



HAL
open science

Decision making under uncertainty in Parkinson's disease with Rem sleep behavior disorder

Ana Luísa Marques, Bruno Pereira, Michela Figorilli, Tiphaine Vidal, Paul Deffarges, Franck Durif, Livia Fantini

► **To cite this version:**

Ana Luísa Marques, Bruno Pereira, Michela Figorilli, Tiphaine Vidal, Paul Deffarges, et al.. Decision making under uncertainty in Parkinson's disease with Rem sleep behavior disorder. *Sleep Medicine*, 2022, 90, pp.214-221. 10.1016/j.sleep.2022.01.025 . hal-03647511

HAL Id: hal-03647511

<https://hal.science/hal-03647511v1>

Submitted on 20 Apr 2022

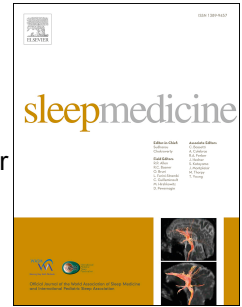
HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Journal Pre-proof

Decision Making Under Uncertainty In Parkinson's Disease With Rem Sleep Behavior Disorder

Ana Marques, MD, PhD, Bruno Pereira, PhD, Michela Figorilli, MD, PhD, Tiphaine Vidal, Paul Deffarges, Franck Durif, MD, PhD, Livia Fantini, MD, PhD



PII: S1389-9457(22)00035-1

DOI: <https://doi.org/10.1016/j.sleep.2022.01.025>

Reference: SLEEP 5195

To appear in: *Sleep Medicine*

Received Date: 5 November 2021

Revised Date: 13 January 2022

Accepted Date: 30 January 2022

Please cite this article as: Marques A, Pereira B, Figorilli M, Vidal T, Deffarges P, Durif F, Fantini L, Decision Making Under Uncertainty In Parkinson's Disease With Rem Sleep Behavior Disorder, *Sleep Medicine*, <https://doi.org/10.1016/j.sleep.2022.01.025>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Elsevier B.V. All rights reserved.

DECISION MAKING UNDER UNCERTAINTY IN PARKINSON'S DISEASE WITH REM SLEEP BEHAVIOR DISORDER

Ana MARQUES, MD, PhD¹; Bruno PEREIRA, PhD²; Michela FIGORILLI, MD, PhD¹; Tiphaine VIDAL³; Paul DEFFARGES¹; Franck DURIF, MD, PhD¹; Livia FANTINI, MD, PhD⁴.

1. Université Clermont Auvergne, CNRS, Clermont Auvergne INP, Institut Pascal, Clermont-Ferrand University Hospital, Neurology department, 63000, Clermont-Ferrand, FRANCE
2. Clermont-Ferrand University Hospital, Biostatistics department, 63000, Clermont-Ferrand, FRANCE
3. Université Clermont Auvergne, CNRS, Clermont Auvergne INP, Institut Pascal, Clermont-Ferrand University Hospital, Centre Mémoire Ressource Recherche, 63000, Clermont-Ferrand, FRANCE
4. Université Clermont Auvergne, CNRS, Clermont Auvergne INP, Institut Pascal, Clermont-Ferrand University Hospital, Neurophysiology department, 63000, Clermont-Ferrand, FRANCE

Correspondence to:

Ana Marques

Neurology Department, Parkinson expert center, CHRU Gabriel Montpied, 63000 Clermont-Ferrand, FRANCE; +33473751600; ar_marques@chu-clermontferrand.fr

Word count:

Abstract: 256 words

Manuscript: 3204 words

Tables and Figures: 2 tables and 3 figures, 1 appendix

References: 60

Running title: Decision making in PD with and without RBD

Keywords: Iowa Gambling Task; Decision-making; Parkinson's disease; Impulse control disorders; Risk-taking

Financial Disclosure/ Conflict of interest: The authors report no financial disclosure or conflict of interest concerning the research related to the manuscript

Funding sources: None

ABSTRACT:

Background: REM sleep behavior disorder (RBD) is associated with an increased risk to develop Impulse control disorders (ICDs) in Parkinson's disease (PD), however the mechanisms underlying this putative association are still poorly understood. Decision-making impairment, one major neuropsychological dimension that may lead to ICDs, has been reported in idiopathic RBD, but has never been assessed in RBD associated with PD.

Objective: We aimed to assess decision-making abilities under ambiguous situations associated with the presence of RBD in PD patients.

Methods: In this cross-sectionnal study, 60 non-demented PD patients with (PD-RBD, n=40) and without (PD-nRBD, n=20) videopolysomnography-confirmed RBD, and 20 healthy controls matched for gender and age were included. All subjects underwent neurological and neuropsychological examination, including Iowa Gambling task designed to asses decision-making under uncertainty.

Results: IGT total score did not differ between groups ($p=0.851$), however PD-RBD presented, more disadvantageous choices for the last blocks of IGT compared to PD-nRBD ($p=0.001$) and to HC ($p=0.012$). Progression of scores did not differ between HC and PD-nRBD. Multivariate analyses taking into account the value of scores at baseline, as well as the duration of PD, the duration of treatment, the presence of ICDs and MMSE confirmed those results.

Conclusion: Decision making under uncertainty is impaired in PD-RBD compared to PD-nRBD and healthy controls, regardless to the duration of disease, treatment, cognitive status and the presence of ICDs. This could reflect an inability to learn from punishment or reward in PD-RBD, and could explain the increased risk to develop ICDs reported in those patients.

INTRODUCTION

Impulse control disorders (ICDs), defined as behavioral disorders in which a person fails to resist the drive to behave in ways potentially dangerous for himself or for others, are an increasingly recognized non-motor manifestation of Parkinson's disease (PD).[1,2] It has been consistently demonstrated that the main risk factor for the emergence of these psycho-behavioral symptoms is long term dopaminergic replacement therapy, especially dopamine agonists (DA).[1,3] However, not every PD patient treated with DA develop ICDs, suggesting that other non pharmacological factors may influence individual susceptibility for the emergence of these behaviors.[4,5] REM sleep behavior disorder (RBD), a parasomnia that can precede for several years PD motor signs, has been reported to be associated with an increased risk to develop ICDs.[6,7] Although, this remains debated and the mechanisms underlying this putative association are still poorly understood.[8] and could be related to a specific psycho-behavioral profile leading to ICDs, including psychological traits such as cognitive impulsivity and psycho-behavioral decision making impairments.[9,10]

Decision-making impairment is a major neuro-psychological dimension that may lead to impulsive behaviors.[11,12] The Iowa Gambling Task (IGT) is a standardized task which simulates real life decision making in the way that it factors reward and punishment,[13] and has proven sensitive in populations with impulse control problems such as pathological gamblers or substance abusers.[14–17] During IGT, subjects learn to differentiate long-term advantageous from long-term disadvantageous decks of cards through exploration, without explicit rules nor explicit probabilistic contingencies. Few studies have investigated decision-making under uncertainty in PD patients with ICDs and reported conflicting results with one study showing impairment in PD patients with pathological gambling,[18] while two other studies found no difference for the ability to perform IGT between PD patients with various ICDs and without.[19,20] These discrepancies could be explained by the fact that ICDs are multidimensional, and impaired-decision could reflect only one of the possible factor that could lead to ICDs, among motor and cognitive impulsivity (including decision-making, delay discounting, reward and reversal learning).[21] Poorer IGT scores have been reported in isolated RBD group compared to healthy controls,[22,23] but IGT has never been assessed in RBD associated with PD. We hypothesized

that PD patients with RBD could have impaired decision-making compared to PD patients without RBD and to healthy controls, that could predispose them to ICDs. In this study we aimed to compare decision-making under uncertainty, using the Iowa Gambling Task, in PD patients with RBD, without RBD and healthy controls.

METHODS

Design

Sixty non-demented PD patients with (n=40) and without (n=20) RBD, and 20 healthy controls were included in this cross-sectional study, and matched (2:1) for gender and age (± 5 years). Patients were recruited from the Parkinson expert center at Clermont-Ferrand university hospital, and healthy controls were recruited among patient caregivers and a list of volunteers available at our center. Neuropsychological assessment and neurological examination were performed with PD patients under their usual treatment, which had not been modified for at least 4 weeks. The protocol was approved by the local ethical board (2013-A00045-40) and by the national agency for the Safety of Medical and Health products (130176B-31). All the patients gave their written informed consent for participation in this study.

Participants

Patients included were fulfilling the diagnostic criteria for PD (modified United Kingdom Parkinson Disease Society Brain Bank criteria).[24] We excluded PD patients with severe psychiatric disorders (hallucinations, depression or severe anxiety) according to the DSM V as well as those with severe cognitive impairment (MoCA<21). RBD diagnosis was screened using RBD-SQ,[25] and the presence or absence of RBD was confirmed after in-lab nocturnal video-polysomnography in all PD patients, according to ICSD-3 criteria.[26] REM sleep without atonia was assessed according to a widely-used method of visual scoring and percentage of 30-sec epochs with any chin and/or upper limbs EMG activity

was calculated.[27] Subjects with history of psychiatric pathology, PD, with a positive answer to RBD-SQ, with severe cognitive impairment (MoCA<21) or with ICDs were excluded from healthy controls.

Decision-making assessment

PD patients under their usual antiparkinsonian treatment and healthy control subjects underwent the Iowa Gambling Task (IGT),[28] conducted by a trained neuropsychologist (TV, PD). IGT is designed to assess decision-making processes under uncertainty, i.e. it models the development of everyday life long-term profitable strategies against satisfying a need, in this case earning money, without knowing the probabilistic contingencies.[13,29] In this study subjects underwent the original version of the IGT involving four decks of cards (A, B, C and D) (description in **Appendix 1**).

Net scores for the IGT are calculated by the difference between the total number of cards selected from the favourable decks (C and D) minus the total number of unfavourable cards selected (heaps A and B). Total NET score reflects the 100 trials (IGT_TOT), and the NET1, NET2, NET3, NET4, NET5 scores respectively reflect the five successive blocks of 20 trials. Higher net scores therefore signify better performance on the task.

Socio-demographic, neurological and neuropsychological assessment

Socio-demographic data including gender, age, education level was collected for each patient. The severity of PD was evaluated using the modified Movement disorders society Unified Parkinson's disease rating scale (MDS-UPDRS),[30] and Hoehn and Yahr scale.[31] PD duration was also noted as well as dopaminergic treatments doses (expressed as Levodopa equivalent doses (LED) for total antiparkinsonian treatment (Total LED) and for dopamine agonists only (DA LED)).[32] Participants completed the Starkstein scale to assess apathy,[33] and current ICDs were screened using the QUIP questionnaire.[34] PD patients also completed the Ardouin scale of behavior in Parkinson's disease (ASBPD) which is a scale designed to explore neuropsychiatric disorders in PD and including three domains: hypodopaminergic symptoms (anxiety, depression, apathy, irritability), non motor fluctuations and hyperdopaminergic symptoms (hypomanic mood, psychotic symptoms, nocturnal activity, diurnal somnolence, risk-taking behavior, excess motivation, and ICD subitems: compulsive eating and

shopping, pathological gambling, hypersexuality, hobbyism, punning, dopaminergic addiction).[35] Each item is rated on a five-point scale (severe disorder, 4; marked disorder, 3; moderate disorder, 2; mild disorder, 1; absence of disorder, 0), The total ASBPD score ranges from 0 to 84. Scores for hypodopaminergic disorders range from 0 to 20, for non-motor fluctuations from 0 to 8 and for hyperdopaminergic disorders from 0 to 56. The presence of impulsive personality traits of PD patients was assessed using the “Short Urgency, Premeditation (lack of), Perseverance (lack of), Sensation seeking, Impulsive behaviour scale” (short UPPS-P impulsive behaviour scale),[36] which represent distinct facets of impulsivity.

Statistical Analysis

Data storage and management conformed to international guidelines. Continuous data were expressed as mean and standard-deviation or median and interquartile range, according to their statistical distribution. The normality was analyzed using Shapiro-Wilk test. The comparisons between groups (HC, PD-nRBD and PD-RBD) were conducted using ANOVA or Kruskal-Wallis test, when the assumptions of ANOVA were not met. The equality of variances was studied using Bartlett test. When appropriate (omnibus p-value less than 0.05), post-hoc tests for two-by-two multiple comparisons were applied: Tukey-Kramer after ANOVA and Dunn after Kruskal-Wallis test. For categorical data, the comparisons between groups were analyzed with chi-squared or Fisher's exact test. Marginal model estimated using generalized estimating equations (GEE) was performed to compare the improvement of score between groups along the 5 successive blocks evaluating the effects of time (NET 1 to NET 5), group (HC, PD-nRBD and PD-RBD) and their interaction, taking into account between and within subject variability. A Sidak's type I error correction was applied to take into account multiple comparisons. Multivariable analyses were then performed using GEE to adjust results on possible confounders determined according to univariate results and to their clinical relevance: duration of PD, duration of treatment, presence of current ICDs and MMSE. Statistical analyses were performed using Stata software (version 15, StataCorp, College Station, US) with two-sided type I error at 5%, corrected as described above for multiple comparisons.

RESULTS

The socio-demographical and clinical characteristics of the population included in this study are shown in **Table 1**. Our groups differed for MMSE score ($p < 0.001$) (no difference between HC and PD-nRBD ($p = 0.125$); lower scores for PD-RBD compared to HC ($p < 0.001$) and to PD-nRBD ($p = 0.003$). However, all scores were above the cut-off for mild cognitive impairment.[37] MDS-UPDRS I and IV scores were higher in PD-RBD compared to PD-nRBD (respectively $p = 0.03$ and $p = 0.03$).

PD-RBD did not differ from PD-nRBD for any polysomnographic features other than loss of atonia (**Table 2**). There was no between group difference for ASBPd hypodopaminergic subscores, nor for ASBPd apathy subitem. Yet, PD-RBD had higher scores for ASBPd total score ($p = 0.006$), ASBPd non motor fluctuations scores ($p = 0.01$), ASBPd hyperdopaminergic score ($p < 0.001$) compared to PD-nRBD, and ASBPd ICD subitems ($p = 0.001$) compared to PD-nRBD. PD-RBD also presented a higher prevalence of current ICDs screened using QUIP (55%) compared to PD-nRBD (5%) ($p < 0.001$). There was no difference between PD with and without RBD regarding the total impulsivity traits and subdimensions assessed with short UPPS.

IGT_TOT score did not differ between groups ($p = 0.85$), neither did block by block NET1 ($p = 0.10$), NET2 ($p = 0.54$), NET3 ($p = 0.44$) and NET4 ($p = 0.86$) scores. However, there was a significant between group difference for NET5 score ($p = 0.038$), as PD-RBD showed a lower NET 5 score compared to PD-nRBD ($p = 0.012$), whilst there was no difference for this block between HC and PD with or without RBD (respectively $p = 0.47$ and $p = 0.42$) (**figure 1**).

When comparing the improvement of scores along the 5 successive blocks of 20 trials between groups using GEE, we found no difference between HC and PD-nRBD at any time (NET2, NET3, NET4 or NET5 vs NET1), but PD-RBD significantly differed from PD-nRBD ($p=0.001$) and from HC ($p=0.012$) at NET5 compared to NET1. Multivariable analyses taking into account the value of NET at baseline, as well as the duration of PD, the duration of treatment, LED total and LED DA, the presence of current ICDs (screened positive with QUIP) and MMSE confirmed those results (**Figure 2**).

There was no relation between the presence of ICDs and IGT performances all times considered ($p=0.67$), however the evolution of scores along the task improved less in PD with ICDs compared to those without ICDs ($p=0.035$). Yet, multivariable analysis taking into account the presence of RBD, disease and treatment duration, LED total and DA, and MMSE did not confirm this difference ($p=0.064$) (**figure 3**).

DISCUSSION

We report impaired decision making under uncertainty in PD patients with RBD compared to PD patients without RBD and healthy controls, regardless to the duration of disease, treatment, cognitive status and the presence of ICDs. This is the first study assessing IGT performances of PD patients depending on the presence of RBD.

IGT in PD

Numerous studies have previously assessed decision-making under uncertainty in PD, with conflicting results, although a recent meta-analysis confirmed the notion of impaired decision-making as measured by the IGT in PD patients ON dopaminergic medication.[38] The same

study also demonstrated impaired IGT performance in PD patients compared to healthy controls even after short-term medication withdrawal, and no difference in IGT performance between medication status ON and OFF. Those findings argue against the hypothesis that observed decision-making deficits in PD arise from medication-related overdosing of a relatively intact orbitofrontal-ventrostriatal circuits, and rather suggest the role of the disease-related neurodegenerative process itself that could vary depending on subjects. However neither disease duration, nor severity of motor symptoms seem to explain heterogeneity in IGT performance,[38] in line with our results.

It was also recently reported that IGT did not distinguish between PD patients with and without ICDs [19,20] although a trend towards more risky choices was observed in PD with ICDs. Those results are in contrast with another study previously demonstrating low performance in decision-making under ambiguity in PD patients with pathological gambling compared to those without this disorder.[18] As suggested by the authors, these conflicting results may be due to the influence of age on IGT, with a reported preference for disadvantageous decks for ages 60 and above.[20] Henceby, studies reporting no influence of ICD on IGT, [19,20] included older patients than the one reporting impaired decision making during IGT in PD patients with ICD.[18] PD patients included in our study had a mean age similar to those studies with older patients, and yet we found no significant effect of the presence of ICDs for IGT performances when adjusting for disease and treatment duration, treatment doses, presence of RBD and MMSE scores.

Henceby, heterogeneous IGT performance in PD does not appear to be related to dopaminergic drug level, nor to disease duration or severity, but might rather be related to varying disease features across studies, in relation with varying pattern of degeneration. Our results suggest that the presence of RBD, that was not previously assessed in IGT studies conducted in PD, could account for these discrepancies. Thus, RBD that has been reported to be associated with a more

severe phenotype,[39] including cognitive impairment,[40,41] and with a specific psycho-behavioral profile, probably associated with a specific pattern of neurodegeneration leading to an increased risk of impulsive behaviors in PD.[7,42]

IGT in RBD

Only two studies previously assessed decision making using IGT in isolated RBD compared to healthy controls, and reported decision making under ambiguity difficulties in isolated RBD,[22,43] even in a stage where other cognitive functions are relatively well preserved.[23] Isolated RBD showed lower total IGT scores compared to healthy controls, as well as more disadvantageous choices especially in the last block of the task.[22,43] We have also shown an increased prevalence of ICDs in isolated RBD, with altered functional connectivity between the limbic striatum and posterior cortical regions.[44] Those findings suggest that isolated RBD could be associated with impulsive behaviors, in line with the greater propensity to develop ICDs reported in PD patients with RBD.[7,42] As of yet, decision making under uncertainty during IGT had not been investigated in PD patients depending on the presence of RBD. We observed impaired decision making in PD patients with RBD compared to those without RBD and to healthy controls for the last trials during IGT. The altered decision-making that we observed in PD patients with RBD did not affect the total IGT score, nor the firsts blocks of trial, consistent with previous results reporting impaired choices in PD patients generally becoming significant for last blocks,[45,46] and reflecting an inability to learn from previous trials in PD with RBD, whereas HC and PD without RBD learn as the task progresses.[47] In decision-making under ambiguity, the limbic loop and especially the orbital or ventromedial part of the prefrontal cortex, plays a major role in learning from punishment or reward, whereas involvement of executive functions is milder compared to tests assessing decision-making with explicit rules and risk such as the game of dice task.[47] Thus, imaging studies indicate that

IGT performances reflect orbito-frontal cortex,[29,48] and ventral limbic striatum functioning,[49]

Impulsive personality and impulsive behaviors

Surprisingly we found no difference between PD with and without RBD regarding impulsive personality traits (urgency, lack of premeditation, lack of perseverance, sensation seeking) assessed with UPPS, although PD-RBD do have more impulsive behaviors. Other studies failed to identify personality traits differences in isolated RBD compared to healthy controls [50,51]. However impulsive personality traits must be distinguished from impulsive behaviors state. Indeed, impulsive behaviors have been reported in isolated RBD without any difference compared to healthy controls regarding impulsivity traits assessed with UPPS,[44] in line with our results. A discrepancy between the presence of florid ICD signs reported by clinical follow-up and in self-reported impulsivity scales in one hand,[52]and performances of patients in psycho-behavioral tests on the other hand, has previously been reported in PD,[21,52–54] reflecting the heterogeneous entity of impulsivity that is not a unitary phenomenon.

Very few studies have assessed simultaneously multiple impulsive domains (personality traits and psycho-behavioral state) in PD, despite the heterogeneous nature of impulsivity. A study recently reported no correlation between different impulsivity tests (impulsivity traits, decision under implicit risk (with and without losses), and delay discounting, and structural brain correlation associated with each test were divergent.[55] Impulsiveness personality traits appeared to be associated with atrophy of dorso-lateral prefrontal cortices, whereas impaired decision making under implicit risk with losses (IGT) was associated with increased volume of left nucleus accumbens and atrophy of left insula. In line with these results, altered functional connectivity between the ventral limbic striatum and posterior cortical regions has been reported to be associated with impulsive behaviors in isolated RBD, but not with impulsive

traits.[44] Another study highlighted that different components of impulsivity were associated with distinct variations on structural connectivity.[56] Particularly, the variance explained by structural connectivity was higher for impulsive behaviors as compared to questionnaire data, suggesting that impulsive personality traits should be distinguished from behavioral indices of impulsivity assessed either during real daily life or during psycho-behavioral tasks. Altogether those results show that the choice of a specific instrument will lead to different conclusion regarding impulsivity, and that impulsivity studies conclusions might be irrelevant for modes of impulsivity other than the one targeted, and this should be considered in further studies.

ICDs and RBD: neural correlates

Extensive neuroimaging research has attempted to identify neural correlates and predictors of decision impulsivity, yet neural patterns associated with impulsivity vary substantially across studies, likely due to non specific methodologies. Functional connectivity underpinnings decision impulsivity in general population involved multiple brain systems including default mode network, salience network, sensori-motor network, dorsal attention and ventral network, in line with the notion that impulse control is subtended by complex information communication across numerous resting state networks.[57] Those findings are aligned with the presence of disrupted connectivity within three core resting state networks (Salience, default mode and central executive networks) observed in PD patients with ICDs,[58] and in drug naïve PD patients who will develop ICDs at follow up,[59] confirming that preexisting limbic network connectivity changes could represent a risk factor for the emergence of ICDs.[60] The observation of limbic striatal hypoconnectivity in isolated RBD patients associated with impulsive behaviors,[44] suggest that RBD could be a potential marker of risk of these brain network modifications enhancing the risk of ICDs in PD.

Limitations

Our study has some limitations that should be acknowledged. First, the presence of RBD was polysomnography-confirmed in the PD group with and without ICDs, whereas RBD were only screened using a questionnaire in the control group. Thus, the presence of subclinical iRBD cannot be completely ruled out in the control group. Moreover, a comparison of decision making under ambiguity between PD-RBD and isolated RBD is lacking and would be interesting in further studies. Another limitation is the multidimensional aspect of decision making and of IGT, which precludes any clear conclusion regarding which specific component of decision making is altered in RBD and which is the most associated with the emergence of impulsive behaviors. Further studies assessing the wide range of decision-making dimensions (executive functions, learning from reward and from punishment, delay discounting, estimation of the value of an outcome during the anticipation of the outcome or during the effective reception) are warranted in order to understand the complexity of the psycho-behavioral profile associated with this RBD in PD.

CONCLUSION

PD patients with RBD have impaired decision-making under uncertainty compared to PD patients without RBD and to healthy controls, regardless to the duration of disease, treatment, cognitive status and the presence of ICDs. This could reflect an inability to learn from punishment or reward in PD with RBD, and could explain the increased risk to develop ICDs reported in those patients.

REFERENCES

- [1] Voon V, Sohr M, Lang AE, Potenza MN, Siderowf AD, Whetteckey J, et al. Impulse control disorders in Parkinson disease: a multicenter case--control study. *Ann Neurol* 2011;69:986–96. <https://doi.org/10.1002/ana.22356>.
- [2] Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* 2010;67:589–95. <https://doi.org/10.1001/archneurol.2010.65>.
- [3] Corvol J, Artaud F, Cormier-Dequaire F, Rascol O, Durif F, Derkinderen P, et al. Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology* 2018;91:e189–201. <https://doi.org/10.1212/WNL.0000000000005816>.
- [4] Marques A, Durif F, Fernagut P. Impulse control disorders in Parkinson's disease. *J Neural Transm Vienna* 2018;125:1299–312. <https://doi.org/10.1007/s00702-018-1870-8>.
- [5] Weintraub D. Impulse control disorders in Parkinson's disease: prevalence and possible risk factors. *Parkinsonism Relat Disord* 2009;15 Suppl 3:S110-113. [https://doi.org/10.1016/S1353-8020\(09\)70794-1](https://doi.org/10.1016/S1353-8020(09)70794-1).
- [6] Fantini ML, Figorilli M, Arnulf I, Zibetti M, Pereira B, Beudin P, et al. Sleep and REM sleep behaviour disorder in Parkinson's disease with impulse control disorder. *J Neurol Neurosurg Psychiatry* 2017. <https://doi.org/10.1136/jnnp-2017-316576>.
- [7] Lu H-T, Shen Q-Y, Zhao Q-Z, Huang H-Y, Ning P-P, Wang H, et al. Association between REM sleep behavior disorder and impulsive-compulsive behaviors in Parkinson's disease: a systematic review and meta-analysis of observational studies. *J Neurol* 2019. <https://doi.org/10.1007/s00415-019-09588-3>.
- [8] Fantini ML, Fedler J, Pereira B, Weintraub D, Marques A-R, Durif F. Is Rapid Eye Movement Sleep Behavior Disorder a Risk Factor for Impulse Control Disorder in Parkinson Disease? *Ann Neurol* 2020;88:759–70. <https://doi.org/10.1002/ana.25798>.
- [9] Weintraub D, Claassen DO. Impulse Control and Related Disorders in Parkinson's Disease. *Int Rev Neurobiol* 2017;133:679–717. <https://doi.org/10.1016/bs.irn.2017.04.006>.
- [10] Franken IHA, van Strien JW, Nijs I, Muris P. Impulsivity is associated with behavioral decision-making deficits. *Psychiatry Res* 2008;158:155–63. <https://doi.org/10.1016/j.psychres.2007.06.002>.
- [11] Poletti M, Bonuccelli U. Impulse control disorders in Parkinson's disease: the role of personality and cognitive status. *J Neurol* 2012;259:2269–77. <https://doi.org/10.1007/s00415-012-6506-6>.
- [12] Linnet J, Møller A, Peterson E, Gjedde A, Doudet D. Inverse association between dopaminergic neurotransmission and Iowa Gambling Task performance in pathological gamblers and healthy controls. *Scand J Psychol* 2011;52:28–34. <https://doi.org/10.1111/j.1467-9450.2010.00837.x>.
- [13] Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994;50:7–15. [https://doi.org/10.1016/0010-0277\(94\)90018-3](https://doi.org/10.1016/0010-0277(94)90018-3).
- [14] Grant S, Contoreggi C, London ED. Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia* 2000;38:1180–7. [https://doi.org/10.1016/s0028-3932\(99\)00158-x](https://doi.org/10.1016/s0028-3932(99)00158-x).

- [15] Goudriaan AE, Oosterlaan J, de Beurs E, van den Brink W. Decision making in pathological gambling: a comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and normal controls. *Brain Res Cogn Brain Res* 2005;23:137–51. <https://doi.org/10.1016/j.cogbrainres.2005.01.017>.
- [16] Petry NM. Substance abuse, pathological gambling, and impulsiveness. *Drug Alcohol Depend* 2001;63:29–38. [https://doi.org/10.1016/s0376-8716\(00\)00188-5](https://doi.org/10.1016/s0376-8716(00)00188-5).
- [17] Linnet J, Røjskjaer S, Nygaard J, Maher BA. Episodic chasing in pathological gamblers using the Iowa gambling task. *Scand J Psychol* 2006;47:43–9. <https://doi.org/10.1111/j.1467-9450.2006.00491.x>.
- [18] Rossi M, Gerschovich ER, Gerschovich ER, de Achaval D, Perez-Lloret S, Cerquetti D, et al. Decision-making in Parkinson's disease patients with and without pathological gambling. *Eur J Neurol* 2010;17:97–102. <https://doi.org/10.1111/j.1468-1331.2009.02792.x>.
- [19] Bentivoglio AR, Baldonero E, Ricciardi L, De Nigris F, Daniele A. Neuropsychological features of patients with Parkinson's disease and impulse control disorders. *Neurol Sci* 2013;34:1207–13. <https://doi.org/10.1007/s10072-012-1224-5>.
- [20] Biars JW, Johnson NL, Nespeca M, Busch RM, Kubu CS, Floden DP. Iowa Gambling Task Performance in Parkinson Disease Patients with Impulse Control Disorders. *Arch Clin Neuropsychol Off J Natl Acad Neuropsychol* 2019;34:310–8. <https://doi.org/10.1093/arclin/acy036>.
- [21] Hlavatá P, Linhartová P, Šumec R, Filip P, Světlák M, Baláž M, et al. Behavioral and Neuroanatomical Account of Impulsivity in Parkinson's Disease. *Front Neurol* 2019;10:1338. <https://doi.org/10.3389/fneur.2019.01338>.
- [22] Sasai T, Miyamoto T, Miyamoto M, Iwanami M, Abe T, Matsuura M, et al. Impaired decision-making in idiopathic REM sleep behavior disorder. *Sleep Med* 2012;13:301–6. <https://doi.org/10.1016/j.sleep.2011.09.012>.
- [23] Delazer M, Högl B, Zamarian L, Wenter J, Ehrmann L, Gschliesser V, et al. Decision making and executive functions in REM sleep behavior disorder. *Sleep* 2012;35:667–73. <https://doi.org/10.5665/sleep.1828>.
- [24] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–4.
- [25] Nomura T, Inoue Y, Kagimura T, Uemura Y, Nakashima K. Utility of the REM sleep behavior disorder screening questionnaire (RBDSQ) in Parkinson's disease patients. *Sleep Med* 2011;12:711–3. <https://doi.org/10.1016/j.sleep.2011.01.015>.
- [26] Darien, IL. The international Classification of Sleep Disorders Third edition. *Am. Acad. Sleep Med.*, 2014.
- [27] Frauscher B, Iranzo A, Gaig C, Gschliesser V, Guaita M, Raffelseder V, et al. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. *Sleep* 2012;35:835–47. <https://doi.org/10.5665/sleep.1886>.
- [28] Bechara A. Iowa Gambling Task Professional Manual. vol. Version 1, ed B. Raton. (Lutz: Psychological Assessment Resources, Inc.). 2007.
- [29] Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain J Neurol* 2000;123 (Pt 11):2189–202. <https://doi.org/10.1093/brain/123.11.2189>.

- [30] Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. *Mov Disord* 2007;22:41–7. <https://doi.org/10.1002/mds.21198>.
- [31] Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;17:427–42.
- [32] Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord Off J Mov Disord Soc* 2010;25:2649–53. <https://doi.org/10.1002/mds.23429>.
- [33] Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 1992;4:134–9. <https://doi.org/10.1176/jnp.4.2.134>.
- [34] Weintraub D, Hoops S, Shea JA, Lyons KE, Pahwa R, Driver-Dunckley ED, et al. Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Mov Disord* 2009;24:1461–7. <https://doi.org/10.1002/mds.22571>.
- [35] Rieu I, Martinez-Martin P, Pereira B, De Chazeron I, Verhagen Metman L, Jahanshahi M, et al. International validation of a behavioral scale in Parkinson's disease without dementia. *Mov Disord Off J Mov Disord Soc* 2015;30:705–13. <https://doi.org/10.1002/mds.26223>.
- [36] Cyders MA, Littlefield AK, Coffey S, Karyadi KA. Examination of a short English version of the UPPS-P Impulsive Behavior Scale. *Addict Behav* 2014;39:1372–6. <https://doi.org/10.1016/j.addbeh.2014.02.013>.
- [37] Goldman JG, Holden S, Bernard B, Ouyang B, Goetz CG, Stebbins GT. Defining optimal cutoff scores for cognitive impairment using Movement Disorder Society Task Force criteria for mild cognitive impairment in Parkinson's disease. *Mov Disord Off J Mov Disord Soc* 2013;28:1972–9. <https://doi.org/10.1002/mds.25655>.
- [38] Evens R, Hoefler M, Biber K, Lueken U. The Iowa Gambling Task in Parkinson's disease: A meta-analysis on effects of disease and medication. *Neuropsychologia* 2016;91:163–72. <https://doi.org/10.1016/j.neuropsychologia.2016.07.032>.
- [39] Duarte Folle A, Paul KC, Bronstein JM, Keener AM, Ritz B. Clinical progression in Parkinson's disease with features of REM sleep behavior disorder: A population-based longitudinal study. *Parkinsonism Relat Disord* 2019;62:105–11. <https://doi.org/10.1016/j.parkreldis.2019.01.018>.
- [40] Marques A, Dujardin K, Boucart M, Pins D, Delliaux M, Defebvre L, et al. REM sleep behaviour disorder and visuoperceptive dysfunction: a disorder of the ventral visual stream? *J Neurol* 2010;257:383–91. <https://doi.org/10.1007/s00415-009-5328-7>.
- [41] Jozwiak N, Postuma RB, Montplaisir J, Latreille V, Panisset M, Chouinard S, et al. REM Sleep Behavior Disorder and Cognitive Impairment in Parkinson's Disease. *Sleep* 2017;40. <https://doi.org/10.1093/sleep/zsx101>.
- [42] Fantini M, Macedo L, Zibetti M, Sarchioto M, Vidal T, Pereira B, et al. Increased risk of impulse control symptoms in Parkinson's disease with REM sleep behaviour disorder. *J Neurol Neurosurg Psychiatry* 2015;86:174–9. <https://doi.org/10.1136/jnnp-2014-307904>.
- [43] Delazer M, Högl B, Zamarian L, Wenter J, Ehrmann L, Gschliesser V, et al. Decision making and executive functions in REM sleep behavior disorder. *Sleep* 2012;35:667–73. <https://doi.org/10.5665/sleep.1828>.

- [44] Marques A, Roquet D, Matar E, Taylor NL, Pereira B, O'Callaghan C, et al. Limbic hypoconnectivity in idiopathic REM sleep behaviour disorder with impulse control disorders. *J Neurol* 2021. <https://doi.org/10.1007/s00415-021-10498-6>.
- [45] Perretta JG, Pari G, Beninger RJ. Effects of Parkinson disease on two putative nondeclarative learning tasks: probabilistic classification and gambling. *Cogn Behav Neurol Off J Soc Behav Cogn Neurol* 2005;18:185–92. <https://doi.org/10.1097/01.wnn.0000187939.81541.1d>.
- [46] Mimura M, Oeda R, Kawamura M. Impaired decision-making in Parkinson's disease. *Parkinsonism Relat Disord* 2006;12:169–75. <https://doi.org/10.1016/j.parkreldis.2005.12.003>.
- [47] Brand M, Labudda K, Markowitsch HJ. Neuropsychological correlates of decision-making in ambiguous and risky situations. *Neural Netw* 2006;19:1266–76. <https://doi.org/10.1016/j.neunet.2006.03.001>.
- [48] Li X, Lu Z-L, D'Argembeau A, Ng M, Bechara A. The Iowa Gambling Task in fMRI images. *Hum Brain Mapp* 2010;31:410–23. <https://doi.org/10.1002/hbm.20875>.
- [49] Tanabe J, Thompson L, Claus E, Dalwani M, Hutchison K, Banich MT. Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. *Hum Brain Mapp* 2007;28:1276–86. <https://doi.org/10.1002/hbm.20344>.
- [50] Postuma RB, Lang AE, Massicotte-Marquez J, Montplaisir J. Potential early markers of Parkinson disease in idiopathic REM sleep behavior disorder. *Neurology* 2006;66:845–51. <https://doi.org/10.1212/01.wnl.0000203648.80727.5b>.
- [51] Sasai T, Inoue Y, Matsuura M. Do patients with rapid eye movement sleep behavior disorder have a disease-specific personality? *Parkinsonism Relat Disord* 2012;18:616–8. <https://doi.org/10.1016/j.parkreldis.2011.12.010>.
- [52] Bayard S, Joly E, Ghisletta P, Rossignol A, Herades Y, Geny C, et al. A multidimensional approach to impulsivity in Parkinson's disease: measurement and structural invariance of the UPPS Impulsive Behaviour Scale. *Psychol Med* 2016;46:2931–41. <https://doi.org/10.1017/S0033291716001586>.
- [53] Aumann MA, Stark AJ, Hughes SB, Lin Y-C, Kang H, Bradley E, et al. Self-reported rates of impulsivity in Parkinson's Disease. *Ann Clin Transl Neurol* 2020;7:437–48. <https://doi.org/10.1002/acn3.51016>.
- [54] Marín-Lahoz J, Pagonabarraga J, Martínez-Horta S, Fernández de Bobadilla R, Pascual-Sedano B, Pérez-Pérez J, et al. Parkinson's Disease: Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity. *Front Psychiatry* 2018;9:465. <https://doi.org/10.3389/fpsy.2018.00465>.
- [55] Marín-Lahoz J, Martínez-Horta S, Sampedro F, Pagonabarraga J, Horta-Barba A, Bejr-Kasem H, et al. Measuring impulsivity in Parkinson's disease: a correlational and structural neuroimaging study using different tests. *Eur J Neurol* 2020;27:1478–86. <https://doi.org/10.1111/ene.14235>.
- [56] Mosley PE, Paliwal S, Robinson K, Coyne T, Silburn P, Tittgemeyer M, et al. The structural connectivity of discrete networks underlies impulsivity and gambling in Parkinson's disease. *Brain* 2019;awz327. <https://doi.org/10.1093/brain/awz327>.
- [57] Cai H, Chen J, Liu S, Zhu J, Yu Y. Brain functional connectome-based prediction of individual decision impulsivity. *Cortex J Devoted Study Nerv Syst Behav* 2020;125:288–98. <https://doi.org/10.1016/j.cortex.2020.01.022>.
- [58] Tessitore A, Santangelo G, De Micco R, Giordano A, Raimo S, Amboni M, et al. Resting-state

brain networks in patients with Parkinson's disease and impulse control disorders. *Cortex J Devoted Study Nerv Syst Behav* 2017;94:63–72. <https://doi.org/10.1016/j.cortex.2017.06.008>.

[59] Tessitore A, De Micco R, Giordano A, di Nardo F, Caiazzo G, Siciliano M, et al. Intrinsic brain connectivity predicts impulse control disorders in patients with Parkinson's disease. *Mov Disord Off J Mov Disord Soc* 2017;32:1710–9. <https://doi.org/10.1002/mds.27139>.

[60] Navalpotro-Gomez I, Kim J, Paz-Alonso PM, Delgado-Alvarado M, Quiroga-Varela A, Jimenez-Urbieta H, et al. Disrupted salience network dynamics in Parkinson's disease patients with impulse control disorders. *Parkinsonism Relat Disord* 2020;70:74–81. <https://doi.org/10.1016/j.parkreldis.2019.12.009>.

Journal Pre-proof

FIGURES CAPTIONS

Figure 1. Iowa Gambling Task block by block score (A) and total score (B) in PD patients with and without RBD and HC. * Block by block comparisons showed lower performance on NET5 block for PD-RBD compared to PD-nRBD ($p=0.038$); ** univariate GEE kinetic analysis showed lower performance in PD-RBD compared to PD-nRBD ($p=0.001$) and to Healthy controls ($p=0.012$).

Figure 2. Influence of the presence of RBD and other demographic and clinical features of PD on IGT performances variation (using multivariate GEE regression). DA LED: Dopamine agonists Levodopa equivalent dose; ICD: impulse control disorder; MMSE: mini mental status evaluation; NET baseline: IGT score for the first block; NET2-3-4-5 evolution: evolution of IGT score for the second-third, fourth, fifth block compared to baseline; TOT LED: Total Levodopa equivalent dose.

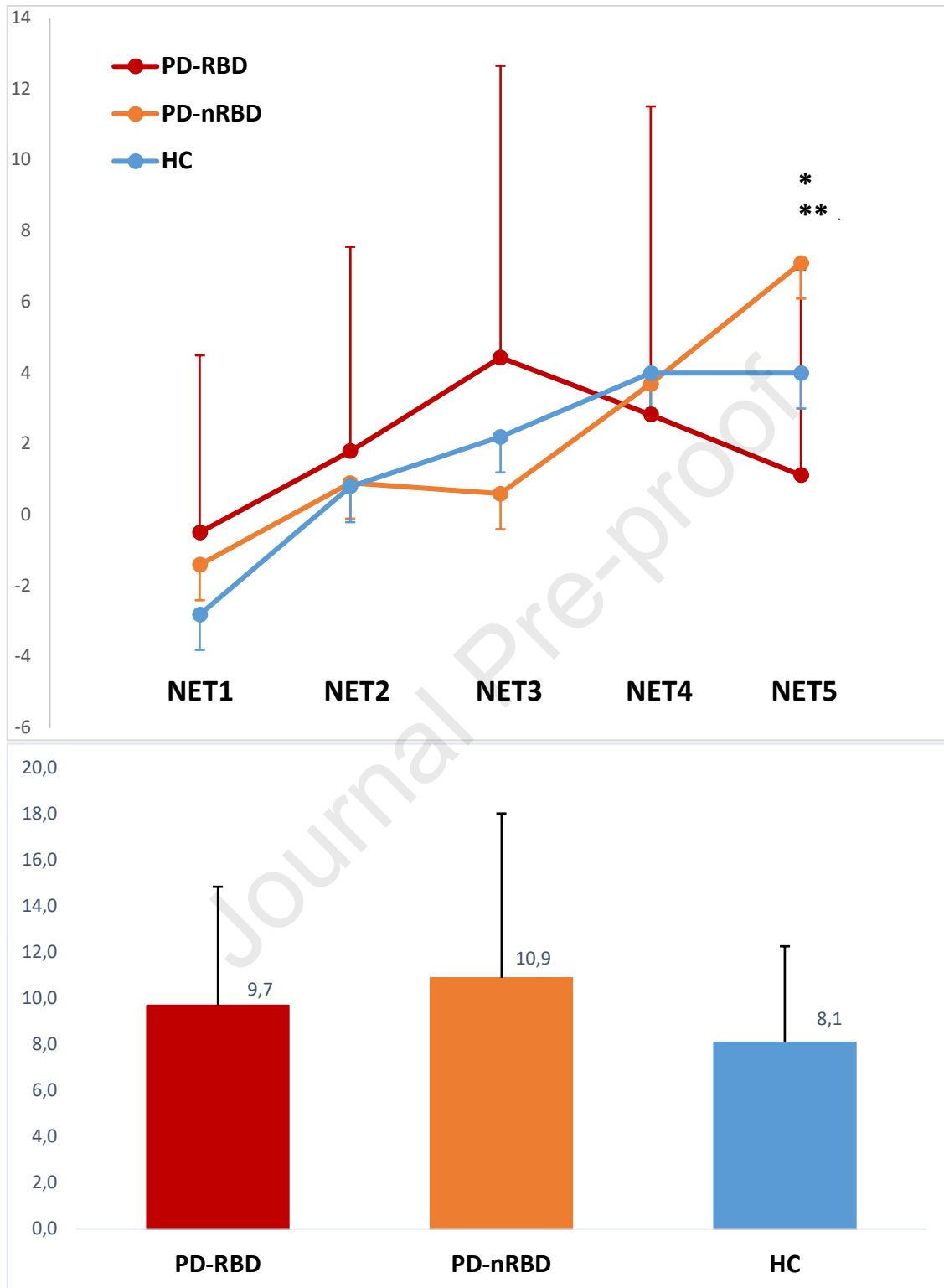
Figure 3. Influence of the presence of ICDs and other demographic and clinical features of PD on IGT performances variation (using multivariate GEE regression). DA LED: Dopamine agonists Levodopa equivalent dose; ICD: impulse control disorder; MMSE: mini mental status evaluation; NET baseline: IGT score for the first block; NET2-3-4-5 evolution: evolution of IGT score for the second-third, fourth, fifth block compared to baseline; TOT LED: Total Levodopa equivalent dose.

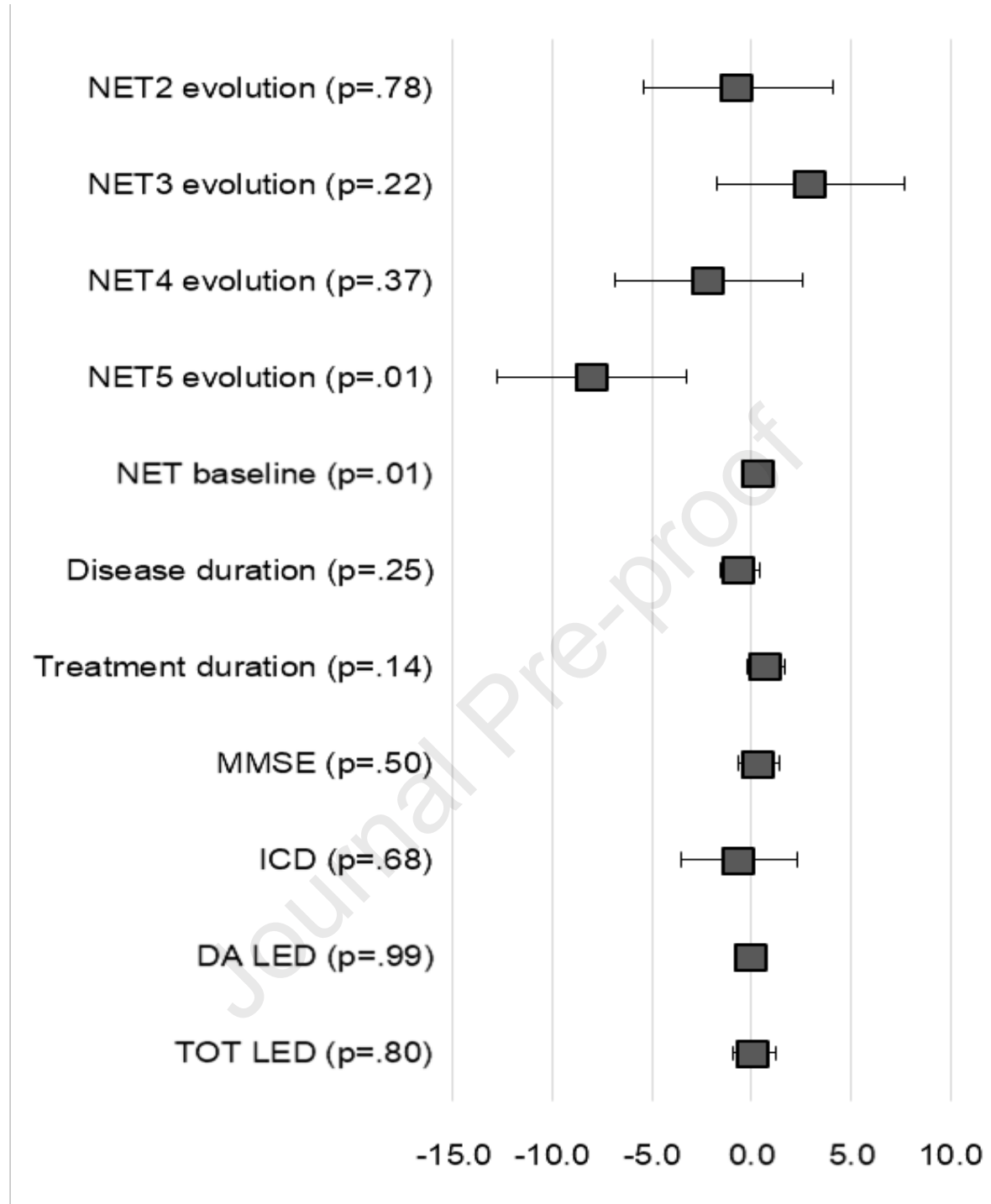
	PD-RBD (n=40)	PD-nRBD (n=20)	HC (n=20)	p
Age	63.75 ± 7.1	61.06 ± 9.7	60.5 ± 7.9	0.25
Gender (M/F)	24/16	12/8	12/8	
Education level (y)	11.8 ± 3.3	12.6 ± 3.2	15.5 ± 5.1	0.06
MMSE (0 to 30)	28.1 ± 1.34	29.2 ± 0.95	29.7 ± 0.57	<0.001
Disease duration (y)	8.55 ± 4.8	5 ± 2.4	NA	0.003
Age of PD onset (y)	55.2 ± 9.3	56.1 ± 9.2	NA	0.69
Treatment duration (y)	7.7 ± 5.0	4.8 ± 2.4	NA	0.02
LED total (mg/day)	832.6 ± 471.6	582.4 ± 351.8	NA	0.06
LED agonists (md/day)	139.8 ± 123.6	121.8 ± 137.5	NA	0.48
DA users n (%)	28 (70%)	10 (50%)	NA	0.13
Hoehn and Yahr	2.14 ± 0.73	1.73 ± 0.73	NA	0.052
MDS-UPDRS total	37.7 ± 19.6	29.1 ± 12.1	NA	0.07
<i>MDS-UPDRS I</i>	2.55 ± 2.19	1.23 ± 1.82	NA	0.03
<i>MDS-UPDRS II</i>	10.92 ± 6.30	8.76 ± 4.74	NA	0.31
<i>MDS-UPDRS III</i>	19.4 ± 11.8	16.3 ± 8.01	NA	0.33
<i>MDS-UPDRS IV</i>	4.87 ± 4.06	2.45 ± 2.43	NA	0.03
ESS	12.5 ± 4.7	10.4 ± 5.8	NA	
UPPS TOT	93.2 ± 39.7	97.4 ± 32.5	NA	0.69
<i>Urgency</i>	25.5 ± 10.9	25.9 ± 8.8	NA	0.89
<i>Lack of Premeditation</i>	25.1 ± 12.1	25.1 ± 11.0	NA	0.99
<i>Lack of Perseverance</i>	21.7 9.9	21.7 9.4	NA	0.99
<i>Sensation Seeking</i>	20.8 10.7	24.6 10.2	NA	0.20
ASBPD TOT	9.1 ± 8.3	3.6 ± 2.4	NA	0.006
<i>ASBPD Part I</i>	2.5 ± 3.1	1.7 ± 1.6	NA	0.39
<i>ASBPD Part II</i>	0.9 ± 1.6	0.1 ± 0.4	NA	0.01
<i>ASBPD Part III</i>	3.9 ± 4.1	0.9 ± 1.4	NA	<0.001
<i>ASBPD ICD</i>	2.74 ± 2.8	.63 ± 1.2	NA	0.001
<i>ASBPD apathy</i>	0.36 ± 0.78	0.21 ± 0.53	NA	0.48
QUIP screening positive	22 (55%)	1 (5%)	NA	<0.001

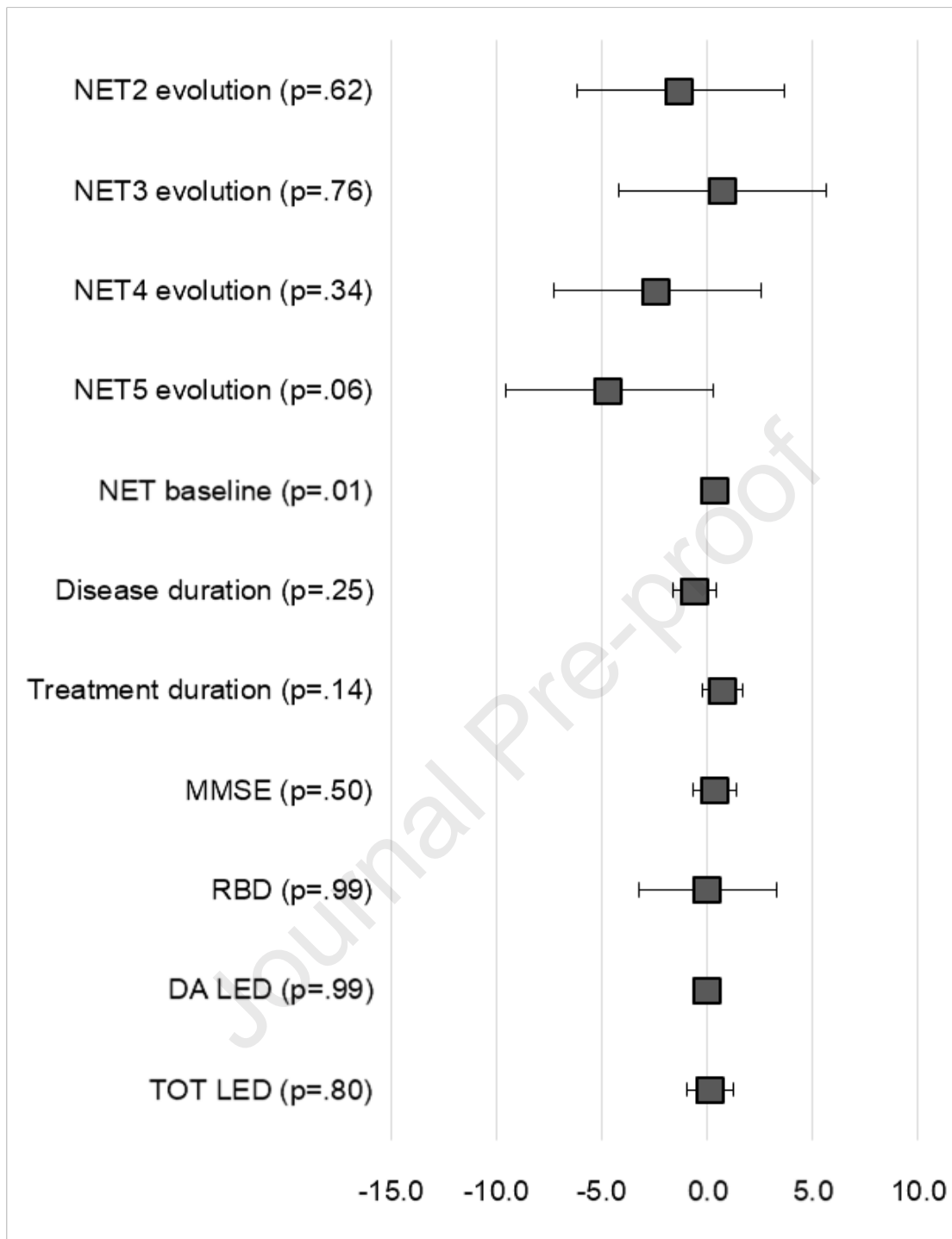
Table 1. Demographical and clinical characteristics of the studied population. Results expressed as means ± standard deviation. ASBPD: Ardouin scale of behavior in Parkinson's disease; ASBPD Part I (Hypodopaminergic symptoms); ASBPD Part II (Non motor fluctuations); ASBPD Part III (Hyperdopaminergic symptoms; DA: dopamine agonists; ESS: Epworth Sleep scale; LED: levodopa equivalent dose; ICDs: impulse control disorders; MDS-UPDRS: movement disorders society unified Parkinson's disease rating scale

	PD-RBD (n=40)	PD-nRBD (n=20)	p
Total Bed Time (mn)	440 ± 55.4	467 ± 38.5	0.06
Total Sleep Time (mn)	340 ± 72.7	344 ± 78.5	0.86
Sleep Efficiency	77.7 ± 13.9	73.8 ± 16.8	0.34
Number of awakenings	24.5 ± 11.9	26.8 ± 12.6	0.48
Arousal index	8.4 ± 5.6	8.6 ± 5.5	0.9
Wake after sleep onset (mn)	77.7 ± 45.6	89 ± 68.4	0.45
N1 sleep (%)	10.8 ± 8.1	8.7 ± 5.5	0.33
N2 sleep (%)	58.2 ± 13.2	57.2 ± 11.5	0.78
N3 sleep (%)	20.1 ± 13.5	21.4 ± 11.6	0.72
REM sleep (%)	10 ± 6.9	12.7 ± 7.1	0.18
REM sleep duration (mn)	34.5 ± 25.8	45.7 ± 31.6	0.14
RSWA (%)	54.1 ± 27	8.5 ± 5.8	<0.001
Periodic limb movement index	25.1 ± 28.8	21.1 ± 39.2	0.66
Apnea Hypopnea index	5.0 ± 12.7	3.9 ± 4.8	0.73

Table 2. videopolysomnographic features of PD patients with and without RBD. REM: Rapid Eyes movement. RSWA: REM sleep without atonia expressed as the percentage of 30-sec epochs with any chin + upper limbs EMG activity







- IGT was used to assess decision making under uncertainty in PD with and without RBD
- Decision making impairment was reported in PD with RBD vs. without RBD and controls
- This impairment was regardless to cognitive status, disease duration and treatment.
- RBD in PD could be associated with an inability to learn from punishment or reward
- This could explain the increased risk to develop ICDs reported in PD patients with RBD

Journal Pre-proof