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Dopaminergic medication increases reliance on current information in Parkinson's disease

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The neurotransmitter dopamine is crucial for decision-making under uncertainty, but its computational role is still a subject of intense debate. To test its potential roles, we invited patients with Parkinson's disease (PD), who have less internally generated dopamine, to participate in a visual decision-making task in which uncertainty in both prior and current sensory information was varied. Behaviour during these tasks is often predicted by Bayesian statistics. We found that many aspects of uncertainty processing were conserved in PD patients: they could learn the prior uncertainty and utilize both prior and current sensory information. As predicted by prominent theories, we found that dopaminergic medication influenced the weight given to sensory information. However, as PD patients learned, this bias disappeared. In addition, throughout the experiment the patients exhibited lower sensitivity to current sensory uncertainty compared with age-matched controls. Our results provide empirical evidence for the idea that dopamine levels, which are affected by PD and the drugs used for its treatment, influence the reliance on new information.

Every day we face decisions that have associated uncertainty. They may range from very important, life-changing situations (for example, 'Should I marry this person?' or 'Which career should I choose?') to minor decisions, some of which we make without even noticing (for example, 'What is that object in the sky?'). When making a decision, we combine information from the past, called 'prior' information (for example, 'How trustworthy has this person shown to be?' or 'What types of objects generally appear in the sky?') with current sensory information, or 'likelihood' (for example, 'What am I feeling now?' or 'What is the shape of that object?'). Correctly combining these pieces of information is the key to effective decision-making.

To understand how people (and their brains) make these decisions, we can use a normative approach; for instance, we can ask what people should be doing if they were to optimally compute information, and then compare it with what they are actually doing. Bayesian theory gives us such a framework. Specifically, it tells us that the statistically optimal way to make decisions based on uncertain information is to use both prior and current sensory information and, moreover, to combine them according to their respective relative uncertainties, relying more on current information when prior information is more uncertain, and vice versa[1,2]. One may then expect that if someone has more uncertain prior information (for example, because they have trouble storing and keeping prior information) or a more uncertain likelihood (for example, due to perception problems), this would result in an over-reliance or under-reliance on current information. In this way, the Bayesian framework can give us insights into the specific information (or lack thereof) a person has, and allow the characterization of apparent abnormal behaviour under a normative light[3].

As uncertainty processing and appropriate weighing of prior and current information is essential for decision-making, understanding how the brain performs these calculations seems of extreme importance. Previous laboratory research has indicated that the putamen is particularly important in this process, with activity in the putamen correlating with increased prior uncertainty and also with individuals' tendencies to sense and attend to current versus prior information[4]. However, from functional magnetic resonance imaging data alone it is not possible to know in which of these processes putamen activity could have a causal role. Better understanding the role of the putamen may shed light on how the brain performs the computations necessary for decision-making under uncertainty.

The existing literature shows that activity in the putamen either directly or indirectly affects decision-making under uncertainty. For example, putamen activity has been associated with ambiguity[5] and also learning[6,7]. Interestingly, when a person is learning a motor sequence, their putamen activity decreases after training but remains high when the sequence is random[6,7]. We could interpret these studies as putamen activity signalling for prior uncertainty, which decreases with learning but stays high when the sequence is random or when the probabilities of events are unknown. Another interpretation is that it promotes focusing on current incoming information, which would equally predict the observed data. As activity in the putamen is severely compromised in people who suffer from Parkinson's disease (PD),[8] we can study PD patients to ask fundamental questions about the role of the putamen in decision-making.

PD leads to a depletion of dopamine[8], one of the main transmitters in the putamen, and this neurotransmitter probably mediates at least some of the putamen's influence on decision-making under uncertainty. Indeed, dopamine has been associated with uncertainty[9–11]. However, its precise role is still unclear and subject to intense debate[10,12,13]. Besides its best-known role in reward prediction error[14,15], it has been proposed that dopamine is involved in attention and the saliency of stimuli[12,16,17]. It has also been proposed that dopamine regulates the weight given to bottom-up current sensory information (likelihood) versus top-down prior beliefs[10,11,18,19], and that it codes for uncertainty in the current stimulus[10,11,18]. Furthermore, dopamine has been implicated in learning[17,20,21], and hence could be crucial for learning the uncertainty of a given event. To distinguish between these ideas, we can compare PD patients with healthy participants on a task that allows the disambiguation of different aspects of decision-making under uncertainty[4].

Previous studies have shown that PD patients have impairments in decision-making. In particular, they have trouble reacting to unexpected events[18], task switching[22] and using negative feedback[23].

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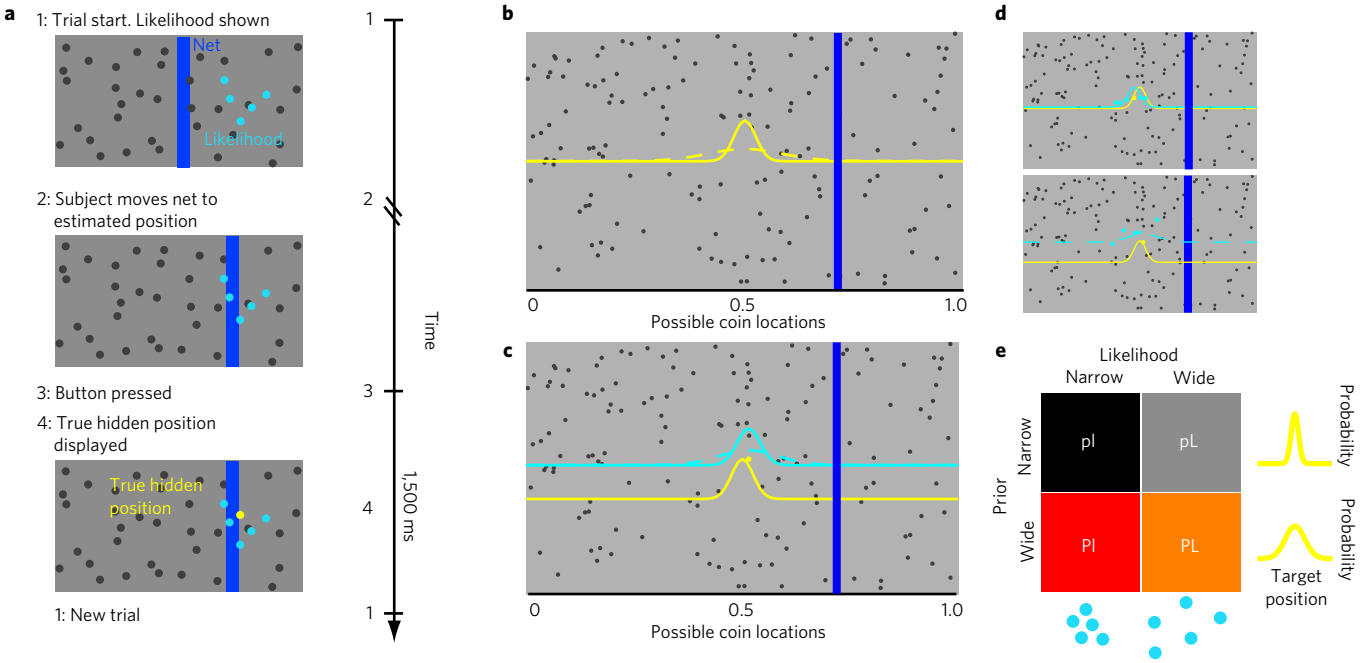

Figure 1 | Experimental setup. a, Illustration of the task. Participants guess the position of a hidden target (the 'coin', represented by the yellow dot) using a net (vertical blue bar), which they can displace horizontally. At the onset of each trial, participants receive noisy information about the position of the hidden target in the form of a set of five blue dots (the current sensory information, or 'likelihood'). Participants then move the net to the guessed position and press the mouse button to confirm their choice, after which the true target position is displayed. A new trial then begins 1,500 ms later. Left, illustration of the computer display that was presented to the participants. Right, typical time course of a trial. **b**, Represented are the two prior distributions from which the target coin could be drawn. They are both Gaussian distributions for which the mean is the center of the screen (0.5) and only the variance is different. The solid yellow line is the low variance (small uncertainty) prior distribution (p) and the yellow dashed line is the high variance (large prior uncertainty) distribution (P). These distributions were overlaid on the screen that the participants could see. The screen corresponds to the state space and varies from 0 (left corner) to 1 (right corner). **c**, In each trial, after the coin was drawn from one of the prior distributions (yellow dot), five likelihood dots were drawn from a second Gaussian distribution (likelihood distribution), where the mean was the position of the coin on that trial and the variance was either low (small likelihood uncertainty, l; solid light blue line) or high (large likelihood uncertainty, L; dashed light blue line). **d**, Represented is a sample trial of a low prior, low likelihood uncertainty condition (top) and a low prior, high likelihood uncertainty condition (bottom). Note that when playing, only the likelihood dots (in light blue) and the net (vertical blue bar) were shown from the beginning of the trial, and the coin (yellow dot) was shown after the participant made a choice. The distributions were never explicitly shown. **e**, The four conditions of the experiment. The experiment consisted of a two-by-two factorial design, with two types of 'prior' (p, narrow prior; P, wide prior) and two types of 'likelihood' (l, narrow likelihood; L, wide likelihood). The wider conditions are the ones with more associated uncertainty.

It seems reasonable to assume that some of these deficits may result from the wrong processing of uncertainty information; for example, a diminished capacity to attend to external cues. Studying how PD patients learn and deal with uncertainty in prior and current sensory information may help in understanding the specific challenges PD patients face when making decisions.

In the present study, we invited PD patients and age-and-gender-matched controls to perform a decision-making task in which both prior and current uncertainty were independently varied. Patients performed the task once 'on' dopaminergic medication (more dopamine in their system) and once 'off' medication (less dopamine). We hypothesized that if the putamen directly stores prior uncertainty information, PD patients would have trouble reacting to the different prior uncertainties. Alternatively, if dopaminergic activity mediated by the putamen signals the weight given to current versus prior information, we would expect PD patients off medication to rely less on current sensory information. Finally, if dopamine is directly involved in signalling uncertainty in current sensory information[10,11,18], we may expect PD patients to react similarly to sensory stimuli with different uncertainties. By studying how PD patients and controls reacted to the different changes in uncertainty, we were able to analyse these hypotheses independently.

Participants performed a visual decision-making task, during which they guessed the position of a hidden target ('coin') on a screen (see Fig. 1a). They received noisy (uncertain) visual information about the position of the target in the form of a cloud of dots centred on the true target position. To accurately estimate the target position, participants could use both prior information, obtained from the distribution of previous target positions, and current sensory information (the 'likelihood'), obtained from the displayed cloud of dots (see Methods and Fig. 1). The conditions comprised a two-by-two factorial design (Fig. 1e), with two levels of prior uncertainty (wide, more uncertain prior: 'P'; and narrow, less uncertain prior: 'p') and two levels of likelihood uncertainty (wide, more uncertain likelihood: 'L'; and narrow, less uncertain likelihood: 'l') for a total of four conditions (pl, pL, Pl and PL). Participants performed the task twice, with PD patients performing it once on medication (shortly after taking their dopaminergic medication) and once off medication (dopaminergic medication withdrawn overnight), counterbalanced across participants. By varying prior and current sensory uncertainty and comparing the results among PD patients with different dopaminergic medication levels and healthy controls, we studied the specific effects of the disease and of dopaminergic medication on decision-making under uncertainty.

To analyse a participant's reactions to changes in uncertainty in both prior and current sensory information (likelihood) we made, for each condition, a linear regression of the participant's estimated coin position in each trial as a function of the centroid of the cloud of dots;

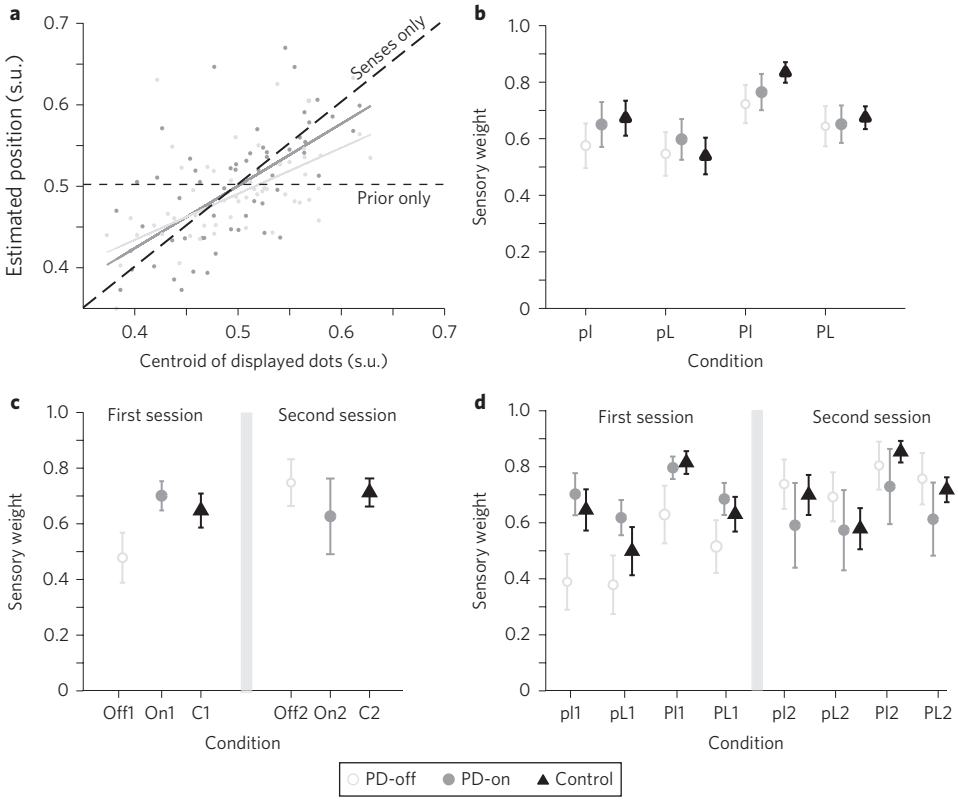

Figure 2 | Relative weight given to current information (sensory weight). a, One participant's estimated target position (in screen units (s.u.)) as a function of current sensory information (here, the centroid of the displayed cloud of dots (s.u.)). The slope of this regression is the 'sensory weight', with 1 corresponding to full reliance on current sensory information (black dashed line), and 0 corresponding to no reliance on current sensory information (black dotted line). In light grey are the data and linear regression from one participant off medication (small prior uncertainty, large likelihood uncertainty condition, pL), and in dark grey are the data from the same participant in the same condition but on-medication ($n=75$ trials for both). **b**, Average sensory weights ± s.e.m. for PD patients off medication (open light grey circles, $n=15$), PD patients on medication (filled dark grey circles, $n=15$) and controls (black triangles, $n=15$), divided per condition (pl, pL, Pl and PL), but not separated by session. **c**, Same as **b**, but data are shown separated by sessions and averaged by condition. **d**, Same as **b**, but divided per session.

that is, as a function of the mean of the current sensory information (see Fig. 2a and Methods). The slope of this regression represented the relative weight on current sensory information, which we call the 'sensory weight'. When people rely exclusively on current information, this slope/sensory weight is 1, whereas when they completely ignore current sensory information (for example, they rely only on prior knowledge) this weight is 0 (Fig. 2a). Note that if we assume that PD patients are using only prior or current sensory information, the weight on prior information is just the sensory weight subtracted from 1 (ref. [2]). Intuitively, and if they behave according to the statistical optimum predicted by Bayesian statistics, the sensory weight should be higher when participants think the current information is more reliable and when their prior information is more uncertain[2]. Hence, if and how the value of this weight changes according to the uncertainty in current and prior information can serve as a proxy to tell us whether participants are detecting and reacting to changes in uncertainty.

The sensory weights within the PD population were significantly affected by both prior uncertainty and likelihood uncertainty ($F_{1,101}=17.51$, $P<0.0001$, 95% confidence interval for mean difference (CI): 0.055 to 0.153, for the main effect of 'prior uncertainty', P > p; and $F_{1,101}=7.64$, $P=0.007$, 95% CI: 0.019 to 0.118, for the main effect of 'likelihood uncertainty', l > L; repeated-measures analysis of variance (ANOVA) with prior, likelihood, session and medication type as fixed factors; Fig. 2b). PD patients showed increased sensory weights when the current information (likelihood) was more reliable and also when the prior information was more uncertain (see Fig. 2b for the average weights under less uncertain (l) versus more uncertain (L) likelihood conditions; and under more uncertain (P) versus more reliable (p) prior conditions). Furthermore, the weights were highest in the Pl condition, when the prior information was more uncertain and the likelihood information more reliable, and lowest in the pL condition, when the opposite was the case. This indicates that PD patients noticed differences in both prior and current sensory uncertainty and, moreover, they reacted to them in a way qualitatively predicted by Bayesian statistics[2,24] (see Supplementary Information and Supplementary Fig. 1 for quantitative predictions). Thus, in our experiment, PD patients were able to detect changes in both prior and current sensory uncertainty and modify their behaviour accordingly.

To examine the effects of dopaminergic medication, we compared PD patients' weights when they were 'on' their medication (that is, shortly after having taken their medication; 'PD-on') with their weights when they were 'off' their medication (that is, at least 12 hours after having taken medication; 'PD-off'). We made this comparison within-participant to directly analyse the effect of medication independent of participant-specific effects, and we counterbalanced the order in which participants started the experiment (on versus off) to distinguish the effects of medication from the session effects. We found that PD patients, on average, had lower sensory weights when they were off medication compared with when they were on medication ($F_{1,101}=4.16$, $P=0.044$, 95% CI: 0.001 to 0.100, for the main effect of medication, PD-on > PD-off,

using the same ANOVA as above; see the slopes in Fig. 2a, as well as Fig. 2b–d). Note that this effect of medication was independent of any session effects. For six of the PD patients, the increase in weight with dopaminergic medication was significant even at the individual level. Administration of dopaminergic medication resulted in PD patients, on average, placing an increased weight on current information.

The results also revealed session effects. As stated above, participants performed the task twice, with patients performing it once on medication and once off medication (order randomized). For the PD population, session number had a significant main effect on the average weight given to current information ($F_{1,101}=15.59$, $P=0.0001$; 95% CI: 0.049 to 0.147; $2>1$; Fig. 2). Analysing each session independently, we observed that in the first session, PD patients off medication had lower average sensory weights compared with PD patients on medication ($t_{13}=2.2$, $P=0.046$, 95% CI: 0.004 to 0.440; unpaired t-test; Fig. 2c,d), but this difference disappeared in the second session ($t_{13}=-0.78$, $P=0.45$, 95% CI, −0.456 to 0.214; unpaired t-test). Note that this is a between-participants effect. To better analyse the potential session effects, we calculated the starting and ending weights for each session (obtained using the first and last 15 trials of each condition, respectively). For the initial weights (first session) there was a striking difference between PD patients who started off medication and those who started on medication, with PD patients off medication starting with significantly lower sensory weights ($U_{8,7}=50$, $P=0.009$; Mann–Whitney U-test; see Supplementary Information and Supplementary Fig. 2 for more in-depth analyses of the changes in weights across time). At the end of the first session, this difference shortened, with patients off medication still with lower weights, but not significantly so ($U_{8,7}=42$, $P=0.12$; Mann–Whitney U-test). In the second session, PD patients who were then off medication had starting weights even higher than patients on medication, although not significantly so ($U_{7,8}=18$, $P=0.28$; Mann–Whitney U-test). Note that the PD patients off medication in the second session were the ones on medication in the first session, suggesting a time/experience effect. This session effect may also help explain the smaller influence of dopaminergic medication in some participants. Thus, although at the start of the experiment PD patients off medication placed significantly lower weight on current information relative to patients on medication, experience with the task made this difference disappear.

If dopamine signalling in the putamen mediates the relative weight given to sensory information (as suggested by the observed increased weight on senses while on medication), we may expect to see a relation between the effect of dopaminergic medication and time since PD diagnosis. Research has shown that while the early stages of PD are associated with the specific localized loss of dopaminergic neurons in the putamen, as the disease progresses the loss becomes more generalized and starts affecting other areas in the brain, as well as other neurotransmitter/neuromodulator pathways[8]. Thus, one may expect dopaminergic medication to be particularly effective during the early stages of PD[8,25]. To test this hypothesis, we analysed the difference in weights when the patients were on versus off medication and correlated them with the time since their PD diagnoses. Time since diagnosis (in months) was, indeed, strongly negatively correlated with how much patients changed their average weights between the on and off medication states ($r=-0.77$, $P=0.002$; Spearman's rank correlation). This seems to be a specific effect of time since diagnosis and not age, as age was not significantly correlated with change in weights ($r=-0.31$, $P=0.27$; Spearman's rank correlation). These results suggest that as the disease advances, dopaminergic medication may become ineffective in producing a change in behaviour.

To study the specific effects of the disease, we compared the behaviour of PD patients in this task with the behaviour of age- and-gender-matched controls (see Supplementary Information for behavioural analyses within controls). Using the average weights

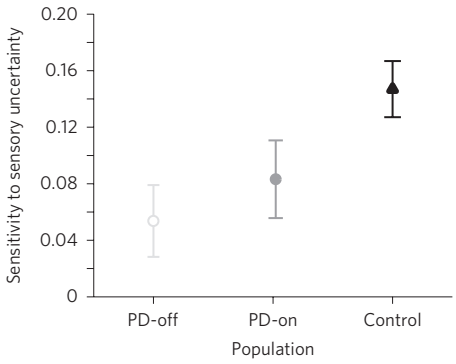

Figure 3 | Sensitivity to likelihood uncertainty, separated by population type. Mean ± s.e.m. sensitivity to likelihood uncertainty (including both sessions) for PD patients off medication (open light grey circle), PD patients on medication (closed dark grey circle) and controls (black triangle).

of both sessions and medication states, no significant difference is found between patients and controls ($F_{1,120}=0.21$, $P=0.65$, 95% CI: −0.198 to 0.126, for the main effect of population type; repeated-measures ANOVA with population, prior and likelihood type as fixed factors; Fig. 2). However, we saw that both session number and medication state affected these weights; therefore, we decided to look at the starting weights for the first session and separately analyse PD patients on medication and off medication. The starting weights of PD patients off medication were significantly lower than those of controls ($U_{7,15}=18$, $P=0.017$, Mann–Whitney U-test; similar to Fig. 2c,d), while there was no significant difference between the weights of PD patients on medication and those of controls ($U_{8,15}=59$, $P=0.97$, Mann–Whitney U-test). Together, our results show that PD patients off medication started the task relying less on current information (compared with patients on medication or controls), and that this changed with experience with the task.

Analysing the interactions between population type (patients or controls) and prior and likelihood effects can give us an idea of whether or not PD patients and controls react similarly to changes in prior and likelihood uncertainty. There was no significant interaction between population type and reactions to prior uncertainty ($F_{1,120}=1.02$, $P=0.32$, for the prior and population interaction term; same ANOVA as used previously; see Supplementary Information for additional analyses on reactions to prior uncertainty). In contrast, we found a significant interaction effect between population type and reactions to likelihood uncertainty ($F_{1,120}=8.44$, $P=0.007$). These results suggest that PD patients and controls react similarly to changes in prior uncertainty, but differently to changes in current sensory uncertainty (likelihood uncertainty).

To better understand how PD patients differ from controls in their reactions to changes in likelihood uncertainty, we directly analysed their 'sensitivity to likelihood uncertainty'; that is, the difference in weights between conditions of different likelihood uncertainty. Medication state had no significant effect on the average sensitivity to likelihood uncertainty ($t_{14}=0.776$, $P=0.45$, 95% CI: −0.052 to 0.111; paired t-test; Fig. 3), hence we combined the data from PD patients on and off medication. PD patients reacted significantly less to changes in likelihood uncertainty compared with controls ($F_{1,29}=8.44$, $P=0.007$, 95% CI: 0.023 to 0.134; repeated-measures ANOVA with population and session as fixed factors), while session number had no significant effect ($F_{1,29}=1.35$, $P=0.25$, 95% CI: −0.023 to 0.086; see Supplementary Information for control analyses ruling out motoric and visual confounds). When the prior uncertainty was lower, the difference between PD patients and controls was salient: the change in likelihood uncertainty did not significantly change PD patients' behaviour

($t_{14}=1.33$, $P=0.20$, 95% CI: −0.025 to 0.106, for mean change; one-sample *t*-test; Fig. 2), while controls showed a solid effect ($t_{14}=5.01$, $P=0.0002$, 95% CI: 0.077 to 0.191; one-sample *t*-test). When the prior was more uncertain, both groups showed an effect of likelihood uncertainty ($t_{14}=4.45$, $P=0.0005$, 95% CI: 0.050 to 0.142 and $t_{14}=7.17$, $P<10^{-5}$, 95% CI: 0.112 to 0.208, for patients and controls, respectively; one-sample *t*-test), having higher sensory weights when sensory information was more precise. Together, these results show that PD patients were less responsive to changes in the uncertainty of the current stimulus compared with controls, and this was particularly evident when there was less prior uncertainty.

So far, we have looked at participants' average behaviour, but analysing how participants react to trial-by-trial variations in sensory uncertainty gives us a more fine-grained understanding of their behaviour. If PD patients can react to fast changes in sensory uncertainty and behave according to the predictions of a statistically optimal observer, we would expect a negative correlation between the specific sensory uncertainty associated with a given trial and a participant's sensory weight on that trial. This is what we observed. Both PD patients and controls showed consistently negative correlations (albeit of small amplitude) between the standard deviation of a trial's cloud of dots and the weight they placed on senses on that trial (correlations consistently lower than 0: $t_{14}=-6.05$, $P=0.00003$, 95% CI: −0.091 to −0.044 for correlations in PD patients; and $t_{14}=-6.61$, $P=0.00001$, 95% CI: −0.117 to −0.060 for controls; one-sample *t*-tests over Pearson's correlation coefficients; see Supplementary Information; Fig. 4). However, PD patients off medication showed weaker correlations compared with controls ($t_{28}=2.18$, $P=0.038$, 95% CI: 0.002 to 0.076, for the mean difference between correlations; unpaired *t*-test over mean Pearson's correlation values across groups), while there was no significant difference between PD patients on medication and controls ($t_{28}=0.10$, $P=0.92$, 95% CI: −0.043 to 0.048; unpaired *t*-test; Fig. 4). Furthermore, when dividing per prior block, we find that PD patients showed stronger negative correlations in the block with higher prior uncertainty than in the block with lower prior uncertainty ($t_{14}=-2.6$, $P=0.021$, 95% CI: −0.093 to −0.009; paired *t*-test). These results indicate that the PD patients detected trial-by-trial changes in current sensory uncertainty and responded appropriately, but this trial-by-trial reaction was weaker when there was less prior uncertainty or when patients were off medication.

In terms of task performance, PD patients had higher errors (i.e. higher standard deviations between their estimated position and the target coin's position) when uncertainty in prior or in likelihood was higher ($F_{1,103}=16.67$, $P<10^{-4}$, P>p, 95% CI: 0.006 to 0.018, for prior main effects; $F_{1,103}=106.53$, $P<10^{-16}$, L > l, 95% CI: 0.024 to 0.036 for likelihood main effects, rmANOVA with prior and likelihood uncertainty as fixed factors), being the highest when both uncertainties were higher (PL condition). This is to be expected, given that higher posterior uncertainty (uncertainty after incorporating both prior and current information) should result in overall larger errors (see Supplementary Information for additional analysis).

Our goal was to understand how dopamine and PD affect decision-making under uncertainty. Namely, we wanted to know how PD patients, who have deficits in dopaminergic transmission (especially in the putamen), react to changes in prior and current sensory uncertainty, what relative weight they place on each of these two types of information, and what the effect of dopaminergic medication is on these behaviours.

We found that PD patients were able to react to changes in both prior and current sensory uncertainty, and they did so in a way predicted by Bayesian statistics. We also found that dopaminergic medication affected the weight given to current versus prior information, with PD patients off medication relying less on current information compared with patients on medication (within and between participant effects) or age-matched controls. Finally, we discovered that although PD patients could still learn the different prior uncertainties to the same level as controls, they were impaired at reacting to changes in sensory uncertainty.

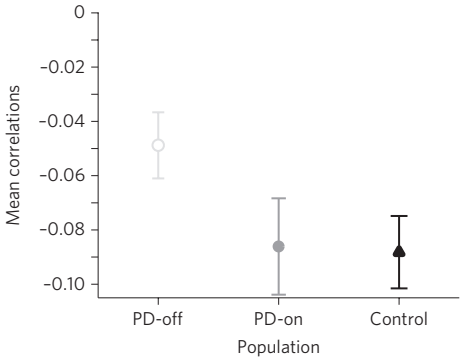

Figure 4 | Reaction to trial-by-trial changes in likelihood uncertainty. Mean ± s.e.m. Pearson's correlation values between a trial's specific likelihood/sensory uncertainty (s.d. of the cloud of dots shown in that trial) and the relative weight placed on sensory information in that trial (see Supplementary Methods for details) for PD patients off medication (open light grey circles), PD patients on medication (closed dark grey circle) and controls (black triangle), averaged across sessions (15 PD patients and 15 controls).

If dopaminergic transmission in the putamen directly signals prior uncertainty, we would expect PD patients to be impaired at learning and adapting to prior uncertainty. However, PD patients off medication were still able to learn prior uncertainty to the same level as controls. Dopamine and the putamen have been previously implicated in learning associated with some tasks[17,20,21]. Notably, however, they are not required for learning associated with all types of tasks. For example, in a study of PD patients, it was found that the dopaminergic drug state (on versus off) affected performance but not learning[26]. Dopaminergic medication increased learning in some tasks but decreased learning in others[21,27]. It has been proposed that dopaminergic medication may sometimes increase tonic dopamine levels in unaffected areas ('overloading' them), preventing phasic dips from being effective and so decreasing performance in tasks that require those areas[27]. Thus, although PD patients have dopamine deficits that affect transmission in the putamen, the patients in our task could still adapt to the different prior uncertainties, suggesting that the prior uncertainty information participants used did not come from there.

The finding that PD patients were still able to learn and use prior uncertainty provides mixed support to the results of a recent paper studying PD patients in a binary discrimination task[28]. In that study, PD patients were not able to use prior information, but still seemed to be sensitive to it. Although, in their study, the specific effects of prior uncertainty and of dopamine medication were not analysed (all PD patients were on medication), both studies revealed a potentially interesting dissociation between learning and the uncertainty of prior information (as in our task) and using prior information in a binary discrimination task (where the mean and variance of the prior uncertainty cannot be dissociated). This dissociation is interesting as it suggests that PD may affect the learning and use of the mean or the variance of prior information differently. Previous studies have found that the the mean and variance of prior information can be encoded separately[4,29] and that they generalize differently[30]. Alternatively, it may be that the use of prior information is affected in a visual discrimination task (as in ref. [28]), but not in a estimation task (such as ours). Follow-up studies to understand whether PD patients react to the mean and variance of prior information in different ways, and how their performance may be differently affected in a discrimination or an estimation task, would be very interesting.

PD patients off medication started with a lower average weight on current information compared with controls. We found both a within-participant and a between-participant effect of dopaminergic medication on the weight given to sensory information, with the administration of dopaminergic medication resulting in an increase in the sensory weight. This effect was strongest in early-stage PD patients, who have a more specific localized loss of dopaminergic neurons in the putamen. These results are in accordance with theories suggesting that dopamine affects the relative weight given to current bottom-up sensory evidence (likelihood) versus top-down prior information[10,18,19], and indicate that dopaminergic medication (and potentially dopamine itself) can increase the relative weight given to current information.

PD patients reacted to changes in the uncertainty of current sensory information, but less so than controls. Furthermore, this lower sensitivity was particularly pronounced in the context of more certain prior information. These results agree with the results obtained by Galea *et al.*[18], which showed that PD patients were slower to change their behaviour in response to an improbable stimulus when this stimulus was delivered in the context of an overall predictable sequence (that is, more certain prior information), but not when the sequence was unpredictable (uncertain prior information)[18]. Together, these results are compatible with a role of dopamine in directing attention to current stimuli[12,16,17]. Increased attention would give current sensory information more weight in general, and also enable the person to better detect its uncertainty, and hence respond appropriately to it. Furthermore, this could explain the asymmetry observed: more uncertain prior information may be in itself a drive for increased attention to current stimuli, and hence this may compensate for a patient's general lack of attention to it. However, to really know what dopamine is coding for, one should directly record dopaminergic activity[9,15,31]. Future studies with direct neural recordings; for example, in PD patients undergoing deep brain stimulation surgery[31], could measure the specific response of dopaminergic neurons to changes in current sensory uncertainty to verify if the observed lower sensitivity could indeed be due to dopamine promoting attention to current information and/or directly encoding its uncertainty[10,18,19].

We cannot be sure that the cause for the behavioural differences we observed in PD patients were specifically related to the putamen, as transmission from other structures is also affected in PD. Nevertheless, the putamen seems to be the brain structure most severely compromised in PD[8], and so it is likely that the observed effects are at least partly due to deficient dopaminergic transmission in the putamen. Furthermore, as mentioned previously, we saw significant effects of dopaminergic medication on the sensory weights of early-stage PD patients, whose deficits are more localized to the putamen[8]. It would be interesting to perform a similar study with other patient populations that have deficits in transmission in the putamen to see whether similar behaviours are observed.

We found that PD patients' behaviour could be captured successfully by a Bayesian framework. However, quantitatively, the weights obtained both for patients and controls were not exactly the 'statistically optimal' weights assuming the imposed variances. This could be because PD patients (and controls) were 'irrational'; that is, they had all the information available (including the imposed uncertainties) but still did not behave in a statistically optimal way. However, it is also possible (and, in our view, likely) that the participants' subjective prior and likelihood variances were not identical to the imposed ones, and this could explain the observed behaviour. The participants' subjective variances are unobservable (at least behaviourally), and hence can only be inferred. The goal of Bayesian statistics, in this context, is not to say that people are 'rational' or 'irrational', but instead to give a framework by which to understand the subjective information people are using in perception and decision-making. Adopting a Bayesian framework allowed us to find that PD can affect the sensitivity to likelihood uncertainty and the relative weight on senses, and promises to explain decision-making deficits in PD under a normative light[22,23].

While some patients in our experiment were taking only levodopa as dopaminergic medication, others were also taking dopamine agonists or monoamine oxidase B inhibitors, which have different effects on phasic and tonic dopamine and different decay times[25]. It is possible that if our sample had been more homogeneous, we would have seen even stronger medication effects. For example, increased tonic dopamine levels could have prevented us from seeing a stronger phasic response on uncertainty processing[27]. Here, we looked at the general effect of medication, but future studies could analyse the specific effect of different types of medication on these behaviours.

In our task, although we made sure that all participants had enough cognitive ability to understand our task, we did not explicitly assess IQ, years of education or income. Hence, we cannot be sure whether the differences we found between groups (for example, controls and PD patients) were related to the disease or to general differences in socioeconomic statuses. Nevertheless, the healthy controls recruited were mainly spouses or other close family members, who we assume would naturally match for most socioeconomic status measures. Most of our results should not suffer from this problem, as they are within-participant comparisons. Future studies could investigate whether the results we found within our PD group can be generalized to other tasks and groups.

The neural signalling of uncertainty is among the central topics in computational neuroscience[1,32]. However, preciously little is known about the way the brain actually solves those problems. There is an increasing volume of literature using functional magnetic resonance imaging studies to ask how neural activities change with uncertainty[4,5,33], but these studies cannot directly address the causal roles of brain areas or neurotransmitters. Here, we have used a different approach and started with a patient population that should, according to multiple theories, have deficits in the signalling of uncertainty. Our findings of retained prior uncertainty learning, a lower reliance on current information in PD patients off medication and a lower sensitivity to changes in current sensory uncertainty promise to inform the development of new theories about the representation of uncertainty.

Methods

Participants. In total, 15 PD patients (9 women; 62.8 ± 9.6 years old) and 15 age-matched controls (8 women; 63.4 ± 11.6 years old) participated in the experiment. Written informed consent was obtained for all participants. All protocols were approved by the Northwestern University Institutional Review Board. Additional details, including inclusion and exclusion criteria, can be found in the Supplementary Methods.

General procedure. PD patients completed two test sessions, one about 1 h after they had taken their regular dopaminergic medication (on medication) and one after overnight withdrawal from dopaminergic medication (off medication). The session order was counterbalanced across patients (randomly), so in total eight patients started on medication, and seven started off medication. Control participants also completed two test sessions, and the results reported for controls were the average of the results obtained in the two sessions.

Coin catching task. Participants performed a decision-making task in which they had to guess the position of a hidden coin on a screen[4] (Fig. 1a). They were told the cover story of a coin being tossed into a pond and informed that their task was to guess where the coin had fallen. They could not see the coin, but they could see five blue dots that were the 'splashes' produced by the coin falling in. They were told that the person who threw the coin aimed, albeit imperfectly, at the centre of the screen (mean of the prior information). They were also told that, between blocks, the thrower changed, and the new one might be better or worse at throwing (thus indirectly informing them that the variance of the prior information had changed). To estimate the coin position, participants could use (although they were never explicitly told so) both the likelihood of the coin's position, obtained from the 'splashes', and prior information (the distribution of previous coin locations). There was no temporal deadline; that is, participants had

as long as they needed to submit their response. See Supplementary Methods for additional details.

Data availability. Data are available from the corresponding author on reasonable request.

Code availability. Code to produce the results shown here is available from the corresponding author on reasonable request.

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Author contributions

Both authors designed the experiment. I.V. ran the experiments and analysed the data (with the supervision of K.P.K.). Both authors wrote the manuscript.

Additional information

Supplementary information is available for this paper.

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Competing interests

The authors declare no competing interests.