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STN anticipates gamblers decision

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Abstract

Economic decision-making is disrupted in individuals with gambling disorder, an addictive behavior observed in Parkinson's Disease (PD) patients receiving dopaminergic therapy. The subthalamic nucleus (STN) is involved in the inhibition of impulsive behaviors; however its role in impulse control disorders and addiction is still unclear. Here, we recorded STN local field potentials (LFPs) in PD patients with and without gambling disorder during an economic decision-making task. Reaction times analysis showed that for all patients the decision whether to risk preceded task onset. We compared then for both groups the STN LFP preceding high and low risk economic decisions. We found that risk avoidance in gamblers correlated with larger STN LFP low frequency (<12 Hz) fluctuations preceding task onset. In particular, the amplitude of low frequency LFP fluctuations carried significant information about future decisions. Decisions of patients not affected by gambling disorder were instead not correlated with pre-task STN LFP. Our results suggest that STN activity preceding task onset affects risk decisions by pre-emptively inhibiting attraction to high but unlikely rewards in favor of a long-term payoff.

Significance statement

Economic decision making relies on a balance between impulsiveness and rationality, which is disrupted in individuals with gambling disorder. Parkinson's Disease (PD) patients receiving dopaminergic therapy are at higher risk of developing this disorder. Here, we compared the neural activity recorded in the Subthalamic Nucleus of PD patients with and without gambling disorder during an economic decision-making task. We found that neural activity in this area is different in gamblers and that is possible to estimate gamblers' attitude toward risk on single bets based on the observed low frequency extracellular fluctuations. These findings will help clarifying the role of the Subthalamic Nucleus in decision making, and pave the way to PD therapies with a lesser risk of cognitive side-effects.

Introduction

Humans make fast and efficient decisions even when the outcomes associated to each option are probabilistic, as is often the case in real life. Economic decision-making can be impaired in psychiatric or neurological pathological condition, such as the gambling disorder (GD), a problematic addictive behavior (American Psychiatric Association, 2013) with a particularly high incidence in Parkinson's disease (PD) patients receiving dopamine replacement therapy (~5% against ~1% over the whole population) (Santangelo et al., 2013; Weintraub et al., 2015). Understanding the psyco-pathophysiological mechanisms of GD in PD patients would improve PD and GD therapies and would further inform the neural basis of economic decision-making. PD patients with GD (GDPs) are more likely than PD patients without GD (NGDPs) to follow the impulse of betting despite the negative consequences of such action. However, their behavior is non deterministic, as they resists to their propensity to risk a significant fraction of times that the option of a high risk choice is presented. Human behavior is known to strongly depend on internal bias (Kahneman and Tversky, 1979) that can often be associated to specific neural features (De Martino, 2006; Sacré et al., 2016). What are then the neural correlates of the trial-to-trial variations of the attitude toward risk in GDPs? In particular, what happens when GDPs manage to overcome their general behavioral tendency and avoid risk?

We investigated the hypothesis that subthalamic nucleus (STN) activity reflects the internal state determining the attitude toward risk on a single trial basis, given the wealth of data indicating an involvement of this region in decision making. Studies about stop signal tasks (Ray et al., 2012; Alegre et al., 2013) and high conflict tasks (Frank et al., 2007; Brittain et al., 2012) have shown that the STN is involved in reactive inhibition (i.e., behavioral inhibition triggered by the STN activity following stimulus presentation) (Aron, 2011; Jahanshahi et al., 2015b, 2015a). The STN is also involved in proactive inhibition (Aron, 2011; Jahanshahi et al., 2015b), since the STN activity preceding stimulus presentation leads to inhibition of upcoming impulses to initiate a movement (Favre et al., 2013; Benis et al., 2014; Obeso et al., 2014). The STN inhibitory role is not limited to motor control, but extends to impulse control in cognition and emotion (Jahanshahi et al., 2015b); however, its role in GD and other impulse control disorders is still unclear (Jahanshahi et al., 2015a; Zavala et al., 2015). Electrodes implanted in the STN for deep brain stimulation (DBS) in PD patients have been used to investigate correlations between decision-making and spike rates (Zaghloul et al., 2012) and low-frequency local field potentials (LFP) in the STN (Cavanagh et al., 2011; Herz et al., 2016; Zénon et al., 2016). Crucially, it has been shown that STN LFPs differ between GDPs and NGDPs in the following conditions: i) at rest (Rodriguez-Oroz et al., 2011), ii) while making a choice between two known

options (Rosa et al., 2013a), and iii) when evaluating the consequences of a choice (Fumagalli et al., 2015). However, STN activity preceding options presentation has never been analyzed to assess the correlation between STN and risk propensity in GDPs and/or NGPDs.

To clarify this relationship we compared the behavior and the STN LFP of GDPs and NGDPs choosing between high-risk (HR) and low-risk (LR) economic options (see Materials and Methods). We found no correlation between STN LFP and NGDPs risk attitude. GDPs risk attitude was instead determined before options presentation, and the low frequency (<12 Hz) component of STN LFP within that interval significantly correlated with future decisions.

Materials and Methods

Experimental Design

Patients, clinical data analysis and neurosurgical procedures

The LFP study involved twelve patients with advanced PD, already scheduled for a subthalamic implant in order to treat their motor symptomatology. All the patients provided their written informed consent either for STN DBS and LFP study. The study was approved by the institutional review board and conformed to the declaration of Helsinki.

Complete analysis of patients' clinical data, details of neurosurgical procedures, LFP signal pre-processing, and of economic task design are described below and in Tables 1-2.Briefly, enrolled patients were classified as Patients with Gambling Disorder (GDPs) or without it (NGDPs) according to DSM-5 diagnostic criteria (American Psychiatric Association, 2013); gambling history was ascertained during a structured psychiatric and behavioral interview whilst gambling behavior was scored by using the South Oaks Gambling Screen (SOGS) (Lesieur, HR and Blume, SB, 1987).Groups were formed first selecting six GDP volunteers and then forming a matching group of six NGDPs.

All patients underwent a one-stage bilateral stereotactic subthalamic implant, according to standard procedures (Zangaglia et al., 2009; Franzini et al., 2012). During the economic task, LFPs were simultaneously captured from the contact pair 0-2 of the DBS electrodes (Figure 1D). We enrolled also seventeen healthy subjects comparable to patients group for age and education. These subjects performed exactly the same two-alternative forced choice task as PD patients for behavior comparison.

We collected clinical data such as gender, age, disease duration, disease onset, preoperative therapy (levodopa equivalent daily dose - LEDD and dopamine agonist dosage in LEDD), preoperative score on the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS III), in off and on

medication conditions. All patients underwent a complete cognitive and psychological evaluation, including Mini Mental State Examination (MMSE) (Folstein et al., 1975)and State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983), to exclude cognitive, mood and anxiety disorders. Clinical data are reported in Table 1; GDPs and NGDPs groups were comparable for demographic and PD characteristics, except for a significant difference in SOGS score (Table 1, bottom row). The final set size was 6 for each group. This number was sufficient to perform descriptive statistics and also to perform within group significant ($p<0.05$) paired Wilcoxon test between conditions. However, results on reaction time statistics, LFP fluctuations comparison and information measurements were computed normalizing subject-wise the variables and then pooling trials within all subjects on the same group to increase the robustness of the results (see subsection "Dataset limitations").

All patients underwent a one-stage bilateral stereotactic subthalamic implant, according to standard procedures (Zangaglia et al., 2009; Franzini et al., 2012). Briefly, initial STN coordinates were determined by matching the patient's preoperative brain CT and MRI fused images with a digitized stereotactic atlas. Combined electrodes for both intraoperative recording and macrostimulation were then used to check and choose the correct location of the definitive STN lead. Each implanted lead (DBS Lead Model 3389, Medtronic, Minneapolis, MN, USA) has four cylindrical contacts (1.27 mm in diameter, 1.5 mm in length, placed 2 mm apart, center-to-center) denominated 0–1–2–3, beginning from the ventral contact. After implant, the extracranial section of the STN lead was connected to an externalized extension wire in order to permit the LFP recordings. A complete 2D and 3D reconstruction of STN lead location was ascertained by combining the findings of the Medtronic Stealth Station TREON plus Navigation System with the findings of Medtronic Optivise^{TM} software: three-dimensional anatomy of basal ganglia was adapted to the brain geometry of each patient by overlaying the pre-operative and postoperative MRI or computed tomography scans onto the software atlas. STN leads were considered as correctly positioned only if two or more contacts included the STN. A 2D reconstruction of STN lead contacts 1 location is provided in Figure 2 (referred to GDP #6), whilst a 3D reconstruction of STN leads location (also referred to GDP #6) is provided in Figure 1D. Stereotactic coordinates for all subjects are reported in Table 2. After the end of LFP recording, the STN leads were connected by tunneled extension to the implantable pulse generators (Activa PC Neurostimulator Model 37601 or Activa SC Neurostimulator Model 37603, Medtronic Inc, Minneapolis, USA), placed in a subclavicular subcutaneous pouch.

Economic decision-making task

Participants were seated in front of a computer screen in a lighted room. All patients were studied in the "on levodopa" condition. Pairs of stimuli (two of the four letters: *A, B, C, D*) were presented on the screen in white on a black background (Figure 1C). We call "trial" each options presentation followed by a choice, and "session" the set of the trials for each subject. Subjects were asked to choose a stimulus by pressing one of the two keyboard keys, corresponding to the stimulus on the left or right of the screen. Subjects were informed that each letter can lead to win or to lose money and that the goal was to maximize accumulated money. Note that due to obvious ethical and clinical considerations involving in particular patients with gambling disorder, patients were not rewarded with real money, but with points presented as virtual money. Fast reaction times and behavioral differences between GDP and NGDP indicate that this virtual money was perceived in a way similar to real money. Starting money accumulated was 0 €. The letters *B* and *C* were the high risk (HR) options leading to a +100 € win 20% of the times, and to a 70 € loss 80% of the times (Figure 1A). *A* and *D* were the low risk (LR) options leading to a +60 €win 80% of the times, and to a 30 €loss 20% of the times (Figure 1A). Note that the expected value of LR is +42 € while the expected value of HR is -36 €, i.e., in the long term the LR option leads to an accumulated money increase while the HR option leads to an accumulated money decrease. We defined two options with different expected value since we wanted to investigate a defining characteristic of impulse control disorders, i.e., the failure to resist a drive even if it is causing harm to the subject or others (Weintraub et al., 2006; American Psychiatric Association, 2013). In our experimental design this corresponds to the inability to refrain from selecting the high risk option even if it leads to a loss.

Six different stimulus pairs (*A vs B, A vs C, A vs D, B vs C, B vs D, C vs D*) were presented. Four of them were conflictual (C) since the subject had to choose between one HR and one LR option: *B vs D, A vs B, C vs D, A vs C*. Two were Equivalent Choice (EC) since the options outcomes were identical: both HR (*B* vs *C*) or both LR (*A* vs *D*). Participants were instructed to choose between the two options, but there was no time restraint, i.e. reaction time was freely chosen. Each choice was followed by two visual feedbacks, the first lasting one second and displaying the previous choice outcome (i.e., the money won or lost during the last trial) and the second lasting 1.5 seconds indicating the total amount of money accumulated since the beginning of the session. Finally, 0.8 seconds of black screen preceded the next stimulus presentation. Overall, starting from the second stimulus, each presentation started exactly 3.3 seconds after the subject response to the previous presentation (see Figure 1C).

The experimenter did not reveal the probability to win associated to each letter, hence the task incorporated a learning phase. Each session was preceded by 12 trials (two for each stimulus pair) for

patients to learn the difference between HR and LR. This learning phase duration was previously found to be sufficient for patients to define their strategy (Rosa et al., 2013b). Following the 12 trials training set, 6/6 GDPs showed a preference for the HR option suggesting that patients learned that the two options were associated to different reward contingencies. Learning phase presentations are not included in behavior or LFP analysis. Following the end of the learning phase two thirds of the trials (60/90) were Conflictual (C) and the rest of the trials were Equivalent Choice (EC): both HR (15/90) or both LR (15/90). For 1/6 GDPs the session ended earlier after 13 EC LR, 12 EC HR and 51 conflictual trials. For 1/6 NGDPs 5 conflictual trials were later discarded due to failure in recording reaction time.

Statistical analysis

Complete description of analysis of subjects' choices and of processing and analysis of LFP signal preceding options presentation is reported below. Briefly, risk avoidance (probability of choosing LR option in conflictual trials) and reaction times (time interval between options presentation and behavioral response) of GDPs and NGDPs have been compared under different conditions with unpaired Wilcoxon test. Reaction times were then normalized for the average reaction time of each patient and compared across the conditions separately for GDPs and NGDPs with Kruskal-Wallis test corrected for multiple comparisons.

Data processing and part of the statistical analysis was performed in Matlab[tm] (Natick USA). Two and three way repeated measures tests were performed in SPSS (IBM).

Unless otherwise stated figures report median value of the variables and interval of confidence of median value, computed as (Chambers et al., 1983)

$$\boldsymbol{median\ c.i.} = \pm \frac{\mathbf{1.57} * (\boldsymbol{75th\ percentile} - \boldsymbol{25th\ percentile})}{\sqrt{\boldsymbol{samples\ number}}} \qquad (1)$$

Behavioral performance analysis

The behavioral variables collected for each trial during the task were the reaction time (RT), the type of choice (LR, HR) and the money accumulated from the beginning of the task. Risk avoidance (RA) was defined as the fraction of times LR was chosen in conflictual trials (number of LR choices in conflictual trials divided per the number of conflictual trials), and reaction time (RT) as the interval between options presentation and option selection by pressing the corresponding button. Risk avoidance of GDPs (n=6) and NGDPs (n=6) is compared in Figure 1B with paired Wilcoxon test. Risk avoidance of healthy subjects (n=17), GDPs (n=6) and NGDPs (n=6) is compared with Kruskal Wallis

test corrected for multiple comparisons. For the reaction time analysis we divided the trials in four sets given by the type of trial and the following decision: C LR, EC LR, EC HR, C HR. The number of trials in each set was 139 (C LR), 87 (EC LR), 88 (EC HR), 212 (C HR) in GDPs and 219 (C LR), 90 (EC LR), 90 (EC HR), 136 (C HR) in NGDPs. Group-trial type interaction was evaluated with two-way ANOVA in SPSS[tm]. GDPs and NGDPs reaction times were compared overall and for each trials set with Wilcoxon test. Correlation between RTs ratio and RA was computed with *corr* function in Matlab[tm].

We computed for each subject RA in the subset of trials in which the accumulated money was above or below the session average, and we compared with a Wilcoxon signed rank test the two RA in GDPs and NGDPs. Interaction between accumulated money and group was evaluated with two-way ANOVA with repeated measures in SPSS[tm]. Finally, we measured the extent to which the decisions in conflictual trials (C) in each trial depended by the previous outcome (PO) as follows. If the subjects' choice was a Bernoulli process the risk avoidance after each of the four possible POs (the patient chose LR/HR and Won/Lost) would be independent from the outcome

$$\boldsymbol{RA_B(PO) =< RA > \ \forall\, PO} \qquad (2)$$

The estimated number of LR choices following each outcome in a memoryless process is then

$$\boldsymbol{Exp_B(LR|PO) =< RA > * occurrences\ of\ PO\ before\ C} \qquad (3)$$

We compared the observed number of LR choices in conflictual trials following each PO with the number expected in case the decisions were memoryless. We used the squared differences between expected and observed value as chi square measure of the goodness of the memoryless fit, i.e. of the extent to which the decisions are independent from previous outcome. In Figure 3D we compared the chi square between GDPs and NGDPs with Wilcoxon test (*ranksum* function, Matlab[tm]).

Local Field Potential (LFP) recording and processing

During the economic task, LFPs were simultaneously captured from the contact pair 0-2 of the DBS electrodes (Figure 1D). Signals were preamplified, differentially amplified (100000×) and digitized with 1024 Hz sampling rate through the Galileo BE Light EEG amplification system (EBNeuro Spa, Florence, Italy). Acquired LFPs were preprocessed by applying a 5th order zero-delay Butterworth bandpass filter in the range [0.5 50] Hz in order to remove very low frequency artifacts and high frequency noise. A narrow 50 Hz notch filter was also applied to remove electrical noise.

Since we are not looking for inhibition of motion we did not expect to find any preferred correlation between area of the recording within STN (left or right) and hand motion (ipsilateral and contralateral) but rather a global coordinated inhibition involving both areas. Hence, for the sake of robustness we averaged the LFP signal coming from the two recording tips (Figure 1C).

Figure 1C displays voltage values of (averaged) LFP recording for single sessions to show absolute values of behavior-dependent fluctuations. However, all the analysis described in the next subsection, involving multiple sessions, are performed on z-scored LFPs, to remove the variability associated to the different recording conditions across sessions and focus on the intra-session LFP variations.

Analysis of relationship between LFP and behavior

To focus on risk attitude instead of on decision-encoding neural activity, we analyzed the LFP recorded in the 3.3 seconds between the behavioral response to the $(n-1)^{th}$ presentation and the visual onset of the n^{th} presentation (see subsection "*Economic decision-making task"*). We obtained then for each session a set of LFP recording intervals of the same duration.

First we discarded LFPs associated to EC trials (30 trials, see above) as followed by a forced choice and then not useful to understand the relationship between LFP and response.

Conflictual choice trials were then divided into

i) C trials followed by choice of the high risk option LFP_{CHR}

ii) C trials followed by choice of the low risk option LFP_{CLR}

These datasets were the objects of the analysis. For each session we performed the analyses described below

LFP spectral analysis

Power spectral density was computed with *pwelch* Matlab function over the whole window, and over the three functional sub-intervals (see above). We compared the median power over LR and HR trials for the six subjects of each group with two-sided Wilcoxon rank test (*signrank* function Matlab). We compared median values across all trials between the six subjects in the GDP and the six subjects in the NGDP group with Kruskal Wallis test (*kruskalwallis* function Matlab).

We computed the information about future behavior conveyed by three frequency bands: low frequency]1 12] Hz, beta [12 30] Hz, low gamma [30 50[Hz. Spectral information was computed by using as neural signal S (see below) the average log-power of each band in each trial.

Low frequency fluctuations analysis

We analyzed the relationship between the evolution of low frequency LFP in the interval of interest by applying a low pass filter at 12 Hz (5^{th} order Butterworth filter) and computing the average value of the LFP for each of the three intervals (see above) for each trial. We performed on the resulting signal analyses both at the single subject level and comparing all trials of the same group.

Subject level analysis: First we compared for all the subjects in each group for each interval the average value of the LFP preceding HR and LR decisions, to test for significant differences. Then, we evaluated the correlation between LFP value and propensity to risk for each subject dividing the single trial average LFPs computed above into four equipopulated percentiles and counting the fraction of trials within each group of LFP that were followed by a low risk decision (a LFP-averaged risk avoidance). We subtracted from this value the overall risk avoidance of each subject, to see how the LFP modulates risk avoidance. We used these values for two tests. First, we tested (Pearson correlation test, Matlab *corrcoef* function) whether the values of the LFP and the risk avoidance correlated for each interval and condition. Second, we tested whether particularly high values of LFP were associated to a significant discrepancy of risk avoidance from mean value. We compared with a paired Wilcoxon test (*signrank* function Matlab) the average risk avoidance with the LFP-dependent risk avoidance for each LFP percentile.

Group level analysis: In a second set of analysis we grouped the trials for each combination of patient condition (GDP vs NGDP) and following choice (LR, HR), for a total of 2 conditions x 3 intervals x 2 choices = 12 groups each containing >100 LFP values. We computed the ANOVA three-fold interaction tests for the three factors (with SPSS). As the data were not distributed normally, we computed the test on LFP ranks (Conover and Iman, 1981). As interaction was significant we computed a second analysis separating LFP value from GPD and NGDP. We computed the interaction for factors intervals and choice with two-way ANOVA with unbalanced design (*anovan* function Matlab). We computed the significance of the difference of LFP between choices for each condition and interval with a Wilcoxon rank sum test (*ranksum* function Matlab).

Finally, low frequency LFP information was computed by using as neural signal S (see below) the average value of LFP over each interval in each trial.

Mutual information between LFP and behavior

Mutual information between a set of behaviors B and a set of neural signals S is defined as (Shannon, 1948)

$$I(B;S) = \sum_{s\in S, b\in B} P(b)P(s|b)log_2\frac{P(s|b)}{P(s)} \quad (4)$$

Where P(b) and P(s) are the absolute probability across all trials of observing a given behavior b from the set B or given neural signal s from set S, and P(s|b) the conditional probability of observing the neural signal s in trials in which the (following) behavior is b.

Here, we considered as set of behaviors the two possible responses: B=[HR, LR]. We computed then the mutual information between this set and different sets of neural signals. First we considered the average power of the three LFP bands over the whole window of interest (see above), then the average value of the low-passed LFP over each the three different functional intervals (see above). Information was computed with Information BreakDown Toolbox in Matlab (Magri et al., 2009)

We tackled the information bias due to the limited data set (Panzeri et al., 2007) with the following four steps:

- we grouped together all the trials from all patients from each group so to have a sufficiently high number of trials/stimulus
- we limited the number of bins of the signal to four (equipopulated), coherently with the binning used in the correlation study (see above) which ensures a conservative but stable measure of information (Ince et al., 2012)
- we applied the Panzeri-Treves bias correction (Treves and Panzeri, 1995)
- we compared the resulting values of information with those obtained with 200 bootstrap repetitions (Magri et al., 2009). We considered as being significant only values of information having $p<0.05$ of being generated with a bootstrap procedure, which gives a conservative estimate of information significance (Ince et al., 2012).

Dataset limitations

The two groups of patients whose behavior and neural activity we compare in the present work are composed by six patients each. This group size is sufficient to obtain statistically significant within and across group comparisons, so we performed several analyses considering each subject separately (see *subject level analysis* above). However, to improve the robustness of our conclusions we performed a second set of analysis by pooling trials of all subjects from the same group (see *group level analysis* above).

In reaction time analysis we compensated for the relatively small sample size by pooling together data from all subjects within the same group after normalizing to the median response time of each subject

(Sacré et al., 2016). Average z-scored LFPs from all subjects in the same condition were grouped for analysis of variance. Mutual information analysis was computed grouping the normalized neural activity (PSD, z-scored LFP) preceding LR or HR decisions of all subjects (Ince et al., 2012) of each group (see Materials and Methods for details). Note that these analyses were complemented by the subject-wise analysis of the LFP PSD and of the correlation between LFP and risk avoidance.

Results

The patients were asked to perform a two-alternative forced-choice task choosing between two letters presented on a screen (see Materials and Methods and Table 1 for details). The letters were associated to a probabilistic economic outcome (Figure 1A and Materials and Methods). The HR option (letters *B* and *C*) had a high maximum reward (+100 €) associated to a low probability (20%), and a negative expected value (-36 €); the LR option (letters *A* and *D*) had a lower maximum reward (+60 €) associated to a high probability (80%), and a positive expected value (+42 €) (Rosa et al., 2013a; Fumagalli et al., 2015). Each session consisted in 90 trials, preceded by a short learning phase (see Materials and Methods). Two thirds of the trials were Conflictual (C), i.e., the subject had to choose between HR and LR. The others were Equivalent Choices (ECs), i.e., both letters were associated with either HR or LR. The choice outcome and the total amount of money accumulated from the beginning of the session were displayed on the screen (Figure 1C, top) during the 3.3 s interval between each option selection and the following option presentation.

The patients performed the task four days after DBS surgery, when the extensions connected to the extracranial part of the STN lead were accessible for LFP recordings (see Materials and Methods, Figure 1D, Figure 2, and Table 2 for details). The analysis focused on the interval that preceded options presentation (Figure 1C bottom and Materials and Methods) to identify the features of the STN LFP signal correlated to the behavioral bias given by the attitude toward risk (Sacré et al., 2016). The selected interval also ensures that STN activity was not motion-related.

Decision bias precedes options presentation

Gambling disorder, as all impulse control disorders, is characterized by a difficulty in resisting to a drive even if this leads to a personal loss (Weintraub et al., 2006; American Psychiatric Association, 2013). This is in our case corresponds to preference toward the HR option even if the expected value is negative. We characterized for each patient the ability to resist this drive and select the most convenient option by means of the risk avoidance (RA), measured as the fraction of times LR was chosen on

conflictual trials. RA was significantly lower for GDPs than for NGDPs (inter-median difference (IMD) = -0.16; Wilcoxon test (WT), p=0.013, Figure 1B), and all GDPs showed a preference for the HR option (RA<0.5 for 6/6 GDPs, sign test p=0.031). This finding was consistent with behavioral screenings acquired prior to the recording sessions (see Materials and Methods). Although only 4/6 NGDPs selected a low risk strategy (RA>0.5) over the whole task, the risk avoidance of NGDPs and a control group of healthy subjects (see Materials and Methods) did not differ significantly (IMD = -0.058; WT, p=0.99).

We compared for the two patients groups the reaction time (RT) of each decision, i.e., the interval between the options presentation and the response (Figure 3A). As expected (Napier et al., 2015), the RTs of GDPs were overall faster when compared to those of NGDPs (IMD = -188 ms; WT, p=0.044). However, when we took into account both factors "group" and "trial type" in determining the RTs we found a significant interaction between the two factors (two way mixed ANOVA F(3,1052)=3.59, p=0.013). Note that significance of interaction holds without subjects pooling (two way mixed ANOVA with repeated measure on ranks F(3,30)=3.847, p=0.019). Conflictual and Equivalent Choices RTs (neglecting the response type) were not significantly different neither in GDP (KW test, p=0.55) nor in NGDP (KW test, p=0.21). RTs were then analyzed separately for each patient group taking into account trials type and response. GDPs had faster RTs than NGDPs only on trials in which two HR options were presented (EC-HR trials) (IMD = -423 ms; WT, p=0.015). During trials in which two LR options were presented (EC-LR) GDPs were actually slower, although not significantly (IMD = +37 ms, WT, p=0.94). Hence, the tendency of GDPs to make decisions more quickly than NGDPs strongly depended on the options presented.

The relative RTs (normalized to the median RT of each subject) across trial type for each patients group were then compared to understand how RTs were modulated by the trial type. Reaction times across trial types were significantly different for GDPs (Figure 3B, left, Kruskal Wallis test with Tukey Kramer correction for multiple comparisons (KWMC), p=0.0035). Post-hoc analysis revealed that the relative RTs of GDPs were significantly shorter on EC-HR trials than on EC-LR trials (IMD= -0.20; p=0.012). Also for NGDPs reaction times across trial types were significantly different (Figure 3B, right, KWMC, p=0.0066). Post-hoc analysis revealed that for NGDPs the relative RTs on EC-HR trials were significantly longer than on EC-LR trials (IMD=+0.35; KWMC, p=0.01). In other words, GDPs reaction was slower when presented with two LR options, while NGDPs reaction was slower when presented with two HR options, even if in both cases there was no decision to be taken. These findings are compatible with a decision bias occurring before options presentation (favoring usually LR for

NGDPs and HR for GDPs). RTs on EC trials were slower when the preferred option was not available, requiring subjects to switch their decision strategy. Consistent with these findings, the ratio of RTs on EC-HR and on EC-LR trials sets strongly correlated with risk avoidance across both GDPs and NGDPs (R=0.89, Pearson correlation test (PCT), p=0.0001). A similar correlation was also observed in healthy subjects (R=0.53, PCT, p=0.028). These results suggest that both GDPs and NGDPs had a strong decision bias before the options were presented and that RTs depended largely on the agreement between the planned response and the options available.

As expected, neither GDPs nor NGDPs behaved deterministically in conflictual trials, as each subject took a specific decision on each single trial. We examined then whether the single trial decision was more affected by a global evaluation of the strategy or by a reaction to recent decision/outcome history. One possible global strategy would be that subjects modulate their risk attitude according to money accumulated from the beginning of the session, for instance due to a saturating utility curve (Bernoulli, 1954). The relationship between RA and accumulated money was significantly different in the two groups (two way mixed ANOVA with repeated measures $F(1,10)=5.69$, $p=0.0382$). The RA of NGDPs was significantly lower when the accumulated money was lower than session average (IMD=-0.13; paired WT, p=0.031). For 2/6 NGDPs the increase in the risky behavior associated to low accumulated money was so strong ($\Delta RA = -.32$ and $\Delta RA = -.23$) to lead to an overall risky strategy ($RA<0.5$).The accumulated money did not exert instead any impact on GDPs RA (IMD=0.0097; paired WT, p=0.81). We examined then whether RA was specifically influenced by the outcome of the decision took in the preceding trial (LR/HR followed by Loss or Win): we computed for each group the discrepancy between the overall RA and RA given the previous outcome (PO). A two-way ANOVA indicated that the discrepancy was different between the two groups ($F[1,40]=14.4$, $p<0.001$) and for different POs ($F[3,40]=7.3$, $p=0.001$) with a significant interaction between the two factors ($F[3,40]=3.2$, $p=0.034$), as is shown in Figure 3C. We measured then for each subject how consistently the sequence of decisions in conflictual trials could be approximated by a Bernoulli process in which each choice is independent (see Materials and Methods). The influence of the previous outcome on RA was significantly higher in GDPs than in NGDPs (chi square distance from Bernoulli process, IMD= 2.42, WT, p=0.041, Figure 3D). This indicates that GDPs decisions were significantly more influenced than NGDPs by the preceding decision's outcome. Overall these results define an interval in between the display of the previous decision consequence and the onset of the following trial where neural activity could affect the risk attitude of GDP patients.

Band-wise STN LFP spectral content correlates with patient condition, but not with risk avoidance

We first analyzed the spectral content of STN LFP recorded in the whole interval for GDPs and NGDPs. The two groups did display significant differences in spectral content over the whole session (KW test, $p=0.25$). The peak of the relative difference in power between the two groups was found at 19 Hz (relative difference in power =204%), with a striking resemblance with the spectral difference between PD patients with and without impulse control disorder found in (Rodriguez-Oroz et al., 2011) (Figure 4A).

We compared then for each group separately the power spectra in intervals preceding HR and LR choices in conflictual trials (Figure 4B-C). The spectra did not show significant differences (KW test $p>0.5$ for both groups). The peaks of the relative difference in power between the two conditions were found below beta band and were much smaller than in the previous comparison (28% at 6 Hz for GDPs and 27% at 9 Hz for NGDPs). The window of interest was divided into three intervals, characterized by different screen display (Figure 1C, top). Different intervals were likely to be associated to different neural activity. We wondered then if the spectra in the three intervals were different for different future choices in the two groups. This was not the case, as there was no significant Choice x Interval interaction (two-way ANOVA with repeated measures, $F(2,30)=0.27$, $p=0.7$ for NGDPs and $F(2,30)=1.2$, $p=0.3$ for GDPs).

These results suggest that the overall STN LFP spectrum did not correlate with future choice. To further corroborate this conclusion we computed the amount of information about future decision carried trial-wise by the average power of the beta band ([12 30] Hz), of the low frequencies below beta (]1 12] Hz), and of the gamma-range frequencies above beta ([30 50[Hz) (see Materials and Methods). We found that no band carried significant information about future choice in GDPs or NGDPs (Figure 4D-E, $p>0.05$, bootstrap test).

STN low frequency fluctuations correlate with risk avoidance in GDPs, but not in NGDPs

The fact that the power of a neural signal does not carry information about a given behavioral feature does not imply that the signal is not informative, as information might be encoded in the signal phase, e.g., in the timing of the fluctuations of the signal relatively to the behavioral time frame. Indeed, although band-wise spectral analysis did not capture significant correlations between STN LFP and risk avoidance, we investigated whether the low-pass filtered LFP of GDPs in the interval of interest was

different when preceding conflictual trials ending with an HR or LR decision. Note that fluctuations of LFP bandpassed in beta and above had interval averages close to zero.

When analyzing the LFP subject-wise we found a significant Choice x Interval x Group interaction (Three Way mixed ANOVA with repeated measures $F(6,60)=2.31$, $p=0.046$) hence we analyzed separately the two groups. In GDPs we found a significant Choice x Interval interaction (Two way mixed ANOVA with repeated measures $F(6,30)=3.894$, $p=0.005$) so we analyzed each interval separately. We compared the median low frequency LFP preceding HR and LR choices in the three intervals for each GDP (Figure 5A-C). We found that LFP tended to be higher for HR (Wilcoxon Rank Test (WRT), $p=0.094$) in the first interval, while was significantly higher for LR in the second (WRT, $p=0.031$) and displayed no differences in the third interval (WRT, $p=0.438$). We wondered then if the LFP activity in the different intervals correlated subject-wise with changes in risk avoidance (Figure 5D-F). We found that risk avoidance was significantly anti-correlated with LFP activity in the first interval ($R= -0.57$, PCT, $p=0.0035$) and significantly correlated with LFP activity in the second interval ($R=0.70$, PCT, $p=0.0001$), while we found no correlation between LFP in the third interval and behavior ($R= -0.38$, PCT, $p=0.063$), coherently with results in Figure 5A-C. In particular, for 6/6 subjects trials with LFP in the 75^{th} percentile in the first/second interval were associated to a decrease/increase in risk avoidance (WRT, $p=0.0313$ for both intervals, Figure 5D-E).

In order to perform further analysis overcoming the limited number of subjects available, we grouped then all the trial-averaged LFPs for the two groups (Figure 6A). Also when considering groups data, GDPs and NGDPs displayed a different level of activity across the different intervals (significant Group x Choice x Interval interaction $F(2,2106)=5.82$, $p= 0.003$, three way ANOVA on ranks) and hence were analyzed separately. In the GDP group, we found a significant interaction Choice x Interval for the LFP average value over the three intervals (two-way ANOVA $F(2,1047)=3.55$, $p=0.029$), then we analyzed each interval separately (Figure 6B). The average LFP in the first interval was considerably lower in trials preceding LR decisions (WRT, $p=0.0024$), while the opposite was true for the second interval (WRT, $p=0.0012$), and no decision-related difference was found in the third interval (WRT, $p=0.12$). This indicates that in GDPs HR and LR decisions are associated to significantly different pattern of LFP activity before options presentation. As the two intervals in which we found significant differences were associated to the presentation of the results of the previous decision, we performed for each interval a two-way analysis taking into account the factors “future decision” and “outcome of previous decision”. We found that there was no significant interaction between the two factors ($F(1,347)<0.2$, $p>0.7$ for the first two intervals, $F(1,347)=3.4$, $p=0.065$ for the last interval).

Indeed, when considering only trials following a loss (Figure 6C), the LFP were significantly different for the first two intervals (WRT; p=0.016 and p=0.027 respectively) and tended to be different in the third one (WRT; p=0.084). When considering only trials following a win (Figure 6D), the LFPs were significantly different for the second interval (WRT; p=0.023) and tended to be different in the first one (WRT; p=0.070). No significant difference was instead found between LFPs preceding the same future choice but following different previous outcomes (WRT: p>0.1 for all intervals and both future choices). We can consider then the difference between the LFPs associated to different future decisions to be largely independent from the previous outcome. Finally, we computed the mutual information (see Materials and Methods) between LFP activity in the different intervals preceding options presentation and the following selected option (Figure 6E). We found that LFP in the first two intervals carried significant information ($p<0.05$, bootstrap test with Bonferroni correction) about future choices. These results shows that in GDPs low frequency fluctuations in STN LFP preceding option presentations are correlated to risk avoidance in the following trial, suggesting that STN activity might play a role in determining the risk bias for this group. In other words, the STN carries information about the ability of GDPs to choose in the next future a safe option against their general bias toward risk, suggesting that STN might be involved in this behavioral suppression, as observed in different behavioral tasks (Jahanshahi et al., 2015b). Note that STN LF LFP in GDPs did correlate with future choice, but, for a given choice, did not correlate with reaction time (Pearson correlation test, $p>0.2$ for every condition and interval), coherently with results reported in (Zénon et al., 2016), suggesting that STN LF LFP correlated with reward evaluation rather than with conflict.

We repeated for NGDPs the same subject-wise analysis performed for GDP, and we found no LFP x Interval interaction (two-way ANOVA repeated measures $F(6,30)=0.558$, $p=0.76$). Indeed we did not find any difference between LFP preceding HR or LR (WRT, $p>0.15$ for all intervals, Figure 7A-C) nor LFP-RA significant correlation ($|R|<0.25$, PCT, $p>0.2$ for all intervals, Figure 7(D-F)) for any interval. The low frequency LFPs in NGDPs were relatively unrelated to the following decisions (Figure 8A). We found no significant interaction Choice x Interval for the LFP average value over the three intervals (two-way ANOVA $F(2,1059)=0.07$, $p=0.93$), and in no interval we found significantly different LFPs associated to the future decisions (Figure 8B, WRT, $p>0.3$ for all intervals). Note that NGDPs LF LFP did not correlate to reaction times either ($p>0.05$ for all intervals and conditions). Finally, in no interval low frequency LFP of NGDPs STN carried significant information about future choices ($p>0.05$ bootstrap test with Bonferroni correction, Figure 8C).

The stronger correlation between behavior and STN activity before option presentation observed in GDPs compared to NGDPs is coherent with the fact that previous outcomes contribute much more in GDPs decisions (Figure 3D). Moreover, the lack of significant correlation between STN activation and risk avoidance in NGDPs supports the hypothesis that the STN plays a crucial role in suppressing unsafe urges (Aron, 2011). This suppression might then be present only in GDPs who have an unsafe urge to take risks but not in NGDPs who spontaneously lean towards a safer choice.

Discussion

We compared behavior and STN neural activity of Parkinson's Disease patients with and without gambling disorder during an economic decision making task. The main differences in the behavioral responses were related to reaction times and structure of decision making. First, the longest/shorter reaction times for NGDPs were for equivalent choice trials in which the options were both HR/LR respectively, while the opposite was true for GDPs. This suggested the possibility that the choice was strongly biased before option presentations and that patients needed time to change strategy when the pre-selected option was not available. Second, we found that GDPs decisions were strongly affected by the outcome of the immediately preceding trial, while this was not true for NGDPs. This indicated that GDPs decisions were determined in the interval between two consecutive trials.

The results of our analysis of the STN activity demonstrated indeed that, when a subject affected by gambling disorder faces economic choices, the STN activity preceding options presentations correlates with the ability to select the low risk option (with a larger expected value) despite the overall preference toward risky options. We argue that this suggests that the STN plays a role in determining upcoming economic decisions by opposing pathological risk propensities. The seminal paper by Frank et al. (Frank et al., 2007) showed that STN sends a "Global No-go" signal that "temporarily prevents the execution of any response" in the "face of conflict", after the options have been presented. This behavioral phenomenon is referred to as "Reactive Global Stopping" (Aron, 2011; Jahanshahi et al., 2015b). The results presented here are compatible with the hypothesis that the STN might serve also as a "Proactive Selective Control" (Aron, 2011), i.e., a complementary function that prepares to stop a selected response tendency in an upcoming task. In other words, our results support the idea that the role of STN goes beyond putting decisions on hold after a conflict is detected, but includes suppressing an undesired behavior after an internal bias toward an unfavorable action is detected.

We have in particular found future decisions to be correlated with interval-dependent STN LFP fluctuations in the low frequencies (LF, <12 Hz) below the beta band ([12 30] Hz). These two frequency bands have different functional properties in STN (Jahanshahi et al., 2015a). In particular, LF and beta band in STN LFP have been linked to different aspects of decision making (Rodriguez-Oroz et al., 2011), with LF being primarily associated to reward level (Zénon et al., 2016) and risk (Rosa et al., 2013a) while beta is primarily associated with conflict (Brittain et al., 2012). A recent work links low frequency STN activity with the "level of cautiousness" of subjects presented with an ambiguous perceptual discrimination (Herz et al., 2016). This is coherent with results establishing a specific functional link between low frequency STN activity and the medial prefrontal cortex, while beta band correlates with motor cortex (Rodriguez-Oroz et al., 2011; Herz et al., 2016; Horn et al., 2017). While the motor role of STN is usually associated to beta band, cognitive functions have been found to be related to different frequencies below the beta band. In order to keep our results as general as possible and avoid frequency band hand-picking we considered everything below the beta band as low frequency. Our results support the view of such low frequencies being related in STN to cognitive functions.

We have here observed a significant relationship between STN activity and future decisions. The first limitation of this finding is that we do not have a mechanistic explanation for this finding. One hypothesis might be that an outcome inducing a decrease in the risk drive triggers an activation of the STN, which we observe as a large low frequency deflection in the LFP, followed by a decrease in activity, which we observe as a slow rebound in the LFP. This hypothesis could be tested by modulating the different intervals of the task. The second limitation is that correlation obviously does not imply causality. A direct test of causality and not mere correlation between STN and future behavior would be to properly stimulate the STN of GDPs in the interval between economic risk trials and observe the expected reduction in risky behavior. Such a test would also be the first step toward an electroceutical therapy for gambling disorder.

The cognitive role of STN may generalize to non-Parkinsonian individuals. In fact, the inhibitory role of STN in decision-making seems to be qualitatively similar for PD patients and healthy subjects (Frank et al., 2007) because it is probably not affected by the neurological disease or dopamine medication (only by DBS, which is off in our case). Our results support the hypothesis put forth by Jahanshai et al. (Jahanshahi et al., 2015b) that proposes that the STN contributes to proactive inhibition via its functional connections through the striatum (Majid et al., 2013) (known to be involved in impulsivity (Buckholtz et al., 2010)) to the prefrontal cortex (Cavanagh et al., 2011; Rodriguez-Oroz et

al., 2011), an area strongly related to human decision-making in the face of uncertain outcomes (Bechara et al., 1994; Domenech and Koechlin, 2015). Our findings suggest that STN might take part to proactive selective inhibition by suppressing the impulsive attraction of GDPs for the risk associated to high but unlikely rewards and favor a rational preference for options associated to positive expected value. This interpretation also accounts for the lack of influence of STN in NGDPs, due to the fact that risk propensity is missing or weaker in NGDPs and hence no suppression is needed. Our results and this interpretation are coherent with the results in an identical task presented in (Rosa et al., 2013b) in which low frequency STN LFP modulation were associated to conflictual stimuli in GDPs but not in NGDPs. Additionally, the role of STN in high conflict tasks (Frank et al., 2007) and difficult moral decisions (Fumagalli et al., 2011; Fumagalli and Priori, 2012) can be interpreted within this framework. The lack of proactive selective inhibition might underlie most impulse control disorders, which indeed show a high rate of comorbidity (Weintraub et al., 2015), and might have overlapping neural mechanisms (Averbeck et al., 2014). The STN may then play a role in other impulse control disorders. Our findings about the relationship between risky decisions and STN activity in GDPs lay the ground for innovative pharmacological and neuromodulatory strategies that target the STN to efficiently tackle addiction and impulse control disorders.

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Figure captions

Figure 1. Economic task and STN LFP recordings. (A) Letters, wins (W) and loss (L) probability (P) and value (€), and expected values (EV) associated with Low Risk (LR) and High Risk (HR) options. (B) Risk avoidance in GDPs (n=6) and NGDPs (n=6). Bars represent median confidence interval. (C) Window of interest (3.3 s preceding options presentation). Top: sequence of visual stimuli in the window of interest. Bottom: processing of recorded LFP: raw data from right and left leads, and average LFP. (D) 3D reconstruction of STN location of the STN (blue structures) and of the Medtronic 3389 DBS™ leads (red cylinders) with 0-3 contacts in one example GDP subject (#6). CA and CP indicate the anterior and posterior commissure.

Figure 2. 2D reconstruction of recording coordinates. Location of STN (pale blue lines) and of Medtronic 3389 DBS ™ contact 1 in GDP # 6 (already shown in Figure 1D). R, right, L, Left, CA, anterior commissure, CP, posterior commissure, PM, middle point between CA and CP line. CO, MRI coronal view; SW, MRI sagittal view; AX, MRI axial (transverse) view; Sup, superior; Inf, inferior; A, anterior; P, posterior.

Figure 3. Risk avoidance bias precedes options presentation. (A) Comparison of reaction times in GDP (n=6) and NGDP (n=6). From left to right: over all conditions, Low Risk choice in Conflictual (C-LR) and Equivalent Choice (EC-LR) trials, High Risk choice in Equivalent Choice (EC-HR) and Conflictual (C-HR) trials. (B) Relative reaction times (RT) for the different conditions pooling all sessions of each patient group. The dashed line indicates the median RT. (C) Modulation of Risk Aversion due to previous outcome (PO) for GDPs (purple) and NGDPs (green). (D) Chi-square discrepancy between observed responses and expected responses in an equivalent memoryless Bernoulli process for GDPs (n=6) and NGDPs (n=6). Bars and error bars represent median and median confidence interval, respectively, for all panels. Horizontal line inserts highlight significant differences reporting p value (see Results for details) for all panels.

Figure 4. Spectral modulations of Subthalamic Nucleus Local Field Potential and future decisions. (A) Average Power Spectrum of STN LFP preceding options presentations over all trials for patients with gambling disorder (GDPs) and without (NGDPs). Dashed lines indicate Beta band [12-30 Hz]. (B) Average Power Spectrum of STN LFP preceding options presentations over all Low Risk (LR) and

774 High Risk (HR) tasks for patients with gambling disorder (GDPs). (C) Same as (B) for patients without
775 gambling disorder (NGDPs). (D) Mutual information between future choice and average power of the
776 different bands for GDPs. White bars and error bars represent respectively median and 75th percentile
777 of bootstrap information (see Material and Methods). (E) Same as (D) for NGDPs.
778
779 **Figure 5.** Subject-wise correlation between low frequency STN LFP preceding options presentation
780 and risk avoidance in GDPs. (A-C) Comparison of the average value of GDPs LFP in the three
781 intervals for the two conditions. Title reports significance of Wilcoxon Rank Test. (D-F) Modulation
782 from average Risk Avoidance associated to trials in which LFP averaged over the three different
783 intervals belongs to the four percentiles. Markers and bars indicate medians and range over GDP.
784 Circle indicates significant difference from average value ($p<0.05$, Wilcoxon rank test)
785
786 **Figure 6.** Group-wise correlation between low frequency STN LFP preceding options presentation and
787 risk avoidance in GDPs. (A) Grand average of z-scored LFP preceding task in which GDPs opted for
788 HR (red) or LR (blue) option. Areas indicate median value confidence. Horizontal dotted line
789 represents $z=0$. Vertical dashed lines indicate the interval in which the outcome of previous choice, the
790 accumulated money, and the blank screen are displayed. See Figure 1C for details. (B) Average value
791 of GDPs LFP in the three intervals for the two conditions. Markers indicate $p<0.05$ significant
792 difference. (C) Same as panel B, considering only trials in which the outcome of the previous choice
793 was a loss. (D) Same as panel B, considering only trials in which the outcome of the previous choice
794 was a win. (E) Mutual information between LFP levels in the different intervals and future choice
795 (black bars). White bars and associated error indicate average and 75th percentile bootstrap information
796 over 200 permutations (see Materials and Methods). Marker indicate $p<0.05$ significance of
797 information (bootstrap test with Bonferroni correction)
798
799 **Figure 7.** Subject-wise correlation between low frequency STN LFP preceding options presentation
800 and risk avoidance in NGDPs. (A-C) Comparison of the average value of NGDPs LFP in the three
801 intervals for the two conditions. Title reports significance of Wilcoxon Rank Test. (D-F) Modulation
802 from average Risk Avoidance associated to trials in which LFP averaged over the three different
803 intervals belongs to the four percentiles. Markers and bars indicate medians and range over NGDP.
804
805 **Figure 8.** Group-wise correlation between low frequency STN LFP preceding options presentation and
806 risk avoidance in NGDPs. (A) Grand average of z-scored LFP preceding task in which NGDPs opted

807 for HR (red) or LR (blue) option. Areas indicate median value confidence. Horizontal dotted line
808 represents z=0. Vertical dashed lines indicate the interval in which the outcome of previous choice, the
809 accumulated money, and the blank screen are displayed. See Figure 1C for details. (B) Average value
810 of NGDPs LFP in the three intervals for the two conditions. (C)Mutual information between LFP levels
811 in the different intervals and future choice (black bars). White bars and associated error indicate
812 average and 75th percentile bootstrap information over 200 permutations (see Materials and Methods).
813
814

Tables

Patient	Age at implant (years)	Gender	Disease duration at implant (years)	Preoperative therapy		Pre-operative UPDRS III score	MMSE	SOGS	BIS	Y1-S-TAI	Y2-STAI
				LEDD (mg)	DA in LEDD (mg)						
Cohort 1: GDPs											
1	49	M	8	1400	0	73.9	26.6	7	18	29	41
2	41	M	15	550	0	73.5	24.6	9	7	20	34
3	52	M	4	200	0	50.0	27.1	10	24	35	28
4	60	F	6	940	240	61.3	27.5	5	26	55	53
5	78	F	10	1200	280	56.2	30	7	19	46	35
6	48	M	10	900	0	71.1	27.6	15	22	48	36
Mean (SD)	*53.0 (10.0)*		*8.8 (3.8)*	*865.0 (435.0)*	*86.6 (134.5)*	*64.3 (10.0)*	*27.2 (1.7)*	*8.8 (3.5)*	*19.3 (6.7)*	*38.8 (13.1)*	*37.8 (8.5)*
Cohort 2: NGDPs											
1	67	F	14	2275	420	38.2	28.49	0	26	41	46
2	63	F	9	257,5	70	62.9	26.27	0	22	22	38
3	60	F	14	1550	350	70.3	28.27	1	25	52	54
4	64	F	11	910	0	61.5	29.27	0	22	33	39
5	47	M	10	820	240	58.0	25.89	0	14	38	31
6	61	F	11	1100	210	60.7	NA	0	NA	39	47
Mean (SD)	*60.0 (6.0)*		*11.5 (2.1)*	*1152.1 (691.5)*	*215 (160)*	*58.6 (10.8)*	*27.6 (1.5)*	*0.2 (0.4)*	*21.8 (4.7)*	*37.5 (9.8)*	*42.5 (8.1)*
p-value	*p>0.05*	*p>0.05*	*p>0.05*	*p>0.05*	*p>0.05*	*p>0.05*	*p>0.05*	*p<0.05*	*p>0.05*	*p>0.05*	*p>0.05*

Table 1. Patients' demographic and clinical characteristics.

LEED: Levodopa Equivalent daily dose; DA: dopamine agonist; UPDRS III: Unified Disease Rating - scale motor score; MMSE: Mini-mental state examination; SOGS: South Oaks Gambling Screen; BIS: Barratt Impulsiveness Scale; Y1-Y2 STAI: State-Trait Anxiety Inventory.; NA: not available. Patients with Gambling Disorder (GDs) and patients without Gambling Disorders (NGDs) were compared with a paired t-test for age and disease duration at implant, preoperative therapy, preoperative UPDRS motor score, preoperative MMSE, SOGS, BIS and Y2-STAI, stereotactic coordinates; with the Fisher exact

824 test for gender. Differences were considered significant if $p<0.05$. Data were expressed as mean ±
825 standard deviation (SD).
826

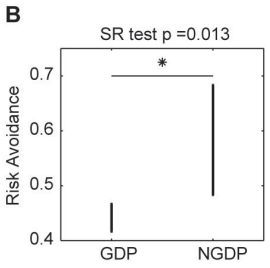
Patient	Contact 1 stereotactic coordinates	
	Right X, Y, Z	Left X, Y, Z
Cohort 1: GDPs		
1	12.4, -4.7, -0.3	11.3, -6.1, -4.7
2	11.2, -3.4, -3,1	11.4, 6.6, -6.7
3	13.0, 1.3, -3.0	10.3, -0.3, -3.3
4	11.6, -3.0, -1.5	10.3, -4.1, -1.6
5	10.9, -1.4, -3.1	11.9, -2.9, -5.5
6	13.1, -1.3, -3.6	9.9, 0.3, -6.9
Mean (SD)	*12.0(0.9),-2(2),-2.4(1.2)*	*10.8(0.8),-1.1(4.4),-4.8(2)*
Cohort 2: NGDPs		
1	9.8, 4.2, 0.75	11.8, -6.2, -1.8
2	11.7, -3.4, -4.2	11.8, -3.2, -4.0
3	9.6, -1.9, -5.1	10.3, -4.4, -5.0
4	10.7, -1.2, -2.6	11.3, -3.1, -2.1
5	12.4, -2.8, -4.3	12.1, -4.0, -3.7
6	13.6, -4.5, -3.8	11.3, -3.0, -4.0
Mean (SD)	*11.3(1.6),-1.6(3),-3.2(1.2)*	*11.4(0.6),-3.9(1.2),-3.4(1.2)*
p-value	*p>0.05*	*p>0.05*

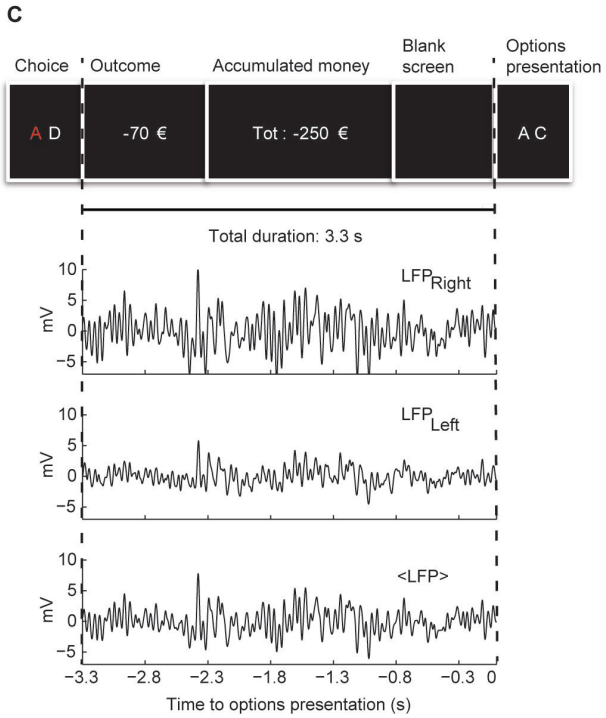
Table 2. STN lead contact 1 stereotactic coordinates

Stereotactic coordinates of subthalamic leads' contact 1 were rendered according to the anterior commissural–posterior commissural (AC–PC) line and the mid-commissural point (MCP) between AC-PC line; X = mm lateral from AC-PC line; Y = mm anterior (+) or posterior (-) from MCP; Z = mm depth according to AC–PC line (-, if ventral; +, if dorsal). Differences were considered significant if $p<0.05$. Data were expressed as mean ± standard deviation (SD).

A

		HR (B,C)	LR (A,D)
W	P	20%	80%
	€	+100	+60
L	P	80%	20%
	€	-70	-30
EV	€	-36	+42





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