

Subthalamic involvement in monetary reward and its dysfunction in parkinsonian gamblers

INTRODUCTION

Pathological gambling (PG) is an impulse control disorder that manifests in 2.2–7% of patients with Parkinson's disease (PD). Although the underlying neural mechanisms remain controversial, parkinsonian patients with PG show enhanced risk propensity, especially when assuming dopamine agonist drugs.

The dopaminergic reward circuit, a neural network that participates in developing and monitoring motivated behaviours,¹ includes the subthalamic nucleus (STN). Local field potentials (LFPs) recorded from macroelectrodes implanted in the STN for deep brain stimulation (DBS) show specific low-frequency oscillations in patients with PD with impulsive control disorders at rest and in patients with PG during the preparation of conflictual economics decisions.^{2 3} No study has yet investigated STN involvement in monetary reward processing, namely the phase that follows economics decisions,

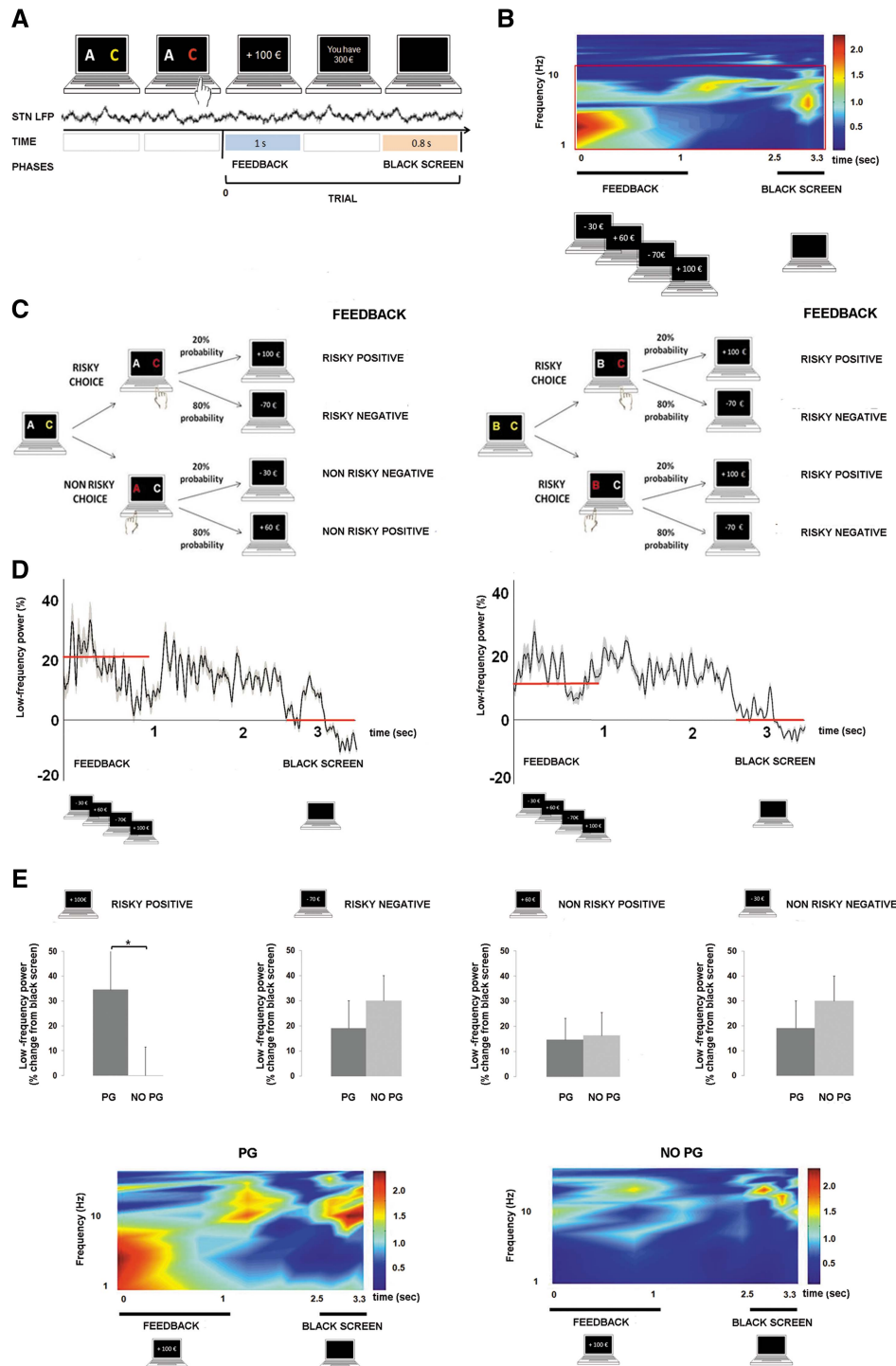


Figure 1 (A) The economics decision task. Each trial comprised two phases: the 'feedback' phase displaying the money won or lost after the patient's choice, and the 'black screen'. The red letters show the patient's choice. (B) The time-frequency plot for the grand average subthalamic nucleus local field potential (STN LFP) power in all trials in patients with and without pathological gambling (PG). Note that the principal power changes during the feedback phase involved the low-frequency band. (C) Feedback obtained during the economics task in conflictual and non-conflictual trials. On the left, an example showing a conflictual trial between a non-risky stimulus 'A' and a risky stimulus 'C'. On the right, an example showing a non-conflictual trial between two risky stimuli 'B' and 'C'. We classified four types of feedback according to risk taking: risky positive (+100€), risky negative (-70€), non-risky positive (+60€), non-risky negative (-30€). The task was designed to reward non-risky stimuli choices, so that the larger the number of non-risky stimuli choices, the higher was the amount of money earned. (D) On the left, the grand average of low-frequency power modulations in conflictual trials during the feedback phase and the black screen phase in all parkinsonian patients with and without PG. Low-frequency power modulations are expressed as percentage changes from the black screen phase. Red horizontal lines represent the mean low-frequency power during the feedback and black screen phases. On the right, the grand average for low-frequency power modulations in non-conflictual trials. Note that in all patients STN LFP low-frequency power increased during feedback in both conflictual and non-conflictual trials. (three-way analysis of variance (ANOVA), $p < 0.05$). (E) Histograms represent changes in low-frequency STN LFP power during feedback in patients with and without PG in conflictual trials. Error bars represent the SE of the estimated mean. Below, time-frequency plots for the grand average STN LFP power during risky positive feedback. Low-frequency power during risky positive feedback is significantly lower in patients without than in patients with PG (post hoc ANOVA, $p < 0.05$).

when participants face the outcome of their choice in patients with PD. Besides helping to understand the mechanisms underlying PG, this knowledge could promote the optimisation of therapies for impulse control disorders.

We investigated the STN's role in risk-related monetary reward in parkinsonian patients. To do so, we studied the reward-related STN LFPs changes in patients with PD with and without PG engaged in an economics decision task.

MATERIALS AND METHODS

We enrolled 12 patients with PD 4 days after STN DBS macroelectrode positioning surgery as described elsewhere³ (for clinical details, see table 1 from Ref. 3, patients number 1–4, 8–12, 14, 15, 17). Of the 12 patients, 6 met the criteria for PG according to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR). All patients gave informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board. Patients were tested with the economics decision task (figure 1A,C) during bilateral STN LFP recording from DBS macroelectrode contact pair 0–2.

LFPs were preamplified, filtered (band pass 2–512 Hz), differentially amplified ($\times 100\,000$) and digitised with a 1024 Hz sampling rate through the Galileo BE Light EEG amplification system (EBNeuro Spa, Florence, Italy). LFPs were analysed off-line with Matlab software (V7.10, The MathWorks, Natick, Massachusetts, USA). First, to identify the main activated LFP frequency band during economics feedback, we ran a time–frequency analysis. Then, to obtain the mean frequency band power in conflictual and non-conflictual task conditions during the two *task phases* (black screen, feedback) for each *type of feedback* (risky positive, risky negative, non-risky positive, non-risky negative), we applied the Hilbert transform.³

For behavioural analyses, the economics strategy each patient used during task performance was evaluated by calculating the sum of risky choices in conflictual trials. Differences between economics strategies in patients with and without PG were tested in a one-way analysis of variance (ANOVA) using PG (*presence, absence*) as between factor.

A one-sample Kolmogorov-Smirnov test was performed with electrophysiological data to verify whether they have normal distributions. To assess whether STN LFP activity recorded during black screen could be used as the baseline, we first compared mean power during the black

screen in conflictual and non-conflictual trials using a two-way repeated measures ANOVA with between factor PG and within factor *type of feedback*.

After calculating the percentage power change from the baseline for each trial,³ a three-way repeated measures ANOVA with between factor PG, first within factor *task phases* and second within factor *type of feedback* was run for conflictual trials. A similar three-way ANOVA was run for non-conflictual trials. One patient was excluded from the analysis on non-conflictual trials for artefacts due to electrode extension cable movement. Differences were considered significant at $p < 0.05$.

RESULTS

During the economics task, patients with PG adopted a significantly more risk-taking behavioural strategy than patients without PG ($F(1,10)=7.99$; $p=0.017$).

The one-sample Kolmogorov-Smirnov test showed that LFPs in the task phases and in the types of feedback have a normal distribution ($p > 0.05$ for all variables).

In all patients, the time–frequency plot for STN LFPs averaged across all trials showed that the principal power modulations during the feedback phase involved low-frequency power (from 2.25 ± 0.87 to 12.08 ± 0.29 Hz; figure 1B).

When we applied the Hilbert transform, the two-way ANOVA showed that the factors PG and *feedback type* and their interactions had no significant effects on low-frequency power during the black screen phase in conflictual ($F(3,66)=1.45$; $p > 0.05$) and non-conflictual trials ($F(3,60)=1.38$; $p > 0.05$). We therefore considered the STN LFP low-frequency band power recorded when we displayed the black screen as the baseline.

Global three-way ANOVA showed significantly higher low-frequency power during feedback than during black screen in conflictual (*task phases*, $F(1,22)=9.25$; $p=0.005$) and non-conflictual trials (*task phases*, $F(1,20)=4.45$; $p=0.047$; figure 1D).

Three-way ANOVA detected a significant interaction between the three factors only in conflictual trials ($PG \times task phases \times feedback type$, $F(3,66)=2.73$; $p=0.050$). Post hoc ANOVA showed a significant interaction ($PG \times feedback type$, $F(1,22)=2.74$; $p=0.050$). Post hoc ANOVA showed significant differences between patients with and without PG only during risky positive feedback ($F(1,22)=5.07$; $p=0.034$). Specifically, when patients received a positive feedback after a risky choice, percentage changes in low-

frequency power were significantly lower in parkinsonian patients without than with PG (figure 1E).

DISCUSSION

In general, our results first provide the neurophysiological evidence that the human STN is involved in monetary reward. Specifically, we found that the reward-related STN neural activity recorded during an economics decision task shows distinct patterns in parkinsonian patients who gamble and those who do not: whereas in gamblers, low-frequency power increases during all types of monetary feedback, that is, during winning and losing, in non-gamblers, it remains unchanged during the risky positive feedback, a low probable and high win that in the long run leads to loss. This neurophysiological pattern reflects the behavioural strategy adopted by patients. Patients without PG used a risk-avoiding strategy, for instance, they tended to choose stimuli associated with small but more probable positive rewards (in our economics task, a non-risky positive feedback). Conversely, patients with PG used a risk-taking strategy, and preferred large and less probable positive rewards (in our task, a risky positive feedback). These results suggest that the specific neurophysiological activity in non-gamblers that remains unchanged during risky positive feedback behaviourally reflects their scarce tendency to choose this option. Conversely, neurophysiological activity in patients who gamble is modulated indifferently by reward and gamblers behaviourally use a disadvantageous strategy.

Therefore, we conjecture that the specific STN LFP reward-related pattern in response to the risky positive feedback depends on the value that the STN 'attributes' to it in orienting the economics choice: in patients with PG it suggests an impaired learning in discriminating economics rewards.

To understand the reward circuit better, future research should also investigate cortical modulation. It should also check whether the feedback task involves other cognitive processes related to decision-making, including inhibition, learning, probability encoding, stimuli salience and reward encoding. Nonetheless, in general, our results confirm previous reports on STN low-frequency involvement in emotional and decisional processes⁴ and agree with reports that STN DBS can variably modulate efficacy in using feedback and regulate impulsivity.⁵

Our previous findings on the preparation of economics decision in parkinsonian

patients with PG showed a subthalamic dysfunction that makes their decisional threshold highly sensitive to risky options.³ In this study, we extend these results, suggesting that STN activity is also affected by reward and that PG could be related to a reward circuit disorder.

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