# DEVELOPMENT OF A PREDICTIVE MODEL OF IMPULSE CONTROL DISORDER IN PARKINSON´S DISEASE USING CLINICAL, NEUROPSICHOLOGICAL, GENETIC AND NEUROPHYSIOLOGICAL DATA AS RISK MARKERS

**Juan Marín Lahoz**

**Doctoral Thesis**

# DEVELOPMENT OF A PREDICTIVE MODEL OF IMPULSE CONTROL DISORDER IN PARKINSON'S DISEASE USING CLINICAL, NEUROPSICHOLOGICAL, GENETIC AND NEUROPHYSIOLOGICAL DATA AS RISK MARKERS


**Juan Marín Lahoz**

**Directors**

Jaime Kulisevsky, Thesis Director

Javier Pagonabarraga, Thesis Director

Frederic Sampedro, Thesis Director

**Tutor**

José Aguilera



Universitat Autònoma de Barcelona

Programa de Doctorat en Neurociencies

Institut de Neurociencies

September 2019

To the patients, who we drove crazy

**Certificate of direction**

Dr Jaime Kulisevsy Bojarski, PhD in Medicine, head of the Movement Disorders Unit in the Neurology Department of Hospital de la Santa Creu I Sant Pau, Barcelona, Javier Pagonabarraga Mora PhD in Medicine, consultant of the Movement Disorders Unit in the Neurology Department of Hospital de la Santa Creu I Sant Pau, Barcelona and Frederic Sampedro Santaló PhD in Medicine and MSc in Biomedical and Electrical Engeniering, researcher of the Movement Disorders Research group in the Hospital Sant Pau Research institute

**CERTIFY:**

That the work DEVELOPMENT OF A PREDICTIVE MODEL OF IMPULSE CONTROL DISORDER IN PARKINSON'S DISEASE USING CLINICAL, NEUROPSICHOLOGICAL, GENETIC AND NEUROPHYSIOLOGICAL DATA AS RISK MARKERS presented by Juan Marín Lahoz to qualify for Doctor in Neurosciences for the Universitat Autònoma de Barcelona has been done under our direction and the supervision of his tutor Dr José Aguilera and meets all the requirements to be presented and defended in the presence of the corresponding Thesis Committee.

Dr. Jaime Kulisevsky Dr. Javier Pagonabarraga Dr. Frederic Sampedro

# Aknowledgements

This thesis is the product of a little obsession. An obsession about how madness could be induced through PD treatment. An obsession about how we, neurologist were inducing iatrogenesis. I want to thank Dr. Pagonabarraga because he was the first that told me about it. He also showed me how in spite of his knowledge, his interest and efforts, he was powerless. He was also the one who showed me the next step: to go to Boulder Colorado where Frank and O'Reily had developed -and validated with real life experiments- computational models of health and Parkinson's that seemed to explain striking facts about decisions in Parkinson's. Finally I want to thank him for his help and his enthusiasm.

In 2012 I went to Boulder, CO. Although I never had the time, or the computational knowledge or both to fix the problems that precluded their Parkinson's model to correctly simulate dopamine agonists, the period I spent there changed my understanding about the basal ganglia, for good. Besides, I learned there some tools that probed to be extremely useful. Thank you Randy.

As I was running into welfare in 2013, I talked to Dr Kulisevky. He not only helped with some concepts or to get the financial support needed. He allowed me to investigate what I was looking for, even if impulse control disorder had not been in the pipeline of his research group. Furthermore, financing my ideas, he somehow let down the support for some of his ideas. This is remarkable. In 2017, when both my life and my thesis come across their biggest hurdle he was also helpful.

Saul Martinez not only has made many of the patient assessments of this thesis, he can take credit for the use of the feedback related negativity to evaluate reward in Parkinson's. This idea was great. And was our main longitudinal bet. The reason this was not included in our first study is probably because at that time Saul spent a a great part of his working time in other hospitals so we could not share our ideas. Ramón was the first neuropsychologist I worked with, he taught me many things and when he left, he trained Andrea to supersede him. Andrea not only did a great job. She shared with me the huge load of the logistics of our cohort. Without her, our sample would have been decimated, twice ($0.9^2$=81%).

About the 2017 hurdle, when I think again, my tears come back. My wife and my daughter were in life danger and when you are in need, you see what other people are made of. Off course I have one of the most heretic fan clubs in the world: my family. They were always there supporting me; my parents the most, and not only at that time, always. They did just anything. Nonetheless, I already knew what my family was made of. My colleges were the ones whose help overwhelmed me and that help was also decisive for the research. Chus and Nacho visited my patients. Chus even treated those with migraine that were not in the movement disorder clinic. Nacho and Helena visited the ones in the cohort. Dr Sampedro came into our group at that time. Until then, he was a loud collaborator for me. When he first knew about my circumstances he said: "I can help with anything, I know English". He did not fully honor the truth, it is not just English what he knows. But more important than what he knows is that what he does not know he learns. Then he applies it and when

he does, the result is usually better than if one had just known. He was so helpful that I felt obligated to make him my director, and that decision probed to be one of the best.

The hurdle was overcome and the thesis took off again thanks to many people, but especially to the strongest ones in my life, the ones who were in danger. My wife Cristina and my daughter Leyre were the ones that really overcome the hurdle with the help of professionals and friends from Vall d'Hebron Hospital. My wife stop working for two years to take care of Leyre and she delayed her thesis in favor of mine.

Other people directly or indirectly supported this thesis, this includes: Antonia who holds the group and sometimes prevents our unit from becoming lawless, Cristina Izquierdo who keeps Antonia in a state similar to quietude, Ion who made EEG recording and processing possible, Jordi Riba who participated in the design of the longitudinal cohort study, and Jordi Clarimon and Oriol who facilitated the genetics that could not make it into the thesis (but hopefully will make it into the journals).

We also have to thank our financial supporters: the millions of anonymous donors that support la Fundació la Marató de TV3, the Muy Ilustre Administración, the Catalan Government and the Spanish Government and the Parkinson's Progression Markers Initiative which facilitated data for the depression study.

# Contents

## List of publications

1. Marín-Lahoz J, Pagonabarraga J, Martinez-Horta S, Fernandez de Bobadilla R, Pascual-Sedano B, Pérez-Pérez J, Gironell A, Kulisevsky J. Parkinson's Disease: Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity. Front Psychiatry. 2018;9:465. Quartile 1.
2. Marín-Lahoz J, Sampedro F, Martinez-Horta S, Pagonabarraga J, Kulisevsky J. Depression as a Risk Factor for Impulse Control Disorders in Parkinson Disease. Ann Neurol. 2019 Aug 15. Decile 1.

## List of unpublished works

3. Preservation of brain metabolism in recently-diagnosed Parkinson's impulse control disorders. Marín-Lahoz J, Sampedro, Pagonabarraga J, Kulisevsky J et al.
4. Reward processing predicts the development of impulse control disorders in Parkinson's disease. Marín-Lahoz J, Sampedro, Pagonabarraga J, Kulisevsky J et al.

# Introduction

## Parkinson's disease as a motor and neurodegenerative disorder

Parkinson's disease (PD) is the most common and the archetype of hypokinetic disorders. Traditionally it has been identified by its motor signs: slowness (specifically bradykinesia), stiffness, gait disturbance and rest tremor (which is not always present). These signs are so relevant that the diseases other hypokynetic disorders presenting with them are called parkinsonisms. PD is also a neurodegenerative disease. Today it is recognized as the second most frequent neurodegenerative disease and the most frequent neurodegenerative movement disorder. It is together with Alzheimer's disease, one of the most studied neurodegenerative diseases.

Accordingly, since the first occidental description was published by James Parkinson, studies have focused on two areas: to understand why the nervous system is damaged (etiopathogenesis of neurodegeneration) and understand why motor symptoms occur (pathophysiology). Although advances in the knowledge of neurodegeneration cannot be denied, the number of clinical trials conducted with the intention of modifying the evolution of the disease is reduced and the number of treatments approved with the indication to curb neurodegeneration is zero. However, knowledge of the pathophysiology of motor symptoms has allowed the development and approval of almost two dozens of effective drugs to treat motor symptoms belonging to several pharmacological families.

### Motor symptom physiopathology

In humans - as in animals whose movements and behaviors exhibit certain level of complexity and variability - motor orders are not simply generated in the motor cortex (1st motor neuron) and conveyed to the brain stem or spinal cord (2nd motor neuron) and to muscle cells. Although the activation of the first motor neuron can generate and generates movements (due to the contraction of fibers of a muscle), performing normal movements requires coordination of neurons that stimulate muscle fibers of different muscles in complex temporal and topographical patterns. To coordinate the activity of motor neurons, the participation of the thalamus-cortical loop and the basal ganglia is required. The basal ganglia are strongly regulated by dopamine. This is required to select the most appropriate and precise movements in each moment. PD pathological hallmark is the loss of dopaminergic neurons in substantia nigra pars compacta, which is the main supplier of dopamine to the basal ganglia. Dopamine is also a strong regulator of basal ganglia activity. A very simplistic way to understand motor symptoms is the notion that low dopaminergic activity causes a decrease in spontaneous movements, in movement amplitude and speed. Conversely, an excess in dopaminergic activity translates into an increase in movements.

## Treatment

Although it would be an oversimplification to say that the motor symptoms of PD are due to the decrease in dopaminergic activity, this simplification has allowed the development and understanding of most of the available PD treatments. Thus, the main therapeutic strategy is to increase dopaminergic activity in the nigrostriate pathway. These treatments frequently receive the name of dopamine replacement therapy (DRT). This thesis will focus in this kind of therapy due to its effects not only in the motor symptoms but in mood, learning and behavior.

### *L-dopa*

L-dopa (l-3,4-dihydroxyphenylalanine) is the main treatment of PD and a reference to which any dopaminergic treatment is compared. Nowadays it is always used combined with an inhibitor of its peripheral metabolism, either carbidopa or benserazide. L-dopa is an amino acid naturally present in the nervous system since it is the last metabolite of the main route of dopamine synthesis. Providing l-dopa to dopaminergic neurons avoids the need to perform the previous metabolic steps (hydroxylation of phenylalanine to tyrosine and hydroxylation of tyrosine to l-dopa) leaving only one step before the neurotransmitter can be released into the synaptic cleft: the decarboxylation of l-dopa to dopamine.

Since the pharmacodynamics of l-dopa is to facilitate the synthesis of dopamine by the neurons that normally produce it, its effect is subject to the regulatory mechanisms that control normal dopaminergic activity. This is the case at least, while the amount of available dopaminergic neurons is sufficient. However, its pharmacokinetics are very unfavorable: it has a very short blood half-life. In the initial stages of PD, the clinical effects of l-dopa last hours after the drug has disappeared from the blood. In addition, an excess in effect (excessive movements known as dyskinesias) does not appear unless very high doses are used. As the disease progresses, the clinical effect of l-dopa becomes highly correlated with its blood levels. Therefore, a high level of l-dopa in blood eventually causes an excess in effect (dyskinesias), and a low level leads to a lack of effect, (known as wearing off). On the one hand, this narrowing of the therapeutic range makes getting an acceptable symptomatic control with oral l-dopa more and more difficult as time goes on and makes the use of other drugs almost indispensable. On the other hand, the early use of high doses of l-dopa has been associated with an earlier appearance of more severe dyskinesias and motor fluctuations[1], although the mechanisms involved are not completely clarified[2,3]. This also motivates that the use of l-dopa in early disease stages is usually reserved to elderly patients and to situations in which other drugs are contraindicated. Therefore, the current treatment of PD cannot be understood without considering the use of other drugs.

### *Catechol-O-methyltransferase (COMT) inhibitors*

COMT inhibitors act primarily by decreasing the catabolism of l-dopa, they thus modify its pharmacokinetics to make it more favorable. For this reason, they only have clinical effect if they are used in conjunction with l-dopa and their clinical effect cannot be expected to be very different from that of l-dopa. Although this type of drug is useful for reducing motor complications, its use in initial patients advances the onset and increases the risk of dyskinesias[4].

### *Monoamine oxidase B (MAO-B) inhibitors*

MAO-B inhibitors decrease dopamine catabolism in the synaptic cleft. In this way they increase the available amount of dopamine at the synapse greater. This effect is independent of whether the patient is using l-dopa or not, since they affect the catabolism of endogenous dopamine. For this reason, MAO-B inhibitors are useful in monotherapy (this has been shown for selegiline and rasagiline but not for safinamide). There are also some results that suggest that the evolution of PD could be slowed by the use of MAO-B inhibitors [5,6]. However, the maximum efficacy of MAO-B inhibitors is low [7], so they do not avoid or substantially delay the use of other drugs.

### *Dopamine agonists (DA)*

Dopamine agonists are drugs that bind to dopamine receptors selectively and reversibly. As the name implies, they activate dopamine receptors, causing a similar effect on the postsynaptic neuron to that caused by dopamine. Its clinical efficacy has a clear correlation with its concentration in the nervous tissue which in turn correlates with its concentration in blood. For this reason, the duration of the effect depends on their pharmacokinetics: the effect is very long for drugs such as cabergoline and very short for others such as apomorphine or piribedil (at least when their galenics do not provide prolonged absorption). For the same reason, the dopaminergic activity caused by these drugs is not subject to any type of regulation by the circuits in which they act since their effect is, in essence, independent of the activity of dopamine. That is, in situations where the amount of dopamine present in a synapse is physiologically decreased, the dopaminergic activity caused by dopamine agonists will remain the same. This is a difference with respect to the previously commented drugs, which, even though they increase dopaminergic activity, this activity continues to be regulated by the neurons that release dopamine.

Although the half-life of different agonists is very diverse (that of cabergoline is 90 times longer than that of apomorphine), currently common dopamine agonists have an intermediate half-life (between 5 and 12 hours) and are used with galenic presentations that allow them to be administered once a day providing what is known as continuous dopaminergic stimulation.

Another important characteristic of dopamine agonists is that they have different affinity for different dopamine receptors. Dopamine agonists available in the clinics have a greater affinity for the D2 receptor family (which includes D2, D3 and D4) than for the D1 family (which includes D1 and D5). This is partly because the stimulation of peripheral D1 receptors causes hypotension. Within the D2 family, some show an affinity for D2 similar than that for D3 - bromocriptine or apomorphine) while others show a higher affinity for D3 than for D2. This is the case of pramipexole, ropinirole and rotigotine.

For the purpose of this thesis, the abbreviation DA will be reserved to refer to the most commonly used agonists: pramipexole, ropinirole and rotigotine. These drugs have characteristics in common that differentiate them from the rest:

1. Common use as first line of treatment and in different stages of evolution.
2. Available in many countries
3. Continuous dopaminergic stimulation with only one dose per day
4. Greater affinity for D3 than for D2 which in turn is greater than for D1

### *Other antiparkinsonian drugs*

There are other antiparkinsonian drugs whose effect does not rely primarily on the dopaminergic mechanisms. Among them, there are very useful drugs such as amantadine or anticholinergics. However, as their relevance for the purpose of this thesis is limited, their mechanisms of action will not be described.

## Parkinson's disease, a behavioral disorder

Although PD has been regarded as neurodegenerative motor disease for most of its history, since DRT led to a substantial improvement in motor symptoms non-motor symptoms have been increasingly recognized. Currently, non-motor symptoms are recognized to cause a greater burden in PD quality of life than motor symptoms. Cognitive, mood and behavioral disorders represent a large share of non-motor symptoms. This is not surprising as those disorders arise from the same structures than motor symptoms, the brain.

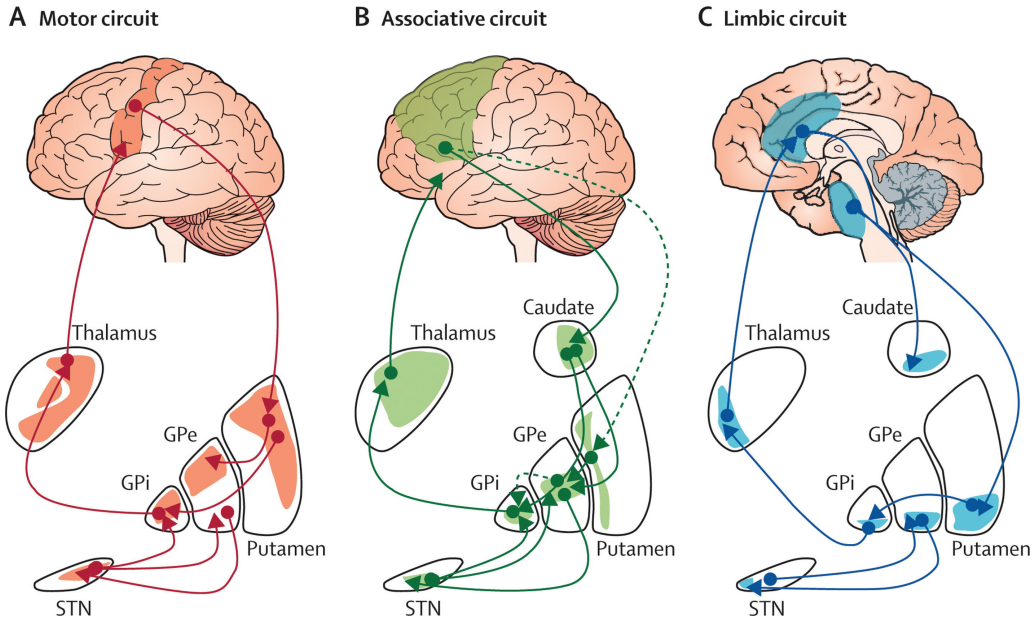


**Figure 1:** Basal ganglia circuits that explain why basal ganglia dysregulation generate symtoms other than motor ones. GPe=globus pallidus pars externa. GPi=globus pallidus pars interna. STN=subthalamic nucleus. From Obeso et al.[8]

### Depression

Depressive symptoms are very common in PD. Although depression is frequently found among patients of chronic disorders, it has been shown that it appears more frequently associated with PD than associated with other chronic diseases[9]. Furthermore, most of the antidepressant drugs with proven effectiveness in depression not associated with PD, have failed to prove a positive effect in PD depression[10]. This is the case of selective serotonin reuptake inhibitors. In some cases is not only that they do not outperform placebo, placebo fully outperforms them[11]. On the contrary, drugs with a greater catecholaminergic effect lead to mood improvements in PD. This has been shown for pramipexole, venlafaxine and tricyclic antidepressants[10]. Pharmacological evidence therefore supports the notion that PD depression is somehow different than depression in other populations.

### Anxiety

Anxiety is also a very common neuropsychiatric PD symptom. More than one quarter of PD patients have anxiety[12]. Although anxiety is related to dopaminergic activity and in some cases strongly responds to DRT optimization (i. e. correct management of non-motor wearing off), in other cases anxiety seems completely independent of DRT and is hard to mitigate[13]. Anxiety is associate to depression in PD [14], nonetheless, there are no current recommendations for the treatment of

anxiety endorsed by the Movement Disorders Society (MDS) because of the lack of sound randomized clinical trials[10].

### Apathy

Unlike depression and anxiety, both common in the general population, isolated apathy is unknown in otherwise healthy humans and is not included in the Diagnostic and Statistical Manual of the American Psychiatric Association, DSM-V [15]. Consequently, apathy is sometimes misdiagnosed as depression. Both apathy and depression share some phenomenology: anhedonia, low activity or decreased enthusiasm. However, depression is characterized by the presence of negative mood and negative thoughts -namely Beck's cognitive triad [16]) about the self, the world and the future that are absent in pure apathy. On the contrary, apathy presents with diminished emotional reactivity, lack of concern for others and indifference (both toward positive or negative events)[17].Some randomized clinical trials have been performed on PD apathy and both rivastigmine and piribedil currently hold recommendations by the MDS[10]. Nonetheless, the efficacy of piribedil has been shown in patients who had been previously withdrawn from DA and the efficacy of DA for apathy in other settings has not been proven[18].

Scales designed to quantify or diagnose apathy and depression usually have very similar items targeting the common symptoms of both disorders[19–23]. Most studies are not designed to discriminate apathy and depression because they rely on scales, this represents an important limitation in this context. Some associations found for PD depression may thus hold for PD apathy. Furthermore, some might be truly related to apathy while their association with depression might be spurious.

## Impulse control disorders (ICD)

Disorders include in the DSM-V under the heading of *Disruptive, Impulse –control and conduct disorders* are unique to the corresponding chapter in that they are either manifested by the violation of others rights or they bring the individual into significant conflict with societal norms and authorities. The archetypal ICDs are pyromania and kleptomania. In the context of PD, the behaviors diagnosed as ICDs are better characterized by the experimentation of pleasure and gratification by the patient. They comprise behaviors and objects of desire that are common in both PD patients and healthy individuals but that have gone out of the individual's restrain and yield negative consequences to the individual and his/her environment. Behaviors that constitute ICD in PD are frequently related to sex, food (eating), shopping, gambling, computers use (especially games and social networks) and a great diversity of hobbies. These behaviors are better understood when they are regarded as behavioral addictions. In fact, in the current version of the DSM, they are not included anymore in the *Disruptive, Impulse –control and conduct disorders* but described under the heading of *Substance-related and addiction disorders.* Nevertheless, the only behavioral addiction that currently has a decisional algorithm in the DSM is pathological gambling. For other behavioral addictions the scientific evidence is considered yet insufficient by de American Psychiatric Association. Although the compulsive behaviors that appear in PD patients could be better understood using the concept of behavioral addictions, for the sake of continuity, this thesis refers to those behaviors as impulse control disorders (ICD).

### ICD epidemiology and consequences

ICD are much more common among common among PD patients than in the general population. Their incidence apparently remains constant among treated patients and the longer a patient receives DRT the higher the cumulated risk. Case reports have been published about severe forms of ICD and probably most neurologist frequently treating PD patients have come across some of them[24]. The burden ICD cause on patients and their relatives has also been reported in cross-sectional studies[25].

### Dopamine agonists withdrawal syndrome

The obvious management of ICD is to withdraw patients from the causative agent; usually DA. Although this is frequently effective[26–28] it is not always easy or even possible[29]. Furthermore, DA withdrawal frequently leads to DAWS: dopamine agonists withdrawal syndrome[30,31]. According to literature, patients suffer from anxiety (91.7%), pain (50%), sweating (41.7%), and anhedonia (16.7%). According to our experience apathy is very common[32]. There are no reports on DAWS treatment except for a randomized trial that studied several problems associated with DA use.[33] Treatments other than DA withdrawal have not proved efficacy[34], therefore prevention is the mainline to fight ICD[29].

## ICD as an avoidable disorder

ICDs are as uncommon in untreated PD patients as in the general population[35–37]. Among PD treatments, the use of dopamine agonists (DA) has been strongly associated with ICDs[35] and patients who have never been exposed to DA exhibit four times less risk than patients who use or have used DA[38]. The longer the exposure and the higher the does the greater ICD risk is[38]. Furthermore, patients receiving drugs of this family for a disorder other than PD also have a high risk of ICD[39,40]. Therefore, we can assume that if we could identify patients at high risk of ICD and keep them away from DA we could avoid a great share of the problem. Conversely, if we could identify patients with very low ICD risk, they might receive DA with greater frequency or even at greater doses than they currently, benefiting from the aforementioned advantages in treating motor and non-motor symptoms. In other words, a better knowledge of individualized ICD risk of each patient would lead to a more personalized PD management and in turn to a greater quality of life.

## Identification of patients at high ICD risk

Although prevention is currently regarded as the main tool to fight PD-ICD[29], currently there are no recommendations for the identification of patients who face higher risk of ICD. Physicians treating PD patients may thus differ in their prudence when prescribing DA, their purposefulness when screening for ICD, their degree of suspicion and the advice they give to patients when the patient receives his/her first DA prescription. Physicians who have greater concern about ICD may have more restrictive prescription habits in relationship with DA especially when facing patients presenting factors that have been related to the presence of ICD.

Some of the factors –other than DRT-related or proposed to be related with ICD are described here:

**Age.** Although there are no studies directly targeting age as a risk factor, younger age is consistently associated to ICD [35,41,37,38].Nonetheless, the independency of younger age as a risk factor is not routinely evaluated and L-dopa sparing medications, including DA, are more commonly used younger patients to prevent or delay motor complications[1].

**Impulsivity** has been associated to ICD in many studies[42–45]. Contrary to age, impulsivity is a latent variable[46] and is not directly measured. Diverse tools have been used to estimate impulsivity including both questionnaires and tasks[47].

Dopaminergic activity is paramount for **reward processing** and dopamine has been implied in additions related or not to catecholaminergic drugs[48], even in addictions not related to substances[49]. Therefore, when behavioral addictions appear in the context of dysregulation of dopamine, the reward processing systems are likely to be involved. DRT has been shown to modify learning reinforced by punishment and reward [50]. Nonetheless reward processing is probably even harder to evaluate than impulsivity and there is a great variety of approaches that include behavioral tasks[51,50], neuroimaging[52,53] and neurophysiology[54,55].

Previous use of **addictive substances** has also been linked to the presence of ICD. This includes alcohol in some studies[56] but not others[35,43,57]. Pathological gambling in the general population has also been linked to alcohol consumption[58]. The research interest on caffeine has been weaker but a longitudinal prospective study has shown a significant association[27]. Tobacco has been consistently linked to ICD[35,43,59,60,57] and studies not finding the association are scarce[56].

Higher scores in **depression** scales have been found in PD patients with ICD than in those without[60], and severity of depression has been related to ICD presence[59] and severity[61]. Nonetheless, the direction of the causality has been questioned as behavioral disorders could lead to depressive symptoms[62]. Furthermore, differences in reward processing have been found in depressed patients in the general population[63].

Few studies have evaluated **family history** of behavioral or substance addictions in relation to PD-ICD[35]. Nonetheless, family history is sometimes regarded as a risk factor[62] due to the associations found in the general population[64] and the heritability of PD-ICD behavior estimated by restricted maximum likelihood (REML) analysis.

In this vein, **genetic** risk factors of PD-ICD have also been reported. Polymorphisms in the dopamine receptor D3 and the subunit epsilon-2 of the Glutamate receptor (known as GRIN2B or NMDAR2B) were linked to PD-ICD in Korean population[65]. A polymorphism in the serotonin receptor 2a (HTR2A) was also linked to PD-ICD in the same sample[66]. However, a study based on a multicenter international cohort prospectively studied these and other polymorphisms and was unable to replicate the findings[67]. This study found association with polymorphisms in the opioid receptor OPRK1 and in the tryptophan hydroxylase 2 whose activity is crucial in serotonin synthesis. Importantly, this study –published after the inception of this thesis- was the first to show how statistical models could be developed to predict the ICD development. The predictive power of the

model was shown deploying receiver operating characteristic (ROC) curves, nonetheless the model itself was not included in the manuscript. To the best of my knowledge, this is the only published article targeting a predictive model for PD-ICD.

Not only there is a lack of predictive strategies, many of the factors regarded as risk factors have not been evaluated in prospective studies. Furthermore, most of the cross-sectional and retrospective studies do not include any information about the time relationship between ICD inception and study inclusion. Their finding could therefore be consequence of the disorder –and not the cause- or be related to treatment modification. Additionally, the identification of cases in case-control studies does not usually come from systematic screening of the population or of cohorts, they are frequently convenient samples. Therefore, most of the knowledge accumulated about PD-ICD may be generated with the influence of selection and information biases[68]. Some of them are detailed in table 1.

| Bias | Type of bias | Consist of | Type of Studies afected | Examples | consequences |
|---|---|---|---|---|---|
| ***Prevalence-incidence (Neyman) bias*** | selection | *excluding the cases whose ICD is not active anymore or are death* | Case control studies based on prevalent cases | 35,43 | Patients with persistent or conspicuous ICD are overrepresented while others are underrepresented |
| ***Unmasking (detection signal) bias*** | Information | *Exposures associated with phenomenology of the disorder but not the disorder itself become suspects* | Potentially anything that makes ICD more apparent like previous gambling or younger age | None demonstrably affected | An unrelated exposure is associated to the disorder |
| ***Non-respondent bias*** | selection | *Some patients respond more frequently to mailed questionnaires than others* | Studies based on mailed quesionnaires | 59,69,60 | Hard to estimate in PD-ICD context. Samples not representative of PD population |
| ***Diagnostic suspicion bias*** | Information | *PD patients with high risk of ICD (those taking DA) are more frequently screened and diagnosed of ICD.* | Studies in which cases and controls are not evaluated with the same diagnostic procedure prior to inclusion. Most case control studies | 42,41 | Increases the strength of the association with the known risk factor and others associated with it |
| ***Exposure suspicion bias*** | Information | *Looking for a exposure with greater effort in cases* | Any study reliying on clinical records any data "flexible" information source | 70 | Increases the association with the exposure |
| ***Recall bias*** | information | *Cases remember exposures better than controls* | Case control studies that include previous exposures | 35,43,61 | Overstimation of the role of recalled exposures |
| ***Family information bias*** | information | *Cases remember related family history better than controls* | Case control studies that include family history | 35 | Overstimation of the importance of family history |

**Table 1:** some of the biases case control studies are at high risk of.

One aim of this thesis was to improve the quality of the evidence about ICD. We have therefore tried to avoid or limit this and other biases through longitudinal studies when possible (second and fourth

work) of through modifications of the basic case-control design. In this sense, the first work, although the sample was based in consecutive PD patients, their status (as cases or controls) was based in the same clinical interview to avoid Neyman bias. This design is not immune to other bias such as recall bias. Nevertheless the main exposures of the study were measured at inclusion avoiding recall bias. The third work used a nested design; all the patients thus came from the same cohort and had gone through the same evaluations. This avoids many of the biases associated with case-control design but does not allow the evaluation of one of the main criteria of causality: the temporality. This applies to the temporal relationship between ICD and the main evaluation; brain metabolism but it does not apply to exposures that were evaluated in the cohort study.

## Hypotheses

1. A comprehensive study of impulse control disorders, and specifically to of its etiology may lead to the identification of patients at higher risk of this disorder. This would be useful to prevent its development.
2. The development of Impulse control disorders in Parkinson's disease is related to an imbalance in reward processing.
3. This imbalance in reward processing can be measured prior to the development of the disorder.
4. Impulsivity reflects the inability to refrain behavior, and therefore higher impulsivity may lead to less refrained behaviors within patients with impulse control disorders.
5. Depression, due to the associated reward imbalance, is linked to impulse control disorders in PD and may act as a risk factor for them.
6. The reward imbalance that leads to impulse control disorder requires not only the use of dopamine agonists but also the preservation of reward areas (compared to Parkinson patients with no impulse control disorder).

## Objectives

1. To identify factors associated to the presence and especially to the development of impulse control disorder to better estimate the risk of this disorder among patients with Parkinson's disease.
2. To investigate whether patients developing impulse control disorders had a reward imbalance (compared to patients who remain free of the disorder) prior to its development.
3. To evaluate the relationship of impulsivity with the presence and severity of impulse control disorders.
4. To evaluate prospectively whether depression, acts as a risk factor of impulse control disorder in Parkinson's disease.
5. To compare brain metabolism of Parkinson patients with new onset impulse control disorders with that of matched Parkinson patients free of behavioral disorders.

## General discussion

The association between DA and impulse control disorders in PD has been known for decades[71,72]. This did not made DA to be a restricted treatment like tolcapone or clozapine. On the contrary, given their proven therapeutic efficacy, they still remain one of the main PD treatments[1].

From a purely scientific point of view, the fact that an available compound induces compulsive-impulsive behaviors to an important proportion of their users is enlightening. It gives strong evidence of the involvement of dopamine in behavioral addictions[73]. From a clinical point of view, the fact that one of the most frequent treatments of one of the most common neurodegenerative diseases exposes patients to a high risk of behavioral disorders is not only alarming but also challenging.

Fortunately, these decades of cumulative evidence have raised the consciousness among neurologists about PD-ICD an avoidable disorder. Nonetheless, the evidence generated in 20 years included little about ICD prevention. As of September the 10th 2019, the search of "impulse control disorders" AND Parkinson in *pubmed.gov* yields 440 results. More than 200 publications were cited in a recent review[62]. And yet, the number of longitudinal observational studies targeting risk factors is 3: one of them is part of this thesis, another was published after the inception of this thesis, and a third was based on mailed surveys[67,69,74] .Moreover, the number of neuroimaging longitudinal studies that includes patients prior to ICD development is only 2[75,76]. Dozens of studies restricted their analysis to the study of problematic and well-stablished ICD, which had been compromising the patients' quality of life for months. From the perspective of a clinical neurologist, evidence could be summarized as follows:

1. **DA are useful** in the treatment of PD
2. Yet, they can **cause** a potentially severe behavioral disorder, **ICD**
3. ICD is a real problem, there are many journal articles on the **burden** they create for patients and families, the decisional **impairment** they cause and the **functional brain changes** they associate. Furthermore, I have visited (or heard of) **patients suffering severe consequences** of ICD.
4. **I cannot identify which patients are at risk** and the main tool to prevent the consequences of ICD is to detect them early because the only risk factor other than DA that comes from longitudinal evidence [77] is male sex. However, male sex has not been replicated in cross-sectional studies (sex is a variable protected from many of the biases of case-control studies), and the evidence comes from a mailed questionnaire study[69]. Besides, avoiding DA in male PD patients would imply that the majority of PD patients would not benefit from this treatment.

This thesis tried to complement the vast literature about PD-ICD. In the first published article we showed that if ICD are screened in consecutive PD patients, they are not associated to impulsivity (as had been found in other case-control studies based in previously known cases). For that, we used two independent measures of impulsivity. Importantly, we subsequently confirmed this result within a longitudinal framework in the unpublished work B. This striking fact was better explained by other

finding: patients with more severe forms of ICD had higher levels of impulsivity. Taken together, these findings raised a strong suspicion of Neyman bias in previously published PD-ICD case control studies: the cases they included represented the most severe and persistent ICD cases. This made us more conscious of the risks of case-control designs. We thus adopted the resolution to longitudinally study PD-ICD. We thus designed unpublished work A and B conjointly to evaluate reward and brain metabolism in ICD. We would have happily designed unpublished work A to longitudinally evaluate PET but it was beyond our budget.

Unpublished work A was thus designed in a way that could avoid many of the problems of traditional case-control studies; we nested it in a cohort. We showed that brain metabolism is preserved in vast regions of the cortex among ICD patients. Due to the design we can ensure the findings are not caused by changes in DRT. With current knowledge, is hard to interpret the higher metabolism as a consequence of ICD, $^{18}$F-FDG-PET scans are not performed during a task but after one hour of resting in a dark room. Besides, most of the areas that showed higher metabolism in PD-ICD than in PD-nonICD are unrelated to reward and addiction, is plausible that a global preservation of brain metabolism precedes ICD.

Unpublished work B is the prospective longitudinal study in which unpublished work A was nested in. Its design is simple: a cohort study in which we evaluated reward processing prior to the appearance of ICD. This required a sample of considerable size whose recruitment lasted about a year. Moreover, it required a long follow up that included several hundreds of visits. This study yielded a number of incident cases a bit lower than expected. Furthermore, the proportion of patients excluded because of previous ICD was much lower than the proportion of cases detected in the first published work. This possibly means that we are using DA more cautiously than we were some years ago. Nevertheless we could detect a significant number of incident ICD cases that allowed us to prove the main hypothesis: reward processing differed between patients at high risk for ICD and those at low risk. Furthermore, it allowed the development of a predictive model, the objective that gave name to this thesis five years ago.

Last but not least, the second published article targeted depression. Depression had been associated to ICD in several samples. However, their design precluded the evaluation of any causal association. Furthermore, reverse causality was plausible (and still is) and pramipexole was a confounding factor, given its well-known association with ICD but being at the same time the only treatment recommended for PD depression by the MDS.. Our cohort study was ongoing and it would have been interesting to evaluate the longitudinal association between depression and subsequent ICD depression in an in-house cohort. However, depression was an exclusion criterion for our cohort because it is linked to FRN differences[63]. We thus took advantage of a multicenter prospective database which had enough information about the required phenomena. Our aim then was to ensure that the association between depression and ICD was not spurious but causal. We wrote probably the first paper on PD-ICD that has causality as the main goal. We showed how depression, at least within a large multicentric cohort, predisposed to ICD development complying with all the ascertainable causality criteria[78]. This work was published in a top journal in this field, which contributes to the diffusion among neurologists required to influence future PD management.

Overall, this thesis has contributed to a better understanding of PD-ICD and to the prevention of them. On the one hand, regarding the understanding:

1. Impulsivity is probably not a cause of ICD, but regulates their expression.
2. Reward processing differences (we do not imply they represent a dysfunction) precede ICD development in PD.
3. PD-ICD patients have a preserved brain metabolism which probably facilitates ICD development.

On the other hand, regarding prevention:

1. Impulsive patients possibly have more severe ICD. DA should probably be used with caution among patients known to be impulsive.
2. Depressed patients and those who require medication to remain free of depressive symptoms have higher ICD risk. This risk is even higher if they receive DA. DA should thus be avoided or used cautiously in depressed patients.
3. Among non-depressed PD patients, their ICD risk can be estimate using a cost-effective and non-invasive tool such as EEG.

Even so, there are still important gaps in the knowledge and the prevention of PD-ICD. We have shown that ICD can be predicted. The next step is probably to predict them in clinical practice. This can be done using genetics or gambling tasks, and probably achieving better results combining them with other factors. . A step further would be the development of models that instead of predicting the risk, predict the benefit of DA avoidance, that is, individual treatment effect models. This requires randomized controlled trials to feed the predictive models, but we think that to prevent ICD, it is worth it.

Finally, from the point of view of the main author, this period has served to grasp a profound knowledge about study design and execution, bias, causality and statistics. Besides, it served learn tools of neuropsychological testing, neurophysiology and neuroimaging.

## Concluding remarks

1. Impulse control disorders appear as a result of a previous reward imbalance.
2. The FRN can be used as a neurophysiological biomarker to evaluate reward processing in Parkinson's disease and also be used to predict future development of impulse control disorders.
3. Although this reward imbalance is probably the mediator of the effect of dopamine agonists, dopamine agonists are neither a sufficient cause nor a necessary cause.
4. The preservation of brain metabolism probably plays a role in the reward imbalance caused by dopamine agonists.
5. Depression acts as a risk factor for impulse control disorder in Parkinson's disease patients. This may be due to the reward dysfunction that underlies Parkinson's depression. Furthermore, depression can be identified easily using several methods available in clinical practice and therefore is one of the easiest methods to identify patients at risk of impulse control disorder.
6. It is not clear whether impulsivity fosters the development of impulse control disorders in Parkinson's disease. However, impulsivity is positively correlated with the manifestations of impulse control disorders: more impulsive patients have more conspicuous behaviors.

## References


1. Fox, S. H. *et al.* International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease: Treatment of Motor Symptoms in PD. *Movement Disorders* **33**, 1248–1266 (2018).
2. de la Fuente-Fernández R. PResynaptic mechanisms of motor complications in parkinson disease. *Arch Neurol* **64**, 141–143 (2007).
3. Voon, V. *et al.* Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. *The Lancet Neurology* **8**, 1140–1149 (2009).
4. Stocchi, F. *et al.* Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: The STRIDE-PD study. *Annals of Neurology* **68**, 18–27 (2010).
5. Olanow, C. W. *et al.* A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease. *New England Journal of Medicine* **361**, 1268–1278 (2009).
6. Cereda, E. *et al.* Efficacy of rasagiline and selegiline in Parkinson's disease: a head-to-head 3-year retrospective case-control study. *J. Neurol.* **264**, 1254–1263 (2017).
7. Tomlinson, C. L. *et al.* Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement Disorders* **25**, 2649–2653 (2010).
8. Obeso, J. A. *et al.* Functional organization of the basal ganglia: Therapeutic implications for Parkinson's disease. *Movement Disorders* **23**, S548–S559 (2008).
9. Nilsson, F. M., Kessing, L. V., Sorensen, T. M., Andersen, P. K. & Bolwig, T. G. Major depressive disorder in Parkinson's disease: a register-based study. *Acta Psychiatr Scand* **106**, 202–211 (2002).
10. Seppi, K. *et al.* Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review: Treatment of the Nonmotor Symptoms in PD. *Movement Disorders* (2019). doi:10.1002/mds.27602
11. Menza, M. *et al.* A controlled trial of antidepressants in patients with Parkinson disease and depression. *Neurology* **72**, 886–892 (2009).

12. pubmeddev & al, B. M., et. Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis. - PubMed - NCBI. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27125963. (Accessed: 5th September 2019)
13. Leentjens, A. F. G. *et al.* Symptomatology and markers of anxiety disorders in Parkinson's disease: A cross-sectional study: Symptomatology and Markers of Anxiety Disorders in PD. *Mov. Disord.* **26**, 484–492 (2011).
14. Dissanayaka, N. N. W. *et al.* Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Mov. Disord.* **25**, 838–845 (2010).
15. Association, A. P. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5*. (American Psychiatric Publishing, 2013).
16. Beck, A. T., Rush, A. J., Shaw, B. F., Emery, G. & more, & 1. *Cognitive Therapy of Depression*. (The Guilford Press, 1987).
17. Pagonabarraga, J., Kulisevsky, J., Strafella, A. P. & Krack, P. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *The Lancet Neurology* **14**, 518–531 (2015).
18. Hauser, R. A. *et al.* Evaluation of rotigotine transdermal patch for the treatment of apathy and motor symptoms in Parkinson's disease. *BMC Neurol* **16**, 90 (2016).
19. Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. & Erbaugh, J. An Inventory for Measuring Depression. *Arch Gen Psychiatry* **4**, 561–571 (1961).
20. Zigmond, A. S. & Snaith, R. P. The hospital anxiety and depression scale. *Acta Psychiatr Scand* **67**, 361–370 (1983).
21. Sheikh, J. & Yesavage, J. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. in *Clinical Gerontology: A Guide to Assessment and Intervention* 165–173 (Routledge, 1986).
22. Starkstein, S. E. *et al.* Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* **4**, 134–139 (1992).

23. Beck, A. T., Steer, R. A., Ball, R. & Ranieri, W. F. Comparison of Beck Depression Inventories-IA and-II in Psychiatric Outpatients. *Journal of Personality Assessment* **67**, 588–597 (1996).
24. Berger, C., Mehrhoff, F. W., Beier, K. M. & Meinck, H.-M. [Sexual delinquency and Parkinson's disease]. *Nervenarzt* **74**, 370–375 (2003).
25. Leroi, I. *et al.* Carer burden in apathy and impulse control disorders in Parkinson's disease. *Int J Geriatr Psychiatry* **27**, 160–166 (2012).
26. Mamikonyan, E. *et al.* Long-term follow-up of impulse control disorders in Parkinson's disease. *Mov. Disord.* **23**, 75–80 (2008).
27. Bastiaens, J., Dorfman, B. J., Christos, P. J. & Nirenberg, M. J. Prospective cohort study of impulse control disorders in Parkinson's disease. *Movement Disorders* **28**, 327–333 (2013).
28. Zhang, S. *et al.* Management of impulse control disorders in Parkinson's disease. *International Psychogeriatrics* **28**, 1597–1614 (2016).
29. Samuel, M. *et al.* Impulse Control Disorders in Parkinson's Disease:Management, Controversies, and Potential Approaches. *Movement disorders* **30**, 150–159 (2015).
30. Thobois, S. *et al.* Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain* **133**, 1111–1127 (2010).
31. Chaudhuri, K. R. *et al.* A Pilot Prospective, Multicenter Observational Study of Dopamine Agonist Withdrawal Syndrome in Parkinson's Disease. *Movement Disorders Clinical Practice* **2**, 170–174 (2015).
32. Thobois, S. *et al.* Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain* **136**, 1568–1577 (2013).
33. Lyons, K. E. *et al.* Orally Disintegrating Selegiline in Parkinson Patients With Dopamine Agonist-Related Adverse Effects: *Clinical Neuropharmacology* **33**, 5–10 (2010).
34. Papay, K. *et al.* Naltrexone for impulse control disorders in Parkinson disease A placebo-controlled study. *Neurology* **83**, 826–833 (2014).

35. Weintraub, D. *et al.* Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch. Neurol.* **67**, 589–595 (2010).
36. Weintraub, D., Papay, K., Siderowf, A. & others. Screening for impulse control symptoms in patients with de novo Parkinson disease A case-control study. *Neurology* **80**, 176–180 (2013).
37. Poletti, M. *et al.* A Single-Center, Cross-Sectional Prevalence Study of Impulse Control Disorders in Parkinson Disease: Association With Dopaminergic Drugs. *Journal of Clinical Psychopharmacology* **33**, 691–694 (2013).
38. Corvol, J.-C. *et al.* Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology* **91**, e189–e201 (2018).
39. Tippmann-Peikert, M., Park, J. G., Boeve, B. F., Shepard, J. W. & Silber, M. H. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. *Neurology* **68**, 301–303 (2007).
40. Martinkova, J., Trejbalova, L., Sasikova, M., Benetin, J. & Valkovic, P. Impulse control disorders associated with dopaminergic medication in patients with pituitary adenomas. *Clin Neuropharmacol* **34**, 179–181 (2011).
41. Djamshidian, A., O'Sullivan, S. S., Wittmann, B. C., Lees, A. J. & Averbeck, B. B. Novelty seeking behaviour in Parkinson's disease. *Neuropsychologia* **49**, 2483–2488 (2011).
42. Voon, V. *et al.* Factors associated with dopaminergic drug–related pathological gambling in Parkinson disease. *Archives of Neurology* **64**, 212–216 (2007).
43. Voon, V. *et al.* Impulse control disorders in parkinson disease: A multicenter case-control study. *Annals of Neurology* **69**, 986–996 (2011).
44. Djamshidian, A. *et al.* Decision-making, impulsivity and addictions: Do Parkinson's disease patients jump to conclusions? *Movement Disorders* **27**, 1137–1145 (2012).
45. Sáez-Francàs, N. *et al.* Factores clínicos y psicopatológicos asociados a los trastornos del control de impulsos en la enfermedad de Parkinson. *Neurología* (2015). doi:10.1016/j.nrl.2015.05.002
46. Loehlin, J. C. & Beaujean, A. A. *Latent Variable Models*. (Routledge, 2017).

47. Nombela, C., Rittman, T., Robbins, T. W. & Rowe, J. B. Multiple modes of impulsivity in Parkinson's disease. *PLoS ONE* **9**, e85747 (2014).

48. Volkow, N. D. & Morales, M. The Brain on Drugs: From Reward to Addiction. *Cell* **162**, 712–725 (2015).

49. Olsen, C. M. Natural Rewards, Neuroplasticity, and Non-Drug Addictions. *Neuropharmacology* **61**, 1109–1122 (2011).

50. Frank, M. J., Seeberger, L. C. & O'reilly, R. C. By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science* **306**, 1940–1943 (2004).

51. Bechara, A. Deciding Advantageously Before Knowing the Advantageous Strategy. *Science* **275**, 1293–1295 (1997).

52. McClure, S. M., Laibson, D. I., Loewenstein, G. & Cohen, J. D. Separate neural systems value immediate and delayed monetary rewards. *Science* **306**, 503–507 (2004).

53. Aracil-Bolaños, I. & Strafella, A. P. Molecular imaging and neural networks in impulse control disorders in Parkinson's disease. *Parkinsonism & Related Disorders* **22 Suppl 1**, S101-105 (2016).

54. Gehring, W. J. & Willoughby, A. R. The Medial Frontal Cortex and the Rapid Processing of Monetary Gains and Losses. *Science* **295**, 2279–2282 (2002).

55. Martínez-Horta, S. *et al.* Apathy in Parkinson's Disease: Neurophysiological Evidence of Impaired Incentive Processing. *J. Neurosci.* **34**, 5918–5926 (2014).

56. Fan, W., Ding, H., Ma, J. & Chan, P. Impulse control disorders in Parkinson's disease in a Chinese population. *Neuroscience Letters* **465**, 6–9 (2009).

57. Zhang, Y., He, A. qi, Li, L., Chen, W. & Liu, Z. guo. Clinical characteristics of impulse control and related disorders in Chinese Parkinson's disease patients. *BMC Neurology* **17**, 98 (2017).

58. Petry, N. M., Stinson, F. S. & Grant, B. F. Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* **66**, 564–574 (2005).

59. Joutsa, J., Martikainen, K., Vahlberg, T., Voon, V. & Kaasinen, V. Impulse control disorders and depression in Finnish patients with Parkinson's disease. *Parkinsonism & Related Disorders* **18**, 155–160 (2012).

60. Callesen, M. B., Weintraub, D., Damholdt, M. F. & Møller, A. Impulsive and compulsive behaviors among Danish patients with Parkinson's disease: Prevalence, depression, and personality. *Parkinsonism & Related Disorders* **20**, 22–26 (2014).

61. Goerlich-Dobre, K. S. *et al.* Alexithymia-an independent risk factor for impulsive-compulsive disorders in Parkinson's disease: Impulsive-Compulsive Disorders & Alexithymia. *Movement Disorders* **29**, 214–220 (2014).

62. Eisinger, R. S. *et al.* Medications, Deep Brain Stimulation, and Other Factors Influencing Impulse Control Disorders in Parkinson's Disease. *Front Neurol* **10**, 86 (2019).

63. Keren, H. *et al.* Reward Processing in Depression: A Conceptual and Meta-Analytic Review Across fMRI and EEG Studies. *Am J Psychiatry* **175**, 1111–1120 (2018).

64. Kessler, R. C. *et al.* Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* **62**, 593–602 (2005).

65. Lee, J.-Y. *et al.* Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease. *Mov. Disord.* **24**, 1803–1810 (2009).

66. Lee, J.-Y., Jeon, B. S., Kim, H.-J. & Park, S.-S. Genetic variant of HTR2A associates with risk of impulse control and repetitive behaviors in Parkinson's disease. *Parkinsonism & Related Disorders* **18**, 76–78 (2012).

67. Kraemmer, J. *et al.* Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* **87**, 1106–1111 (2016).

68. Sackett, D. L. Bias in analytic research. *Journal of Chronic Diseases* **32**, 51–63 (1979).

69. Joutsa, J., Martikainen, K., Vahlberg, T. & Kaasinen, V. Effects of dopamine agonist dose and gender on the prognosis of impulse control disorders in Parkinson's disease. *Parkinsonism & Related Disorders* **18**, 1079–1083 (2012).

70. Rizos, A. *et al.* A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists. *Eur J Neurol* **23**, 1255–1261 (2016).

71. Seedat, S., Kesler, S., Niehaus, D. J. & Stein, D. J. Pathological gambling behaviour: emergence secondary to treatment of Parkinson's disease with dopaminergic agents. *Depress Anxiety* **11**, 185–186 (2000).

72. Molina, J. A. *et al.* Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? *Mov. Disord.* **15**, 869–872 (2000).

73. Ambermoon, P., Carter, A., Hall, W. D., Dissanayaka, N. N. W. & O'Sullivan, J. D. Impulse control disorders in patients with Parkinson's disease receiving dopamine replacement therapy: evidence and implications for the addictions field. *Addiction* **106**, 283–293 (2011).

74. Marín-Lahoz, J., Sampedro, F., Martinez-Horta, S., Pagonabarraga, J. & Kulisevsky, J. Depression as a Risk Factor for Impulse Control Disorders in Parkinson Disease. *Ann. Neurol.* (2019). doi:10.1002/ana.25581

75. Vriend, C. *et al.* Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease: Reduced DaT BR Predates ICD in PD. *Movement Disorders* **29**, 904–911 (2014).

76. Tessitore, A. *et al.* Intrinsic brain connectivity predicts impulse control disorders in patients with Parkinson's disease. *Movement Disorders* **32**, 1710–1719 (2017).

77. Marinus, J., Zhu, K., Marras, C., Aarsland, D. & van Hilten, J. J. Risk factors for non-motor symptoms in Parkinson's disease. *The Lancet Neurology* **17**, 559–568 (2018).

78. Hill, A. B. The Environment and Disease: Association or Causation? *Proc R Soc Med* **58**, 295–300 (1965).

79. Maloney, E. M., Djamshidian, A. & O'Sullivan, S. S. Phenomenology and epidemiology of impulsive-compulsive behaviours in Parkinson's disease, atypical Parkinsonian disorders and non-Parkinsonian populations. *Journal of the Neurological Sciences* **374**, 47–52 (2017).

80. Sobrido, M. J., Dias-Silva, J. J. & Quintáns, B. [Behavioral disorders in Parkinson's disease. Genetic, pharmacological and medico-legal aspects]. *Rev Neurol* **48 Suppl 1**, S43-48 (2009).
81. Weintraub, D. *et al.* Dopamine Agonist Use is Associated with Impulse Control Disorders in Parkinson's Disease. *Arch Neurol* **63**, 969–973 (2006).
82. Isaias, I. U. *et al.* The relationship between impulsivity and impulse control disorders in Parkinson's disease. *Movement Disorders* **23**, 411–415 (2008).
83. Marín-Lahoz, J. *et al.* Parkinson's Disease: Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity. *Front Psychiatry* **9**, 465 (2018).
84. Eisinger, R. S. *et al.* Medications, Deep Brain Stimulation, and Other Factors Influencing Impulse Control Disorders in Parkinson's Disease. *Front. Neurol.* **10**, (2019).
85. Aracil-Bolaños, I. & Strafella, A. P. Molecular imaging and neural networks in impulse control disorders in Parkinson's disease. *Parkinsonism Relat Disord* **22**, S101–S105 (2016).
86. Martini, A. *et al.* Dopaminergic Neurotransmission in Patients With Parkinson's Disease and Impulse Control Disorders: A Systematic Review and Meta-Analysis of PET and SPECT Studies. *Front. Neurol.* **9**, (2018).
87. Biundo, R. *et al.* Brain volume changes in Parkinson's disease and their relationship with cognitive and behavioural abnormalities. *J. Neurol. Sci.* **310**, 64–69 (2011).
88. Pellicano, C. *et al.* Morphometric changes in the reward system of Parkinson's disease patients with impulse control disorders. *J. Neurol.* **262**, 2653–2661 (2015).
89. Biundo, R. *et al.* Patterns of cortical thickness associated with impulse control disorders in Parkinson's disease. *Mov. Disord.* **30**, 688–695 (2015).
90. Imperiale, F. *et al.* Brain structural and functional signatures of impulsive–compulsive behaviours in Parkinson's disease. *Molecular Psychiatry* **23**, 459–466 (2018).
91. Tessitore, A. *et al.* Intrinsic brain connectivity predicts impulse control disorders in patients with Parkinson's disease. *Mov. Disord.* **32**, 1710–1719 (2017).

92. Tessitore, A. *et al.* Resting-state brain networks in patients with Parkinson's disease and impulse control disorders. *Cortex* **94**, 63–72 (2017).

93. Verger, A. *et al.* Brain PET substrate of impulse control disorders in Parkinson's disease: A metabolic connectivity study. *Hum Brain Mapp* **39**, 3178–3186 (2018).

94. Neyman, J. Statistics—Servant of All Science. *Science* **122**, 401–406 (1955).

95. Yakushev, I., Drzezga, A. & Habeck, C. Metabolic connectivity: methods and applications. *Curr. Opin. Neurol.* **30**, 677–685 (2017).

96. Postuma, R. B. *et al.* MDS clinical diagnostic criteria for Parkinson's disease: MDS-PD Clinical Diagnostic Criteria. *Movement Disorders* **30**, 1591–1601 (2015).

97. Emre, M. *et al.* Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders* **22**, 1689–1707; quiz 1837 (2007).

98. Weintraub, D. *et al.* Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Movement Disorders* **24**, 1461–1467 (2009).

99. Weintraub, D. *et al.* Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. *Movement disorders* **27**, 242–247 (2012).

100. Goetz, C. G. *et al.* Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement disorders* **23**, 2129–2170 (2008).

101. Marinus, J., Leentjens, A. F., Visser, M., Stiggelbout, A. M. & van Hilten, J. J. Evaluation of the hospital anxiety and depression scale in patients with Parkinson's disease. *Clinical neuropharmacology* **25**, 318–324 (2002).

102. Pagonabarraga, J. *et al.* Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. *Movement Disorders* **23**, 998–1005 (2008).

103. Ramón Fernández de Bobadilla *et al.* Parkinson's disease-cognitive rating scale: Psychometrics for mild cognitive impairment. *Movement Disorders* **28**, 1376–1383 (2013).

104. Varrone, A. *et al.* EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. *Eur. J. Nucl. Med. Mol. Imaging* **36**, 2103–2110 (2009).

105. Martínez-Horta, S. *et al.* The impact of bilingualism on brain structure and function in Huntington's disease. *Parkinsonism Relat. Disord.* (2018). doi:10.1016/j.parkreldis.2018.09.017

106. Fischl, B. & Dale, A. M. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl. Acad. Sci. U.S.A.* **97**, 11050–11055 (2000).

107. Greve, D. N. *et al.* Cortical surface-based analysis reduces bias and variance in kinetic modeling of brain PET data. *Neuroimage* **92**, 225–236 (2014).

108. Greve, D. N. *et al.* Different partial volume correction methods lead to different conclusions: An (18)F-FDG-PET study of aging. *Neuroimage* **132**, 334–343 (2016).

109. Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M. & Nichols, T. E. Permutation inference for the general linear model. *Neuroimage* **92**, 381–397 (2014).

110. Riba, J., Krämer, U. M., Heldmann, M., Richter, S. & Münte, T. F. Dopamine Agonist Increases Risk Taking but Blunts Reward-Related Brain Activity. *PLoS One* **3**, (2008).

111. Ye, Z., Hammer, A., Camara, E. & Münte, T. F. Pramipexole modulates the neural network of reward anticipation. *Human Brain Mapping* **32**, 800–811 (2011).

112. Dragogna, F. *et al.* Brain metabolism in substance-induced psychosis and schizophrenia: a preliminary PET study. *Neuropsychobiology* **70**, 195–202 (2014).

113. Siri, C. *et al.* Long-term cognitive follow-up of Parkinson's disease patients with impulse control disorders. *Movement Disorders* **30**, 696–704 (2015).

114. Schindlbeck, K. A. & Eidelberg, D. Network imaging biomarkers: insights and clinical applications in Parkinson's disease. *Lancet Neurol* **17**, 629–640 (2018).

115. Pagonabarraga, J. & Kulisevsky, J. Cognitive impairment and dementia in Parkinson's disease. *Neurobiol. Dis.* **46**, 590–596 (2012).

116. Sampedro, F., Marín-Lahoz, J., Martínez-Horta, S., Pagonabarraga, J. & Kulisevsky, J. Dopaminergic degeneration induces early posterior cortical thinning in Parkinson's disease. *Neurobiol. Dis.* **124**, 29–35 (2019).

117. Firbank, M. J. *et al.* Cerebral glucose metabolism and cognition in newly diagnosed Parkinson's disease: ICICLE-PD study. *Journal of Neurology, Neurosurgery & Psychiatry* **88**, 310–316 (2017).

118. Tan, H., Li, X., Wei, K. & Guan, Y. Study on brain glucose metabolic networks in Parkinson's disease patients with visual spatial dysfunction by 18F-FDG PET imaging. *Traditional Medicine and Modern Medicine* **01**, 27–31 (2018).

119. Matthews, D. C. *et al.* FDG PET Parkinson's disease-related pattern as a biomarker for clinical trials in early stage disease. *NeuroImage: Clinical* **20**, 572–579 (2018).

120. Martinez-Horta, S. *et al.* Non-demented Parkinson's disease patients with apathy show decreased grey matter volume in key executive and reward-related nodes. *Brain Imaging Behav* **11**, 1334–1342 (2017).

121. Dujardin, K., Sockeel, P., Delliaux, M., Destée, A. & Defebvre, L. Apathy may herald cognitive decline and dementia in Parkinson's disease. *Movement Disorders* **24**, 2391–2397 (2009).

122. Leroi, I. *et al.* Apathy and impulse control disorders in Parkinson's disease: a direct comparison. *Parkinsonism Relat. Disord.* **18**, 198–203 (2012).

123. Chaudhuri, K. R. *et al.* The burden of non-motor symptoms in Parkinson's disease using a self-completed non-motor questionnaire: A simple grading system. *Parkinsonism & Related Disorders* **21**, 287–291 (2015).

124. Pagonabarraga, J., Marín-Lahoz, J. & Kulisevsky, J. Oral dopamine agonists in the management of Parkinson's disease. in *Parkinson's Disease: Current and Future Therapeutics and Clinical Trials* (eds. Gálvez-Jiménez, N., Fernandez, H. H., Espay, A. J. & Fox, S. H.) (Cambridge University Press, 2016).

125. *Behavioral Addictions: Criteria, Evidence, and Treatment*. (Academic Press, 2014).

126. Rothman, K. J. Causes. *Am. J. Epidemiol.* **104**, 587–592 (1976).

127. Potenza, M. N. Should addictive disorders include non-substance-related conditions? *Addiction* **101**, 142–151 (2006).

128. Kalivas, P. W. & Volkow, N. D. The Neural Basis of Addiction: A Pathology of Motivation and Choice. *Am J Psychiatry* 11 (2005).

129. Hauser, T. U. *et al.* The feedback-related negativity (FRN) revisited: New insights into the localization, meaning and network organization. *NeuroImage* **84**, 159–168 (2014).

130. Walsh, M. M. & Anderson, J. R. Learning from experience: Event-related potential correlates of reward processing, neural adaptation, and behavioral choice. *Neurosci Biobehav Rev* **36**, 1870–1884 (2012).

131. Stiasny-Kolster, K. *et al.* The REM sleep behavior disorder screening questionnaire-A new diagnostic instrument. *Movement Disorders* **22**, 2386–2393 (2007).

132. Marco-Pallares, J. *et al.* Human oscillatory activity associated to reward processing in a gambling task. *Neuropsychologia* **46**, 241–248 (2008).

133. Belouchrani, A., Abed-Meraim, K., Cardoso, J.- & Moulines, E. A blind source separation technique using second-order statistics. *IEEE Transactions on Signal Processing* **45**, 434–444 (1997).

134. Romero, S., Mañanas, M. A. & Barbanoj, M. J. A comparative study of automatic techniques for ocular artifact reduction in spontaneous EEG signals based on clinical target variables: A simulation case. *Computers in Biology and Medicine* **38**, 348–360 (2008).

135. Delorme, A. & Makeig, S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* **134**, 9–21 (2004).

136. Litvan, I. *et al.* Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov. Disord.* **27**, 349–356 (2012).

137. Patton, J. H., Stanford, M. S. & Barratt, E. S. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol* **51**, 768–774 (1995).

138. Mueller, S. T. & Piper, B. J. The Psychology Experiment Building Language (PEBL) and PEBL Test Battery. *Journal of Neuroscience Methods* **222**, 250–259 (2014).

139. Homack, S. Conners' Continuous Performance Test (2nd ed.; CCPT-II). *Journal of Attention Disorders* **9**, 556–558 (2006).

140. Brown, R. I. F. Some contributions of the study of gambling to the study of other addictions. in *Gambling Behavior and Problem Gambling* (eds. Eadington, W. R. & Cornelius, J. A.) (Univ of Nevada Pr, 1993).

141. Griffiths, M. A 'components' model of addiction within a biopsychosocial framework. *Journal of Substance Use* **10**, 191–197 (2005).

142. DeLong, E. R., DeLong, D. M. & Clarke-Pearson, D. L. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* **44**, 837–845 (1988).

143. R Development Core Team (2008). *R: A language and environment for statistical computing.* (R Foundation for Statistical Computing).

144. Wilson, F. P. & Parikh, C. R. Translational Methods in Nephrology: Individual Treatment Effect Modeling. *JASN* **29**, 2615–2618 (2018).

145. Johnston, S. C. *et al.* Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *The Lancet* **369**, 283–292 (2007).

146. Maresh, E. L., Allen, J. P. & Coan, J. A. Increased default mode network activity in socially anxious individuals during reward processing. *Biol Mood Anxiety Disord* **4**, 7 (2014).

147. Volpato, C. *et al.* Dopaminergic Medication Modulates Learning from Feedback and Error-Related Negativity in Parkinson's Disease: A Pilot Study. *Front Behav Neurosci* **10**, (2016).

148. Frank, M. J., Woroch, B. S. & Curran, T. Error-Related Negativity Predicts Reinforcement Learning and Conflict Biases. *Neuron* **47**, 495–501 (2005).

149. Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E. & Donchin, E. A Neural System for Error Detection and Compensation. *Psychol Sci* **4**, 385–390 (1993).

150. Falkenstein, M., Hoormann, J., Christ, S. & Hohnsbein, J. ERP components on reaction errors and their functional significance: a tutorial. *Biological Psychology* **51**, 87–107 (2000).

151. Kang, J.-H. *et al.* Association of Cerebrospinal Fluid β-Amyloid 1-42, T-tau, P-tau181, and α-Synuclein Levels With Clinical Features of Drug-Naive Patients With Early Parkinson Disease. *JAMA Neurol* **70**, 1277–1287 (2013).

## Article 1: Parkinson's Disease: Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 28 September 2018
doi: 10.3389/fpsyt.2018.00465

# Parkinson's Disease: Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity

*Juan Marín-Lahoz*[1,2,3,4], *Javier Pagonabarraga*[1,2,3*†], *Saul Martinez-Horta*[1,2,3], *Ramón Fernandez de Bobadilla*[5,6], *Berta Pascual-Sedano*[1,2,3,6], *Jesús Pérez-Pérez*[1,2,3], *Alexandre Gironell*[1,2,3] *and Jaime Kulisevsky*[1,2,3,6*†]

[1] Movement Disorders Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [2] Biomedical Research Institute (IIB-Sant Pau), Barcelona, Spain, [3] Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain, [4] Institute de Neurociencies Universitat Autonoma de Barcelona, Cerdanyola del Vallès, Spain, [5] Centro Neurológico de Atención Integral, Navarra, Spain, [6] Estudios de Ciencias de la Salud, Universitat Oberta de Catalunya, Barcelona, Spain

OPEN ACCESS

**Edited by:**
Alain Dervaux,
Centre Hospitalier Universitaire (CHU) de Amiens, France

**Reviewed by:**
Mauro Ceccanti,
Università degli Studi di Roma La Sapienza, Italy
Carla Cannizzaro,
Università degli Studi di Palermo, Italy

***Correspondence:**
Javier Pagonabarraga
jpagonabarraga@santpau.cat
Jaime Kulisevsky
jkulisevsky@santpau.cat

[†] These authors have contributed equally to this work

**Specialty section:**
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

**Received:** 20 April 2018
**Accepted:** 06 September 2018
**Published:** 28 September 2018

**Citation:**
Marín-Lahoz J, Pagonabarraga J, Martinez-Horta S, Fernandez de Bobadilla R, Pascual-Sedano B, Pérez-Pérez J, Gironell A and Kulisevsky J (2018) Parkinson's Disease: Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity. Front. Psychiatry 9:465. doi: 10.3389/fpsyt.2018.00465

**Introduction:** Impulse control disorders (ICDs) are a common complication of Parkinson's disease (PD) receiving dopamine agonist (DAA) Impulsivity is considered an underlying mechanism but evidence of this relationship is scarce. To explore the relationship between impulsivity and the presence and severity of ICD in PD.

**Methods:** Prospective cross-sectional study of consecutive PD outpatients. Patients with dementia or previously known ICDs were excluded. Two measures of impulsivity were assessed: Barratt Impulsiveness Scale (BIS-11) for impulsiveness trait (main exposure) and commission errors in the Continuous Performance Test (CE) for motor inhibition. Main outcomes were diagnosis of ICD based on a comprehensive clinical interview and severity of ICD based on the Questionnaire for Impulsive-Compulsive Disorders.

**Results:** Of 100 patients (mean [SD] age, 67.2 [8.8], 54 male), 31 had ICD. Patients with ICDs were 5.3 years younger ($p = 0.01$), used more frequently dopamine agonist ($p = 0.02$), alcohol ($p = 0.009$) and tobacco ($p = 0.02$). They were not more impulsive on BIS-11 (56 vs. 58, $p = 0.23$, adjusted $p = 0.46$) and CE ($p = 0.96$). No relationship was found between dopaminergic medications and impulsivity or ICD severity. Among patients with ICD, impulsivity was correlated with ICD severity (BIS-11 $r = 0.33$, $p = 0.001$, adjusted $p = 0.002$, CE $r = 0.53$, $p = 0.006$). Multivariate regression analysis confirmed the independent predictive role of both measures.

**Conclusions:** Impulsivity is not associated with increased prevalence of ICD in PD but it is strongly linked to ICD severity. When considering dopamine replacement therapy, assessment of impulsivity may be a useful approach to detect those patients at risk of severe forms of ICD.

**Keywords: impulsivity, impulse control disorders, behavioral addictions, Parkinson's disease, severity**

## INTRODUCTION

Impulse control disorders (ICDs) are a common neuropsychiatric complication of Parkinson's disease (PD). By definition, ICDs refer to pathological behaviors characterized by failure to resist an impulse, drive or temptation to perform an act that is harmful. Usually, the affected individual experiences pleasure, gratification, or relief at the time of committing the act (1). Common ICDs in PD include dysfunctional behaviors related to gambling, sex, food intake, shopping, and hobbies. In the context of PD, these and other ICD-related behaviors are increasingly regarded as behavioral addictions (2–4).

ICDs are uncommon in the general population and in untreated PD patients (5–7). Among PD treatments, dopamine agonists (DAA) are strongly associated with ICDs (5). Patients receiving DAA for a disorder other than PD also have a high risk of ICDs (8, 9). However, other risk factors are important for their development and phenomenology as most patients taking DAA will not develop ICDs, and the best clinical-genetic predictive models for the development of ICD symptoms explains only part of the risk (4).

Not only ICD frequency is worrisome, but also for their range of severity. Severity may vary from extremely disruptive addictions causing bankruptcy, divorce, or even criminal prosecution (10, 11) to mild addictive symptoms—usually related to increased creativity or productivity—that may be even perceived as positive for patients' functionality (12, 13). It is also worth noting that 13–39% of patients with ICDs do not experience improvement or remission of the addictions after dopamine agonists withdrawal (3, 14–16). It is therefore important not only to study risk factors for the development of ICDs, but to identify the variables responsible for different prognosis and severity.

Impulsivity is a psychological construct characterized by poor control of thoughts and actions with a propensity to react fast over urges and environmental demands despite potential negative consequences. The definition of impulsivity shares obvious aspects with that of ICDs, and impulsivity is usually considered to have a causal relation with ICDs in PD. Higher scores on the Barratt Impulsiveness Scale (BIS-11), a self-reported questionnaire with semi-quantitative responses, have been observed in PD patients with and without ICDs (17, 18). Other modes of impulsivity, such as deficit of motor inhibition, have also been studied (18). Yet, studies on the influence of impulsivity for the development and clinical manifestations of ICDs in PD are scarce (17, 19).

In the present study, we aimed to explore the relation between impulsivity and frequency and severity of ICDs in PD. We assessed impulsivity and ICDs in PD patients who were taking dopaminergic drugs. Only incident cases of ICDs were included to avoid confounding factors such as changes in dopaminergic medication and a bias toward chronic ICDs. If impulsivity was a true risk factor for ICDs in PD we would expect higher levels of impulsivity in patients with ICDs.

## MATERIALS AND METHODS

Consecutive PD outpatients followed at the Movement Disorders Unit at Hospital de la Santa Creu i Sant Pau were invited to participate. Inclusion criteria were idiopathic PD, active treatment with a dopaminergic agent and last follow up at the same center including ICDs evaluation within the last 6 months. Exclusion criteria were: any other neurological condition, history of brain surgery, dementia according to Movement Disorder Society PD-dementia criteria (20), inability to perform the proposed tasks, use of dopamine antagonists, unstable medical or psychiatric conditions (depression and anxiety under effective and stable treatment were not excluded), and presence of ICD in the previous follow up. Excluding patients with previous ICDs was chosen to get measures of the exposures as close to ICD inception as possible and to avoid bias generated by medication changes and chronicity.

Patients were informed about the study during follow-up visits. If they agreed to participate in the study, they returned for the study evaluation. Patients were not excluded if ICDs were suspected or diagnosed the day they were informed about the study. In such cases, no changes in medication were made before the study protocol was completed (always within a week). All the participants were evaluated by a neurologist trained in movement disorders and a neuropsychologist experienced in PD. All the patients gave written informed consent and the study protocol was approved by the clinical research ethics committee at Hospital de la Santa Creu i Sant Pau. All the study was conducted according to the principles expressed in the Declaration of Helsinki. All the evaluations were performed on medication.

### ICDs Diagnosis and Rating

The presence of ICDs was assessed through a comprehensive clinical interview. ICDs were considered present when the related behavior was dysfunctional according to the components of addiction proposed by Brown (21) and modified by Griffiths (22). This model considers six components that comprise addiction regardless of the involvement of drug use: salience, mood modification, tolerance, withdrawal symptoms, conflict, and relapse. At least 4 of the 6 components needed to be present to consider a behavior as ICD. To diagnose a patient with more than one ICD, each ICD had to be unrelated to the others and considered dysfunctional.

To obtain a semiquantitative measure of severity in patients with a diagnosis of ICD, we used the short version of the questionnaire for impulsive-compulsive disorders in PD (QUIPs) (23) (score range 0–13), the Minnesota Impulsive Disorders Interview (MIDI) (24) (score range 0–56), and the number of different ICDs. The number of ICDs was based on the clinical interview. ICD diagnosis and QUIPs score were considered main outcomes and the other ICD related variables were considered exploratory. The investigator rating the main outcomes was blinded to impulsivity measures.

## Impulsivity Evaluation

Impulsivity was evaluated using two different approaches, the BIS-11 and the PEBL Continuous Performance Test (PCPT). The BIS-11 was designed to assess the personality trait of impulsiveness (25). It has 30 self-reported items grouped in three subtraits: motor, attentional, and nonplanning. We used BIS-11 as a subjective estimator for impulsivity. The PCPT is a continuous performance task programmed in the Psychology Experiment Building Language (26) based on the Conners Continuous Performance Task II (27). The PCPT was designed to assess motor inhibition and sustained attention. Participants have to press a key in response to any capital letter (except X) that appears on the screen. At the same time, they must refrain from responding to lures (any X that appears). Targets are much more common than lures, creating a tendency to respond to lures, an inhibition failure. Commission error rate (CE)—failure to avoid responding to lures—was used as an indirect but objective measure of impulsivity (28). The investigator rating impulsivity measures was blinded to patient outcomes (presence and severity of ICDs).

## PD-Related Variables

We recorded the motor part of Unified Parkinson's Disease Rating Scale (UPDRS-III) (29), Hoehn and Yahr stage (H&Y), age at PD onset, PD duration, and current medical treatment. We calculated the Levodopa equivalent daily dose (LEDD) and the amount of LEDD corresponding to dopamine agonists (agonist-LEDD) according to previously reported conversion factors (30). We also recorded personal use of legal drugs (caffeine, nicotine and alcohol), use of illegal drugs and both personal and family history of alcohol and illegal drugs use disorders.

## Data Analysis

Patients with and without ICD (ICD+/ ICD-) were compared. The chi-squared test was used for discrete variables. When this was inappropriate, the Fischer exact test was used. For most quantitative variables we used mean and Student's *t*-test and for those which did not comply with parametric assumptions we used median and Mann–Whitney *U*-test. We used Pearson correlations in ICD+ patients to analyze the relationship between ICD severity and other variables. Linear regression was used to assess whether impulsivity independently explained ICD severity and to control for motor state (UPDRS III) when comparing medication doses between groups. Logistic regression was used to assed which variables were independently associated with ICD diagnosis. The level of significance was set as $p < 0.05$, 2-sided. Main objectives were the comparison of BIS-11 score between ICD+ and ICD- and the correlation between BIS-11 with severity among ICD+ (measured by QUIPs). Multiple comparison adjustment was performed for these two tests by Bonferroni (using the number of tests performed for impulsivity and ICD diagnosis and for impulsivity and ICD severity). The other statistical analysis were considered exploratory and significance was not adjusted. Confidence intervals (CI) are reported at 95% level. All the statistical analyses were conducted using R version 3.1.3 (31).

# RESULTS

## ICD Frequency

One hundred consecutive PD patients (54 male, age mean ± SD 67 ± 9, education 11 ± 5, age at PD diagnosis 61 ± 9) were recruited and ICDs were diagnosed in 31. Thirty-eight patients had a positive score in QUIPs and 19 in MIDI.

The behaviors causing ICDs were hobbism/punding ($n = 15$), binge-eating ($n = 14$), pathological hypersexuality ($n = 5$), and compulsive shopping ($n = 5$). Hobbism/punding behaviors were tidying ($n = 6$), board games ($n = 3$), social networking ($n = 3$), repairing ($n = 2$), computer assisted edition ($n = 2$), and one case each of compulsive reading, doll handcraft, dancing, and walk-about. Eleven patients had several unrelated ICDs. None had pathological gambling or dopamine dysregulation syndrome.

ICD+ patients were 5.25 years younger at the time of the study (CI 1.24–9.25, $p = 0.01$) and at PD onset ($p = 0.017$). They were also more frequently receiving treatment with a DAA (59.4 vs. 83.9%, CI 4.7–44.1%, $p = 0.02$). No differences were found regarding time since PD diagnosis, Hoehn & Yahr stage, or UPDRS III status (**Table 1**).

Most patients in the sample were taking DAA: 41 used pramipexole, 11 ropinirole, and 15 rotigotine (among ICD+ patients 16, 4 and 6, respectively). No patients used more than one DAA. Average agonist-LEDD was higher in ICD+ patients ($p = 0.012$) but this difference was due to the higher proportion of DAA use in the ICD+ group (59.4% among ICD-, 83.9% among ICD+; chi-square test $p = 0.02$). Among patients taking DAA, no differences were found in agonist-LEDD between ICD+ and ICD- groups ($p = 0.17$). No difference was found after adjusting for UPDRS III ($p = 0.22$). Levodopa dose was similar in both groups ($p = 0.35$) and remained similar after adjusting for UPDRS III ($p = 0.07$). MAO-B inhibitors and amantadine use did not differ between groups ($p = 0.96$ and $p = 0.22$, respectively). LEDD showed a trend toward significance, with higher doses in ICD+ patients ($p = 0.08$). However, after controlling for UPDRS III this difference became clearly significant ($p = 0.008$), indicating that for a comparable degree of motor severity, ICD+ patients were taking higher LEDD.

No differences between ICD- and ICD+ groups were found either in BIS-11 (56.35 vs. 58.33, unadjusted $p = 0.23$, adjusted $p = 0.46$,) or in CE ($p = 0.96$) (**Table 1**). Neither BIS-11 nor CE, were related to LEDD, DAA use or agonist-LEDD (**Table 2**).

None of the patients had begun to consume legal or illegal drugs after PD diagnosis. No association was found between the current amount of alcohol intake and ICDs ($p$ =0.46). However, current alcohol use was associated to ICD (41.5 vs. 12.9%, OR = 5.42, CI = 1.64 - 23.61, $p = 0.003$), and patients with no history of alcohol use had a significantly lower prevalence of ICDs (6.7 vs. 34.5%, OR = 0.13, CI = 0.01-0.95, $p = 0.03$). Most of the participants did not remember the age of first alcohol use and therefore it was not analyzed.

Current tobacco use was associated with ICDs (OR = 5.17, CI = 1.05–34.44, $p = 0.02$), although <10% of our sample were current smokers and the average tobacco consumption did not differ between groups ($p = 0.25$). Lifetime tobacco consumption was more common (52%) but its association with

**TABLE 1 |** Clinical and behavioral description of the sample.

| | ICD- ($n = 69$) | ICD+ ($n = 31$) | $p$-value |
|---|---|---|---|
| Age, years | 68.79 ± 7.82 | 63.55 ± 9.77 | 0.01 |
| Gender, male (%) | 37 (53.6) | 17 (54.8) | 0.91 |
| Age at PD onset, years | 62.5 ± 7.75 | 57.5 ± 9.52 | 0.02 |
| Evolution, months | 65.6 ± 3.76 | 77.8 ± 3.87 | 0.25 |
| UPDRS III | 23.4 ± 9.88 | 19.9 ± 9.65 | 0.11 |
| H&Y* | 2(2-2.5) | 2(2-2) | 0.06 |
| LEDD, mg | 533.1 ± 451.6 | 702.2 ± 416.9 | 0.07 |
| Proportion of agonist use (%) | 41 (59) | 26 (84) | 0.02 |
| QUIPs | 0.06 | 1.84 | <0.001 |
| MIDI | 0.29 | 3.3 | <0.001 |
| BIS-11 | 56.35 ± 7.0 | 58.33 ± 7.72 | 0.23 |
| Motor | 19.31 ± 2.52 | 19.37 ± 2.95 | 0.93 |
| Nonplanning | 20.79 ± 4.07 | 22.23 ± 4.7 | 0.15 |
| Attentional | 16.25 ± 1.98 | 16.73 ± 1.98 | 0.27 |
| PCPT commission errors ratio | 0.378 ± 0.2 | 0.376 ± 0.2 | 0.96 |
| PCPT correct RT, ms | 480 ± 75 | 465 ± 57 | 0.24 |
| PCPT error RT, ms | 447 ± 163 | 426 ± 131 | 0.49 |
| PCPT correct targets ratio | 0.94 | 0.95 | 0.59 |
| Current smokers (%) | 3 (4.3) | 6 (19) | 0.02** |
| Lifetime smokers (%) | 32 (46) | 20 (65) | 0.93 |
| Age at smoking onset | 19.65 ± 4.48 | 15.53 ± 3.11 | <0.001 |
| Current alcohol users (%) | 41 (59) | 27 (87) | 0.006 |
| Lifetime alcohol users (%) | 52 (75) | 30 (97) | 0.009 |
| Lifetime illegal drugs users (%) | 3 (5) | 4 (14) | 0.20** |

*Mean ± standard deviation and proportions are shown unless otherwise specified. t-test is used for central measures and Chi-square for proportions unless other test specified. * Median (interquartile range), Wilcoxon–Mann–Whitney test significance is shown. **Fisher exact test significance is shown.*
*ICD, impulse control disorder; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; QUIPs, Short version of Questionnaire for Impulsive-Compulsive Disorders, MIDI, Minnesota Impulsive Disorders Interview; BIS-11, Barrat Impulsiveness Scale; PCPT, PEBL Continuous Performance Task; RT, reaction time; ms, milliseconds.*

**TABLE 2 |** Correlation matrix of impulsivity and dopaminergic medication.

| | BIS-11 | CE | LEDD | Agonist-LEDD |
|---|---|---|---|---|
| BIS-11 | | $r = 0.03$ | $r = 0.03$ | $r = 0.03$ |
| CE | $p = 0.76$ | | $r = 0.1$ | $r = -0.12$ |
| LEDD | $p = 0.77$ | $p = 0.33$ | | $r = 0.43$ |
| Agonist-LEDD | $p = 0.78$ | $p = 0.22$ | $p < 0.001$ | |

*BIS-11, Barrat Impulsiveness Scale; CE, Commission Error rate in PEBL Continuous Performance Task; LEDD, Levodopa equivalent daily dose (mg/d), Agonist-LEDD, Levodopa equivalent daily dose corresponding to dopamine agonists(mg/d).*

ICDs was not statistically significant (OR = 2.09, CI = 0.81–5.61, $p = 0.09$). However, patients who had begun smoking at 18 years old or younger were more likely to present ICDs than older first time smokers (OR = 7.18, CI 1.29–76.3, $p = 0.01$) and ICD+ patients had started smoking 4 years earlier on average (15.5 vs. 19.7 y.o., $p < 0.001$). Current and previous coffee intake was not related to ICDs ($p = 0.73$ and $p = 0.67$, respectively).

No patient was currently using illegal drugs and previous use was not significantly related to ICD diagnosis (OR = 3.26, CI = 0.51–23.87, $p = 0.19$). No association was found between ICDs and family history of drug or alcohol abuse (OR = 2.48, CI = 0.76–8.02, $p = 0.08$). Only one of the 18 patients who had never consumed alcohol on a regular basis and were not current smokers had ICDs (Fischer exact test $p = 0.01$).

Multiple logistic regression showed that only current alcohol consumption and age were independently associated with ICD diagnosis (**Supplementary material**).

**TABLE 3 |** Correlation matrix of impulsivity and ICD severity among ICD+.

| | BIS-11 | CE | QUIPs | MIDI | N. of ICDs |
|---|---|---|---|---|---|
| BIS-11 | | $r = 0.03$ | $r = 0.33$ | $r = 0.30$ | $r = 0.30$ |
| CE | $p = 0.75$ | | $r = 0.53$ | $r = 0.38$ | $r = 0.53$ |
| QUIPs | $p = 0.001$ | $p = 0.006$ | | $r = 0.68$ | $r = 0.9$ |
| MIDI | $p = 0.002$ | $p = 0.04$ | $p < 0.001$ | | $r = 0.70$ |
| N. of ICDs | $p = 0.003$ | $p = 0.006$ | $p < 0.001$ | $p < 0.001$ | |

*ICD, impulsive control disorders; BIS-11, Barrat Impulsiveness Scale; CE, Commission Error rate in PEBL Continuous Performance Task; QUIPs, Short version of Questionnaire for Impulsive-Compulsive Disorders; MIDI, the Minnesota Impulsive Disorders Interview; N. of ICDs, number of ICDs.*

## ICD Severity

Among ICD+ we studied correlations patients between impulsivity measures and ICD severity measures. BIS-11 and QUIPs correlated significantly ($r = 0.33$, unadjusted $p = 0.001$, adjusted $p = 0.002$). We also found positive, significant correlations between each impulsivity measure and each severity measure, a correlation matrix is shown in **Table 3**. However, no correlation was found between BIS-11 and PCPT commission error rate (Pearson's $r = 0.03$, $p = 0.75$). Other variables related to ICD frequency were not statistically associated to severity measures (**Supplementary Material**).

We performed multiple linear regression analysis to study whether each impulsivity estimator independently explained QUIPs in ICD+ patients. As the other tested variables were not statistically associated with QUIPs, we included as independent variables the ones that were associated with ICD presence except for age of smoking onset (because 32% of the ICD+ patients had never smoked) and history of alcohol use (because only one ICD+ patient had never used it). QUIPs score was the predicted value. We also used bidirectional stepwise regression to select the predictors. Both impulsivity measures—BIS-11 and commission error rate—significantly predicted QUIPs in the "all in" model. Current smoking was also a significant predictor. These were also the only variables selected by bidirectional stepwise regression (**Table 4**).

# DISCUSSION

The present results show a complex interaction between DAA and impulsivity with the presence and severity of ICDs in

**TABLE 4 |** Multiple linear regression models using QUIPs as the dependent variable among ICD+.

| | Adjusted $R^2$ | Estimate | t | *p* |
|---|---|---|---|---|
| **All-in model** | 0.5974 | | | |
| (Intercept) | | −3.55 | −1.82 | 0.08 |
| LEDD | | 0.00006 | 0.13 | 0.90 |
| DAA use | | 0.055 | 0.11 | 0.91 |
| Age | | 0.0007 | 0.037 | 0.97 |
| BIS-11 | | 0.065 | 2.45 | 0.02 |
| CE | | 4.57 | 4.56 | < 0.001 |
| Current alcohol user | | −0.459 | −0.86 | 0.40 |
| Current smoker | | 1.26 | 2.39 | 0.03 |
| **Stepwise, both directions model** | 0.6452 | | | |
| (Intercept) | | −3.52 | −2.63 | 0.01 |
| BIS-11 | | 0.06 | 2.58 | 0.02 |
| CE | | 4.35 | 4.82 | < 0.001 |
| Current Smoker | | 1.24 | 2.57 | 0.02 |

*QUIPs, Short version of Questionnaire for Impulsive-Compulsive Disorders; ICD, impulsive control disorders; LEDD, levodopa equivalent daily dose; DAA, dopamine agonists; BIS-11, Barrat Impulsiveness Scale; CE, Commission Errors.*

PD patients. Contrary to our hypothesis impulsivity was not significantly higher in patients with ICD. However it was associated with higher severity of ICDs. This suggests that the role of impulsivity in ICD presence may be weak or nonexistent but it has an important role regulating ICD severity. The use of DAA, as previously shown, is associated with the presence of ICDs, but not with impulsivity or with ICD severity. Therefore DAA seem to have a critical role in ICD inception but not in their severity.

The fact that LEDD was higher in ICD+ only after controlling for motor severity might indicate that ICDs are related to an imbalance of dopaminergic activity between dorsal and ventral striatum. Higher doses of dopaminergic medication to control motor symptoms could promote overdosing of the ventral striatum (32), but our study is not designed to address this hypothesis.

Other studies have found higher levels of impulsivity in ICD+ patients (17). This discrepancy with our findings may be due to different study designs. Case-control studies select previously diagnosed patients who are more likely to have more severe ICDs (33). Systematic screening of consecutive patients permits to identify less conspicuous but relevant cases. Therefore, our sample, which excluded patients with previously known ICDs, is more likely to be enriched with less severe addictive behaviors. Both approaches are valid and useful to serve different purposes. The selection bias in case-control studies increases the probability to rule out suspected differences because the expected difference between groups is higher. Cross sectional studies such as the present study tend to produce more representative results. Another plausible explanation for the lack of significant differences in impulsivity between ICD+ and ICD- patients is based on the type of ICDs found in our sample. None of our patients had pathological gambling, while other studies analyzing risk factors for ICDs in PD included almost exclusively patients with gambling, a condition known to be highly related to elevated impulsivity (34).

The double dissociation exhibited by impulsivity and dopamine agonist use suggests that dopamine agonist do not cause PD-ICDs by means of fostering impulsivity. Impulsivity promotes the expression of the disorder not restraining the behaviors that constitute it. Conversely, the existence of an impulse able to constitute a disorder, would be caused by the imbalance generated by dopaminergic medication in the reward system (35). Accordingly, impulsive behaviors not generally linked to reward, such as reckless driving or domestic violence are quite rare in PD patients. Nonetheless, a minimum grade of impulsivity may be required as a perfect self-control would preclude any addictive behavior.

As previously reported (5), we found the use of legal drugs are greatly associated to ICDs. Drug use is linked to both reward imbalance and impulsivity, not shedding light on the discussed dissociation. In this sample, alcohol consumption was associated with the presence while tobacco was associated with both presence and severity of ICDs. The use of both drugs precedes ICDs development in this study, therefore they act as risk factors. History of alcohol and tobacco use is easily available information and probably not usually taken into account prior to DAA prescription as it has not been used in predictive models (4).

Our study has several limitations and strengths. The first limitation is that QUIP short has not been properly validated as a measure of ICD severity. However, it is considered sensitive, reliable, easy to answer accurately and able to capture ICD severity (23). A rating scale has been validated for ICD severity, the QUIP rating scale (36). This scale is closely related to QUIP short. To overcome this limitation, MIDI and the number of ICDs have also been studied yielding similar statistical correlations. Second, the design does not probe that impulsivity antecedes ICDs. Prospective studies are necessary to confirm causality. The strengths of our study are: (1) the assessment of two unrelated modes of impulsivity, showing that they were independently related to ICD severity; (2) the use of behavioral addiction criteria to diagnose ICDs, allowing the use of the same criteria independently of the studied behavior; and (3) a sample of systematically interviewed consecutive outpatients, avoiding selection bias.

## CONCLUSIONS

In summary, we found impulsivity is more associated with severity of ICDs than with ICD diagnosis. Conversely, we found DAA are associated the diagnosis of ICDs but are not associated with their severity. We also show how previous and current use of legal drugs is strongly related to the appearance and severity of ICDs. Further research is needed to evaluate whether impulsivity and legal drug use should be taken into account before prescribing DAA, and whether treatment strategies focused on decreasing impulsivity (37) in PD patients with ICDs would help to control these behaviors.

## AUTHOR CONTRIBUTIONS

JM-L conception, design, data collection, data analysis, data interpretation, writing, and editing. JP and JK design, data collection, data interpretation, writing, and editing. RF design and data collection. SM-H data interpretation, writing, and editing. BP-S, AG, and JP-P data collection and editing.

## FUNDING

This work was financially supported by CERCA and CIBERNED funding, and grants from la Marató de TV3 (2014/U/477 and 20142910) and Fondo de Investigaciones Sanitarias del Ministerio de Sanidad y Consumo (PI15/00962 and PI14/02058). JM-L is recipient of a Rio Hortega contract. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. None of the authors have any relationship that could be perceived as a conflict of interest.

## ACKNOWLEDGMENTS

Carolyn Newey revised and edited English and scientific language.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00465/full#supplementary-material

## REFERENCES

1. American Psychiatric Association. *Diagnostic Criteria From DSM-IV-TR*. Washington, DC: The Association (2000).
2. Potenza MN. Non-substance addictive behaviors in the context of DSM-5. *Addict Behav*. (2014) 39:1–2. doi: 10.1016/j.addbeh.2013.09.004
3. Cilia R, Benfante R, Asselta R, Marabini L, Cereda E, Siri C, et al. Tryptophan hydroxylase type 2 variants modulate severity and outcome of addictive behaviors in Parkinson's disease. *Parkins Relat Disord*. (2016) 29:96–103. doi: 10.1016/j.parkreldis.2016.05.017
4. Kraemmer J, Smith K, Weintraub D, Guillemot V, Nalls MA, Cormier-Dequaire F, et al. Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease. *J Neurol Neurosurg Psychiatry* (2016). 87:1106–11. doi: 10.1136/jnnp-2015-312848
5. Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, etal. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol*. (2010) 67:589–95. doi: 10.1001/archneurol.2010.65
6. Weintraub D, Papay K, Siderowf A. Screening for impulse control symptoms in patients with de novo Parkinson disease A case-control study. *Neurology* (2013) 80:176–80. doi: 10.1212/WNL.0b013e31827b915c
7. Poletti M, Logi C, Lucetti C, Del Dotto P, Baldacci F, Vergallo A, et al. A single-center, cross-sectional prevalence study of impulse control disorders in parkinson disease: association with dopaminergic drugs. *J Clin Psychopharmacol*. (2013) 33:691–4. doi: 10.1097/JCP.0b013e3182979830
8. Tippmann-Peikert M, Park JG, Boeve BF, Shepard JW, Silber MH. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. *Neurology* (2007) 68:301–3. doi: 10.1212/01.wnl.0000252368.25106.b6
9. Martinkova J, Trejbalova L, Sasikova M, Benetin J, Valkovic P. Impulse control disorders associated with dopaminergic medication in patients with pituitary adenomas. *Clin Neuropharmacol*. (2011) 34:179–181. doi: 10.1097/WNF.0b013e3182281b2f
10. Berger C, Mehrhoff FW, Beier KM, Meinck H-M. Sexual delinquency and Parkinson's disease. *Nervenarzt* (2003) 74:370–5. doi: 10.1007/s00115-003-1505-6
11. Sobrido MJ, Dias-Silva JJ, Quintáns B. Behavioral disorders in Parkinson's disease. Genetic, pharmacological and medico-legal aspects. *Rev Neurol*. (2009) 48(Suppl 1):S43–48.
12. Kulisevsky J, Pagonabarraga J, Martinez-Corral M. Changes in artistic style and behaviour in Parkinson's disease: dopamine and creativity. *J Neurol*. (2009) 256:816–9. doi: 10.1007/s00415-009-5001-1
13. Joutsa J, Martikainen K, Kaasinen V. Parallel appearance of compulsive behaviors and artistic creativity in Parkinson's disease. *Case Rep Neurol*. (2012) 4:77–83. doi: 10.1159/000338759
14. Mamikonyan E, Siderowf AD, Duda JE, Potenza MN, Horn S, Stern MB, et al. Long-term follow-up of impulse control disorders in Parkinson's disease. *Mov Disord*. (2008) 23:75–80. doi: 10.1002/mds.21770
15. Bastiaens J, Dorfman BJ, Christos PJ, Nirenberg MJ. Prospective cohort study of impulse control disorders in Parkinson's disease. *Mov Disord*. (2013) 28:327–33. doi: 10.1002/mds.25291
16. Zhang S, Dissanayaka NN, Dawson A, O'Sullivan JD, Mosley P, Hall W, et al. Management of impulse control disorders in Parkinson's disease. *Int Psychogeriatr*. (2016) 28:1597–614. doi: 10.1017/S104161021600096X
17. Voon V, Thomsen T, Miyasaki JM, de Souza M, Shafro A, Fox SH, et al. Factors associated with dopaminergic drug–related pathological gambling in Parkinson disease. *Arch Neurol*. (2007) 64:212–6. doi: 10.1001/archneur.64.2.212
18. Nombela C, Rittman T, Robbins TW, Rowe JB. Multiple modes of impulsivity in Parkinson's disease. *PLoS ONE* (2014) 9:e85747. doi: 10.1371/journal.pone.0085747
19. Sáez-Francàs N, Martí Andrés G, Ramírez N, de Fàbregues O, Álvarez-Sabín J, Casas M, et al. Factores clínicos y psicopatológicos asociados a los trastornos del control de impulsos en la enfermedad de Parkinson. *Neurología* (2015) 31:231–8. doi: 10.1016/j.nrl.2015.05.002
20. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. (2007) 22:1689–707; quiz 1837. doi: 10.1002/mds.21507
21. Brown RIF. Some contributions of the study of gambling to the study of other addictions. In: Eadington WR, Cornelius JA, editors. *Gambling Behavior and Problem Gambling*. Reno, NV: Univ of Nevada Pr (1993). pp. 241–72.
22. Griffiths M. A 'components' model of addiction within a biopsychosocial framework. *J Subst Use* (2005) 10:191–7. doi: 10.1080/14659890500114359
23. 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. doi: 10.1002/mds.22571
24. Grant JE. *Impulse Control Disorders: A Clinician's Guide to Understanding and Treating Behavioral Addictions*. 1st ed. New York, NY: W. W. Norton & Company (2008).
25. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol*. (1995) 51:768–74.
26. Mueller ST, Piper BJ. The Psychology Experiment Building Language (PEBL) and PEBL Test Battery. *J Neurosci Methods* (2014) 222:250–9. doi: 10.1016/j.jneumeth.2013.10.024
27. Homack S. Conners' Continuous Performance Test (2nd ed.; CCPT-II). *J Atten Disord*. (2006) 9:556–8. doi: 10.1177/1087054705283578
28. Epstein JN, Erkanli A, Conners CK, Klaric J, Costello JE, Angold A. Relations between continuous performance test performance measures and ADHD behaviors. *J Abnorm Child Psychol*. (2003) 31:543–54. doi: 10.1023/A:1025405216339
29. Fahn S, Elton R. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne D, Goldstein R. editors. *Recent Developments in Parkinson's Disease*. Florham Park, NJ: Macmillan Healthcare Information (1987). pp.153–63.

30. 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*. (2010) 25:2649–53. doi: 10.1002/mds.23429
31. R Development Core Team (2008). *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing. Available online at: http://www.R-project.org
32. Aracil-Bolaños I, Strafella AP. Molecular imaging and neural networks in impulse control disorders in Parkinson's disease. *Parkins Relat Disord*. (2016) 22:S101–05. doi: 10.1016/j.parkreldis.2015.08.003
33. Kopec JA, Esdaile JM. Bias in case-control studies. A review. *J Epidemiol Community Health* (1990) 44:179.
34. Cilia R, Cho SS, van Eimeren T, Marotta G, Siri C, Ko JH, et al. Pathological gambling in patients with Parkinson's disease is associated with fronto-striatal disconnection: a path modeling analysis. *Mov Disord*. (2011) 26:225–33. doi: 10.1002/mds.23480
35. Riba J, Krämer UM, Heldmann M, Richter S, Münte TF. Dopamine agonist increases risk taking but blunts reward-related brain activity. *PLoS ONE* (2008) 3:e2479. doi: 10.1371/journal.pone.0002479
36. Weintraub D, Mamikonyan E, Papay K, Shea JA, Xie SX, Siderowf A. Questionnaire for impulsive-compulsive disorders in Parkinson's Disease-rating scale. *Mov Disord*. (2012) 27:242–7. doi: 10.1002/mds.24023
37. Kehagia AA, Housden CR, Regenthal R, Barker RA, Muller U, Rowe J, et al. Targeting impulsivity in Parkinson's disease using atomoxetine. *Brain* (2014) 137:1986–97. doi: 10.1093/brain/awu117

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Article 2: Depression as a Risk Factor for Impulse Control Disorders in Parkinson Disease.

Annals of Neurology Research Article

# Depression as a Risk Factor for Impulse Control Disorders in Parkinson Disease

Juan Marín-Lahoz MD, Frederic Sampedro PhD, Saül Martinez-Horta MSc, Javier Pagonabarraga MD, PhD, Jaime Kulisevsky MD, PhD

First published: 15 August 2019. https://doi.org/10.1002/ana.25581

## Abstract

**Objective**

To longitudinally evaluate the role of depression in the development of impulse control disorders (ICDs) in Parkinson disease (PD) patients.

**Methods**

Using data from the Parkinson's Progression Markers Initiative, we included PD patients without ICDs at baseline according to the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP). Patients were prospectively evaluated first quarterly and then biannually. Development of an ICD was defined as an increase in QUIP scores during follow-up. Using survival proportional hazard models, we studied the effect of baseline depression on ICD risk. We also evaluated this effect controlling for dopamine agonist use as a time-dependent variable and for other potential confounders.

**Results**

Among 354 patients, 68 were depressed at baseline. The median follow-up was 4.08 years. Depression at baseline was associated with higher ICD risk (hazard ratio [HR] = 1.96, 95% confidence interval [CI] = 1.32–2.9, $p < 0.001$). This risk remained significant after controlling for dopamine agonist use (HR = 1.97, 95% CI = 1.33–2.9, $p < 0.001$), which was also independently linked to ICD development (HR = 1.87, 95% CI = 1.3–2.7, $p < 0.001$). Therefore, depressed patients faced an even higher ICD risk when receiving dopamine agonists. Controlling for multiple potential confounders did not alter these results.

**Interpretation**

Depression predisposes to the development of ICDs in PD. This risk is magnified by dopamine agonists. Dopamine agonists should thus be used cautiously in depressed PD patients. ANN NEUROL 2019

# Appendix A: Preservation of brain metabolism in recently-diagnosed Parkinson's impulse control disorders

**Preservation of brain metabolism in recently-diagnosed Parkinson's impulse control disorders**

Juan Marín-Lahoz, Frederic Sampedro, Javier Pagonabarraga, Jaime Kulisevsky et al.

## Abstract

Impulse control disorders (ICD) are a common and disrupting complication of Parkinson's disease (PD) treatment. Although their relationship with dopaminergic activity is well studied, their brain metabolic correlates are mostly unknown. In this work we studied brain metabolism using brain $^{18}$F-FDG-PET. We performed a case-control study nested within a cohort of PD patients free of ICD at baseline to compare ICD patients right after ICD diagnosis and prior to any treatment modification with matched ICD-free patients. We also compared both PD groups with healthy controls.

When compared with ICD-free PD patients, PD patients with recently diagnosed ICD showed higher glucose metabolism in widespread areas comprising prefrontal cortices, both amygdalae and default mode network hubs ($p<0.05$, corrected). When compared to healthy controls, they did not show hypermetabolism and the only hypometabolic region was the right caudate. In turn, ICD-free patients showed diffuse hypometabolism when compared to healthy controls.

Our results suggest brain metabolism is more preserved in PD patients with ICD than patients without ICD. This metabolic preservation could play a role in ICD development.

## Introduction

Impulse control disorders (ICD) are a common and frequently disabling complication of Parkinson's disease (PD). They represent a group of disorders characterized by an exaggerated increase in pleasurable activities which, even though rarely being noxious per se, can become harmful due to the prominence they acquire in the patient's life. ICD in PD are frequently related to sex, eating, shopping, gambling and a great variety of hobbies[79]. The amplified pursue of these activities leads to personal, social, financial and sometimes even legal consequences to the patients and their relatives [24,80].

ICD are more frequent in PD patients receiving treatment than in the general population, because they are related to dopaminergic replacement, particularly to a frequently used family of drugs, dopamine agonists (DA)[81]. Nevertheless, a great number of PD patients under DA treatment do not develop ICD[35,27]. This suggests that factors other than DA may explain why some patients develop this disorder and others do not. Even though longitudinal studies targeting causality of PD-ICD are scarce[77], several sociodemographic and clinical risk factors identified in cross-sectional studies are usually accepted. These include younger age[35], impulsivity[82,83,44], history of depression[59,60,74], personal history of alcohol or tobacco use and family history of pathological gambling[35,84]. Nonetheless, current predictive models leave a considerable part of this risk unexplained[67].

Studies targeting neural mechanisms of ICD may also help to explain why some patients develop ICD and may lead to strategies to prevent or treat them. In this vein, neuroimage is frequently used to investigate neuropsychiatric symptoms of PD. Neuroimaging studies examining ICD in PD can be classified according to their image modality. Studies targeting the dopaminergic system and the reward circuit have found significant differences such as lower presynaptic dopamine transporter and higher dopamine release related to reward[85,86] in PD-ICD patients. Studies targeting brain structure in this context showed conflicting results[87–90]. Studies targeting resting-state connectivity have found differences between ICD and non-ICD PD patients, but their results are inconsistent[91,92,90]. Finally, one study targeted brain glucose metabolism using PET imaging. It found a relative increase in the right middle and inferior temporal gyri of PD-ICD patients compared to that of patients those without ICD[93].

An important limitation of most neuroimaging studies is that they only considered prevalent ICD cases without specifying either the time elapsed from ICD inception or treatment changes performed after ICD diagnosis. This may alter their findings in two ways: first, they risk of a selection bias: Neyman bias –excluding patients who have recovered from ICD due or not to treatment changes[68,94]. Second, the study findings may be partially or completely related treatment modifications and not to ICD itself.

Nonetheless, two works studied preclinical ICD using a longitudinal neuroimaging setting. These studies found interesting differences in both DAT ligands uptake[75] and resting-state connectivity[91] in patients who were about to develop ICD. Importantly, although the patterns of DAT ligands uptake are similar in patients with ICD and in patients who will develop ICD, connectivity patterns found in preclinical ICD differed from those found in patients with established ICD[90–92]. This divergence could be explained by the fact that functional correlations in PD-ICD evolve with time[90].

Overall, previous neuroimaging findings suggest that timing is a critical issue in the study of the functional brain correlates of PD-ICD. This highlights the necessity of studies targeting a population of recently-diagnosed ICD cases, allowing a comprehensive characterization of the imaging correlates of PD-ICD in the continuum ranging from preclinical, recently-diagnosed and well-established or even treated phenomena. Such studies could also provide useful imaging biomarkers to predict ICD development or monitor therapeutic strategies.

In this work, we describe the brain metabolism in recently-diagnosed PD-ICD patients prior to any treatment modification. We used a prospective cohort of PD patients who were free of ICD when recruited and underwent PET scans closely after ICD inception. We use the relatively widely available $^{18}$F-Fluorodeoxyglucose PET ($^{18}$FDG-PET) imaging modality. This technique has shown several advantages with respect to functional MRI in terms of interpretability, sensitivity, magnetic-artifacts, signal-to-noise ratio and out-of-sample replication at single-level[95]. We profit from structural MRI to study FDG uptake of intracortical and subcortical grey matter ensuring the results are not related to structural differences.

## Materials and Methods

Study design

We conducted a nested case control study within a cohort study of PD patients targeting risk markers for the development of ICDs. Inclusion criteria for the cohort study were PD diagnosis according to the Movement Disorders Society clinical diagnostic criteria[96], informed consent to perform the proposed evaluations, and willingness to take part in biannual follow up visits. Exclusion criteria were the use of neuroleptics, other suspected cause of parkinsonism, dementia[97], inability to perform the proposed evaluations, and current or previous ICD diagnosis -based on the Questionnaire for Impulsive-Compulsive Disorders (QUIP current and QUIP anytime, respectively[98]). This study also comprised a healthy control (HC) cohort with the same criteria (except that excludes PD and any neurological or psychiatric disorder). Participants in the HC cohort also perform the same evaluations.

For this nested case-control study, cases were participants who were diagnosed with PD-ICD in follow-up visits during the first two years of the cohort study. Right after ICD diagnosis, we proposed them to participate in the PET study. The PET scan was performed before any treatment modification and always within a fortnight. For each included PD-ICD case, two matched PD controls (PD-nonICD) were selected. They were PD patients from the same cohort free of ICD, of the same sex, similar age and similar disease duration. Finally, for each PD-ICD patient, an age and sex matched HC who agreed to perform a PET scan was selected from the corresponding cohort. The nested study was planned at the same time as the cohort study and the corresponding informed consent for PET imaging was obtained at the same time the cohort consent was -prior to any evaluation of the cohort study. Nonetheless, patients could decline participating in the PET study and still take part in the cohort study.

The study was designed according to the declaration of Helsinki and was approved by the local ethics committee.

Clinical assessments:

As part of the cohort study, we performed a comprehensive interview targeting ICD to all PD participants every six months, which included the short version of the Questionnaire for Impulsive-Compulsive Disorders in PD (QUIPs)[98]. When an ICD case was detected, we also performed the rating scale version (QUIP-RS) to evaluate its severity[99]. We assessed motor status using part III of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[100], levodopa equivalent daily dose (LEDD) according to previous literature[7], depressive symptoms using the depression subscale of the Hospital Anxiety and Depression Scale (HADS)[20,101], apathy using the Starkstein apathy scale (SAS)[22] and cognition using the Parkinson's Disease Cognitive Rating Scale (PD-CRS)[102,103]. All the evaluations were performed in the on state.

Neuroimaging acquisition and methods:

$^{18}$F-FDG-PET scans were acquired for all participants on a Philips Gemini TF station 60 minutes after the intravenous injection of 277 MBq/ml of radiotracer and following the European Association of Nuclear Medicine procedural guidelines for PET brain imaging[104]. PET scans of PD cases where performed within 15 days of ICD diagnosis and prior to any therapeutic change.

We compared voxelwise brain FDG uptake across groups using the SPM12 software package (http://www.fil.ion.ucl.ac.uk/spm/) and the SnPM toolbox (https://warwick.ac.uk/snpm). We applied a previously-reported PET preprocessing pipeline[105], which included intensity-normalization by a pons-vermis reference region, spatial normalization to MNI space, and smoothing with a Gaussian kernel of 12mm full-width at half maximum (FWHM).

PD patients had an available MRI scan acquired in a 3-Tesla Philips Achieva station within 6 months (median 2.5 months) of the PET scan. None of the patients had abnormalities in T2/FLAIR sequences. We used the T1 sequence to obtain structural information. This sequence was acquired using the following parameters: MPRAGE, Repetition time/Echo time (TR/TE) 500/50 milliseconds, flip-angle=8º, field of view (FOV) =23 cm, in-plane resolution of 256x256 and 1 mm slice thickness. Structural MRI information allowed us to perform a cortical thickness (Cth) and subcortical volumetric group comparison (PD-ICD vs PD-nonICD) using the FreeSurfer 6.0 software package (https://surfer.nmr.mgh.harvard.edu/). The specific methods employed for cortical and subcortical reconstruction of structural T1-MRI images have been fully described elsewhere[106]. Briefly, optimized surface deformation models following intensity gradients are able to accurately identify white matter and gray matter boundaries in the cerebral cortex, from which Cth values are computed at each vertex. On visual inspection, we did not observe reconstruction errors. We subsequently smoothed Cth values in fsaverage space by a vertexwise Gaussian kernel of 10mm FWHM.

Using the information provided by the T1-MRI scans, we performed an additional surface-based intracortical FDG-PET uptake analysis. This approach provides substantial improvements in reliability and detectability of metabolic effects within the cerebral cortex[107]. Additionally, the application of partial volume correction (PVC) techniques allows the correction of PET signal spill-over and also its adjustment by a possible underlying structural atrophy. For this, we used the PetSurfer pipeline (https://surfer.nmr.mgh.harvard.edu/fswiki/PetSurfer)[107,108]. In short, we registered PET images to its associated T1-MRI scans, intensity-scaled with respect to the pons region to obtain relative Standardized Uptake Values (SUVr), partial-volume corrected using the Muller-Gartner method, sampled halfway between the white and pial surfaces, and vertex-wise smoothed using a Gaussian kernel of 10mm FWHM. Methods including MRI were performed only in PD groups as healthy controls had no MRI available.

Statistical analyses

We compared clinical and sociodemographic data across groups using t-test for continuous variables and $X^2$ for categorical variables. We considered significant differences with a p-value<0.05.

We assessed voxelwise and vertexwise neuroimaging differences between groups using a generalized linear model (GLM). We included age and sex as nuisance variables. When comparing PD-ICD and PD-nonICD we also included disease duration and PD-CRS values as nuisance variables. We considered significant the clusters surviving p<0.05 and family-wise error (FWE) correction for multiple-comparison by permutation testing using 5000 permutations[109]. In the PD groups, as they had available T1-MRI imaging, we also compared parceled subcortical volumetric and PVC-SUVr information using the same GLM. For this analysis we used the same significance and correction.

Finally, we studied the Pearson's correlations of ICD severity (QUIP-RS) with the clusters identified in the group analysis. This analysis was considered exploratory and a p-value<0.05 was considered significant.

## Results

One hundred and twelve patients were included in the cohort study. During follow-up, 13 ICD cases were detected. Two patients withdraw their consent for PET scans. Two scans could not be acquired within two weeks for technical reasons, thus they were not acquired to avoid any delay in treatment modification. Finally, we obtained nine PD-ICD PET scans. We selected eighteen PD-nonICD controls for PET imaging. However, one withdrew the consent and two acquisitions were excluded because they were performed using a different scan (i.e. they were performed in a Phillips Vereos). The resulting PD-nonICD group had therefore 15 patients. We included nine matched HC and adquiered the corresponding PET scans. Table 1 describes the sample's clinical and sociodemographic information. No relevant differences were found comparing PD-ICD and PD-nonICD.

| | PD | PD-ICD | PD-nonICD | HC | p-value (PD-ICD vs PD-nonICD) | p-value (PD vs HC) |
|---|---|---|---|---|---|---|
| **n** | 24 | 9 | 15 | 9 | | |
| **Age [years]** | 70.6 ± 7.2 | 70.2±8.4 | 70.8±6.8 | 67.3 ± 6.6 | 0.84 | 0.25 |
| **Sex [%Female]** | 45.8% | 44.4% | 46.7% | 44% | 0.92 | 1 |
| **Education [years]** | 12.2±5.0 | 13.2±5.3 | 11.5±4.9 | 14.11±4.0 | 0.45 | 0.29 |
| **Disease duration [years]** | 5.5 ± 2.4 | 4.5 ± 2.5 | 6.1 ± 2.2 | NA | 0.13 | NA |
| **MDS-UPDRS-III** | 28.8±8.5 | 29.0±6.7 | 28.7±9.6 | 0.77±1.1 | 0.94 | <0.001 |
| **LEDD** | 629.7±262.5 | 634.2±352.4 | 627.1±205.5 | 0±0 | 0.96 | <0.001 |
| **Agonist-LEDD** | 150.5±108.6 | 175.3±91.1 | 135.6±118.3 | 0±0 | 0.37 | <0.001 |
| **QUIP-Short** | 0.6±0.9 | 1.6±0.7 | 0.0±0.0 | 0±0 | <0.001 | <0.001 |
| **QUIP-RS** | 5.4±4.2 | 10.7±2.8 | 0.3±0.5 | NA | <0.001 | NA |
| **PD-CRS** | 89.9 ± 13.9 | 93.1 ± 14.4 | 87.9 ± 13.7 | 105.3±8.1 | 0.39 | 0.002 |
| **HADS-D-Total** | 3.0±2.9 | 2.7±2.1 | 3.3±3.4 | 1.6±2.1 | 0.59 | 0.17 |
| **SAS-Total** | 3.8±3.8 | 5.1±5.0 | 3.0±2.8 | 0.86±1.9 | 0.26 | 0.06 |

**Table 1. Sample's socio-demographic and clinical information. Values are expressed as mean ± standard deviation. PD-CRS: Parkinson's Disease Cognitive Rating Scale, MDS-UPDRS-III: Part III of the Movement Disorders Society Unified Parkinson's Disease Rating Scale, LEDD: Levodopa Equivalent Daily Dose, QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (RS: Rating Scale). HADS-D: Hospital Anxiety and Depression Scale-Depression score, SAS: Starkstein Apathy Scale.NA=not applicable/available.**

As seen in Figure 1A, PD-ICD cases showed higher glucose metabolism than PD-nonICD controls. Given the spatial extent of the resulting voxelwise statistical map, only voxels showing $p<0.005$ voxels are displayed and discussed. The $p<0.05$-map is shown in supplementary Figure S1. This metabolic pattern included the posterior cingulate cortex (PCC), bilateral supramarginal gyrus, right precuneus, bilateral fusiform gyrus, bilateral lingual, parahippocampal gyrus, left anterior insula, bilateral amygdala, bilateral uncus, bilateral inferior orbitofrontal cortex (OFC), right BA10, left BA46, and left BA6. A positive correlation was found between right amygdala SUVr values and QUIP-RS scores within the PD-ICD group, $p=0.028$ (Figure 1B).

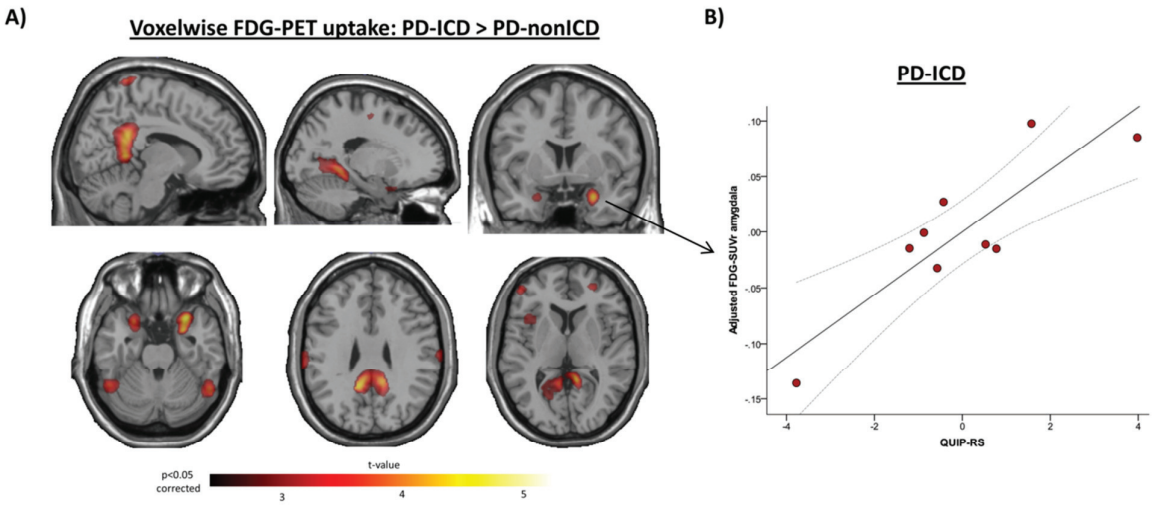


**Figure 1. A) Voxelwise FDG-PET uptake differences between PD-ICD and PD-nonICD, using age, sex, disease duration and PD-CRS as covariates of no interest (p<0.05 FWE). No significant regions were found in the PD-ICD < PD-nonICD contrast. For illustration purposes, only voxels showing p<0.005 are displayed. B) Correlation between FDG-SUVr values in the right amygdala cluster and demeaned QUIP-RS scores within the PD-ICD group, controlling for the same set of covariates.**

The result from intracortical PVC-SUVr analysis (Figure 2) was similar to that of voxelwise uptake analysis. There were not significant differences between PD-ICD and PD-nonICD either in Cth.

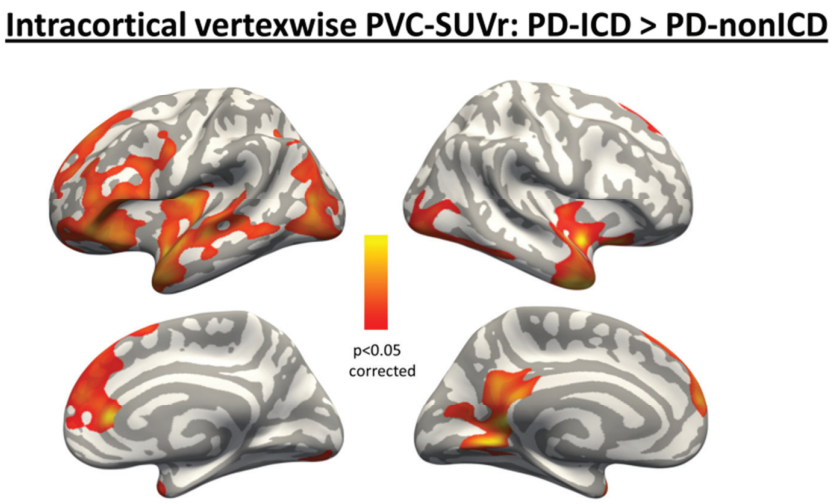


**Figure 2. Cortical vertexwise FDG-PET SUVr differences between PD-ICD and PD-nonICD, using age, sex, disease duration and PD-CRS as covariates of no interest (p<0.05 FWE). No significant regions were found in the PD-ICD < PD-nonICD contrast.**

As vertexwise measures are restricted to cortical structures, we also addressed differences in subcortical PVC-SUVr and volumetric information controlling for the same variables. The following subcortical structures were considered: Caudate, Putamen, Pallidum, Nucleus Accumbens, Thalamus, Amygdala and Hippocampus. The following regions showed higher SUVr values in the PD-ICD group with respect to PD-nonICD: Left Caudate(p=0.022), Right Putamen (p=0.043), Left

Hippocampus (p=0.025) and Right Hippocampus (p=0.025). However none of these survived significance correction by permutations. No significant subcortical structural differences were found.

Finally, in order to investigate whether this uptake difference was driven by an abnormal increase in FDG uptake in PD-ICD patients or rather by a hypometabolism of the PD-nonICD, PD subgroups were compared to HC (Figure 3). Given the spatial extent of the HC vs PD-nonICD statistical map only voxels showing p<0.005 voxels are displayed and discussed. The p<0.05-map is shown in supplementary Figure S2.

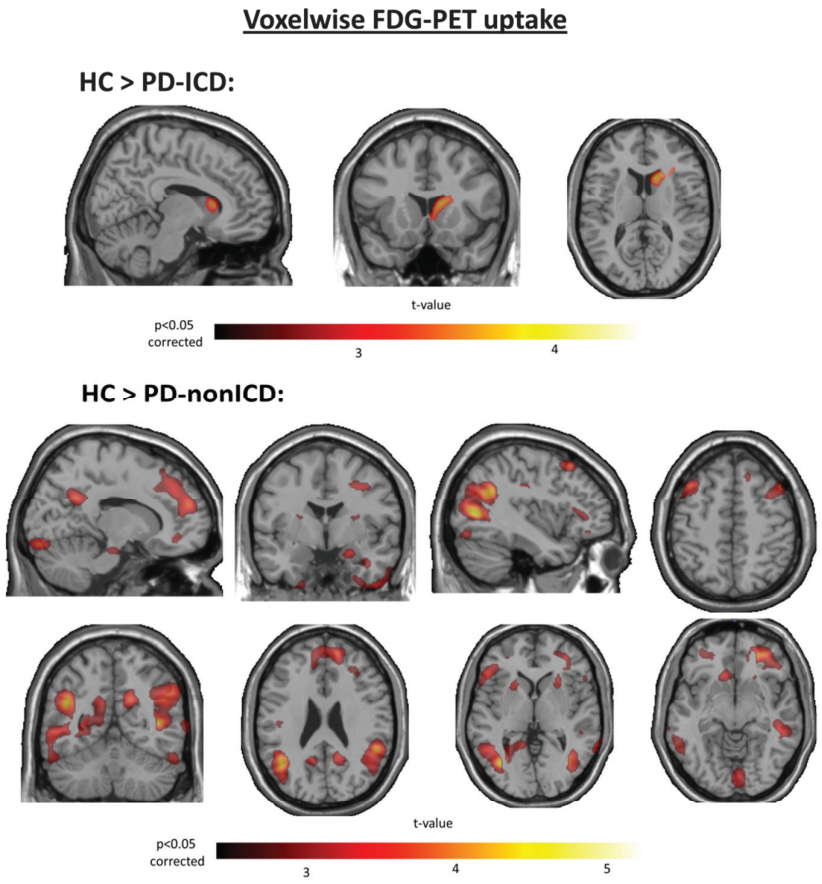


**Figure 3. Voxelwise FDG-PET uptake differences between HC and PD subgroups, using age and sex as covariates of no interest (p<0.05 FWE). No significant hypometabolic regions were found in HC. In the HC > PD-nonICD contrast, for illustration purposes, only voxels showing p<0.005 are displayed.**

None of the PD groups showed hypermetabolism with respect to the HC group (Figure 3). Whereas PD-ICD hypometabolic pattern included only the right caudate, PD-nonICD hypometabolic pattern was widespread and similar to the one obtained by the comparison of PD-ICD and PD-nonICD patients. It included bilateral angular gyrus, bilateral posterior cingulate cortex and precuneus, right amygdala, bilateral putamen, bilateral BA8, left anterior insula, left calcarine sulcus, bilateral fusiform gyrus, bilateral middle temporal lobe, bilateral superior frontal gyrus, bilateral middle orbitofrontal, left anterior cingulate and left subcallosal gyrus.

## Discussion

We report a pattern of significant metabolic preservation in recently-diagnosed PD-ICD patients prior to any medication changes. Importantly, this is one of the few studies addressing both structural and functional correlates of recently diagnosed ICD in the same matched sample of PD patients and healthy controls.

Our results show a diffuse pattern of metabolic brain preservation in PD-ICD patients comparted to PD-nonICD which included critical regions of the reward system (OFC, amygdala, insula) but also key nodes of neurocognitive networks (PCC, parahippocampus) and important heteromodal hubs (supramarginal gryi). This data go in line with previous evidence of lower regional FDG-PET uptake in PD-nonICD patients with respect to PD-ICD [93].

Similar widespread —and sometimes topographically inconsistent— multimodal brain differences in this population have been reported[88–90]. This suggests that the presence of PD-ICD is associated with a global brain state —rather than with well-defined localized abnormalities. Nevertheless, the exploratory correlational analysis showed an association between glucose metabolism in the amygdala and ICD severity. This finding may be related to the greater preservation of the uncinated fasciculus previously found in PD-ICD[90] and suggests a specific role of this structure in ICD.

Overall, these findings reinforce the view of PD-ICD as a multidimensional disorder where an abnormal overdrive of the meso-cortico-limbic pathway in response to DA therapy would require some degree of metabolic preservation of metabolism to take action. This reasoning is supported by the fact that DA alter risk and reward processing in healthy controls[110,111].

The metabolic preservation we found might be related to previously reported PD-ICD associations such as younger age[35], drug-abuse[112], or cognitive preservation[113]. Noteworthy, PD-nonICD patients showed widespread hypometabolism with respect to healthy controls of similar age and sex profiles. Of particular interest is hypometabolism observed in key nodes of the default mode network (DMN) such as the PCC, angular gyri and medial prefrontal cortex.

With the current knowledge of the role of resting-state networks such as the default mode network on cognitive decline in PD[114], and current evidence of neurodegeneration in early PD extending beyond frontostriatal regions[115,116], our findings suggest that, the cortex of PD-ICD patients might be less affected by the disease's neuropathological mechanisms. Correspondingly, the preservation of cortical metabolism observed in PD-ICD patients might explain their lower cognitive decline[113]. Further research is needed for confirmation of this hypothesis. Nonetheless, the metabolic preservation found in PD-ICD could be a possible source of discrepancy among the so-far reported metabolic signatures of PD with respect to HC[117–119].

Opposite findings have been reported for PD apathy. Apathetic patients show a more severe structural[120] compromise, an increased risk of cognitive impairment[121] and a more conservative response in gambling tasks[55]. This backs the idea that apathy and ICD related but opposite phenomena[122].

The main strengths of this study are the use of a longitudinal cohort to attain the adequate timing (before any therapeutic change) of PET scans, the case-control matching that allowed a robust

clinical-imaging avoiding potential confounders, and the absence of significant structural brain differences between PD-ICD and PD-nonICD groups, which could also act as a potential confounding effect. Notwithstanding, this work has some limitations: the sample size is relatively low and its cross-sectional nature limits the interpretation of the results. A cohort study including PET imaging prior to the development of ICD would be desirable, but would require a greater number of PET scans to obtain similar statistical power.

To conclude, we found that preservation of brain glucose metabolism characterize recently-diagnosed ICDs in PD. We hypothesize that this metabolic preservation fosters the appearance of ICD in patients receiving dopaminergic medication. This hypothesis will require a longitudinal design to be confirmed.

**Acknowledgements**

This work was financially supported by CIBERNED, and grants from Fundació la Marató de TV3 (2014/U/477 and 20142910) and Fondo de Investigaciones Sanitarias del Ministerio de Sanidad y Consumo (PI15/00962). None of the supporting organizations played a direct role on the inception, development or publication of this work.

**Author contributions:**

Study design: JML, JK, SMH, IC

Study execution: JML, AHB, SMH, IAB, MC, JP, HBM

Image analysis: FS

Statistical analysis: FS, JML

First draft: JML, FS

Manuscript review: all authors

**Competing interest**

None of the authors has competing interests.

## References


1. Fox, S. H. *et al.* International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease: Treatment of Motor Symptoms in PD. *Movement Disorders* **33**, 1248–1266 (2018).
2. de la Fuente-Fernández R. PResynaptic mechanisms of motor complications in parkinson disease. *Arch Neurol* **64**, 141–143 (2007).
3. Voon, V. *et al.* Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. *The Lancet Neurology* **8**, 1140–1149 (2009).
4. Stocchi, F. *et al.* Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: The STRIDE-PD study. *Annals of Neurology* **68**, 18–27 (2010).
5. Olanow, C. W. *et al.* A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease. *New England Journal of Medicine* **361**, 1268–1278 (2009).
6. Cereda, E. *et al.* Efficacy of rasagiline and selegiline in Parkinson's disease: a head-to-head 3-year retrospective case-control study. *J. Neurol.* **264**, 1254–1263 (2017).
7. Tomlinson, C. L. *et al.* Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement Disorders* **25**, 2649–2653 (2010).
8. Obeso, J. A. *et al.* Functional organization of the basal ganglia: Therapeutic implications for Parkinson's disease. *Movement Disorders* **23**, S548–S559 (2008).
9. Nilsson, F. M., Kessing, L. V., Sorensen, T. M., Andersen, P. K. & Bolwig, T. G. Major depressive disorder in Parkinson's disease: a register-based study. *Acta Psychiatr Scand* **106**, 202–211 (2002).
10. Seppi, K. *et al.* Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review: Treatment of the Nonmotor Symptoms in PD. *Movement Disorders* (2019). doi:10.1002/mds.27602
11. Menza, M. *et al.* A controlled trial of antidepressants in patients with Parkinson disease and depression. *Neurology* **72**, 886–892 (2009).

12. pubmeddev & al, B. M., et. Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis. - PubMed - NCBI. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27125963. (Accessed: 5th September 2019)
13. Leentjens, A. F. G. *et al.* Symptomatology and markers of anxiety disorders in Parkinson's disease: A cross-sectional study: Symptomatology and Markers of Anxiety Disorders in PD. *Mov. Disord.* **26**, 484–492 (2011).
14. Dissanayaka, N. N. W. *et al.* Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Mov. Disord.* **25**, 838–845 (2010).
15. Association, A. P. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5*. (American Psychiatric Publishing, 2013).
16. Beck, A. T., Rush, A. J., Shaw, B. F., Emery, G. & more, & 1. *Cognitive Therapy of Depression*. (The Guilford Press, 1987).
17. Pagonabarraga, J., Kulisevsky, J., Strafella, A. P. & Krack, P. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *The Lancet Neurology* **14**, 518–531 (2015).
18. Hauser, R. A. *et al.* Evaluation of rotigotine transdermal patch for the treatment of apathy and motor symptoms in Parkinson's disease. *BMC Neurol* **16**, 90 (2016).
19. Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. & Erbaugh, J. An Inventory for Measuring Depression. *Arch Gen Psychiatry* **4**, 561–571 (1961).
20. Zigmond, A. S. & Snaith, R. P. The hospital anxiety and depression scale. *Acta Psychiatr Scand* **67**, 361–370 (1983).
21. Sheikh, J. & Yesavage, J. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. in *Clinical Gerontology: A Guide to Assessment and Intervention* 165–173 (Routledge, 1986).
22. Starkstein, S. E. *et al.* Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* **4**, 134–139 (1992).

23. Beck, A. T., Steer, R. A., Ball, R. & Ranieri, W. F. Comparison of Beck Depression Inventories-IA and-II in Psychiatric Outpatients. *Journal of Personality Assessment* **67**, 588–597 (1996).
24. Berger, C., Mehrhoff, F. W., Beier, K. M. & Meinck, H.-M. [Sexual delinquency and Parkinson's disease]. *Nervenarzt* **74**, 370–375 (2003).
25. Leroi, I. *et al.* Carer burden in apathy and impulse control disorders in Parkinson's disease. *Int J Geriatr Psychiatry* **27**, 160–166 (2012).
26. Mamikonyan, E. *et al.* Long-term follow-up of impulse control disorders in Parkinson's disease. *Mov. Disord.* **23**, 75–80 (2008).
27. Bastiaens, J., Dorfman, B. J., Christos, P. J. & Nirenberg, M. J. Prospective cohort study of impulse control disorders in Parkinson's disease. *Movement Disorders* **28**, 327–333 (2013).
28. Zhang, S. *et al.* Management of impulse control disorders in Parkinson's disease. *International Psychogeriatrics* **28**, 1597–1614 (2016).
29. Samuel, M. *et al.* Impulse Control Disorders in Parkinson's Disease:Management, Controversies, and Potential Approaches. *Movement disorders* **30**, 150–159 (2015).
30. Thobois, S. *et al.* Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain* **133**, 1111–1127 (2010).
31. Chaudhuri, K. R. *et al.* A Pilot Prospective, Multicenter Observational Study of Dopamine Agonist Withdrawal Syndrome in Parkinson's Disease. *Movement Disorders Clinical Practice* **2**, 170–174 (2015).
32. Thobois, S. *et al.* Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain* **136**, 1568–1577 (2013).
33. Lyons, K. E. *et al.* Orally Disintegrating Selegiline in Parkinson Patients With Dopamine Agonist-Related Adverse Effects: *Clinical Neuropharmacology* **33**, 5–10 (2010).
34. Papay, K. *et al.* Naltrexone for impulse control disorders in Parkinson disease A placebo-controlled study. *Neurology* **83**, 826–833 (2014).

35. Weintraub, D. *et al.* Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch. Neurol.* **67**, 589–595 (2010).

36. Weintraub, D., Papay, K., Siderowf, A. & others. Screening for impulse control symptoms in patients with de novo Parkinson disease A case-control study. *Neurology* **80**, 176–180 (2013).

37. Poletti, M. *et al.* A Single-Center, Cross-Sectional Prevalence Study of Impulse Control Disorders in Parkinson Disease: Association With Dopaminergic Drugs. *Journal of Clinical Psychopharmacology* **33**, 691–694 (2013).

38. Corvol, J.-C. *et al.* Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology* **91**, e189–e201 (2018).

39. Tippmann-Peikert, M., Park, J. G., Boeve, B. F., Shepard, J. W. & Silber, M. H. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. *Neurology* **68**, 301–303 (2007).

40. Martinkova, J., Trejbalova, L., Sasikova, M., Benetin, J. & Valkovic, P. Impulse control disorders associated with dopaminergic medication in patients with pituitary adenomas. *Clin Neuropharmacol* **34**, 179–181 (2011).

41. Djamshidian, A., O'Sullivan, S. S., Wittmann, B. C., Lees, A. J. & Averbeck, B. B. Novelty seeking behaviour in Parkinson's disease. *Neuropsychologia* **49**, 2483–2488 (2011).

42. Voon, V. *et al.* Factors associated with dopaminergic drug–related pathological gambling in Parkinson disease. *Archives of Neurology* **64**, 212–216 (2007).

43. Voon, V. *et al.* Impulse control disorders in parkinson disease: A multicenter case-control study. *Annals of Neurology* **69**, 986–996 (2011).

44. Djamshidian, A. *et al.* Decision-making, impulsivity and addictions: Do Parkinson's disease patients jump to conclusions? *Movement Disorders* **27**, 1137–1145 (2012).

45. Sáez-Francàs, N. *et al.* Factores clínicos y psicopatológicos asociados a los trastornos del control de impulsos en la enfermedad de Parkinson. *Neurología* (2015). doi:10.1016/j.nrl.2015.05.002

46. Loehlin, J. C. & Beaujean, A. A. *Latent Variable Models*. (Routledge, 2017).

47. Nombela, C., Rittman, T., Robbins, T. W. & Rowe, J. B. Multiple modes of impulsivity in Parkinson's disease. *PLoS ONE* **9**, e85747 (2014).

48. Volkow, N. D. & Morales, M. The Brain on Drugs: From Reward to Addiction. *Cell* **162**, 712–725 (2015).

49. Olsen, C. M. Natural Rewards, Neuroplasticity, and Non-Drug Addictions. *Neuropharmacology* **61**, 1109–1122 (2011).

50. Frank, M. J., Seeberger, L. C. & O'reilly, R. C. By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science* **306**, 1940–1943 (2004).

51. Bechara, A. Deciding Advantageously Before Knowing the Advantageous Strategy. *Science* **275**, 1293–1295 (1997).

52. McClure, S. M., Laibson, D. I., Loewenstein, G. & Cohen, J. D. Separate neural systems value immediate and delayed monetary rewards. *Science* **306**, 503–507 (2004).

53. Aracil-Bolaños, I. & Strafella, A. P. Molecular imaging and neural networks in impulse control disorders in Parkinson's disease. *Parkinsonism & Related Disorders* **22 Suppl 1**, S101-105 (2016).

54. Gehring, W. J. & Willoughby, A. R. The Medial Frontal Cortex and the Rapid Processing of Monetary Gains and Losses. *Science* **295**, 2279–2282 (2002).

55. Martínez-Horta, S. *et al.* Apathy in Parkinson's Disease: Neurophysiological Evidence of Impaired Incentive Processing. *J. Neurosci.* **34**, 5918–5926 (2014).

56. Fan, W., Ding, H., Ma, J. & Chan, P. Impulse control disorders in Parkinson's disease in a Chinese population. *Neuroscience Letters* **465**, 6–9 (2009).

57. Zhang, Y., He, A. qi, Li, L., Chen, W. & Liu, Z. guo. Clinical characteristics of impulse control and related disorders in Chinese Parkinson's disease patients. *BMC Neurology* **17**, 98 (2017).

58. Petry, N. M., Stinson, F. S. & Grant, B. F. Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* **66**, 564–574 (2005).

59. Joutsa, J., Martikainen, K., Vahlberg, T., Voon, V. & Kaasinen, V. Impulse control disorders and depression in Finnish patients with Parkinson's disease. *Parkinsonism & Related Disorders* **18**, 155–160 (2012).

60. Callesen, M. B., Weintraub, D., Damholdt, M. F. & Møller, A. Impulsive and compulsive behaviors among Danish patients with Parkinson's disease: Prevalence, depression, and personality. *Parkinsonism & Related Disorders* **20**, 22–26 (2014).

61. Goerlich-Dobre, K. S. *et al.* Alexithymia-an independent risk factor for impulsive-compulsive disorders in Parkinson's disease: Impulsive-Compulsive Disorders & Alexithymia. *Movement Disorders* **29**, 214–220 (2014).

62. Eisinger, R. S. *et al.* Medications, Deep Brain Stimulation, and Other Factors Influencing Impulse Control Disorders in Parkinson's Disease. *Front Neurol* **10**, 86 (2019).

63. Keren, H. *et al.* Reward Processing in Depression: A Conceptual and Meta-Analytic Review Across fMRI and EEG Studies. *Am J Psychiatry* **175**, 1111–1120 (2018).

64. Kessler, R. C. *et al.* Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* **62**, 593–602 (2005).

65. Lee, J.-Y. *et al.* Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease. *Mov. Disord.* **24**, 1803–1810 (2009).

66. Lee, J.-Y., Jeon, B. S., Kim, H.-J. & Park, S.-S. Genetic variant of HTR2A associates with risk of impulse control and repetitive behaviors in Parkinson's disease. *Parkinsonism & Related Disorders* **18**, 76–78 (2012).

67. Kraemmer, J. *et al.* Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* **87**, 1106–1111 (2016).

68. Sackett, D. L. Bias in analytic research. *Journal of Chronic Diseases* **32**, 51–63 (1979).

69. Joutsa, J., Martikainen, K., Vahlberg, T. & Kaasinen, V. Effects of dopamine agonist dose and gender on the prognosis of impulse control disorders in Parkinson's disease. *Parkinsonism & Related Disorders* **18**, 1079–1083 (2012).

70. Rizos, A. *et al.* A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists. *Eur J Neurol* **23**, 1255–1261 (2016).

71. Seedat, S., Kesler, S., Niehaus, D. J. & Stein, D. J. Pathological gambling behaviour: emergence secondary to treatment of Parkinson's disease with dopaminergic agents. *Depress Anxiety* **11**, 185–186 (2000).

72. Molina, J. A. *et al.* Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? *Mov. Disord.* **15**, 869–872 (2000).

73. Ambermoon, P., Carter, A., Hall, W. D., Dissanayaka, N. N. W. & O'Sullivan, J. D. Impulse control disorders in patients with Parkinson's disease receiving dopamine replacement therapy: evidence and implications for the addictions field. *Addiction* **106**, 283–293 (2011).

74. Marín-Lahoz, J., Sampedro, F., Martinez-Horta, S., Pagonabarraga, J. & Kulisevsky, J. Depression as a Risk Factor for Impulse Control Disorders in Parkinson Disease. *Ann. Neurol.* (2019). doi:10.1002/ana.25581

75. Vriend, C. *et al.* Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease: Reduced DaT BR Predates ICD in PD. *Movement Disorders* **29**, 904–911 (2014).

76. Tessitore, A. *et al.* Intrinsic brain connectivity predicts impulse control disorders in patients with Parkinson's disease. *Movement Disorders* **32**, 1710–1719 (2017).

77. Marinus, J., Zhu, K., Marras, C., Aarsland, D. & van Hilten, J. J. Risk factors for non-motor symptoms in Parkinson's disease. *The Lancet Neurology* **17**, 559–568 (2018).

78. Hill, A. B. The Environment and Disease: Association or Causation? *Proc R Soc Med* **58**, 295–300 (1965).

79. Maloney, E. M., Djamshidian, A. & O'Sullivan, S. S. Phenomenology and epidemiology of impulsive-compulsive behaviours in Parkinson's disease, atypical Parkinsonian disorders and non-Parkinsonian populations. *Journal of the Neurological Sciences* **374**, 47–52 (2017).

80. Sobrido, M. J., Dias-Silva, J. J. & Quintáns, B. [Behavioral disorders in Parkinson's disease. Genetic, pharmacological and medico-legal aspects]. *Rev Neurol* **48 Suppl 1**, S43-48 (2009).
81. Weintraub, D. *et al.* Dopamine Agonist Use is Associated with Impulse Control Disorders in Parkinson's Disease. *Arch Neurol* **63**, 969–973 (2006).
82. Isaias, I. U. *et al.* The relationship between impulsivity and impulse control disorders in Parkinson's disease. *Movement Disorders* **23**, 411–415 (2008).
83. Marín-Lahoz, J. *et al.* Parkinson's Disease: Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity. *Front Psychiatry* **9**, 465 (2018).
84. Eisinger, R. S. *et al.* Medications, Deep Brain Stimulation, and Other Factors Influencing Impulse Control Disorders in Parkinson's Disease. *Front. Neurol.* **10**, (2019).
85. Aracil-Bolaños, I. & Strafella, A. P. Molecular imaging and neural networks in impulse control disorders in Parkinson's disease. *Parkinsonism Relat Disord* **22**, S101–S105 (2016).
86. Martini, A. *et al.* Dopaminergic Neurotransmission in Patients With Parkinson's Disease and Impulse Control Disorders: A Systematic Review and Meta-Analysis of PET and SPECT Studies. *Front. Neurol.* **9**, (2018).
87. Biundo, R. *et al.* Brain volume changes in Parkinson's disease and their relationship with cognitive and behavioural abnormalities. *J. Neurol. Sci.* **310**, 64–69 (2011).
88. Pellicano, C. *et al.* Morphometric changes in the reward system of Parkinson's disease patients with impulse control disorders. *J. Neurol.* **262**, 2653–2661 (2015).
89. Biundo, R. *et al.* Patterns of cortical thickness associated with impulse control disorders in Parkinson's disease. *Mov. Disord.* **30**, 688–695 (2015).
90. Imperiale, F. *et al.* Brain structural and functional signatures of impulsive–compulsive behaviours in Parkinson's disease. *Molecular Psychiatry* **23**, 459–466 (2018).
91. Tessitore, A. *et al.* Intrinsic brain connectivity predicts impulse control disorders in patients with Parkinson's disease. *Mov. Disord.* **32**, 1710–1719 (2017).

92. Tessitore, A. *et al.* Resting-state brain networks in patients with Parkinson's disease and impulse control disorders. *Cortex* **94**, 63–72 (2017).

93. Verger, A. *et al.* Brain PET substrate of impulse control disorders in Parkinson's disease: A metabolic connectivity study. *Hum Brain Mapp* **39**, 3178–3186 (2018).

94. Neyman, J. Statistics—Servant of All Science. *Science* **122**, 401–406 (1955).

95. Yakushev, I., Drzezga, A. & Habeck, C. Metabolic connectivity: methods and applications. *Curr. Opin. Neurol.* **30**, 677–685 (2017).

96. Postuma, R. B. *et al.* MDS clinical diagnostic criteria for Parkinson's disease: MDS-PD Clinical Diagnostic Criteria. *Movement Disorders* **30**, 1591–1601 (2015).

97. Emre, M. *et al.* Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders* **22**, 1689–1707; quiz 1837 (2007).

98. Weintraub, D. *et al.* Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Movement Disorders* **24**, 1461–1467 (2009).

99. Weintraub, D. *et al.* Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. *Movement disorders* **27**, 242–247 (2012).

100. Goetz, C. G. *et al.* Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement disorders* **23**, 2129–2170 (2008).

101. Marinus, J., Leentjens, A. F., Visser, M., Stiggelbout, A. M. & van Hilten, J. J. Evaluation of the hospital anxiety and depression scale in patients with Parkinson's disease. *Clinical neuropharmacology* **25**, 318–324 (2002).

102. Pagonabarraga, J. *et al.* Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. *Movement Disorders* **23**, 998–1005 (2008).

103. Ramón Fernández de Bobadilla *et al.* Parkinson's disease-cognitive rating scale: Psychometrics for mild cognitive impairment. *Movement Disorders* **28**, 1376–1383 (2013).

104. Varrone, A. *et al.* EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. *Eur. J. Nucl. Med. Mol. Imaging* **36**, 2103–2110 (2009).

105. Martínez-Horta, S. *et al.* The impact of bilingualism on brain structure and function in Huntington's disease. *Parkinsonism Relat. Disord.* (2018). doi:10.1016/j.parkreldis.2018.09.017

106. Fischl, B. & Dale, A. M. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl. Acad. Sci. U.S.A.* **97**, 11050–11055 (2000).

107. Greve, D. N. *et al.* Cortical surface-based analysis reduces bias and variance in kinetic modeling of brain PET data. *Neuroimage* **92**, 225–236 (2014).

108. Greve, D. N. *et al.* Different partial volume correction methods lead to different conclusions: An (18)F-FDG-PET study of aging. *Neuroimage* **132**, 334–343 (2016).

109. Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M. & Nichols, T. E. Permutation inference for the general linear model. *Neuroimage* **92**, 381–397 (2014).

110. Riba, J., Krämer, U. M., Heldmann, M., Richter, S. & Münte, T. F. Dopamine Agonist Increases Risk Taking but Blunts Reward-Related Brain Activity. *PLoS One* **3**, (2008).

111. Ye, Z., Hammer, A., Camara, E. & Münte, T. F. Pramipexole modulates the neural network of reward anticipation. *Human Brain Mapping* **32**, 800–811 (2011).

112. Dragogna, F. *et al.* Brain metabolism in substance-induced psychosis and schizophrenia: a preliminary PET study. *Neuropsychobiology* **70**, 195–202 (2014).

113. Siri, C. *et al.* Long-term cognitive follow-up of Parkinson's disease patients with impulse control disorders. *Movement Disorders* **30**, 696–704 (2015).

114. Schindlbeck, K. A. & Eidelberg, D. Network imaging biomarkers: insights and clinical applications in Parkinson's disease. *Lancet Neurol* **17**, 629–640 (2018).

115. Pagonabarraga, J. & Kulisevsky, J. Cognitive impairment and dementia in Parkinson's disease. *Neurobiol. Dis.* **46**, 590–596 (2012).

116. Sampedro, F., Marín-Lahoz, J., Martínez-Horta, S., Pagonabarraga, J. & Kulisevsky, J. Dopaminergic degeneration induces early posterior cortical thinning in Parkinson's disease. *Neurobiol. Dis.* **124**, 29–35 (2019).

117. Firbank, M. J. *et al.* Cerebral glucose metabolism and cognition in newly diagnosed Parkinson's disease: ICICLE-PD study. *Journal of Neurology, Neurosurgery & Psychiatry* **88**, 310–316 (2017).

118. Tan, H., Li, X., Wei, K. & Guan, Y. Study on brain glucose metabolic networks in Parkinson's disease patients with visual spatial dysfunction by 18F-FDG PET imaging. *Traditional Medicine and Modern Medicine* **01**, 27–31 (2018).

119. Matthews, D. C. *et al.* FDG PET Parkinson's disease-related pattern as a biomarker for clinical trials in early stage disease. *NeuroImage: Clinical* **20**, 572–579 (2018).

120. Martinez-Horta, S. *et al.* Non-demented Parkinson's disease patients with apathy show decreased grey matter volume in key executive and reward-related nodes. *Brain Imaging Behav* **11**, 1334–1342 (2017).

121. Dujardin, K., Sockeel, P., Delliaux, M., Destée, A. & Defebvre, L. Apathy may herald cognitive decline and dementia in Parkinson's disease. *Movement Disorders* **24**, 2391–2397 (2009).

122. Leroi, I. *et al.* Apathy and impulse control disorders in Parkinson's disease: a direct comparison. *Parkinsonism Relat. Disord.* **18**, 198–203 (2012).

123. Chaudhuri, K. R. *et al.* The burden of non-motor symptoms in Parkinson's disease using a self-completed non-motor questionnaire: A simple grading system. *Parkinsonism & Related Disorders* **21**, 287–291 (2015).

124. Pagonabarraga, J., Marín-Lahoz, J. & Kulisevsky, J. Oral dopamine agonists in the management of Parkinson's disease. in *Parkinson's Disease: Current and Future Therapeutics and Clinical Trials* (eds. Gálvez-Jiménez, N., Fernandez, H. H., Espay, A. J. & Fox, S. H.) (Cambridge University Press, 2016).

125. *Behavioral Addictions: Criteria, Evidence, and Treatment*. (Academic Press, 2014).

126. Rothman, K. J. Causes. *Am. J. Epidemiol.* **104**, 587–592 (1976).

127. Potenza, M. N. Should addictive disorders include non-substance-related conditions? *Addiction* **101**, 142–151 (2006).

128. Kalivas, P. W. & Volkow, N. D. The Neural Basis of Addiction: A Pathology of Motivation and Choice. *Am J Psychiatry* 11 (2005).

129. Hauser, T. U. *et al.* The feedback-related negativity (FRN) revisited: New insights into the localization, meaning and network organization. *NeuroImage* **84**, 159–168 (2014).

130. Walsh, M. M. & Anderson, J. R. Learning from experience: Event-related potential correlates of reward processing, neural adaptation, and behavioral choice. *Neurosci Biobehav Rev* **36**, 1870–1884 (2012).

131. Stiasny-Kolster, K. *et al.* The REM sleep behavior disorder screening questionnaire-A new diagnostic instrument. *Movement Disorders* **22**, 2386–2393 (2007).

132. Marco-Pallares, J. *et al.* Human oscillatory activity associated to reward processing in a gambling task. *Neuropsychologia* **46**, 241–248 (2008).

133. Belouchrani, A., Abed-Meraim, K., Cardoso, J.- & Moulines, E. A blind source separation technique using second-order statistics. *IEEE Transactions on Signal Processing* **45**, 434–444 (1997).

134. Romero, S., Mañanas, M. A. & Barbanoj, M. J. A comparative study of automatic techniques for ocular artifact reduction in spontaneous EEG signals based on clinical target variables: A simulation case. *Computers in Biology and Medicine* **38**, 348–360 (2008).

135. Delorme, A. & Makeig, S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* **134**, 9–21 (2004).

136. Litvan, I. *et al.* Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov. Disord.* **27**, 349–356 (2012).

137. Patton, J. H., Stanford, M. S. & Barratt, E. S. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol* **51**, 768–774 (1995).

138. Mueller, S. T. & Piper, B. J. The Psychology Experiment Building Language (PEBL) and PEBL Test Battery. *Journal of Neuroscience Methods* **222**, 250–259 (2014).

139. Homack, S. Conners' Continuous Performance Test (2nd ed.; CCPT-II). *Journal of Attention Disorders* **9**, 556–558 (2006).

140. Brown, R. I. F. Some contributions of the study of gambling to the study of other addictions. in *Gambling Behavior and Problem Gambling* (eds. Eadington, W. R. & Cornelius, J. A.) (Univ of Nevada Pr, 1993).

141. Griffiths, M. A 'components' model of addiction within a biopsychosocial framework. *Journal of Substance Use* **10**, 191–197 (2005).

142. DeLong, E. R., DeLong, D. M. & Clarke-Pearson, D. L. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* **44**, 837–845 (1988).

143. R Development Core Team (2008). *R: A language and environment for statistical computing.* (R Foundation for Statistical Computing).

144. Wilson, F. P. & Parikh, C. R. Translational Methods in Nephrology: Individual Treatment Effect Modeling. *JASN* **29**, 2615–2618 (2018).

145. Johnston, S. C. *et al.* Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *The Lancet* **369**, 283–292 (2007).

146. Maresh, E. L., Allen, J. P. & Coan, J. A. Increased default mode network activity in socially anxious individuals during reward processing. *Biol Mood Anxiety Disord* **4**, 7 (2014).

147. Volpato, C. *et al.* Dopaminergic Medication Modulates Learning from Feedback and Error-Related Negativity in Parkinson's Disease: A Pilot Study. *Front Behav Neurosci* **10**, (2016).

148. Frank, M. J., Woroch, B. S. & Curran, T. Error-Related Negativity Predicts Reinforcement Learning and Conflict Biases. *Neuron* **47**, 495–501 (2005).

149. Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E. & Donchin, E. A Neural System for Error Detection and Compensation. *Psychol Sci* **4**, 385–390 (1993).

150. Falkenstein, M., Hoormann, J., Christ, S. & Hohnsbein, J. ERmponents on reaction errors and their functional significance: a tutorial. *Biological Psychology* **51**, 87–107 (2000).

151. Kang, J.-H. *et al.* Association of Cerebrospinal Fluid β-Amyloid 1-42, T-tau, P-tau181, and α-Synuclein Levels With Clinical Features of Drug-Naive Patients With Early Parkinson Disease. *JAMA Neurol* **70**, 1277–1287 (2013).

## Supplementary material

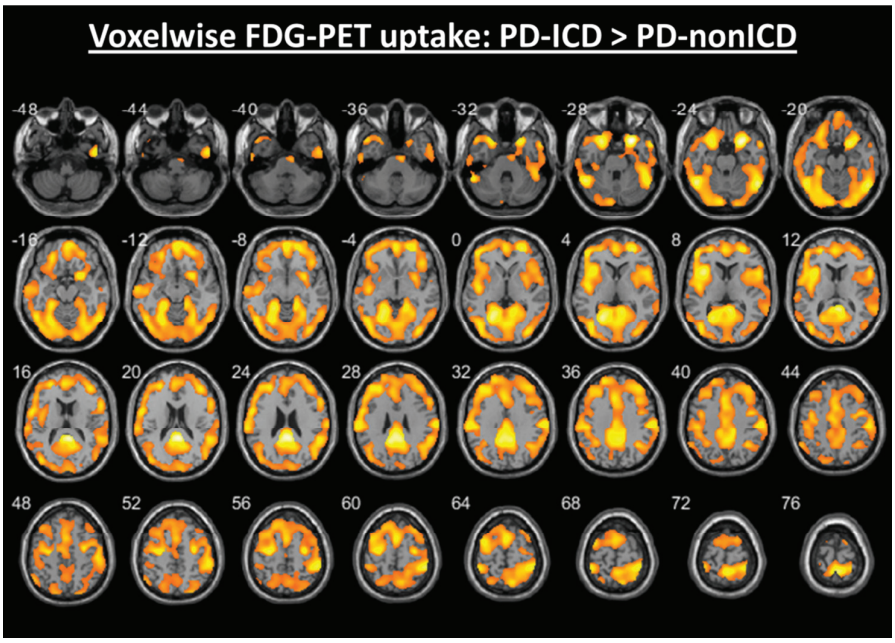


**Figure S1. Numbered axial MNI slices showing voxelwise FDG-PET uptake differences between PD-ICD and PD-nonICD, using age and sex as covariates of no interest (p<0.05 FWE).**

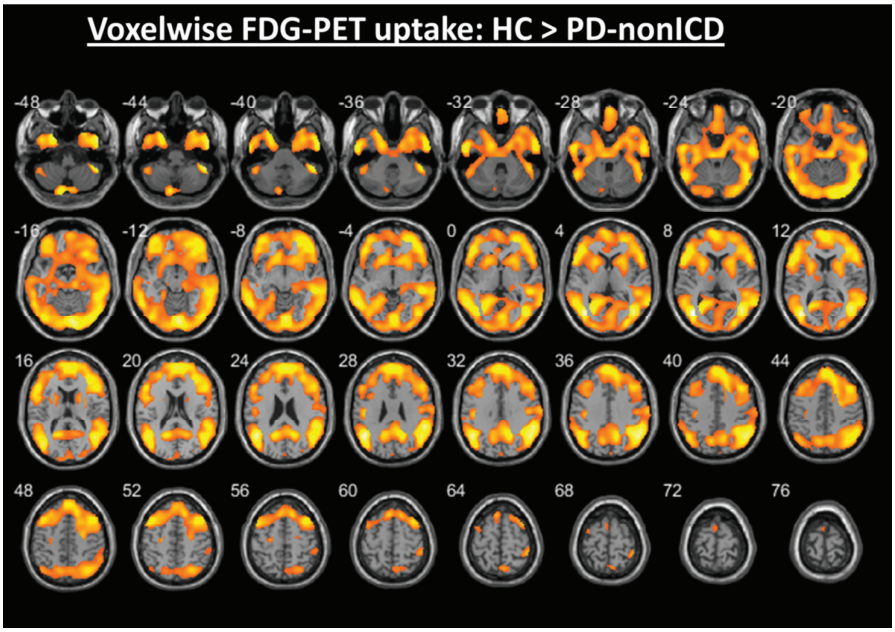


**Figure S2. Numbered axial MNI slices showing voxelwise FDG-PET uptake differences between HC and PD-nonICD, using age and sex as covariates of no interest (p<0.05 FWE).**

## Appendix B: Reward processing predicts the development of impulse control disorders in Parkinson's disease

**Predicting ICD through incentive biomarkers**

Juan Marín-Lahoz, Javier Pagonabarraga, Frederic Sampedro, Jaime Kulisevsky et al.

**Abstract**

**Objective:** To evaluate the usefulness of the feedback related negativity (FRN) -a neurophysiological marker of incentive processing- to predict the development of impulse control disorders (ICD) in Parkinson's disease (PD).

**Methods:** We included a sample of consecutive non-demented PD patients with no ICD history. We recorded FRN signals while they performed a gambling task. We calculated the mean amplitude difference between losses and gains (FRNdiff) to be used as a predictor of future ICD development. We performed prospective biannual follow-up assessments for 3 years to detect incident ICD. Finally, we compared basal FRNdiff of patients who subsequently developed ICD with respect to those who did not, and evaluated its predictive power.

**Results:** 92 patients performed the gambling task with valid EEG records and completed the follow up. Eighteen patients developed ICD during follow up while 74 remained free of ICD during the whole period. Baseline FRNdiff was greater in patients who developed ICD than in those who did not (-2.33 μV vs -0.84μV, p=0.001). No other significant baseline differences in were found. The relationship between FRNdiff remained significant after controlling for dopamine replacement therapy, sex and age (p=0.004). A predictive model based on clinical data yielded a ROC with an area under the curve of 61.3 while the model that also included the FRNdiff had a significantly greater one 79.7 (p=0.003).

**Conclusions:** Our study shows that reward processing differences measured by FRN signals precede ICD development in PD. This neurophysiological marker also permits to identify patients with high risk of ICD development.

## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's. While the hallmark of PD is movement impairment, notably bradykinesia, rigidity, tremor and gait impairment, non-motor symptoms are frequent and disabling[123]. As motor symptoms are mainly due to reduced levels of dopaminergic activity within the basal ganglia, they tend to respond well to dopamine replacement therapy (DRT). Contrarily, non-motor symptoms usually have a poor or absent response to DRT[10]. Furthermore, DRT worsens or even causes some of them[124]. This is the case of impulse control disorders (ICD) which rarely appear in untreated PD patients being particularly associated to DRT with dopamine agonists (DA)[38,74].

ICD are characterized by difficulties to resist an impulse to perform a typically pleasurable activity that is finally harmful to the person or to others. In the context of PD often the implied activities are usually not harmful on their own, but harmful only because of the frequency and salience they acquire[79]. ICDs in the general population typically include kleptomania and pyromania (which are considered disruptive regardless their severity)[15]. However, PD-ICDs usually consist of gratifying activities, performed by many healthy people who do not suffer a behavioral disorder. This is the case of gambling, sex, eating or buying. Gratifying activities that rarely constitute a disorder, when the effect on the performer is comparable to that of drugs[125]. In these cases they are recognized as behavioral addictions in the general population, such as pathological gambling, compulsive buying or hobbism. Although the objects of ICD drive or pulsion are neither qualitatively abnormal nor noxious, ICDs cause significant disability and negatively impact the quality of life of the patient and the caregiver[25]. These complications have potentially devastating social, familial and financial consequences.

Impulsivity is considered to have an important role on PD-ICD as in addictions[43,44] and have been linked to ICD severity[83]. Still, in the case of PD-ICDs, the single most important risk factor is DRT, specifically the use of DA which associate a hazard ratio (HR) of almost 2[62,74]. Notably drug naïve patients have a risk as low as healthy controls.[36] Nevertheless, many patients exposed to DA do not develop ICD[35] and occasionally patients who never received DA do develop the disorder[38]. DA are neither necessary cause nor a sufficient cause for ICD in PD[126].

To date, longitudinal studies of PD-ICD are scarce[69,27,75,67,76,38,74] and most of the evidence comes from cross-sectional studies[53,62]. A recent review by Marinus et al.[77] considered male sex and DA the only proven risk factors because no other factor, including age and impulsivity, was confirmed in prospective studies. DA use is a modifiable risk factor, so avoiding their use could diminish ICD risk. However, DA avoidance usually comes at the cost of higher levodopa use and should not be done systematically until ICD risk is better profiled.

Studies featuring a predictive model for ICD are scarce. Main aim of a previous study which used a predictive model was to confirm the genetic component of PD-ICD and did not include information to apply the model[67]. Thus, it is not easy for treating physicians to prevent PD-ICD.

The objects of ICD drive may be qualitatively normal, but the reward experienced by the affected patient might not be. In this vein, a strong reward is the initial force that drives drug experimentation which is the first step in the way to drug addiction[48]. This is not to say that addiction is maintained by a hyperactive reward system: a reward deficiency is thought to underlay the rapid reward discounting observed both in drug addictions and behavioral addictions[127]. Yet, a high activity in the reward system is required for the initiation of drug addiction and could be also a critical factor in the inception of behavioral additions and PD-ICD[128,125].

Feedback related negativity (FRN) is an event related potential appearing in healthy subjects after meaningful feedback. FRN amplitude is unrelated to whether the feedback comes after a right or wrong decision but depends on whether this decision led to a gain or a loss. The FRN is considered to represent reward prediction error, specifically within the dorsal anterior cingulate cortex[129]. The amplitude difference between the FRN generated after gains and after loses (FRNdiff) has therefore been used as a marker of incentive processing[130]. An experiment conducted in our laboratory showed that the FRN in PD patients without ICD does not differ from that of healthy controls. Interestingly, apathetic PD patients exhibited a lower FRN voltage than patients and controls with normal motivation[55].

We hypothesized that the differences in reward processing suspected to take part in behavioral addictions and PD-ICD could be identified by means of the FRNdiff in PD patients at risk of ICD prior to any behavioral disorder. Furthermore, we propose that the FRNdiff could support a predictive model for PD-ICD.

## Methods

### Patients

We prospectively recruited a cohort of non-demented PD outpatients between December 2015 and December 2016. Inclusion criteria were PD according to the MDS diagnostic criteria[96], Hoehn and Yahr stage up to 3 and full understanding and agreement with the informed consent. Exclusion criteria were brain lesions or any neurodegenerative disorder other than PD, dementia (related to PD[97] or not[15]), any condition related or not to PD disenabling the patient to perform the proposed evaluations (such as illiteracy, severe visual impairment, severe hearing loss or severe motor impairment), ICD history, positive screening for ICD according to QUIP, unpredictable motor fluctuations according to the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) item 4.5 > 1[100], use of dopamine antagonists, patients with a life expectancy under 1 year or having unstable medical conditions and patients taking part in current or recent (4 weeks) clinical trials and patients with untreated or refractory depression.

### Assessments

At baseline each patient was evaluated by a neurologist and a neuropsychologist specialized in movement disorders. This clinical assessment included MDS-UPDRS part III (motor score)[100], total l-dopa equivalent daily dose (LEDD) and DA l-dopa equivalent daily dose (DA-LEDD) according to previous literature[7], and the REM behavior sleep disorder questionnaire[131]. Then, the neuropsychological was performed. FRN acquisition was performed within the next 2 weeks

Patients were followed up for 3 years. Follow up visits were scheduled biannually. They comprised the recording of current medications, current drug use and the evaluation of motivation, particularly impulse control and related disorders. The presence of ICD was considered the main outcome.

#### FRN: Stimuli and procedure

We used a modified version of Gehring's gambling task[55,132]. Each trial begins with a fixation sign (asterisk). After 500 ms, two numbers, 25 and 5, are presented in white against a black background. Participants have to bet on one of these two numbers to increase a starting amount of 1000 (virtual) euro cents. They are instructed to choose one of the two numbers by pressing a button. Immediately after the selection, the numbers change color into red or green. If the selected number turns green, the participant gains the corresponding amount

of Euro cents (i.e., +5 or +25); conversely when the selected number turns red, the participant losses the corresponding amount. This feedback is shown for 1 s. A new trial is initiated after 3 s. The experimental session comprises 4 runs of 92 trials each. In 60 of the 92 trials (65%), the feedback indicates the gain or loss of the exact amount previously shown in white. In the other trials the resulting feedback was greater than the original amount. In 16 of the 92 trials (17.5%), (so-called "boost trials"), wins and losses are doubled (feedback consisting in "10" or "50" shown in green or red). Finally, in the remaining 16 trials, the feedback amount was minimally increased (the possible feedback being 7 or 27). This was done to tease a part the effect of a greater magnitude from the effect of a reduced frequency. Participants are told that they should adjust their choices based on outcomes in each trial in order to increase their gains. However, the task was programmed to yield wins in 50% of the trials and losses in the other 50%.

FRN: Electrophysiological recording

We recorded electroencephalogram (EEG) at a sampling rate of 250Hz from 19 standard scalp sites (Fp1/2, F3/4, C3/4, T3/4, T5/6, P3/4, O1/2, F7/8, Fz, Cz, Pz) referenced to the two mastoid leads using BrainAmp System (Brain Products GmbH, Gilching, Germany), Electro-Cap International electrode caps (Eaton, Ohio, USA) and Brainvision Recorder software (Brain Products GmbH). We registered vertical and horizontal eye movements using two additional bipolar channels for artifact minimization and rejection. We ensure the impedances of recording sites were lower than 5 KΩ. Signals were filtered with a bandpass of 0.1-35 Hz and digitized at a rate of 250 Hz.

FRN: Processing

We processed EEG signals using second-order blind identification (SOBI) to minimize the ocular motion artifacts. SOBI is a blind source separation algorithm based on an eigenvalue decomposition of time-delayed covariance matrices[133,134]. Feedback-locked event related potential (ERP) record window was set from 200 ms before until 1000 ms after the feedback stimulus. We removed any epochs exceeding ±300μV in any channel or ±75μV in Fz from further analysis. Then, we averaged and corrected by baseline -50 to 0 ms time window- the epochs for each condition. Patients with less than 60 epochs for each condition were not analyzed.

We took Fz mean amplitude between 250 and 450 ms following feedback presentation as the FRN value for each condition. For each participant we calculated the FRNdiff as the losses FRN minus gains FRN. EEG signal processing was done using EEGLAB[135] on MATLAB R2016a (The Mathworks, Inc.).

Neuropsychological and behavioral assessment

We assessed global cognitive status by means of the Parkinson's Disease Cognitive Rating Scale (PD-CRS)[102]. The PD-CRS is a cognitive scale validated and recommended in the context of PD[136]. We evaluated anxiety and depression using the Hospital Anxiety and Depression Scale (HADS)[20,101], apathetic symptoms using the Starkstein apathy scale[22] and impulsivity using the Barratt impulsiveness scale (BIS-11)[137] and the commission errors on the PEBL[138] continuous performance task which based on the Conners continuous performance test[139].

Evaluation of motivational disorders

We evaluated the short version of QUIP at each follow up. In the case of a positive answer We also administered the QUIP rating scale(QUIP-RS)[99] and performed a comprehensive interview based on the core components of behavioral addictions[140,141]. The main outcome of the study was the development of ICD according to these criteria as described previously[83].

**Statistical analysis**

We grouped patients according to the development of ICD during follow up and compared baseline characteristics across groups. Categorical variables were compared by means of $\chi 2$ test. For quantitative variables we calculated mean and standard deviation (SD) and compared with t test when parametrical testing was appropriate. When not we calculated medians, ranges and compared them using the Wilcoxon signed-rank test. We also compared baseline FRNdiff.

We deployed two logistic regression models with ICD development as the dependent variable. Both of them included known risks factors as predictors, but one of them also featured the FRNdiff. We assessed the predictability of ICD using a receivers operating characteristic (ROC) of these logistic models. To evaluate whether baseline FRNdiff could enhance predictability we compared the area under the curve (AUC) of both ROC curves. This comparison was made using DeLong's test[142]. The second model –that including the FRNdiff- was also used to assess the independence of the association between baseline FRNdiff and ICD development from known risk factors.

To summarize the information yielded by the logistic regression in a way that has straightforward clinical translation we chose 2 cut-off points: The first one to identify patients whose ICD risk was in the lower quintile and the second one to identify those in the highest quintile. We then calculated the cumulative incidence in both quintiles. We also calculated the median sensitivity and specificity of each cut off using 2000 stratified bootstrap replicates. All the statistical analyses were performed using R version 3.4.3[143].

**Results**

We recruited 120 patients but only 98 performed the gambling task. Twenty patients were excluded: 12 patients screened positive for ICD and 8 had cognitive impairment precluding the execution of the study. Two patients withdraw their consent for the task. Over the 98 patients with EEG registers and 4 were excluded from analysis because they had an insufficient number of trials per condition.

Among the 94 patients with valid registers, 18 developed ICD within the 3 year follow up (ICD+), 74 did not develop ICD (ICD-) and 2 did not perform follow up (2.1%). Patients who developed ICD in follow up were similar to those who did not except for an insignificantly higher cognitive performance (PD-CRS) and DA LEDD. Baseline characteristics are shown in **Table 1**

| | Develop no ICD (74) | Develop ICD (18) | p |
|---|---|---|---|
| Sex, male (%) | 47 (63.5%) | 11 (61.1%) | 0.85 |
| Baseline age | 68.36±9.54 | 66.31±7.37 | 0.4 |
| Age at PD diagnosis | 62.59±9.26 | 62.4±13.66 | 0.94 |
| Time since PD diagnosis | 6.77±2.8 | 5.6±11.78 | 0.44 |
| Education (years) | 11.72±4.83 | 12.67±4.84 | 0.46 |
| MDS-UPDRS III (motor score) | 25.49±6.98 | 24.72±8.88 | 0.7 |
| Modified H & Y stage (median, range) | 2(1-3) | 2(2-2.5) | 0.36 |
| S&E ADL Scale | 90 (70-100) | 90 (70-100) | 0.32 |
| Baseline LEDD | 552.23±313.14 | 584.81±326.48 | 0.7 |
| Dopamine Agonists LEDD | 138.27±112.74 | 193.78±103.69 | 0.07 |
| DA use (%) | 58 (78.4%) | 17 (94.4%) | 0.22 |
| PD-CRS | 87.6±16.37 | 94.72±15.43 | 0.11 |
| HADS A | 3.29±2.62 | 3.88±2.65 | 0.41 |
| HADS D | 2.24±2.75 | 3.06±2.76 | 0.28 |
| SAS | 4.84±5.9 | 5.39±6.35 | 0.73 |
| BIS 11 Total | 53.99±8.2 | 54.28±8.07 | 0.89 |

| | | | |
|---|---|---|---|
| Commision errors | 0.39±0.21 | 0.38±0.27 | 0.94 |
| RBD score | 4.76±3.46 | 6.22±2.76 | 0.26 |

Table 1

**FRN analysis**

The number of EEG epochs averaged and included for analysis did not differ between groups for any of the two main conditions (mean±SD): wins non-developing ICD 173.54±22.83, developing ICD 173.5±25.41 p=1); loses non-developing ICD 171.32±24.91, developing ICD 172.56±20.86 p=0.83).

The mean FRN for wins was 8.998148 ± 5.914293 μV and for loses was 7.870445 ± 5.370835 μV. Feedback-locked averages after wins and losses for the entire patient sample are shown in Figure 1. An upward (negative) deflection was observed starting 250ms after negative feedback (loses).

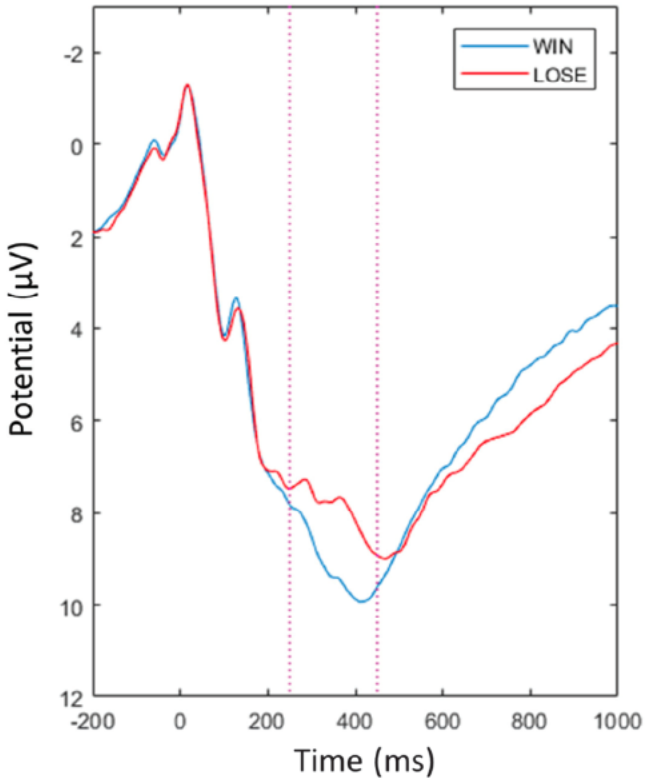


**Figure1** Event related potentials associated with monetary wins and losses. Grand average feedback-locked at Fz for monetary wins and losses.

The FRNdiff of the whole sample was -1.185708±1.646784 µV. For those who did not develop ICD the FRNdiff was -0.84±1.51 µV and for those who did it was-2.3256193 ± 1.57 µV. The difference between both groups was 1.48µV (CI 95% 0.6401139 2.326724, p=0.001). Figure 2 shows FRN for wins and losses of each group and Figure 3 shows FRNdiff of both groups

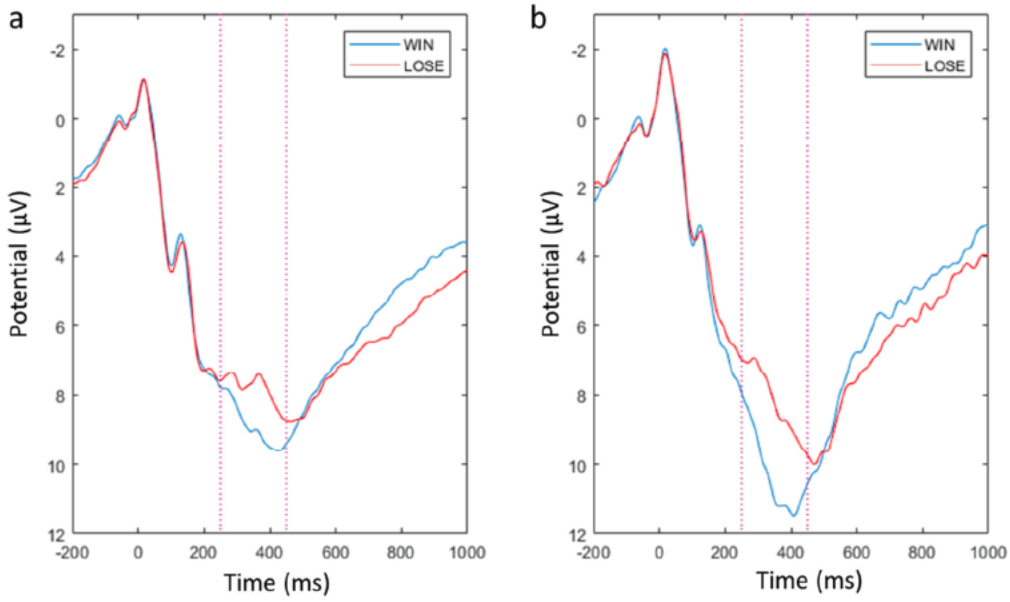


**Figure2** Event related potentials associated with monetary wins and losses for each group: **a)** shows the average feedback-locked at Fz for monetary wins and losses of patients who did not develop ICD and **b)** shows the corresponding waves of those who did develop ICD.

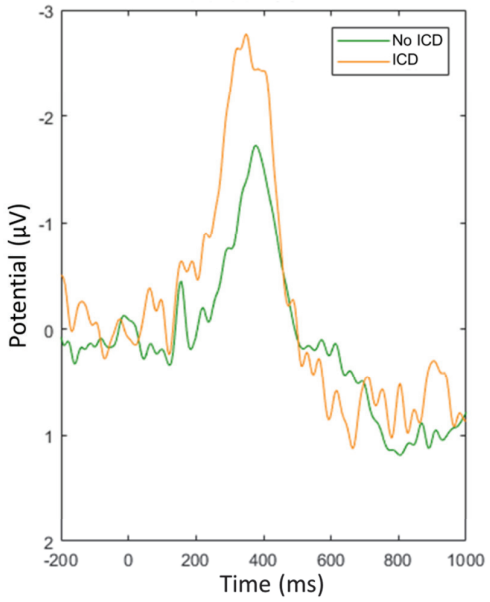


**Figure 3** FRNdiff (difference between losses and gains) at Fz for patients who developed ICD within 3 years of the register (yellow) and those who remained ICD free for the same period (green).

**Predictive models**

ROC curves for the logistic regression models are shown in Figure 4. The clinical model that included sex, DA LEDD, total LEDD, and age as predictors yielded an AUC of 61.3. The model that also included the FRNdiff had an AUC of 79.7. The AUC of the second model was significantly greater (p=0.003). In this model, the FRNdiff resulted a significant and independent predictor of ICD development (p=0.0039). In fact, it was the only significant predictor. Table 2 shows the parameters of the model.

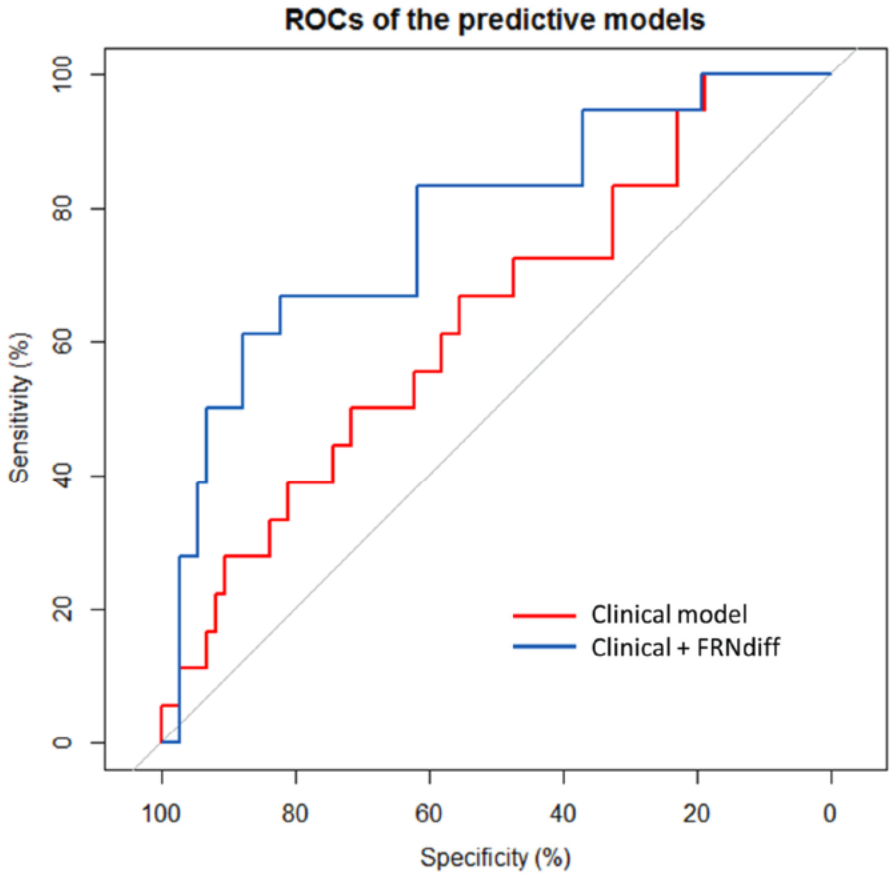


**Figure 4**. Receivers Operating Characteristic (ROC) ot the clinical model with an area of 0.61 and of the clinical and neurophysiological model with an area of 0.8 for the prediction of impulse control disorders (ICD) in the next three years

| | α | β | Significance (p) |
|---|---|---|---|
| Intercept | -1.92 | | 0.47671 |
| Age | | -0.017 | 0.65613 |
| Sex (male) | | 0.39 | 0.53890 |
| DA-LEDD | | 0.0042 | 0.18062 |
| Total LEDD | | 0.0001 | 0.91416 |
| FRNdiff | | −0.53 | 0.00388 |

| | | | |
|---|---|---|---|
| | | | |

Table 2

The formula shows how to apply the coefficients obtained from the logistic model:

$$Y = -1.92 - 0.017 * age + 0.39 * (sex = male) + 4.2 * DA\ LEDD + 0.1 * LEDD - 0.53 * FRNdiff$$

Age is expressed in years, DA LEDD and LEDD in hundreds of mg (dg) and the potential in μV.

Patients in the lower quintile (Y<-2.5) had a three year cumulative incidence of 5.5%, or 1.9 cases/100 patients year. This cut-off yielded a sensitivity of 94% and a specificity of 37%. Patients in the highest quintile (Y>-0.63) had a cumulative incidence of 50% or 20.6 cases/ 100 patients year. This cut-off yielded a sensitivity of 61% and a specificity of 88%. The remaining patients had a cumulative incidence of 14.3% or 5 / 100 patients year.

## Discussion

This is the first longitudinal prospective study aiming ICD prediction recruiting a PD sample *ad hoc.* We report for the first time a predictive model for PD-ICD presented in a way that can be both replicable and transferable –i.e. model βs are included. Previous longitudinal prospective studies that recruited an *ad hoc* cohort did not offer predictive models to the reader[27,69]. A pervious study was not based on a purposive cohort and did not include enough information to validate the model with another cohort or to apply it in the clinical practice[67].

The model developed in this study discriminated patients with low risk (less than 2% per year) and with high risk (more than 20% per year) from the patients with average risk (about 5% per year). The risk of those in the highest quintile was tenfold greater than that of those in the lowest one. This is greater than any HR or OD shown in any other PD-ICD longitudinal study, either prospective or not.

If validated with another cohort, this model could change the way clinicians confront the risk of PD-ICD because many cases could be prevented by avoiding DA in patients at high risk and use them only when indispensable. Conversely, patients with low risk could receive if necessary, DA with greater confidence or even at greater doses. This situation might be considered prognostic targeting[144] and is comparable to the use of the $ABCD^2$ score to decide which patients with atrial fibrillation should receive anticoagulation treatment[145]. However, prognostic targeting presupposes that patients at high risk will benefit the most of an intervention to blunt this risk. This is yet to be proven. Patients facing higher risk of ICD may benefit from DA avoidance less than the average patient, because the relative risk associated with DA use is not necessarily independent of the total risk. Conversely, individual treatment effect models try to identify the patients who will benefit the most from an intervention (regardless of the total risk). They require to fit a predictive model using randomized trial data[144]. Nonetheless they would provide the maximum benefit for every patient.

This is also the first study to identify electrophysiological differences in reward processing preceding ICD development. Previous studies have shown other functional differences prior to the development of ICD. One study evaluated T2* functional connectivity in resting state of 30 drug naïve PD patients that were followed up for three years[76]. It found that a lower anticorrelation between the default mode network and the right central executive was independently associated to the development of ICD. Todate, there are no studies evaluating both resting state connectivity and reward processing. One work examined default mode network activity and gambling in patients with social anxiety[146],but by definition, gambling was not done in resting state. This makes the interpretation of the current results in line with those of resting connectivity too speculative. Moreover, the

sample they evaluated might not be representative of PD population as half of the patients developed ICD in three years (or 20.6 / 100 patients year) which represents an incidence twice of that of other samples[27,74]. Furthermore, each of the patients in the half that remained free of ICD had a QUIP-RS of 0.

Other study targeted dopamine transporter (DAT) availability ($^{123}$I-FP-CIT SPECT uptake) in 71 drug naïve PD patients with SPECTs performed as part of the diagnostic process, prior to study inclusion[75]. They compared the uptake of six ROIs within the basal ganglia between 11 patients who developed ICD and 20 who did not within an average follow up of 2.5 years with the other 40 patients either excluded or lacking follow up. They found 3 of the ROIs to have lower uptake in patients who subsequently developed ICD. This finding has two possible interpretations: patients susceptible to ICD may have greater neurodegeneration within the substantia nigra pars compacta (SNpc) or they may have lower availability of DAT –for a similar number of neurons. Low number of dopamine transporters or lower affinity to the ligand may explain a lower availability. These interpretations are not mutually exclusive. While lower neuron counts in the SNpc would lead to lower dopaminergic activity, lower DAT would lead to higher dopaminergic activity. The relationship between dopaminergic activity and ERPs has been studied in one PD study[147]. They found greater potentials in levodopa on state than in levodopa off state. Taken together these and our results support the idea of greater dopaminergic activity in patients prone to develop ICD. Nonetheless, their study targeted error related negativity in a probabilistic learning paradigm[148]. This potential appears 80-150ms after response[149,150]. Therefore the relationship they found may not hold for the FRN.

In contrast to the evaluation of DAT availability, ERP recording is non-invasive, radiation free and the infrastructure required is much simpler. Our methods can be replicated in any quiet environment with two conventional laptop computers and an EEG recorder. The time required is similar to that of an MRI, but with a simpler setting, and without its contraindications and difficulties. Furthermore, ERP recording is currently cheaper.

Regarding transferability of the results, this study has two limitations. First, although FRN recording is not expensive or time consuming, the patient, the technician and the equipment need to be at the same place. This means that to transfer our findings to the population of a whole country, many registering sites or patient peregrination is required. Nonetheless, data processing can be centralized and automated. Furthermore, FRN recording could take advantage of the EEG recording equipment and technicians that are available in many hospitals and clinics. Still, models based on wet biomarkers would be easier to escalate[151]. Second, as explained above, pure individualized treatment models are

desirable and cannot be obtained from longitudinal prospective cohorts like this one, but require randomized trials.

From the point of view of the ICD knowledge, the evaluation of patients who are drug naïve as well as patients with active ICD and patients with remitted ICD would be desirable. For this study we chose a design that favored applicability.

To conclude, using event related potentials we show that electrophysiological differences in reward processing precede the development of impulse control disorders in PD. We also show that this phenomenon has enough predictive power to deploy preventive strategies in clinical settings. We think that time has come to take full responsibility of what we prescribe in PD and to deploy a coordinated strategy to prevent PD-ICD.

1. Fox, S. H. *et al.* International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease: Treatment of Motor Symptoms in PD. *Movement Disorders* **33**, 1248–1266 (2018).
2. de la Fuente-Fernández R. PResynaptic mechanisms of motor complications in parkinson disease. *Arch Neurol* **64**, 141–143 (2007).
3. Voon, V. *et al.* Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. *The Lancet Neurology* **8**, 1140–1149 (2009).
4. Stocchi, F. *et al.* Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: The STRIDE-PD study. *Annals of Neurology* **68**, 18–27 (2010).
5. Olanow, C. W. *et al.* A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease. *New England Journal of Medicine* **361**, 1268–1278 (2009).
6. Cereda, E. *et al.* Efficacy of rasagiline and selegiline in Parkinson's disease: a head-to-head 3-year retrospective case-control study. *J. Neurol.* **264**, 1254–1263 (2017).
7. Tomlinson, C. L. *et al.* Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement Disorders* **25**, 2649–2653 (2010).
8. Obeso, J. A. *et al.* Functional organization of the basal ganglia: Therapeutic implications for Parkinson's disease. *Movement Disorders* **23**, S548–S559 (2008).
9. Nilsson, F. M., Kessing, L. V., Sorensen, T. M., Andersen, P. K. & Bolwig, T. G. Major depressive disorder in Parkinson's disease: a register-based study. *Acta Psychiatr Scand* **106**, 202–211 (2002).
10. Seppi, K. *et al.* Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review: Treatment of the Nonmotor Symptoms in PD. *Movement Disorders* (2019). doi:10.1002/mds.27602
11. Menza, M. *et al.* A controlled trial of antidepressants in patients with Parkinson disease and depression. *Neurology* **72**, 886–892 (2009).

12. pubmeddev & al, B. M., et. Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis. - PubMed - NCBI. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27125963. (Accessed: 5th September 2019)
13. Leentjens, A. F. G. *et al.* Symptomatology and markers of anxiety disorders in Parkinson's disease: A cross-sectional study: Symptomatology and Markers of Anxiety Disorders in PD. *Mov. Disord.* **26**, 484–492 (2011).
14. Dissanayaka, N. N. W. *et al.* Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Mov. Disord.* **25**, 838–845 (2010).
15. Association, A. P. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5*. (American Psychiatric Publishing, 2013).
16. Beck, A. T., Rush, A. J., Shaw, B. F., Emery, G. & more, & 1. *Cognitive Therapy of Depression*. (The Guilford Press, 1987).
17. Pagonabarraga, J., Kulisevsky, J., Strafella, A. P. & Krack, P. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *The Lancet Neurology* **14**, 518–531 (2015).
18. Hauser, R. A. *et al.* Evaluation of rotigotine transdermal patch for the treatment of apathy and motor symptoms in Parkinson's disease. *BMC Neurol* **16**, 90 (2016).
19. Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. & Erbaugh, J. An Inventory for Measuring Depression. *Arch Gen Psychiatry* **4**, 561–571 (1961).
20. Zigmond, A. S. & Snaith, R. P. The hospital anxiety and depression scale. *Acta Psychiatr Scand* **67**, 361–370 (1983).
21. Sheikh, J. & Yesavage, J. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. in *Clinical Gerontology: A Guide to Assessment and Intervention* 165–173 (Routledge, 1986).
22. Starkstein, S. E. *et al.* Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* **4**, 134–139 (1992).

23. Beck, A. T., Steer, R. A., Ball, R. & Ranieri, W. F. Comparison of Beck Depression Inventories-IA and-II in Psychiatric Outpatients. *Journal of Personality Assessment* **67**, 588–597 (1996).
24. Berger, C., Mehrhoff, F. W., Beier, K. M. & Meinck, H.-M. [Sexual delinquency and Parkinson's disease]. *Nervenarzt* **74**, 370–375 (2003).
25. Leroi, I. *et al.* Carer burden in apathy and impulse control disorders in Parkinson's disease. *Int J Geriatr Psychiatry* **27**, 160–166 (2012).
26. Mamikonyan, E. *et al.* Long-term follow-up of impulse control disorders in Parkinson's disease. *Mov. Disord.* **23**, 75–80 (2008).
27. Bastiaens, J., Dorfman, B. J., Christos, P. J. & Nirenberg, M. J. Prospective cohort study of impulse control disorders in Parkinson's disease. *Movement Disorders* **28**, 327–333 (2013).
28. Zhang, S. *et al.* Management of impulse control disorders in Parkinson's disease. *International Psychogeriatrics* **28**, 1597–1614 (2016).
29. Samuel, M. *et al.* Impulse Control Disorders in Parkinson's Disease:Management, Controversies, and Potential Approaches. *Movement disorders* **30**, 150–159 (2015).
30. Thobois, S. *et al.* Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain* **133**, 1111–1127 (2010).
31. Chaudhuri, K. R. *et al.* A Pilot Prospective, Multicenter Observational Study of Dopamine Agonist Withdrawal Syndrome in Parkinson's Disease. *Movement Disorders Clinical Practice* **2**, 170–174 (2015).
32. Thobois, S. *et al.* Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain* **136**, 1568–1577 (2013).
33. Lyons, K. E. *et al.* Orally Disintegrating Selegiline in Parkinson Patients With Dopamine Agonist-Related Adverse Effects: *Clinical Neuropharmacology* **33**, 5–10 (2010).
34. Papay, K. *et al.* Naltrexone for impulse control disorders in Parkinson disease A placebo-controlled study. *Neurology* **83**, 826–833 (2014).

35. Weintraub, D. *et al.* Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch. Neurol.* **67**, 589–595 (2010).

36. Weintraub, D., Papay, K., Siderowf, A. & others. Screening for impulse control symptoms in patients with de novo Parkinson disease A case-control study. *Neurology* **80**, 176–180 (2013).

37. Poletti, M. *et al.* A Single-Center, Cross-Sectional Prevalence Study of Impulse Control Disorders in Parkinson Disease: Association With Dopaminergic Drugs. *Journal of Clinical Psychopharmacology* **33**, 691–694 (2013).

38. Corvol, J.-C. *et al.* Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology* **91**, e189–e201 (2018).

39. Tippmann-Peikert, M., Park, J. G., Boeve, B. F., Shepard, J. W. & Silber, M. H. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. *Neurology* **68**, 301–303 (2007).

40. Martinkova, J., Trejbalova, L., Sasikova, M., Benetin, J. & Valkovic, P. Impulse control disorders associated with dopaminergic medication in patients with pituitary adenomas. *Clin Neuropharmacol* **34**, 179–181 (2011).

41. Djamshidian, A., O'Sullivan, S. S., Wittmann, B. C., Lees, A. J. & Averbeck, B. B. Novelty seeking behaviour in Parkinson's disease. *Neuropsychologia* **49**, 2483–2488 (2011).

42. Voon, V. *et al.* Factors associated with dopaminergic drug–related pathological gambling in Parkinson disease. *Archives of Neurology* **64**, 212–216 (2007).

43. Voon, V. *et al.* Impulse control disorders in parkinson disease: A multicenter case-control study. *Annals of Neurology* **69**, 986–996 (2011).

44. Djamshidian, A. *et al.* Decision-making, impulsivity and addictions: Do Parkinson's disease patients jump to conclusions? *Movement Disorders* **27**, 1137–1145 (2012).

45. Sáez-Francàs, N. *et al.* Factores clínicos y psicopatológicos asociados a los trastornos del control de impulsos en la enfermedad de Parkinson. *Neurología* (2015). doi:10.1016/j.nrl.2015.05.002

46. Loehlin, J. C. & Beaujean, A. A. *Latent Variable Models*. (Routledge, 2017).

47. Nombela, C., Rittman, T., Robbins, T. W. & Rowe, J. B. Multiple modes of impulsivity in Parkinson's disease. *PLoS ONE* **9**, e85747 (2014).

48. Volkow, N. D. & Morales, M. The Brain on Drugs: From Reward to Addiction. *Cell* **162**, 712–725 (2015).

49. Olsen, C. M. Natural Rewards, Neuroplasticity, and Non-Drug Addictions. *Neuropharmacology* **61**, 1109–1122 (2011).

50. Frank, M. J., Seeberger, L. C. & O'reilly, R. C. By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science* **306**, 1940–1943 (2004).

51. Bechara, A. Deciding Advantageously Before Knowing the Advantageous Strategy. *Science* **275**, 1293–1295 (1997).

52. McClure, S. M., Laibson, D. I., Loewenstein, G. & Cohen, J. D. Separate neural systems value immediate and delayed monetary rewards. *Science* **306**, 503–507 (2004).

53. Aracil-Bolaños, I. & Strafella, A. P. Molecular imaging and neural networks in impulse control disorders in Parkinson's disease. *Parkinsonism & Related Disorders* **22 Suppl 1**, S101-105 (2016).

54. Gehring, W. J. & Willoughby, A. R. The Medial Frontal Cortex and the Rapid Processing of Monetary Gains and Losses. *Science* **295**, 2279–2282 (2002).

55. Martínez-Horta, S. *et al.* Apathy in Parkinson's Disease: Neurophysiological Evidence of Impaired Incentive Processing. *J. Neurosci.* **34**, 5918–5926 (2014).

56. Fan, W., Ding, H., Ma, J. & Chan, P. Impulse control disorders in Parkinson's disease in a Chinese population. *Neuroscience Letters* **465**, 6–9 (2009).

57. Zhang, Y., He, A. qi, Li, L., Chen, W. & Liu, Z. guo. Clinical characteristics of impulse control and related disorders in Chinese Parkinson's disease patients. *BMC Neurology* **17**, 98 (2017).

58. Petry, N. M., Stinson, F. S. & Grant, B. F. Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* **66**, 564–574 (2005).

59. Joutsa, J., Martikainen, K., Vahlberg, T., Voon, V. & Kaasinen, V. Impulse control disorders and depression in Finnish patients with Parkinson's disease. *Parkinsonism & Related Disorders* **18**, 155–160 (2012).

60. Callesen, M. B., Weintraub, D., Damholdt, M. F. & Møller, A. Impulsive and compulsive behaviors among Danish patients with Parkinson's disease: Prevalence, depression, and personality. *Parkinsonism & Related Disorders* **20**, 22–26 (2014).

61. Goerlich-Dobre, K. S. *et al.* Alexithymia-an independent risk factor for impulsive-compulsive disorders in Parkinson's disease: Impulsive-Compulsive Disorders & Alexithymia. *Movement Disorders* **29**, 214–220 (2014).

62. Eisinger, R. S. *et al.* Medications, Deep Brain Stimulation, and Other Factors Influencing Impulse Control Disorders in Parkinson's Disease. *Front Neurol* **10**, 86 (2019).

63. Keren, H. *et al.* Reward Processing in Depression: A Conceptual and Meta-Analytic Review Across fMRI and EEG Studies. *Am J Psychiatry* **175**, 1111–1120 (2018).

64. Kessler, R. C. *et al.* Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* **62**, 593–602 (2005).

65. Lee, J.-Y. *et al.* Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease. *Mov. Disord.* **24**, 1803–1810 (2009).

66. Lee, J.-Y., Jeon, B. S., Kim, H.-J. & Park, S.-S. Genetic variant of HTR2A associates with risk of impulse control and repetitive behaviors in Parkinson's disease. *Parkinsonism & Related Disorders* **18**, 76–78 (2012).

67. Kraemmer, J. *et al.* Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* **87**, 1106–1111 (2016).

68. Sackett, D. L. Bias in analytic research. *Journal of Chronic Diseases* **32**, 51–63 (1979).

69. Joutsa, J., Martikainen, K., Vahlberg, T. & Kaasinen, V. Effects of dopamine agonist dose and gender on the prognosis of impulse control disorders in Parkinson's disease. *Parkinsonism & Related Disorders* **18**, 1079–1083 (2012).

70. Rizos, A. *et al.* A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists. *Eur J Neurol* **23**, 1255–1261 (2016).

71. Seedat, S., Kesler, S., Niehaus, D. J. & Stein, D. J. Pathological gambling behaviour: emergence secondary to treatment of Parkinson's disease with dopaminergic agents. *Depress Anxiety* **11**, 185–186 (2000).

72. Molina, J. A. *et al.* Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? *Mov. Disord.* **15**, 869–872 (2000).

73. Ambermoon, P., Carter, A., Hall, W. D., Dissanayaka, N. N. W. & O'Sullivan, J. D. Impulse control disorders in patients with Parkinson's disease receiving dopamine replacement therapy: evidence and implications for the addictions field. *Addiction* **106**, 283–293 (2011).

74. Marín-Lahoz, J., Sampedro, F., Martinez-Horta, S., Pagonabarraga, J. & Kulisevsky, J. Depression as a Risk Factor for Impulse Control Disorders in Parkinson Disease. *Ann. Neurol.* (2019). doi:10.1002/ana.25581

75. Vriend, C. *et al.* Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease: Reduced DaT BR Predates ICD in PD. *Movement Disorders* **29**, 904–911 (2014).

76. Tessitore, A. *et al.* Intrinsic brain connectivity predicts impulse control disorders in patients with Parkinson's disease. *Movement Disorders* **32**, 1710–1719 (2017).

77. Marinus, J., Zhu, K., Marras, C., Aarsland, D. & van Hilten, J. J. Risk factors for non-motor symptoms in Parkinson's disease. *The Lancet Neurology* **17**, 559–568 (2018).

78. Hill, A. B. The Environment and Disease: Association or Causation? *Proc R Soc Med* **58**, 295–300 (1965).

79. Maloney, E. M., Djamshidian, A. & O'Sullivan, S. S. Phenomenology and epidemiology of impulsive-compulsive behaviours in Parkinson's disease, atypical Parkinsonian disorders and non-Parkinsonian populations. *Journal of the Neurological Sciences* **374**, 47–52 (2017).

80. Sobrido, M. J., Dias-Silva, J. J. & Quintáns, B. [Behavioral disorders in Parkinson's disease. Genetic, pharmacological and medico-legal aspects]. *Rev Neurol* **48 Suppl 1**, S43-48 (2009).
81. Weintraub, D. *et al.* Dopamine Agonist Use is Associated with Impulse Control Disorders in Parkinson's Disease. *Arch Neurol* **63**, 969–973 (2006).
82. Isaias, I. U. *et al.* The relationship between impulsivity and impulse control disorders in Parkinson's disease. *Movement Disorders* **23**, 411–415 (2008).
83. Marín-Lahoz, J. *et al.* Parkinson's Disease: Impulsivity Does Not Cause Impulse Control Disorders but Boosts Their Severity. *Front Psychiatry* **9**, 465 (2018).
84. Eisinger, R. S. *et al.* Medications, Deep Brain Stimulation, and Other Factors Influencing Impulse Control Disorders in Parkinson's Disease. *Front. Neurol.* **10**, (2019).
85. Aracil-Bolaños, I. & Strafella, A. P. Molecular imaging and neural networks in impulse control disorders in Parkinson's disease. *Parkinsonism Relat Disord* **22**, S101–S105 (2016).
86. Martini, A. *et al.* Dopaminergic Neurotransmission in Patients With Parkinson's Disease and Impulse Control Disorders: A Systematic Review and Meta-Analysis of PET and SPECT Studies. *Front. Neurol.* **9**, (2018).
87. Biundo, R. *et al.* Brain volume changes in Parkinson's disease and their relationship with cognitive and behavioural abnormalities. *J. Neurol. Sci.* **310**, 64–69 (2011).
88. Pellicano, C. *et al.* Morphometric changes in the reward system of Parkinson's disease patients with impulse control disorders. *J. Neurol.* **262**, 2653–2661 (2015).
89. Biundo, R. *et al.* Patterns of cortical thickness associated with impulse control disorders in Parkinson's disease. *Mov. Disord.* **30**, 688–695 (2015).
90. Imperiale, F. *et al.* Brain structural and functional signatures of impulsive–compulsive behaviours in Parkinson's disease. *Molecular Psychiatry* **23**, 459–466 (2018).
91. Tessitore, A. *et al.* Intrinsic brain connectivity predicts impulse control disorders in patients with Parkinson's disease. *Mov. Disord.* **32**, 1710–1719 (2017).

92. Tessitore, A. *et al.* Resting-state brain networks in patients with Parkinson's disease and impulse control disorders. *Cortex* **94**, 63–72 (2017).

93. Verger, A. *et al.* Brain PET substrate of impulse control disorders in Parkinson's disease: A metabolic connectivity study. *Hum Brain Mapp* **39**, 3178–3186 (2018).

94. Neyman, J. Statistics—Servant of All Science. *Science* **122**, 401–406 (1955).

95. Yakushev, I., Drzezga, A. & Habeck, C. Metabolic connectivity: methods and applications. *Curr. Opin. Neurol.* **30**, 677–685 (2017).

96. Postuma, R. B. *et al.* MDS clinical diagnostic criteria for Parkinson's disease: MDS-PD Clinical Diagnostic Criteria. *Movement Disorders* **30**, 1591–1601 (2015).

97. Emre, M. *et al.* Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders* **22**, 1689–1707; quiz 1837 (2007).

98. Weintraub, D. *et al.* Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Movement Disorders* **24**, 1461–1467 (2009).

99. Weintraub, D. *et al.* Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. *Movement disorders* **27**, 242–247 (2012).

100. Goetz, C. G. *et al.* Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement disorders* **23**, 2129–2170 (2008).

101. Marinus, J., Leentjens, A. F., Visser, M., Stiggelbout, A. M. & van Hilten, J. J. Evaluation of the hospital anxiety and depression scale in patients with Parkinson's disease. *Clinical neuropharmacology* **25**, 318–324 (2002).

102. Pagonabarraga, J. *et al.* Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. *Movement Disorders* **23**, 998–1005 (2008).

103. Ramón Fernández de Bobadilla *et al.* Parkinson's disease-cognitive rating scale: Psychometrics for mild cognitive impairment. *Movement Disorders* **28**, 1376–1383 (2013).

104. Varrone, A. *et al.* EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. *Eur. J. Nucl. Med. Mol. Imaging* **36**, 2103–2110 (2009).

105. Martínez-Horta, S. *et al.* The impact of bilingualism on brain structure and function in Huntington's disease. *Parkinsonism Relat. Disord.* (2018). doi:10.1016/j.parkreldis.2018.09.017

106. Fischl, B. & Dale, A. M. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl. Acad. Sci. U.S.A.* **97**, 11050–11055 (2000).

107. Greve, D. N. *et al.* Cortical surface-based analysis reduces bias and variance in kinetic modeling of brain PET data. *Neuroimage* **92**, 225–236 (2014).

108. Greve, D. N. *et al.* Different partial volume correction methods lead to different conclusions: An (18)F-FDG-PET study of aging. *Neuroimage* **132**, 334–343 (2016).

109. Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M. & Nichols, T. E. Permutation inference for the general linear model. *Neuroimage* **92**, 381–397 (2014).

110. Riba, J., Krämer, U. M., Heldmann, M., Richter, S. & Münte, T. F. Dopamine Agonist Increases Risk Taking but Blunts Reward-Related Brain Activity. *PLoS One* **3**, (2008).

111. Ye, Z., Hammer, A., Camara, E. & Münte, T. F. Pramipexole modulates the neural network of reward anticipation. *Human Brain Mapping* **32**, 800–811 (2011).

112. Dragogna, F. *et al.* Brain metabolism in substance-induced psychosis and schizophrenia: a preliminary PET study. *Neuropsychobiology* **70**, 195–202 (2014).

113. Siri, C. *et al.* Long-term cognitive follow-up of Parkinson's disease patients with impulse control disorders. *Movement Disorders* **30**, 696–704 (2015).

114. Schindlbeck, K. A. & Eidelberg, D. Network imaging biomarkers: insights and clinical applications in Parkinson's disease. *Lancet Neurol* **17**, 629–640 (2018).

115. Pagonabarraga, J. & Kulisevsky, J. Cognitive impairment and dementia in Parkinson's disease. *Neurobiol. Dis.* **46**, 590–596 (2012).

116. Sampedro, F., Marín-Lahoz, J., Martínez-Horta, S., Pagonabarraga, J. & Kulisevsky, J. Dopaminergic degeneration induces early posterior cortical thinning in Parkinson's disease. *Neurobiol. Dis.* **124**, 29–35 (2019).

117. Firbank, M. J. *et al.* Cerebral glucose metabolism and cognition in newly diagnosed Parkinson's disease: ICICLE-PD study. *Journal of Neurology, Neurosurgery & Psychiatry* **88**, 310–316 (2017).

118. Tan, H., Li, X., Wei, K. & Guan, Y. Study on brain glucose metabolic networks in Parkinson's disease patients with visual spatial dysfunction by 18F-FDG PET imaging. *Traditional Medicine and Modern Medicine* **01**, 27–31 (2018).

119. Matthews, D. C. *et al.* FDG PET Parkinson's disease-related pattern as a biomarker for clinical trials in early stage disease. *NeuroImage: Clinical* **20**, 572–579 (2018).

120. Martinez-Horta, S. *et al.* Non-demented Parkinson's disease patients with apathy show decreased grey matter volume in key executive and reward-related nodes. *Brain Imaging Behav* **11**, 1334–1342 (2017).

121. Dujardin, K., Sockeel, P., Delliaux, M., Destée, A. & Defebvre, L. Apathy may herald cognitive decline and dementia in Parkinson's disease. *Movement Disorders* **24**, 2391–2397 (2009).

122. Leroi, I. *et al.* Apathy and impulse control disorders in Parkinson's disease: a direct comparison. *Parkinsonism Relat. Disord.* **18**, 198–203 (2012).

123. Chaudhuri, K. R. *et al.* The burden of non-motor symptoms in Parkinson's disease using a self-completed non-motor questionnaire: A simple grading system. *Parkinsonism & Related Disorders* **21**, 287–291 (2015).

124. Pagonabarraga, J., Marín-Lahoz, J. & Kulisevsky, J. Oral dopamine agonists in the management of Parkinson's disease. in *Parkinson's Disease: Current and Future Therapeutics and Clinical Trials* (eds. Gálvez-Jiménez, N., Fernandez, H. H., Espay, A. J. & Fox, S. H.) (Cambridge University Press, 2016).

125. *Behavioral Addictions: Criteria, Evidence, and Treatment*. (Academic Press, 2014).

126. Rothman, K. J. Causes. *Am. J. Epidemiol.* **104**, 587–592 (1976).

127. Potenza, M. N. Should addictive disorders include non-substance-related conditions? *Addiction* **101**, 142–151 (2006).

128. Kalivas, P. W. & Volkow, N. D. The Neural Basis of Addiction: A Pathology of Motivation and Choice. *Am J Psychiatry* 11 (2005).

129. Hauser, T. U. *et al.* The feedback-related negativity (FRN) revisited: New insights into the localization, meaning and network organization. *NeuroImage* **84**, 159–168 (2014).

130. Walsh, M. M. & Anderson, J. R. Learning from experience: Event-related potential correlates of reward processing, neural adaptation, and behavioral choice. *Neurosci Biobehav Rev* **36**, 1870–1884 (2012).

131. Stiasny-Kolster, K. *et al.* The REM sleep behavior disorder screening questionnaire-A new diagnostic instrument. *Movement Disorders* **22**, 2386–2393 (2007).

132. Marco-Pallares, J. *et al.* Human oscillatory activity associated to reward processing in a gambling task. *Neuropsychologia* **46**, 241–248 (2008).

133. Belouchrani, A., Abed-Meraim, K., Cardoso, J.- & Moulines, E. A blind source separation technique using second-order statistics. *IEEE Transactions on Signal Processing* **45**, 434–444 (1997).

134. Romero, S., Mañanas, M. A. & Barbanoj, M. J. A comparative study of automatic techniques for ocular artifact reduction in spontaneous EEG signals based on clinical target variables: A simulation case. *Computers in Biology and Medicine* **38**, 348–360 (2008).

135. Delorme, A. & Makeig, S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* **134**, 9–21 (2004).

136. Litvan, I. *et al.* Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov. Disord.* **27**, 349–356 (2012).

137. Patton, J. H., Stanford, M. S. & Barratt, E. S. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol* **51**, 768–774 (1995).

138. Mueller, S. T. & Piper, B. J. The Psychology Experiment Building Language (PEBL) and PEBL Test Battery. *Journal of Neuroscience Methods* **222**, 250–259 (2014).

139. Homack, S. Conners' Continuous Performance Test (2nd ed.; CCPT-II). *Journal of Attention Disorders* **9**, 556–558 (2006).

140. Brown, R. I. F. Some contributions of the study of gambling to the study of other addictions. in *Gambling Behavior and Problem Gambling* (eds. Eadington, W. R. & Cornelius, J. A.) (Univ of Nevada Pr, 1993).

141. Griffiths, M. A 'components' model of addiction within a biopsychosocial framework. *Journal of Substance Use* **10**, 191–197 (2005).

142. DeLong, E. R., DeLong, D. M. & Clarke-Pearson, D. L. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* **44**, 837–845 (1988).

143. R Development Core Team (2008). *R: A language and environment for statistical computing.* (R Foundation for Statistical Computing).

144. Wilson, F. P. & Parikh, C. R. Translational Methods in Nephrology: Individual Treatment Effect Modeling. *JASN* **29**, 2615–2618 (2018).

145. Johnston, S. C. *et al.* Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *The Lancet* **369**, 283–292 (2007).

146. Maresh, E. L., Allen, J. P. & Coan, J. A. Increased default mode network activity in socially anxious individuals during reward processing. *Biol Mood Anxiety Disord* **4**, 7 (2014).

147. Volpato, C. *et al.* Dopaminergic Medication Modulates Learning from Feedback and Error-Related Negativity in Parkinson's Disease: A Pilot Study. *Front Behav Neurosci* **10**, (2016).

148. Frank, M. J., Woroch, B. S. & Curran, T. Error-Related Negativity Predicts Reinforcement Learning and Conflict Biases. *Neuron* **47**, 495–501 (2005).

149. Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E. & Donchin, E. A Neural System for Error Detection and Compensation. *Psychol Sci* **4**, 385–390 (1993).

150. Falkenstein, M., Hoormann, J., Christ, S. & Hohnsbein, J. ERP components on reaction errors and their functional significance: a tutorial. *Biological Psychology* **51**, 87–107 (2000).

151. Kang, J.-H. *et al.* Association of Cerebrospinal Fluid β-Amyloid 1-42, T-tau, P-tau181, and α-Synuclein Levels With Clinical Features of Drug-Naive Patients With Early Parkinson Disease. *JAMA Neurol* **70**, 1277–1287 (2013).