola et al., 2014; Santangelo et al., 2017; Vriend et al., 2014b; Weintraub and Claassen, 2017). In sum, without overlooking the influence of demographic/clinical confounders in neuroimaging studies (e.g., clinical stage, age at onset of PD, disease duration; Ekhtiari et al., 2017; Santangelo et al., 2017) and common problems of imaging (heterogeneous data processing and paradigms, sample size, etc), it seems that improving neurofunctional analyses requires a more careful consideration of the cognitive functions of interest.

3. The need for a stronger neurocognitive footing

The existing literature on the neural bases of PD-ICDs faces challenges of consistency and validity (e.g., Ekhtiari et al., 2017), but has nonetheless provided important theoretical and therapeutic insights. In particular, it now seems obvious that ICDs have no unitary explanation. It is therefore necessary to disentangle and identify the neural and neurochemical bases of each potentially dysfunctional process underlying ICDs. This constitutes a prerequisite towards understanding the interactions among different functional networks and distinguishing causes, correlates and individual susceptibility factors of PD ICDs.

To this aim, a stronger neurocognitive footing is necessary. There are important confounds in the available literature because psychological functions are conceptual and flexible constructs that integrate a variable number of computational processes. The only way to control the involvement of these processes is to use sophisticated psychological (i.e., neurocomputational) models in combination with sophisticated behavioral tasks. Various behavioral protocols have been developed and are now used routinely in clinical investigations to define subcomponents of impulsivity in other pathologies. Examples are Temporal Discounting and probability discounting tasks assessing different aspects of impulsive choice, Stop Signal Reaction Time and Go-NoGo tasks assessing different aspects of response inhibition, Choice Serial Reaction Time tasks assessing premature responding, etc (Dalley

and Robbins, 2017; Napier et al., 2015; Voon et al., 2017). These protocols have been used in the study of Obsessive Compulsive Disorders, Attention Deficit Hyperactivity Disorder and Substance Use Disorders (Fineberg et al., 2014; Voon, 2014). It is very surprising that only a few studies on PD-ICDs (N=6) have combined standard behavioral protocols with neuroimaging methods targeting precisely the underlying psychological processes. The majority of the available studies rather searched for non-specific correlates of ICDs clinical scores. However, neither the MIDI (Minnesota Impulsive Disorders Interview; Christenson et al., 1994), the QUIP (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; Weintraub et al., 2009), or the BIS-11 (Barratt Impulsiveness Scale-11; Patton et al., 1995) provide clinical scores that reflect the multidimensional nature of impulsivity in terms of dysfunctional neurocognitive mechanisms (Ekhtiari et al., 2017). This calls for more neuroimaging research using event-related fMRI or electromagnetic recordings for their potential to provide access to fine-grain processes, provided that advanced and valid psychological models are used for design and interpretation. In that sense, the main limitation of the approach we are promoting is the inherent limit of cognitive work in humans. There are conflicting models and the use of one or another may lead to conflicting results with the risk of introducing even more confusion in clinical investigations (e.g., Ballanger et al., 2009). However, combining brain activity recordings with appropriate behavioral tasks precisely allows testing the physiological plausibility of the underlying psychological models (e.g., Criaud et al., 2017; Criaud and Boulinguez, 2013), which neuropsychological batteries or purely behavioral studies cannot achieve. To that extent, any future improvement, refutation or enrichment of a psychological model will provide an opportunity for neuroimaging studies to further disentangle actual confounds in clinical research.

Separating all possible sources of dysfunction may be highly valuable in uncovering new therapeutic opportunities. This might help clarifying the complex link between PD-ICDs and DA dysfunction and treatment (e.g., Antonelli et al., 2014), and might open possible perspectives for the major issue of non-DA therapeutic solutions in PD (Fox et al., 2008; Fox, 2013). For instance, recent

work on the neural and neurochemical bases of response inhibition has identified the key role of the noradrenergic (NA) system (Albares et al., 2015b; Chamberlain et al., 2009, 2006; Chamberlain and Robbins, 2013; Chamberlain and Sahakian, 2007; Robbins and Arnsten, 2009; Spay et al., 2018). Other clues point to the involvement of the serotonergic (5HT) system (Dalley and Robbins, 2017; Eagle et al., 2008; Paterson et al., 2012). Dysfunction of specific inhibitory processes in PD patients with ICDs might thus be treated with NA or 5HT pharmacological agents (Kehagia et al., 2014; Rae et al., 2016; Ye et al., 2015, 2016). To illustrate how entering into detailed neural mechanisms of response control can be fruitful, let's mention the case of proactive inhibitory control, a central mechanism controlling the initiation of response, that has recently been modeled in healthy subjects (e.g., Criaud et al., 2017, 2012; Jaffard et al., 2008, 2007; Wardak et al., 2012). The function of this gating mechanism is to lock movement initiation processes in order to avoid automatic responses to external or internal stimuli in uncertain contexts, or when the situation requires saving time to settle on the best option. A dysfunction of this basic motor inhibitory mechanism can induce not only action impulsivity, but also choice impulsivity. Its neural substrates involve brain regions that have been identified in many of the studies reviewed here (supplementary motor area, medial prefrontal cortex, precuneus, striatum, subthalamic nucleus). Using appropriate behavioral protocols and brain recordings, it has been possible to demonstrate the alteration of this pivotal mechanism in PD and the associated dysfunction of the NA system (Albares et al., 2015b; Ballanger et al., 2009; Ballanger et al., 2014; Criaud et al., 2016; Spay et al., 2018). Based on this insight, a phase 2 clinical trial testing the efficacy of clonidine for the treatment of ICDs in PD is currently running (ClinicalTrials.gov Identifier: NCT03552068). This is a potentially promising approach, that would avoid fiddling with the dopaminergic treatment, and thus reduce the risk of worsening motor symptoms or developing dopamine agonist withdrawal syndrome (Samuel et al., 2015).

Nonetheless, another key source of confusion arises from the fact that all these neurocognitive processes strongly interact (e.g., Antonelli et al., 2011; Antonelli and Strafella, 2014; Bari and

Robbins, 2013; Criaud and Boulinguez, 2013; Dalley and Robbins, 2017; Robbins et al., 2012). This means that identifying each possible dysfunction independently of all others by means of specific behavioral protocols will not be enough. The next step should consist in assessing interactions between processes, trying to build mechanistic models **integrating** possible sources of dysfunction leading to ICDs **and states favoring the development of ICDs**. The identification of sources **and modulators** is a prerequisite for future studies which will then have the opportunity to implement computational approaches to understand these interactions. In this effort, electroencephalography (EEG) may be useful. First because EEG provides a direct measure of brain activity, by contrast with blood flow imaging (Logothetis, 2008). Second because EEG has the necessary temporal resolution for distinguishing processes that are close in time. Third because EEG offers high functional discrimination power by means of spectral analyses. Indeed, distinct cortical functions are expressed in distinct frequency bands (Albares et al., 2015a; Siegel et al., 2012). Since recent methods now offer efficient source separation and localization solutions, EEG is certainly a highly suitable tool for future neurocomputational investigations of the multidimensional system supporting various forms of impulsive **and compulsive behaviors** (Albares et al., 2015a).

4. Conclusion

There is much to gain from incorporating strong psychological models **and methods** into clinical and neuroimaging studies of PD-ICDs. Indeed, PD-ICDs are multidimensional and remain difficult to understand thoroughly by simply linking global clinical scores to overall changes in brain activity or connectivity with paradigms that do not allow the targeting of specific neurocognitive mechanisms. A lot of work still needs to be done to explore more efficiently the possible ways in which pioneering studies in the field may help managing ICDs in PD. In this respect, identifying patients at high risk **of developing drug-induced ICDs** is of tremendous importance. As inspired by extensive investigations in psychiatric conditions (Bari and Robbins, 2013; Dalley and Robbins, 2017; Robbins

et al., 2012) neurocognitive subtypes could be differently associated with the DA, NA and 5HT systems. Characterizing ICDs-related neurocognitive dysfunctions using more sophisticated behavioral paradigms and brain activity recordings might thus offer the possibility to improve personalized therapeutic pharmacological approaches.

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Figure legends

Figure 1: Molecular imaging findings in PD-ICDs. This literature provides important insights on PD-ICDs etiology by revealing various dopaminergic alterations in ICDs+ compared to ICDs- (see Aracil-Bolaños and Strafella, 2016; Vriend, 2018; Weintraub and Claassen, 2017 for extensive reviews). At the postsynaptic level, lower D2/3 dopamine receptor (D2/3r) availability in the ventral striatum was demonstrated using [11C]Raclopride during performance of a gambling task (Steeves et al., 2009), exposure to reward-related cues (O’Sullivan et al., 2011; Wu et al., 2015) but also at baseline (Steeves et al., 2009). One study showed lower D3r availability in the ventral striatum in ICDs+ using [11C]-(+)-PHNO (Payer et al., 2015). These observations are consistent with higher endogenous DA release or higher DA tone in the ventral striatum, i.e., a “hyperdopaminergic state”. Yet, this could also reflect reduced D2/3r density or more pronounced DA degeneration. One study using [11C]-FLB-457 found greater D2/3r availability in the anterior cingulate cortex (ACC) in ICDs both at rest and during a gambling task, possibly due to lower DA tone or increased D2/3r expression. There was also a lower gambling-induced change in D2/3r availability in the midbrain, where auto-receptors dominate, suggesting impaired homeostatic control over striatal DA release (Ray et al., 2012). At the presynaptic level, lower DAT availability in the striatum (Premi et al., 2016; Voon et al., 2014), and more specifically in the ventral striatum (Cilia et al., 2010; Lee et al., 2014) is a consistent finding in [123I]-FP-CIT SPECT studies. This is often interpreted as reduced striatal DAT levels rather than advanced degeneration, since reduced striatal DAT levels better account for the hyperdopaminergic state observed in [11C]Raclopride studies (Dreyer, 2014; Steeves et al., 2009; Voon et al., 2014). These alterations have been shown to predate ICD development in retrospective (Vriend et al., 2014a) and prospective studies (Smith et al., 2016). Abnormalities of extrastriatal DAT availability were also identified in two studies (Lee et al., 2014; Premi et al., 2016) in the ventromedial prefrontal cortex (vmPFC), the posterior cingulate cortex (PCC), the insula and the inferior frontal gyrus (IFG). Finally,

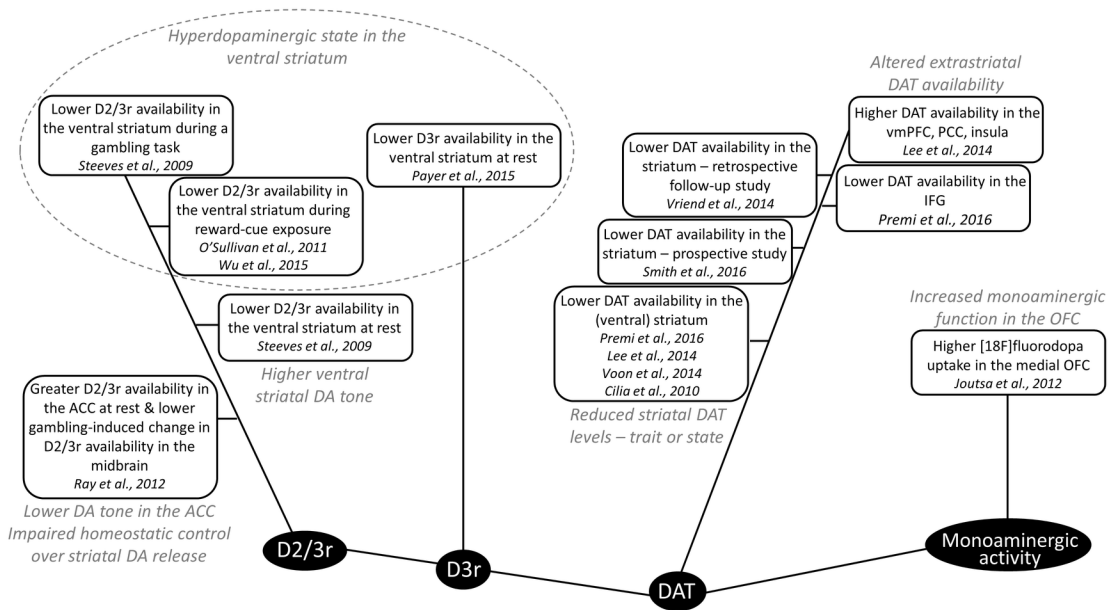
one study using [18F]Fluorodopa showed higher tracer uptake at rest in the medial orbitofrontal cortex (OFC) in ICDs+ (Joutsa et al., 2012).

Figure 2: Flow chart of publication selection procedure based on PRISMA guidelines (www.prisma-statement.org).

Figure 3: Differences in functional connectivity (A) or task-related activation (B) between PD patients with (ICDs+) or without ICDs (ICDs-). For the sake of clarity, only regions involved in Group effects (and not Group x Medication effects) are reported. The heterogeneity of the methods as well as the results (in terms of location and direction of group differences) makes it difficult to extract a clear and coherent picture.

Table legends

Table 1: Functional neuroimaging studies examining the brain mechanisms that differentiate PD patients with ICDs from PD patients without ICDs.



DOPAMINERGIC ALTERATIONS IN PD-ICDS

Literature search (11/10/2018)

Database: Pubmed, Web of Science

Search teams: ((Impuls* OR Gamb*) AND (Parkinson) AND (Imaging OR fMRI OR PET OR Blood flow))

Search results (n=210)

Articles screened on the basis of title and abstract

Inclusion criteria: PET regional cerebral blood flow (rCBF) or fMRI studies, including PD patients with current ICDs (ICDs+) as well as a control group of PD patients without ICDs (ICDs-), and reporting at least one of the two contrasts ICDs+ > ICDs- or ICDs- > ICDs+

Exclusion criteria: review articles, conference abstracts, animal studies, case-reports, metabolism or neurotransmission PET studies.

Excluded (n=192)

*Molecular Imaging studies
Discussed in Figure 1*

Included (n=18)

Manuscript review and application of inclusion and exclusion criteria

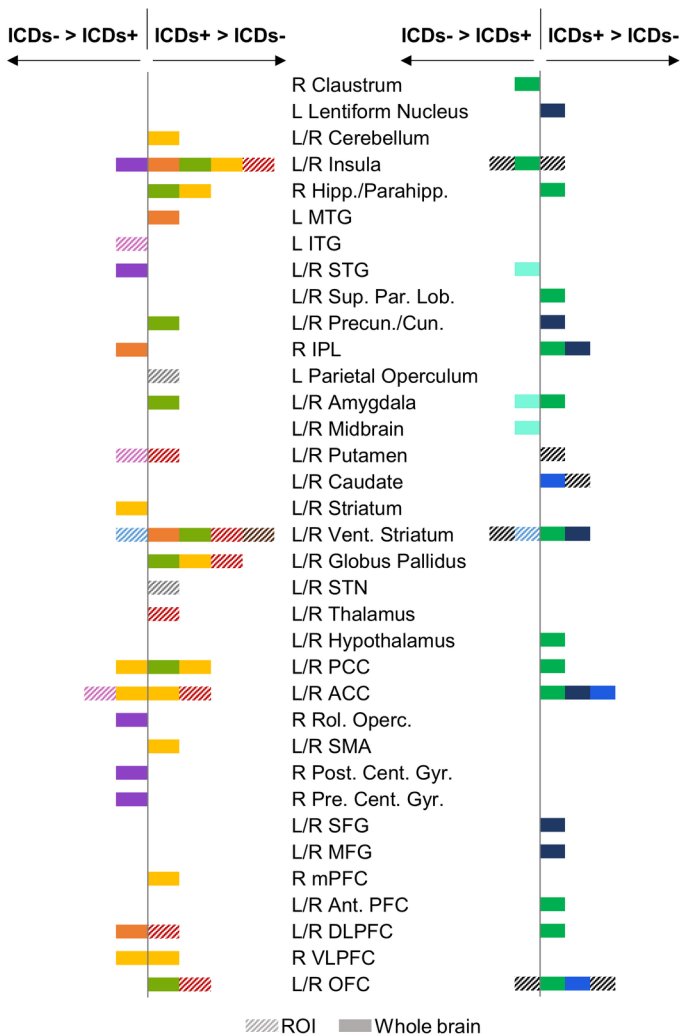
Excluded (n=4):

- Case-report (n=1)
- Did not include PD patients with current ICDs (n=3)

Included (n=14, including 15 experiments)

Resting state (n=9)
fMRI (n=7) – SPECT (n=2)

Task-based activations (n=6)
PET (n=1) – fMRI (n=5)



Intrinsic activity

RS rCBF

FC



Task-related activity

Risk-taking

Incentive learning

Motivation



Table 1: Functional neuroimaging studies examining the brain mechanisms that differentiate PD patients with ICDs from PD patients without ICDs.

Studies		Populations	Neuroimaging		Behavioral tasks and targeted neurocognitive mechanisms			Results	
		ICDs+/ICDs- /HC	Tool Signal	Processing methods	Authors' rationale	NOI BT	ROI		
#1	Imperiale , 2017	PD-ICDs 35/50/50 Interview QUIP-RS= 21.9± 10.2/NR ON	fMRI BOLD	Intrinsic activity FC - ICA	"to investigate [...] functional alterations in PD-ICB patients compared with healthy controls and PD no-ICB cases"	/	Major RSNs	ICDs+ > ICDs- ICDs- > ICDs+ ICDs+ > HC HC > ICDs+	[FC within and between RSNs] Ø [FC within Sensorimotor Network] R Precentral Gyrus - R Postcentral Gyrus - R Rolandic Operculum - R STG - L Insula [FC between RSNs] Ø [FC within Visual Network] L and R Middle Occipital Gyrus - R Lingual Gyrus - L Fusiform Gyrus - R Cerebellum Vermis 4-5 - R Cerebellum Crus 1 [FC between RSNs] Ø [FC within and between RSNs] Ø
#2	Tessitore, 2017	PD-ICDs 15/15/24 Interview MIDI=6.8± 3.2/0.4±0.5 ON	fMRI BOLD	Intrinsic activity FC - ICA	"to assess whether the presence of ICD in PD patients may determine abnormalities in the intrinsic neural networks connectivity"	/	Major RSNs	ICDs+ > ICDs- ICDs- > ICDs+ ICDs+ > HC HC > ICDs+	[FC within SN and DMN] L and R Insula - R Ventral Striatum - L Middle Temporal Gyrus [FC within Right CEN] R DLPFC – R IPL [FC within Right CEN] R Angular Gyrus [FC within SN and DMN] ACC – Precuneus
#3	Cilia, 2008	PD-PG ¹ 11/40/29 DSM-IV SOGS=7.6± 2.8/1.1±0.4 ON	SPECT rCBF	Intrinsic activity RS activation	"to determine whether PD patients with PG exhibit differential brain activity compared with matched PD controls and healthy controls"	/	Whole brain	PG+ > PG- PG- > PG+ PG+ > HC HC > PG+	[rCBF peak/extended to] R OFC/Insula - R Hippocampus/Parahippocampal Gyrus - R Amygdala - R Ventral Pallidum/Nucleus Accumbens - L Insula - R and L Precuneus/Cuneus/PCC [rCBF] Ø [rCBF peak/extended to] R Hippocampus/ Parahippocampal Gyrus - R Insula/OFC/ Striatum - R Caudate/Insula - R Putamen/ Insula [rCBF] Ø

#4	Cilia, 2011	PD-PG ¹ 15/15/15 DSM-IV SOGS=7.5± 2.7/0.9±0.5 ON	SPECT rCBF	Intrinsic activity FC Intrinsic activity Effective connectivity	"to identify the critical neural interactions that differentiated PD gamblers from matched controls"	/	Seeds: regions whose activity correlated with SOGS scores	PG+ > PG- PG- > PG+	[Covariance between regions not functionally connected in PG-] R ACC and Insula, SMA, Cerebellum – R VLPFC and Ventral Pallidum - R mPFC and PCC – R Parahippocampal Gyrus and Insula [Lack of covariance between] R VLPFC and ACC, PCC – R ACC and Striatum
							Seeds: R VLPFC, R mPFC, R ACC, R PCC, L Striatum, R Insula, R Parahippocampal Gyrus	PG+ < PG-/HC	[Main finding] Disconnection of the Striatum from ACC <i>Correlation analysis</i> Activity correlated with SOGS scores: [positive correlation] R VLPFC, R mPFC, R ACC, R PCC, R Rostral SMA, R Anterior Superior Temporal Gyrus, L Striatum, L and R Insula, R Parahippocampal Gyrus - [negative correlation] L Fusiform Gyrus, Cerebellum.
#5	Carriere, 2015	PD-ICDs 19/17/16 Interview QUIP=NR ON	fMRI BOLD	Intrinsic activity FC - Seed-based	"ICDs would be associated with alterations in corticostriatal connectivity and especially the connectivity between the ventral striatum and cortical limbic regions"	/	Seeds: Bilateral Dorsal Caudate, Ventral Striatum, Anterior and Posterior Putamen	ICDs- > ICDs+ ICDs+ > ICDs- ICDs+ <> HC	[FC from L Anterior Putamen, disconnection] L Inferior Temporal Gyrus – L ACC ⁶ Ø ⁶ Ø ⁶
#6	Petersen, 2018	PD-ICDs 19/18 Interview QUIP-RS= 35.9±9.7/18. 9±11.1 ON DAA + OFF L-DOPA / OFF	fMRI BOLD	Intrinsic activity FC - Seed-based	"we hypothesized that DAA-treated PD patients with this behavioral phenotype [ICDs] have increased functional connectivity between the ventral striatum and components of the limbic striato-pallido-thalamo-cortical loop" - "Because amygdala activity has also been linked with reward-motivated behaviors [...], we additionally examined amygdala connectivity with reward network components."	/	Seeds: Bilateral Ventral Striatum, Bilateral Amygdala Seeds: Bilateral Ventral Striatum, Bilateral Amygdala - Connectivity to 12 target bilateral mesocorticolimbic ROIs	ICDs+ > ICDs- ICDs- > ICDs+ ICDs+ > ICDs- ICDs- > ICDs+ <i>Group x Medication</i>	[Volxewise analysis - FC from ventral striatum] L and R Thalamus/Basal Ganglia/Subgenual ACC/Lateral OFC/DLPFC Ø [ROI-based analysis - FC from ventral striatum] Dorsal ACC - OFC - Insula - Putamen - Globus Pallidus - Thalamus Ø Ø

#10	Voon, 2011	PD-PG/CB 11/11 DSM-IV/ McElroy criteria ON/OFF DAAs	fMRI BOLD	Task-related activity Event-related	“we hypothesized that dopamine agonists would be associated with greater risk taking and lower ventral striatal activity in patients with ICD relative to Parkinson’s disease controls.”	Risk Taking Gambling Task Box-car convolved with HRF on decision phase (4s) with risk as a parametric regressor	<i>Whole brain</i>	ICDs+ > ICDs- <i>Group effect</i> ICDs- > ICDs+ <i>Group effect</i> <i>Group x Medication</i> <i>Behavioral results</i> ⁵	[Risk-taking related activation] L and R ACC, L and R Caudate, L OFC [Risk-taking related activation] Ø [Risk-taking related activation - Increased ON versus OFF in ICDs- but decreased activity ON versus OFF in ICDs+] L and R Ventral Striatum [Proportion of risky choices] No Group effect (p=0,96)– No Medication x Group effect (p=0,19)
#11	Van Eimeren, 2010	PD-PG 7/7 DSM-IV ON/OFF DAAs	PET rCBF	Task-related activity Block-design	“we reasoned that in contrast to controls, gamblers may show DA-induced hypoactivity of inhibitory frontolimbic networks encompassing the lateral OFC and the rostral cingulate zone.”	Risk Taking Card selection game with probabilistic feedback, neutral and financial variant Task > Rest	<i>Whole brain</i>	ICDs- > ICDs+ <i>Group effect</i> <i>Group x Medication</i>	L and R Midbrain, L and R Superior Temporal Gyrus, R Amygdala [Increased activity ON versus OFF in ICDs- but decreased activity ON versus OFF in ICDs+] L lateral OFC, R Rostral Cingulate Zone, R Amygdala, L Ventral Anterior External Pallidum
#12	Politis, 2013	PD-HypS ¹ 12/12 Based on Voon, 2006 ON/OFF	fMRI BOLD	Task-related activity Block-design	"hypersexuality in Parkinson’s disease could be associated with increased processing in brain regions linked to sexual motivation and cue reactivity"	Motivation Watching sexual cues ³ Sexual cues > Neutral cues, Sexual cues > Other cues ⁴	OFC, ACC, PCC, Amygdala, Ventral Striatum, Hypothalamus <i>Whole brain</i>	HypS+ > HypS- HypS+ > HypS-	[Sexual versus neutral, ON and OFF] L and R OFC - L and R ACC - L and R PCC - L Amygdala - L and R Ventral Striatum - L and R Hypothalamus [Sexual versus others, ON and OFF] L and R OFC - L and R ACC - L and R PCC - L and R Ventral Striatum - L and R Hypothalamus [Sexual versus neutral, ON and OFF] L and R OFC - L and R ACC - L and R PCC - L Amygdala - L and R Ventral Striatum - L and R Hypothalamus - L and R Anterior PFC - L and R Superior Parietal Lobule - R IPL [Sexual versus others, ON and OFF] L and R OFC - L and R ACC - L and R PCC - L and R Ventral Striatum - L and R Hypothalamus – R and L DLPFC – R anterior PFC – R Parahippocampal Gyrus

								HypS- > Hyps+ [Sexual versus neutral, OFF] L and R Insula - R Claustrum	
								<i>Behavioral results</i> [Sexual desire after-before sexual stimuli exposure] OFF: HypS-= 0.28 ± 0.26, HypS+= 1.04 ± 0.32, p=0.08; ON: HypS-=0.80 ± 0.52, HypS+=3.23 ± 0.51, p<0,01	
#13	Frosini, 2010	PD-PG ¹ 7/7 DSM-IV OFF	fMRI BOLD	Task-related activity Block-design	Gambling related cues would result in activation patterns similar to those related to craving in drug addictions	Motivation Watching gambling cues ³ Gambling cues > Neutral cues	<i>Whole brain</i>	PG+ > PG- <i>Behavioral results</i>	[Gambling cues related activation] L and R ACC – L and R Medial Frontal Gyrus – L and R Superior Frontal Gyrus – L and R Precuneus – R IPL – L Ventral Striatum – L Lentiform Nucleus [Gambling urge after gambling stimuli exposure] PG+=7.10 ± 1.8, PG-= 1.3 ± 0.9, p<0.05.
#14	Voon, 2010	PD-PG/CB 11/11/16 DSM-IV/ McElroy criteria ON/OFF DAAs	fMRI BOLD	Task-related activity Computational modelling	“dopamine agonists would be associated with faster learning from gain outcomes along with greater ventral striatal positive δ activity in [ICDs] compared to PD controls”	Incentive Learning Probabilistic gain and loss learning task PE and PO activity: PE entered as a parametric modulator for the outcome phase (3s) – PO entered as a parametric modulator for the stimulus phase (3s)	<i>ROIs: Striatum, Amygdala, OFC, Insula</i>	ICDs+ > ICDs- <i>Group effect</i> ICDs- > ICDs+ <i>Group effect</i>	[PO activity, gain condition] L and R OFC [Positive PE activity, gain condition] R Posterior Putamen – L OFC [Negative PE activity, gain condition] Ø [PO activity, loss condition] L Dorsolateral Striatum [Positive PE activity, loss condition] Ø [Negative PE activity, loss condition] L Anterior Insula – L Dorsomedial Caudate – L Dorsolateral Striatum [PO activity, gain condition] Ø [Positive PE activity, gain condition] Ø [Negative PE activity, gain condition] R Ventral Striatum – R OFC [PO activity, loss condition] L and R OFC – R Anterior Insula [Positive PE activity, loss condition] L/R OFC [Negative PE activity, loss condition] L and R OFC, R Anterior Insula

<i>Group x Medication</i>	<p>[PO activity, gain condition] Greater increase under DAAs in L Ventral Striatum and lower decrease under DAAs in R Posterior Insula in ICDs+ than in ICDs-</p> <p>[Positive PE activity, gain condition] Greater increase under DAAs in L and R Posterior Putamen, R Insula and L Dorsomedial Striatum and lower decrease under DAAs in L and R OFC in ICDs+ than in ICDs-</p> <p>[Negative PE activity, gain condition] Ø</p> <p>[PO activity, loss condition] Lower decrease under DAAs in L Dorsomedial, Ventral Striatum and L and R Anterior Insula in ICDs+ than in ICDs-</p> <p>[Positive PE activity, loss condition] Greater increase under DAAs in L and R Anterior Insula and R Ventral Striatum in ICDs+ than in ICDs-</p> <p>[Negative PE activity, loss condition] Lower decrease under DAAs in L and R Anterior Insula, R OFC and L Putamen in ICDs- than in ICDs+</p>
<i>Behavioral results</i>	<p>[Gain learning] No main effects – Group x medication interaction: Higher percentage of gain cue choices and faster learning rate under DAAs in ICDs+ but not in ICDs-⁵</p> <p>[Loss learning] No main effects – Group x medication interaction: Lower percentage of correct responses and lower learning rate under DAAs in ICDs- but not in ICDs+⁵</p>

¹: with other ICD co-occurrence in some patients. – ²: ICD status was determined using the MGS (Massachusetts Gambling Screen) for pathological gambling, the MIDI for hypersexuality and buying, and the DSM-IV-TR research criteria for compulsive eating. – ³: No responses required – ⁴: Gambling, food, and dopaminergic cues – ⁵: The reader is referred to the whole article for the complete results – ⁶: The reader is referred to the whole article for the results of the exploratory analysis using a less stringent criteria for significance – HypS+/-: PD patients with/without hypersexuality – ICDs+/-: PD patients with/without ICDs – PG+/-: PD patients with/without PG – CB: Compulsive Buying – HC: Healthy Controls – MIDI: Minnesota Impulsive Disorders Interview – QUIP-RS: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale – DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – MGS: Massachusetts Gambling Screen – SOGS: South Oaks Gambling Screen – DAAS: Dopamine Agonists – NR: Non-Reported – FC: Functional Connectivity – RS: Resting state – BT: Behavioral task – NOI: Neurocognitive processes Of Interest – ROI: Regions Of Interest approach – RSNs: Resting State Networks – BART: Balloon Analogue Risk Task – PE: Prediction Error – PO: Predicted Outcome – ACC: Anterior Cingulate Cortex – CEN: Central Executive Network – DLPFC: Dorsolateral Prefrontal Cortex – DMN: Default Mode Network – GPe: External portion of the Globus Pallidus – GPi: Internal portion of the Globus Pallidus – IPL: Inferior Parietal Lobule – mPFC: Medial Prefrontal Cortex – OFC: Orbitofrontal Cortex – PCC: Posterior Cingulate Cortex – SMA: Supplementary Motor Area – SN: Salience Network – STG: Superior Temporal Gyrus – VLPFC: Ventrolateral Prefrontal Cortex – Ø : No areas concerned by significant modification of activity/connectivity for the corresponding contrast.