# Predicting Impulse Control Disorders in Parkinson Disease through Incentive Biomarkers

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**Objective:** This study was undertaken to evaluate whether the feedback-related negativity (FRN)—a neurophysiological marker of incentive processing—can be used to predict the development of impulse control disorders (ICDs) in Parkinson disease (PD).

**Methods:** The longitudinal cohort consisted of consecutive nondemented 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 30 months to detect incident ICDs. Finally, we evaluated how basal FRNdiff was associated with posterior development of ICDs using survival models.

**Results:** Between October 7, 2015 and December 16, 2016, we screened 120 patients. Among them, 94 patients performed the gambling and 92 completed the follow-up. Eighteen patients developed ICDs during follow-up, whereas 74 remained free of ICDs. Baseline FRNdiff was greater in patients who developed ICDs than in those who did not ($-2.33\mu V$ vs $-0.84\mu V$, $p = 0.001$). No other significant baseline differences were found. The FRNdiff was significantly associated with ICD development in the survival models both when not adjusted (hazard ratio [HR] = 0.73, 95% confidence interval [CI] = 0.58–0.91, $p = 0.006$) and when controlling for dopamine replacement therapy, sex, and age (HR = 0.74, 95% CI = 0.55–0.97, $p = 0.035$). None of the impulsivity measures evaluated was related to ICD development.

**Interpretation:** Reward-processing differences measured by FRN signals precede ICD development in PD. This neurophysiological marker permits identification of patients with high risk of ICD development.

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Parkinson disease (PD) is the second most common neurodegenerative disease. Although the hallmark of PD is motor symptoms, nonmotor symptoms constitute a major cause of disability and caregiver burden in PD.[1] Some of them have a poor response to dopamine replacement therapy,[2] and others are caused or aggravated by it. This is the case of impulse control disorders (ICDs), which are associated with treatment with dopamine agonists (DAs)[3,4] and almost absent in drug-naïve patients.[5]

ICDs are characterized by difficulty resisting an impulse to perform a typically pleasurable activity that is finally harmful. In the context of PD, ICDs usually involve

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activities that are harmful not on their own, but only because of the frequency and salience they acquire.[6] Nevertheless, ICDs cause significant disability and negatively impact the quality of life of PD patients and their caregivers.[7]

In the general population, these rewarding compulsive actions not directed toward drugs are increasingly referred as behavioral addictions. Pathological gambling is included as a behavioral addiction in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition.[8] Both in the general population and for PD, the brain effects of these activities are comparable to that of drugs.[8–10]

PD-associated ICDs (PD-ICDs) are potentially preventable. However, DA avoidance may come at the cost of worse motor control or higher L-dopa use and should not be done systematically but only when benefits outweigh the risks. This would require ICD risk to be profiled by risk factors or biomarkers. To date, most of the evidence comes from cross-sectional studies.[10,11] A recent review[12] considered sex and DAs the only risk factors, because no other factor—not even age and impulsivity—had been confirmed in prospective studies. We later found in a prospective study that also depression acts as a risk factor.[4]

A strong reward is considered important in the initiation of drug addiction,[13] and a highly active reward system might be needed to transform normal activities into behavioral addictions or PD-ICDs.[9,14] The feedback-related negativity (FRN) is an event-related potential used to evaluate reward and incentive processing.[15,16] The FRN is considered to represent reward prediction error, specifically within the dorsal anterior cingulate cortex.[16] The amplitude difference between the FRN generated after gains and after losses (FRNdiff) has been used to evaluate reward-processing.[16] In a previous study, we showed that apathetic PD patients have a reduced FRNdiff, whereas PD patients without apathy have a normal amplitude compared to healthy controls.[17] These results highlighted the involvement of diminished incentive processing in the downregulation of motivated behavior and illustrated the usefulness of the FRN to evaluate motivational disorders in PD.

In the present study, we aimed to evaluate whether the differences in reward-processing can be detected prior to the development of ICDs among PD patients. We hypothesized that an FRNdiff would be associated with future development of ICDs among PD patients free of ICDs. We further hypothesized that the FRNdiff could be used to predict ICD development.

## Patients and Methods

### Study Design and Patients

We performed a monocentric longitudinal cohort study at Hospital of the Holy Cross and Saint Paul, Barcelona, Spain. The protocol, patient information, and consent form were approved by the institutional review board (Hospital of the Holy Cross and Saint Paul Clinical Research Ethics Committee), and written consent was obtained with full comprehension of the study from each patient before any study procedure. The study was designed and executed according with the Declaration of Helsinki. We prospectively recruited an ad hoc cohort of nondemented PD outpatients between October 7, 2015 and December 16, 2016. Inclusion criteria were PD diagnosis according to the London Brain Bank diagnostic criteria,[18] Hoehn and Yahr stage up to 3, and full understanding of and agreement with the informed consent. Exclusion criteria were brain lesions or any neurodegenerative disorder other than PD, dementia,[8,19] any condition–related or not to PD–disenabling the patient from performing the proposed evaluations, ICD history according to the electronic medical records, positive screening for past or present ICDs according to the short version of Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP), use of dopamine antagonists, a life expectancy < 1 year, unstable medical conditions, current or recent (4 weeks) participation in clinical trials, and untreated or refractory depression. Participants were recruited from the same outpatient movement disorders clinic.

### Assessments

At baseline, each patient was evaluated by a neurologist and a neuropsychologist specializing in movement disorders. This clinical assessment included Movement Disorder Society–Unified Parkinson's Disease Rating Scale part III (motor score),[20] total L-dopa equivalent daily dose (LEDD), DA L-dopa equivalent daily dose (DA LEDD),[21] and REM Behavior Sleep Disorder Questionnaire.[22] Then, a neuropsychological examination was performed (detailed below). FRN acquisition was performed within the next 2 weeks.

Follow-up visits were scheduled biannually (+6, +12, +18, +24, and +30 months) to detect ICDs. They comprised the recording of current medications, and the evaluation of impulse control and related disorders. The presence of ICDs at any time point was considered the main outcome of the study. The biannual evaluations were included to allow early detection for a metabolical study of ICDs,[23] not to measure time to development of ICDs.

***FRN: Stimuli and Procedure.*** We used a modified version of Gehring's gambling task.[17] Each trial begins with a fixation sign (asterisk). After 500 milliseconds, 2 numbers, 25 and 5, are presented in white against a black background. Participants have to bet on 1 of these 2 numbers

to increase the starting amount of 1,000 (virtual) Euro cents. They are instructed to choose 1 of the 2 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 (ie, +5 or +25); conversely, when the selected number turns red, the participant losses the corresponding amount. This feedback is shown for 1 second. A new trial is initiated after 3 seconds. The experimental session comprises a total of 368 trials (4 runs of 92 trials). Participants are told that they should adjust their choices based on outcomes in each trial 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 2 mastoid leads using the BrainAmp System (Brain Products, Gilching, Germany), Electro-Cap International (Eaton, OH) electrode caps, and BrainVision Recorder software (Brain Products). We registered vertical and horizontal eye movements using 2 additional bipolar channels for artifact minimization and rejection. We ensured the impedances of recording sites were <5kΩ. Signals were filtered with a bandpass of 0.1–35Hz and digitized at a rate of 250Hz.

***FRN: Processing.*** We processed EEG signals using SOBI (second-order blind identification) to minimize the ocular motion artifacts. It is a blind source separation algorithm based on an eigenvalue decomposition of time-delayed covariance matrices.[24] The feedback-locked event-related potential recording window was set from 200 milliseconds before until 1,000 milliseconds 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-millisecond time window the epochs for each condition. Patients with <60 epochs for each condition were not analyzed.

Event-related potentials were quantified measuring the mean amplitude between 250 and 450 milliseconds following feedback presentation for each condition (win and loss) at each midline electrode (Fz, Cz, Pz). The FRN was identified as the negative deflection in the event-related potential during this interval. For each participant, we calculated the FRNdiff as the FRN in loss condition minus the FRN in win condition at Fz, the closer electrode to the FRN generator, in which the potential is greater.[15,16] EEG signal processing was done using EEGLAB[25] on MATLAB R2016a (MathWorks, Natick, MA).

***Neuropsychological and Behavioral Assessment.*** We assessed global cognitive status by means of the Parkinson's Disease Cognitive Rating Scale (PD-CRS).[26] The PD-CRS is a cognitive scale validated and recommended by the Movement Disorders Society for cognitive evaluation in PD.[27] We evaluated anxiety and depression using the Hospital Anxiety and Depression Scale[28] and apathy symptoms using the Starkstein Apathy Scale.[29] Impulsivity and risk taking were evaluated by several measures: the Barratt Impulsiveness Scale (BIS11) for impulsivity as a trait, commission errors on the Psychology Experiment Building Language Continuous Performance Task based on the Conners Continuous Performance Test for motor inhibition, the Kirby Delay Discounting Task (DDT) for delay discounting, the Iowa Gambling Task (IGT) for implicit risk with potential losses, the Balloon Analog Risk Task (BART) for implicit risk without losses, and the Game of Dice Task (GDT) for explicit risk.[30] Details on all the impulsivity evaluations except for the GDT are described elsewhere.[31] The GDT is a task inspired by the IGT and the Rogers Risk Task.[32] It was designed to yield explicit risk choices that remain stable and obvious during the task. Participants have to choose among 4 kinds of dice bets; 2 of those bets are risky and unprofitable and 2 of them are not. The measure derived from this task is the number of safe trials minus the number of risky trials, ranging from −18 to +18. The interpretation is as follows: lower scores represent greater impulsivity or risk taking for commission errors, IGT, and GDT, whereas higher scores represent higher impulsivity or risk taking for BIS11, DDT, and BART.

***Evaluation of ICDs.*** We evaluated the short version of QUIP at each follow-up and performed a comprehensive interview based on the core components of behavioral addictions.[9,33] The main outcome of the study was the development of a significant ICD according to this interview. In the cases where an ICD was detected, we also administered the QUIP Rating Scale (QUIP-RS).[34] The evaluator of ICDs was blinded to electrophysiological studies during all follow-up.

***Statistical Analysis.*** We grouped patients according to the development of ICDs 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 groups with $t$ test when appropriate.

When not, we calculated medians and ranges and compared groups using the Wilcoxon signed-rank test.

A repeated measures analysis of variance (ANOVA) was performed with electrode (Fz, Cz, Pz) and condition (win and loss) as within-subject factors to evaluate the effects of the condition. Then the outcome (ICD+ and ICD− during follow-up) was included as between-groups factor (mixed ANOVA). Greenhouse–Geisser correction was used for sphericity. We plotted the FRN and the FRNdiff for each condition and compared the FRNdiff between ICD− and ICD+ using *t* test and then adjusting potential confounders using a general lineal model.

We conducted a survival analysis to evaluate the relationship between the FRNdiff and ICD development at each time point. For this purpose, we used Cox proportional hazard models (time-to-event analysis). We first deployed a model with no covariates and then an adjusted model including known risk factors as covariates. This adjusted model was considered the main goal of the study.

To ensure any association between ICD development and FRNdiff was not driven by changes in the medication after baseline (eg, less DA use during follow-up among patients with greater FRNdiff at baseline would lead to a false association between FRNdiff and the outcome), we deployed another Cox model including DA dose at each time point as a time-dependent covariate. To ensure any association between ICD development and FRNdiff was not driven by use of DAs prior to baseline, we also deployed a Cox model including DA accumulated doses. We explored the inclusion of any other available variables to improve the model. For this purpose, we used bidirectional stepwise regression.

We explored the classification capabilities of the FRNdiff and the predictability of ICDs using logistic regression and receiver operating characteristic (ROC) curves. Although logistic regression cannot deal with dropout in the way survival models do, we decided to include this exploratory analysis to offer an easily interpretable result and to make the current results comparable to previous studies that have used this methodology.[35] We utilized 2 logistic regression models with ICD development as the dependent variable. Both of them included clinical variables, but one of them also featured the FRNdiff. For each model, we generated a ROC curve, and then we compared the area under the curve (AUC) of both ROC curves using DeLong test.[36] To show a potential clinical application of the information yielded by the FRN-based model, we chose 2 cutoff points, the first one to identify patients with low ICD risk (lowest quintile according to the model) and the second one to identify patients at high risk (highest quintile). We then calculated the cumulative incidence in both quintiles. We also provide the cutoff with highest balanced accuracy. We also calculated the median sensitivity and specificity of each cutoff using 2,000 stratified bootstrap replicates.

For all analyses, statistical significance threshold (alpha) was 0.05 (2-tailed). We estimated that a sample size of 11 in the smaller group (patients developing ICDs), completing the follow-up, would be required to provide 0.8 power with the aforestated alpha. As no references of FRNdiff in PD-ICDs had been published, we assumed the difference between patients who develop and who remain free of ICDs to be at least 1.76μV (same difference we had found between PD with and without apathy).[17] To calculate the size required for the full cohort, we took into account previously published incidence rate(1 ICD case per 100 patient-months).[37] However, as this rate corresponds to a cohort in which all the patients were receiving DAs (and we planned to include patients regardless of their use of DA), we counted on a lower incidence rate, 0.6, for the cohort sample size calculation. Assuming follow-up losses of 25%, inclusion of 91 participants was required. All the statistical analyses were performed using R version 3.4.3.[38] Data used for this study are available upon reasonable request.

## Results

We recruited 120 patients, but only 98 performed the gambling task. Twenty patients were excluded; 12 patients screened positive for an ICD, and 8 had cognitive impairment precluding the execution of the study evaluations. Two patients withdraw their consent for the task. From the 98 patients with EEG registers, 4 were excluded from analysis because they had an insufficient number of valid trials per condition (Fig 1).

Among the 94 patients with valid registers, 18 developed ICDs within the 30-month follow-up (ICD+),

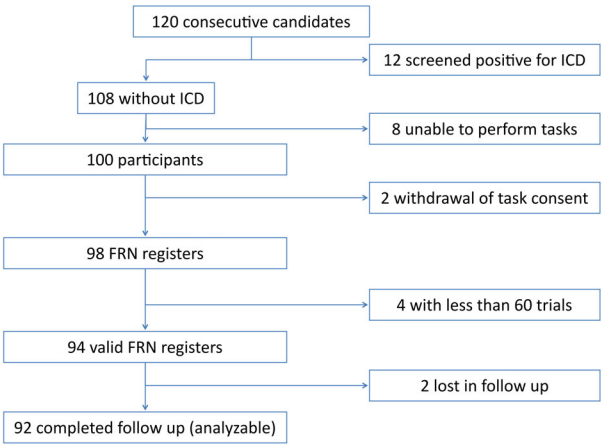


**FIGURE 1: Patient flowchart. FRN = feedback-related negativity; ICD = impulse control disorders. [Color figure can be viewed at www.annalsofneurology.org]**

74 did not develop an ICD (ICD−), and 2 did not perform follow-up (2.1%). The mean proportion of visit completion was 0.67 (interquartile range = 0.6–0.8). Nevertheless, all the patients included completed several follow-up visits, and the median follow-up was 2 years. There was no association between dropout rate and the evaluated variables: age, evolution, medication, impulsivity measures, motor status, and FRNdiff.

Patients who developed ICDs in follow-up were similar to those who did not, although they had higher cognitive performance (PD-CRS) and DA LEDD (both not statistically significant). Baseline characteristics are shown in Table 1.

**TABLE 1. Baseline Characteristics**

| Characteristic | ICD−, n = 74 | ICD+, n = 18 | *p* |
|---|---|---|---|
| Sex, male, n (%) | 47 (63.5%) | 11 (61.1%) | 0.85 |
| Baseline age, yr | 68.36 ± 9.54 | 66.31 ± 7.37 | 0.4 |
| Age at PD diagnosis, yr | 62.59 ± 9.26 | 62.4 ± 13.66 | 0.94 |
| Time since PD diagnosis, yr | 6.77 ± 2.8 | 5.6 ± 11.78 | 0.44 |
| Education, yr | 11.72 ± 4.83 | 12.67 ± 4.84 | 0.46 |
| MDS-UPDRS III | 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, mg | 552.23 ± 313.14 | 584.81 ± 326.48 | 0.7 |
| DA LEDD, mg | 138.27 ± 112.74 | 193.78 ± 103.69 | 0.07 |
| Accumulated LEDD, g | 711.27 ± 1,065.99 | 490.58 ± 447.77 | 0.18 |
| Accumulated DA LEDD, g | 178.75 ± 222.4 | 197.23 ± 253.53 | 0.78 |
| DA use, % | 58 (78.4%) | 17 (94.4%) | 0.22 |
| PD-CRS | 87.6 ± 16.37 | 94.72 ± 15.43 | 0.11 |
| HADS anxiety | 3.29 ± 2.62 | 3.88 ± 2.65 | 0.41 |
| HADS depression | 2.24 ± 2.75 | 3.06 ± 2.76 | 0.28 |
| SAS | 4.84 ± 5.9 | 5.39 ± 6.35 | 0.73 |
| RBD score | 4.76 ± 3.46 | 6.22 ± 2.76 | 0.26 |
| BIS11 Total | 53.99 ± 8.2 | 54.28 ± 8.07 | 0.89 |
| Commission errors | 0.39 ± 0.21 | 0.38 ± 0.27 | 0.94 |
| DDT low *k* | 0.29 ± 1.15 | 0.12 ± 0.32 | 0.30 |
| DDT high *k* | 0.49 ± 1.71 | 0.67 ± 1.84 | 0.72 |
| GDT | 4.62 ± 8.57 | 6.22 ± 8.17 | 0.47 |
| IGT | 0.36 ± 21.12 | 3.53 ± 19.12 | 0.57 |
| BART | 35.41 ± 12.07 | 34.9 ± 8.28 | 0.85 |

BART = Balloon Analogue Risk Task; BIS11 = Barratt Impulsiveness Scale; DA = dopamine agonist; DDT = Delayed Discount Task; GDT = Game of Dice Task; H&Y = Hoehn and Yahr; HADS = Hospital Anxiety and Depression Scale; ICD = impulse control disorder; ICD− = PD patients who remain free of ICDs during the 30-month follow-up; ICD+ = PD patients free of ICDs at baseline who develop the disorders during the 30-month follow-up; IGT = Iowa Gambling Task; *k* = hyperbolic discounting rate; LEDD = L-dopa equivalent daily dose; MDS-UPDRS III = Movement Disorder Society–Unified Parkinson's Disease Rating Scale part III (motor score); PD = Parkinson disease; PD-CRS = Parkinson's Disease Cognitive Rating Scale; RBD = rapid eye movement sleep behavior disorder; S&E ADL = Schwab and England Activities of Daily Living; SAS = Starkstein Apathy Scale.

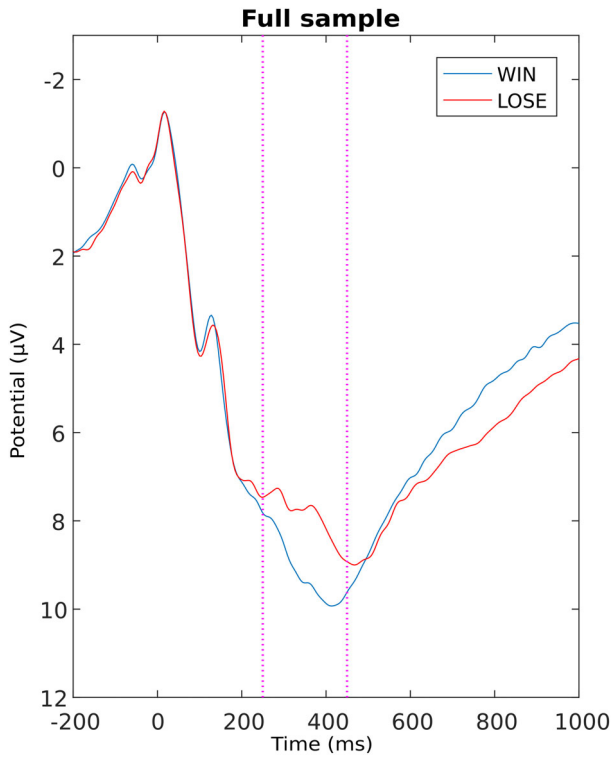


**FIGURE 2: Event-related potentials associated with monetary wins and losses. Grand average is feedback-locked at Fz for monetary wins and losses. [Color figure can be viewed at www.annalsofneurology.org]**

### *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 ICD− were 173.54 ± 22.83, and wins ICD+ were 173.5 ± 25.41 ($p = 1$); losses ICD− were 171.32 ± 24.91, and losses ICD+ were 172.56 ± 20.86 ($p = 0.83$).

The mean FRN for wins was 9 ± 5.91μV and for losses was 7.87 ± 5.37μV. Feedback-locked averages after wins and losses for the entire patient sample are shown in Figure 2. An upward (negative) deflection was observed starting 250 milliseconds after negative feedback (losses).

The repeated measures ANOVA on the mean amplitude of the FRN with condition (win vs loss) and electrode (Fz, Cz, Pz) as within-subject factors showed the main effects of condition ($F_{1,92} = 46.94$, $p < 0.001$) and electrode ($F_{1.56,143.58} = 116.4$, $p < 0.001$) and the interaction condition by electrode ($F_{1.6,146.79} = 13.504$, $p < 0.001$). The mixed ANOVA with the same within-subject factors and the outcome (ICD+, ICD−) as between-group factor showed a significant interaction of condition by outcome ($F_{1,89} = 10.66$, $p = 0.002$). Electrode, condition, and their interaction remained significant, whereas outcome and its interaction with electrode were not significant ($p > 0.1$).

The FRNdiff of the whole sample was −1.19 ± 1.65μV. For those who did not develop an ICD, the FRNdiff was −0.84 ± 1.51μV, and for those who did it was −2.33 ± 1.57μV. The difference between both groups was 1.48μV (95% confidence interval [CI] = 0.64–2.33, $p = 0.001$). Figure 3 shows the FRN for wins and losses of each group, and Figure 4 shows FRNdiff of both groups. The difference between both

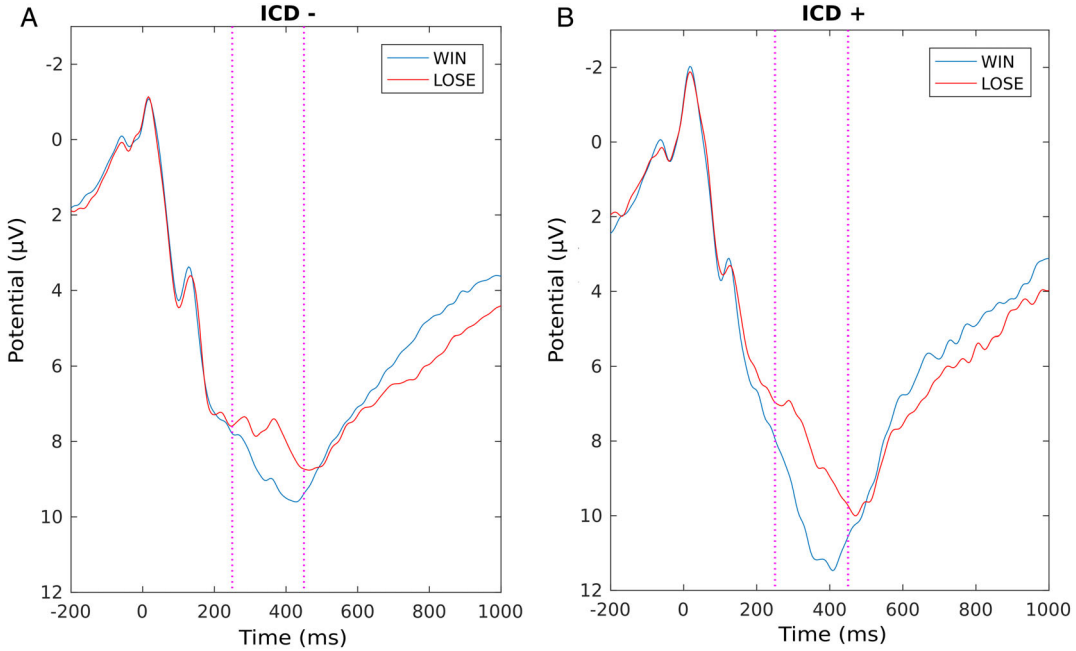


**FIGURE 3: Event-related potentials associated with monetary wins and losses for each group. (A) Average feedback-locked at Fz for monetary wins and losses of patients who did not develop an impulse control disorder (ICD). (B) Corresponding waves of those who did develop ICDs. [Color figure can be viewed at www.annalsofneurology.org]**

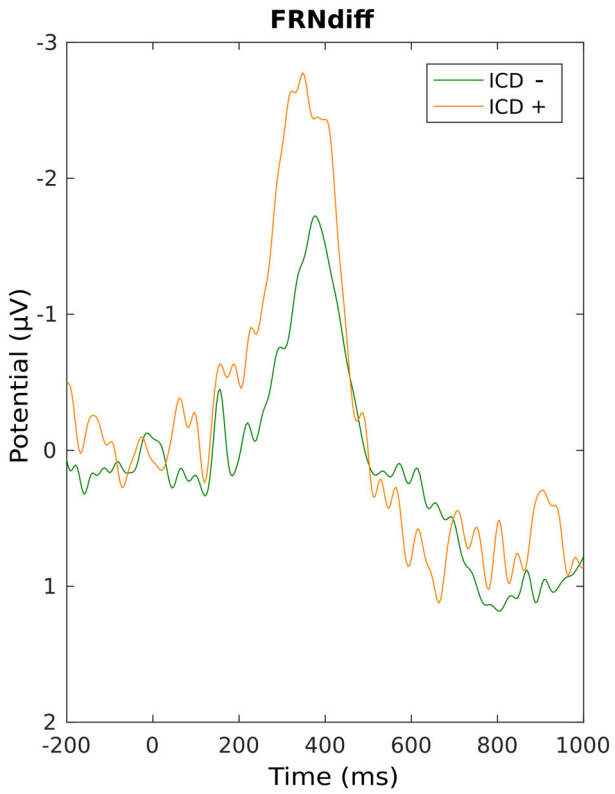


**FIGURE 4: Difference between losses and gains (FRNdiff) at Fz for patients who developed an impulse control disorder (ICD) within 30 months of the register (ICD+) and those who remained ICD-free for the same period (ICD−). [Color figure can be viewed at www.annalsofneurology.org]**

groups was also significant after controlling for potential confounders (DA LEDD, LEDD, and age; −1.40μV, 95% CI = −2.22 to −0.58, $p = 0.001$) and for cumulative doses instead of current ones (−1.33μV, 95% CI = −2.13 to −0.53, $p = 0.001$).

### *Survival Model*

The FRNdiff was significantly associated with ICD development, with a hazard ratio (HR) of 0.73 (95% CI = 0.58–0.91, $p = 0.006$). When sex, DA LEDD, total LEDD, and age were included as covariates, the FRNdiff remained significantly associated with ICD development (HR = 0.74, 95% CI = 0.55–0.97, $p = 0.035$). None of the other covariates was significant.

The replacement of baseline DA dose with current dose yielded a similar result (HR = 0.73, 95% CI = 0.56–0.96, $p = 0.024$). The model with accumulated DA doses was also similar (HR = 0.69, 95% CI = 0.51–0.91, $p = 0.01$). In both cases, the covariates remained nonsignificant. The stepwise selection could not find any variable that could improve the model.

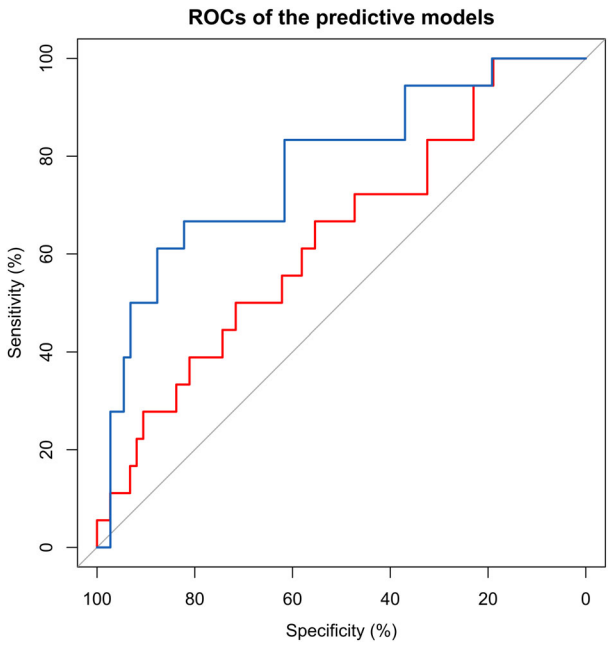


**FIGURE 5: Receiver operating characteristic curves (ROCs) of the clinical model with an area of 0.61 and of the clinical and neurophysiological model with an area of 0.8 for the prediction of impulse control disorders in the next 3 years. [Color figure can be viewed at www.annalsofneurology.org]**

### *Classification Models*

To better show the utility of FRNdiff as a predictor, we performed ROC curves for a logistic model including the same variables (with or without the inclusion of the FRNdiff). These curves are shown in Figure 5. The clinical model yielded an AUC of 0.61. The model that also included the neurophysiological potential had an AUC of 0.8. The AUC of the second model was significantly greater ($p = 0.003$). The cutoff for higher balanced accuracy was −1.97μV (specificity = 80.8%, sensitivity = 72.2%).

Table 2 shows the parameters of the full logistic model. The formula shows how to apply the coefficients obtained from the logistic model:

$$Y = -1.92 - 0.017*age + 0.39*(sex = male) + 4.2*DA\,LEDD + 0.01*LEDD - 0.53*FRNdiff$$

Age is expressed in years, DA LEDD and LEDD in hundreds of milligrams, and the potential in microvolts.

Patients in the lower quintile (Y < −2.576) had a cumulative incidence of 5.26%, or 2.1 cases/100 patient-years. This cutoff yielded a sensitivity of 94.4% and a specificity of 37%. Patients in the highest quintile (Y > −0.63) had a cumulative incidence of 55.6% or 22.2 cases/100 patient-years. This cutoff yielded a sensitivity of 55.6% and a specificity of 89%. The remaining patients had a cumulative incidence of 12.9% or 5.2/100 patient-years.

**TABLE 2. Parameters of the Full Logistic Model**

| Parameter | A | β | *p* |
|---|---|---|---|
| Intercept | −1.92 | | 0.48 |
| Age | | −0.017 | 0.66 |
| Sex (male) | | 0.39 | 0.54 |
| DA LEDD | | 0.0042 | 0.18 |
| Total LEDD | | 0.0001 | 0.91 |
| FRNdiff | | −0.53 | 0.004 |

DA LEDD = LEDD accounted for by dopamine agonists; FRNdiff = difference between the amplitude feedback-related negativity generated after gains and after losses; LEDD = L-dopa equivalent daily dose.

The use of accumulated doses did not improve the classification model.

Although the goal of this study was to evaluate the predictive capabilities of the FRN when used in combination with known risk factors, we profited from the opportunity to explore the relationship of multiple modes of impulsivity (and risk taking) with ICD development in a longitudinal cohort, even if none of them was significantly associated with ICD development on their own. We evaluated the predictive power of all these measures combined in an additive model (multivariate logistic regression). Due to covariance between low and high *k*, the mean between them was included instead of including both. None of them was significantly associated with ICD development (minimum $p = 0.43$ for BART). A survival analysis did not show a significant association between any impulsivity or risk measures and ICD development in this cohort (minimum $p = 0.35$ for BART).

## Discussion

To the best of our knowledge, this is the first longitudinal prospective study of ICD prediction recruiting a PD sample ad hoc. Among a sample of patients with PD free of ICDs, we found that those who were going to develop an ICD had greater FRNdiff amplitude than those who were not. We also found that this difference was useful to predict ICD development. Consequently, we report for the first time a predictive model for PD-ICDs presented in a way that can be both replicable and transferable (ie, model parameters are included). Previous longitudinal prospective studies that recruited an ad hoc cohort did not offer prediction.[37,39]

A previous study offered a genetic predictive model.[35] This study was not based on an ad hoc cohort but on the Parkinson Progression Markers Initiative (PPMI) cohort.[40] It used extensive genotyping to evaluate heritability and included a predictive model of ICDs based on genetics. It had nevertheless some limitations that prevented its use as a clinical predictive tool. First, ICD diagnosis was based on a screening scale, which is useful to find an association but might be considered not stringent enough for a predictive clinical model. Second, the model parameters were not reported, making its application difficult elsewhere. Finally, the polymorphisms associated with ICD development in the PPMI cohort—found in opioid receptor kappa (*OPRK1*) and tryptophan hydroxylase (*TPH2*)—diverge from the polymorphisms identified in other populations.[41–43] This divergence raises the concern that ICD-related polymorphisms may be different in populations with different genetic backgrounds. In this vein, our method is based on the FRN, which reflects incentive processing in the anterior cingulate cortex not only in humans but in other mammals.[44,45] The conservation of this event-related potential across species suggests that the genetic background among humans is of little relevance for this application. In the current study, in addition to the survival analysis, we report our results using logistic regression and ROC curves so the current results can be better interpreted in relation to the aforementioned PPMI genetic study.

This is also the first study to identify electrophysiological differences in reward-processing preceding ICD development. This difference was independent of known risk factors. Previous studies have shown other functional differences prior to the development of ICDs. One study evaluated magnetic resonance imaging (MRI) functional connectivity in resting state of 30 drug-naïve PD patients who were followed up for 3 years.[46] It found that a lower anticorrelation between the default mode network and the right central executive network was independently associated with the development of ICDs. However, the sample evaluated might not be representative of the PD population, as half of the patients developed ICDs within 3 years (or 20.6/100 patient-years), which represents very high incidence compared to other samples.[4,37] Furthermore, each of the patients in the half who remained free of ICDs had a QUIP-RS of 0. The relationship between resting state connectivity and reward-processing has not yet been studied. This makes the interpretation of the current results in line with those of resting connectivity too speculative.

Another study targeted dopamine transporter (DAT) availability ($^{123}$I-FP-CIT single photon emission computed tomography [SPECT]) in 71 drug-naïve PD patients with SPECT performed as part of the diagnostic process prior to study inclusion.[47] They compared the

uptake of 6 regions of interest (ROIs) within the basal ganglia between 11 patients who developed ICDs 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 ICDs. This finding has 2 possible interpretations; patients susceptible to ICDs 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. A low number of DATs or lower affinity to the ligand may explain a lower availability. These interpretations are not mutually exclusive. Whereas fewer neurons in the SNpc would lead to lower dopaminergic activity, fewer DATs in each neur would lead to higher dopaminergic activity. The relationship between dopaminergic activity and event-related potentials has been studied in one PD study.[48] It found greater error-related potentials in L-dopa on state than in L-dopa off state, but it did not include FRN evaluation. Taken together, these and our results might support the idea of greater dopaminergic activity in patients prone to develop ICDs. Nonetheless, this study used a probabilistic learning paradigm and targeted error-related negativity,[49] a potential that appears 80 to 150 milliseconds after response representing error, not feedback value. Therefore, the relationship they found may not hold for the FRN.

In contrast to the evaluation of DAT availability, FRN recording is noninvasive and radiation free, and the infrastructure required is much simpler. Our methods can be replicated in any quiet environment with 2 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, FRN recording is currently cheaper than both MRI and $^{123}$I-FP-CIT SPECT.

This study may also shed some light on the relationship between impulsivity and ICDs. It is to the best of our knowledge the only prospective study evaluating the relationship between several measures of impulsivity and ICD development, and we did not find any association. This may reinforce the results of our previous study in which we found that impulsivity was associated with ICD severity but not ICD presence,[33] as previous evidence of the relationship between impulsivity and ICD presence comes from case–control studies.

The model developed in our study discriminated patients with low risk (2% per year) and with high risk (>20% per year). If validated with another cohort, this model could change the way clinicians confront the risk of PD-ICDs, because many cases could be prevented by avoiding DAs in patients at high risk, using them only when indispensable. Conversely, patients at low risk could receive DAs with greater confidence or even at greater doses.

This strategy might be considered prognostic targeting[50] and is similar to common practices like the use of the $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke) score to decide which patients with atrial fibrillation should receive anticoagulation treatment.[51] Prognostic targeting presupposes that patients at high risk will benefit the most from an intervention to blunt this 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 fitting a predictive model using randomized trial data.[50] Nonetheless, the development of an individual treatment effect model for PD-ICDs would provide the maximum benefit for every patient regardless of the risk.

Regarding transferability of the results, this study has 2 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 whole population, many registering sites or patient travel is required. Nonetheless, data processing can be centralized and automated. Furthermore, FRN recording could take advantage of the EEG equipment and technicians currently in use. Nonetheless, models based on wet biomarkers would be easier to escalate. 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. It would also be desirable to include patients with depression due to its known relationship with ICD development. Their exclusion in the present study due to its known relationship with the FRN precluded us from evaluating its role in FRN predictive models. Furthermore, the exclusion of depressed patients may limit the interpretation of apathy and anxiety scores due to the high correlation between these variables.

From the point of view of ICD knowledge, the evaluation of patients who are drug-naïve as well as patients with active ICDs and patients with remitted ICDs would be desirable. For this study, we chose a design that favored applicability (as the results can be applied to a larger prevalent population), but future studies with large cohorts of drug-naïve subjects are warranted.

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 the time has come to take full responsibility for what we prescribe in PD and to deploy a coordinated strategy to prevent PD-ICDs.

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## Author Contributions

J.M.-L., S.M.-H., and J.K. contributed to conception and design of the study. J.M.-L., S.M.-H., J.P., A.H.-B., I.A.-B., H.B.-k., F.S., and A.C. contributed to acquisition and analysis of data. J.M.-L., J.P., F.S., S.M.-H., and J.K. contributed to drafting the text or preparing the figures.

## Potential Conflicts of Interest

Nothing to report.

## References

1. Chaudhuri KR, Sauerbier A, Rojo JM, et al. The burden of non-motor symptoms in Parkinson's disease using a self-completed non-motor questionnaire: a simple grading system. Parkinsonism Relat Disord 2015;21:287–291.
2. Seppi K, Chaudhuri KR, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. Mov Disord 2019;34:180–198.
3. Corvol J-C, Artaud F, Cormier-Dequaire F, et al. Longitudinal analysis of impulse control disorders in Parkinson disease. Neurology 2018; 91:e189–e201.
4. Marín-Lahoz J, Sampedro F, Martinez-Horta S, et al. Depression as a risk factor for impulse control disorders in Parkinson disease. Ann Neurol 2019;86:762–769.
5. Weintraub D, Papay K, Siderowf A. Parkinson's Progression Markers Initiative. Screening for impulse control symptoms in patients with de novo Parkinson disease: a case-control study. Neurology 2013;80: 176–180.
6. Maloney EM, Djamshidian A, O'Sullivan SS. Phenomenology and epidemiology of impulsive-compulsive behaviours in Parkinson's disease, atypical parkinsonian disorders and non-parkinsonian populations. J Neurol Sci 2017;374:47–52.
7. Leroi I, Harbishettar V, Andrews M, et al. Carer burden in apathy and impulse control disorders in Parkinson's disease. Int J Geriatr Psychiatry 2012;27:160–166.
8. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Publishing, 2013.
9. Rosenberg KP, Feder LC. *Behavioral addictions: criteria, evidence, and treatment*. 1st ed. London, UK; Waltham, MA: Academic Press, 2014.
10. Aracil-Bolaños I, Strafella AP. Molecular imaging and neural networks in impulse control disorders in Parkinson's disease. Parkinsonism Relat Disord 2016;22:S101–S105.
11. Eisinger RS, Ramirez-Zamora A, Carbunaru S, et al. Medications, deep brain stimulation, and other factors influencing impulse control disorders in Parkinson's disease. Front Neurol 2019;10:86.
12. Marinus J, Zhu K, Marras C, et al. Risk factors for non-motor symptoms in Parkinson's disease. Lancet Neurol 2018;17:559–568.
13. Volkow ND, Morales M. The brain on drugs: from reward to addiction. Cell 2015;162:712–725.
14. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 2005;162:1403–1413.
15. Gehring WJ, Willoughby AR. The medial frontal cortex and the rapid processing of monetary gains and losses. Science 2002;295: 2279–2282.
16. Hauser TU, Iannaccone R, Stämpfli P, et al. The feedback-related negativity (FRN) revisited: new insights into the localization, meaning and network organization. Neuroimage 2014;84:159–168.
17. Martínez-Horta S, Riba J, de Bobadilla RF, et al. Apathy in Parkinson's disease: neurophysiological evidence of impaired incentive processing. J Neurosci 2014;34:5918–5926.
18. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.
19. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22: 1689–1707. quiz 1837.
20. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129–2170.
21. Tomlinson CL, Stowe R, Patel S, et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010; 25:2649–2653.
22. Stiasny-Kolster K, Mayer G, Schäfer S, et al. The REM sleep behavior disorder screening questionnaire—a new diagnostic instrument. Mov Disord 2007;22:2386–2393.
23. Marín-Lahoz J, Sampedro F, Horta-Barba A, et al. Preservation of brain metabolism in recently diagnosed Parkinson's impulse control disorders. Eur J Nucl Med Mol Imaging 2020;47:2165–2174.
24. Belouchrani A, Abed-Meraim K, Cardoso J-F, Moulines E. A blind source separation technique using second-order statistics. IEEE Trans Signal Process 1997;45:434–444.
25. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134:9–21.

26. Pagonabarraga J, Kulisevsky J, Llebaria G, et al. Parkinson's Disease-Cognitive Rating Scale: a new cognitive scale specific for Parkinson's disease. Mov Disord 2008;23:998–1005.
27. Litvan I, Goldman JG, Tröster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society task force guidelines. Mov Disord 2012;27:349–356.
28. Marinus J, Leentjens AF, Visser M, et al. Evaluation of the Hospital Anxiety and Depression Scale in patients with Parkinson's disease. Clin Neuropharmacol 2002;25:318–324.
29. Starkstein SE, Mayberg HS, Preziosi TJ, et al. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992;4:134–139.
30. Brand M, Labudda K, Kalbe E, et al. Decision-making impairments in patients with Parkinson's disease. Behav Neurol 2004;15:77–85.
31. Marín-Lahoz J, Martínez-Horta S, Sampedro F, et al. Measuring impulsivity in Parkinson's disease: a correlational and structural neuroimaging study using different tests. Eur J Neurol 2020;27:1478–1486.
32. Rogers RD, Owen AM, Middleton HC, et al. Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. J Neurosci 1999;19:9029–9038.
33. Marín-Lahoz J, Pagonabarraga J, Martinez-Horta S, et al. Parkinson's disease: impulsivity does not cause impulse control disorders but boosts their severity. Front Psychiatry 2018;9:465.
34. Weintraub D, Mamikonyan E, Papay K, et al. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. Mov Disord 2012;27:242–247.
35. Kraemmer J, Smith K, Weintraub D, et al. Clinical-genetic model predicts incident impulse control disorders in Parkinson's disease. J Neurol Neurosurg Psychiatry 2016;87:1106–1111.
36. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–845.
37. Bastiaens J, Dorfman BJ, Christos PJ, Nirenberg MJ. Prospective cohort study of impulse control disorders in Parkinson's disease. Mov Disord 2013;28:327–333.
38. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2008 Available at: http://www.R-project.org.
39. 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 Relat Disord 2012;18:1079–1083.
40. Marek K, Jennings D, Lasch S, et al. The Parkinson progression marker initiative (PPMI). Prog Neurobiol 2011;95:629–635.
41. Lee J-Y, Lee EK, Park SS, et al. Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease. Mov Disord 2009;24:1803–1810.
42. Lee J-Y, Jeon BS, Kim H-J, Park S-S. Genetic variant of HTR2A associates with risk of impulse control and repetitive behaviors in Parkinson's disease. Parkinsonism Relat Disord 2012;18:76–78.
43. Castro-Martínez XH, García-Ruiz PJ, Martínez-García C, et al. Behavioral addictions in early-onset Parkinson disease are associated with DRD3 variants. 2018. Available at: http://linkinghub.elsevier.com/retrieve/pii/S1353802018300117. Accessed January 29, 2018.
44. Vezoli J, Procyk E. Frontal feedback-related potentials in nonhuman primates: modulation during learning and under haloperidol. J Neurosci 2009;29:15675–15683.
45. Warren CM, Hyman JM, Seamans JK, Holroyd CB. Feedback-related negativity observed in rodent anterior cingulate cortex. J Physiol Paris 2015;109:87–94.
46. Tessitore A, De Micco R, Giordano A, et al. Intrinsic brain connectivity predicts impulse control disorders in patients with Parkinson's disease. Mov Disord 2017;32:1710–1719.
47. Vriend C, Nordbeck AH, Booij J, et al. Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease. Mov Disord 2014;29:904–911.
48. Volpato C, Schiff S, Facchini S, et al. Dopaminergic medication modulates learning from feedback and error-related negativity in Parkinson's disease: a pilot study. 2016. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5075574/. Accessed September 8, 2019.
49. Frank MJ, Woroch BS, Curran T. Error-related negativity predicts reinforcement learning and conflict biases. Neuron 2005;47:495–501.
50. Wilson FP, Parikh CR. Translational methods in nephrology: individual treatment effect modeling. J Am Soc Nephrol 2018;29:2615–2618.
51. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–2870.