Subjective estimates of uncertainty and volatility during gambling predict impulsivity after subthalamic deep brain stimulation for Parkinson's disease

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1 ABSTRACT

Subthalamic deep brain stimulation (DBS) for Parkinson's disease (PD) may modulate chronometric and instrumental aspects of choice behaviour, including motor inhibition, decisional slowing, and value sensitivity. However, it is unknown whether subthalamic DBS affects more complex aspects of decision-making, such as estimating the uncertainty around the probability of obtaining rewarding outcomes and the tendency of this probability to change over time. In this study, 38 participants with PD played a slot-machine in a virtual casino prior to subthalamic DBS (whilst 'on' medication) and again, 3-months postoperatively (whilst 'on' stimulation). Gambling behaviour during game play reflected self-reported measures of impulsivity, as quantified by the Barratt Impulsiveness Scale. We fit several computational models, including a hierarchical model of decision-making in the presence of uncertainty (the Hierarchical Gaussian Filter, HGF) and a reinforcement learning model (based on the Rescorla-Wagner formalism), to choices during slot machine play. The HGF was superior in accounting for the behaviour of our participants. Estimates of the perceptual model parameters, which encoded a participant's uncertainty regarding the winning probability of the slot machine and its volatility, were significantly associated with impulsivity. Moreover, preoperative parameter estimates enabled significant out-of-sample predictions of the maximum postoperative change in impulsivity during longitudinal follow up. Our findings suggest that impulsivity in PD patients may be underpinned by uncertainty, and implicate a role for the subthalamic nucleus in the modulation of outcome certainty.

2 INTRODUCTION

The subthalamic nucleus (STN) is a subcortical nucleus of central pathophysiological relevance for Parkinson's disease (PD). In PD, STN neurons display abnormal patterns of burst firing[1] and low-frequency synchronisation of local field potentials.[2] By modulating this pathological network activity, subthalamic deep brain stimulation (DBS) for PD improves motor symptoms such as bradykinesia, tremor and rigidity.[3] However, STN-DBS has also been linked to neuropsychiatric symptoms, particularly impulsivity,[4,5] an issue of substantial clinical importance. The STN is a second input station to the basal ganglia, receiving direct cortical projections from the frontal lobe ('hyperdirect' pathway).[6] This route permits basal ganglia inhibitory tone to be directly modulated by cortical regions. Functional and structural brain imaging support the role of this pathway in motor inhibition.[7,8] Following STN-DBS, participants with PD make commission errors (errors in which participants execute an erroneous action) [9] and take longer to cancel an action,[10] suggesting an impairment in action restraint. Errors in the Stroop [11] and random number generation tasks [12] suggest increased sensitivity to cognitive interference and impaired task-switching. When faced with decisional conflict, patients with subthalamic DBS speed up rather than slow down their decision-making.[13,14] These findings suggest a role for the STN in 'braking' cognitive-associative circuits in the basal ganglia. It is not clear, however, whether such chronometric aspects of decision-making are sufficient to explain the complex picture of impulsivity after STN-DBS.[15] For example, subthalamic DBS may modulate contingencies in reinforcement learning,[16,17] suggesting a role for the STN in valuation.

A potential computational mechanism underlying impulsivity is uncertainty. If the longer-term outcomes of actions are not (or do not seem to be) predictable, prospective thinking may be replaced by seeking immediately available outcomes – a policy that would manifest behaviourally as impulsivity.[18] More specifically, subjective uncertainty about environmental dynamics, or the longer-term consequences of actions, has been associated with a tendency to reduce reflection and long-term planning, and favour short-term over long-term outcomes.[19-21] For example, PD participants with impulse control disorders (ICDs) 'jump to conclusions' in an information collection task (the beads task) more quickly than PD participants without ICDs, a finding that relates informational uncertainty to impulsivity.[22] A computational modelling study of behaviour across three tasks commonly used to probe impulsivity (information sampling, temporal discounting and novelty bias) suggested that PD participants with ICDs are more uncertain about the relationship between possible actions and future rewards than patients without ICDs.[23] Based on these findings, we hypothesised that changes in impulsivity after STN-DBS may relate to estimates of uncertainty about future rewards.

A paradigmatic approach to inference and learning under uncertainty uses Bayes' theorem to understand how prior knowledge (represented as a probability distribution known as the *prior*) is combined with new information from the environment (the *likelihood*) in order to update beliefs (the *posterior*). To obtain the posterior, a Bayesian agent inverts a 'generative' model (that describes how noisy sensory data result from environmental states); this corresponds to perception. Inferring environmental states from noisy sensory data allows the agent to plan actions that take into account the uncertainty of the environment.[24] Human behaviour often closely resembles those of Bayesian agents, for example, during low level sensory processing,[25,26] sensorimotor learning,[27,28] and higher-level reasoning,[29] although approximations to ideal Bayesian inference are likely required for most domains of cognition.[30-32]

Critically, a Bayesian perspective can accommodate multiple forms of uncertainty, beyond sensory noise. For example, the agent's environment might change over time. In order to account for this higher-order uncertainty (or volatility), Bayesian agents are able to modulate the rate at which they learn (update their beliefs). This learning rate can be linked to an agent's encoding of volatility.[33-35] For instance, in more volatile environments, estimates of uncertainty (and thus learning rate) should be higher so that more emphasis is given to very recent information; at the same time, predicting the longer-term consequences of actions becomes more difficult. This link between uncertainty and decision-making may be of crucial importance for impulsivity.[23] Furthermore, individual differences in approximate Bayesian inference plausibly contribute to inter-individual variability in behaviour. Such differences can be quantified using models with subject-specific parameters.[34] For example, individual differences could concern the estimation of environmental volatility [36] or the formation of unusually confident or 'precise' beliefs.[37]

Here, we applied a hierarchical Bayesian model (the Hierarchical Gaussian Filter, HGF) to behavioural data from 38 participants with PD who played a virtual casino before and after subthalamic DBS. By allowing participants to vary their bet size, switch between slot machines and place 'double or nothing' bets, we could estimate how participants not only inferred the trial-by-trial probability of winning, but also updated higher-order beliefs about the likelihood of a machine running 'hot' or 'cold', and the fluctuation of machines between these states. These model-based estimates afford us an individual profile of how each participant represented (and responded to) environmental uncertainty. We assessed these findings against standard measures of impulsivity derived from clinical assessment and questionnaires, focusing our attention on self-reported impulsivity as measured by the Barratt Impulsiveness Scale (BIS). Our computational analysis examines how DBS changes the manner in which persons with PD engage in Bayesian belief updating, and whether subject-specific estimates of uncertainty and volatility prior to DBS may predict impulsivity postoperatively.

3 MATERIALS AND METHODS

3.1 Subjects

Prior to the commencement of data collection, the full protocol was approved by the Human Research Ethics Committees of the Royal Brisbane & Women's Hospital, the University of Queensland, the QIMR Berghofer Medical Research Institute and UnitingCare Health. All research was performed in accordance with relevant guidelines and regulations. All participants gave written, informed consent to participate in the study.

Thirty-eight participants with PD undertaking STN-DBS were consecutively recruited at the Asia-Pacific Centre for Neuromodulation in Brisbane, Australia. All participants met the UK Brain Bank criteria for PD [38]. No participants met the Movement Disorder Society criteria for dementia.[39] The PD subtype and the Hoehn and Yahr stage at device implantation was recorded.[40] Patients underwent bilateral implantation of Medtronic 3389 or Boston Vercise electrodes in a single-stage procedure. Stimulation was commenced immediately using microelectrode recording data to identify the optimal contact. Further contact testing took place over the following week as an inpatient, with participants returning to the DBS centre following discharge for further stimulation titration, guided by residual motor symptoms. Further details have previously been reported.[41,42]

3.2 Neuropsychiatric Assessment

Impulsivity amongst participants was assessed with patient and clinician-rated instruments prior to STN-DBS and subsequently 2 weeks, 6 weeks, 13 weeks and 26 weeks postoperatively (see Supplementary Figure 1 for a study flowchart). A range of measures were obtained, to account for the fact that impulsivity is not a unitary construct. These included the Barratt Impulsiveness Scale 11 (BIS) and second-order factors attentional, motor and non-planning;[18] the Questionnaire for Impulsive-Compulsive disorders in PD Rating Scale (QUIP-RS);[43] the delay discounting task;[44] the Excluded letter fluency task (ELF);[45] and the Hayling test.[46] Further information on these instruments is detailed in the Supplementary Information. Additional neuropsychiatric symptoms were captured with the Beck Depression Inventory II (BDI);[47] the Empathy Quotient (EQ);[48] the Geriatric anxiety inventory (GAI);[49] and the Apathy Scale.[50] At each visit, PD motor symptoms were assessed using the UPDRS Part III motor examination.[51] Dopaminergic medication was recorded and converted to a levodopa-equivalent daily dose (LEDD) value.[52]

3.3 Design and Setting

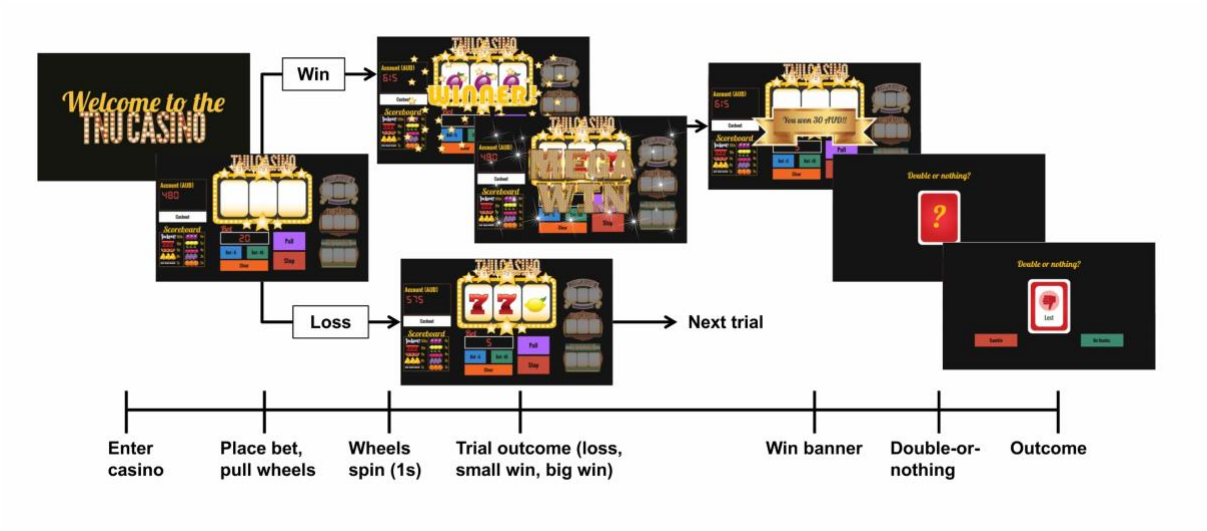
Participants completed the experimental task prior to DBS and at 13-weeks post-DBS. Participants were 'on' medication and stimulation for all assessments. We opted against a counterbalanced 'off' and 'on' DBS assessment at the same visit for several reasons. First, our aim was to provide a naturalistic insight into the subtle behavioural changes that emerge as patients transition from dopaminergic therapies to subthalamic stimulation; changes in levodopa equivalent daily dose were included as co-variates in our analyses. Second, our experience is that many patients would not tolerate the DBS 'off' state without severe discomfort. Thirdly, despite allowing DBS washout, plastic network effects of chronic DBS may persist and contaminate findings in an on-off design.

3.4 Task

We employed a modified version of an established slot machine gambling paradigm validated in healthy controls.[19] Subjects read an instruction screen and played through 5 training trials, after which they entered a 'virtual' casino, starting with 2000 AUD available to gamble and playing 100 trials (Figure 1). The win-loss likelihood of the slot machines was predetermined and changed at regular intervals. On completion of the task, participants received a small monetary reward proportional to their total winnings. The naturalistic gambling task allows for risk-taking and impulsive behaviour to be expressed and offers four actions on each trial, each of which reflect exploration, and thereby, risk-taking.

(i) Bet Increase: increasing the amount wagered on consecutive trials (minimum of 5 cents per bet, no maximum)
(ii) Machine-Switch: switching between slot machines (four machines in total)
(iii) Casino Switch: cashing out and switching 'virtual' casino days
(iv) Double-Up: engaging in a secondary double-or-nothing gamble on certain win trials

As in our previous work,[19] these responses, together with trial-wise outcome information (wins/losses), served as the input for our computational models (for a brief summary, see below). Details on the paradigm and computational modelling can be found in prior work [19] and the Supplementary Material.



Legend to Figure 1

Figure 1 | Slot machine gambling paradigm The task consists of 100 trials. On every trial, subjects are able to place a bet of unlimited magnitude, switch slot machines or 'cash out', exiting the casino and returning again on another 'virtual' day. The overall win probability is 25%, with wins split into big wins and small wins. The two possible types of losses are near-misses, in which the first two wheels are the same and the third is different (i.e. AAB) or a true loss, in which all the wheels are different (i.e. ABC). A more detailed breakdown of trial outcomes can be found in the Supplementary Information. For each loss trial, subjects are taken directly to the beginning of the next trial. On selected win trials, subjects are given 3 seconds to decide whether or not to engage in a 'double-or-nothing' option. If the subject elects to engage in this gamble, a card flips over revealing the result, and subjects are taken to the next trial. If the subject does nothing, or decides not to gamble, he or she is taken to the next trial. The trajectory of win-loss outcomes is fixed, ensuring comparable inference upon perceptual and response parameters across participants.

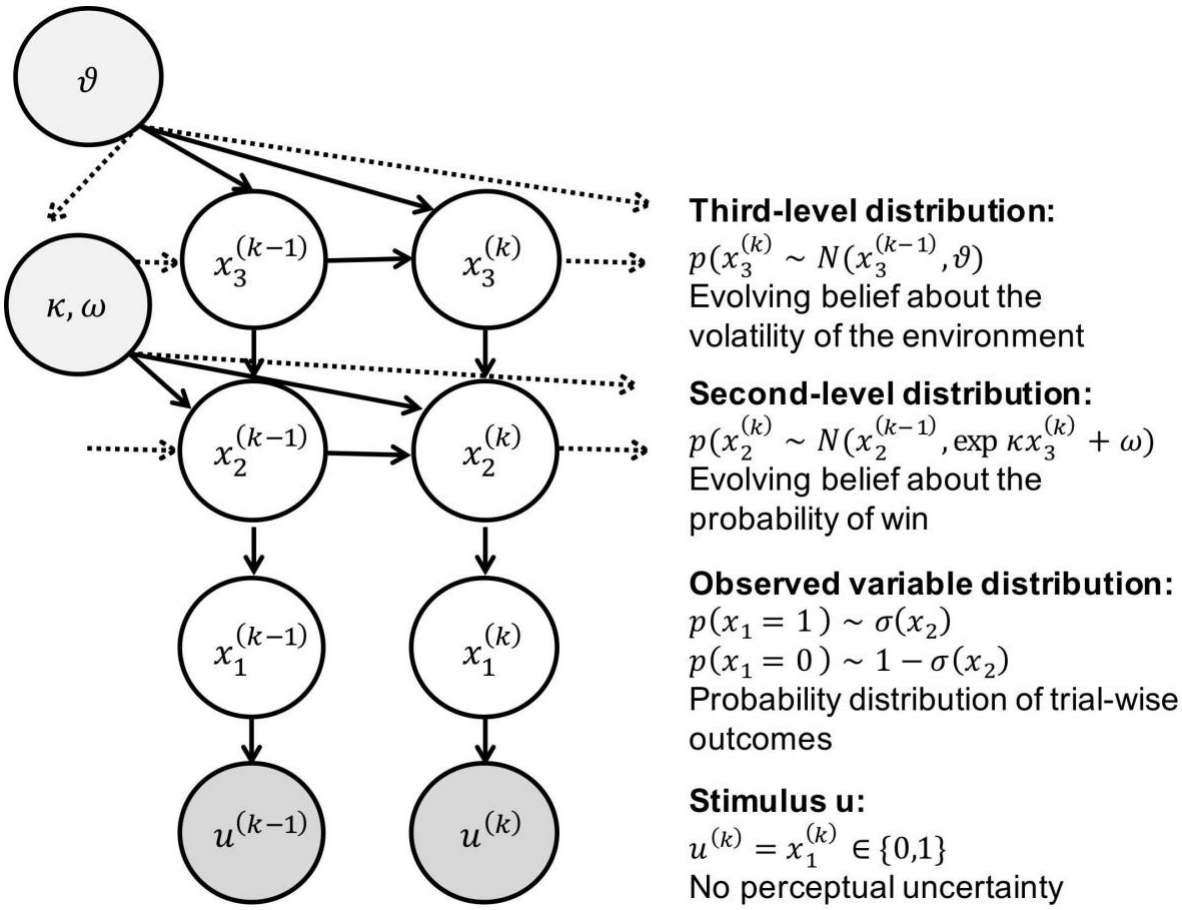
3.5 Computational Modelling

3.5.1 The Hierarchical Gaussian Filter (HGF)

The HGF is a hierarchical Bayesian model [34,35] (Figure 2) where each level of the hierarchy encodes distributions of environmental variables (in ascending complexity) that evolve as Gaussian random walks. The hierarchical levels are coupled such that each state determines how quickly the next lower state evolves, with the lowest hierarchical level representing sensory events. Inversion of this 'perceptual model' produces subject-specific parameter estimates that determine the nature of the coupling between levels of the HGF. Inverting this model under generic (mean-field) approximations results in analytical belief-update equations, in which trial-wise belief updates are proportional to prediction errors (PEs) weighted by uncertainty (or its inverse, precision). The subject-specific parameters shape an individual's approximation to ideal Bayesian inference, specifically how phasic and tonic volatility impacts trial-wise estimates of uncertainty at all levels of the hierarchy. Posterior estimates of HGF parameters can thus be regarded as a compact summary of an individual's uncertainty processing during an experiment. Furthermore, in a 'response model', trial-wise beliefs are probabilistically linked to observed trial-wise decisions. Inverting both perceptual and response models allows for estimating the parameters; this corresponds to Bayesian inference (of an observer) on Bayesian inference (of an agent).[24] An informal description is given below and a formal summary is provided in the Supplementary Material.

3.5.2 The Perceptual Model

The HGF is used to infer how an individual subject learns about hierarchically-coupled environmental quantities under different forms of uncertainty (including volatility). In our case, the lowest level of the HGF, x_1, represents the trial-wise binary outcome (win or loss) in the slot machine. This derives from a sigmoid transformation of x_2 representing probability in logit space (i.e., whether the machine is currently "hot" or "cold"). x_2 evolves as a Gaussian random walk whose step size is a function $f_2(x_3)$ of a third-level variable, x_3, which performs a Gaussian random walk of its own. x_3 represents the slot machine's 'volatility', the speed at which it fluctuates between 'hot' and 'cold' states. The coupling function f_2 between levels, contains subject-specific parameters κ and ω, that underlie an individual's approximation to ideal Bayesian inference. Finally, the parameter ϑ at the highest level denotes how quickly volatility itself is changing (meta-volatility). A detailed derivation of the exact equations can be found in Mathys *et al* (2014).[34]



Legend to Figure 2

Figure 2 | The Hierarchical Gaussian Filter (HGF) $u^{(k)}$ represents binary observations (true wins=1, and losses=0, in the case of the slot machine). Binary inputs are represented on the first level, $x_1^{(k)}$ via a Bernoulli distribution, around the probability of win or loss, $x_2^{(k)}$. In turn, $x_2^{(k)}$ is modelled as a Gaussian random walk, whose step-size is governed by a combination of $x_3^{(k)}$, via coupling parameter κ, and a tonic volatility parameter ω. $x_3^{(k)}$ also evolves as a Gaussian random walk over trials, with step size ϑ (meta-volatility). In this investigation, after observing trial-wise outcomes (win or lose), the gambler updates her belief about the probability of win on a given trial k ($x_2^{(k)}$), as well as how swiftly that slot machine is moving between being 'hot' (high probability of win) or 'cold' $x_3^{(k)}$ (low probability of win). On any trial, the ensuing beliefs then provide a basis for the gambler's response, which may be to increase the bet size, 'double up' after a win, switch to a new slot machine or leave the casino.

3.5.3 The Response Model

The response model maps a subject's beliefs (obtained by inverting the perceptual model under given parameter values) to observed gambling behaviour. Here, we use a sigmoidal response model [34]; if this function is steep, there is a close relationship between current perceptual beliefs and betting behaviour. Conversely, a gentler sigmoidal slope results in a lower-precision belief-behaviour mapping. This response function has a parameter, β, the decision 'temperature', which determines the steepness of the sigmoid and thus the degree of stochasticity in the belief-to-choice mapping. In this paper, we test the following two variants of this response model,

(i) 'Standard' HGF: $\beta = constant$, i.e., the mapping from beliefs to behaviour is fixed across the experiment. This parameter is estimated for each subject.

(ii) 'Uncertainty-driven' HGF: $\beta = 1/\sigma_2^{(k)}$, where $\sigma_2^{(k)}$ is the variance of the inferred probability of win on trial k. That is, the response behaviour dynamically adapts to the precision of the subjects' belief about the hotness or coldness of the machine.

3.5.4 Perceptual Variable

Based on previous work that examined different computational models of our slot machine paradigm,[19] the perceptual variable used here was simple: a binary variable in which wins were represented by 1 and losses by 0.

3.5.5 Response Variable

The response variable is a binary representation of actions associated with risk taking. It is constructed using a logical OR operator on four choices during the slot machine paradigm: bet increases, machine switches, double-ups and casino switches. For each trial, the response variable takes a 1 when any of these four events occur, and 0 otherwise. For details, please see Supplementary Table 1.

3.5.6 Reinforcement Learning

As an alternative model, we used a classical associative learning model, Rescorla-Wagner (RW), often used in reinforcement learning (RL).[53] The RW model updates the probability of a win on trial k by combining the probability on trial k-1 with a PE weighted by a constant learning-rate. Hence, in contrast to the HGF, the RW model does not have a dynamic learning rate over trials, nor can it account for different forms of perceptual uncertainty. Here, we combine the RW learning rule with the same sigmoidal response model described above, with free parameter β, that we estimate on a subject-specific

basis. This results in a model that is (i) structurally not dissimilar but less complex than the HGF and (ii) almost identical to the RL model used in a prior investigation of learning after STN-DBS.[17]

3.5.7 Model Inversion

The HGF and RW models were inverted using population Markov-Chain Monte Carlo (MCMC) sampling.[54] Parameter estimation in the HGF is classically 'fully Bayesian' and requires a selection of priors, which influence parameter estimation to a lesser or greater degree. In order to minimise this influence, we used a novel empirical Bayesian inference scheme for the HGF where a Gaussian group-level distribution of parameters is constructed from samples across the group. This group-level empirical prior is then used to obtain posterior parameter estimates in each subject (Supplementary Figure 2).

3.5.8 Model Comparison

As described above, we considered two competing hypotheses of how subjects might incorporate uncertainty into their choice of actions, i.e., two different belief-to-choice mappings in the response model for the HGF (the 'Standard' and 'Uncertainty-driven' models). These two versions of the HGF were compared with the RW model. As we were primarily interested in the pre-DBS to post-DBS change, we selected the winning model for the pre-DBS measurements. We then evaluated if the parameter estimates of that winning model changed postoperatively. Estimates of the negative free energy (log model evidence) were computed using thermodynamic integration.[54] The negative free energy balances goodness of fit with a complexity penalty. Group-level free energy estimates were compared to select a winning model.

3.6 Data Analysis

3.6.1 General Considerations

All computational modelling and model inversion was performed using MATLAB (Mathworks), employing custom scripts developed from the HGF toolbox version 3 in the open source software TAPAS (http://www.translationalneuromodeling.org/tapas/). Multiple regression analyses were performed using the regstats function in the MATLAB Statistics Toolbox. For all analyses involving multiple comparisons, native p-values are presented, accompanied by Holm-Bonferroni correction at α=0.05. To test the significance of individual regressors in multiple regression models, post hoc t-tests were performed.

Neuropsychiatric assessment data from baseline, prior to DBS, was compared with data gathered at 13-weeks post-DBS, when the gambling task was repeated. To test for differences in pre-DBS and post-DBS questionnaire scores and model parameter estimates, a paired t-test was employed when the data were normally distributed and the Wilcoxon signed-rank test otherwise, where distribution was assessed using the Lilliefors test. Gambling behaviours (such as bet increases and machine switches) were also compared at both intervals. Gambling behaviours were regressed against clinical measures of impulsivity to determine significant relations. After determining the winning computational model, model parameter estimates were extracted for each participant and regressed against clinical measures of impulsivity to determine significant associations and predictors of postoperative impulsivity. Based on previous work showing a significant association between BIS scores and both slot machine behaviour and HGF-based estimates of uncertainty encoding,[19] we focused our analyses on the BIS and its subscales.

We were particularly interested in examining whether the computational characterisation of individual uncertainty estimates prior to DBS could predict clinically-relevant changes in impulsivity at any time point after DBS. This follows the 'generative embedding' approach, in which individual predictions are not derived from measured data but from parameter estimates obtained by a generative model.[55,56] Importantly, the optimal BIS cut-off score for clinically-significant impulsivity varies by age and disease,[57] with only one existing investigation specific to a PD cohort.[58] Therefore, we examined whether we could predict the maximum postoperative increase in impulsivity, as measured by the BIS, from each participant's parameter estimates obtained at baseline, using regression and cross-validation.

3.6.2 Cross-Validation

In order to evaluate the out-of-sample predictability of the maximum change in BIS by pre-DBS model parameter estimates, a leave-one-out cross-validation was performed. A null distribution was constructed by shuffling the labels of either the dependent variable (when testing the full regression model) or the independent variable of interest (when testing a single regressor, ϑ) in the training set, using the resultant regression model to perform an out-of-sample prediction for the validation set. The out-of-sample sum-squared error of our model was then compared to this null distribution in order to assess the significance of our prediction (for details, see Supplementary Information).

4 RESULTS

4.1 Participant Characteristics

Participants were a predominantly middle-aged sample, with a bias towards male gender and akinetic-rigid/mixed phenotype over tremor (Table 1). Most participants had bilateral disease with consequent impairment of functioning in their activities of daily living.

4.2 Neuropsychiatric Assessment Pre- and Post-DBS

Concerning symptoms of primary interest (Table 2), there was a significant post-DBS decrease in impulsivity, as measured by the BIS Total, compared to baseline. There was also a near-significant decrease in self-reported symptoms of depression (BDI) and a highly significant reduction of motor symptoms UPDRS Part III Motor Examination, with a corresponding significant reduction in requirement for dopaminergic therapy (LEDD). There were no significant changes in other measures of impulsivity, including the Hayling test, the Excluded Letter Fluency task and the delay discounting task. Comparable to the BIS, the QUIP-RS total score demonstrated a trend towards a reduction at 13-weeks post-DBS, but this did not reach significance.

For symptoms of secondary interest (and subscales), see Supplementary Table 2. There was considerable variance across assessment scores at each interval (Supplementary Figure 3).

The BIS and the BDI showed a significant positive correlation at each time point (ρ_{pre}=0.46, p=0.003; ρ_{post}=0.53, p<0.001), and both showed (near-)significant changes from pre- to post-DBS (Table 2). Therefore, to rule out that impulsivity-related findings were driven by changes in depression, the BDI was included as a covariate when regressing behaviour and model parameter estimates against BIS scores. Whilst the LEDD is conceivably related to impulsivity, it did not correlate with the BIS total (ρ_{pre}=-0.126, p=0.450; ρ_{post}=-0.042, p=0.799) and was therefore not included in these regression analyses. However, the QUIP and LEDD correlated strongly at both time points (ρ_{pre}=0.42, p=0.008); ρ_{post}=0.44, p = 0.005), with LEDD decreasing significantly post-DBS. There were no significant correlations between LEDD and the other measures of impulsivity (ELF Rule Violations, Hayling AB Error Score and Delay Discount K). Based on previous work using this task and modelling framework,[19] we focused our attention on exploring impulsivity as measured by the BIS.

Table 1: Demographic and clinical characteristics of PD cohort (n=38)

	Number	% total	Mean (SD), Median (Range)
Gender			
Male	25	65.8	
Female	13	34.2	
Clinical Subtype			
Akinetic-Rigid	13	34.2	
Mixed	18	47.4	
Tremor	7	18.4	
Age (Years)			61.9 (±9.3), 65 (35 - 76)
Hoehn & Yahr Stage			2.7 (±0.6), 2.5 (1.5 - 4)
Years Since Diagnosis			8.5 (±4.6), 7 (2 - 21)

Table 2: Neuropsychiatric Assessment Data Pre- and Post-DBS

	Pre-DBS	Post-DBS	Max Impairment	Pre- vs. Post-DBS		
Behavioural Measure	*Mean (SD), Median (Range)*			*t-stat*	*p-value*	*Adj. p-value*
BIS	60.2 (±7.4), 60 (44 - 76)	57.8 (±9.5), 58 (40 - 75)	2.3 (±6.4), 3 (-14 - 17)	2.66	0.011‡	0.033*
BDI-II	11.1 (±5.1) 11 (1 - 22)	8.4 (±6.6) 6 (1- 29)	1.3 (±7.1), 0 (-12 - 18)	2.29	0.028‡	0.056
QUIP-RS	21.4 (±15.7), 19 (0 - 63)	17.2 (±15.8), 14 (0 - 55)	5.1 (±13.5), 4 (-25 - 37)	1.78	0.084	0.084
UPDRS Part III Motor	37.7 (±17.0), 37 (10 - 91)	30.9 (±12.7), 32 (8 - 60)	N/A	3.47	0.001‡	0.004**
Levodopa equiv. daily dose (LEDD)	1032.9 (±599.4), 988 (0 - 3450)	334.9 (±199.8), 329 (0 - 825)	N/A	8.59	<0.001‡	<0.001**
				Chi-square	*p-value*	
ELF Rule Violations	9.7 (±5.3), 9 (0 - 24)	8.4 (±5.0), 8 (1 - 18)	3.0 (±6.5), 1 (-6 - 19)	20.2	0.12	0.360
Hayling AB Error Score	11.4 (±11.1), 8 (0 - 38)	9.4 (±11.3), 5 (0 - 45)	6.2 (±12.0), 6 (-19 - 30)	23.6	0.13	0.360
Delay Discount K	0.034 (±0.067) 0.016 (0.00016 - 0.25)	0.036 (±0.049) 0.016 (0.00016 - 0.25)	0.041 (±0.077) 0.0128 (-0.15 - 0.25)	12.6	0.18	0.260

*Significance codes: ‡Indicates significant native p-values, before multiple comparison correction. **p*<0.01, **p*<0.05 *where p-values are Holm-Bonferroni corrected for multiple comparisons.*

4.3 Gambling Behaviour

4.3.1 Gambling Behaviour Pre- and Post-DBS

At the group level, there were no significant differences in the behaviour of participants on the slot machine from pre- to post-DBS (Supplementary Table 3). Due to subjects not engaging in the 'casino switch' option, this variable was eliminated from regression analyses.

4.3.2 Pre-DBS Regression of Gambling Behaviour on BIS scores

We studied the relationship between pre-DBS gambling behaviour and pre-DBS impulsivity as measured by the BIS (Table 3). The BDI was included in this regression in order to control for changes in clinical state attributable to depressive symptoms. The overall preoperative model including the BDI total was significantly associated with the BIS Total score [$F_{(4,33)}$=3.024, p=0.031]. Post-hoc t-tests on task behaviour revealed that no behavioural variable was significantly related to the BIS individually. When subscales of the BIS were examined, gambling behaviour associated significantly with the BIS Attentional subscale [$F_{(4,33)}$=4.094, p=0.008], where higher bet sizes corresponded to higher attentional impulsivity ($t_{(37)}$=2.303, p = 0.028) (Supplementary Table 4).

4.3.3 Post-DBS Regression of Gambling Behaviour on BIS scores

The full model of postoperative gambling behaviour was also significantly associated with BIS total score [$F_{(4,33)}$=4.920, p=0.003] (Table 3). Again, post-hoc t-tests revealed that no task behaviour was significant on its own. When subscales of the BIS were examined, gambling behaviour correlated significantly with the BIS Attentional subscale [$F_{(4,33)}$=8.123, p<0.001]. Post-hoc t-tests revealed that higher bet sizes ($t_{(37)}$=2.604 p=0.014) and more frequent double or nothing gambles ($t_{(37)}$=2.589 p=0.014) corresponded to higher BIS Attentional scores (Supplementary Table 5).

Post-DBS, higher bets and more frequent machine switches were significantly associated with higher QUIP-RS scores (Supplementary Table 6). No other measures of impulsivity were significantly associated with pre- or post-DBS slot machine activity.

Table 3 | Slot Machine Behaviour

Pre-DBS Slot Machine Behaviour and Pre-DBS BIS

	Independent Variables (*b*)						
Dependent Variables	**Bet Size**	**Machine Switch**	**Double-up**	**BDI**	R^2	**F-stat**	**p-value**
BIS-11 Total	0.034	0.338	-0.077	0.821	0.268	3.024	0.031*

Post-DBS Slot Machine Behaviour and Post-DBS BIS

	Independent Variables						
Dependent Variables	**Bet Size**	**Machine Switch**	**Double-up**	**BDI**	R^2	**F-stat**	**p-value**
BIS-11 Total	0.018	0.128	0.263	0.712	0.374	4.920	0.003**

*b values are standardized regression coefficients. **p<0.01, *p<0.05.*

Table 4 | Log model parameters, Pre- and Post-DBS

	Pre-DBS	**Post-DBS**
ω	-11.453 (9.672; -30.45 – -0.326)	-6.819 (6.041; -17.892 – -0.842)
ϑ	-6.959 (1.946; -14.288 – -2.649)	-6.003 (1851; -9.840 – -0.973)
β	0.442 (1.848; -4.747 – 2.416)	-0.114 (2.372; -7.582 – 2.572)

Group means are reported with standard deviations and range in parentheses. Model parameters are reported in log space.

4.4 Computational Modelling

As described above, we were primarily interested finding pre-DBS predictors for post-DBS changes in impulsivity. We therefore first determined, using Bayesian model comparison, which of our three models best explained pre-DBS behaviour, before evaluating whether the parameter estimates of this winning model changed postoperatively and predicted maximum postoperative BIS scores. Bayesian model comparison selected the 'standard' HGF (with a subject-specific decision temperature in the response model) as the winning model, with a group-level Bayes factor of approximately 11, compared to the next best model (the Rescorla-Wagner model) (Figure 3).

4.4.1 Changes in Model Parameter Estimates Pre- to Post-DBS

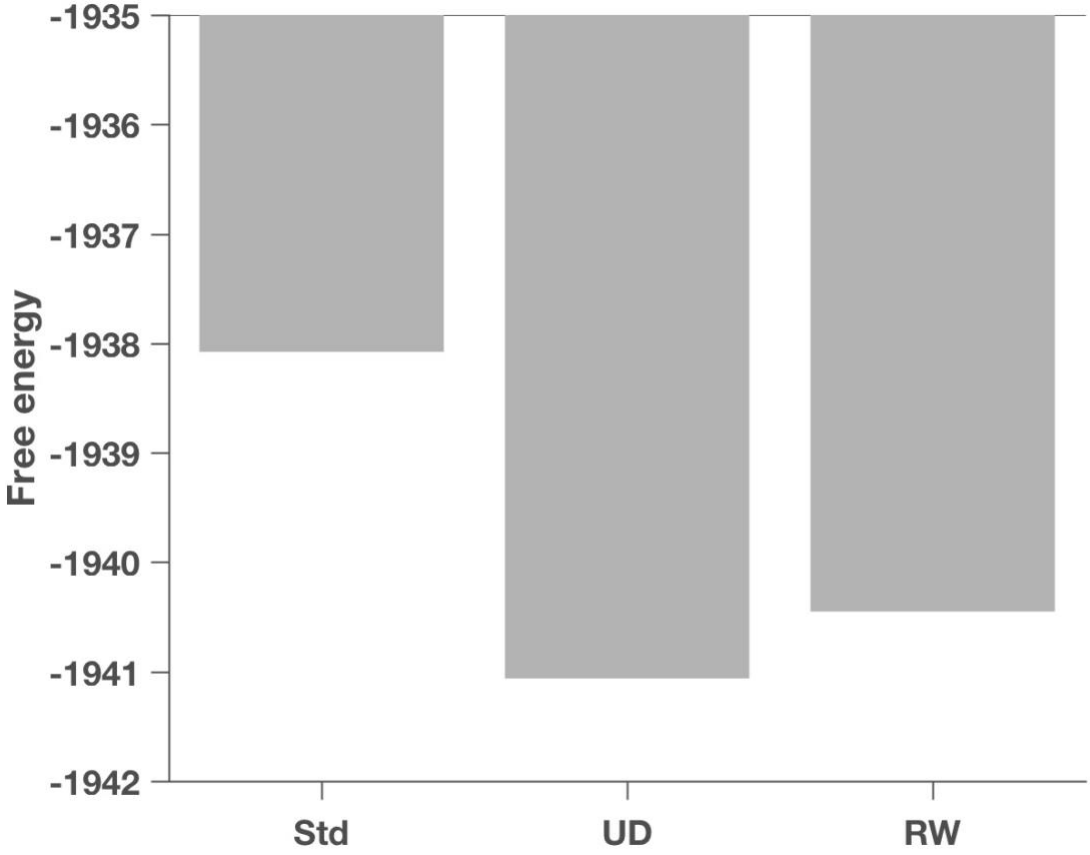
Estimates of both HGF model perceptual parameters ω and ϑ significantly increased postoperatively, implying larger subjective estimates of uncertainty (specifically, volatility) after DBS (Table 5 and Figure 4). ω represents the tonic component of environmental volatility; i.e., how quickly the likelihood of winning on a given slot machine is changing. By contrast, ϑ represents the general tendency for this volatility to change (meta-volatility).

4.4.2 Pre-DBS Regression of Model Parameter Estimates on BIS scores

The full regression model (including the estimates of preoperative perceptual parameters ω and ϑ) was significantly associated with BIS Total [$F_{(3,34)}$=4.093, p=0.014] (Table 5). Post-hoc t-tests on model parameter estimates revealed that no single parameter was significantly related to the BIS.

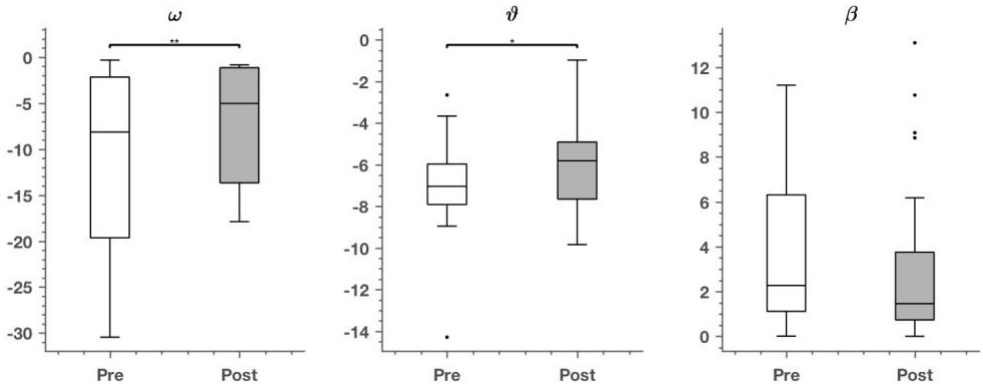
4.4.3 Post-DBS Regression of Model Parameter Estimates on BIS scores

The full regression model was significantly associated with BIS Total [$F_{(3,34)}$=10.183, p<0.001] (Table 5). Post-hoc t-tests revealed that ω was a significant regressor ($t_{(34)}$ =2.863, p=0.014). The positive regression coefficient for ω implied that the greater the subjective estimate of tonic volatility, the higher the BIS score.



Legend to Figure 3

Figure 3 | Model Comparison Results Bayesian model comparison results across the Standard (Std), Uncertainty-driven (UD) and Rescorla Wagner (RW) models, pre- and post-DBS. Shown here are the group-level free energy values for the three models, Std, UD and RW. Pre-DBS model free energies are F_{Std}=-1938.08, F_{UD}=-1941.06, and F_{RW}=-1940.45. The winning model pre-DBS is the standard HGF. The group-level difference in free energy compared to the next best model (the Rescorla-Wagner model) is 2.37, corresponding to a Bayes factor of approx. 11.



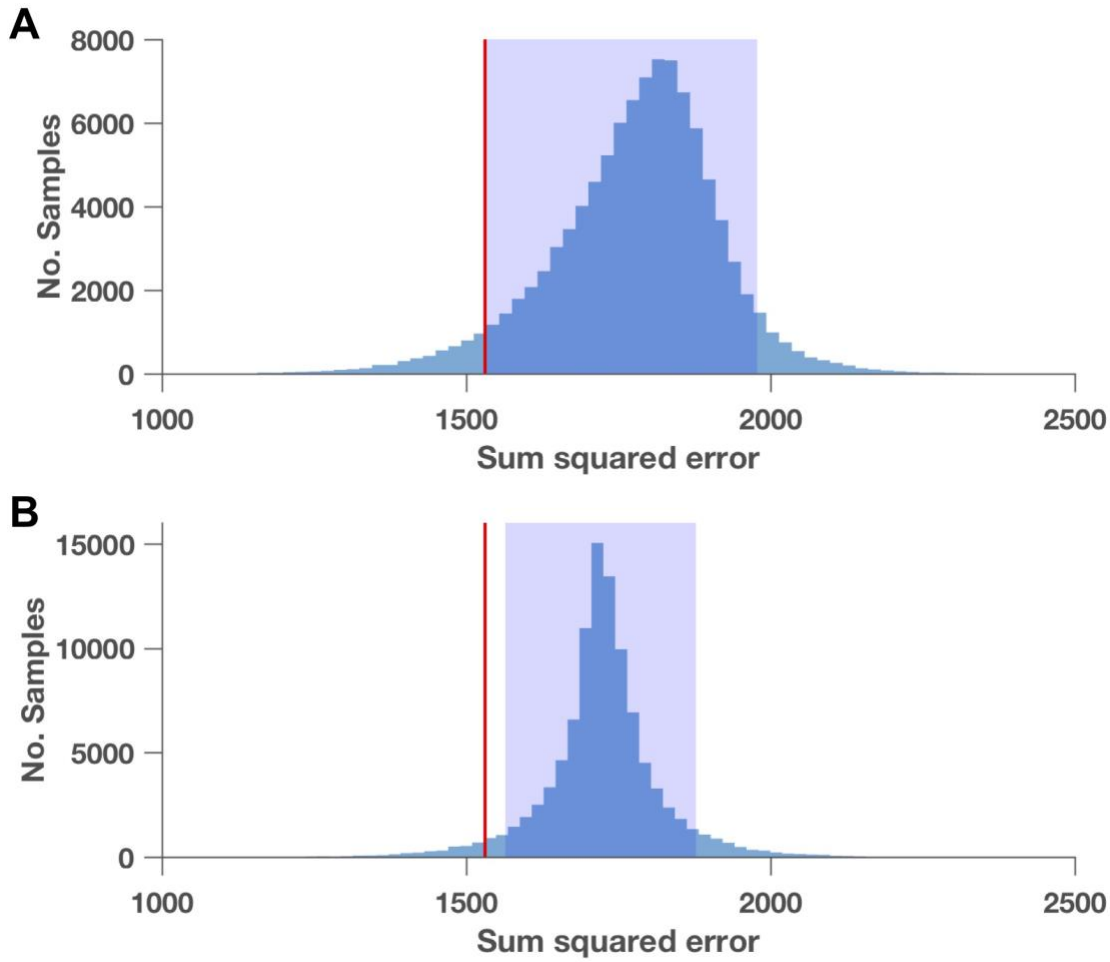
Legend to Figure 4

Figure 4 | Computational Model Parameters, Pre- and Post-DBS: Log model parameter estimates are displayed pre- and post-DBS. For the box plots, the central line indicates the median of the distribution, and the top and bottom edges of the box represent the 25th and 75th percentiles respectively. The whiskers extend to the farthest data points that are included in the distribution and are not considered outliers. A paired t-test was performed on all pairs. Significant differences were observed in estimates of parameter ω ($t_{(37)}$=-3.22, p<0.01) and in estimates of parameter ϑ ($t_{(37)}$=-2.256, p=0.03). p-values are Holm-Bonferroni corrected for multiple comparisons.

4.4.4 Pre-DBS Model Parameter Estimates Predict Post-DBS Impulsivity

We next regressed the estimates of ω and ϑ at baseline against the maximum postoperative increase in impulsivity, as measured by the BIS. Pre-DBS parameter estimates, along with pre-DBS BDI were significantly associated with the maximum postoperative increase in impulsivity [$F_{(3,34)}$=3.235, p=0.034] (Table 5). Post-hoc t-tests revealed that ϑ was significantly related to the maximum change in BIS ($t_{(37)}$=2.301, p=0.027). Notably, the BDI alone did not predict the maximum change in BIS [$F_{(1,36)}$=3.6418, p=0.0643]. The positive regression coefficient for ϑ implied that the higher the subjective global volatility estimates pre-DBS (i.e., the more uncertain a participant was about whether the tendency of slot machines to oscillate between 'hot' and 'cold' states was changing), the larger the subsequent postoperative increase in BIS.

To validate the predictive nature of this model, we performed a leave-one-out cross validation procedure (Figure 5). The sum squared error of the full model (red), with labels correctly assigned, is exactly at the boundary of the 95% confidence interval for the null distribution (plot A) The out-of-sample predictive power is also significant (p=0.032) for the individual regressor ϑ (plot B). The normalized root-mean-squared error (NRMSE) for the out-of-sample prediction is 0.21, where NRMSE is defined as the root-mean-squared error over the range of our dependent variable. Notably, parameters of the RW model (the runner-up model in our model comparison) neither had an in-sample association with the maximum BIS Increase [F=1.438, p=0.249] nor out-of-sample predictive power (p=0.385) (Supplementary Table 7),



Legend to Figure 5

Figure 5 | Cross validation results: The blue histogram represents the sum squared error of the out of sample predictions under the null hypotheses. Plot A displays the null distribution for the omnibus F-test, in which the dependent variable (BIS) is shuffled between participants in the training set, in order to make an out-of-sample prediction. Plot B shows the null distribution for the t-test on ϑ, in which ϑ is shuffled in the training set. In both plots, the shaded area indicates the 95% confidence interval of the null distribution. Shown in red is the sum-squared-error of the predictive model for both tests, based on perceptual parameters inferred from the gameplay of participants prior to DBS.

Table 5 | Perceptual Model Parameters

Pre-DBS Model Parameters and Pre-DBS BIS

	Independent Variables					
Dependent Variables	ω	ϑ	**BDI**	R^2	**F-stat**	**p-value**
BIS-11 Total	0.102	0.621	0.719	0.265	4.093	0.014*

Post-DBS Model Parameters and Post-DBS BIS

	Independent Variables					
Dependent Variables	ω	ϑ	**BDI**	R^2	**F-stat**	**p-value**
BIS-11 Total	0.751^	-0.836	0.720	0.473	10.183	<0.001***

Pre-DBS Model Parameters Predicting Max BIS Increase

	Independent Variables					
Dependent Variables	ω	ϑ	**BDI**	R^2	**F-stat**	**p-value**
Max BIS Increase	0.015	1.198^	0.363	0.222	3.235	0.034*

b values are standardized regression coefficients. ***p<0.001, **p<0.01, *p<0.05. ^ *Indicates significant t-statistics, Holm-Bonferroni corrected for multiple comparisons.*

5 DISCUSSION

In this study, we employed a naturalistic gambling task and a hierarchical Bayesian model (for inference on subject-specific estimates of uncertainty) in order to investigate impulsive decision-making in patients with PD undertaking subthalamic DBS. We found that parameter estimates representing different forms of uncertainty (volatility) changed significantly from pre- to postoperative conditions. In particular, there was a significant increase in ϑ, the parameter that captures a gambler's uncertainty about changes in the tendency of slot machines to oscillate between 'hot' and 'cold' states (meta-volatility). There was also a postoperative increase in a second parameter, ω, that reflects a gambler's uncertainty about how quickly the probability of winning on a given slot machine was changing (volatility).

Notably, these model-based estimates of subjective uncertainty related to postoperative impulsivity. For example, the maximum postoperative increase in BIS was significantly associated with preoperative ϑ estimates. Most importantly, our model-based estimates also allowed for out-of-sample predictions: leave-one-out cross validation demonstrated that the regression model as a whole, but also ϑ individually, significantly predicted the maximum postoperative change in BIS (Figure 5).

Increased estimates of uncertainty accelerate the rate of learning at higher hierarchical levels, which could engender maladaptive learning at lower levels of the hierarchy. A high learning rate means suppressing top-down expectations, and may impair learning about probabilistically aberrant events. This offers a parallel but computationally distinct account of the stimulation-related learning changes described previously,[17] in which reduced positive and negative instrumental outcome sensitivity was reported as a consequence of neurostimulation. Similar to prior work, we also find a positive relationship between model-based estimates of uncertainty and impulsivity.[19,20,22,23] A plausible computational account of impulsivity is that high subjective uncertainty leads to lack of predictability and increases a tendency for exploration.

In our participants, neurostimulation may interact with the physiology of the STN and alter the computations it implements. A tripartite functional organisation of the STN into limbic, associative and motor subregions is suggested by primate and human studies, [59,60] with electrode implantation targeted to the dorsolateral sensorimotor region to address motor symptoms of PD.[61] Yet, the small size of the STN means that leakage of current from a stimulating contact in this region could still modulate subthalamic regions with greater connectivity to fronto-striatal networks. The more ventral and medial the stimulating contact, the more likely these networks are to be affected by DBS. Previous investigations have suggested that the site of subthalamic stimulation can modulate cognitive [62] and

psychiatric symptoms.[63,64] Further work is required to determine if the site of stimulation affects the magnitude of changes in uncertainty estimation observed here.

In a non-surgical population, persons with PD withdrawn from medication display a characteristic impairment in reward learning and may show enhanced punishment sensitivity.[65] However, whilst dopamine replacement enhances the ability to learn from positive outcomes, learning from negative outcomes is impaired.[65] From the HGF perspective, an agent with increased uncertainty at higher levels would be expected to show both decreased reward and punishment learning, as surprise to both positive and negative unexpected outcomes would be reduced (see Lawson *et al*, 2017).[66] However, if LEDD reduction is a principal driver of a change in behaviour, then a selective impairment in positive outcome representation would be observed. This suggests that LEDD changes may have a secondary role, but further careful experiments will be necessary to address this question.

We did not observe significant correlations between behaviour or parameters inferred from slot machine play with other estimates of impulsivity including the excluded letter fluency task, the Hayling test and the delay discounting task. This reflects the compound nature of inhibitory control, which may implicate discrete subcortical and cortical regions and may evidence differential patterns of expression amongst impulsive endophenotypes.[67,68] For example, the Hayling and ELF tasks are more commonly included amongst measures of task-switching and conflict interference, whilst the delay discounting task assesses impatience. Alternative paradigms may be required to capture participant-wise behaviour amongst these constructs.

We note that the lack of a counterbalanced on-off stimulation design is a potential limitation of our study but suggest that our longitudinal design is more reflective of the natural clinical course taken by persons with PD in the clinic. Our participants simply would not have tolerated an extended DBS washout and we hypothesise that the younger age of participants in the study of Seymour *et al* may have facilitated their crossover design.[17]

In summary, this study suggests that hierarchically related forms of uncertainty (volatility and meta-volatility) change after subthalamic DBS in PD. Our results demonstrate that a naturalistic assessment of gambling behaviour in a virtual casino is useful for investigating impulsivity in PD: behavioural measures on this task and model-based estimates of subjective uncertainty (volatility) related significant to BIS scores, both pre- and postoperatively (Tables 3, 5). Increased uncertainty about environmental volatility may be maladaptive, as informed predictions about the world are necessary for learning from errors about trial-wise outcomes. We therefore posit a cognitive mechanism for the genesis of impulsive behaviour in this population. Finally, the potential of our model to predict changes in postoperative impulsivity from game play (Figure 5) could be most valuable in PD, given the significant, but poorly

quantified risks relating to surgical (neurostimulation) and medical (dopamine agonist) treatments. If those at a higher risk of neuropsychiatric harm could be identified, this would improve the nature of treatment choice and informed consent and the effectiveness of clinical follow-up.

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6.1 Data availability statement

The HGF toolbox is part of the open source TAPAS software and available for download at http://www.translationalneuromodeling.org/tapas. The gambling paradigm is provided for download on a git repository at https://github.com/saeepaliwal/breakspear_slot_machine.git. The analysis pipeline is provided at https://github.com/saeepaliwal/dbs_pd_analysis_pipeline.git. A de-identified data set containing neuropsychiatric assessment and gambling data can be provided by Dr Philip Mosley (Philip.Mosley@qimrberghofer.edu.au) on application, subject to institutional review board approval.

6.2 Financial disclosures / conflicts of interest

All authors report no conflict of interest

6.3 Funding agencies

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6.4 Author Contribution Statement

Paliwal: Task design, statistical analysis, writing of first draft of manuscript*
Mosley: Data collection, statistical analysis, writing the first draft of the manuscript *
Breakspear: Critical comments on study design and manuscript
Coyne: Supervision of data collection, critical comments on manuscript
Silburn: Supervision of data collection, critical comments on manuscript

Aponte: Collaborated on model inversion and cross validation

Mathys: Collaborated on model inversion and cross validation

Stephan: Task design, supervision of data analysis, contributions to manuscript writing

* These authors contributed equally to the work

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