doi:10.1093/brain/awy298 BRAIN 2019: 142; 146–162 | 146

BRAIN
A JOURNAL OF NEUROLOGY

Wait and you shall see: sexual delay discounting in hypersexual Parkinson's disease

Romuald Girard,[1,2,3,*] Ignacio Obeso,[1,2,4,*] Stéphane Thobois,[5,6,7] Seongmin A. Park,[1,2] Tiphaine Vidal,[8,9] Emilie Favre,[6] Miguel Ulla,[8] Emmanuel Broussolle,[2,6,7] Paul Krack,[10,11] Franck Durif[8,9] and Jean-Claude Dreher[1,2]

*These authors contributed equally to this work.

Patients with Parkinson's disease may develop impulse control disorders under dopaminergic treatments. Impulse control disorders include a wide spectrum of behaviours, such as hypersexuality, pathological gambling or compulsive shopping. Yet, the neural systems engaged in specific impulse control disorders remain poorly characterized. Here, using model-based functional MRI, we aimed to determine the brain systems involved during delay-discounting of erotic rewards in hypersexual patients with Parkinson's disease (PD+HS), patients with Parkinson's disease without hypersexuality (PD – HS) and controls. Patients with Parkinson's disease were evaluated ON and OFF levodopa (counterbalanced). Participants had to decide between two options: (i) wait for 1.5 s to briefly view an erotic image; or (ii) wait longer to see the erotic image for a longer period of time. At the time of decision-making, we investigated which brain regions were engaged with the subjective valuation of the delayed erotic reward. At the time of the rewarded outcome, we searched for the brain regions responding more robustly after waiting longer to view the erotic image. PD+HS patients showed reduced discounting of erotic delayed rewards, compared to both patients with Parkinson's disease and controls, suggesting that they accepted waiting longer to view erotic images for a longer period of time. Thus, when using erotic stimuli that motivate PD+HS, these patients were less impulsive for the immediate reward. At the brain system level, this effect was paralleled by the fact that PD+HS, as compared to controls and PD – HS, showed a negative correlation between subjective value of the delayed reward and activity of medial prefrontal cortex and ventral striatum. Consistent with the incentive salience hypothesis combining learned cue–reward associations with current relevant physiological state, dopaminergic treatment in PD+HS boosted excessive 'wanting' of rewards and heightened activity in the anterior medial prefrontal cortex and the posterior cingulate cortex, as reflected by higher correlation with subjective value of the option associated to the delayed reward when ON medication as compared to the OFF medication state. At the time of outcome, the anterior medial prefrontal/rostral anterior cingulate cortex showed an interaction between group (PD+HS versus PD – HS) and medication (ON versus OFF), suggesting that dopaminergic treatment boosted activity of this brain region in PD+HS when viewing erotic images after waiting for longer periods of time. Our findings point to reduced delay discounting of erotic rewards in PD+HS, both at the behavioural and brain system levels, and abnormal reinforcing effect of levodopa when PD+HS patients are confronted with erotic stimuli.

1 Neuroeconomics, Reward and Decision-making Team, Institut des Sciences Cognitives Marc Jeannerod, Centre National de la Recherche Scientifique, UMR 5229, 69675 Bron, France
2 University Claude Bernard Lyon, Lyon 1, 69100 Villeurbanne, France
3 Section of Neurosurgery, The University of Chicago Medicine and Biological Sciences, Chicago, IL 60637, USA
4 HM Hospitales – Centro Integral en Neurociencias HM CINAC, 28938, Móstoles, Madrid, Spain
5 Université de Lyon, Université Claude Bernard Lyon 1, Faculté de Médecine Lyon Sud Charles Mérieux, 69921 Oullins, France
6 Neurologie C, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Lyon, France
7 Physiopathology of basal ganglia, Institut des Sciences Cognitives Marc Jeannerod, Centre National de la Recherche Scientifique, UMR 5229, 69675 Bron, France

Received May 29, 2018. Revised September 21, 2018. Accepted October 4, 2018. Advance Access publication December 22, 2018

8 Neurology Department, CHU de Clermont-Ferrand, 63000 Clermont-Ferrand, France
9 University Clermont Auvergne, EA 7280, Clermont Ferrand, France
10 University Grenoble Alpes, Grenoble Institut des Neurosciences, Grenoble, France, Inserm U1216, Grenoble, France
11 Movement Disorders Unit, Neurology Department, CHU de Grenoble, Grenoble, France

Correspondence to: Dr Jean-Claude Dreher
CNRS UMR 5229
Reward and Decision-making Team
Centre de Neurosciences Cognitives
67 Bd Pinel, 69675 Bron, France
E-mail: dreher@isc.cnrs.fr

Correspondence may also be addressed to: Dr Ignacio Obeso
Centro Integral en Neurociencias A.C. (CINAC)
Puerta del Sur HM Hospitales, 28938, Madrid, Spain
E-mail: iobeso.hmcinac@hmhospitales.com
http://www.somoshmcinac.com

Keywords: impulsivity; decision-making; delay discounting; functional MRI; hypersexuality

Abbreviations: GLM = general linear model; ICD = impulse control disorder; mPFC = medial prefrontal cortex; PD+/−HS = Parkinson's disease with/without hypersexuality; vmPFC = ventromedial prefrontal cortex

Introduction

Impulse control disorders (ICDs) are serious psychiatric complications in patients with Parkinson's disease treated with dopaminergic agents. They comprise compulsive, repetitive and, ultimately, harmful behaviours including compulsive gambling or shopping, sexual behaviours, binge-eating, as well as punding and excessive hobbyism. ICDs are mostly induced by dopamine agonists in about 17% of patients with Parkinson's disease and more rarely by levodopa (6.9%) (Molina *et al.*, 2000; Weintraub *et al.*, 2010; Voon *et al.*, 2011*b*, 2017). ICDs can have dramatic consequences for patients and their families with high risk of financial ruin, divorce, loss of employment or prosecution (Weintraub and Claassen, 2017).

The role of an abnormal sensitization of the mesolimbic dopaminergic system has been constantly reported in ICDs (Voon *et al.*, 2017). In addition, several anatomical and functional MRI studies in patients with Parkinson's disease with ICDs have shown dysfunctions in limbic and cortico-subcortical circuits engaged in risk-taking, reward-learning, reducing punishment learning and outcome evaluation as well as cognitive control difficulties (Santangelo *et al.*, 2017). These abnormalities mostly consist of dysfunctions of the ventral striatum and cortico-limbic areas as well as abnormal connectivity between the mesolimbic and meso-cortical regions (Cilia *et al.*, 2010; Rao *et al.*, 2010; van Eimeren *et al.*, 2010; Voon *et al.*, 2011*b*; Politis *et al.*, 2013; Cerasa *et al.*, 2014; Piray *et al.*, 2014; Biundo *et al.*, 2015; Carriere *et al.*, 2015; Claassen *et al.*, 2017; Tessitore *et al.*, 2017; Valli *et al.*, 2017; Petersen *et al.*, 2018). However, most of these studies have enrolled patients with Parkinson's disease with either various forms of ICDS or only pathological gambling (Steeves *et al.*, 2009; Cilia *et al.*, 2010, 2011; Rao *et al.*, 2010; van Eimeren *et al.*, 2010; O'Sullivan *et al.*, 2011; Voon *et al.*, 2011*b*, 2014; Joutsa *et al.*, 2012; Ray *et al.*, 2012; Politis *et al.*, 2013; Cerasa *et al.*, 2014; Piray *et al.*, 2014; Vriend *et al.*, 2014; Biundo *et al.*, 2015; Carriere *et al.*, 2015; Tessitore *et al.*, 2017; Petersen *et al.*, 2018).

The neural mechanisms that underlie each type of ICD specifically, such as hypersexuality, remain unclear. So far, only one functional MRI study has investigated the neural circuitry related to Parkinson's disease hypersexuality (Politis *et al.*, 2013). This study showed significant increased activity over limbic regions (i.e. orbitofrontal cortex, anterior cingulate cortex and ventral striatum) in patients with Parkinson's disease with hypersexuality (PD+HS) when passively viewing erotic images (Politis *et al.*, 2013). However, no study has, so far, investigated the brain networks associated with cost/benefit decisions related to sexual stimuli in PD+HS patients.

Decision-making consists of choosing among available options based on a valuation of their potential costs and benefits. Models of decision-making used in neuroeconomics propose that the desirability of outcomes expected from alternative options can be quantified by assigning a subjective value to each option under consideration. This valuation process allows the brain to weight the likely benefits and costs resulting from an action and to select the option with the highest subjective value. A domain in which the valuation process has proven particularly efficient in describing choice behaviour is delay discounting, which refers to the finding that animals tend to value immediate rewards more than delayed rewards. Here we hypothesized that hypersexuality in Parkinson's disease encompasses a dysfunctional valuation system when considering available options related to sexual stimuli.

Previous delay discounting experiments in Parkinson's disease and ICD have used monetary rewards as incentives

(Steeves *et al.*, 2009; Cilia *et al.*, 2010, 2011; Rao *et al.*, 2010; van Eimeren *et al.*, 2010; O'Sullivan *et al.*, 2011; Voon *et al.*, 2011*b*, 2014; Joutsa *et al.*, 2012; Ray *et al.*, 2012; Politis *et al.*, 2013; Cerasa *et al.*, 2014; Piray *et al.*, 2014; Vriend *et al.*, 2014; Biundo *et al.*, 2015; Carriere *et al.*, 2015; Tessitore *et al.*, 2017; Petersen *et al.*, 2018). Patients with Parkinson's disease with ICD tested with monetary rewards showed elevated discounting over short delays (immediate option is preferred) but not those without ICD (Voon *et al.*, 2010). In a study using a Kirby delay discounting questionnaire with future monetary rewards, patients with Parkinson's disease with ICD (mixed subtypes) also showed higher delay discounting, suggesting less tolerance for delay gratification (Housden *et al.*, 2010), replicated in ICD with pathological gambling (Voon *et al.*, 2010). However, these previous studies have not considered the role that specific reward types may play on a specific ICD, such as hypersexuality.

According to the incentive sensitization theory of addiction, there is a 'sensitization' or hypersensitivity to the incentive salience of drugs and drug-associated stimuli (Robinson and Berridge, 1993). Incentive sensitization produces a bias of attentional processing towards drug-associated stimuli and pathological motivation for drugs (compulsive 'wanting') (Robinson and Berridge, 1993, 2000). In behavioural addictions, by extension, excessive 'wanting' and compulsive pursuit of specific reward types may result, triggered by cues previously learned to be associated with rewards (Berridge and Robinson, 1998; Grant and Kim, 2001; Everitt and Wolf, 2002; Fadardi and Cox, 2009; Brevers *et al.*, 2011*a*). This hypothesis is supported by clinical observations indicating that exposure to addiction-related cues induces specific attentional biases and feelings of craving in addicted populations (Fadardi and Cox, 2009; Brevers *et al.*, 2011*b*). For example, abstaining smokers attribute higher reward value to cigarette cues than to neutral cues that are equally predictive of reward (Freeman *et al.*, 2013), and there is a motivational bias favouring monetary rewards in pathological gamblers as compared to erotic stimuli (Sescousse *et al.*, 2013). Similarly, here, we tested whether PD+HS patients are hypersensitive to erotic cues, related to their specific behavioural addiction, leading to a critical imbalance in incentive motivation for erotic rewards.

We used a model-based functional MRI and a delay discounting paradigm with real delay (waiting for a few seconds) as a cost and viewing erotic stimuli (i.e. stimuli that drive their excessive 'wanting' of rewards) for longer as the benefits to specifically assess the behavioural and neural mechanisms engaged in valuation of primary rewards but, this time, in PD+HS. We previously demonstrated that healthy young heterosexual males accepted waiting longer to see the erotic images for longer, and we identified the ventral striatum and ventromedial prefrontal cortex (vmPFC) as the core components engaged in delay discounting of erotic images (Prevost *et al.*, 2010). Using a similar paradigm, we hypothesized that Parkinson's disease with hypersexuality would show reduced delay discounting due to enhanced incentive salience of erotic rewards lasting for longer (i.e. PD+HS should prefer to choose to wait for longer to view erotic images for longer) and differential activity in the valuation system relative to Parkinson's disease without hypersexuality (PD − HS) and healthy controls. Moreover, because ICDs, including hypersexuality, are often considered as side effects of dopaminergic therapy (Lim *et al.*, 2008; Weintraub *et al.*, 2010), we tested whether dopaminergic medication in PD+HS would modulate subjective valuation of the option leading to the delayed erotic reward as well as the erotic reward outcome following a longer delay duration.

Materials and methods

Patients

Twenty-seven right-handed and non-demented male patients with idiopathic Parkinson's disease were enrolled in the study. All patients met UK Brain Bank diagnostic criteria for Parkinson's disease (Hughes *et al.*, 1992) and, because of the difficulty in recruiting this cohort, three University Hospital Movement Disorders clinics participated in the recruitment (Lyon, Clermont-Ferrand and Grenoble, France). Thirteen exhibited ongoing hypersexual ICD (PD+HS; $n = 13$, mean age = 58.5 ± 8.3 years), more or less associated with other ICDs as assessed by the Ardouin Scale of Behaviour in Parkinson disease (ASBPD, sexual items scores >2 of 4) (Rieu *et al.*, 2015). Diagnosis and presence of ICD was established by a clinical interview with an experienced neurologist (S.T., P.K., F.D., E.B.) and then further confirmed by the neuropsychologist (E.F., T.V.) using the ASBPD.

A group of patients with Parkinson's disease without HS (PD − HS; $n = 14$, mean age = 57.0 ± 9.0 years) were also included as a disease control group. Absence of ICD was also confirmed by a clinical interview and using the ASBPD. In both patient groups, absence of dementia [Mattis Dementia Rating Scale (DRS) score > 123; Frontal Assessment Battery (FAB) score > 16 (Dubois *et al.*, 2000), and depression (Hamilton Anxiety and Depression Scale; HADS) score < 18 (Zigmond and Snaith, 1983)] were considered as inclusion criteria. Patients' impulsivity levels were evaluated using the Barratt Impulsivity Scale-III (Patton *et al.*, 1995). Psychiatric history was evaluated with the MINI International Neuropsychiatric Interview (MINI) (Sheehan *et al.*, 1998) to control for potential confounding factors in patients' history (no history of alcohol or drug abuse). Motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale Part III in ON and OFF medication conditions during a levodopa challenge. Patients received chronic levodopa (L-DOPA) treatment in combination with dopamine agonists (ropinirole, pramipexole, rotigotine) and/or rasagiline (Table 1).

Fourteen healthy male volunteers were recruited as controls (right handed, mean age = 54.4 ± 5.0 years). None had any neurological disorder, psychiatric illness, head injury, or history of alcohol or drug abuse (as measured with the above neuropsychological tools). The study was approved by the Joint Ethics Committee of the Hôpital Neurologique and informed consents were obtained from all participants prior to the beginning of the study (registration number 22036S).

Table 1 Demographics of parkinsonian patients and control subjects

	Control	PD+HS	PD – HS	Control versus PD+HS	Control versus PD – HS	PD+HS versus PD – HS
Demographics						
Number of subjects	14	13	14			
Age (±SD)	54.4 (±5.0)	58.5 (±8.3)	57 (±9.0)	0.1	0.3	0.5
Disease duration (±SD)	NA	7.5 (±2.1)	6.8 (±2.6)	NA	NA	0.2
Clinical and neuropsychological test scores (±SD)						
UPDRS III Off	NA	33.2 (±11.2)	28.4 (±9.1)	NA	NA	0.2
UPDRS III On	NA	11.1 (±5.1)	12.6 (±6.0)	NA	NA	0.5
$LEDD_{total}$	NA	973.1 (±422.6)	1068.7 (±398.8)	NA	NA	0.5
$LEDD_{L\text{-}DOPA}$	NA	709.7 (±361.3)	779.8 (±412.0)	NA	NA	0.6
$LEDD_{DA}$	NA	282.1 (±185.1)	295.1 (±161.3)	NA	NA	0.8
$HADS_{Depression}$	4.0 (±4.3)	6.3 (±2.7)	5.3 (±4.4)	0.1	0.4	0.4
$HADS_{Anxiesty}$	5.9 (±3.1)	8.5 (±3.2)	7.3 (±2.8)	0.05	0.2	0.3
BIS-III	56.4 (±4.6)	62.7 (±8.0)	54 (±8.7)	0.01*	0.3	0.007*
FAB	16.9 (±1.1)	15.9 (±1.6)	16.5 (±1.2)	0.1	0.4	0.4
ASBPD (sexual item)	0	2.1 (±0.5)	0	0.001	1	0.001
MDRS	137 (±3.8)	134.2 (±5.8)	137.3 (±4.0)	0.1	0.8	0.9

*Significant statistical difference.

ASBPD = Ardouin Scale of Behaviour in Parkinson Disease; BIS-III = Barratt Impulsivity Scale; FAB = Frontal Assessment Battery; HADS = Hamilton Anxiety Depression Scale; LEDD = levodopa equivalent daily dose; MDRS = Mattis Dementia Rating Scale; NA = not applicable; SD = standard deviation; UPDRS-III = Unified Parkinson's Disease Rating Scale part III.

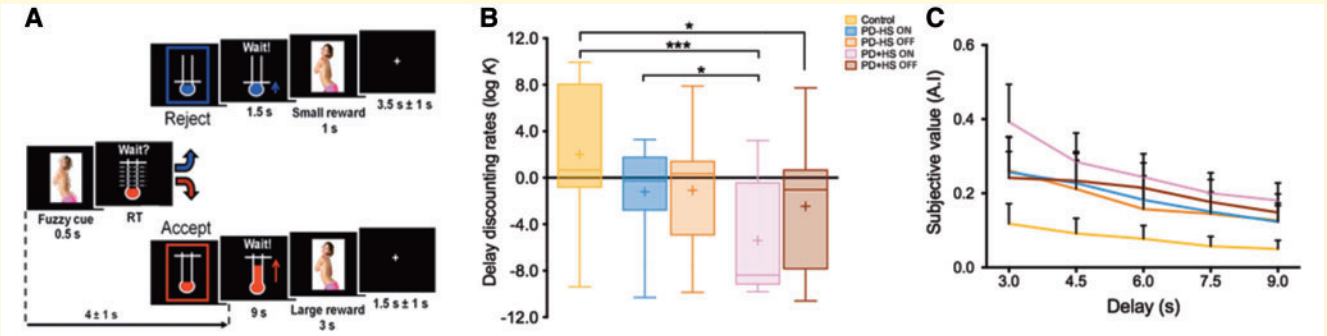

Figure 1 Delay-discounting task. (**A**) In each trial, a fuzzy erotic picture briefly appeared on the screen and was followed by the instruction 'Wait?', along with a thermometer indicating one of five possible levels of the proposed delay period to wait, ranging from 3 to 9 s for the delay. Subjects had to decide between the costly option and a default option having a minimal cost (1.5 s of waiting), depending on the incentive cue and the level of waiting proposed. If they accepted to wait the cost proposed, they had to wait passively during the proposed delay period before seeing the erotic picture a longer time (large reward). Otherwise, if they refused, they had to wait passively for a shorter delay period before seeing the erotic picture clearly for a short time period (small reward). The outcome and the intertrial interval lasted for a total of 4.5 s plus a jitter of ± 1 s in both options, avoiding that subjects adopted the strategy of choosing the default option more often to see more pictures. (**B**) Behavioural results. The mean average of the delay discounting rates (logK) did not show any difference between controls and PD – HS patients either ON or OFF medication. However, the mean delay discounting rates were higher in PD+HS patients both ON ($P = 0.001$) and OFF ($P = 0.04$) medication than in controls. In addition, the PD+HS patients ON medication showed higher delay discounting rates than PD – HS patients ON medication ($P = 0.03$). No difference was observed when both parkinsonians groups were OFF medication. (**C**) In every group, the normalized subjective value decreased when the subjects had to wait longer to see the erotic image clearly ($P < 0.001$). *$P < 0.05$, ***$P < 0.001$. Results are shown as box-and-whisker plots with each box representing the 2.5–97.5 percentile. The line within the box indicates the median. The plus symbol within the box represents the mean.

Delay discounting task

Subjects had to weight the cost and benefit of each option based on both the fuzzy cue and the proposed level of waiting period (delay). The levels of delays ($n = 5$) were randomly presented across sessions with an average of 12 trials per level. Each trial started with the presentation of a cue (0.5 s) representing an erotic fuzzy picture of a naked woman (Fig. 1A). The instruction cue 'Wait?' along with a graduated thermometer indicated a level of delay period of between 3 and 9 s. Subjects had to decide whether they chose the costly option (i.e. wait longer) to see the fuzzy cue clearly for 3 s (large

reward), or chose the default option (i.e. wait for a fixed short period of time of 1.5 s) to view the picture only for 1 s (small reward). Subjects pressed a response button using their forefinger to accept the costly option and the middle finger to reject it. Following the subject's choice, the thermometer was framed in a red rectangle if they decided to accept the costly option, and in a blue rectangle otherwise. Subjects then waited until the required time had elapsed and the thermometer was filled up to the indicated level. At the outcome, the erotic picture was displayed clearly for 3 s or 1 s according to subject's choice (i.e. costly or default option). The duration of the display of the cue plus the proposition (i.e. instruction screen) was a fixed time of 4 s ± 1 s. If the subject did not make a decision during the allocated time, the trial was aborted and the instruction 'Pay attention' was displayed for 2 s. The trial ended with an intertrial interval of 1.5 s plus a jitter of ±1 s when subjects accepted the offer to wait for longer and 3.5 s ± 1 s when they decided to reject this offer.

During the functional MRI scanning, three sessions (lasting around 9 min) were performed, composed of 20 trials each. After each functional MRI scanning acquisition, all subjects were asked to rate the 60 fuzzy cues displayed during the experiment. For each fuzzy image, the participants had to consider 'How much would I like to see this fuzzy picture in clear?', and rate the cue using a visual–analogue scale ranging from 1 ('I do not want to see the fuzzy picture in clear at all') to 9 ('I extremely want to see the fuzzy picture in clear') with an increment of 0.1. This rating score was then used to assess the subjective value for each image displayed.

For all patients with Parkinson's disease, the functional MRI acquisition was performed twice. To counterbalance the order of the acquisition, half of the patients with Parkinson's disease were scanned 1 h after a levodopa challenge (single supraliminar levodopa dose intake corresponding to 150% of the usual morning dose), and then the following day after at least 12-h overnight antiparkinsonian drugs withdrawal. The other half were scanned the same day: after 12-h overnight antiparkinsonian drugs withdrawal and 1 h after a levodopa challenge (single supraliminar levodopa dose intake corresponding to 150% of the usual morning dose). Controls had one functional MRI session.

Statistical methods

The behavioural data analyses were performed using a two-way ANOVA with medication (ON versus OFF) and group (PD+HS, PD − HS and controls) for delay discounting rates (logK) and acceptance rates (Supplementary Figs 1 and 2). In addition, a three-way ANOVA was performed using subjective values associated to the levels of delay, medication and group as variables. *Post hoc* follow-up tests were performed using Fisher's least significant difference (LSD) to correct for multiple comparisons. The betas estimated extracted for each group were compared using a two-sample *t*-test. Statistical analyses were conducted using SPSS statistical software (IBM Corporation, Armonk, NY, USA).

Computational model and parameter estimation

We implemented the softmax decision rule to assign a probability (P_I) to choose a given option given the subjective value of that option (V_I for immediate option; V_D for the delayed option) where β is a parameter representing the degree of stochasticity of the subject's behaviour.

$$P_I = \frac{e^{\beta V_I}}{e^{\beta V_I} + e^{\beta V_D}} \quad (1)$$

We used a discounted utility model to compute the subjective value associated with each option and to provide an accurate fit to subjects' choices in this task (Kable and Glimcher, 2007). This model states that the discounted utility (V) of a reward of magnitude (R) associated to a delay (d) can be expressed as follows:

$$V = \frac{R}{1 + Kd} \quad (2)$$

by which the utility is discounted in a standard hyperbolic fashion (Mazur, 1987). K is a discount rate parameter, which quantifies an individual's tendency to discount the delay. That is, a person with a high K shows a steep devaluation of rewards as they become more delayed. According to traditional models of intertemporal choice valuation, impulsivity—the propensity to choose the immediate option leading to smaller rewards—can be captured by a function of K.

We used each participant's trial-by-trial choice behaviour to fit the free parameters of the model, and asked to what extent the model explains the participant's choices on trial, t (C_t). Model fitting was estimated with log posterior density (lpd) given the parameters θ ($\theta = \{K, \beta\}$). The lpd was measured based on the probabilities to the choices of each participant on each of the T trials, computed as:

$$lpd = \prod_{t=1}^{T} \log p_{post}(C_t|\theta) = \prod_{t=1}^{T} \log \int p(C_t|\theta) p_{post}(\theta) d\theta \quad (3)$$

We fitted the parameters of the model to each participant's choice data. To facilitate model fitting, we used a regularizing prior that favoured realistic values for the parameters (Daw, 2011). Concretely, both K and β were searched within the boundary of positive values (0–∞). To do this, we set the prior distribution of K as the probabilistic density function (PDF) of inverse gamma (0.001, 0.001) and the prior distribution of β as the PDF of inverse gamma (2, 3). We optimized the model parameters by minimizing the negative log posterior density (lpd) of the data given different settings of the model parameters ($\theta = \{K, \beta\}$) using a Bayesian statistical model with STAN (Carpenter *et al.*, 2017). We finally normalized the subjective value among the different levels of delay and the groups using a min-max normalization approach.

Functional MRI data analysis

The functional MRI neuroimaging datasets were preprocessed and analysed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The four initial scans of each functional MRI series were discarded. Images were spatially realigned to the first image from the first session using a six-parameter, rigid-body transformation, and unwrapped to correct for geometric distortions. Scan artefacts were detected and repaired using average intensity and scan-to-scan motion performing the artefact repair algorithm implemented in ArtRepair SPM toolbox. For each participant, the T_1-weighted

anatomical image was co-registered to the mean EPI (echo planar imaging), and segmented into white and grey matter. The grey matter and EPI were then normalized using standard Montreal Neurological Institute space template conforming to the Talairach orientation system by applying a 12-parameter affine transformation followed by a non-linear warping. The computed transformation parameters were applied to all of the functional images, interpolated to a final isotropic voxel size of 3 mm^3. Finally, a spatial smoothing was performed using a Gaussian kernel with full-width at half-maximum of 8 mm and finally, scaled across scans. After a quality check of the post-processing images, two controls, one PD+HS and three PD – HS patients ON L-DOPA and two PD+HS and three PD – HS patients OFF L-DOPA were discarded from the functional MRI analysis due to motion artefacts during data acquisition or because functional MRI data were not acquired during all blocks (participants not being able to perform the task entirely).

After preprocessing, statistical parametric maps were computed from local magnetic resonance signals, as an event-related design using linear multiple regression. Because we focused on discounting of the delayed reward, only trials where the subjects chose the delayed reward were analysed.

GLM1: functional MRI data statistical analysis at the decision-making and outcome phases

For each subject, functional MRI time series were regressed onto a main linear regression model (GLM) modelling three phases including the decision-making stage, delay and outcome. The decision-making phase was represented by an impulse function convolved with a canonical haemodynamic response function (HRF). The delay and the outcome phases were modelled using a boxcar function, whose duration was equal to the duration of the corresponding event, convolved with a HRF. The decision-making regressor was parametrically modulated by the estimated subjective value of the option associated with the delayed reward, while the outcome regressor was modulated by the level of delay (to investigate whether outcomes associated with longer delays engage specific brain regions). The linear contrasts of regression coefficients were computed for each subject. The data were then high-pass filtered (128 s cut-off) to remove low-frequency drifts and serial correlations were accounted for by an autoregressive model of the first order.

The linear contrasts of regression coefficients associated with the parametric modulation of the subjective value of the delayed option and the blood oxygen level-dependent (BOLD) activity at the decision-making phase were then taken to a group level random-effects analysis. A second-level ANOVA was performed to assess the differences in parametric modulation of subjective value and BOLD activity between controls and Parkinson's disease patients with and without hypersexuality regardless of their medication. To study the effect of dopaminergic treatment in patients with Parkinson's disease, we also assessed the differences in the parametric modulation of subjective value conducting a mixed-effect ANOVA analysis including the two groups of patients (PD – HS and PD+HS) and their medication state (ON and OFF) as factors. Finally, the same mixed-effect ANOVA analysis was also conducted at the outcome phase.

GLM2 and GLM3: functional MRI data statistical analysis at the decision-making phase

We performed two additional GLMs to study the effects of the incentive value of the cue (i.e. ratings) and the level of proposed delay (i.e. costs) in the brain regions correlating with the subjective value of the delayed erotic rewards. These additional GLMs were performed to plot the graphs of parameter estimates as a function of the levels of delay (GLM2) and as a function of categories of rating of the fuzzy cue (GLM3). For GLM2, five regressors were used to account for each of the delay cost-enduring level at the time of the decision. For GLM3, we collapsed the ratings into four categories (bins) to ensure a sufficient number of repetitions in each bin and to generate robust statistics. Thus, four regressors were used to account for each of these bins at the decision-making phase. In addition, the delay cost-enduring, and the outcome phases were modelled for each trial in both GLM2 and GLM3 (Prevost *et al.*, 2010).

All phases were modelled using a canonical HRF convolved whether with an impulse function for the decision phase, or using a boxcar function, whose duration is equal to the duration of the stimuli, for the cost-enduring and the outcome phases. For additional details on the methods, see the online Supplementary material.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of local ethical restrictions and protection of privacy of study participants.

Results

Clinical characteristics

Antiparkinsonian treatments and demographic or clinical characteristics (age, gender, disease duration, UPDRS-III ON and OFF scores) were similar between PD+HS and PD – HS patients. Both patient groups showed significant differences between their medication conditions (P's < 0.001). Except two patients, most PD+HS exhibited, in addition to hypersexuality, other ICDs [compulsive shopping ($n = 1$); binge eating ($n = 8$); hobbyism ($n = 9$); hyperactivity ($n = 5$)]. In the PD+HS group, one patient had one score greater than hypersexuality (hobbyism). Higher impulsivity levels (measured by BIS-III) and hypersexuality behaviours (assessed by ASBPD) were found in PD+HS as compared to PD – HS patients (Table 1). Psychiatric history (MINI) between groups showed different percentages across two variables showing larger percentages in PD+HS major depressive disorder and social phobia history (Supplementary material).

Behavioural results

An ANOVA with delay discounting rates, group and medication as factors revealed a significant group effect [$F(1,36) = 6.65$, $P = 0.003$]. *Post hoc* group comparisons demonstrated that PD+HS patients had lower discount rates during delay discounting task than controls [log k: $t(24) = -3.80$, $P = 0.001$; $t(24) = -2.12$, $P = 0.04$ for ON and OFF medication, respectively] (Fig. 1B). While medicated, PD+HS patients showed significantly lower discounting rates than PD − HS patients [log k: $t(24) = -2.20$, $P = 0.03$]. No difference in discounting rates was observed between the two groups while OFF medication. The results show that PD+HS accepted to wait for longer to see erotic images for longer while medicated. Discount rates of PD+HS showed no significant correlations with hypersexual behaviours and impulsive clinical scores.

An ANOVA with the subjective value and group (controls, PD − HS and PD+HS), delay levels and medication as factors revealed a significant subjective value effect [$F(1,36) = 32.00$, $P < 0.001$] suggesting decreased choices when the delay to see the erotic rewards increased (Fig. 1C). In addition, an interaction between level of delay × group × medication [$F(1,36) = 2.15$, $P = 0.03$] was observed. To follow-up on such an interaction, *post hoc* comparisons showed significant differences between controls and PD+HS across delay levels [ON medication: level 1, $t(25) = 2.39$, $P = 0.02$; level 2, $t(25) = 2.19$, $P = 0.03$; level 3, $t(25) = 2.30$, $P = 0.03$; level 4, $t(25) = 2.35$, $P = 0.02$; level 5, $t(25) = 2.49$, $P = 0.02$] without significant differences with PD − HS versus controls (P's > 0.05) suggesting specific behavioural effect on the increased subjective value of erotic images in hypersexuality. No differences were detected between PD+HS and PD − HS patients. For additional behavioural results, refer to the Supplementary material.

Functional MRI results

Subjective valuation phase

The vmPFC correlated with subjective value of the delayed erotic rewards in controls and PD−HS compared to PD+HS

We first identified brain activity differentially correlating with the subjective value of the option leading to the delayed reward at the time of the decision-making phase. The comparison between controls and parkinsonian patients with and without hypersexuality, regardless of medication, showed that activity in the medial PFC, including the vmPFC (Fig. 2A and Table 2) was differently correlated with the subjective value of the delayed reward. Indeed, the activity in the vmPFC [Brodmann area (BA) 8 and 10] was negatively correlated with the subjective value of the delayed reward in PD+HS, while it was positively correlated with this subjective value in the controls and PD − HS groups (Fig. 2A).

To understand the correlations with subjective value better, we plotted the parameter estimates as a function of the levels of delay (GLM2) and categories of rating of the fuzzy cues (GLM3). The activity of the vmPFC for both controls and PD − HS increased for greater ratings of the fuzzy cue and decreased with longer delays (Fig. 2A). On the other hand, activity in the vmPFC of the PD+HS showed a distinct pattern since it did not decrease for both longer delays and greater rating.

Ventral striatum correlated with subjective value of the delayed reward in PD−HS

The comparison of the parametric regression of subjective value and the BOLD activity between controls and patients with Parkinson's disease with and without hypersexuality showed, regardless of medication state, that activity in the right ventral striatum was significantly positively correlated with the subjective value of delayed erotic rewards in both controls and PD − HS (Fig. 2B and Table 3), but not in PD+HS. The parameter estimates as a function of the levels of delays (GLM2) and categories of rating of the fuzzy cue (GLM3) showed the same pattern in the right ventral striatum for both controls and PD − HS patients (Fig. 2B). Indeed, activity in these regions increased for higher ratings and decreased with longer delays. However, the activity in the right ventral striatum decreased for higher ratings in PD+HS (while the relationship with longer delay was not significant).

Medial prefrontal and posterior cingulate cortices were differentially modulated by dopaminergic medication

A significant interaction between medication and group (PD+HS and PD − HS) was observed over the medial prefrontal cortex (BA 10), extending in the orbitofrontal cortex (BA 10, 47) and the lateral PFC (BA 9, 45, 46), the posterior cingulate (BA 31), and the bilateral insula (BA 13) (Fig. 3 and Table 3).

In addition, activity in the anterior medial prefrontal (BA 8, 9 and 10) and posterior cingulate cortices of PD+HS participants ON medication showed higher correlation with subjective value of the delayed option compared to the OFF medication condition (Fig. 3 and Table 3).

Outcome phase

Medial prefrontal cortex correlated with increasing delay in PD+HS on medication

An interaction between medication (ON and OFF medication) and group (PD+HS and PD − HS) showed that viewing erotic rewards after waiting for a longer period of time induced a robust mPFC activation (BA 9 and 10). Activation of this region was positively correlated with the delay at the time of rewarded outcome (i.e. when viewing the erotic image in clear) in medicated PD+HS. Conversely, PD+HS OFF medication showed a negative correlation with delay, similar to what is observed in PD − HS patients (Fig. 4 and Table 4).

In addition, direct comparison between ON and OFF medication conditions in PD+HS, revealed that a more dorsal mPFC region showed higher correlation with subjective value of the delayed erotic rewards when

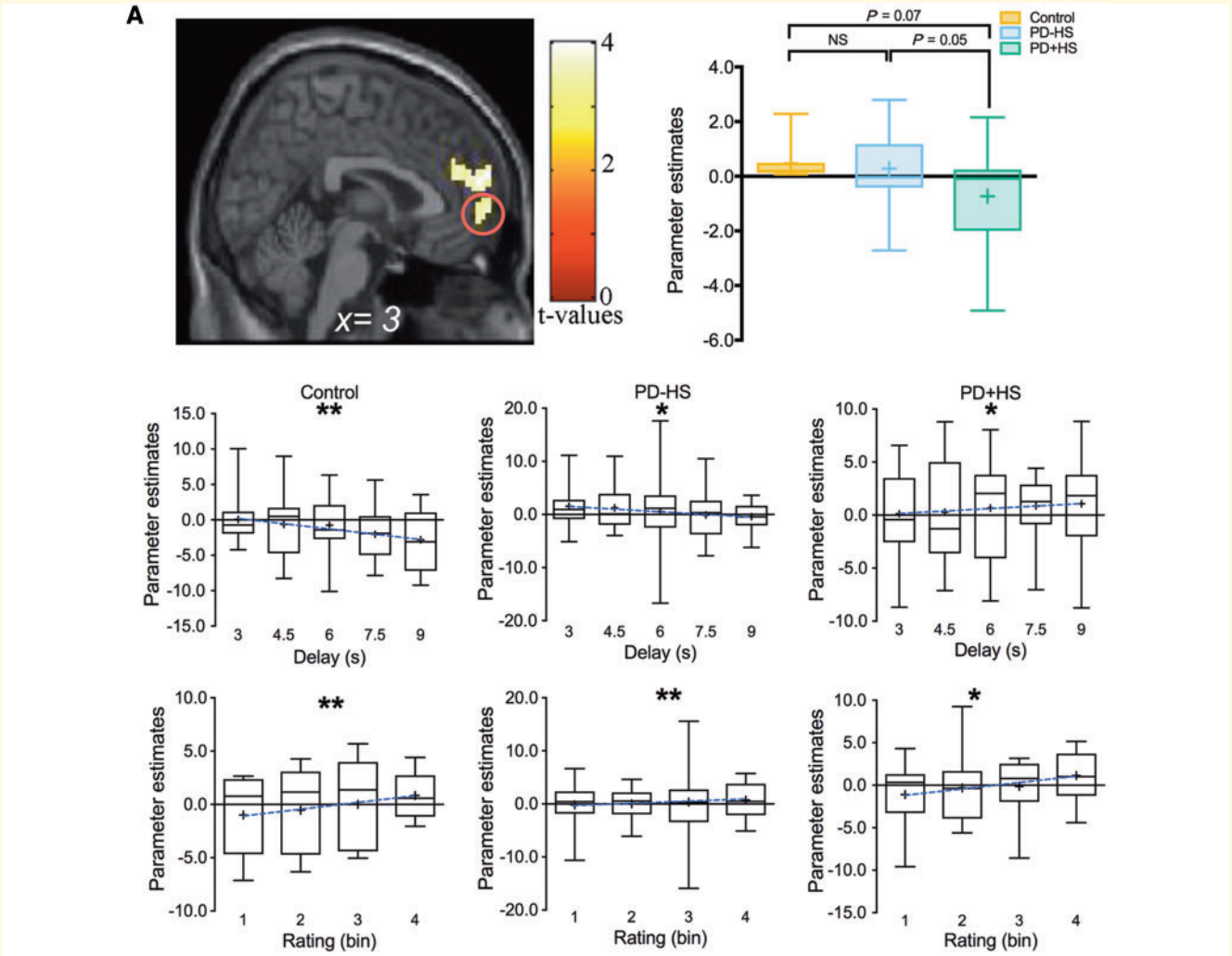

Figure 2 Comparison between controls and parkinsonian subjects with and without hypersexuality showed distinct correlated activity in the vmPFC regardless of the medication condition. (**A**) *Top*: The activity in the vmPFC was differently correlated between controls and parkinsonian patients with and without hypersexuality, regardless of their medication state ($P < 0.001$, uncorrected; SVC FWE corrected; for display purposes extended threshold = 27 voxels). The activity in the vmPFC was negatively correlated with the subjective value of delayed erotic rewards in PD+HS patients, while it was positively correlated in the control subjects and PD − HS patients. *Bottom*: The percentage BOLD change as a function of the five levels of costs (*top*) or four categories of rating of the cue (*bottom*) showed increased activity for greater ratings while it decreased with longer delays in controls and PD − HS patients. However, PD+HS patients showed a distinct pattern where the activity in the vmPFC increased for both longer delays and greater ratings. (**B**) *Top*: The activity in the right ventral striatum was differently correlated between controls and parkinsonian patients with and without hypersexuality, regardless of their medication state ($P < 0.001$, uncorrected; SVC FWE corrected; for display purposes extended threshold = 88 voxels). The activity in the right ventral striatum was not correlated with the subjective value of delayed erotic rewards in PD+HS patients, but it was positively correlated in controls and PD − HS patients. *Bottom*: The percentage BOLD change as a function of the levels of delay (*top*) and rating of the fuzzy cues grouped in four categories (*bottom*) showed an increased activity for greater ratings while it decreased with longer delays in controls and PD − HS patients. However, the BOLD activity decreased for both higher rating and levels in PD+HS patients. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Results are shown as box-and-whisker plots with each box representing the 2.5–97.5th percentile. The line within the box indicates the median. The plus symbol within the box represents the mean.

comparing ON to OFF medication (ON > OFF medication, Supplementary Table 1).

Discussion

Using for the first time a decision-making paradigm specifically dedicated to hypersexual behaviours in Parkinson's disease, we found that PD+HS patients ON medication accepted waiting longer to view erotic images compared to PD − HS patients. At the brain system level, we provide evidence of an altered valuation process in PD+HS influenced by sexual stimuli and dopaminergic medication in the anterior medial prefrontal and posterior cingulate cortices as well as ventral striatum. More precisely, PD+HS showed differential correlation with subjective value in the vmPFC

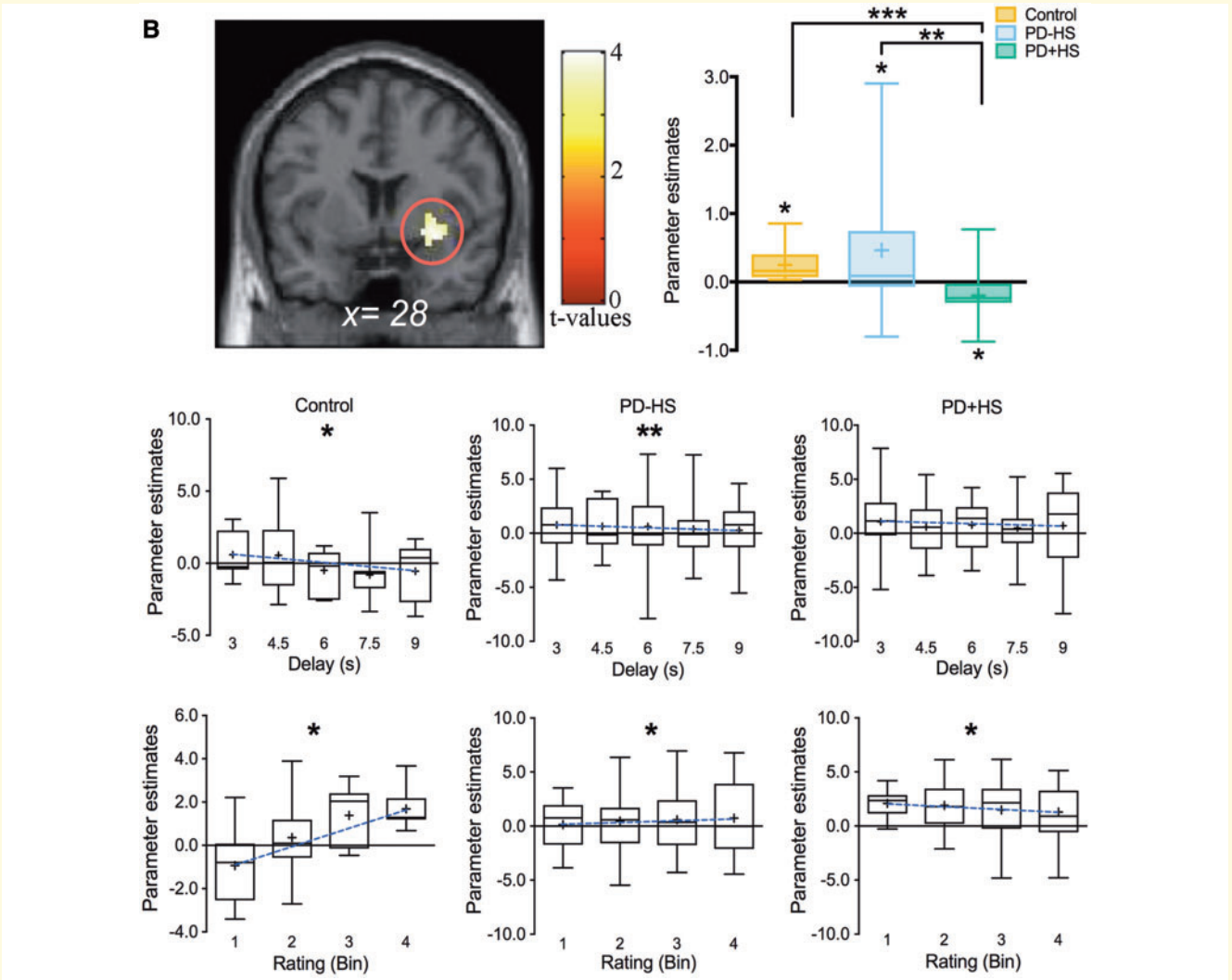

Figure 2 Continued.

and ventral striatum compared to PD – HS and controls, due to altered representations of delay cost in the vmPFC and to the incentive of the cue in the ventral striatum. Moreover, dopaminergic treatment increased the correlation between the subjective value of the delayed option and medial prefrontal as well as posterior cingulate cortices in PD+HS only. Finally, at the outcome phase, when PD+HS patients were ON medication, activity in the medial prefrontal cortex was positively correlated with the delay duration previously experienced.

Delay discounting in patients with Parkinson's disease with hypersexuality

Our behavioural results clearly demonstrate that PD+HS patients accepted to wait longer to view erotic images for longer. Thus, they discounted less delayed erotic stimuli, compared to PD – HS and controls. This result could seem contradictory with several lines of evidence showing that patients with Parkinson's disease suffering from ICD have increased monetary delay discounting, perhaps reflecting higher impulsivity to earn fast money for subsequent gambling activities (Housden *et al.*, 2010; Djamshidian *et al.*, 2011; Vitale *et al.*, 2011; Voon *et al.*, 2011*b*, 2017; Leroi *et al.*, 2013; Claassen *et al.*, 2015). However, all these studies have used money as a reward. Although such secondary reward may be well suited for specific ICD such as pathological gambling, monetary reward appears less appropriate to determine the neural mechanisms underlying hypersexuality in Parkinson's disease. Indeed, hypersexual patients with Parkinson's disease are more likely to be motivated by sexual images and to show changes in choice behaviour specifically related to their hypersexuality. Our findings emphasize that ICDs cannot be considered as a unitary class of psychiatric disorder characterized by impulsivity, but that Parkinson's disease patients with hypersexuality, compulsive shopping or

Table 2 Brain regions showing their activity differently correlated with subjective value of the cost reward between healthy controls and parkinsonian patients

Anatomical structure (Brodmann area)	x	y	z	T-value
Frontal				
Right medial frontal gyrus (BA 10)*	3	58	15	4.02
Right superior frontal gyrus (BA 8 and 9)	15	53	23	3.83
Right inferior frontal gyrus (BA 47)	36	31	−8	3.52
Right precentral gyrus (BA 44)	48	17	6	3.31
Left medial frontal gyrus (BA 10)*	0	57	1	3.77
Left superior frontal gyrus (BA 9)*	−12	50	29	3.92
Left inferior frontal gyrus (BA 44 and 46)	−50	29	16	3.57
Left precentral gyrus (BA 6)	−50	−3	13	3.43
Left middle frontal gyrus (BA 8)	−27	36	46	3.42
Hippocampus				
Left hippocampus	−33	−44	6	3.6
Insula				
Insula (BA 13)	27	−32	16	3.2
Cingulate				
Right anterior cingulate	0	37	−1	3.48
Right posterior cingulate (BA 23)	3	−46	23	3.18
Left anterior cingulate (BA 32 and 33)	−6	9	25	3.37
Left cingulate gyrus (BA 24)	−9	6	28	3.48
Thalamus				
Right thalamus	9	−27	2	3.77
Right cerebellum				
Right culmen	6	−28	−10	3.48
Basal nuclei				
Left caudate	−9	8	14	3.32
Brainstem				
Left red nucleus	0	−16	−3	3.7
Right substantia nigra	12	−25	−5	3.33

*$P < 0.05$ FWE cluster-wise corrected.
The coordinates are given within the framework standardized stereotaxic brain area atlas of Talairach and Tournoux. All areas were significant at $P < 0.001$, uncorrected.

pathological gambling behave differently in distinct delay discounting tasks using different types of rewards (Voon *et al.*, 2011*a*). This underlines the great interest of our study that associates specific stimuli to a specific ICD. One possible reason explaining why there is enhanced delay discounting in pathological gamblers for monetary rewards but reduced delay discounting for erotic rewards in PD+HS is the use of a specific reward for a particular ICD. While small amounts of money now may be seen as a better option than larger amounts later to pathological gamblers because they need fast cash to gamble immediately, PD+HS patients may be prepared to wait a few seconds to experience erotic images for longer. Consistent with this interpretation, patients with Parkinson's disease with binge-eating also do not show enhanced delay discounting, whereas pathological gamblers or compulsive shoppers with Parkinson's disease do (Voon *et al.*, 2011*b*). This indicates that both behaviour and pathophysiology may differ depending on the type of ICD, possibly as different neurobiological substrates correspond to different reward types (Sescousse *et al.*, 2013). Although several cognitive dysfunctions in ICD are detected when formal evaluations are carried out, such as set-shifting or abstraction abilities (Santangello *et al.*, 2017), we suggest that under ICD-relevant stimuli, PD+HS patients improve performance and may bypass impulsive-related or frontal-type deficits and are prepared to wait a few seconds to see erotic images for longer. Therefore, our results reinforce the interest of carefully dissociating the different forms of ICD and to assess each type of ICD (such as hypersexuality here) using dedicated rewards.

Neural signature of delayed discounting in hypersexual Parkinson's disease

We observed altered medial prefrontal cortex (mPFC) functioning in patients with hypersexuality while evaluating the option to wait to view erotic images for longer. Indeed, this brain region showed a negative correlation with subjective value of the delayed reward in PD+HS (Fig. 2A, top right). When investigating the respective contribution of the effects of delay and rating of the cues (subjective value being approximately the ratio of rating divided by the delay cost), this negative correlation with subjective value observed in

Table 3 Brain regions correlated with subjective value of the cost reward in the interaction between medication condition (ON and OFF dopaminergic medication) and group (PD+HS and PD − HS), at the decision phase

Anatomical structure (Brodmann area)	x	y	z	T-value
Frontal				
Right medial frontal gyrus (BA 6 and 9)	9	44	26	4.63
Right paracentral lobule (BA 6)*	12	−22	46	4.43
Right postcentral gyrus (BA 4)	15	−36	58	3.83
Right superior frontal gyrus (BA 6 and 8)	27	31	52	3.74
Right inferior frontal gyrus (BA 44, 45, 46 and 47)*	36	22	−10	4.72
Right precentral gyrus (BA 4, 6 and 44)*	53	−4	48	4.38
Left paracentral lobule (BA 31)	0	−16	46	4.25
Left sub gyrus (BA 6)	−18	2	53	3.18
Left superior frontal gyrus (BA 8 and 10)	−24	34	49	3.61
Left middle frontal gyrus (BA 6, 8, 9, 46 and 47)	−30	−10	43	3.86
Left precentral gyrus (BA 9)	−42	18	36	3.51
Left inferior frontal gyrus (BA 9, 45 and 46)	−50	29	16	4.11
Temporal				
Right superior temporal gyrus (BA 22, 39 and 41)	48	−4	−7	4.11
Right middle temporal gyrus (BA 39)	56	−64	21	3.20
Left angular gyrus (BA 39)	−45	−72	29	3.49
Left superior temporal gyrus (BA 38)*	−50	−4	−9	4.54
Left middle temporal gyrus (BA 21 and 39)	−59	−10	−9	3.95
Left superior temporal gyrus (BA 22)	−59	−47	17	3.50
Parietal				
Right precuneus (BA 7)	15	−60	48	3.73
Right inferior parietal lobule (BA 40)	39	−28	41	3.54
Right postcentral gyrus (BA 3 and 43)	48	−15	18	3.82
Left precuneus (BA 7)	−21	−54	48	4.07
Left superior parietal lobule (BA 7)	−27	−63	43	3.57
Left postcentral gyrus (BA 2)	−45	−28	36	3.41
Left angular gyrus (BA 39)	−45	−69	38	3.18
Left supramarginal gyrus (BA 40)	−59	−43	31	3.51
Left inferior parietal lobule (BA 40)	−59	−29	27	3.47
Insula				
Right insula (BA 13)*	27	−29	19	4.49
Left insula (BA 13)*	−33	22	3	4.15
Cingulate				
Right cingulate gyrus (BA 31)	12	−37	33	3.18
Left anterior cingulate	−9	40	2	4.72
Thalamus				
Right thalamus	9	−27	2	3.97
Left thalamus	−9	−21	−1	3.96
Hippocampus				
Right parahippocampal gyrus (BA 28)	24	−28	−8	3.17
Left parahippocampal gyrus (BA 27 and 30)	−24	−30	−8	3.54
Basal nuclei				
Right lateral globus pallidus	15	−4	7	3.47
Right putamen	33	−18	2	3.51
Right claustrum	36	5	−2	4.45
Left putamen	−27	5	−2	4.01
Midbrain				
Left red nucleus*	−3	−16	−6	4.52

*$P < 0.05$ FWE cluster-wise corrected.
The coordinates are given within the framework standardized stereotaxic brain area atlas of Talairach and Tournoux. All areas were significant at $P < 0.001$ uncorrected.

the mPFC in PD+HS patients was mainly guided by a positive correlation with delay duration. This may reflect that in PD+HS patients, the vmPFC does not code increasing delay as a cost but rather as a means to obtain erotic rewards for longer. In contrast to PD+HS patients, the anterior mPFC activation was positively correlated with subjective value of the delayed reward in PD-ICD and controls. Furthermore, in both controls and PD − HS patients,

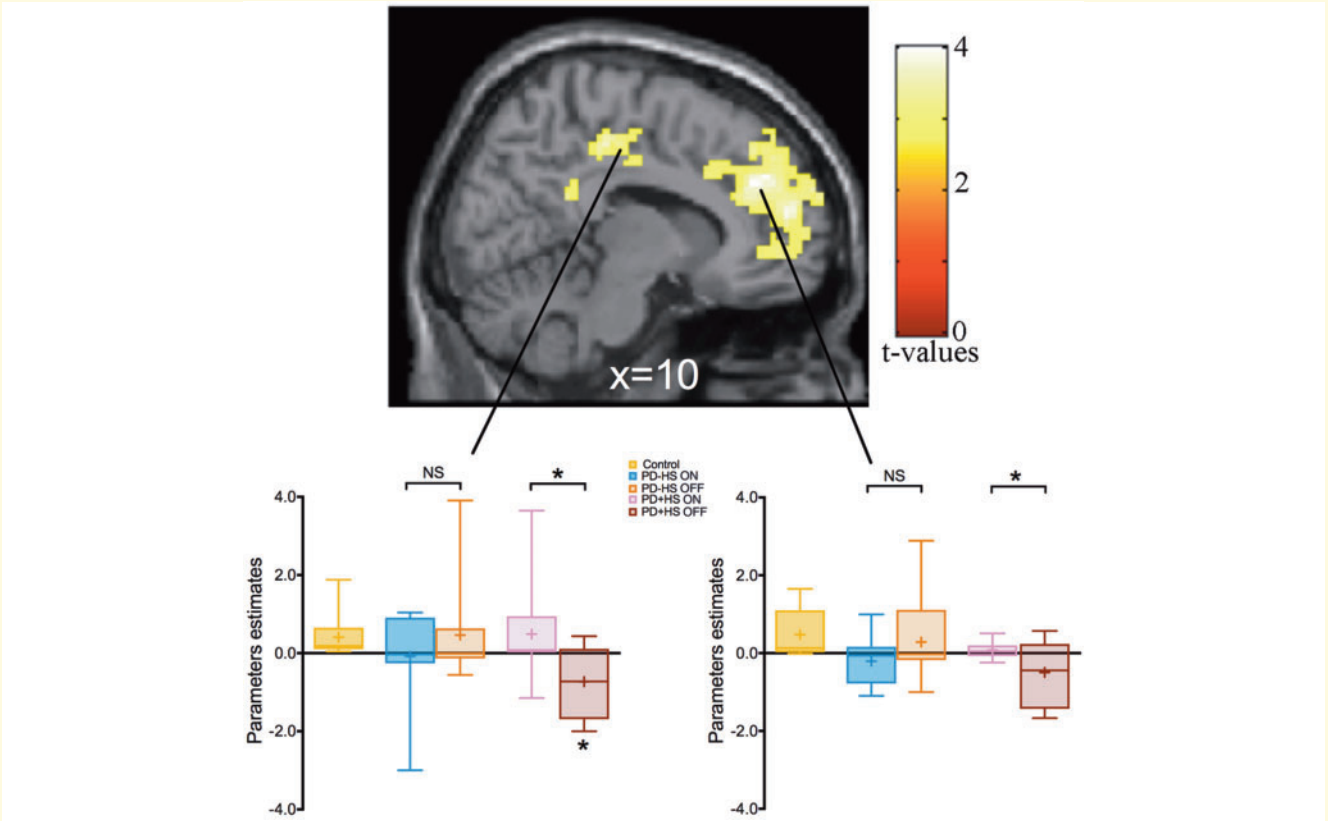

Figure 3 Interaction between medication (ON versus OFF) and group (PD − HS versus PD+HS) at the time of the valuation of the option leading to the delayed reward. Difference in correlation between the subjective values of the delayed erotic rewards and the BOLD signal were observed over the mPFC and the posterior cingulate ($P < 0.001$, uncorrected, SVC FWE corrected). Only the PD+HS subjects ON medication showed a significant increased correlated activity with subjective value in the prefrontal ($P < 0.03$) and posterior cingulate ($P < 0.01$) cortices compared to OFF medication. Controls are included in the parameters estimates for viewing purposes. *$P < 0.05$. Results are shown as box-and-whisker plots with each box representing the 2.5–97.5 percentile. The line within the box indicates the median. The plus symbol within the box represents the mean.

activity in this region correlated negatively with longer delays to get the reward, reflecting that delay was effectively valued as a cost in this region. In addition, a positive correlation was observed between vmPFC activity and rating of the fuzzy cues in all groups, consistent with the role of this area in coding the incentive value of such cues, as demonstrated in young controls (Prevost *et al.*, 2010) and PD+HS patients (Politis *et al.*, 2013). Altogether, these findings may point to a neurobiological marker of hypersexual patients with Parkinson's disease, in which mPFC value enduring the delay not as a cost but as a means to view the erotic reward for longer.

Similar to the vmPFC response pattern, the ventral striatum activity correlated negatively with subjective value in PD+HS patients, but positively in PD − HS patients and controls. When inspecting the respective contribution of the rating of the cue and of the delay to get the reward, ventral striatal activity decreased as a function of the rating of the cues in PD+HS, contrary to what was observed in controls and PD − HS patients who showed increasing activity with higher ratings (Fig. 2B, bottom). This indicates a ventral striatal dysfunction in the evaluation of incentive value of the fuzzy cue in PD+HS, despite increased willingness to wait to view the erotic reward for longer. This finding is of great interest with respect to the role of the ventral striatum in motivation since it is known to normally correlate positively with subjective value in healthy subjects (Kable and Glimcher, 2007; Prevost *et al.*, 2010; Tricomi and Lempert, 2015). Increased risk-taking and default of risk evaluation in patients with Parkinson's disease with ICD (gambling or compulsive shopping) has been associated with decreased ventral striatum activity (Voon *et al.*, 2011*a*). Taken together, the present results suggest that PD+HS patients exhibit changes of ventral striatum activity that may reflect blunted sensitivity to reward predicting cues, known as a reward deficiency syndrome (Comings and Blum, 2000; Volkow *et al.*, 2002). This fits well with functional connectivity and anatomical studies showing a disconnection between ventral striatum and a large network including orbitofrontal cortices (Cilia *et al.*, 2011; Petersen *et al.*, 2018) as well as reduced accumbens nucleus volume (Biundo *et al.*, 2015) in patients with Parkinson's disease with ICDs.

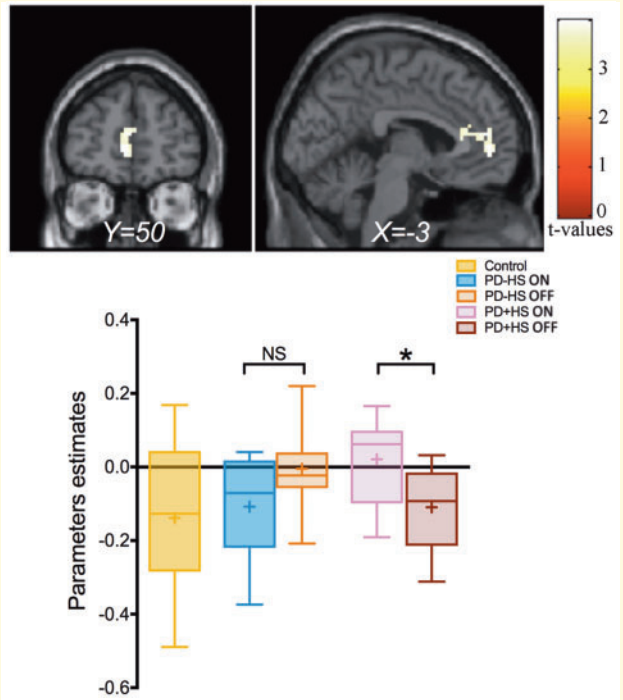

Figure 4 Activity in the prefrontal cortex is modulated by dopaminergic treatment during the outcome phase. A mixed-effect ANOVA analysis including the two groups of patients (PD – HS and PD+HS) and their medication state (ON and OFF dopaminergic medication) showed a difference at the outcome phase in the correlation between the activity of the mPFC and the duration of the delay to view the erotic reward ($P < 0.001$, uncorrected). Region of interest showed a positive correlation with the duration of the delay to view the erotic reward and the activity in the mPFC and a negative correlation while OFF medication ($P = 0.01$) in medicated PD+HS patients only. Controls are included in the parameters estimates for viewing purposes. *$P < 0.05$. Results are shown as box-and-whisker plots with each box representing the 2.5–97.5 percentile. The line within the box indicates the median. The plus symbol within the box represents the mean.

Table 4 Brain regions correlated with the level of the expected reward in the interaction between medication condition and group at the outcome phase

Anatomical structure (Brodmann area)	x	y	z	T-value
Frontal				
Right medial frontal gyrus (BA 10)*	3	55	17	3.51
Left superior frontal gyrus (BA 9)	−15	56	29	3.42
Parietal				
Left angular gyrus (BA 39)	−45	−61	32	3.71
Cingulate				
Right cingulate gyrus (BA 32)	3	29	24	3.20
Right anterior cingulate (BA 24)	9	31	2	3.38
Left anterior cingulate (BA 24 and 32)*	−6	48	−2	3.53
Basal nuclei				
Right caudate	9	9	17	3.31
Left caudate	−6	8	3	3.35

*$P < 0.05$ FWE cluster-wise corrected.
The coordinates are given within the framework standardized stereotaxic brain area atlas of Talairach and Tournoux. All areas were significant at $P < 0.001$, uncorrected.

Impact of dopaminergic medication

A negative correlation between subjective value of the delayed reward and medial prefrontal and posterior cingulate cortices activity was observed in PD+HS patients while OFF dopaminergic medication (Fig. 3). This correlation became positive under medication in PD+HS patients. In contrast, PD – HS patients did not show a reverse pattern of correlation with subjective value when ON versus OFF L-DOPA. Previous studies have linked activation of the mPFC to anticipation of rewards and explicit ratings of anticipated pleasure (Kringelbach, 2005; Sescousse *et al.*, 2015) and engagement of the posterior cingulate cortex to cue specificity in reward desire (Garavan *et al.*, 2000). The mPFC has also been associated with subjective valuation of delayed primary/secondary rewards and cognitive control mechanisms during adaptive decisions (Kable and Glimcher, 2007; Isoda and Hikosaka, 2008; Prevost *et al.*, 2010; Cho *et al.*, 2013). However, we cannot rule out the possibility of ICD being a consequence of reduced prefrontal top-down inhibitory control deficits (van Eimeren *et al.*, 2010) in controlling enhanced reward desire received from ventral striatum (for review see Napier *et al.*, 2015).

The particular impact of dopaminergic medication in PD+HS patients may relate to the incentive salience hypothesis, which combines learned conditioned-unconditioned stimuli associations with current relevant physiological states (Robinson and Berridge, 1993, 2001; Berridge, 2007; Zhang *et al.*, 2009). According to this hypothesis, modulation of incentive salience adaptively guides motivated behaviour to appropriate rewards. Yet, when the mesolimbic circuitry, including the mPFC and ventral striatum go awry, such as in behavioural addiction, excessive 'wanting' and compulsive pursuit of rewards may result, triggered by cues previously learned to be associated with rewards (Grant and Kim, 2001; Everitt and Wolf, 2002; Berridge and Robinson, 2003; Fadardi and Cox, 2009; Brevers *et al.*, 2011*a*). In our sample, while medicated, PD+HS patients showed significantly lower discounting rates than PD – HS patients, indicative of increased wanting of the erotic rewards. Consequently, while taking medication, PD+HS patients accepted to wait for longer to see the erotic images. Hence, dysfunctional bottom-up limbic (with probable top-down dysfunction) inputs may boost the excessive wanting seen in PD+HS. Overall, our study adds evidence to the incentive salience hypothesis role in ICD.

Animal studies have shown that there is a synergy between elevated dopamine levels and phasic encounters with the Pavlovian cue (Zhang *et al.*, 2009; Berridge, 2012) and sensitization by dopaminergic drugs can lead to exaggerated pursuit of sexual rewards (Fiorino and Phillips, 1999;

Nocjar and Panksepp, 2002; Afonso *et al.*, 2009; Pfaus, 2010; Frohmader *et al.*, 2011; Stolzenberg and Numan, 2011). Consistent with these findings, we observed that mPFC activity was potentiated by dopaminergic medication in PD+HS patients at the time of the decision (Fig. 3). That is, patients with PD+HS while medicated, who were willing to wait to view erotic rewards for longer, showed a significant difference in the correlation with subjective value of the delayed reward in the mPFC and posterior cingulate cortices (as compared to OFF medication). This interaction between medication and presence/absence of hypersexuality observed in the mPFC and posterior cingulate cortices reflects differential valuation of the delayed reward in PD+HS patients according to medication condition (Fig. 3). Similarly, consumption of the psychostimulant methamphetamine, which leads to increased dopamine release, is often associated with heightened sexual desire, arousal and pleasure and these factors have been identified as primary motivation for drug use (Semple *et al.*, 2002; Schilder *et al.*, 2005; Green and Halkitis, 2006). Methamphetamine abuse is also commonly associated with loss of inhibitory control of sex behaviour or sexually compulsive behaviour (Halkitis *et al.*, 2001; Rawson *et al.*, 2002; Green and Halkitis, 2006).

Our findings support the hypothesis that PD+HS patients show heightened mesocorticolimbic response (especially in the mPFC and posterior cingulate cortices) while ON L-DOPA therapy, but also blunted reward system reactivity when OFF medication. Consistent with these findings, in the only published study to date on PD+HS, dopaminergic administration increased activity in a brain network including the mPFC and posterior cingulate cortex during passive viewing of sexual stimuli (Politis *et al.*, 2013). This increased activity correlated with higher sexual desire under dopaminergic medication. Interestingly, increased ventral striatum activity triggered by dopaminergic drugs as well as increased mesolimbic dopamine release have also been correlated with ICD severity (Joutsa *et al.*, 2012; Claassen *et al.*, 2017). Furthermore, previous neuroimaging studies with different types of ICD have reported increased activity in the mPFC in patients with Parkinson's disease with ICD under dopamine agonists using arterial-spin labelling MRI measures of cerebral blood flow at rest (Claassen *et al.*, 2017). Studies focusing on risk anticipation have also shown that dopamine agonists increase risk-taking in patients with Parkinson's disease with ICDs that is accompanied by lower ventral striatal, orbitofrontal and anterior cingulate activity (Voon *et al.*, 2011*a*).

Brain system engaged at the time of the rewarded outcome

At the time of the rewarded outcome, activity in the mPFC was positively correlated with the experienced delay to obtain this reward in the PD+HS group ON medication. Meanwhile, an opposite pattern was found OFF medication. This indicates that while PD+HS patients view the erotic image for a longer period, medication boosts the relationship between the duration of the waiting period and mPFC activity. It has been suggested that dopamine drugs may release inhibition in a local mPFC circuit that may contribute to excessive seeking of sexual behaviour (Politis *et al.*, 2013). In a previous functional MRI study, while ON medication, PD+HS patients passively viewing erotic images showed increased activity over a network including the anterior mPFC (Politis *et al.*, 2013). These results parallel animal studies reporting exaggerated sexual behaviour with increased sexual searching as a consequence of dopaminergic drug administration (Fiorino and Phillips, 1999; Afonso *et al.*, 2009).

Our findings support the hypothesis that dopaminergic medication increased mPFC sensitivity to erotic rewards both at the time of choice and outcome, which may contribute to hypersexuality. The fact that drug-induced hypersexuality in Parkinson's disease only develops in the context of repeated medication use and that it does not occur acutely, but progressively in *de novo* patients both suggest a causal role of dopaminergic medication on hypersexuality (Giladi *et al.*, 2007; Smith *et al.*, 2016).

The current study needs further replication with larger cohorts. Our sample was limited to a precise clinical characteristic with the obvious difficulties of recruitment. Moreover, being a medication-related problem, some patients are under frequent modification of medication regimes that excludes them from research programmes. Hence, the current sample is small but with highly defined clinical and neurophysiological features (several clinical neuropsychological and neurological measures, behavioural and neuroimaging data) that makes a homogeneous, unique and highly valuable sample.

The implication of our results is to characterize the brain networks that turn aberrant in ICD to later guide potential interventions over specific targets circuits or brain regions (such as vmPFC). The use of brain stimulation protocols to revert cortical and subcortical activity may turn key in stopping excessive behaviour, a trend already showing positive results in addiction (Diana *et al.*, 2017). Hence, if delimiting with further tasks and ICD cohorts is completed, specific brain stimulation treatments could arise as plausible therapeutic tools.

Conclusion

The present study, focusing on hypersexuality in Parkinson's disease using dedicated erotic stimuli, reveals large commonalities with other ICDs in terms of dysfunctional brain system. This relates to exaggerated activity in response to appetitive stimuli in the ventral striatum, anterior mPFC and posterior cingulate cortex (Schott *et al.*, 2008; O'Sullivan *et al.*, 2011). However, such neural activity has often been associated with artificial or experimental scenarios where patients were not actively deciding, hence

with little behavioural participation. Rather, the use of stimuli that specifically corresponds to one ICD subtype and require active participation of patients, seems the way forward to guarantee maximal closeness to the current problematic.

Acknowledgements

We thank Safa Louati and Pierre Wydoodt for help analysing the demographic data and adapting the task to patients with Parkinson's disease. We thank the CERMEP staff for help during scanning and patients for their participation.

Funding

This research was funded by research grants from the 'France Parkinson' foundation ('Grand appel d'offre'), a PhD fellowship from the ADR CIBLE (2009), National Research Agency (ANR) (grant number ANR-11-IDEX-0007) to J.C.D. This work was performed within the framework of the LABEX ANR-11-LABEX-0042 of Université de Lyon, within the program 'Investissements d'Avenir'. This work was also supported by grants from the Agence Nationale pour la Recherche (ANR 'Brain Choice' n°14-CE13-0006) to J.C.D.

Competing interests

The authors declare no competing financial interests. S.T. received fees from Teva, Medtronic, Novartis, UCB, Aguettant and grants from France Parkinson, Fondation pour la Recherche Médicale outside the present work. P.K. reports grants and personal fees from Medtronic, Boston Scientific, UCB, grants from St Jude Medical France, Edmond J and Lily Safra Foundation, Movement Disorder Society, French Ministry of Health (PHRC), INSERM, France Parkinson, Swiss National Science Foundation, ROGER DE SPOELBERCH Foundation, Centre National Recherche Scientifique, Orkyn, and Homeperf, outside the submitted work.

Supplementary material

Supplementary material is available at *Brain* online.

References

Afonso VM, Mueller D, Stewart J, Pfaus JG. Amphetamine pretreatment facilitates appetitive sexual behaviors in the female rat. Psychopharmacology 2009; 205: 35–43.

Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology 2007; 191: 391–431.

Berridge KC. From prediction error to incentive salience: mesolimbic computation of reward motivation. Eur J Neurosci 2012; 35: 1124–43.

Berridge KC, Robinson TE. Parsing reward. Trends Neurosci 2003; 26: 507–13.

Berridge K, Robinson T. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 1998; 28: 309–69.

Biundo R, Weis L, Facchini S, Formento-Dojot P, Vallelunga A, Pilleri M, et al. Patterns of cortical thickness associated with impulse control disorders in Parkinson's disease. Mov Disord 2015; 30: 688–95.

Brevers D, Cleeremans A, Tibboel H, Bechara A, Kornreich C, Verbanck P, et al. Reduced attentional blink for gambling-related stimuli in problem gamblers. J Behav Ther Exp Psychiatry 2011a; 42: 265–9.

Brevers D, Cleeremans A, Bechara A, Laloyaux C, Kornreich C, Verbanck P, et al. Time course of attentional bias for gambling information in problem gambling. Psychol Addict Behav 2011b; 25: 675–82.

Carpenter B, Gelman A, Hoffman MD, Lee D, Goodrich B, Betancourt M, et al. Stan: a probabilistic programming language. J Stat Softw 2017; 76: 32.

Carriere N, Lopes R, Defebvre L, Delmaire C, Dujardin K. Impaired corticostriatal connectivity in impulse control disorders in Parkinson disease. Neurology 2015; 84: 2116–23.

Cerasa A, Salsone M, Nigro S, Chiriaco C, Donzuso G, Bosco D, et al. Cortical volume and folding abnormalities in Parkinson's disease patients with pathological gambling. Parkinsonism Relat Disord 2014; 20: 1209–14.

Cho SS, Pellecchia G, Aminian K, Ray N, Segura B, Obeso I, et al. Morphometric correlation of impulsivity in medial prefrontal cortex. Brain Topogr 2013; 26: 479–87.

Cilia R, Cho SS, van Eimeren T, Marotta G, Siri C, Ko JH, et al. Pathological gambling in patients with Parkinson's disease is associated with fronto-striatal disconnection: a path modeling analysis. Mov Disord 2011; 26: 225–33.

Cilia R, Ko JH, Cho SS, van Eimeren T, Marotta G, Pellecchia G, et al. Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. Neurobiol Dis 2010; 39: 98–104.

Claassen DO, Stark AJ, Spears CA, Petersen KJ, van Wouwe NC, Kessler RM, et al. Mesocorticolimbic hemodynamic response in Parkinson's disease patients with compulsive behaviors. Mov Disord 2017; 32: 1574–83.

Claassen DO, van den Wildenberg WP, Harrison MB, van Wouwe NC, Kanoff K, Neimat JS, et al. Proficient motor impulse control in Parkinson disease patients with impulsive and compulsive behaviors. Pharmacol Biochem Behav 2015; 129: 19–25.

Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. Prog Brain Res 2000; 126: 325–41.

Daw ND. Trial-by-trial data analysis using computational models. In Decision making, affect, and learning: attention and performance XXIII. Vol. 23. Oxford Scholarship Online; 2011. 3–38. doi: 10.1093/acprof:oso/9780199600434.001.0001.

Diana M, Raij T, Melis M, Nummenmaa A, Leggio L, Bonci A. Rehabilitating the addicted brain with transcranial magnetic stimulation. Nat Rev Neurosci 2017; 18: 685–693.

Djamshidian A, O'Sullivan SS, Wittmann BC, Lees AJ, Averbeck BB. Novelty seeking behaviour in Parkinson's disease. Neuropsychologia 2011; 49: 2483–8.

Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. Neurology 2000; 55: 1621–6.

Everitt BJ, Wolf ME. Psychomotor stimulant addiction: a neural systems perspective. J Neurosci 2002; 22: 3312–20.

Fadardi JS, Cox WM. Reversing the sequence: reducing alcohol consumption by overcoming alcohol attentional bias. Drug Alcohol Depend 2009; 101: 137–45.

Fiorino DF, Phillips AG. Facilitation of sexual behavior and enhanced dopamine efflux in the nucleus accumbens of male rats after D-amphetamine-induced behavioral sensitization. J Neurosci 1999; 19: 456–63.
Freeman TP, Morgan CJA, Brandner B, Almahdi B, Curran HV. Dopaminergic involvement in effort-based but not impulsive reward processing in smokers. Drug Alcohol Depend 2013; 130: 109–14.
Frohmader KS, Lehman MN, Laviolette SR, Coolen LM. Concurrent exposure to methamphetamine and sexual behavior enhances subsequent drug reward and causes compulsive sexual behavior in male rats. J Neurosci 2011; 31: 16473–82.
Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, et al. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry 2000; 157: 1789–98.
Giladi N, Boroojerdi B, Korczyn AD, Burn DJ, Clarke CE, Schapira AH, et al. Rotigotine transdermal patch in early Parkinson's disease: a randomized, double-blind, controlled study versus placebo and ropinirole. Mov Disord 2007; 22: 2398–404.
Grant JE, Kim SW. Demographic and clinical features of 131 adult pathological gamblers. J Clin Psychiatry 2001; 62: 957–62.
Green AI, Halkitis PN. Crystal methamphetamine and sexual sociality in an urban gay subculture: an elective affinity. Cult Health Sex 2006; 8: 317–33.
Halkitis PN, Parsons JT, Stirratt MJ. A double epidemic: crystal methamphetamine drug use in relation to HIV transmission among gay men. J Homosex 2001; 41: 17–35.
Housden CR, O'Sullivan SS, Joyce EM, Lees AJ, Roiser JP. Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors. Neuropsychopharmacology 2010; 35: 2155–64.
Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55: 181–4.
Isoda M, Hikosaka O. A neural correlate of motivational conflict in the superior colliculus of the macaque. J Neurophysiol 2008; 100: 1332–42.
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: 1079–83.
Kable JW, Glimcher PW. The neural correlates of subjective value during intertemporal choice. Nat Neurosci 2007; 10: 1625–33.
Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci 2005; 6: 691–702.
Leroi I, Barraclough M, McKie S, Hinvest N, Evans J, Elliott R, et al. Dopaminergic influences on executive function and impulsive behaviour in impulse control disorders in Parkinson's disease. J Neuropsychol 2013; 7: 306–25.
Lim S-Y, Evans AH, Miyasaki JM. Impulse control and related disorders in Parkinson's disease. Ann N Y Acad Sci 2008; 1142: 85–107.
Mazur JE. An adjusting procedure for studying delayed reinforcement. In Commons ML, Mazur JE, Nevin JA, Rachlin H, editors. Quantitative analyses of behavior. The effect of delay and of intervening events on reinforcement value. Vol. 5. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.; 1987. p. 55–73.
Molina JA, Sainz-Artiga MJ, Fraile A, Jimenez-Jimenez FJ, Villanueva C, Orti-Pareja M, et al. Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? Mov Disord 2000; 15: 869–72.
Napier TC, Corvol J-C, Grace AA, Roitman JD, Rowe J, Voon V,et al. Linking neuroscience with modern concepts of impulse control disorders in Parkinson's disease. Mov Disord 2015; 30: 141–9.
Nocjar C, Panksepp J. Chronic intermittent amphetamine pretreatment enhances future appetitive behavior for drug- and natural-reward: interaction with environmental variables. Behav Brain Res 2002; 128: 189–203.
O'Sullivan SS, Wu K, Politis M, Lawrence AD, Evans AH, Bose SK, et al. Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. Brain 2011; 134 (Pt 4): 969–78.
Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol 1995; 51: 768–74.
Petersen K, Van Wouwe N, Stark A, Lin YC, Kang H, Trujillo-Diaz P, et al. Ventral striatal network connectivity reflects reward learning and behavior in patients with Parkinson's disease. Hum Brain Mapp 2018; 39: 509–21.
Pfaus JG. Dopamine: helping males copulate for at least 200 million years: theoretical comment on Kleitz-Nelson et al. (2010). Behav Neurosci 2010; 124: 877–80; discussion 81–3.
Piray P, Zeighami Y, Bahrami F, Eissa AM, Hewedi DH, Moustafa AA. Impulse control disorders in Parkinson's disease are associated with dysfunction in stimulus valuation but not action valuation. J Neurosci 2014; 34: 7814–24.
Politis M, Loane C, Wu K, O'Sullivan SS, Woodhead Z, Kiferle L, et al. Neural response to visual sexual cues in dopamine treatment-linked hypersexuality in Parkinson's disease. Brain 2013; 136 (Pt 2): 400–11.
Prevost C, Pessiglione M, Metereau E, Clery-Melin ML, Dreher JC. Separate valuation subsystems for delay and effort decision costs. J Neurosci 2010; 30: 14080–90.
Rao H, Mamikonyan E, Detre JA, Siderowf AD, Stern MB, Potenza MN, et al. Decreased ventral striatal activity with impulse control disorders in Parkinson's disease. Mov Disord 2010; 25: 1660–9.
Rawson RA, Gonzales R, Brethen P. Treatment of methamphetamine use disorders: an update. J Subst Abuse Treat 2002; 23: 145–50.
Ray NJ, Miyasaki JM, Zurowski M, Ko JH, Cho SS, Pellecchia G, et al. Extrastriatal dopaminergic abnormalities of DA homeostasis in Parkinson's patients with medication-induced pathological gambling: a [11C] FLB–457 and PET study. Neurobiol Dis 2012; 48: 519–25.
Rieu I, Martinez-Martin P, Pereira B, De Chazeron I, Verhagen Metman L, Jahanshahi M, et al. International validation of a behavioral scale in Parkinson's disease without dementia. Mov Disord 2015; 30: 705–13.
Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 1993; 18: 247–91.
Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 2000; 95 (Suppl 2): S91–117.
Robinson TE, Berridge KC. Incentive-sensitization and addiction. Addiction 2001; 96: 103–14.
Schilder AJ, Lampinen TM, Miller ML, Hogg RS. Crystal methamphetamine and ecstasy differ in relation to unsafe sex among young gay men. Can J Public Health 2005; 96: 340–3.
Santangelo G, Raimo S, Barone P. The relationship between impulse control disorders and cognitive dysfunctions in Parkinson's Disease: a meta-analysis. Neurosci Biobehav Rev 2017; 77: 129–47.
Schott BH, Minuzzi L, Krebs RM, Elmenhorst D, Lang M, Winz OH, et al. Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. J Neurosci 2008; 28: 14311–19.
Semple SJ, Patterson TL, Grant I. Motivations associated with methamphetamine use among HIV+ men who have sex with men. J Subst Abuse Treat 2002; 22: 149–56.
Sescousse G, Barbalat G, Domenech P, Dreher JC. Imbalance in the sensitivity to different types of rewards in pathological gambling. Brain 2013; 136 (Pt 8): 2527–38.
Sescousse G, Li Y, Dreher JC. A common currency for the computation of motivational values in the human striatum. Soc Cogn Affect Neurosci 2015; 10: 467–73.
Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic

psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59 (Suppl 20): 22–33; quiz 4–57.
Smith KM, Xie SX, Weintraub D. Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. J Neurol Neurosurg Psychiatry 2016; 87: 864–70.
Steeves TD, Miyasaki J, Zurowski M, Lang AE, Pellecchia G, Van Eimeren T, et al. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. Brain 2009; 132 (Pt 5): 1376–85.
Stolzenberg DS, Numan M. Hypothalamic interaction with the mesolimbic DA system in the control of the maternal and sexual behaviors in rats. Neurosci Biobehav Rev 2011; 35: 826–47.
Tessitore A, De Micco R, Giordano A, di Nardo F, Caiazzo G, Siciliano M, et al. Intrinsic brain connectivity predicts impulse control disorders in patients with Parkinson's disease. Mov Disord 2017; 32: 1710–19.
Tricomi E, Lempert KM. Value and probability coding in a feedback-based learning task utilizing food rewards. J Neurophysiol 2015; 113: 4–13.
Valli M, Mihaescu A, Strafella AP. Imaging behavioural complications of Parkinson's disease. Brain Imaging Behav 2017, in press. doi: 10.1007/s11682-017-9764-1.
van Eimeren T, Pellecchia G, Cilia R, Ballanger B, Steeves TD, Houle S, et al. Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD. Neurology 2010; 75: 1711–16.
Vitale C, Santangelo G, Trojano L, Verde F, Rocco M, Grossi D, et al. Comparative neuropsychological profile of pathological gambling, hypersexuality, and compulsive eating in Parkinson's disease. Mov Disord 2011; 26: 830–6.
Volkow ND, Fowler JS, Wang GJ. Role of dopamine in drug reinforcement and addiction in humans: results from imaging studies. Behav Pharmacol 2002; 13: 355–66.
Voon V, Gao J, Brezing C, Symmonds M, Ekanayake V, Fernandez H, et al. Dopamine agonists and risk: impulse control disorders in Parkinson's disease. Brain 2011a; 134 (Pt 5): 1438–46.
Voon V, Mole TB, Banca P, Porter L, Morris L, Mitchell S, et al. Neural correlates of sexual cue reactivity in individuals with and without compulsive sexual behaviours. PLoS One 2014; 9: e102419.
Voon V, Napier TC, Frank MJ, Sgambato-Faure V, Grace AA, Rodriguez-Oroz M, et al. Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update. Lancet Neurol 2017; 16: 238–50.
Voon V, Pessiglione M, Brezing C, Gallea C, Fernandez HH, Dolan RJ, et al. Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors. Neuron 2010; 65: 135–42.
Voon V, Reynolds B, Brezing C, Gallea C, Skaljic M, Ekanayake V, et al. Impulsive choice and response in dopamine agonist-related impulse control behaviors. Psychopharmacol. 2010; 207: 645–59.
Voon V, Sohr M, Lang AE, Potenza MN, Siderowf AD, Whetteckey J, et al. Impulse control disorders in Parkinson disease: a multicenter case–control study. Ann Neurol 2011b; 69: 986–96.
Vriend C, Nordbeck AH, Booij J, van der Werf YD, Pattij T, Voorn P, et al. Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease. Mov Disord 2014; 29: 904–11.
Weintraub D, Claassen DO. Impulse control and related disorders in Parkinson's Disease. Int Rev Neurobiol 2017; 133: 679–717.
Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 2010; 67: 589–95.
Zhang J, Berridge KC, Tindell AJ, Smith KS, Aldridge JW. A neural computational model of incentive salience. PLoS Comput Biol 2009; 5: e1000437.
Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–70.