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Valence-dependent influence of serotonin depletion on model-based choice strategy

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Human decision-making arises from both reflective and reflexive mechanisms, which underpin goal-directed and habitual behavioural control. Computationally, these two systems of behavioural control have been described by different learning algorithms, model-based and model-free learning, respectively. Here, we investigated the effect of diminished serotonin (5-hydroxytryptamine) neurotransmission using dietary tryptophan depletion (TD) in healthy volunteers on the performance of a two-stage decision-making task, which allows discrimination between model-free and model-based behavioural strategies. A novel version of the task was used, which not only examined choice balance for monetary reward but also for punishment (monetary loss). TD impaired goal-directed (model-based) behaviour in the reward condition, but promoted it under punishment. This effect on appetitive and aversive goal-directed behaviour is likely mediated by alteration of the average reward representation produced by TD, which is consistent with previous studies. Overall, the major implication of this study is that serotonin differentially affects goal-directed learning as a function of affective valence. These findings are relevant for a further understanding of psychiatric disorders associated with breakdown of goal-directed behavioural control such as obsessive-compulsive disorders or addictions.

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INTRODUCTION

Flexible behaviour is crucial for adapting to the environment. When choosing an action, we use multiple strategies to obtain potential reward and to avoid potential punishment. Studies on humans and other animals suggest the existence of 'reflective' or goal-directed responses that depend on prospective consideration of future actions and their consequent outcomes in contrast to 'reflexive' or habitual responses that relies on retrospective experience with good and bad outcomes.[1–3]

Computationally, two behavioural control systems have been proposed to arise from different learning algorithms, model-based and model-free learning.[3,4] Specifically, a model-based strategy was linked to the goal-directed behavioural control, whereas a model-free strategy, which presumes choices based on previously reinforced actions, suggests shared similarities with habitual control.[3] Nevertheless, it is likely that habitual behaviour exceeds a simple reinforcement learning model-free mechanism.[5]

These two (often competitive) behavioural control strategies may depend on distinct neuronal systems, and more specifically on limbic (model-free) and on cognitive (model-based) corticostriatal circuits.[1,6,7] Chemical neuromodulation of these systems by the ascending monoaminergic projections has only recently been addressed. Namely, numerous studies have focused on the role of dopamine (DA) as a signal of positive prediction error in model-free learning.[8–10] Interestingly, administration of the dopaminergic precursor, levodopa, to healthy volunteers shifted behavioural performance to a model-based over a model-free strategy.[11]

In contrast, the question whether serotonin (5-hydroxytryptamine, 5-HT), another monoamine neurotransmitter, influences the degree to which behaviour is governed by either model-based or model-free systems has not been previously addressed. Serotonin is sometimes considered to be in an opponent, or alternatively in a synergistic, functional relationship with brain DA with respect to behavioural choice.[12]

Recent data show that manipulation of 5-HT can selectively produce effects on both appetitive and aversively motivated behaviour.[13,14] Consequently, 5-HT might influence the degree to which behaviour is governed by either model-based or model-free systems in both reward and punishment conditions.

In particular, selective activation of 5-HT neurons of the raphé nucleus promoted long-term optimal behaviour by facilitating waiting for the delayed rewards.[15,16] In contrast, low serotonin increased delayed reward discounting.[17] Consequently, lower serotonin neurotransmission may affect the prospective consideration of behavioural choices and consequently shift the balance between two behavioural controllers towards model-free behaviour. Under punishment, lowering of serotonin levels promoted lose-shift associative learning[18,19] and reduced the pavlovian inhibitory bias to aversive stimuli,[20,21] which potentially might shift the balance towards goal-directed behaviour.

To test these hypotheses formally, we designed a novel version of a model-based versus model-free paradigm based on a two-step sequential choice task[22] that dissociated the reward and punishment conditions. This task discriminates model-based and model-free behavioural strategies (Figure 1a). On each trial in stage 1, subjects made an initial choice between two stimuli, which led with fixed probabilities to one of two pairs of stimuli in stage 2. Each of the four second-stage stimuli was associated with

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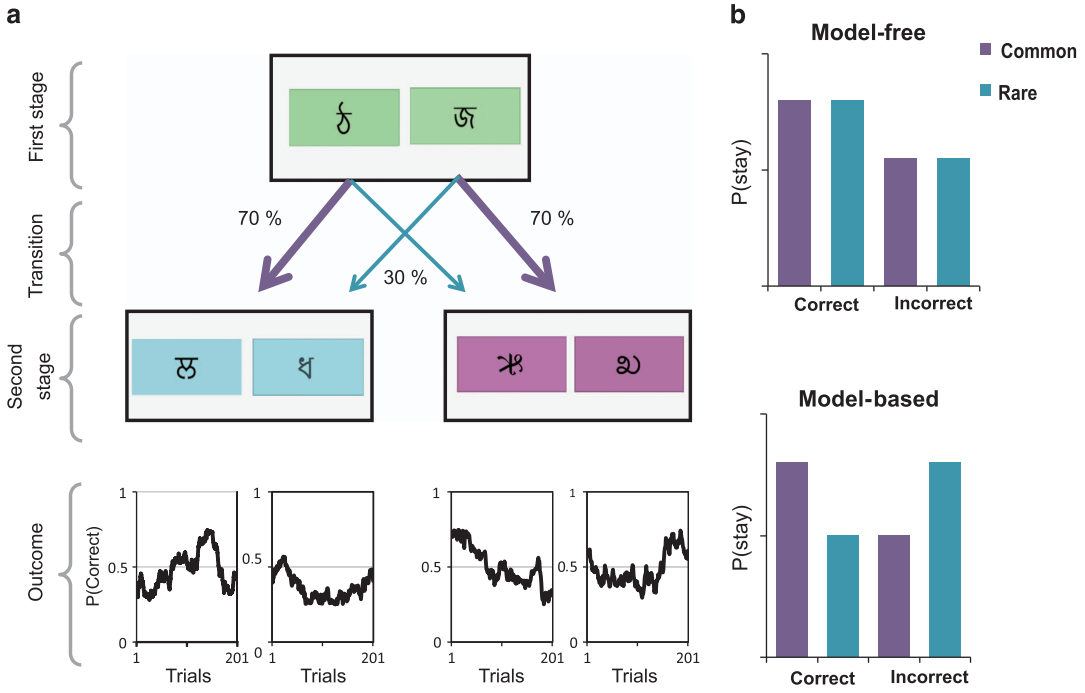

Figure 1. Two-stage decision-making task. Task. (**a**) On each trial (first stage), the initial choice between two stimuli (left-right randomised) led with fixed probabilities (transition) to one of two pairs of stimuli in stage 2. Each of the four second-stage stimuli was associated with probabilistic outcome: monetary reward in the reward or loss in the punishment version of the task. All stimuli in second stage were associated with probabilistic outcome, which changed slowly and independently across the trials. (**b**) Model-based and model-free strategies predict different choice patterns by which outcome obtained after the second stage affected subsequent first-stage choices. In the model-free system, the choices are driven by the reward or the no loss, which increase the chance of choosing the same stimulus on the next trial independently of the type of transition (upper row). In a model-based system, the choices of the stimuli on the next trial integrate the transition type (lower row).

probabilistic monetary reward (in the reward version of the task) or loss (in the punishment version of the task) (Figure 1a and Supplementary Experimental Procedures). As shown in Figure 1b, model-based or model-free learning are theoretically predicted to produce different patterns by which the events on a trial affect the subsequent first-stage choice. In particular, considering the first-stage choice (stay or shift) as a function of two factors, the transition probability (common or rare) and outcome (reward or punishment), model-free reinforcement learning predicts only a main effect of outcome, whereas the signature of model-based reinforcement learning is an interaction of reward by transition probability. Previous studies on healthy volunteers have shown an intermediate pattern (i.e., using both model-based and model-free strategies) of choice preference on this task, supporting evidence for both behavioural strategies.[22]

To influence serotonin neurotransmission, we used the dietary acute TD procedure in healthy volunteers, which induces a selective and transient reduction of central 5-HT in the human brain.[23–25]

METHODS

Experimental procedure

Session. A total of 44 participants were assigned to receive either the TD or the placebo (BAL) mixture in a randomised, placebo-controlled, double-blind order (Supplementary Information 1). They were asked to abstain from food and alcohol 12 h before the testing session. Upon arrival, participants completed questionnaires, gave a blood sample for the biochemical measures and ingested either the BAL or the TD drink. To ensure stable and low tryptophan (TRP) levels, behavioural testing was performed and the second blood sample was taken after a resting period of 5 h.

TD and biochemical procedures

TRP was depleted by ingestion of a liquid amino acid load that did not contain TRP but did include other large neutral amino acids (LNAAs) (see Supplementary Information 2 for biochemical composition of mixtures). Plasma total amino acid concentrations were measured by means of high-performance liquid chromatography with fluorescence end-point detection and precolumn sample derivatisation. The TRP:ΣLNAAs ratio was calculated as an indicator of central serotoninergic function.[25] The obtained values were entered in repeated measures analysis of variance (ANOVA) with time as a dependent factor and group as an independent factor.

Task

We used the two-stage decisional task with separate reward and punishment conditions (Supplementary Information 3). The reward version of the task was identical to the previously published task by Daw *et al.*[22] Briefly, on each trial in stage 1, subjects made an initial choice between two stimuli, which led with fixed probabilities (70 and 30% of choices) to one of two pairs of stimuli in stage 2. Each of the four second-stage stimuli was associated with probabilistic £1 monetary reward (in the reward version of the task) or loss (in the punishment version of the task), with probability varying slowly and independently over time (0.25 to 0.75). The punishment version had a different colour code and stimuli set on the first and second task stages. Both versions of the task had the same transition probabilities and dynamic range of the reward or the punishment probability. Participants completed 201 trials for each task version divided into three sessions. The order of performance of the task versions was counterbalanced and the two versions were separated by at least 1 h.

Before the experiment, all subjects underwent the self-paced computer-based instructions explaining the structure of the task and providing practice examples. Overall, the subjects were instructed to win as much money as they could in the reward version and to avoid monetary loss in the punishment version of the task. Participants were told that they would

be paid for the experiment depending on their cumulative performance in both task versions. They were paid a flat amount of £60 at the end of the experiment.

Behavioural analysis

Before analysis, we applied the arcsin transformation to the non-normally distributed behavioural variables and log transformation to the reaction times that allowed the normalisation of the data, with Shapiro–Wilk test < 0.05 for all variables in both groups.

For both versions of the task, we performed two types of analyses: one a factorial analysis of shifting and staying behaviour (which makes few computational assumptions), and the second the fit of a more structured computational model (Supplementary Information 4).

In the factorial analysis, stay probabilities at the first stage (the probability to choose the same stimulus as in the previous trial), transition probability on the previous trial (common (70%) or rare (30%)) and outcome (loss/no loss or reward/no reward) and group (TD or BAL) were entered into three-way mixed-measures ANOVA.

In a computational-fitting analysis, we fit a previously described hybrid model (Supplementary Information 4)[22] to choice behaviour, estimating free parameters for each subject separately by the method of maximum likelihood. This model contains a separate term for model-free temporal difference algorithm and model-based reinforcement-learning algorithm.

Model selection was performed with a group-level random-effect analysis of the log-evidence obtained for each tested model and subject (Supplementary Information 5). The estimated parameters were fitted to the winning model (see Supplementary Information 5 for parameters optimisation) and were compared between the groups using multivariate ANOVA analysis after normality distribution test and square root transformation of the non-normally distributed variables.

RESULTS

A total of 22 TD and 22 control (BAL) healthy volunteers were included in the study in a double-blind, counterbalanced design. The groups were matched by gender, age and had no differences in IQ level (Supplementary Table S1).

Post-procedure biochemical analysis showed that TD robustly decreased the TRP:ΣLNAAs ratio relative to the BAL group (main effect of group: $F_{(1,42)} = 41.595$, $P < 0.0001$; main effect of time: $F_{(1,42)} = 5.402$, $P = 0.025$; group × time interaction: $F_{(1,42)} = 41.916$, $P < 0.0001$). *Post hoc* analysis showed significant ($t_{42} = 10.634$, $P < 0.0001$) reduction of serum TRP concentration in the TD group (mean ± s.d.: 75.78 ± 23.07%), but not in BAL (mean ± s.d.: 25.00 ± 2.5%, $t_{42} = 1.6$, $P = 0.18$). There was no effect of task order or an interaction of task order with TD (both $F_{(1,42)} < 1.0$).

We considered staying and shifting of responses as direct markers of model-free and model-based learning. Using mixed-measures ANOVA, we examined the probability of staying or shifting at the first task stage dependent on the between-subjects factor of group (TD or BAL) and within-subject factors of task valence (reward or punishment), outcome (rewarded, non-rewarded, punished or unpunished) and transition probability on the previous trial (common (70%) or rare (30%)).

We found main effects of group ($F_{(1,41)} = 4.22$, $P = 0.046$), outcome ($F_{(1,41)} = 17.06$, $P < 0.0001$) and transition probability ($F_{(1,41)} = 32.16$, $P < 0.0001$), but no main effect of valence ($F_{(1,41)} = 1.46$, $P = 0.22$). Across all subjects and conditions, the finding of both a main effect of outcome and outcome × transition probability interaction ($F_{(1,41)} = 28.24$, $P < 0.0001$) showed that the subjects used both model-free and model-based strategies, respectively. Importantly, the outcome × transition probability interaction (the signature of model-based learning) was significantly modulated by TD (outcome × transition probability × group interaction ($F_{(1,41)} = 6.21$, $P = 0.017$)), and this modulation was itself further modulated by valence (valence × outcome × transition probability × group interaction ($F_{(1,41)} = 11.55$, $P = 0.001$)). There

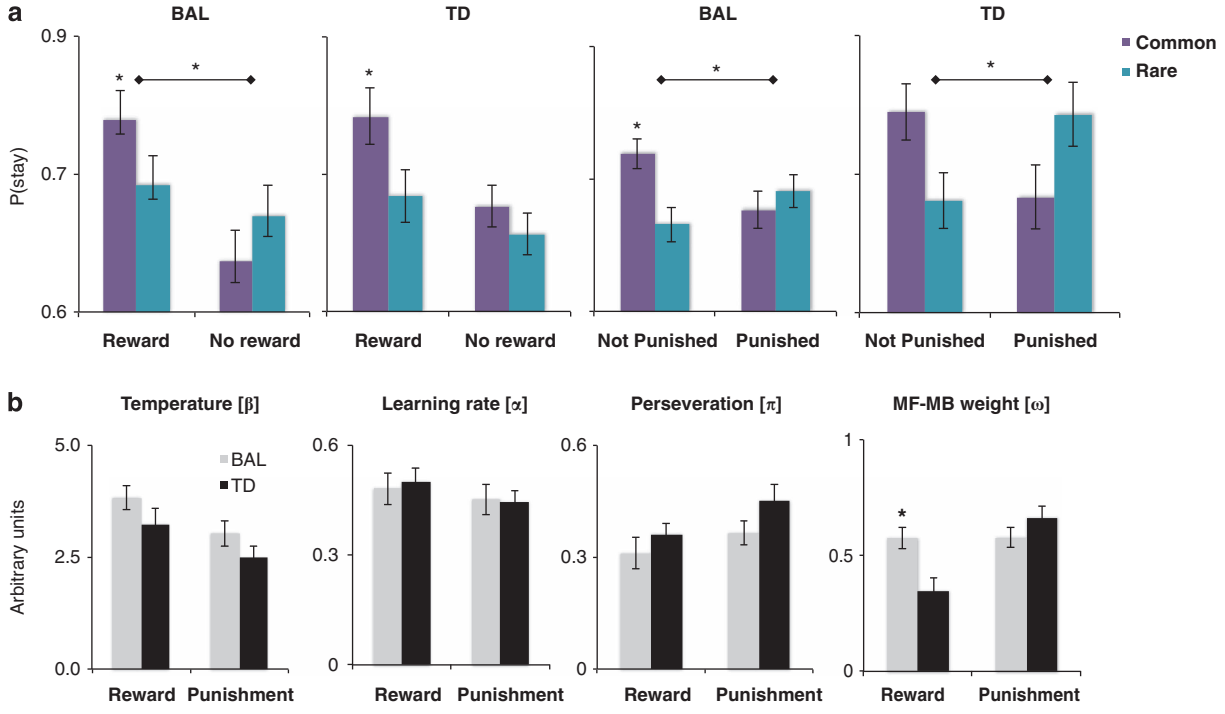

Figure 2. (**a**) Factorial (stay-shift) behavioural results. Separate analysis of task valence showed a mixed choice strategy in BAL and a shift to a model-free choice strategy in the TD group in the reward condition. In the loss condition, the significant interaction between outcome × transition in the TD group indicates a shift of behavioural choice towards a model-based strategy. (**b**) Computationally fitted behavioural results before arscin transformation. Compared with BAL, the TD group showed a significant difference in the weighting factor ω in reward condition. BAL = control group; TD = TRP-depleted group. *$P < 0.05$.

was no outcome × group interaction ($F_{(1,41)} = 0.78$, $P = 0.38$), suggesting an absence of effect of TD on model-free learning.

These results indicate that TD affects model-based behaviour in a way that depends on valence, justifying further analyses separated by task valence (reward versus punishment) and by group (TD versus BAL) (Figure 2a).

This analysis of task valence showed a main effect of outcome (i.e., reward or no reward) ($F_{(1,42)} = 26.18$, $P < 0.0001$), transition probability ($F_{(1,42)} = 4.87$, $P = 0.033$) and an outcome × transition probability × group interaction ($F_{(1,42)} = 6.63$, $P = 0.014$) in the reward version. *Post hoc* separate comparisons of BAL versus TD showed a main effect of outcome ($F_{(1,21)} = 14.62$, $P = 0.001$) and an outcome × transition probability interaction ($F_{(1,21)} = 6.65$, $P = 0.018$) in the BAL group only (Figure 2a), indicating both model-free and model-based components in choice performance, in accordance with previous results.[22] In the TD group, the only significant main effect was that of outcome ($F_{(1,21)} = 11.58$, $P = 0.003$) suggested a behavioural shift to the model-free strategy (Figure 2a).

In the punishment version, there were main effects of transition probability ($F_{(1,42)} = 7.88$, $P = 0.008$) with a significant outcome × transition probability interaction ($F_{(1,42)} = 18.80$, $P < 0.0001$), but no main effect of outcome (i.e., loss or no loss) ($F_{(1,42)} = 0.24$, $P = 0.62$). Overall, this result shows that subjects were aware of the task structure and demonstrated model-based behaviour in this task version. *Post hoc* analysis showed a mixed strategy (both model-free and model-based components in choice performance) in BAL: main effect of outcome ($F_{(1,21)} = 8.04$, $P = 0.01$) and outcome × transition probability interaction ($F_{(1,21)} = 4.77$, $P = 0.04$). For TD, there was only a significant outcome × transition interaction ($F_{(1,21)} = 12.07$, $P = 0.002$), suggesting the use of a model-based strategy in this version of the task (Figure 2a). Overall, these results suggest that TD reduces model-based learning in the reward condition, while promoting it in the punishment condition.

In addition to the preceding factorial analysis of staying-shifting behaviour, we examined these results more closely by fitting participants' choices to a computational model of the learning process, so as to estimate the effects of our manipulations in terms of the parameters of the model, which have interpretations in terms of specific computational processes.[22] We first used model selection (Supplementary Tables S2 and SI.5) to determine which parameters should be included to optimally model the data. In this analysis, we fitted the behavioural data with computational models of increasing complexity from a pure model-free reinforcement-learning model Q-SARSA (two free parameters) to more complex 'hybrid' models involving both model-based and model-free learning (four free parameters).

Similar to previous reports,[11] the model with the best fit for the data in each group of subjects (TD and BAL) and task valence (reward versus punishment) had four free parameters controlling both model-based and model-free learning: learning rate α, softmax temperature β (control the choice randomness), perseverance index ρ (captures perseveration ($\rho > 0$) or shifting ($\rho < 0$) in the first-stage choices) and the weighting factor ω, which provides an index of the relative engagement of a model-free versus model-based behavioural choices (where lower scores indicate a shift to habitual model-free choices and higher scores indicate a shift to model-based choices).

In accordance with data for stay and shift behaviour in the reward condition, a multivariate ANOVA showed that, compared with the BAL group, the TD group had a lower ω ($F_{(1,39)} = 6.93$, $P = 0.012$) and a trend to a higher perseverance index ($F_{(1,37)} = 2.99$, $P = 0.092$). In contrast, there was no significant difference between the groups in the parameters of the loss version of the task (see also Supplementary Table 4, Figure 2b and Supplementary Information 6).

The analysis of choice reaction times showed no difference between the groups on the first or second stages of the task (all $P > 0.1$) or between loss and reward version of the task (all $P > 0.1$). There were more omitted trials in the punishment version of the task in both groups, but no difference between the groups ($F < 1.0$). Finally, there was no difference between the groups in cumulative learning in both versions of tasks (reward: $F_{(1,42)} < 0.1$, loss: $F_{(1,42)} = 1.31$, $P = 0.25$).

DISCUSSION

The balance between model-based and model-free behavioural control is suggested to determine at least some aspects of our decisional process, being framed as a competition and/or co-operation between a flexible prospective goal-directed system and fixed retrospective system.[4]

Here, we investigated the modulatory role of serotonin in the balance between these two systems, and provide evidence that diminished serotonin neurotransmission, effected by TD, influences goal-directed behaviour while leaving intact the model-free choice strategy. Overall, in the reward condition, TD impaired goal-directed behaviour and shifted the balance towards the model-free strategy. However, this effect changed with motivational valence. In the punishment condition, the factorial analysis pointed to an increase of behavioural goal-directness, although a secondary computational model-fitting analysis failed to fully corroborate this second result. Both animal[23] and human studies[26] have suggested a selective TD effect on central serotonin, with no effect on DA and norepinephrine neurotransmission; hence, these findings are likely to be neurochemically specific.

These effects of TD support a dual role for 5-HT mechanisms in the choice strategy balance depending on outcome valence. Modulation of the representation of average reward rate is a possible mechanism of shifting of the behavioural balance in either reward or punishment conditions. This interpretation grows out of several ideas from the modelling literature: first, that serotonin may help report average reward[27,28] and, second, that this quantity should affect the tendency to use model-based choice, as it represents the opportunity cost (or in the punishment condition, benefit) of time spent deliberating.[29,30] More specifically, in the 'average-case' reinforcement-learning model, the average reward is a signal that provides an estimation of the overall 'goodness' or 'badness' of the environment[27] (also see the Supplementary Information 6 for further discussion on this point).

A tonic serotonergic signal has been previously suggested to report average reward rate over long sequences of trials, either positively[27] or negatively.[28] Lowering serotonin neurotransmission in the brain via the TD procedure would result in increases in the average reward signal representation and a shift toward model-free responding. The opportunity cost considerations of Keramati *et al*[30] offer an explanation of the effect of TD on the reward condition. Finally, as for the punishment condition, the opportunity cost of time inverts and becomes a benefit (as any time spent not being punished is better than average[31]), which may help explain why the sign of the effect reverses in this condition (also see the Supplementary Information 6 for further discussion on this point).

One can also argue that the effects observed here might ultimately result from a nonspecific 5-HT depletion effect on cognitive functions that affects performance on the two-stage task. Indeed, there are quite consistent deleterious effects of 5-HT depletion on working memory,[32] which may prevent engagement in model-based strategies.[33] However, in that case, we would have expected promotion of model-free behavioural choice, independent of valence, but that result was not observed here.

Confidence or uncertainty about the choice at different levels (i.e., confidence about reward outcome or higher level confidence about that belief) could also potentially affect results. Numerous

studies have shown the main effect of uncertainty to be on the modulation of learning rates.[34,35] However, as we did not observe any difference in learning rates between the groups in either valence conditions, it is also unlikely that effects on choice confidence could explain the reported results.

Low serotonin has been also showed to prone the risky decisions in reward condition[36,37] and risk-aversion under the punishment.[38] However, how the risk influences the goal-directed behaviours remains unclear, and further studies are needed to address this point.

Finally, in view of the proposed functional interaction of 5-HT with brain DA and evidence for the influence of DA in the balance between model-based and model-free strategies, it is possible that the effect of TD was mediated ultimately via interactions with the DA system. TD had the opposite effect to that of levodopa administration[11] by alteration of the model-based strategy. This would argue for synergy or co-operation between the DA and 5-HT systems. Nonetheless, a recent study has shown highly parallel effects of selective 5-HT depletion in rats and TD in humans on a similar task measuring increases in impulsive behaviour,[39] suggesting that the effects of TD are likely to be mediated via 5-HT loss. However, our results will ultimately require confirmation using other means to reduce central 5-HT function,[40] although there are no other clear-cut means to do this in human volunteers. The effects of nonspecific 5-HT receptor agents, for example, would be difficult to interpret. However, it would be of theoretical, as well as clinical, value to test the effects of enhanced 5-HT neurotransmission produced by administration of selective serotonin re-uptake inhibitors. In addition, there are no available data to clarify how DA modulates behavioural choice in the punishment condition of the task and therefore the nature of any possible interaction with the 5-HT system. However, it has been reported following either DA D2 receptor blockade or Parkinson's disease, which is characterised by diminished striatal DA neurotransmission, that there is greater attention to stimuli associated with punishment than with reward.[8,9,41] We also did not show a specific effect of 5-HT depletion on model-free or habitual response in the behavioural analysis. The two-step task or model-free reinforcement learning has been suggested not to fully capture habit expression; further studies focusing on conventional over-training and testing in extinction may help clarify the effect of 5-HT depletion on habit.[5]

The major implication of this study is that 5-HT contributes to both appetitive and aversive learning, an increasingly supported view.[13,42,43] As model-free and model-based learning appear to have different anatomical correlates within the corticostriatal circuitry, as shown by functional neuroimaging[44–46] and rodent lesion studies,[1,47] it could be speculated that decreases in central 5-HT neurotransmission may affect these types of learning at different anatomical locations.

Finally, our findings are also of clinical interest, as impairment of goal-directed responses has been put forward as a theoretical framework for a range of psychiatric disorders.[48] In particular, impairment of goal-directed behavioural control has been evidenced in obsessive-compulsive disorders, as well as in substance addictions and eating disorders.[49,50,51]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

Supplementary Information

Valence-dependent influence of serotonin depletion on model-based choice strategy

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SI 1. Participants' inclusion criteria and characteristics

The East of England-Essex Research Ethics Committee approved this study. Participants were recruited from university-based advertisements and from Cambridge BioResource (www.cambridgebioresource.org.uk) and gave informed consent prior to participation. The inclusion criteria were as follows: age 18 – 45 years, no history of neurological or psychiatric disorders as assessed with the Mini International Neuropsychiatric Inventory (1), no regular or recreational use of drugs including nicotine, no significant physical illness and not currently taking any type of regular medication (except contraceptive pills for women).

Supplementary Table 1. Participants' demographic and behavioural data

	BAL (n=22)	TD (n=22)	t	p
Age	27.78 ± 1.61	30.50 ± 1.84	0.139	0.890
Men (number)	11	10	0.091*	0.762*
IQ	120.67 ± 1.96	120.20 ± 1.62	0.037	0.879
BDI	3.54 ± 0.92	3.05 ± 0.79	0.413	0.682
STAI, trait	46.84 ± 1.30	44.88 ± 0.10	-0.975	0.335
STAI, state	44.23 ± 1.04	45.62 ± 0.97	-1.264	0.213
STAI, state, post-procedure	41.26 ± 1.26	44.33 ± 1.09	-1.64	0.293

*- chi square test; Reported as means ± SEM values, TD = tryptophan depleted group; BAL = control group. BDI = Beck Depression Inventory; STAI = Spielberg State-Trait Anxiety Inventory (STAI).

SI. 2 Session schedule and tryptophan depletion procedure

Participants were assigned to receive either the tryptophan depleting drink (TD) or the placebo mixture in a randomized, placebo-controlled, double blind order.

Prior to participation, participants were asked to abstain from food and alcohol 12 hours before the testing session. Upon arrival in the morning, they completed questionnaires, gave a blood sample for the biochemical measures and ingested either the placebo or the TD drink. To control for mood and anxiety state, we administrated the Beck Depression Inventory (BDI) (2) and the Spielberg State-Trait Anxiety Inventory (STAI) (3). A proxy of an intelligence quotient (IQ) was measured using the National Adult reading Test (NART) (4). To ensure stable and low tryptophan levels, the behavioral testing was performed and the second blood sample taken after a resting period of approximately 5 hours. Low-protein snacks (biscuits, vegetable sandwiches and fruits) were provided to the participants during the waiting period.

In the TD procedure, tryptophan was depleted by ingestion of a liquid amino acid load that did not contain tryptophan but did include other large neutral amino acids (LNAAs). Amino acid mixtures (SHS International, Liverpool, UK) were as follows: TD: L-alanine, 4.1 g; L-arginine, 3.7 g; L-cystine, 2.0 g; glycine, 2.4 g; L-histidine, 2.4 g; L-isoleucine, 6 g; Lleucine, 10.1 g; L-lysine, 6.7 g; L-methionine, 2.3 g; Lproline, 9.2 g; L-phenylalanine, 4.3 g; L-serine, 5.2 g; Lthreonine, 4.9 g; L-tyrosine, 5.2 g; and L-valine, 6.7 g. Total: 75.2 g. Placebo: same as ATD, plus 3.0 g of L-tryptophan. Total: 78.2 g.

The drinks were prepared by stirring the mixture and lemon–lime flavouring into 200 ml tap water.

Plasma total amino acid concentrations (tyrosine, valine, phenylalanine, isoleucine, leucine, and tryptophan) were measured by means of high-performance liquid chromatography with fluorescence end-point detection and precolumn sample derivatization. The tryptophan/large neutral amino acid (TRP:ΣLNAAs) ratio was calculated as an indicator of central serotonergic

function. The obtained values were entered in repeated measures ANOVA with time as a dependent and group as independent factors.

SI 3. Task

We used the two-stage decision task with reward and punishment conditions implemented by MATLAB 2010a and Cogent 2000.

The reward version of task was identical to previously published task by Daw et al. (2011). The punishment version had a different colour code and stimuli set on the first and second task stages. Both versions of the task had the same transition probabilities and dynamic range of the reward or the punishment.

Before the experiment, all subjects underwent the self-paced (approximately 10 min) computer-based instructions explaining the structure of the task and providing practice examples. Overall, the subjects were instructed to win as much money as they could in the reward version and to avoid monetary loss in the punishment version of the task. The order of performance of the versions of the task was counter-balanced and the two versions were separated by at least 1 hour.

On each trial in Stage 1, subjects made an initial choice between two stimuli, which led with fixed probabilities (70 % and 30 % of choices) to one of two pairs of stimuli in Stage 2. Each of the four second-stage stimuli was associated with a probabilistic monetary reward (in the Reward version of the task) or loss (in the Punishment version of the task), with probability varying slowly and independently over time (0.25 to 0.75), as shown in Fig 1A.

On each stage of the task, participants had 2 seconds to make a decision. The transition time between the stages was 1.5 seconds. If no response was performed within 2 seconds, the trial was aborted (indicated by red cross on the stimuli). No outcome was associated with omitted

trials. The reward was a picture of a one-pound coin. The punishment was a monetary loss of £1, indicated as a one pound coin overlaid with a red cross. Participants completed 201 trials for each task version divided into 3 sessions (with a mean duration of session of approximately 9 minutes). The omitted trials were discarded from the analysis for each task version and for each participant.

Participants were told that they would be paid for the experiment depending on their cumulative performance in both task versions. They were paid a flat amount of £60 at the end of the experiment.

The mean cumulative earnings for both groups were as follows: (Mean ± SD), Reward: TD - 28.21 ± 0.96 £; BAL - 28.50 ± 0.99 £; Loss: TD - 25.50 ± 1.06 £; BAL - 27.59 ± 0.85 £.

The task was a part of a larger tests battery and was generally performed as the 1st and the 3d task in the battery order. The mean time between the drink intake and task performance was respectively 5 and 6.5 hours.

SI 4. Computational model

The detailed description of the hybrid model is provided in Daw et al. (2011). The algorithm included both model-based and model-free subcomponents, which allowed for mapping each state-action pair to its expected future value.

The model-free strategy was computed using the SARSA (λ) temporal difference learning. At each stage *i* of each trial *t,* the value for the each state-action pair was calculated as follows:

$$Q_{TD}(s_{i,t}, a_{i,t}) = Q_{TD}(s_{i,t}, a_{i,t}) + \alpha_i \delta_{i,t}$$

where $\delta_{i,t} = r_{i,t} + Q_{TD}(s_{i+1,t}, a_{i+1,t}) - Q_{TD}(s_{i,t}, a_{i,t})$ and α_i is a free learning parameter. The full model allows different learning rates α_1 and α_2 for the two task stages. The reinforcement

eligibility parameter (λ) determines the update of the first-stage action by the second-stage prediction error as follows: $Q_{TD}(s_{1,t}, a_{i1,t}) = Q_{TD}(s_{1,t}, a_{1,t}) + a_1\lambda\delta_{2,t}$.

The model-based reinforcement-learning algorithm was computed by mapping state-action pairs to a transition function and assuming that participants choose between two possibilities, as follows: $P(S_B \mid S_A, a_A) = 0.7$, $P(S_C \mid S_A, a_B) = 0.7$ for the common or $P(S_B \mid S_A, a_A) = 0.3$ $P(S_C \mid S_A, a_B) = 0.3$ for the rare transition, where S is a state (first stage: S_A; second stage: S_B and S_C), and a is an action (two actions - a_A and a_B).

The action value (Q_{MB}) was computed at each trial from the estimates of the transition probabilities and rewards and was defined for the first stage as follows:

$$Q_{MB}(s_A, a_i) = P(s_B \mid s_A, a_i) \max_a Q_{TD}(s_B, a) + P(s_C \mid s_A, a_i) \max_a Q_{TD}(s_C, a)$$

Finally, to connect the values to choices, the weighted sum of the model-free and model-based values was computed for the first stage as defined:

$$Q_{net}(s_A, a_j) = w\, Q_{MB}(s_A, a_j) + (1\text{-}w)\, Q_{TD}(s_A, a_j)$$

where *w* is the weighting parameter.

Assuming that two approaches coincide at the second stage, and that $Q_{MB} = Q_{TD}$, at the second stage $Q_{net} = Q_{MB} = Q_{TD}$. Then, the probability of a choice is the softmax equation for Q_{net}:

$$P(a_{i,t} = a \mid s_{i,t}) = \frac{\exp(\beta_i [Q_{net}(s_{i,t}, a) + p * rep(a)])}{\Sigma_{a'} \exp(\beta_i [Q_{net}(s_{i,t}, a) + p * rep(a)])}$$

where the free inverse temperature parameters (β_i) control the choice randomness, and *p* captures perseveration ($p > 0$) or switching ($p < 0$) in the first-stage choices. In total, the fully parameterized model contains 7 free parameters ($\beta 1$, $\beta 2$, $\alpha 1$, $\alpha 2$, λ, π, ω), with special cases of pure model-based ($\omega = 1$) and model-free ($\omega = 0$) models.

SI 5. Parameters optimization and model selection procedure.

We optimized model parameters by maximizing the Laplace approximation to the model evidence with Matlab's fmincon function. To ensure convergence the number of function iterations and evaluation of fmincon function were increased from the default value to 1000 000. The Laplace approximation to the model evidence (log of posterior probability) was calculated as: $LPP = \log(\sum P(D|M,\theta)))$,

where D, M and θ represent the data, model and model parameters respectively, assuming the parameters distributed as follows: learning rate betapdf(lr1,1.1,1.1), temperature gampdf(beta1,1.2,5), perseveration normpdf(ps,0,1) and finally model-free/model-based weighting parameter betapdf(w,1.1,1.1). The same approach has been used in a previous study in (Daw et al Neuron 2011).

The probability corresponds to the marginal likelihood, which is the integral over the parameter space of the model likelihood weighted by the prior on free parameters. This probability increases with the likelihood (which measures the accuracy of the fit) and is penalized by the integration over the parameter space (which measures the complexity of the model). The model evidence thus represents a trade-off between accuracy and complexity and can guide model selection.

Model selection was performed with a group-level random-effect analysis of the log-evidence obtained for each model and subject, using the VB-toolbox (5)

(https://code.google.com/p/mbb-vb-toolbox/). This procedure estimates the expected frequencies of the model (denoted PP) and the exceedance probability (denoted XP) for each model within a set of models, given the data gathered from all subjects. Expected frequency quantifies the posterior probability, i.e. the probability that the model generated the data for any randomly selected subject. This quantity must be compared to chance level (one over the number of models in the search space). Exceedance probability quantifies the belief that the model is more likely than all the other models of the set, or in other words, the confidence in the model having the highest expected frequency.

SI 6. Parameters correlation.

Across all subjects, we found the following correlations of model parameters that survived Bonferroni correction of multiple comparisons: in the Loss version of the task - a significant correlation between β and π ($r = -0.482$, $p = 0.002$) and in the Reward version of the task - between α and β ($r = -0.420$, $p = 0.006$).

SI 7 Supplementary discussion

Here, we investigated the modulatory role of serotonin in the balance between these two systems and provide evidence that diminished serotonin neurotransmission, effected by TD, influences goal-directed behaviour while leaving intact the model-free choice strategy. Overall, in the reward condition TD impaired goal-directed behaviour and shifted the balance towards the model-free strategy. However, this effect changed with motivational valence. In the punishment condition, the factorial analysis pointed to an increase of behavioural goal-directness, although a secondary computational model-fitting analysis failed to fully corroborate this second result. Both animal (6) and human studies (7) have suggested a selective TD effect on central serotonin, with no effect on dopamine and norepinephrine neurotransmission, hence these findings are likely to be neurochemically specific.

These effects of TD support a dual role for 5-HT mechanisms in the choice strategy balance depending on outcome valence. Modulation of the representation of average reward rate is a possible mechanism of shifting of the behavioural balance in either reward or punishment conditions. This interpretation grows out of several ideas from the modelling literature: first, that serotonin may help to report average reward (8, 9) and second, that this quantity should affect the tendency to employ model-based choice since it represents the opportunity cost (or in the punishment condition, benefit) of time spent deliberating (10, 11). More specifically, in the 'average-case' reinforcement-learning model, the average reward is a signal that provides an estimation of the overall 'goodness' or 'badness' of the environment (8). Theoretically, this quantity plays an important role in numerous aspects of choice; for instance, it characterizes the opportunity cost of time (9, 10): if the average reward is high, then any time spent *not* earning reward is relatively more costly. This opportunity cost effect might affect the balance between model-based and model-free behaviour (11). If the brain allocates time to deliberating (to produce model-based behaviour) by balancing the opportunity cost of time spent this way against the rewards gained (by making improved decisions) from doing so, then when the average reward is high, model-free responding is more favored (11).

Meanwhile, a tonic serotonergic signal has been previously suggested to report average reward rate over long sequences of trials, either positively (8) or negatively (9). Putting these two points together, then, on the latter suggestion, lowering serotonin neurotransmission in the brain via the TD procedure would result in increases in the average reward signal representation and a shift toward model-free responding. Keramati et al's (11) opportunity cost considerations thus offer an explanation of the effect of TD on the reward condition. Finally, as for the punishment condition, the opportunity cost of time inverts and becomes a benefit (since any time spent not being punished is better than average (12)), which may help

to explain why the sign of the effect reverses in this condition (please, also see the SI 6 for further discussion on this point).

A related interpretation of the results reported here might be that TD differentially affects the impact or desirability of the rewards or punishments themselves: again, by Keramati's (11) logic, model-based deliberation will be more (or less) worth engaging in the better (or worse) is the outcome thus obtained. Note that in the current model, condition-wise changes in the scaling of rewards should be reflected in changes in the estimated temperature parameter β; in other words, choices should become more or less deterministic. We did not see any such effects. However, this prediction is specific to the softmax choice rule assumed here, and would not be expected under other plausible forms like a Luce choice rule.

Supplementary Table 2. Values of the best model parameters in all subjects.

Name	**α**	**β**	**π**	**ω**
Lower limit	0	0	-Inf	0
Upper limit	1	Inf	Inf	1
Mean	3.2314	0.4331	0.4447*	0.5062
Median	2.7235	0.4614	0.3434	0.5304
Max	10.8778	0.9693	1.6741	0.9831
Mean	0.4281	0.0004	0.0089	0.0064

Mean ± SEM. *$t(87)=11.4$, $p < 0.001$.

Supplementary Table 3: Model selection results

	Model 1	**Model 2**	**Model 3**	**Model 4**
DF	**2 (α, β)**	**3 (α, β, ω)**	**3 (α, β, π)**	**3 (α, β, π , ω)**
All subjects (XP)	0	0	0	1
All subjects (EF)	0.0009±0.0003	0.0015±0.0005	0.0069±0.0007	**0.9906±0.0011**
Bal/Rew (XP)	0	0	0	**1**
Bal/Rew (EF)	0.0031±0.0023	0.0060±0.0036	0.0164±0.0039	**0.9745±0.0073**
Bal/Pun (XP)	0	0	0	**1**
Bal/Pun (EF)	0.0024±0.0022	0.0031±0.0028	0.0153±0.0046	**0.9791±0.0073**
TD/Rew (XP)	0	0	0	**1**
TD/Rew (EF)	0.0051±0.0030	0.0086±0.0042	**0.0569±0.0081*†**	**0.9294±0.0104*†**
TD/Pun (XP)	0	0	0	**1**
TD/Pun (EF)	0.0029±0.0024	0.0047±0.0031	0.0309±0.0057	**0.9615±0.0084**

DF - degree of freedom; XP - model exceedance probability; EF - model expected frequency; Bal – control group; TD - tryptophan depleted group. Expected frequencies are reported as Mean ± SEM. * $t(21) > 2.9$, $p < 0.01$, paired t-test compared to the TD punishment task. † - $t(42) > 3.5$, $p < 0.01$, unpaired t-test compared to the Bal reward task.

Supplementary Table 4. Parameters Values of the best-fitting computational model before arscin transformation

Parameter	TD group	BAL group
Reward condition :		
Learning rate (α)	0.48 ± 0.05	0.49 ± 0.04
Choice temperature (β)	3.23 ± 0.32	3.80 ± 0.44
Perseverance index (π)	0.36 ± 0.04	0.31 ± 0.03
Weighting factor (ω)	0.34 ± 0.05	0.57 ± 0.06
Punishment condition :		
Learning rate (α)	0.44 ± 0.05	0.45 ± 0.05
Choice temperature (β)	2.48 ± 0.34	3.02 ± 0.37
Perseverance index (π)	0.44 ± 0.06	0.36 ± 0.04
Weighting factor (ω)	0.66 ± 0.06	0.57 ± 0.04

Supplementary Figure 1. Computational models comparisons.

(A) Shows the first level choices as a function of the outcome (correct: 1£ in reward condition and 0£ in punishment condition; incorrect: 0£ in reward condition or -1£ in punishment condition) and transition probability of the real and virtual subjects (model simulation) across all conditions and groups: n = 88. Data are shown for the four different computational models. (B) Model-based index and perseveration index (see definition in the text) as a function computational models.

Supplementary Figure 2.

The figure depicts the effect of valence (reward versus punishment) in the posterior probability of the model 3 (with perseveration, without model-based) and 4 (with perseveration and model-based) as a function of pharmacological manipulation (BAL = balanced; TD = acute tryptophan depletion). TD causes an increase in the frequency of the model 3 and a concomitant decrease of the frequency of the model 4 in the reward compared to the punishment condition.

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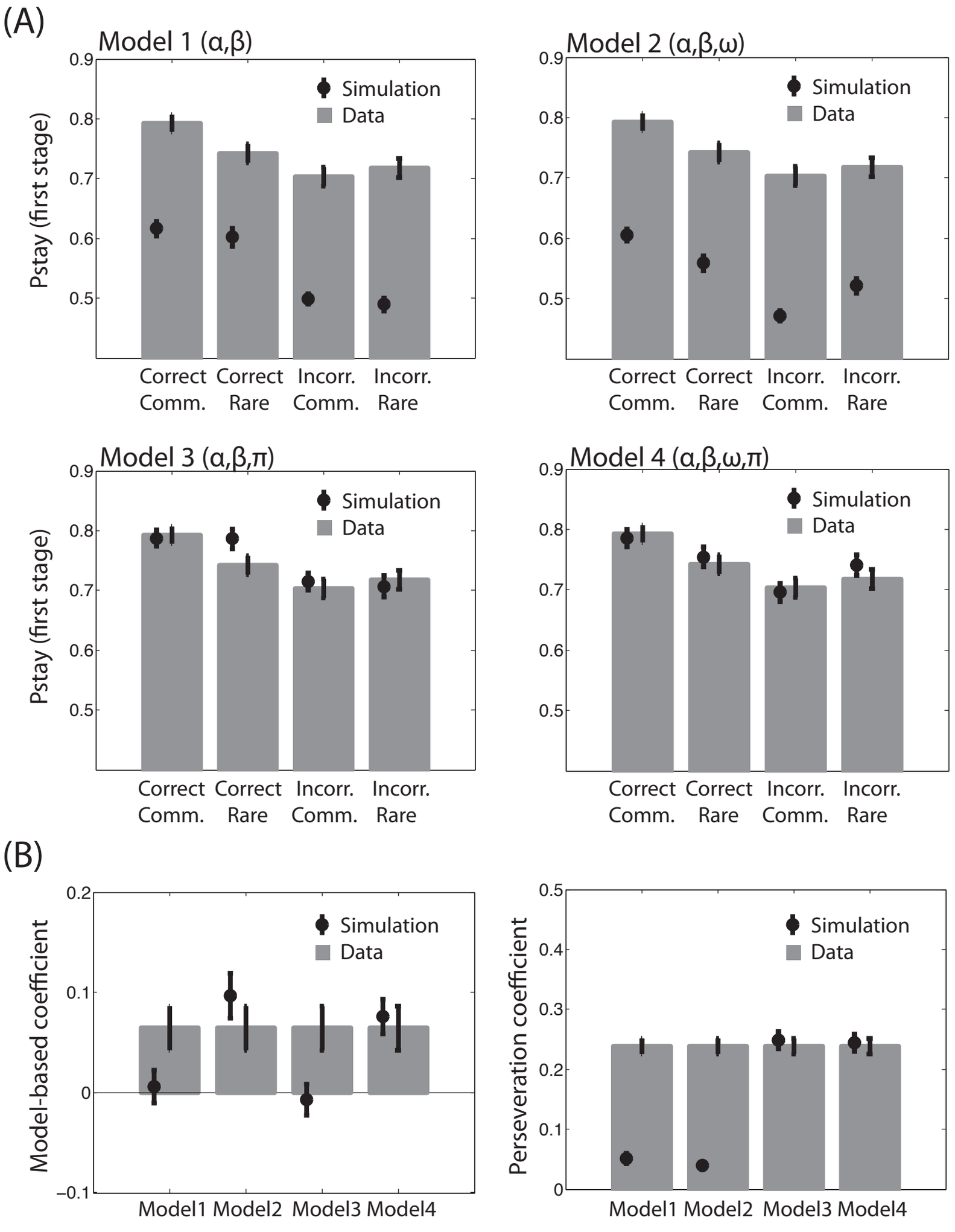
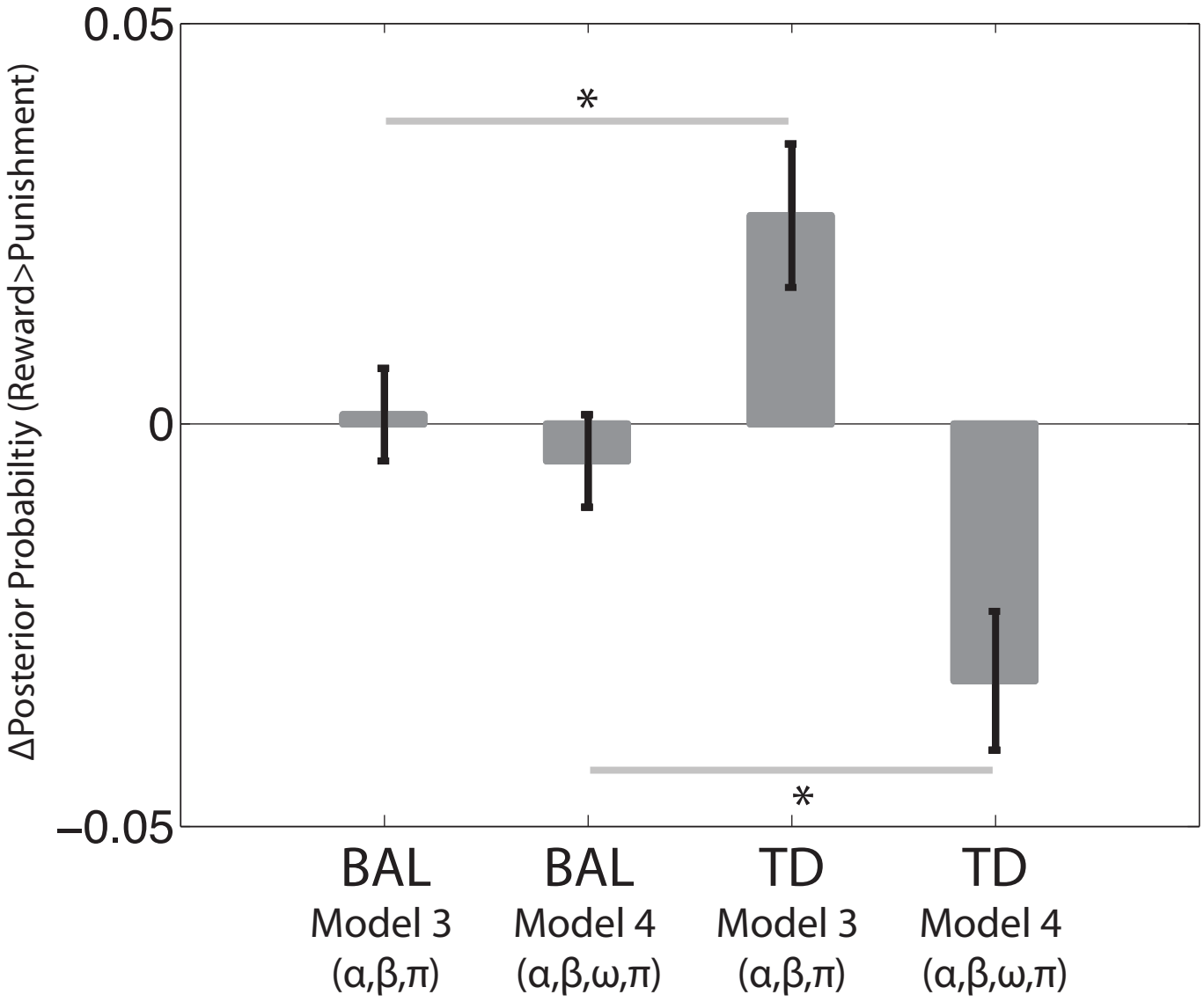

(A)
Model 1 (α,β)
Model 2 (α,β,ω)
Model 3 (α,β,π)
Model 4 (α,β,ω,π)
Simulation
Data
Pstay (first stage)
0.9
0.8
0.7
0.6
0.5
Correct Comm.
Correct Rare
Incorr. Comm.
Incorr. Rare
(B)
Model-based coefficient
0.2
0.1
0
−0.1
Perseveration coefficient
0.5
0.4
0.3
0.2
0.1
0
Model1
Model2
Model3
Model4


0.05
0
−0.05
ΔPosterior Probabiltiy (Reward>Punishment)
*
*
BAL
Model 3
(α,β,π)
BAL
Model 4
(α,β,ω,π)
TD
Model 3
(α,β,π)
TD
Model 4
(α,β,ω,π)