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# Neural correlates of impulse control behaviors in Parkinson's disease: Analysis of multimodal imaging data

Hamzah Baagil [a,b], Christian Hohenfeld [a,b], Ute Habel [c,d], Simon B. Eickhoff [e,f], Raquel E. Gur [g], Kathrin Reetz [a,b,*], Imis Dogan [a,b]

[a] Department of Neurology, RWTH Aachen University, Pauwelsstraße 30, Aachen, Germany
[b] JARA-BRAIN Institute Molecular Neuroscience and Neuroimaging, Research Center Jülich and RWTH Aachen University, Germany
[c] Department of Psychiatry, Psychotherapy and Psychosomatics, RWTH Aachen University, Pauwelsstraße 30, Aachen, Germany
[d] JARA-BRAIN, Jülich-Aachen Research Alliance, Institute of Brain Structure-Function Relationships, Aachen, Germany
[e] Institute for Systems Neuroscience, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany
[f] Institute of Neuroscience and Medicine, Brain and Behaviour (INM-7), Research Center Jülich, Germany
[g] Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

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ABSTRACT

*Background:* Impulse control behaviors (ICB) are frequently observed in patients with Parkinson's disease (PD) and are characterized by compulsive and repetitive behavior resulting from the inability to resist internal drives.
*Objectives:* In this study, we aimed to provide a better understanding of structural and functional brain alterations and clinical parameters related to ICB in PD patients.
*Methods:* We utilized a dataset from the Parkinson's Progression Markers Initiative including 36 patients with ICB (PDICB+) compared to 76 without ICB (PDICB-) and 61 healthy controls (HC). Using multimodal MRI data we assessed gray matter brain volume, white matter integrity, and graph topological properties at rest.
*Results:* Compared with HC, PDICB+ showed reduced gray matter volume in the bilateral superior and middle temporal gyrus and in the right middle occipital gyrus. Compared with PDICB-, PDICB+ showed volume reduction in the left anterior insula. Depression and anxiety were more prevalent in PDICB+ than in PDICB- and HC. In PDICB+, lower gray matter volume in the precentral gyrus and medial frontal cortex, and higher axial diffusivity in the superior corona radiata were related to higher depression score. Both PD groups showed disrupted functional topological network pattern within the cingulate cortex compared with HC. PDICB+ vs PDICB- displayed reduced topological network pattern in the anterior cingulate cortex, insula, and nucleus accumbens.
*Conclusions:* Our results suggest that structural alterations in the insula and abnormal topological connectivity pattern in the salience network and the nucleus accumbens may lead to impaired decision making and hypersensitivity towards reward in PDICB+. Moreover, PDICB+ are more prone to suffer from depression and anxiety.

## 1. Introduction

Parkinson's disease (PD) is associated with a spectrum of non-motor symptoms including cognitive, autonomic and neuropsychiatric abnormalities (Schapira et al., 2017). PD patients may experience changes in affective or goal-directed behaviors that can manifest as impulsivity

*Abbreviations:* AD, axial diffusivity; CSF, cerebrospinal fluid; DLPC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; ESS, Epworth Sleepiness Scale; FA, fractional anisotropy; FWHM, full width at half maximum; GDS, Geriatric Depression Scale; GM, gray matter; HC, healthy controls; H&Y, Hoehn and Yahr rating scale; HVLT-R, Hopkins Verbal Learning Test-Revised; ICB, impulse control behaviors; LEDD, Levodopa Equivalent Daily Dose; MD, mean diffusivity; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; OFC, orbitofrontal cortex; PD, Parkinson's disease; PDICB-, Parkinson's disease patients without impulse control behaviors; PDICB+, Parkinson's disease patients with impulse control behaviors; PPMI, Parkinson's Progression Markers Initiative; QUIP, Questionnaire for Impulsive-Compulsive Disorders; RBD, REM sleep behavior disorder; RD, radial diffusivity; SDMT, Symbol-Digit Modalities Test; STAI, State-Trait Anxiety Inventory; TBSS, Tract-Based Spatial Statistics; TIV, total intracranial volume; VBM, voxel-based morphometry; WM, white matter.

* Corresponding author at: Department of Neurology, RWTH Aachen University, Pauwelsstraße 30, 52074 Aachen, Germany.
*E-mail address:* k.reetz@fz-juelich.de (K. Reetz).

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(Eisinger et al., 2019). Impulse control behaviors (ICB) are commonly observed in PD patients and are characterized by compulsive and repetitive behavior that can be excessive and harmful resulting from the inability to resist internal drives (Fantini et al., 2019; Izzo et al., 2019; Weintraub et al., 2015). These behaviors include pathological gambling, hypersexuality, compulsive shopping, eating disorders (Fantini et al., 2019; Weintraub, 2019) and other compulsive-related disorders such as punding, hoarding and compulsive PD medication use (Gatto and Aldinio, 2019). In the general population the prevalence of ICB varies from 0.2 to 5.3 % (Weintraub et al., 2015). The estimated prevalence of PD patients with ICB varies from 20 % to 46 % (Corvol et al., 2018; Weintraub and Claassen, 2017). Determining the true frequency of ICB in the general population and in PD patients represents a significant challenge since several variables must be considered, including regular and standardized assessment tools, dopaminergic medication (L-dopa or dopamine agonists), medication dose, disease duration as well as ethnic and cultural backgrounds (Gatto and Aldinio, 2019; Weintraub and Claassen, 2017).

Previous studies suggest that dysregulation in the dopaminergic system in PD plays a considerable role in the development of ICB (Eisinger et al., 2019; Gatto and Aldinio, 2019; Vriend, 2018; Weintraub et al., 2015). Dopamine replacement therapy, which is used in PD to restore dopamine depletion in the substantia nigra, can also affect meso-cortico-limbic circuitry (Meyer et al., 2019; Vriend, 2018). Over-stimulation of the meso-cortico-limbic pathway may cause abnormal motivation and reward-related decision making and thus increase the risk for ICB (Martini et al., 2018).

Another highly relevant clinical aspect is the relationship between non-motor symptoms and ICB in PD. Studies have reported associations between depression, anxiety and REM sleep behavior disorder (RBD) with ICB (Cao et al., 2022; Fantini et al., 2019). There is evidence that PD patients differ concerning their cognitive profiles (Rottschy et al., 2013), akinetic-rigid PD being associated with a faster cognitive decline especially in executive functions compared to tremor-dominant PD (Michels et al., 2022; Wojtala et al., 2019). A recent meta-analysis by Martini and colleagues reported worse set-shifting and reward-related decision making for PDICB+ patients compared with PDICB- suggesting the importance of executive function deficits in ICB (Martini et al., 2018).

Neuroimaging studies have yielded important insight into brain dysfunctions associated with ICB in PD. Structural imaging studies on ICB in PD have shown inconsistent results. While some studies observed cortical thinning in the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPC), globus pallidus externa and corpus callosum in PDICB+ compared with PDICB- patients (Biundo et al., 2015; Ruitenberg et al., 2018; Yoo et al., 2015), others showed an increase in cortical thickness in the anterior cingulate cortex and OFC in PDICB+ patients (Pellicano et al., 2015; Tessitore et al., 2016). In contrast, some studies reported no morphometric differences between PDICB+ and PDICB- patients (Carriere et al., 2015; Ricciardi et al., 2018). There are only a few diffusion tensor imaging (DTI) studies on ICB in PD reporting white matter alterations in the corpus callosum, parahippocampal, pedunculopontine, uncinate fasciculus, cingulate cortex in PDICB+ patients compared with PDICB- and controls (Canu et al., 2017; Imperiale et al., 2018). Some resting-state fMRI studies have reported reduced functional connectivity (Carriere et al., 2015; Hammes et al., 2019a) between the frontal regions and the limbic circuit as well as executive and default mode networks, while others reported increased connectivity (Koh et al., 2020; Petersen et al., 2018). Nevertheless, there is a general agreement that disruptions between the anterior cingulate cortex and the ventral striatum seem to play an important role in the development of ICB in PD patients (Girard et al., 2019; Petersen et al., 2018; Tessitore et al., 2017a). However, given the inconsistent findings, further research is required, and a multimodal approach might help to understand the structural and functional alterations related to ICB in PD.

Utilizing a dataset from the Parkinson's Progression Markers Initiative (PPMI) we aimed to provide a better understanding of the mediating factors as well as the neural correlates underlying ICB in PD using a multimodal neuroimaging approach including structural, diffusion, and resting state fMRI. We hypothesized to find dysfunctions in regions related to reward processing, decision making, and emotion regulation including the ventral striatum, the prefrontal cortex, the insula, the amygdala and the cingulate cortex in PD patients with ICB. We analyzed functional topological network pattern within the limbic and salience networks, regions that have been associated with ICB. We also expected PD patients with ICB to have higher rates of sleep disorders, depression, and anxiety compared with those without ICB.

## 2. Methods

### 2.1. Study population

We utilized a dataset from the Parkinson's Progression Markers Initiative (PPMI) which is available online (https://www.ppmi-info.org/data). The PPMI is an observational, international, multicenter study designed in parts to identify PD progression biomarkers and improve understanding of disease etiology (Marek et al., 2018, 2011). All subjects were enrolled after obtaining informed consent. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines after approval of the ethics committees. PD subjects were only eligible if diagnosis was confirmed by dopamine transporter (DAT) imaging demonstrating dopaminergic deficit consistent with PD in addition to clinical features of the disease. We selected only participants who underwent 3T MRI scanning and T1 MPRAGE acquisition to create a homogeneous dataset. Of the PPMI database this was mainly the case for measurements at the timepoint 4 years following PD diagnosis, at which most PD patients were identified having ICB as assessed by Questionnaire for Impulsive-Compulsive Disorders (QUIP)-Current-Short, the most commonly used validated self-reported screening tool in PD patients (Weintraub et al., 2009). The inclusion criteria were the presence of one or more of ICB including pathological gambling, compulsive buying, hypersexuality, compulsive eating, punding, dopamine dysregulation syndrome or hobbyism based on cutoff scores described previously (Weintraub et al., 2009), $\geq$ 1 affirmative answer, for the PD patients with ICB (PDICB+) group. PD patients without ICB (PDICB-) and healthy controls (>40 years of age) were included in the study, if they showed no presence of any ICB in the QUIP. Subjects were only excluded if imaging data failed specific quality control criteria. This resulted in 36 PD patients with ICB (PDICB+), 76 PD patients without ICB (PDICB-), and 61 healthy controls (HC). For DTI analysis data was available of 36 PDICB+, 75 PDICB-, and 40 HC subjects; and for resting-state fMRI 21 PDICB+, 44 PDICB-, and 18 HC subjects were included in final analyses. Due to data availability, 5 additional HC subjects from the PPMI database were included from a different timepoint where resting state fMRI data was available since the sample size would otherwise be too small.

### 2.2. Motor and non-motor assessments

Clinical assessments included Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Hoehn and Yahr scales. The standardized acquisition of PPMI data includes, amongst others, brain imaging, clinical, and neuropsychological assessments. Neurobehavioral tests included the Geriatric Depression Scale (GDS-Short version) and State-Trait Anxiety Inventory (STAI). A cut-off score of $\geq$ 5 points was used to consider an individual of having depression symptoms assessed by GDS (Alden et al., 1989). Neuropsychological testing included the Montreal Cognitive Assessment (MoCA) to assess global cognitive function; the Hopkins Verbal Learning Test-Revised (HVLT-R) to assess memory; Benton Judgment of Line Orientation 15-item version to assess visuospatial function; Symbol-Digit Modalities Test (SDMT) to assess processing speed and attention; Letter-Number

sequencing to assess working memory; and semantic fluency to assess executive function and semantic memory. Sleep disorder was assessed with the REM Sleep Behavior Disorder Questionnaire (RBDSQ) and Epworth Sleepiness Scale (ESS). The dosage of PD medication for each participant was converted to a Levodopa Equivalent Daily Dose (LEDD) (Tomlinson et al., 2010). For normally distributed data one-way Analysis of Variance (ANOVA) was performed to assess group differences (PDICB+, PDICB-, and HC) in motor and non-motor symptoms. Kruskal-Wallis test was used if the data violated the normal distribution. In case of a significant difference ($p < 0.05$), *post hoc* two-sample T-tests or a Mann-Whitney U-tests were used.

### 2.3. MRI data acquisition

The imaging data were acquired on a 3-Tesla Siemens MRI scanner. T1-weighted images were acquired using 3D MPRAGE sequence (TR = 2300 ms, TE = 3 ms, TI = 900 ms, flip angle = 9°, acquisition matrix = 240 × 256, 176 sagittal slices and slice thickness = 1 mm). DTI data were obtained using a two-dimensional echo-planar sequence (TR = 900 ms, TE = 88 ms, flip angle = 90°, 64 gradient directions with a *b*-value of 1000 s/mm$^2$ and one b0 image, acquisition matrix = 1044 × 1044 and slice thickness = 2 mm). Resting-state fMRI scans were acquired using echo-planar sequence (TR = 2400 ms, TE = 25 ms, flip angle = 80°, 210 slices and slice thickness = 3.3 mm).

### 2.4. Analysis of structural MRI data

For processing and analysis of structural MRI data, we used the Computational Anatomy Toolbox version 12.7 (CAT12.7) (http://www.neuro.uni-jena.de/cat/) based on the Statistical Parametric Mapping Software version 12 (SPM12) (Welcome Department of Imaging Neuroscience Group, London, UK; https://www.fil.ion.ucl.ac.uk/spm/) running on the MATLAB R2019b environment (The Mathworks, Natick, MA, USA). Regional gray matter (GM) and white matter (WM) differences were analyzed by means of voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Good et al., 2001). All T1-weighted images were checked and manually realigned in SPM12, with the origin set to the anterior commissure to ensure a common orientation and improve spatial registration, prior to the automated preprocessing of CAT12. T1-weighted images were spatially normalized to a template brain image using an affine and non-linear registration (DARTEL and Geodesic Shooting), corrected for bias field inhomogeneities, and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Modulated and normalized GM and WM images were smoothed using 8 mm full width at half maximum (FWHM) Gaussian Kernel. Morphological differences between PDICB+, PDICB-, and controls were tested using one-way ANOVA and by including age, gender, and total intracranial volume (TIV) as covariates. In case of a significant difference, *post hoc* two-sample T-tests were used. In addition, we conducted correlation analysis to assess the relationships between brain volumes and MDS-UPDRS parts I and III as well as risk factors associated with ICB including depression scale (GDS), anxiety scale (STAI), and REM sleep disorder questionnaire (RBDSQ) with age, gender, and TIV as covariates of no interest within each of group corrected for multiple comparisons across the whole brain. A nonparametric permutation test with 5000 permutations was used to assess significance at $p < 0.05$ family-wise error (FWE) corrected using threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009).

### 2.5. Analysis of diffusion MRI data

Diffusion data were preprocessed and analyzed using FMRIB Software Library version 6.0 (FSL; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (Jenkinson et al., 2012). First, images were brain extracted using FSL Brain Extraction Tool (BET) (Smith, 2002) to remove non-brain tissue. Next, FSL eddy tool was used to correct for eddy currents and subject movements (Andersson and Sotiropoulos, 2016). Slices with outlying data points were corrected by the Gaussian Process prediction (Andersson et al., 2016) to minimize signal loss. Finally, diffusion tensors were fitted on corrected diffusion-weighted images using the FSL DTIFIT toolbox, thereby generating maps of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD).

Voxel-wise statistical analysis of the FA data was carried out using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) as part of FSL (Smith et al., 2004). Prior to TBSS analysis, all images were reoriented to standard space for data control. All subjects' FA data were then aligned into a common space, the FMRIB58_FA, using the nonlinear registration tool FNIRT (Andersson et al., 2007a, 2007b). Next, a mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. The threshold for the mean FA skeleton was 0.2 to avoid too much cross-subject variability and statistical interference by gray matter. Each subject's aligned FA data was then projected onto this skeleton. The same statistical tests as for the structural analysis were applied (see above). Similar to the structural data, a nonparametric permutation test with 5000 permutations was used to assess significance at $p < 0.05$ FWE-corrected using TFCE. Maps of MD, AD, and RD were also compared in an analogous fashion.

### 2.6. Analysis of resting-state fMRI data

We used graph theory analysis to characterize functional properties of brain networks. Graph contains nodes and edges, where nodes represent brain regions and edges the connection between regions. Graph theory analysis can give information on the connections of brain regions with the rest of the brain, the length of these connections or the relationship with their nearest regions. We specifically looked at the salience network and limbic regions including the anterior cingulate cortex, middle cingulate gyrus, insula, amygdala, nucleus accumbens, and the ventral tegmental area. These regions have been shown to be associated with ICB in PD.

For preprocessing of functional data tools from FSL were employed via a wrapper package implemented in R (R Core Team 2020, https://www.R-project.org/). Functional data was skull stripped, co-registered to an anatomical scan of the same session and then transformed into standard space. Further time courses of cerebrospinal fluid and white mater were extracted from the data based on coordinates; data was then motion and slice scan-time corrected. Movement parameters as well as time course of cerebrospinal fluid and white matter were then regressed out of the data. Time courses were then extracted for 166 regions available in the AALv3.1 atlas (Rolls et al., 2020), and band-pass filtered with cut-offs of 0.01 and 0.15 Hz. The time courses obtained from preprocessing were correlated pair-wisely and the resulting correlation matrix was used to construct an undirected graph with regions as nodes and correlations as edge weights. Loops representing correlations of a region with itself were removed from the graph.

For analysis proportional thresholding was applied to the graphs. A common value for binarization was sought across all subjects by determining the largest possible threshold for inclusion of edges that would still keep the graphs as one component. If the threshold was near-zero for a subject, this data set was removed from the analysis, as this pointed towards failed co-registration or a too narrow field of view at acquisition – resulting in the exclusion of one subject. The lowest of the so obtained threshold of non-excluded subjects was then applied to all datasets, leading to equal sized graphs for all subjects. Next, we examined the motion parameters, determining whether motion for subjects exceeded 2 mm translation or 2° rotation. Subjects exceeding these values were also excluded from further analysis, resulting in the exclusion of 9 subjects.

For analyzing differences between groups, we computed the following measures: mean distance (the average length of all geodesics, i.e. the shortest paths) and diameter (the longest geodesic). At the regional level, we computed local efficiency (the mean distance between

a node's neighbors), local transitivity (proportion of possible connections between a node's neighbors and the total possible connections, betweenness (the number of times geodesics traverse a node), closeness (the inverse of the average geodesic to all other nodes), hubness (a metric indicating importance of a node), and degree (the total number of a node's connections). Nodal measures were compared as average between groups as well as for all regions included in this analysis. For comparisons between groups, we used a twofold approach: On the one hand we calculated linear models to characterize effects of individual groups and an ANOVA based on these models to characterize overall group effects. On the other hand, we also used Bayesian linear modelling, providing a more robust and nuanced, but also computationally heavier alternative to frequentist models. Using the implementation from the rstanarm package (Stan, 2022) we did fit models with weakly informative Gaussian priors and 4 Markov-chains with 2000 iterations each were used, with the first 1000 iterations for burn-in. To describe effects in frequentist terms, we used p-values as measure of effect existence. For Bayesian modelling we report the proportion of values in the region of practical equivalence (% ROPE) as measure of effect significance, and the probability of direction (pd) as measure of effect existence. We report all results with $p < 0.05$ and $pd > 0.97$ as threshold for likely existence of effects and %ROPE < 2.5 as threshold for probable significance of the effect controlled by age and gender. For MDS-UPDRS parts I and III, dopaminergic medication, depression scale (GDS), anxiety scale (STAI), and REM sleep disorder questionnaire (RBDSQ), we performed Pearson's product-moment correlations with graph measures corrected for multiple comparisons across the salience and limbic regions.

## 3. Results

### 3.1. Demographics and clinical assessments

In the PDICB+ group, 28 patients showed a single ICB, and 8 patients have multiple ICB. Most frequently observed ICB was hobbyism (31 %), followed by compulsive eating (22 %), hypersexuality (8%), and compulsive buying, punding and dopamine dysregulation syndrome (each 6 % respectively). Regarding age, gender, and years of education, all three groups were comparable (Table 1). For the clinical measures, the PDICB+ group showed higher score than PDICB- on the MDS-UPDRS part I ($p = 0.004$), which assesses non-motor experiences of daily living. In all other clinical measures, including motor score (MDS-UPDRS part III and Hoehn and Yahr score) and disease duration PDICB+ did not differ from PDICB-. The total LEDD was only slightly higher for the PDICB+ group compared with PDICB- ($p = 0.1$). Although number of patients receiving dopamine agonists was higher for the PDICB+ group (64 %) compared with PDICB- (38 %) ($p = 0.01$), the mean dopamine agonist dosage across those receiving dopamine agonists did not differ between groups.

Concerning cognition, the groups PDICB+, PDICB-, and HC only differed in the symbol digit modalities test which assesses processing speed and attention. Both PD groups scored lower compared with HC ($p = 0.004$ for PDICB+ and $p = 0.03$ for PDICB-). The groups also differed in severity of anxiety, depressive symptoms, and sleep disorder. Mean depression scores (GDS) were higher for both PD groups than HC ($p < 0.001$), and PDICB+ scored higher compared with PDICB- ($p = 0.03$). Depressive symptoms (GDS $\geq 5$ points) were more frequent in PDICB+ (33 %) than in PDICB- (12 %) ($p = 0.006$) and HC (5 %) ($p < 0.001$). Both PDICB+ and PDICB- scored higher on the state-anxiety test (STAI-state) than HC ($p < 0.001$ and $p = 0.009$ for PDICB+ and PDICB-, respectively). Between the PD groups, there was a tendency towards higher state-anxiety levels within the ICB+ group compared with the ICB- group ($p = 0.09$). In the trait-anxiety test (STAI-trait), PDICB+ subjects showed higher levels of anxiety compared with PDICB- and HC ($p = 0.02$ and $p < 0.001$, respectively). PDICB- trait-anxiety levels showed a tendency towards higher scores compared with HC ($p = 0.07$).

**Table 1**
Demographics, clinical, motor and non-motor assessments between PDICB+, PDICB-, and HC.

| | PDICB+ ($n = 36$) | PDICB- ($n = 76$) | HC ($n = 61$) | *P*-value |
|---|---|---|---|---|
| Age (years) | 65.7 (9.0) | 63.9 (10) | 64.1 (7.6) | 0.6[a] |
| Gender (males) | 24/36 | 52/76 | 42/61 | 1.0[b] |
| Education (years) | 15.7 (3.4) | 15.5 (2.5) | 16.5 (2.9) | 0.2[a] |
| Duration of PD (years) | 4.3 (0.7) | 4.4 (1.0) | – | 0.8[c] |
| MDS-UPDRS-I | 11.2 (6.3) †† | 7.5 (5.3) | – | 0.004[c] |
| MDS-UPDRS-II | 10.8 (7.5) | 9.2 (6) | – | 0.3[c] |
| MDS-UPDRS-III | 20.3 (14.1) | 20.8 (11.5) | – | 0.5[c] |
| H&Y | 1.9 (0.8) | 1.8 (0.5) | – | 0.8[c] |
| Total LEDD (mg) | 615 (231) | 586 (45) | – | 0.1[c] |
| Dopamine agonists (number of patients) | 23/36 (64 %) † | 29/76 (38 %) | – | 0.01[b] |
| Dopamine agonists LEDD (mg) | 186 (111) | 209 (152) | – | 0.7 [c] |
| **Cognition** | | | | |
| MoCA | 26.7 (3.7) | 27.6 (2.4) | 28.1 (1.1) | 0.2[a] |
| SDMT | 37.2 (13) * | 40.6 (11.1) * | 46.2 (10) | 0.002[d] |
| HVLT free recall | 23.9 (6.2) | 24.9 (5.5) | 25.7 (4.1) | 0.5[a] |
| LNS | 9.7 (3.7) | 10.6 (2.8) | 11.1 (2.4) | 0.1[a] |
| JOLO | 25.4 (4) | 26.1 (3.8) | 26.7 (3.2) | 0.3[a] |
| Semantic fluency | 50.9 (15.3) | 48.8 (11.6) | 51.1 (10.4 | 0.5[d] |
| **Mood questionnaires** | | | | |
| GDS score | 3.5 (2.8) **/† | 1.9 (1.9) ** | 1.1 (2.3) | < 0.001[a] |
| GDS | 12/36 (33 %) **/† | 9/76 (12 %) | 3/61 (5 %) | < 0.001[b] |
| State anxiety (STAI) | 35.6 (10.5) ** | 30.5 (7.6) * | 26.6 (6.9) | < 0.001[a] |
| Trait anxiety (STAI) | 36.4 (10.5) **/† | 30.9 (8.4) | 27.5 (6.7) | < 0.001[a] |
| **Sleep questionnaires** | | | | |
| RBD | 21/36 (58 %) ** | 33/76 (43 %) ** | 7/61 (11 %) | < 0.001[b] |
| ESS | 19/36 (53 %) **/† | 24/76 (32 %) ** | 4/61 (7 %) | < 0.001[b] |
| **Types of ICB** | | | | |
| Hypersexuality | 3 (8 %) | – | – | – |
| Compulsive buying | 2 (6 %) | – | – | – |
| Compulsive eating | 8 (22 %) | – | – | – |
| Hobbyism | 11 (31 %) | – | – | – |
| Punding | 2 (6 %) | – | – | – |
| DDS | 2 (6 %) | – | – | – |
| Multiple ICB | 8 (22 %) | – | – | – |

Data are given as means values (SD). Abbreviations: PD, Parkinson's disease; HC, healthy controls; ICB, Impulse Control Behaviors; MDS-UPDRS, Movement Disorders Society-Unified Parkinson Disease Rating Scale; H&Y, Hoehn and Yahr scales; LEDD, Levodopa Equivalent Daily Dose; MoCa, Montreal Cognitive Assessment; SDMT, Symbol-Digit Modalities Test; HVLT, Hopkins Verbal Learning Test; LNS, Letter-Number Sequencing; JOLO, Benton Judgment of Line Orientation; GDS, Geriatric Depression Scale; STAI, State-Trait Anxiety Inventory; RBD, REM sleep behavior disorder; ESS, Epworth Sleepiness Scale; DDS, Dopamine dysregulation syndrome.
A cut-off score of ≥5 points was used to consider an individual of having probable RBD assessed solely by RBD screening questionnaire.
A cut-off score of ≥5 points was used to consider an individual of having depression symptoms assessed by GDS.
Significant difference in PDICB+/PDICB- compared with HC at *P < 0.05 or **P < 0.001.
Significant difference in PDICB+ compared with PDICB- at †P < 0.05 or ††P < 0.001.
[a] Kruskal-Wallis test.
[b] $\chi^2$ test.
[c] Mann-Whitney test.
[d] One-way ANOVA.

Both PDICB+ (58 %) and PDICB- (43 %) were more likely to have RBD (RBDSQ ≥ 5 points) compared with HC (11 %; $p < 0.001$ for both comparisons; PDICB+ vs PDICB-: $p = 0.1$. The group of PDICB+ was more affected by daytime sleepiness (ESS ≥ 10 points) compared with PDICB- and HC (p = 0.03 and p < 0.001, respectively; prevalence was 53 % for PDICB+, 32 % for PDICB- and 7 % for HC).

### 3.2. Voxel-based morphometry

Between the three groups (PDICB+, PDICB-, and HC) there were significant GM differences. Reduced GM volume was found in PDICB+ compared with HC in the bilateral superior temporal gyrus extending to the left anterior insula, the left inferior frontal gyrus, and right amygdala, bilateral middle temporal gyrus, and the right middle occipital gyrus extending to the right angular gyrus (Fig. 1A, Table 2). In addition, volume reduction in PDICB+ compared with PDICB- was observed in the left anterior insula (Fig. 1B). Including risk factors of ICB as covariates (i.e., dopaminergic medication dose, depression-, trait anxiety-, and RBDSQ-score, respectively), GM volume reduction in the anterior insula remained for PDICB+ compared with PDICB-, however the difference was marginally below the threshold of significance after adjusting depression or RBDSQ (p = 0.07 and p = 0.09, respectively). No other significant volume differences were observed between the two PD groups or between PDICB- and HC. There were no significant differences in WM volumes between the three groups.

In the PDICB+ group, the right precentral gyrus (r = -0.379, p = 0.02) and the medial frontal cortex (right: r = -0.492, p = 0.002; left: r =

**Table 2**
Significant gray matter volume reductions in PDICB+ patients compared with PDICB- and HC.

| Anatomical region | L/R | Cluster extent | MNI co-ordinates x | y | z | $P_{FWE-corr}$ |
|---|---|---|---|---|---|---|
| PDICB+ < HC | | | | | | |
| Superior temporal gyrus, insula | L | 11,294 | −32 | 5 | −23 | 0.001 |
| Superior temporal gyrus, amygdala | R | 359 | 30 | 5 | −18 | 0.03 |
| Middle occipital gyrus, angular gyrus | R | 1489 | 44 | −74 | 32 | 0.01 |
| Middle temporal gyrus | L | 1680 | −56 | −53 | 5 | 0.02 |
| | R | 405 | 53 | −45 | 3 | 0.03 |
| PDICB+ < PDICB- | | | | | | |
| Insula, inferior frontal gyrus | L | 1038 | −32 | 8 | 3 | 0.03 |

Results of voxel-based morphometry are shown at $p < 0.05$ Family-Wise Error (FWE) corrected using Threshold-Free Cluster Enhancement (TFCE). MNI co-ordinates are cluster local maxima.

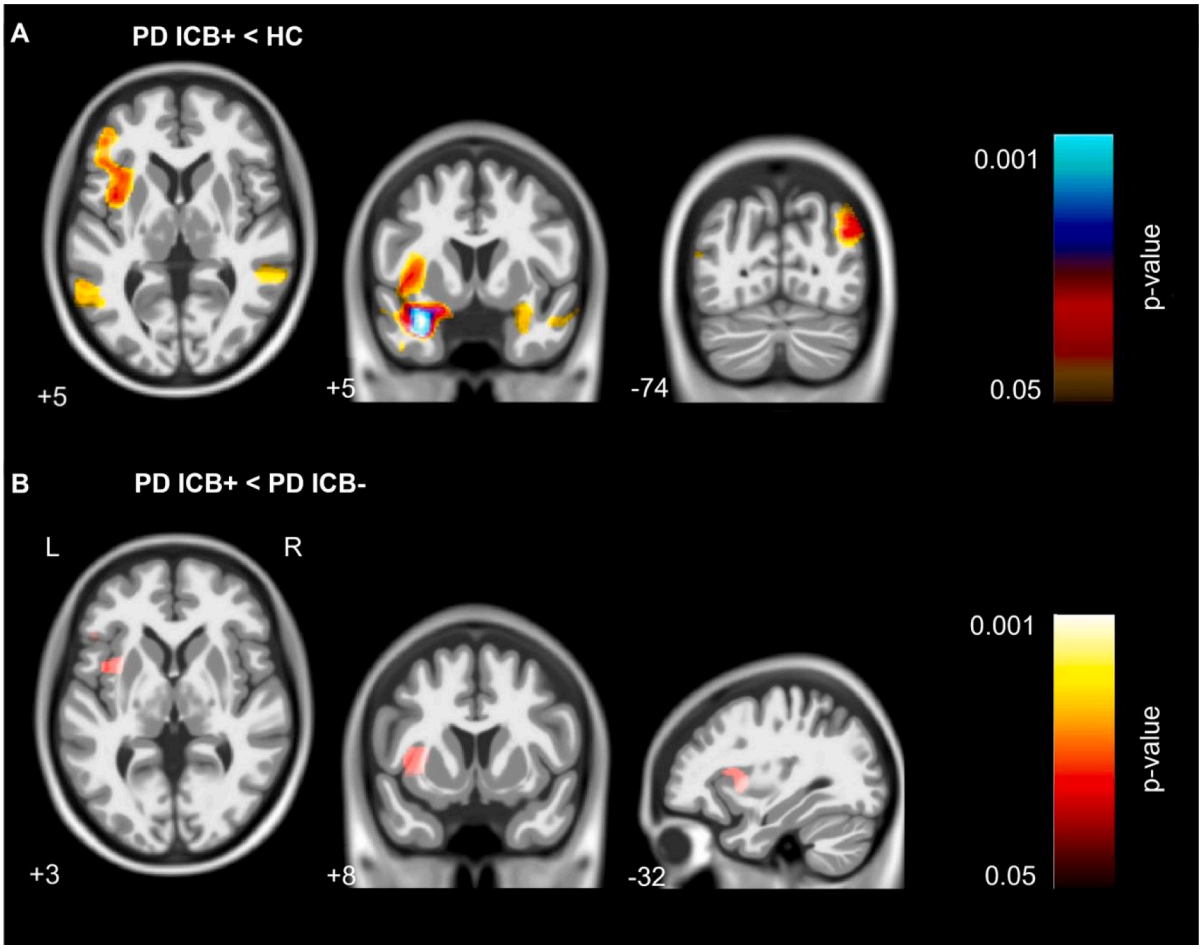


**Fig. 1.** Significant gray matter volume loss in PDICB+ compared with HC (A) and PDICB+ compared with PDICB- (B). Results are shown at $p < 0.05$ Family-Wise Error (FWE) corrected using Threshold-Free Cluster Enhancement (TFCE) with age, total intracranial volume (TIV) and gender as covariates. L/R, left/right. Co-ordinates in MNI space; color bars represent *P*-values.

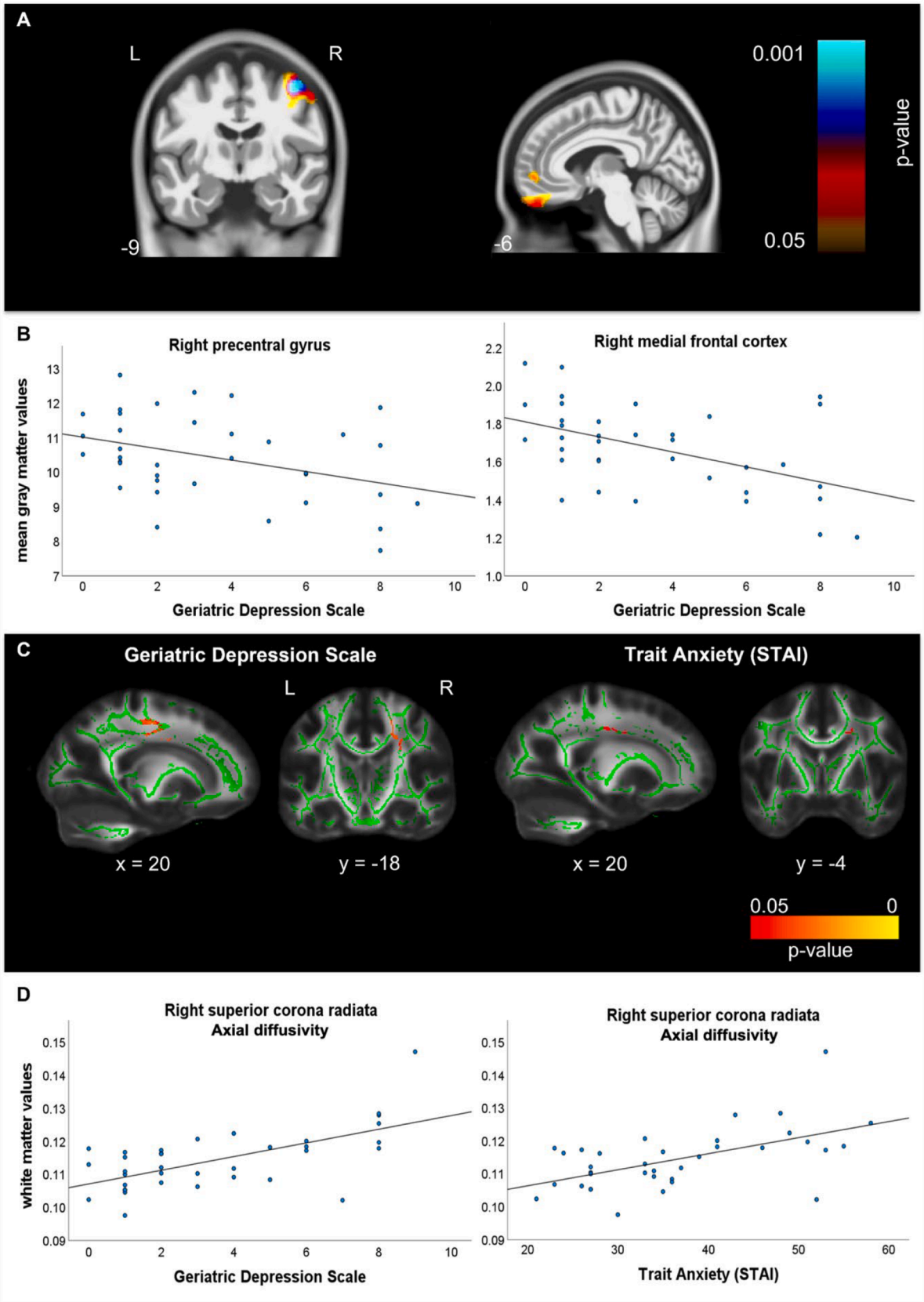


**Fig. 2.** Significant correlations of gray matter volume and white matter values (axial diffusivity) with the Geriatric Depression Scale (A and C) and trait anxiety (C). Scatter plots demonstrating the associations between regional volume loss (B) and Geriatric Depression Scale; (D) mean axial diffusivity and Geriatric Depression Scale and trait anxiety score (STAI). Results are shown at $p < 0.05$ Family-Wise Error (FWE) corrected using Threshold-Free Cluster Enhancement (TFCE) with age, total intracranial volume (TIV) and gender as covariates. L/R, left/right. Coordinates in MNI space; color bars represent *P*-values.

-0.365, p = 0.03) volumes correlated negatively with depression scores (Fig. 2A and B).

### 3.3. Diffusion imaging results

There were no significant WM differences in FA, MD, AD and RD between the three groups. In PDICB+ higher depression score (r = 0.635, p < 0.001) and trait-anxiety score (r = 0.631, p < 0.001) were associated with an increase in AD values in the right superior corona radiata (Fig. 2C and D).

### 3.4. Graph topological analyses

At the global level there were differences in the mean distance between the three groups. Pairwise comparison revealed lower mean distance values for PDICB- as compared to HC. Between the patient groups, there were no differences regarding whole graph measures.

At the regional level PDICB+ showed differences compared to PDICB- in the salience network and limbic regions. PDICB+ (vs PDICB-) had lower values of closeness mainly in the right anterior cingulate cortex, bilateral insula, and the left nucleus accumbens (Fig. 3). In addition, PDICB+ had lower degree and hubness in the left nucleus accumbens compared with PDICB-. Including risk factors (dopaminergic medication dose, depression-, trait anxiety-, and RBDSQ-score) as covariates, respectively, the same brain regions and graph measures were significant; except that differences in degree and hubness in the nucleus accumbens were marginally below significance after including depression or trait anxiety as covariates (p = 0.08 and p = 0.05, respectively).

The differences between PDICB+ and HC comprised reduced betweenness in the left nucleus accumbens, and higher local transitivity and local efficiency values in the right anterior cingulate cortex. As compared to HC, the PDICB- group showed higher values of nodal degree and closeness in bilateral anterior cingulate cortex, bilateral middle cingulate gyrus and bilateral insula. PDICB- (vs HC) also showed lower betweenness values in the right anterior cingulate cortex and the right ventral tegmental area. Increased local transitivity and local efficiency for PDICB- was observed in the bilateral anterior cingulate cortex and left middle cingulate gyrus. In addition, PDICB- had higher values of hubness in the right anterior cingulate cortex and the right insula.

There were no significant correlations for all three groups between graph measures and MDS-UPDRS parts I and III, dopaminergic medication, depression scale (GDS), anxiety scale (STAI), or REM sleep disorder questionnaire (RBDSQ).

## 4. Discussion

In this study we demonstrated that PD patients with ICB showed gray matter reductions in the left anterior insula compared to patients without ICB and HC. In addition, loss of gray matter volume in the

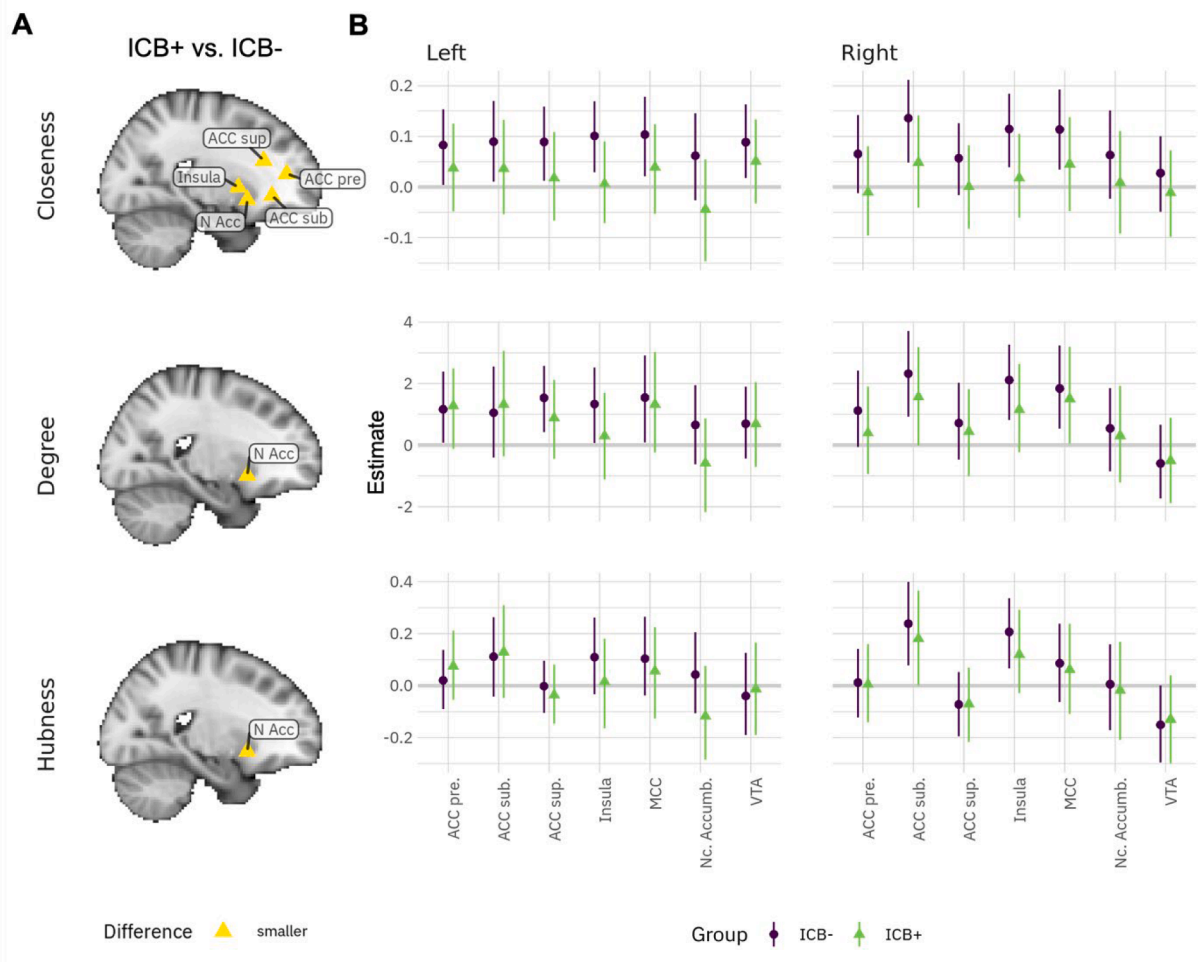


**Fig. 3.** Differences in functional topological network pattern between PDICB+ compared with PDICB- (A). Estimates from the Bayesian linear model shown in relation to HC = 0 (B). Error bars represent 95 % credible intervals. ACC sub, Anterior cingulate cortex subgenual; ACC pre, Anterior cingulate cortex pregenual; ACC sup, Anterior cingulate cortex supracallosal; MCC, middle cingulate and paracingulate gyri; N acc, Nucleus accumbens; VTA, Ventral tegmental area; ICB+, PD patients with ICB symptoms; ICB-, PD patients without ICB.

superior and middle temporal gyrus and the right middle occipital gyrus was observed in the PDICB+ group compared with controls. PD patients with ICB seemed to be more affected by depression and anxiety symptoms compared to those without ICB. Higher depression scores in PDICB+ were related to lower gray matter volume in the precentral gyrus and medial frontal cortex, and to higher axial diffusivity in the superior corona radiata. Finally, PDICB+ compared with PDICB- had abnormal topological connectivity pattern in the salience network and limbic region, specifically in the nucleus accumbens, the anterior cingulate cortex, and the insula.

Similar to previous findings, we observed that PD patients with ICB showed comorbid affective symptoms and behavioral traits including depression and anxiety (Gatto and Aldinio, 2019; Martini et al., 2018; Voon et al., 2011b). Certainly, the pathophysiology related to different subtypes of ICB and associated affective symptoms is complex and multifactorial. Recently, two subtypes of PD have been postulated: a *body-first* (bottom up) subtype, where alpha-synuclein pathology originates in the autonomic or enteric nervous system and spreads to the brain, and a *brain-first* (top-down) subtype, in which pathology arises in the brain (often in the limbic system) and descends through the brainstem into periphery (Berg et al., 2021; Horsager et al., 2020). Other studies have also reported the association and additional risk factors of depression and anxiety in ICB (Joutsa et al., 2012; Vela et al., 2016; Voon et al., 2011c; Weintraub and Mamikonyan, 2019). However, whether these comorbidities are risk factors for the development of ICB, or a result of ICB symptoms remains unclear. Nevertheless, PD patients with depression and anxiety should be monitored closely for ICB symptoms since these patients seem to be more vulnerable (Marín-Lahoz et al., 2019). In this study, correlation analysis within the PDICB+ group also revealed higher depression score related to reduced gray matter volume in the medial frontal cortex, a region which has been associated with ICB and depression (de Hemptinne et al., 2021; Imperiale et al., 2018; Schmaal et al., 2017; Voon et al., 2011c). The medial frontal cortex is known to be involved in cognitive control, reward, and affective processes (Putnam and Chang, 2021; Ridderinkhof et al., 2004). An intact prefrontal cortex is important for successful top-down regulation of inhibitory control and is strongly modulated by reward-related events (Euston et al., 2012). Evidence suggests that there is a reduced top-down inhibitory control in ICB (Cilia and Van Eimeren, 2011; Theis et al., 2021). Interestingly, our correlation analysis also revealed an association between higher depression and anxiety scores and an increase in AD values in the superior corona radiata which contains efferent fibers from the frontal lobe down to the basal ganglia (Gage and Baars, 2018). However, this implication should be treated with caution and rather exploratory, since there were no significant differences regarding DTI measures between the groups, and the interpretation of AD is challenging and still not fully understood (Alexander et al., 2007; Zhang and Burock, 2020). Abnormalities in the superior corona radiata have also been observed in depressive patients and in young individuals with anxiety (van Velzen et al., 2020; Yang et al., 2020).

The insula is an important region of the limbic system (Mesulam and Mufson, 1982). Due to its connectivity to the basal ganglia and other cortical regions such as the frontal, temporal, parietal and cingulate cortices, the insula is integrated in a wide range of different functions including cognitive, affective, sensory, and autonomic processes (Cauda et al., 2011; Chikama et al., 1997; Kurth et al., 2010). Metabolic and structural alterations in the insula have been observed in PD (Christopher et al., 2014). Our results indicate distinct morphological changes in the anterior insula in PD patients with ICB compared to patients without ICB, while both groups did not differ regarding demographics, duration of PD or motor severity (MDS-UPDRS-III). Decreased dopamine D2 receptor availability in the insular cortex of PD patients has been reported to correlate with novelty seeking, a trait associated with risk taking impulsive behavior (Kaasinen et al., 2004). Reduced gray matter volume in the insula was observed in cocaine-dependent individuals and correlated with impulsivity and attentional control (Ersche et al., 2011; Moreno-López et al., 2012). In healthy individuals the anterior insula cortex has been shown to play an important role in successful inhibition of impulsive reactions (Dambacher et al., 2013). Another study also found atrophy in the insula, orbitofrontal cortex (OFC), and anterior cingulate cortex in PD patients with pathological gambling compared with healthy controls (Cerasa et al., 2014). However, it is important to note that compared to PDICB- patients, they only found atrophy in the OFC. This might be explained by the small sample size and the restrictive inclusion of PD patients with pathological gambling. In this study, we included all ICB subtypes and ICB-related behaviors since dividing the patients in different subtypes would have reduced the sample size considerably. In line with previous findings, we found structural alterations in the superior and middle temporal gyrus in PDICB+ compared with HC (Imperiale et al., 2018; Markovic et al., 2017). Earlier studies suggest the importance of the medial temporal lobe in complex decision-making tasks especially during intertemporal choice, as damage to this region can lead to impairment of this cognitive function (Gupta et al., 2009; Gutbrod et al., 2006; Palombo et al., 2015).

In contrast to other studies, we did not find white matter abnormalities between PDICB+ patients compared with PCICB- and controls. Diffusion tensor imaging studies on ICB in PD patients are relatively sparse. Two studies using probabilistic tractography have reported white matter alterations in the uncinate fasciculus, corpus callosum, parahippocampal and pedunculopotine tracts in PDICB+ patients as compared to PDICB- and controls (Canu et al., 2017; Imperiale et al., 2018). In both studies they applied different analysis method, and the disease duration (around 9 years), motor severity (UPDRS-III) and total dopaminergic medication (LEDD) were much higher compared with this sample. Earlier neuropathological PD studies have shown different stages of neural degeneration starting in the motor and limbic areas spreading to the associative and prefrontal lobes (Braak et al., 2004; Braak and Braak, 2000). In PD patients it has been shown that gray matter volume, cortical thickness and diffusion metrics correlated with motor severity (Pereira et al., 2012; Schuff et al., 2015; Zhan et al., 2012).

As shown in previous studies, dopaminergic medications can alter connectivity between the ventral striatum and the anterior cingulate cortex leading to impaired reward-based learning (Girard et al., 2019; Petersen et al., 2018). Patients receiving dopamine agonists were 2 to 3 times at higher risk of developing ICB compared with patients not treated with them (Weintraub et al., 2010). Our study also found that the number of patients receiving dopamine agonists was higher in the PDICB+ group compared with PDICB- (64 % vs 38 %). The highly selective affinity of most dopamine agonists for dopamine D3 receptors (Gerlach et al., 2003), which are abundant in the ventral striatum and important for reward processing, is thought to be a major risk factor for ICB (Ahlskog, 2011; De Micco et al., 2018).

Degeneration of dopaminergic neurons in PD has been shown to affect mainly the sensorimotor-nigrostriatal pathway and to a lesser extent the mesocorticolimbic circuit, leading to the hyperdopaminergic theory (Cilia and Van Eimeren, 2011; Napier et al., 2015). This theory suggests that, while dopaminergic medication helps to counteract dopamine deficiency in the basal ganglia motor loops, it leads to overstimulation of the relatively intact mesocorticolimbic circuit (Cools et al., 2006). Increased functional connectivity at rest within the salience network has been reported in PD patients with ICB (Tessitore et al., 2017a, 2017b). Many studies support the idea that dysfunctions in reward processing and decision making in PDICB+ patients are due to the hyperdopaminergic state (Cools et al., 2006; Voon et al., 2011c; Vriend, 2018). However, this does not explain why many patients do not develop ICB. In contrast, Theis and colleagues proposed recently the hypodopaminergic theory (Theis et al., 2021), based on imaging studies showing weaker dopaminergic input into the ventral striatum as a premorbid vulnerability to develop ICB (Smith et al., 2016; Van Eimeren et al., 2010; Voon et al., 2014; Vriend et al., 2014). This is further supported by Hammes and colleagues, who reported reduced dopamine

synthesis in the nucleus accumbens associated with higher QUIP-RS score, a validated test to quantify severity of ICB in PD (Hammes et al., 2019b). Furthermore, patients with more severe ICB had weaker functional connectivity between the nucleus accumbens and the rostral anterior cingulate cortex (Hammes et al., 2019a). PD patients with ICB compared with those without have also been reported to show reduced dopamine receptor (D2/D3) expression in the ventral striatum (Stark et al., 2018). Interestingly, reduced dopamine synthesis capacity was also found in individuals with drug addiction and binge eaters (Majuri et al., 2017; Wu et al., 1997). In agreement with the hypodopaminergic theory, we found that PD patients with ICB showed reduced connectivity from the nucleus accumbens to other parts of the salience and limbic network indicated by lower nodal degree compared to PDICB- patients. The observed changes in the nucleus accumbens, the anterior cingulate cortex and the insula can be linked to dysfunctions in reward processing, decision making and risk taking. Similar findings of reduced functional connectivity within the salience network and the fronto-striatal pathway have been reported in individuals with obsessive–compulsive disorder (Chen et al., 2018) and internet gaming disorder (Dong et al., 2021). In addition, studies focusing on risk-taking tasks observed decreased activity in the ventral striatum in PDICB+ compared with PDICB- patients (Rao et al., 2010; Voon et al., 2011a). The nucleus accumbens is a major part of the ventral striatum and a central component of the limbic system, receiving - amongst others - input from the prefrontal cortex, amygdala, thalamus, and the ventral tegmental area (Groenewegen et al., 1999). Thus, integrating information from cortical and limbic regions, the nucleus accumbens regulates goal-directed behaviors. Indeed, selective lesions of the nucleus accumbens in a rodent model was linked to increased impulsive choice selection in a delay-discounting task (Cardinal et al., 2001).

Several limitations must be considered in this study. Unfortunately, due to data availability and quality, it was not possible to include all participants for all analyses of the different imaging modalities. Especially for the resting-state fMRI data we also had to exclude participants due to motion parameters to avoid any systematic bias. Our analysis of functional topological network pattern was limited to the limbic and salience networks, leaving any possible disruptions in other networks undetected. In addition, we cannot evaluate the possible effect of dopaminergic treatment since MRI scans were acquired during “ON” state for PD patients. However, ICB in PD have been closely associated with dopaminergic treatment and thus specific changes related to ICB might more likely be present during “ON” state (Claassen et al., 2011). Another limitation is that the role of depression and anxiety regarding the observed brain alterations remains to be understood and cannot be sufficiently addressed in this study. While the observed group differences were at large stable after adjusting for non-motor symptoms, it is difficult to estimate the potential effect of depression and anxiety on ICB-related group differences. Mood and anxiety disorders are closely related to ICB, and we also found associations between affective symptoms and volume loss in the frontal regions for patients with ICB. In fact, there is evidence suggesting common pathophysiological mechanisms of ICB and depression in PD patients (Vriend et al., 2014). In their review, Vriend and colleagues suggest that aberrations in the ventral striatum and the anterior cingulate cortex, as part of the limbic cortico-striatal-thalamocortical circuit, are associated with both ICB and depression in PD. Therefore, these brain regions may indicate a common neurobiological substrate underlying both mood disorders and abnormal reward-related behavior. Further, ICB was assessed by the short version of QUIP which may overestimate ICB rates and does not give information on symptom severity and duration (Weintraub et al., 2013). Additional semi-structured interviews and further assessments certainly help to tackle this issue. Correlation of ICB symptom severity and duration with MRI measures could provide further important insight. Analyses of different subtypes of ICB was not possible due to the small sample size. However, subtypes of ICB might be associated with distinct structural and functional alterations and thus future studies on specific subtypes might help to facilitate and improve treatment strategies for this complex disease. Nevertheless, this multimodal study, utilizing a dataset from the PPMI cohort, provides a holistic insight into the structural and functional brain dysfunctions and clinical parameters associated with ICB in PD.

## 5. Conclusions

We have shown that ICB in PD is related to structural and functional alterations in the salience and limbic regions, presumably leading to impaired decision making and reward processing. Moreover, ICB in PD is closely associated with depression and anxiety symptoms, which were related to structural disruptions in frontal regions that may suggest dysfunction in top-down inhibitory control. Future longitudinal studies with larger sample sizes are needed to elucidate the potential effects of risk factors on brain alterations in ICB and to clarify the extent to which common pathophysiological mechanisms exist between these disorders.

## Author Contributions

Study concept and design: Hamzah Baagil, Imis Dogan, Kathrin Reetz.

Drafting of the manuscript: Hamzah Baagil.

Critical revision of the manuscript: Imis Dogan, Kathrin Reetz, Christian Hohenfeld, Ute Habel, Simon B. Eickhoff, Raquel E. Gur.

Statistical analysis: Hamzah Baagil, Imis Dogan, Christian Hohenfeld.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

The authors do not have permission to share data.

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