Incentive-driven decision-making networks in de novo and drug-treated Parkinson's disease patients with impulsive-compulsive behaviors: A systematic review of neuroimaging studies

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Key words: Parkinson's disease; impulsive-compulsive behavior; impulse control disorder; neuroimaging; motivation; de novo; dopaminergic treatment; cognitive control; incentive-driven decision-making; MRI.

Conflict of Interest: AA has received compensation for consultancy and speaker related activities from UCB, Boehringer Ingelheim, AbbVie, Zambon, Bial, Ever Pharma, Neuroderm, Therevance, Biogen; he receives research support from Chiesi Pharmaceuticals, Lundbeck, Horizon 2020 - PD_Pal Grant 825785, Ministry of Education University and Research (MIUR) Grant ARS01_01081, Cariparo Foundation. He serves as consultant for Boehringer–Ingelheim for legal cases on pathological gambling. RB has received a research grant by the Ministry of Health under Grant Number GR-2016-02361986. ST has received lecture honoraria from Abbvie and Pfizer, support for educational activities from FB Health and Pfizer, and travel grants from CSL Behring. AM, LW, CP, GL, SC, NE: none.

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ABSTRACT

Background: In Parkinson's disease (PD), impulsive-compulsive behaviors (ICBs) may develop as side-effect of dopaminergic medications. Abnormal incentive-driven decision-making, which is supported by the cognitive control and motivation interaction, may represent an ICBs signature. This systematic review explored whether structural and/or functional brain differences between PD patients with vs without ICBs encompass incentive-driven decision-making networks.

Methods: Structural and functional neuroimaging studies comparing PD patients with and without ICBs, either de novo or medicated, were included.

Results: Thirty articles were identified. No consistent evidence of structural alteration both in de novo and medicated PD patients were found. Differences in connectivity within the default mode, the salience and the central executive networks predate ICBs development and remain stable once ICBs are fully developed. Medicated PD patients with ICBs show increased metabolism and cerebral blood flow in orbitofrontal and cingulate cortices, ventral striatum, amygdala, insula, temporal and supramarginal gyri. Abnormal ventral striatum connectivity with anterior cingulate cortex and limbic structures was reported in PD patients with ICBs.

Discussion: Functional brain signatures of ICBs in PD encompass areas involved in cognitive control and motivational encoding networks of the incentive-driven decision-making. Functional alterations predating ICBs may be related to abnormal synaptic plasticity in these networks.

INTRODUCTION

In Parkinson's disease (PD), treatment of motor symptoms is provided by dopamine replacement therapies (DRT). However, in an estimated 30% of cases, DRT trigger impulsive-compulsive behaviors (ICBs) [1]. Individuals with ICBs are unable to resist or have diminished control over an appetitive urge, such as craving, to engage in behaviors that include gambling, sexual activity, eating, shopping. Engaging in such behaviors gives rise to feelings of pleasure or hedonia, but, left uncontrolled, can lead to relationship breakdown, financial difficulties, and health problems [2]. Despite the pervasive nature of ICBs in PD and their negative impact, much remains to be elucidated about their neural correlates.

Each decision made to engage in a hedonic activity is a result of weighing up the predicted benefits of following that particular goal, traded-off against the mental effort involved in achieving the goal (or in resisting the urge to engage in that behavior) versus the alternative option(s) that are not pursued [3]. There is a consensus of opinion that cognitive control and motivation are both intrinsic and closely interrelated aspects of 'incentive-driven decision-making' and will therefore impact on the extent to which the goal directed behavior is regulated, or not as in the case of ICB.

Cognitive control reflects the ability to flexibly organize and control the selection and deployment of on-going cognitive processes that include attention, memory, action-planning, and co-ordinate their activity to ensure successful delivery of goals in multitask environments [4].

Motivation can be defined as follows 'when an external or internal incentive alters the biological system (i.e., generates a 'motivated state') to stimulate an observable change in behavior' [3]. In other words, motivational states can be induced by offering rewards or negative incentives that lead to changes in cognitive control and influence behavior [5]. This highly dynamic and (two-way) interactive relationship is further influenced by individual differences in sensitivity to reward and punishment [5,6] and by modulation of the dopaminergic system, e.g. by DRT [7].

Cognitive neuroscience research suggests that incentive-driven decision-making reflects interactions between at least two brain networks on which cognitive control and motivational signals separately rely [3]. Cognitive control relies on frontal regions that interact via a local and global hierarchical structure. The motor and premotor cortices and the frontal eye fields, which together support sensory-motor control, are at the lowest level of the hierarchy. Rostrolateral prefrontal cortex occupies the intermediate level and has responsibility for domain-specific control of behavior, forming 'schema' from specific episodic information. At the apex of the hierarchy, and residing between caudal and rostral lateral prefrontal cortex, lies the mid-dorsolateral prefrontal cortex that supports domain-general control based on abstract rules and concepts [4].

A parallel and synergistic network is suggested to govern the intensity of cognitive control amongst the networks conveying motivational signals [8]. This network is modulated by dopamine, and comprises the ventral striatum, the anterior cingulate cortex and, minimally, the dorsomedial frontal cortex. The latter interacts with rostrolateral and dorsolateral prefrontal cortex during performance monitoring and prediction error detection, implying that the two systems work together in 'deciding' whether the salience or value of the incentives are worth increasing the strength of control and accepting the greater subjective cost that control involves [9–11].

This systematic review is aimed to explore whether ICBs are associated to abnormal structural and/or functional activation of the brain areas part of the cognitive control and motivational networks supporting incentive-driven decision-making. Brain signatures of de novo PD patients were also explored as putative markers of ICB vulnerability.

Our systematic review included magnetic resonance imaging (MRI) and perfusion brain positron emission tomography (PET) or single-photon emission computed tomography (SPECT) imaging studies. Neuropharmacological PET or SPECT studies were not included as a recently published systematic review and meta-analysis explored this topic [12].

METHODS

A systematic review was conducted to verify whether ICBs in PD are associated with changes in the brain structures supporting cognitive control and the network conveying motivational signals. Studies were selected if they compared PD patients with one or more ICB (ICB+) to those without any ICB (ICB-). Findings are presented separately for de novo PD patients and those treated with DRT.

Inclusion and exclusion criteria

We applied the following inclusion criteria: 1) between-group comparison between ICB+ and ICB- PD patients; 2) ICB status determined using standardized interviews with published criteria and/or rating scales with evidenced construct validity, and defined rates of sensitivity and specificity; 3) neuroimaging studies reporting grey matter structure using voxel-based morphometry (VBM) performed on structural MRI (sMRI), white matter connectivity using diffusion tensor imaging/ diffusion weighted imaging analysis (DTI)/(DWI) performed on sMRI, functional activation and functional connectivity using blood oxygen level dependent (BOLD) signal in functional MRI

(fMRI), or brain perfusion using PET or SPECT at rest to investigate changes in regional cerebral blood flow.

We excluded studies including PD patients with dementia, other neurological conditions other than PD, or with alcohol or any substance use disorder either at the moment when they were tested or in the past, because these conditions might be independently associated with structural and functional brain changes. Studies not screening for the absence of all ICB types in the ICB- groups were not included.

Literature search strategy

On the 10th of August 2018, PubMed, Cochrane, EBSCO, and ISI Web of Science databases were searched for peer-reviewed papers in English, Spanish or Italian published since database inception. The search was further updated on the 30th of March 2020. The protocol of the systematic review was pre-registered in PROSPERO (ID: CRD42018106365).

RESULTS

Search results

Overall, 30 papers were included in the systematic review. Description of the systematic review's phases is provided as Supplementary Material.

Of the included 30 papers, 12 evaluated structural alterations [13–24], 12 evaluated functional alterations [25–36], and 6 included both structural and functional measures [37–42]. The study of Hammes et al. [18] was included in the structural section only, as no between groups analysis was done in functional alteration analysis. The study of Tessitore [33] was included in the functional section only as the sample and the structural alteration analysis were the same as Tessitore et al. [14]. The PRISMA diagram is shown in Figure 1.

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Data extraction

The main outcomes for the structural imaging studies were the differences between ICB+ and ICB- groups in cortical and subcortical grey matter density measured with VBM, cortical thickness (Cth), and subcortical white matter tract metrics assessed using DTI/DWI.

The main outcomes for the functional studies were the differences between ICB+ and ICB- groups in connectivity during resting state fMRI (rs-fMRI), brain perfusion during resting state, using PET or SPECT and brain activation during task performance using fMRI.

STRUCTURAL STUDIES

De novo PD patients

Three studies examined ICBs in de novo PD patients (Table 1). Two were longitudinal [22,42], and the other one was cross-sectional in design [21].

Both longitudinal studies examined differences in local grey matter density using VBM [22,42], although Ricciardi et al. [17] also measured Cth. Zadeh et al. [16] examined subcortical white matter tracts using DTI.

Demographic and clinical characteristics of the three studies are listed in Supplementary Table 1 and described in Supplementary Material.

Cortical and subcortical volume. Baseline and follow-up VBM measures did not dissociate between groups of de novo patients who went on to develop ICBs from those who did not [22,42].

Cortical thickness. There was no difference in Cth at either baseline or follow-up between groups of de novo patients who went on to develop ICBs from those who did not [22].

Subcortical diffusion tensor imaging study. The single cross-sectional study evidenced decreased bilateral white matter connectivity in the cortico-thalamic tract, the cortico-pontine tract, the corticospinal tract, the superior cerebellar peduncle, and the middle cerebellar peduncle in de novo ICB+ compared to ICB- patients [21].

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Dopaminergic replacement therapy-medicated PD patients

A total of 15 cross-sectional studies reported sMRI findings associated to ICBs in medicated PD patients (Table 2).

Three studies reported grey matter cortical volume using VBM [13,19,40]. Seven reports explored subcortical volumes for a set of a priori regions of interest using sMRI [14,15,18,24,38–40]. Cth

was reported in 9 studies [14,15,18,19,23,24,37–39], and subcortical white matter changes using DTI/DWI were described in further four studies [16,17,20,38].

Demographic and clinical characteristics of the 15 studies are listed in Supplementary Table 2 and described in Supplementary Material.

Cortical and subcortical volume studies. One study reported evidence of increased cortical volume in the inferior frontal gyrus bilaterally, and the right-side caudal anterior cingulate between the ICB+ vs ICB- groups [15]. No other differences were detected at cortical level.

Two studies reported volume reduction in the left [24] and right [14] nucleus accumbens, whereas two other studies found no volumetric differences [18,41] between groups. Borderline reduction of right external globus pallidus volume was reported in one study [40]. On the other hand, no between-groups volumetric differences were found in either the caudate nucleus, the globus pallidus, the putamen, [18,24,38,41], the thalamus [24,38,41], the habenula [39], the hippocampus [18,24,38,41] or the amygdala [18,24,38,39,41], although one study reported increase left amygdala volume in ICB+ [14]. Finally, one study reported volume reduction in the central and middle anterior (genu) corpus callosum of ICB+ vs ICB- [14].

Cortical thickness studies. Five of the nine studies examining Cth found abnormalities in ICB+ vs ICB-, although the direction of thickness varied, while four studies reported no differences [15,23,37,41].

Structures with cortical thinning included the left superior frontal and precentral gyri [14,38], right postcentral gyrus [19], pars orbitalis [14,39], pars opercularis, left postcentral area, rostral middle frontal area, superior and inferior parietal areas, lingual and parahippocampal gyri, bilateral caudal middle frontal and supramarginal areas [14], middle temporal gyrus and temporal pole [24].

On the other hand, increased Cth was observed in the rostral anterior cingulate cortex and frontal pole [18], the left anterior cingulate cortex, left medial and lateral orbitofrontal cortex, left parahippocampal cortex, and left isthmus of the cingulate cortex [19].

Subcortical diffusion tensor imaging studies. Three studies examined white matter integrity using fractional anisotrophy (FA), mean diffusivity (MD) [17,20,38], axial and radial diffusivity (RadD) [17,38], and one study investigated structural connectivity [16].

Structural degeneration (i.e., decreased FA and increased MD and RadD) was reported in the left uncinate fasciculus and parahippocampal tract (i.e, both decreased FA and increased MD/RadD) [38], and in pedunculopontine tract on the left [17] and right sides (i.e., increased RadD and MD) [38]. However, preserved white matter integrity (i.e., increased FA) was also reported in the anterior corpus callosum, partial left thalamic radiations, right dorsal and posterior cingula, right internal capsule (genu and posterior limbs), right superior temporo-occipital lobes, and right thalamic radiations [20]. The fibers of the corpus callosum were reported to be both more robust (i.e., increased FA) [20] and disrupted (i.e., increased RadD and MD) compared to ICB- [17,38].

A gambling task revealed that greater impulsivity was associated with lower structural connectivity between the left/right ventral striatum and the ventromedial prefrontal cortex in ICB+, with the opposite effect in ICB- [16].

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FUNCTIONAL STUDIES

De novo PD patients

Functional imaging correlates of ICBs in de novo PD patients have been investigated in one longitudinal study only using rs-fMRI (Table 3).

Demographic and clinical characteristics of the study are reported in Supplementary Table 3 and described in Supplementary Material.

Resting-state fMRI. At baseline, patients who went on to develop ICBs showed increased connectivity in the left orbitofrontal cortex, decreased connectivity in the left supramarginal gyrus, left precuneus and right middle temporal gyrus compared to patients without ICBs at follow-up.

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Dopaminergic replacement therapy-medicated PD patients

Seventeen cross-sectional functional imaging studies investigated ICBs in medicated PD (Table 4).

Two studies reported measures of brain metabolism using resting state PET [33,41]. Three reports explored cerebral blood flow measures, two of them using resting state SPECT ON-medication [25,26], and one using arterial-spin-labelling ON- and OFF-medication [34]. Five studies reported BOLD signal using task-based fMRI. Patient performance was examined on the temporal

discounting task ON- and OFF-medication [35], reward-related visual cues OFF- [29] and ON-medication [30,32] and the Iowa Gambling task ON-medication only [27]. Further six studies investigated spontaneous low frequency BOLD fluctuations using rs-fMRI [28,31,37–40]. Only a single study to date has examined changes in dynamic functional connectivity over time and this was conducted in ON-medicated patients [36].

Demographic and clinical characteristics of the 17 studies are listed in Supplementary Table 4 and described in Supplementary Material.

Resting-state fMRI studies

ICB+ vs ICB- comparison showed reduced connectivity between the basal ganglia nuclei and frontal cortical areas [40], between the habenula and left frontal and precentral cortices, and between right amygdala and hippocampus [39] and in the dorsolateral prefrontal cortex and inferior parietal cortex [28], and between the left anterior putamen and the left inferior temporal and anterior cingulate gyrus, but no difference in connectivity in the ventral striatum [37].

On the other hand, ICB+ compared to ICB- showed increased connectivity between the ventral striatum and limbic structures [31], between the striatum and the habenula, the amygdala, the thalamus and bilaterally [39], in the right ventral striatum and bilateral insula, and in the left middle temporal gyrus [28].

In the single study that examined dynamic functional connectivity over time, ICB+ vs ICB- were found to be engaged for longer in a brain configuration pattern characterized by strong ‘within’ network connections between superior temporal lobe, fronto-insular and cingulate cortices, at the expense of connectivity with other networks. The same study also reported increased local efficiency within the superior temporal lobe, fronto-insular and cingulate cortices [36].

Resting-state brain perfusion and brain metabolism

Two studies found increased metabolism in the right middle and inferior temporal gyri [33], and in the orbitofrontal cortex, amygdala, insula, posterior cingulate cortex, parahippocampus and supramarginal gyri [41] when comparing ICB+ to ICB- patients. Increased regional cerebral blood flow was also evident in the orbitofrontal cortex, hippocampus, amygdala, insula, and the ventral pallidum in ICB+ patients vs ICB- ones [25]. However, OFF-medication, there was no difference in regional cerebral blood flow in the striatum and frontal cortex, whilst ON-medication increased regional cerebral blood flow in these structures was reported in ICB+ vs ICB- [34].

Connectivity was decreased between anterior cingulate cortex and the striatum [26] and the left caudate and the right parahippocampus [33], but increased between the right middle, the inferior temporal gyri, the mesocorticolimbic system, and orbitofrontal regions [33].

Task-based fMRI studies

Task-based fMRI studies consistently showed increased activation of reward-related areas; ICB+ patients with gambling disorder showed increased BOLD signal in the anterior cingulate cortex, medial and superior frontal gyri, the precuneus, inferior parietal lobule, and ventral striatum after gambling-related visual cue exposure in comparison to ICB- ones [29]. A similar functional brain activation profile has been reported in PD patients with hypersexuality after exposure to visual sexual cues [32,35]. The BOLD signal was also reported to be increased in the ventral striatum of ICB+ patients with dopamine dysregulation syndrome (compulsive craving of dopaminergic medication) after exposure to drug-related cues as compared to ICB- ones [30].

On a temporal discounting task, subjective value of the delayed reward was negatively correlated with activity in the ventromedial prefrontal cortex and ventral striatum in ICB+, with the opposite pattern in ICB- patients [35]. ICB+ vs ICB- showed increased BOLD signal in the right subthalamic nucleus, right inferior frontal gyrus, and right ventral striatum while performing the Iowa Gambling Task [27].

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DISCUSSION

The main objective for this systematic review was to report whether ICBs in PD are marked by abnormal brain structures and functional networks in areas related to incentive-driven decision-making, and whether brain changes predate ICB onset.

The main findings from structural imaging studies were inconclusive. There was no consistent association between ICB, both in medicated and de novo PD patients, and changes in VBM, Cth, or white matter tracts in lateral prefrontal areas related to domain-specific and domain-general cognitive control [4], or in medial prefrontal cortex and subcortical structures implicated in motivation and salience response.

On the other hand, results from functional imaging studies were more consistent, revealing four key findings.

The first key finding is that changes in resting-state networks activation were most consistently reported in the salience network, the central executive network (CEN) and the default mode network (DMN), both in medicated and de novo patients. Medicated ICB+ showed reduced functional connectivity within the CEN and increased connectivity in the DMN and salience network [28]. The same results were reported in de novo PD patients who later developed ICBs, except for the DMN that showed decreased connectivity compared to ICB- patients [42]. The DMN is active during internally-directed thoughts such as mind wondering, and it is suspended during cognitively-demanding tasks and goal-directed behaviors. It includes the ventromedial prefrontal cortex, posterior cingulate cortex, inferior parietal cortex and medial temporal lobe. The CEN is engaged when a cognitively demanding task or a goal-directed behavior requiring attention is being performed, and is composed by the dorsolateral prefrontal cortex and inferior parietal cortices [28,43]. The salience network is activated by salient or rewarding stimuli (cognitive, emotional or homeostatic) therefore facilitating the DNM/CEN switching. It includes limbic-paralimbic structures, such as anterior insula, the anterior cingulate cortex, and the ventral striatum. In summary, resting-state networks findings highlight abnormal functional connectivity within regions involved in cognitive control (i.e., CEN) and in motivational processing (i.e., salience network) [4,8] which predate ICBs and remain stable once are fully developed. A limitation of the static functional connectivity studies is that connectivity is time-invariant. Dynamic functional connectivity takes into account the time-variant dynamic coupling that exists between nodes in a network [44,45]. The study by Navalpotro-Gomez et al. (2020) is the only one to date to examine time-variant functional connectivity of ICB in PD, and found that ICB+ were engaged across time in a brain configuration pattern characterized by lack of between-network connections at the expense of strong within-network connections in temporal, frontoinsular and cingulate cortices, all key nodes of the salience network. The increased temporal predominance of this state may be a consequence of, or lead to a reduction in the frequency of transitions between brain states, which is important for neural flexibility mediated through reconfiguration of general brain state organization [44]. The abnormally high connectivity within the salience network may lead ICB+ patients to long and unregulated motivational states focused on or abnormally weighted towards reward-seeking behaviors. We may speculate that, along time, synaptic plasticity related to craving causes long-term potentiation in incentive-driven decision-making networks, as supported by evidence of ICB development years after DRT initiation [46]. Once DRT doses is decreased, ICB may remit although it will reappear if patients are exposed to the same dose.

The second key finding is that resting-state studies showed changes that mainly reflect an increase in brain metabolism [33,41] and cerebral blood flow [25,34] in brain areas belonging to the incentive-driven decision-making networks, such as the orbitofrontal cortex, amygdala, insula, ventral striatum, posterior cingulate cortex, parahippocampus and hippocampus, middle and inferior temporal, and supramarginal gyri. It has been suggested that the enhanced overdrive of the mesocorticolimbic system in response to DRT requires preserved metabolism to take action, and this may explain why ICB- patients, who show lower metabolic preservation are less keen to develop ICB under DRT [41].

The third key finding is that resting-state studies showed abnormal ventral striatal connectivity in ICB+. Ventral striatum show increased connectivity with limbic structures (e.g., habenula, amygdala, thalamus, insula) [28,31,39], and decreased connectivity with the anterior cingulate cortex [26]. Furthermore, increased cerebral blood flow in the ventral striatum and frontal cortex is evident when ON- but not OFF-medication [34]. Taken together these results not only evidence that ventral striatum is a brain area consistently associated with ICBs in PD but also that it is sensitive to the effect of DRT in ICB+ group only. Abnormal frontostriatal connectivity may disrupt integration of cognitive control and motivational inputs during incentive-driven decision-making.

The fourth key finding is that task-based fMRI studies showed increased rather than decreased BOLD signal during exposition to reward-related cues, and during tasks measuring risk-taking and temporal discouting in the subthalamic nucleus, inferior frontal gyrus and ventral striatum, anterior and posterior cingulate cortex, ventromedial prefrontal cortex, and orbitofrontal cortex [27,29,30,35]. The pattern of activation is generalized across ICBs type albeit each study focused on a specific and different ICB.

METHODOLOGICAL CONSIDERATIONS

Some limitations should be acknowledged (Supplementary Table 5).

First, in some studies ICBs were diagnosed using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease [21,22,40], which is a validated screening tool with high sensitivity (94%) but low specificity (72%) to ICBs in PD, thereby possibly inflating the number of false positive subjects. Other studies used the Minnesota Impulsive Disorders Interview only [19,28], without specifying how the ICBs not included in the interview (i.e. binge-eating, punding/hobbyism, and dopamine dysregulation syndrome) were investigated. Although screening questionnaires are easily administrable and time-saving tools, ICBs should always be confirmed by

a clinical interview based on diagnostic criteria. Caregiver should also be interviewed separately to confirm the diagnosis. Between-studies heterogeneity in procedures to ascertain ICB may account for the discrepancy in their findings.

Second, most of the studies were constrained by small sample size, with the smallest including 7 ICB+ and 7 ICB- [29], the largest including 58 ICB+ and 52 ICB- [14], and none of them reporting power analysis calculation. Underpowered studies may not detect a true effect and may reduce the likelihood for a significant result to reflect a true effect [47]. When economic resources are limited, larger samples can be obtained through collaborative research or using available shared databases [48].

Third, protocols of acquisitions and data analysis were not uniform across studies thereby limiting comparison. There is variability in scan duration, pre-processing and analysis, statistical threshold and methods to correct for multiple comparisons, with more liberal statistical thresholding procedure such as the false discovery rate, which in some cases may have inflated the false positive rate [14,17,19,21,25,29,30,32,39]. Methodological differences can explain the lack of consistency in the results reported in this systematic review. For example, the inclusion of the ventral caudate and putamen in the ventral striatum seed region, rather than the nucleus accumbens alone [31,37]. Replication studies using the same acquisition and analysis protocol are needed.

Fourth, a potential bias factor in resting-state studies is whether patients are in ON or OFF state. Most of the studies did not provide information to ensure that patients were in a stable ON state during MRI scan that may be long-lasting. Strategies that could be adopted include two resting-state sessions to increase reliability, exclude patients with unpredictable ON-OFF changes, or measure delta changes between motor symptoms score ON vs OFF-medication.

Fifth, ICB+ and ICB- were not always fully matched for clinical variables that may predict or be associated with ICBs, thus these covariates might have contributed to neuroimaging findings. For example, in some studies ICB+ patients had higher levels of apathy and depression compared to ICB- ones [17,36,38,39]. The lack of consistency in the results may be due to between-studies differences in PD duration (>10 years), co-presence of non-motor symptoms other than ICBs, or gender imbalance, since gender has been differently associated with specific ICB types [49]. Disease-related gender-specific patterns of intrinsic brain connectivity, which may be differently affected by DRT, have been reported [50].

Finally, multiple vs. single ICBs showed higher right temporal metabolism [33], although no structural differences [18], suggesting neurobiological differences across ICB subtypes. However, ICBs subtypes heterogeneity within and across studies, and presence of more than one ICB in many

patients, including those focusing on a single ICB [25,26,29,30,32,35,39], did not allow separate ICB subtype analyses.

CONCLUSIONS

Imaging studies have provided evidence of functional differences between ICB+ and ICB- in brain regions encompassing cognitive control and motivational processing networks, whose interactions support incentive driven decision-making.

In the last decade over 500 studies on ICBs in PD ranging from clinical to neuroimaging and genetic risk factors have been published [51], however we still miss a firm understanding of ICBs neural signature. With a better understanding of ICBs underpinnings, pharmacological and/or non-pharmacological interventions targeting specific brain areas may be developed.

ACKNOWLEDGMENTS We would like to thank Giorgia Albanese and Omar Ferro for the technical support. The work has been supported by a PhD scholarship from Keele University, UK.

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FIGURE LEGENDS

Figure 1. PRISMA diagram of the study (www.prisma-statement.org). **Legend.** ICBs, impulsive-compulsive behaviors; MRI, magnetic resonance imaging.

Table 1

Table 1. Key details of the three structural studies on de novo patients including imaging technique, patient numbers, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICB diagnosis	ICB type: N	Matched variables	Unmatched variables	Differences in brain regions	Findings: ICB+ vs ICB-
Longitudinal								
Ricciardi et al. 2017	VBM, Cth	ICB+: 42 ICB-: 42	QUIP	NR	Sex, age, education, PD duration, H&Y, UPDRS-III, DA-LEDD, GDS	LEDD total: ICB+>ICB-; MoCA: ICB+<ICB-; STAI: ICB+>ICB-	No differences	ICB+ = ICB-
Tessitore, De Micco et al. 2017	VBM	ICB+: 15 ICB-: 15	QUIP-rs; clinical interview	HS:6; BE:5; GD:2; CS:2	Sex, age, education, PD duration, H&Y, UPDRS-III, total LEDD; DA-LEDD, BDI-II, MMSE	NR	No differences	ICB+ = ICB-
Cross-sectional								
Zadeh et al. 2018	Diffusion MRI connectometry	ICB+: 21 ICB–: 68	QUIP	HS: 1; CS: 1; BE: 8; Hobbyism: 2; Punding: 5; walking/driving+HS: 2; BE+ punding: 1; CS+HS: 1; CS+BE+punding: 1	Sex, age, education, PD duration, H&Y, UPDRS-III, MoCA score	GDS: ICB+<ICB-	Decreased bilateral white matter connectivity in the cortico-thalamic tract, the cortico-pontine tract, the corticospinal tract, the superior and middle cerebellar peduncles	ICB+ ↓

Legend. BDI-II: Beck depression inventory II; BE: binge-eating; CS: compulsive shopping; CTh: cortical thickness; DA-LEDD: dopamine agonists equivalent daily dose; GD: gambling disorder; GDS: geriatric depression scale; H&Y: Hoehn & Yahr score; HS: hypersexuality; ICB: impulsive compulsive behaviour; ICB+: PD patients with ICB; ICB-: PD patients without ICB; MMSE: Mini-mental state examination; MoCA: Montreal cognitive assessment; MRI: magnetic resonance imaging; NR: not reported; PD: Parkinson's disease; ref.: reference; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease; QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – rating scale; STAI: State-Trait anxiety inventory; Total LEDD: levodopa equivalent daily dose total; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score; VBM: voxel-based morphometry.

Table 2

Table 2. Key details of the ten structural studies on DRT patients including imaging technique, patient numbers, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICB diagnosis	ICB type: N	Matched variables	Unmatched variables	Differences in brain region*	Findings: ICB+ vs ICB-
Cross-sectional								
Biundo et al. 2011	VBM	ICB+: 33 ICB-: 24	MIDI; DSM-IV-TR criteria; clinical interview (patient and carergiver)	HS: 11; CS: 9; GD: 1; punding: 2; ICB-M: 12	Sex, PD duration, UPDRS-III, total LEDD, DA LEDD, BDI, MMSE	Age: ICB+<ICB-**	No differences	ICB+ = ICB-
Biundo et al. 2015	CTh Subcortical volumes	ICB+: 58 ICB-: 52	QUIP-rs; MIDI; clinical interview (patient and carergiver)	HS: 6; CS: 7; GD: 2; hoarding: 2; impulsive aggression: 1; M-ICB: 40	Sex, education, H&Y, UPDRS-III, DA-LEDD, MMSE, BDI-II	age**; age at PD onset: ICB+<ICB-; PD duration: ICB+>ICB-**; total LEDD: ICB+>ICB-**	CTh: left precentral and postcentral area, superior frontal and rostral middle frontal area, pars orbitalis, pars opercularis, superior and inferior parietal areas, lingual and parahippocampal gyrus, and bilaterally in the caudal middle frontal and supramarginal areas. Subcortical volumes: right NAc, and in the central and middle anterior corpus callosum; Left amygdala	ICB+ ↓ ICB+ ↓ ICB+ ↑
Canu et al. 2017	DTI	ICB+: 21 ICB-: 28	Clinical interview (patient/caregiver) and semi-structured interview	Punding: 21	Sex, age, education, age at PD onset, PD duration, H&Y, UPDRS-III, LEDD, MMSE, HAMA	Depression (HDRS): ICB+>ICB-**; Apathy scale: ICB+>ICB-**	Genu of corpus callosum adjusting for depression and apathy scores; left PPT adjusting for severity of depression only	ICB+ ↓
Carriere et al. 2015	CTh	ICB+: 19 ICB-: 17	QUIP; semi-structured interview	HS: 14; GD: 7; BE: 7; CS: 5	Sex, age, PD duration, H&Y, UPDRS-III, total LEDD, DA-LEDD, MMSE	NR	No differences	ICB+ = ICB-
Hammes et al. 2020	CTh	ICB+: 18 ICB-: 44	QUIP-rs	GD: 3; HS: 11; CS:5; BE: 10; M-ICB: 7	NR	NR	CTh: no differences	ICB+ = ICB-
Hlavata et al. 2020	CTh	ICB+: 8 ICB-: 16	Clinical interview	GD: 5; HS: 2; CS: 1; BE: 3; hobbyism: 1; punding: 1; hoarding: 1; pedantry: 1; excessive cleaning: 1	NR	NR	CTh: no differences Subcortical volumes: bilateral pars orbitalis, right caudal anterior cingulate	ICB+ = ICB- ICB+↑
Imperiale et al. 2018	CTh DTI	ICB+: 35 ICB-: 50	QUIP; clinical interview	GD: 4; HS: 4; CS: 1; BE: 3; punding: 15; DDS: 5; BE+ punding: 1; GD + punding: 1; DDS + punding: 1	Sex, age, education, age at PD onset, PD duration, H&Y, UPDRS-III, total LEDD, DA-LEDD, MMSE	Depression (HDRS): ICB+>ICB-**; Apathy scale: ICB+>ICB-**	CTh: left superior frontal and precentral gyri. DTI: GM: no differences WM: left parahippocampal tract and right PPT, genu of the corpus callosum, bilateral uncinate fasciculus	ICB+ ↓ ICB+ = ICB- ICB+↓
Marin-Lahoz et al. 2020	CTh Subcortical volumes	ICB+: 9 ICB-: 15	QUIP; QUIP-rs; clinical interview	HS: 2; BE: 3; hobbyism: 3; BE + hobbyism: 1	Sex, age, education, age at PD onset, PD duration, UPDRS-III, total LEDD, DA-LEDD	NR	CTh: no differences Subcortical volumes: no differences.	ICB+ = ICB- ICB+ = ICB-
Markovic et al. 2017	CTh Subcortical volumes	ICB+: 22 ICB-: 30	Interview including a semi-structured part (patients and caregivers)	Punding: 17; Punding + BE: 2; Punding + GD: 1; Punding + DDS: 1; Punding + HS: 1	Sex, age, education, age at PD onset, PD duration, H&Y, UPDRS-III, total LEDD, DA-LEDD	NR	CTh: right pars orbitalis of the inferior frontal gyrus Subcortical volumes investigated (habenula and amygdala): no differences	ICB+ ↓ ICB+ = ICB-

Mosley et al. 2019	DWI	ICB+: 17 ICB-: 40	QUIP-rs; semi-structed interview	GD: 10; HS: 9; BE: 1; CS: 3; DDS: 2; hobbyism: 1	Age, PD duration, H&Y, total LEDD	NR	In a gambling task, increased structural connectivity between VS and vmPFC	ICB+↑
Pellicano et al. 2015	CTh Subcortical volumes	ICB+: 18 ICB-: 18	QUIP; Semi-structured interview (DSM-IV-TR)	GD: 4; HS: 3; BE: 1; CS: 1; HS+CS: 2; GD+CS: 1; HS+BE: 1; GD+ DDS: 1; HS+GD+BE: 1; CS+BE+internet: 1; HS+BE+CS: 1; HS+GD+BE+CS: 1	Sex, age, age at PD onset, total LEDD, DA-LEDD, LD-LEDD, MMSE	PD duration: ICB+>ICB-**, UPDRS-III (OFF medication): ICB+>ICB-**; H&Y: ICB+>ICB-	CTh: rostral ACC and frontal pole Subcortical volumes: no differences	ICB+↑ ICB+ = ICB-
Prasad et al. 2018	CTh Subcortical volumes	ICB+: 11 ICB-: 15	QUIP-rs	HS: 1; punding: 3; hobbyism: 1; DDS: 2; HS+CS: 1; BE+hobbyism: 1; GD+hobbyism: 1; HS+BE+CS+DDS+punding: 1	Age, age at PD onset, disease duration, UPDRS-III (OFF), H&Y, total LEDD, LD-LEDD	DA-LEDD: ICB+>ICB-	Cth: right middle temporal gyrus and bilateral temporal pole Subcortical volumes: left nucleus accumbens	ICB+ ↓ ICB+ ↓
Ruitenberg et al. 2018	VBM	ICB+: 21 ICB-: 30	QUIP	GD: 1; HS: 9; CS: 7; BE: 11; others: 6; (9 were in combination)	Sex, age, age at PD onset, PD duration, UPDRS-III, total LEDD, MoCA, NART-R	NR	Right GPe (uncorrected threshold only)	ICB+ ↓
Tessitore et al. 2016	VBM surface based CTh	ICB+: 15 ICB-: 15	MIDI	HS: 13; BE: 8; GD: 1	Sex, age, education, PD duration, H&Y, UPDRS-III, total LEDD, DA-LEDD, HAM-D, HADS, MMSE	—	VBM: no differences CTh: Left ACC, left medial frontal cortex, left lateral OFC, left parahippocampal cortex, and left isthmus of cingulate cortex; Right postcentral gyrus	ICB+ = ICB- ICB+↑ ICB+ ↓
Yoo et al. 2015	DTI	ICB+: 10 ICB-: 9	DSM-IV-TR	GD: 2; HS: 1; CS+BE: 4; CS+BE+HS: 1; GD+HS+BE:1; CS+BE+HS+GD:1	Sex, age, PD duration, H&Y, UPDRS-III, total LEDD, DA-LEDD, GDS, MMSE	NR	Anterior corpus callosum, partial left thalamic radiations, right dorsal and posterior cingulum, right internal capsule (genu and posterior limbs), right superior temporo-occipital lobes, and right thalamic radiations	ICB+↑

Legend. ACC: anterior cingulate cortex; BDI: Beck depression inventory; BDI-II: Beck depression inventory II; BE: binge eating; CS: compulsive shopping; CTh: cortical thickness; DA-LEDD: dopamine agonists equivalent daily dose; DDS: dopamine dysregulation syndrome; DSM-IV-TR: Diagnostic and statistical manual of mental disorders – fourth edition text revision; DTI: diffusion tensor imaging; DWI: diffusion weighted imaging; GD: gambling disorder; GDS: geriatric depression scale; GM: grey matter; GPe: external portion of the globus pallidus; HADS: Hospital anxiety and depression scale; HAMA: Hamilton anxiety rating scale; HAM-D: Hamilton depression rating scale; HDRS: Hamilton depression rating scale; HS: hypersexuality; H&Y: Hoehn & Yahr score; ICB: impulsive compulsive behaviour; ICB+: PD patients with ICB; ICB-: PD patients without ICB; LD-LEDD: levodopa equivalent daily dosage levodopa only; M-ICB: multiple ICB; MIDI: Minnesota Impulsive Disorders Interview; MMSE: Mini-mental state examination; MoCA: Montreal cognitive assessment; MRI: magnetic resonance imaging; NAc: nucleus accumbens; NART-R: National adult reading test-revised; OFC: orbitofrontal cortex; PD: Parkinson's disease; PPT: pedunculopontine tract; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease; QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – rating scale; ref.: reference; Total LEDD: levodopa equivalent daily dose total; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score; VBM: voxel-based morphometry; vmPFC: ventromedial prefrontal cortex; VS: ventral striatum; WM: white matter. *comparison between ICB+ vs ICB- ** variable differing between groups but included as covariate in the analyses.

Table 3

Table 3. Key details of the single functional study on de novo patients including imaging technique, patient numbers, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICB diagnosis	ICB type: N	Matched variables	Unmatched variables	Differences in brain region*	Findings: ICB+ vs ICB-
Longitudinal								
Tessitore, De Micco et al. 2017	rs-fMRI	ICB+: 15 ICB-: 15	QUIP-rs; clinical interview	HS: 6; BE: 5; GD:2; CS:2	Sex, age, education, PD duration, H&Y, UPDRS-III, Total LEDD, DA-LEDD, BDI-II, MMSE	NR	Increased connectivity in the left OFC within the SN; DMN coupling with the right CEN	ICB+↑
							Decreased connectivity in the left supramarginal gyrus within the right CEN; the left precuneus and right middle temporal gyrus within the DMN	ICB+ ↓

Legend. BDI-II: Beck depression inventory II; BE: binge eating; CEN: central executive network; CS: compulsive shopping; DA-LEDD: dopamine agonists equivalent daily dose; DMN: default-mode network; GD: gambling disorder; HS: hypersexuality; H&Y: Hoehn & Yahr score; ICB: impulsive compulsive behaviour; ICB+: PD patients with ICB; ICB-: PD patients without ICB; MMSE: Mini-mental state examination; NR: not reported; OFC: orbitofrontal cortex; PD: Parkinson's disease; QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – rating scale; Ref.: reference; rs-fMRI: resting state functional magnetic resonance imaging; SN: salience network; Total LEDD: levodopa equivalent daily dose total; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score. *comparison between ICB+ vs ICB-.

Table 4

Table 4. Key details of the thirteen functional studies on DRT patients including imaging technique, patient numbers, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICB diagnosis	ICB type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs ICB-
Cross-sectional									
Carriere et al. 2015	rs-fMRI	ICB+: 19 ICB-: 17	QUIP; semi-structured interview	HS:14; GD:7; BE: 7; CS: 5	Sex, age, PD duration, H&Y, UPDRS-III, total LEDD, DA-LEDD, MMSE	NR	Patients assessed after having received their usual antiparkinsonian medication	Decreased functional connectivity between left anterior putamen, left inferior temporal and anterior cingulate gyri	ICB+ ↓
Cilia et al. 2008	SPECT	ICB+: 11 ICB-: 40	DSM-IV-TR; SOGS	GD: 4; GD+HS+BE:4; GD +HS+CS:1; GD +HS+CS+IA:1; GD +BE+HS+IA+CS :1	Sex, age, age at PD onset, PD duration, H&Y, UPDRS-III, total LEDD, DA-LEDD, GDS, MMSE	NR	Patients assessed in the morning during medication use	Increased brain perfusion: right OFC to insula, right hippocampus to parahippocampal gyrus, right amygdala, right ventral pallidum to NAc, left insula, right precuneus to cuneus and PCC, left precuneus to cuneus and PCC.	ICB+↑
Cilia et al. 2011	SPECT	ICB+: 15 ICB-: 15	DSM-IV-TR; SOGS	NR	Sex, age, PD duration, H&Y, UPDRS-III, total LEDD, DA-LEDD, GDS, MMSE	NR	Patients assessed in the morning on-medication	Connectivity analysis: lack of covariance between the VLPFC and ACC, PCC; between the ACC and VS Presence of covariance of ACC with insula, supplementary motor area, and cerebellum; VLPFC with ventral pallidum; medial prefrontal cortex with PCC; parahippocampal gyrus with insula	ICB+ ↓ ICB+↑
Claassen et al. 2017	ASL (ON/OFF)	ICB+: 17 ICB-: 17	QUIP; semi-structured interview (patient and spouse)	Hobbyism:11; HS: 10; CS: 4; BE:12	Sex, age, PD duration, UPDRS-III (OFF medication), total LEDD, DA-LEDD, AMNART, CESD-R, MoCA	UPDRS-III (ON medication): ICB+<ICB-;	Before MRI scan, patients assessed by UPDRS III in the on-DA and off-Dopamine (LD + DA) state. Off condition: withdrawal for at least 36 hours for DA and 16 hours for LD. On condition: after taking prescribed DA medication, having withheld LD for at least 16 hours	OFF state: no differences ON state: CBF increase in VS and frontal cortex, (ICB-: no CBF increase)	ICB+=ICB- ICB+↑
Frosini et al. 2010	Task-based fMRI (gambling-related visual cues and neutral stimuli)	ICB+: 7 ICB-: 7	DSM-IV-TR	GD:5; GD+ HS:1; GD+BE:1	Age, PD duration, UPDRS-III, total LEDD, DA-LEDD, MMSE	NR	MRI scan performed after overnight drug washout (at least 12 hours)	Increased cue-related BOLD response bilaterally in the ACC, medial and superior frontal gyri and precuneus with right prevalence, right inferior parietal lobule, and left VS	ICB+↑
Girard et al. 2019	Task-based fMRI (temporal discounting ON/OFF)	ICB+: 13 ICB-: 14	Arduin scale; clinical interview	HS: 2; HS+CS: 1; HS+BE: 8; HS+hobbyism: 9; HS+hyperactivity : 5	Age, PD duration, UPDRS-III (ON and OFF), total LEDD, LD-LEDD, DA-LEDD	NR	MRI scan performed both ON and OFF in counterbalanced order, one day apart. ON: 1h after a levodopa challenge (single supraliminar levodopa	ON medication, when exposed to erotic picture after waiting for longer periods: increase activity in the anterior medial prefrontal/rostral ACC. ICB+ negative correlation between subjective value of the delayed reward and activity in the medial	ICB+↑

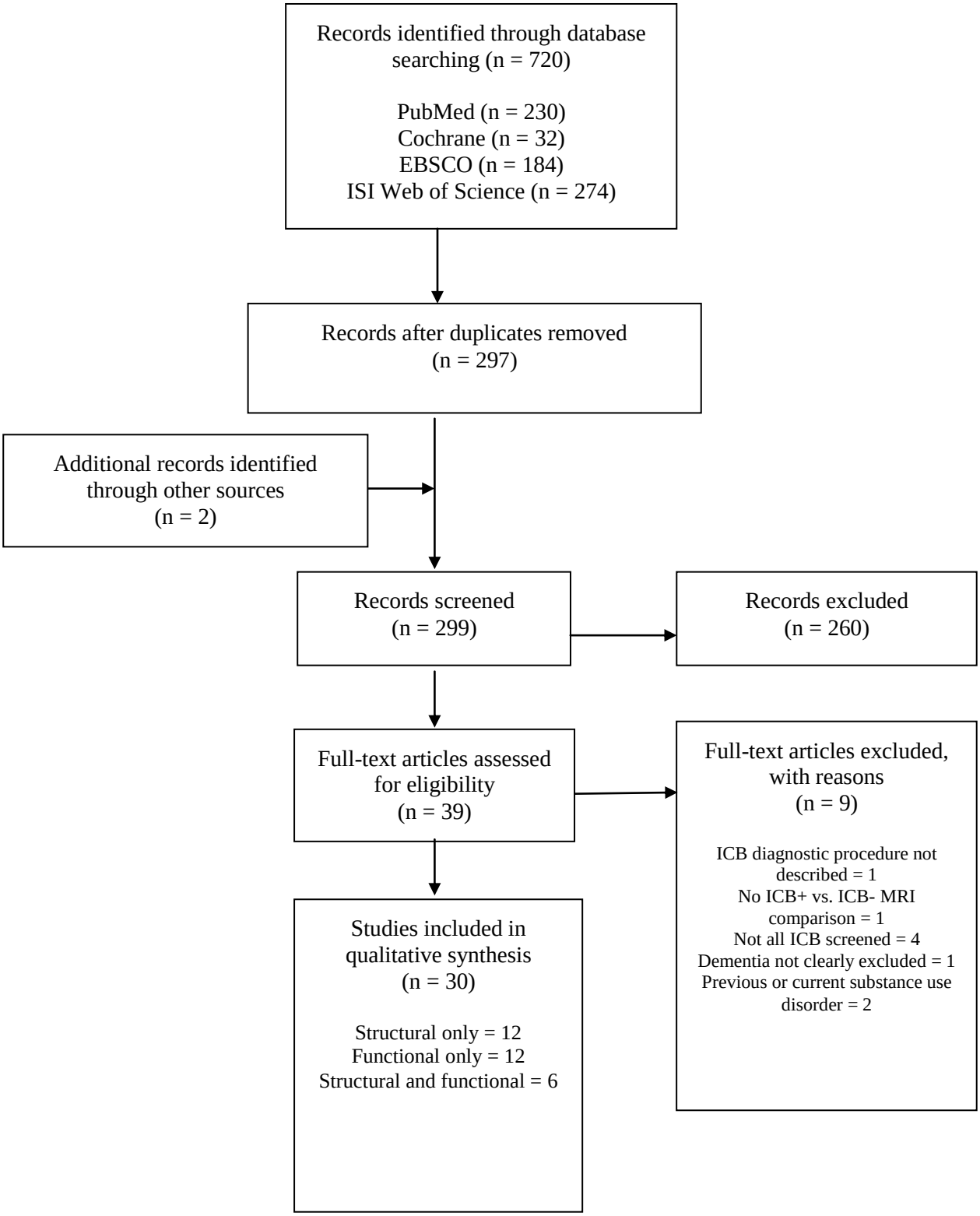
							dose intake corresponding to 150% of the usual morning dose). OFF: after at least 12-h overnight antiparkinsonian drugs withdrawal	prefrontal cortex and VS (opposite pattern in ICB-).	
Imperiale et al. 2018	rs-fMRI	ICB+: 35 ICB-: 50	QUIP; clinical interview	GD: 4; HS: 4; CS: 1; BE: 3; punding: 15; DDS: 5; BE+ punding: 1; GD + punding: 1; DDS+ punding: 1	Sex, age, education, age at PD onset, PD duration, H&Y, UPDRS-III, total LEDD, DA-LEDD, MMSE	Depression (HDRS): ICB+>ICB-**; Apathy scale: ICB+>ICB-**	NR	Decreased functional connectivity of the right precentral gyrus, rolandic operculum and superior temporal gyrus within the sensorimotor network	ICB+ ↓
Loane et al. 2015	Task-based fMRI (rewarding cues and neutral stimuli, ON/OFF)	ICB+: 6 ICB-: 12	Clinical interview	All DDS with at least another ICB (GD; BE; HS; BE+ GD; BE+HS)	Sex, age, PD duration, total LEDD, LD-LEDD, DA-LEDD, MMSE	UPDRS-III (ON and OFF medication): ICB+>ICB-	Participants scanned in OFF medication condition and in ON medication condition after receiving an oral dose of LD 45 min prior to the scan starting. Motor performance was assessed with the UPDRS-III at baseline and immediately before scanning to ensure response to medication	Both ON and OFF medication (neural-cues): increased BOLD activity in the VS, ACC, BA 6, IFG and midbrain post drug-cues vs. neutral-cues exposure: increased BOLD activity in VS, ACC, BA 6, IFG and midbrain.	ICB+↑
Marin-Lahoz et al. 2020	PET	ICB+: 9 ICB-: 15	QUIP; QUIP-rs; clinical interview	HS: 2; BE: 3; hobbyism: 3; BE+hobbysm: 1	Sex, age, education, age at PD onset, PD duration, UPDRS-III, total LEDD, DA-LEDD	NR	All the neuroimaging acquisitions were performed in ON state	Glucose metabolism in PCC, bilateral supramarginal gyrus, right precuneus, bilateral fusiform gyrus, bilateral lingual, parahippocampal gyrus, left anterior insula, bilateral amygdala, bilateral uncus, bilateral inferior OFC, right BA10, left BA46, and left BA6	ICB+ ↑
Markovic et al. 2017	rs-fMRI	ICB+: 22 ICB-: 30	Interview including a semi-structured part (patients and caregivers)	Punding:17; Punding + BE: 2; Punding + GD: 1; Punding + DDS: 1; Punding + HS:1	Sex, age, education, age at PD onset, PD duration, H&Y, UPDRS-III, total LEDD, DA-LEDD	NR	NR	Increased connectivity of the left habenula and the thalamus and striatum bilaterally and left posterior cingulum; between the right habenula and dorsal thalamus bilaterally; between the left amygdala and the thalamus bilaterally and left striatum; between the right amygdala and the left thalamus and caudate	ICB+ ↑
								Decreased connectivity between the left habenula and the left frontal cortex; between the right habenula and the left posterior parietal regions; between the right amygdala and the right hippocampus	ICB+ ↓
Navalpotro-Gomez et al. 2020	rs-fMRI	ICB+: 16 ICB-: 20	QUIP; QUIP-rs; clinical interview	HS: 3; BE: 2; CS: 1; HS+BE: 2; GD+BE: 1; CS+hobbyism: 2; BE+ hobbyism: 3; HS+CS+BE:	Sex, age, education, premorbid IQ, PD duration, UPDRS-III, H&Y, total LEDD, DA-LEDD	NR	PD patients were studied under the effect of their usual dopaminergic medication.	Engaged for a longer time in a brain configuration patter characterized by enhanced within-network functional connectivity in temporal, frontoinsular, and cingulate cortices, key nodes of the SN	ICB+ ↑

				1; HS+CS+ punding+hobbyism: 1					
Paz-Alonso et al. 2020	Task-based fMRI (Iowa Gambling Task)	ICB+: 18 ICB-: 17	QUIP; QUIP-rs; clinical interview	HS: 3; BE: 3; HS+BE: 2; GD+BE: 1; CS+hobbyism: 2; BE+ hobbyism: 3; HS+CS+BE: 1; HS+CS+ punding+hobbyism: 1; HS+CS+BE+punding: 1; CS+BE+hobbyism:1	Sex, age, education, premorbid IQ, PD duration, UPDRS-III, H&Y, total LEDD, DA-LEDD	NR	All assessments and MRI scanning of PD patients were done in the morning while they were still under the effect of their first regular dose of dopaminergic medication.	During IGT performance, hyperactivation in right subthalamic nucleus, right IFG, right VS	ICB+ ↑
Petersen et al. 2018	rs-fMRI (ON/OFF)	ICB+: 19 ICB-: 18	QUIP; semi-structured interview (patient and spouse)	Hobbyism:12; BE:13; HS:12; CS:4	Sex, age, PD duration, total LEDD, DA LEDD, CES-D	NR	Patients refrain from taking all dopaminergic medications prior to the off-dopamine therapy scan (16 h for LD, 36 h for DA) For the on-DA scan, patients took their prescribed DA dosage (but not LD)	Increased connectivity between VS and the dorsal anterior cingulate gyrus, OFC, insula, putamen, globus pallidus, and thalamus. No main effect for drug.	ICB+ ↑
Politis et al. 2013	Task-based fMRI (sexual cues, rewarding cues and neutral stimuli, ON/OFF)	ICB+: 12 ICB-: 12	Proposed operational diagnostic criteria	HS:4; HS+CS:2; HS+DDS:2; HS+CS+BE:2; HS+ GD +BE+CS:1; HS+DDS+GD+BE:1	Sex, age, PD duration, UPDRS-III (ON and OFF medication), total LEDD, MMSE	LD LEDD: ICB+<ICB-; DA LEDD: ICB+>ICB-	Patients scanned in OFF medication condition and in ON medication condition after receiving an oral dose of LD 45 min prior to the scan starting. Motor performance was assessed with the UPDRS-III at baseline and immediately before scanning to ensure response to medication (defined as >25% improvements in UPDRS-III scores)	Sexual cues vs neutral stimuli: Increased BOLD activity in the OFC, ACC, PCC, left amygdala, VS, hypothalamus, anterior prefrontal cortex, superior parietal lobule, lateral right inferior parietal lobule (in ON and OFF) Decreased BOLD activity in the insula and right claustrum (in the OFF scan only)	ICB+ ↑ ICB+ ↓
Ruitenberg et al. 2018	rs-fMRI	ICB+: 21 ICB-: 30	QUIP	GD: 1; HS:9; CS:7; BE:11; others:6; 9 multiple ICBs	Sex, age, age at PD onset, PD duration, UPDRS-III, total LEDD, MoCA, NART-R	NR	Patients were tested while their symptoms were being well controlled by DRT. UPDRS-III was used to assess motor symptoms	Increased connectivity between the left subthalamic nucleus and the left parietal operculum	ICB+ ↑
Tessitore, Santangelo al. 2017	rs-fMRI	ICB+: 15 ICB-: 15	MIDI	HS:13; BE:8; GD:1	Sex, age, education, PD duration, H&Y, UPDRS-III, total	--	Patients were assessed in the morning during the ON medication state	Increased activity in bilateral insula and right ventral striatum (SN), and left middle temporal gyrus (DMN)	ICB+ ↑

					LEDD, DA-LEDD, HAM-D, HADS, MMSE			Decreased activity in DLPFC and the inferior parietal cortices (CEN)	ICB+ ↓
Verger et al. 2018	PET	ICB+: 18 ICB-: 18	MIDI; DSM-IV-TR; clinical interview	GD:4; HS: 2; CS:3 GD+HS:4; CS+ GD:3; CS+ HS:3; ICB+DDS:3	Sex, age, PD duration, H&Y (OFF medication), UPDRS-III (ON and OFF medication), total LEDD, DA-LEDD, Mattis scale, BDI, LARS	NR	NR	Increased metabolism in right middle and inferior temporal gyri	ICB+ ↑
								Increased positive connectivity with right middle and inferior temporal gyri and right middle temporal gyrus, right middle and inferior frontal gyri, right middle and superior temporal gyri and parietal inferior lobule	ICB+ ↑
								Increased negative connectivity with right middle and inferior temporal gyri and left caudate and right parahippocampal gyrus	ICB+ ↑

Legend. ACC: anterior cingulate cortex; AMNART: American version of the national adult reading test; ASL: arterial spin labeling; BA: Brodmann Area; BDI: Beck Depression Inventory; BE: binge eating; BOLD: blood oxygen level dependent signal; CBF: cerebral blood flow; CEN: central executive network; CESD-R: Center for Epidemiologic Studies Depression Scale Revised; CS: compulsive shopping; DA: dopamine agonists; DA-LEDD: dopamine agonists equivalent daily dose; DDS: dopamine dysregulation syndrome; DSM-IV-TR: Diagnostic and statistical manual of mental disorders – fourth edition text revision; DLPFC: dorsolateral prefrontal cortex; DMN: default mode network; DRT: drug replacement therapy; fMRI: functional magnetic resonance imaging; GD: gambling disorder; GDS: geriatric depression scale; HADS: Hospital anxiety and depression scale; HAM-D: Hamilton depression rating scale; H&Y: Hoehn & Yahr score; HS: hypersexuality; IA: internet addiction; ICB: impulsive compulsive behaviour; ICB+: PD patients with ICB; ICB-: PD patients without ICB; IFG: inferior frontal gyrus; LARS: Lille Apathy Rating Scale; LD-LEDD: levodopa equivalent daily dosage levodopa only; LD: levodopa; MIDI: Minnesota Impulsive Disorders Interview; MMSE: Mini-mental state examination; MoCA: Montreal cognitive assessment; MRI: magnetic resonance imaging; NAc: nucleus accumbens; NART-R: National adult reading test-revised; OFC: orbitofrontal cortex; PET: positron emission tomography; PCC: posterior cingulate cortex; PD: Parkinson's disease, ref.: reference; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease; QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – rating scale; rs-fMRI: resting state functional magnetic resonance imaging; SOGS: South Oaks gambling screen test; SN: salience network; SPECT: single photon emission computed tomography; Total LEDD: levodopa equivalent daily dose total; UPDRS-III: Unified Parkinson's disease rating scale part III (motor subscale) score; VLPFC: ventrolateral prefrontal cortex; vmPFC: ventromedial prefrontal cortex; VS: ventral striatum; *comparison between ICB+ vs ICB-.

Figure 1


Records identified through database searching (n = 720)
PubMed (n = 230)
Cochrane (n = 32)
EBSCO (n = 184)
ISI Web of Science (n = 274)
Records after duplicates removed (n = 297)
Additional records identified through other sources (n = 2)
Records screened (n = 299)
Records excluded (n = 260)
Full-text articles assessed for eligibility (n = 39)
Full-text articles excluded, with reasons (n = 9)
ICB diagnostic procedure not described = 1
No ICB+ vs. ICB- MRI comparison = 1
Not all ICB screened = 4
Dementia not clearly excluded = 1
Previous or current substance use disorder = 2
Studies included in qualitative synthesis (n = 30)
Structural only = 12
Functional only = 12
Structural and functional = 6