Stimulation of the human ventral tegmental area increases strategic betting

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Abstract

Learning is a fundamental aspect of human behaviour and is essential for adapting to new environments and situations. The ventral tegmental area is a critical brain area containing neurons that release dopamine to signal reward, drive learning, and bias decision-making. Human data on ventral tegmental area's effects on cognition are scarce, and no studies have causally manipulated the human ventral tegmental area. Here we studied a unique group of patients who had deep brain stimulation surgery in the ventral tegmental area, to improve pain due to trigeminal autonomic cephalalgias refractory to medical therapy.

In this study, we asked how deep brain stimulation, which aimed to inhibit the ventral tegmental area, affected reward-related learning and decision-making. Patients performed a reversal learning task while their deep brain stimulation was switched on vs. off, in a powerful within-subject design. In the task, patients learned to choose between two options to win money, based on previous outcomes, but also made post-decision bets based on whether they thought they were likely to win. This allowed us to also investigate the effect of electrical stimulation within the ventral tegmental area on betting behaviour.

We found that stimulation did not affect learning in this group of patients but led to a more strategic betting behaviour. First, stimulation reduced the bias where healthy people tend to bet similarly to the previous trial. Second, when on stimulation, bets were more strongly linked to the actual value of the choice. The data indicate that disrupting ventral tegmental area signals by electrical stimulation reduces the perseverative betting bias, permitting more strategic decision-making. We

interpret this to mean that mesolimbic dopaminergic signals in humans may be important in producing persistence of reward-driven behaviours over time.

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Introduction

We are confronted with hundreds of decisions each day, spanning from simple choices to the resolution of intricate problems, with uncertain outcomes. To decide between options we must evaluate and compare them, guided by learning from previous experiences.[1,2] Learning and evaluation are subject to a range of biases, leading humans to act in suboptimal ways under certain conditions.[3–5]

A central brain circuit involved in learning and evaluation is the dopaminergic projection from the ventral tegmental area (VTA). The VTA is situated in the midbrain and is origin to the mesolimbic pathway projecting to the ventral striatum, and the mesocortical pathways projecting to the prefrontal cortex (PFC).[6,7] This mesolimbic dopaminergic pathway is activated by both anticipatory reward signals and unexpected reward outcomes. While unexpected outcomes generate classic reward prediction errors, anticipatory dopamine (DA) signals may also contribute to learning by encoding reward expectations, leading to the view that VTA signals are necessary for reinforcement learning.[8–12] However, it may also be involved in signalling aversive stimuli, or even neutral but salient (unexpected) events. Evidence from animal studies has shown both a reduction of DA activity within the mesolimbic pathway as well as increased DA release within the Nucleus accumbens (NAcc) in response to aversive stimuli.[13–15] Moreover, different anatomical parts of the VTA are activated and suppressed by aversive foot shocks[15] suggesting a complex role, more nuanced than simple reinforcement.[16,17] Dysregulation within these pathways has been implicated in addiction and substance abuse disorders, where aberrant reward processing leads to, for example, maladaptive behaviours such as compulsive drug-seeking.[18] Moreover, parallel projections from these VTA neurons to the prefrontal cortex and the mesocortical pathway, are integral to higher-order cognitive functions such as working memory and executive control which provide 'top-down' modulation of decision-making.[19] Disruptions or changes in DA signalling in these pathways may lead to either detrimental or beneficial changes in behaviour (e.g., working memory and executive dysfunction due to dopaminergic depletion in the PFC of patients diagnosed with Parkinson's disease (PD) or improvement of working memory after dopaminergic treatment in patients with Attention deficit hyperactivity disorder).[20–22] More recent evidence, however, suggests a more complex, likely u-shaped relationship between DA and optimal cognitive control, which amongst others, depends on individual baseline DA levels and a dynamic balance between cognitive flexibility and stability.[23] DA release in the PFC modulates the balance between goal-directed and habitual behaviours, thereby influencing the ability to weigh potential rewards against associated costs and consequences. Supporting this view, dysfunction in mesocortical DA may lead to a variety of neuropsychiatric disorders characterized by impaired evaluative decision-making, such as addiction, impulse control disorders or schizophrenia.[18,24,25]

VTA DA projections to the ventral striatum may be important not only for reward prediction error signals for learning[26] but may also promote risk-seeking/gambling behaviour,[27] via the opponent roles of the direct and indirect pathways. Phasic DA release is generally implicated in modulating decision-making based on reward prediction error signalling and reinforcement learning, directing future decision towards more desirable outcomes, whereas tonic DA signalling is postulated to modulate gradually changing reward values and DA-mediated motivation.[28–30] More specifically, VTA-to-ventral striatum dopamine projections are needed for positive reinforcement learning[31] and impulse control has been shown to be closely linked to activity within the VTA-Nucleus accumbens network in a rat model, potentially leading to impulsive behaviour in the context of reduced and increased activity therein.[32] While VTA lesioned rats have shown perseverant behaviour,[33] other animal work showed that inhibiting VTA activity may also reduce incentive salience.[34] In humans, mesolimbic activation is associated with gambling disorders,[35–38] but a direct causal link with VTA is lacking. Lesions to VTA and its connections have been studied in rodents, leading to reduced reward-seeking habitual biases[39] and reinforcement deficits that can be reversed by DA agonists, pointing to the importance of an intact mesoaccumbens pathway in reward-related behaviour.[31] In unlesioned animals, however, D2 agonist injection directly into the ventral striatum actually impairs reversal learning (RL).[40] Data on causal manipulations within in these regions in humans are naturally lacking, and clinical studies disagree on the role of DA in reinforcement learning.[41] This leaves a major open question: What role does the human VTA play in reinforcement learning and evaluation?

A small cohort of patients have undergone surgical implantation of electrodes into the VTA through which electrical stimulation can be given directly, known as deep brain stimulation (DBS), as a treatment for therapy refractory pain.[42] These patients were diagnosed with trigeminal autonomic cephalalgias (TAC), a rather rare group of headache disorders characterized by attacks of severe, strictly unilateral cranial pain associated with ipsilateral cranial autonomic features. Clinically, they can further be subclassified as cluster headache, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). While the underlying cause for these disorders remains elusive, a complex involvement of several neurotransmitters has been hypothesised, with a central role of dopaminergic overactivity, measured by elevated DA plasma levels in patients diagnosed with cluster headache.[43] These disorders can sometimes be difficult to treat and represent a large burden on patients' quality of life. VTA DBS has been shown to help alleviate these symptoms in patients where pain is refractory to other less invasive treatment options,[42,44] potentially by disrupting hypothalamic overstimulation.[43] It, however, also provides a unique opportunity to causally manipulate VTA, to ascertain its role in reinforcement learning, decision-making and risk-taking behaviour, as it allows for directly comparing electrical stimulation with no-stimulation in the same individual. Data on the effect of trigeminal autonomic headache disorders on cognitive performance is scarce. During pain attacks, cognition was found to be overall worse,[45] which could in part be explained by pain processing requiring additional attentional resources.[46] Some studies have, however, also reported poorer executive functioning, working memory, language, and selective attention in pain-free intervals compared to healthy controls.[47,48] No studies have specifically studied the effect of TAC on reversal learning, to our knowledge.

In our study we used a probabilistic RL task to gauge the effects of VTA stimulation on risky decision-making and learning.[49] This task required participants to attempt to select the more rewarding of two options on offer, while the probability of reward varied independently for the two options across trials. After the choice, but before the outcome, participants chose an amount of money to gamble on each trial. This allowed us to assess learning as well as risk-taking behaviour. A previous study using this task showed that healthy participants exhibit a typical betting strategy, and their bets were biased. Their strategy was to bet higher after a win when staying with the previous choice, and conversely, bet less when switching choices.[49] People were also biased to bet similarly to how they bet on the previous trial, irrespective of the option chosen. This previous bet bias could be due to persistence of learned value signals contributing to decision confidence and led to a seemingly irrational betting strategy. The biases were lessened in patients with ventromedial PFC lesions,[50] which could indicate that medial prefrontal lesions disrupt contextual biases from being integrated, in some cases ultimately leading to more rational decisions.

We investigated the effect of electrical stimulation via DBS within the VTA and its effect on learning and betting behaviour. Based on animal data we expected that electrical stimulation would inhibit phasic DA release.[51] A detailed study of electrical stimulation of the VTA in awake macaque monkeys suggests that stimulation above 100 Hz suppresses neural firing[51]. Data on the effect of VTA stimulation in humans is not available; however, in patients with STN DBS, field evoked potentials show sustained suppression during high-frequency (100 Hz) stimulation[52]. We therefore expected high frequency DBS to VTA to disrupt phasic DA signalling. Consequently, stimulation should reduce learning from rewards but also reduce positive reward expectation that drives reward seeking and betting.

Material and methods

Participants

Patients were recruited from the UCLH Headache and Facial Pain Outpatient Clinic and were included if they had a past medical history of either therapy refractory cluster headache, SUNCT (Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) or SUNA (Short-lasting unilateral neuralgiform headache attacks with autonomic symptoms) and had received VTA DBS for pain management.

Surgical procedure/anatomical target

DBS lead placement was performed under general anaesthesia and guided by stereotactic MRI. This method has been outlined previously for other DBS targets.[53,54] The first reported case of DBS for chronic cluster headache was in 2001 and yielded encouraging outcomes.[56] Although the target was originally presumed to lie within the posterior hypothalamus, subsequent work refined the effective stimulation site to a region posterior and inferior to the hypothalamus, localised within the ventral tegmental area of the midbrain.[57,58] This region borders the mamillary bodies and red nucleus.[44] The targeted anatomical site was the VTA ipsilateral to the attacks or bilateral for patients where pain was side alternating. The position of the most distal contact on the Medtronic 3389 lead was established on an axial 1.5 T T2-weighted stereotactic MRI slice, situated immediately above the mammillary bodies, anteromedial to the hypointense red nucleus, and posterolateral to the hypointense mammillothalamic tract. Every DBS lead was implanted with a final position of <1 mm of the designated target.[42,55] Individual active contact locations for all subjects included in this study are demonstrated in **Supplementary Fig 1** and the group average in **Figure 1A**.

Ten patients (49.4 ± 14.9 years, 6 female, **Tbl 1**) completed the task four times in total. Patients were tested with their DBS electrodes switched on/off, off/on respectively in two separate sessions in a powerful randomised double-cross-over design (see **Fig 1B**). We chose this design to mitigate order effects and learning, while minimising problems associated with counterbalancing in a small sample size. They were randomised for the order of testing and a Nurse Specialist programmed the DBS as appropriate. This was followed by a waiting period of 30 minutes to allow for the effects of the DBS change (such as mild dizziness, light-headedness) to settle and for potential visual symptoms (e.g., transient double-vision) to fade. This time frame was chosen following protocols of previous DBS studies where even shorter "wash-in/wash-out" periods have been used[52]. At the time of the testing no symptoms were reported by the patients. However, the presence of transient effects when stimulation was changed meant that blinding for the state of their DBS programming was not possible. Furthermore, 16 healthy, age-matched controls completed the same task on one occasion (54.3 ± 15.09 years, 7 female).

The study was approved by the UCLH Research Ethics Committee (IRAS Number: 203446, patient cohort) as well as the Fulham NRES Ethics committee (18/LO/2152, healthy controls) and written informed consent was obtained in accordance with the Declaration of Helsinki.

Learning task

The task, stimuli, analysis and modelling followed those previously published.[49] Participants were seated 70 cm in front of a computer in a dimly lit room. They were required to select one of two options displayed on the screen (A or B/red or blue, see **Fig 1C**). After choosing, they decided how much money to bet on this option. Subsequently they either won or lost the amount bet. The probability of winning after selecting a particular option was either 30% or 70%, with each option's value changing (reversing) independently, on average every 12 trials (see **Fig 1D**). It was explained to the participants that the values of the options were independent, such that sometimes, both A and B might win and at other times both might lose. With independently changing win probabilities was not always optimal to bet high,[59] and participants were informed that they might sometimes have to bet low, for example, if they were expecting to lose. Each session consisted of 136 trials. The goal was to maximise the money in the bank by the end of the task.

Statistical analysis

General analysis

We first quantified simple performance measures. The total amount won, proportion of wins and mean bet level were compared. Each variable was compared in two ways. First, stimulation effects were compared on vs. off within the patient group, pooling data from both testing days. Second, patients were compared with healthy controls, pooling together on and off data from each patient. This was done using mixed linear effects models in R (nlme package fitted using restricted maximum likelihood method) and Matlab. A random intercept was included to factor out inter-subject variability and predictors were z-scored within subjects. Results between z-scored and non-z-scored predictors did not differ qualitatively; we report statistics of non-z-scored values subsequently. The alpha level was set at 0.05.

Computational model of betting

The modelling was identical to that in previous work.[49] We fitted choices (A vs. B) on each trial. The model estimated the relative subjective values of the options, which were updated based on the outcomes of previous trials. The value-learning rule used was the standard Rescorla-Wagner rule, wherein the value of the chosen item was updated depending on whether it resulted in a win or a loss.

$$Q_{t+1}^{c} \leftarrow Q_{t}^{c} + \alpha(R_t - Q_t^c) \qquad (1)$$

where Q^c is the value of the chosen item on trial t, and the reward R_t is 0 or 1 to indicate a win, irrespective of the bet. The value of the unchosen item remained unchanged by the updating process.

$$Q_{t+1}^{u} \leftarrow Q_{t}^{u} \qquad (2)$$

where $\mathrm{Q}_{\mathrm{t}}^{\mathrm{u}}$ is the value of the unchosen item. Choice proceeds according to a softmax rule

$$choose_t^c \sim \beta \cdot (Q_t^c - Q_t^u) \qquad (3)$$

with a logistic choice function.

The model consisted of three equations: (1) reward prediction updating for the chosen item, (2) no update for the value of the unchosen item, and (3) softmax rule for option selection. Two free parameters, the learning rate (α) and the inverse temperature (β), were estimated using maximum likelihood with a Gibbs sampler (JAGS). Model fits were independent for each session and generated an estimated subjective value for each option on each trial.

To assess the effects of modelled value on betting, we then used mixed effects linear models, in R using the lmer function. Variables used as predictors were z-scored within subjects and a random intercept was included. Results between z-scored and non-z-scored predictors did not differ; we, hence, report statistics of non-scored values.

These models were used to examine how people chose to bet, based on their previous experiences. The model thus factors out the fact that different people may have different means and scaling of their bets and subjective values and focuses only on relationships of within-subject trial-to-trial variation in these values. For the linear models, we used an ordinal scale from 1 to 5 for the bets. Since the spacing of the five bet options were approximately logarithmically spaced, this corresponds approximately to the log-bet. Fixed effects were quantified as t-statistics, yielding a 2-tailed p-value for each factor of interest. The full model, to determine whether VTA DBS stimulation strengthened value-based choice while attenuating previous trial bias, can be written as:

$$bet_t \sim Q_t^c \times stim + bet_{t-1} \times stim \qquad (4)$$

To visualise these effects, choices and bets were plotted as a function of the modelled values on each trial inferred from the Rescorla-Wagner learner. To account for the varying range of modelled values across participants, the values were binned according to quantiles within each subject. Choices and bets were averaged for each subject within each bin. Then the mean and standard error across subjects was plotted for each bin. The bins were determined using a sliding window approach based on 25 percentiles. The x-coordinate for plotting each bin is the mean of the bin centres for each subject. This method corresponds roughly to the mixed models' inclusion of a random intercept. It is important to note that this visualization method approximated the inclusion of a random intercept in the mixed models, but all statistical analyses were performed using the aforementioned linear mixed models.

Results

No effect of DBS on simple learning measures

First, we looked at simple performance measures and used the general linear model to quantify the effect of stimulation on these. The total amount won (**Fig 2A**) at the end of the task did not significantly differ between stimulation on and off (F(1, 9) = 0.83, *p* = .39) nor between the patients and the healthy controls (F(1, 24.3)= 1.62), *p*= .22). This also applied to the proportion of trials won at the end of the task, with no effect of stimulation (F(1, 9) = 0.83, *p* = .39) nor of group (patients vs healthy F(1, 24.3) =1.62, *p* = .21).

To ask whether VTA stimulation affected learning strategy, we split trials according to whether the participant previously won or lost and quantified the proportion of trials on which they stuck with their last decision or switched to the other option. A rational strategy might be to switch option after losing (win-stay, lose-switch). **Fig 2B** shows the mean proportion of trials where participants stuck to their previous choices split according to if they won or lost on the previous trial. As expected, in both groups, participants were more likely to stick with the option chosen previously if that option had won compared to if it had lost (patients: F(1, 27)= 13,26, *p* = .001, HC: F(1, 46.1) = 44.99; *p* < .001). There was no significant difference in this effect between groups (group x previous-win interaction F(1, 46.1) = 3.54, *p* = .066, with a possible weak trend for patients to learn less) nor between stimulation on vs. off (F(1, 27)= 0.077, *p* =.78). This simple behavioural analysis thus revealed no effect of DBS on learning.

VTA DBS increased strategic betting

Next, we asked whether VTA stimulation affected betting. To quantify betting strategy, we split the amount bet on different trials according to whether the participant stuck to or switched their choice, and according to whether they had won or had lost on the previous trial (**Fig 2C**). As expected, healthy controls bet more after they had won, but only when they stuck to the same option. They bet less if they switched to the other option. This win-stay interaction was also seen in the VTA patients but only when DBS was on. This effect was absent when stimulation was off, resulting in a three-way interaction (previous-win x stick-or-switch x stimulation F(1,5403.2) = 5.7, *p* = .017). This result points to less strategic betting when DBS was switched off. Within this model patients bet higher overall when off stimulation than on (main effect of stimulation F(1, 5403.0) = 8.71, *p* = .003), but no interaction between previous wins and stimulation (stim x previous-win F(1, 5403.1) = 1.72, *p* = .19), or the effect of sticking vs switching (stick x stim F(1, 5403.2) = 1.44, *p* = .23) was found. Comparing healthy controls with the average of patients on and off stim, there was a 3-way interaction, where patients showed an overall weaker strategic effect at betting (previous win x stay x group: controls vs. patients, F(1, 8662.5) = 12.13, *p* <.001) – meaning that while controls bet much more on win-stay trials, this was overall weaker in patients (see also **Fig 2D**). Note that this between-group analysis collapses across the effect of stimulation. This remained significant even when comparing only the first session of patient data to healthy controls.

No effect of VTA DBS on Learning model parameters

The lack of effect of VTA stimulation on learning could have arisen because win-stay analysis is a crude measure, ignoring variability that would be expected based on longer-term choice and reward history. To account for this, learning behaviour was modelled using a standard Rescorla-Wagner rule (details see methods) fitting the learning rate and decision noise. Using the mean deviance as goodness of fit, this model was more confident in predicting the choices of the cohort of healthy controls (d = 244.23) than those of patients independent of the stimulation status (on: d = 360.15 off: d = 362.26).

There was no main effect of stimulation (F(1, 9) = 0.19; *p* = .67) or group (patients vs controls F(1, 22.85) = 1.74; *p* = .20) on modelled learning rates (**Fig 3A**). There was also no significant effect of stimulation on decision noise (inverse temperature (β), **Fig 3B**, F(1, 9) = 0.01; *p* = .94). When compared to the cohort of healthy controls, however, patients had higher decision noise (F(1, 23.03) = 4.77; *p* = .039) suggesting either a weaker representation of value or more attentional lapses in this cohort (for probability of choice modelled to value of choice see **Fig 3C)**.

VTA DBS strengthened value-based choice while attenuating previous trial bias

The model yields the expected value of the chosen option (Q), corresponding to the estimated probability of it leading to a win. This allowed us to fit the amount bet as a function of value (**Fig 3D).** Overall people bet more when the chosen option had a higher value. Patients bet more on trials where the chosen option was more valuable according to the model (F(1, 5436) = 15.94, *p* < .001). Stimulation modulated the slope with which the chosen option's value determined bets (Q_t^c × stim: *F*(1, 5436) = 14.95; *p* < .001), with greater value sensitivity when participants are on stimulation as compared to off. This mirrors the simple strategy analysis of **Fig 2C**. Comparing patients to controls, patients bet more overall than controls (F(1, 8721) = 55.48; *p* < .001), while controls showed an overall more conservative betting strategy. Betting was modulated by the value of the chosen option more strongly in controls than patients (Q_t^c × group: controls vs patients F(1, 8721) = 210.7, *p* < .001).

Finally, we asked whether patients show the bias seen in healthy people to bet similarly to the bet on the previous trial. To visualise this, we factored out the value of the chosen option and split the residuals of the current trial's bet according to the bet level on the previous trial (**Fig 3E**). We asked how much bets were biased by the previous bet. A positive slope indicates that the current trial's bet was predicted by the amount bet on the previous trial. Stimulation reduced this slope, suggesting that it abolished the bias induced by the previous trial. Patients showed a reduced betting bias when their stimulation was on compared to off, i.e., stimulation made their betting strategy more rational (*stim x previous bet:* F(1, 5414) = 17.79; *p* < .001). When comparing patients with controls, patients showed an overall decreased decision bias (F(1, 8683 = 363.41, *p* < .001).

Discussion

The VTA is believed to be critical for signalling reward, but its various downstream roles in learning, decision-making and risk remain poorly understood. Here, we present the first human causal manipulation of this area in a rare cohort of patients. We found that DBS stimulation within the human VTA did not affect learning but altered betting patterns. Specifically in these patients, neuromodulation of the VTA reduced betting, increased strategic betting and reduced previous-trial biases.

Reinforcement learning facilitates adaptive decision-making by keeping track of the values of different actions to guide subsequent behaviour.[60] Previous evidence suggests DA inputs to the striatum are crucial for learning by reinforcement in animals. This is because DA neurons within the VTA signal reward prediction errors, which are discrepancies between expected and actual rewards.[61] Recent evidence, however, has not always supported a role for DA in human RL.[41,62,63] Why might this be? More recent theories paint a more nuanced picture of the role of VTA DA in learning and decision-making, signalling a mixture of information about reward types[64], sensory prediction errors,[65] belief states[66] and distributional codes.[67] According to the theory of opponent actor learning, the direct and indirect striatopallidal pathways implement parallel learning of positive and negative outcomes,[68] allowing an organism to measure both the value and risk of an action. A recent computational model implicates DA – both tonic and phasic – in modulating the bias between direct and indirect pathways, with higher DA driving stronger risk preferences.[26] Learning actions from outcomes may itself be a *composite* of multiple processes such as task representation,[69] strategy formation, working memory,[70] episodic memory[71] and sequencing – in addition to simple reinforcement learning. These processes involve a variety of anatomical structures such as the dorsolateral PFC,[72] the orbitofrontal cortex,[73] amygdala,[74] hippocampus[75] and the striatum besides the VTA.[76] Moreover, performance on learning tasks may rely on not only reinforcement-based systems such as VTA-NAcc, but also on working memory or episodic memory.[77,78] Thus, PFC or hippocampus may act as fallback systems that can assist when reward-based RL is disrupted reducing motivational biases on decision-making and enhancing cognitive control over betting strategies. In primates, while ventral striatum lesions impair learning,[79] depletion of mesocortical DA is not sufficient to impair RL.[80] Accordingly, while some human studies have found that levels of DA may affect both learning from rewards and the expression of prior learning in the decision-making process,[68,81] other studies have not supported this.[41] We, therefore, have reasons to believe that humans may employ several decision-making sub-systems in parallel to solve a simple reward learning problem. This redundancy might explain why disruption of VTA did not affect learning. An alternative reason for the lack of effect on learning could be that DBS did not sufficiently suppress VTA DA. If so, then reward prediction error signals themselves might not have been attenuated, but tonic dopamine signals could have been reduced, making the recent wins more salient while betting.

Conversely, dopaminergic projections from VTA to PFC may have a range of other functions that do not pertain directly to learning. The mesocortical dopaminergic pathway is integral to higher-order cognitive functions such as motivation, working memory, goal-directed control over habitual behaviour and risk preference.[76,82,83] Disruptions or changes in DA signalling in these pathways may lead to either detrimental or beneficial changes in behaviour.[20–22] In rodents, mesolimbic dopamine drives risky behaviour[84,85] and may influence the integration of past experiences into current decision-making processes. In line with this, bilateral destruction of the VTA in rodents also reduced habitual biases by down-regulation of habitual behaviour[39]. The removal of previous-trial biases suggests that VTA-DBS might disrupt the encoding of recent reward history, thus promoting a more value-driven approach to betting in our cohort when stimulation was on. In general, this may indicate that while DA is important for RL in humans, it also contributes to habit-related responding and risk preference. This would align well with our finding that overall betting levels were reduced by inhibitory DBS to VTA (**Fig 2C**). While stimulation increased strategic betting in individual patients, when off DBS the patients were actually less strategic than controls. Thus, one could interpret the increase as restoring normal strategic betting in patients who at baseline had reduced strategic betting. Betting behaviour in general may rely on a cognitive model of the task including inferences about volatility or rules. VTA DA may play a role in generating these beliefs and predictions[66] and therefore help set up longer term schemas that control betting. Disrupting this process could abolish the biases we observe in healthy people to bet similar to the previous trial. Indeed, in computational models, decreased dopaminergic signalling (at least within the striatum) leads to diminished emphasis on past rewards and more adaptive decision-making strategies,[86] supporting the above reasoning.

One difficulty in interpreting studies involving DBS is that we do not know the precise effect of electrical stimulation – especially on VTA neurons. DBS has been used therapeutically for many years in PD, dystonia and psychiatric conditions. Despite this, the specific neuronal and neurochemical effects of DBS remain difficult to quantify in terms of excitation or inhibition. Animals work suggests that the location, frequency and timing of stimulation are major determinants of the effects of DBS. For example, studies of subthalamic nucleus (STN) DBS show increased dopaminergic activity in animals[87–89] but not in human patients with PD. Despite amelioration of symptoms during STN stimulation, DA release was not increased, potentially due to the underlying disease pathology.[90,91] While DBS to several brain areas is used to treat PD, the VTA is not targeted, since mesolimbic dopamine is relatively preserved in these patients.[92] A recent rodent model, however, showed a reduction in NAcc dopamine levels by 42% after high frequency VTA DBS in an addiction model.[93] Moreover, the stimulation in our study may not have specifically been dopaminergic as there is also evidence from animal studies for altered serotonergic,[94] glutamatergic[95] and GABAergic[96,97] activity following electrical stimulation. Indeed, VTA GABA projections to NAcc may drive learning from negative outcomes.[98] Optogenetic activation and inactivation of VTA DA neurons can both positively and negatively bias behaviour. This suggests a combination of dopaminergic as well as non-dopaminergic contributions to VTA function.

Based on the stimulation parameters in our patients, we expected that VTA DBS in this cohort would *inhibit* DA release in the mesolimbic pathway. The overall more strategic betting on electrical stimulation could align with this hypothesis: DA release may drive biases by increasing general reward expectation after a win. This in turn could explain the seemingly improved metacognition due to intermittent "lesioning" through DBS. This also concords with fMRI studies where worse performance in the IOWA gambling task is associated with an *increased* connectivity between VTA and brain areas critically involved in the reward/punishment system.[99] DA activation plays a crucial role in addiction and can reinforce betting behaviour in gambling disorders[100] and is also coupled with altered brain activity in the fronto-striatal reward circuit.[101,102] Recent rodent work showed a relatively complex interaction between the VTA and frontal cortex, encoding rewards, predictions, prediction errors and also uncertainty and decision context.[103] Our results, hence, demonstrate that interpreting VTA as directing learning via RPEs may be oversimplistic.

If the interpretation that VTA stimulation in our patients inhibited DA neuron activity is correct, this would then imply that VTA reward prediction error signals may not be essential for learning, at least in our patients. This could be consistent with reward prediction errors being computed and represented in many other brain areas including medial frontal cortex and striatum (for review see [96]). In primates, blocking dopamine transporters increased novelty seeking but did not affect learning.[104] In rats, RL was paradoxically improved by DA blockade in ventral striatum, whereas nigrostriatal DA was required for learning.[105] Different roles have been proposed for D1 and D2 receptor modulation, within different subregions of the striatum, in different stages of RL, pointing to a potential "alternative route" in the cohort of our study.

An additional consideration in our opportunistic study is that our patients were operated for pain. Hypodopaminergic states caused by chronic pain have been observed in both human and animal data[5,106,107] which may need to be taken into consideration when interpreting dopaminergic mechanisms. On debriefing, patients in our study reported no changes in pain when their DBS settings were changed. However, we cannot rule out that VTA-DBS affects performance in our task, for example by affecting attention, even if tests of global cognition in this cohort pre vs post VTA DBS surgery remained unchanged.[108] Moreover, we were unable to double-blind patients in this study, so metacognitive effects cannot be ruled out.

In summary, this is the first study in humans reporting the effect of electrical stimulation within the VTA on learning and betting behaviour. We found reduced decision biases and more strategic betting strategies on stimulation, without impairment of reinforcement learning. This finding contrasts with animal studies, where VTA dopamine has been shown to be crucial for learning from unexpected rewards.[109] The discrepancy may be due to differences in the neural circuitry involved in humans versus animals, or it may reflect the ability of other brain regions to compensate for VTA disruption in humans. Our results provide a unique insight into the potentially dopaminergic effects of VTA DBS pointing towards a positive effect of stimulation on evaluative cognition. Unravelling the role of mesolimbic DA in decision-making, risk-taking behaviour and learning holds promise for advancing both our understanding of brain function and health and disease.

Data availability

The data generated and analysed during the current study are available on the OSF repository https://osf.io/6eg5a.

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Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1 Study design and experimental setup. (A) Lateralised group average volume of tissue activation by DBS in MNI template (ICBM 152 T2 Non-linear Symmetric). Individual volumes of tissue activation were modelled using Brainlab Elements Guide-XT and co-registered, lateralised, and averaged using FSL 6 (FMRIB). Visualisation is made using FSLeyes software (FSL 6). On the left picture a schematic representation of a DBS electrode (yellow) was added for illustrative purposes. (B) Study design: Ten patients with TAC who previously underwent DBS surgery were enrolled. They were randomly assigned to one of two groups and tested on-off as well as off-on in a randomised double crossover design. After DBS was switched on/off there was a waiting period of 30 minutes to allow for DBS effects to settle. The task had a duration of approximately 20 minutes. 16 age-matched healthy controls we recruited separately and tested on one occasion only. (C) Task setup: participants were asked to choose one of two options and select a bet for this choice by clicking on the respective dice. (D) The probability of winning was either 30 % or 70% and changed over time on average every 16 trials independently.

Figure 2 Performance by simple learning measures. (A) The amount won during the task did not statistically differ between the 10 headache patients and the group of healthy controls ($p = .22$), or more importantly between the two stimulation settings (on vs off, $p = .39$). (B) Trials were split according to whether participants previously won or lost, and the proportion of trials on which the option choice was the same ("stay") or different ("switch") was calculated. Looking at this parameter, there was no significant difference between VTA stimulation settings ($p = .78$), nor between the controls and the patients. All participants were significantly more likely to stick with a choice if it previously won (*$p = .001$, **$p > .001$). (C) The amount bet on trials was split according to whether the participant stuck to or switched their choice, and according to whether they won or lost on the previous trial. Comparing on vs off stimulation, patients bet less strategically when VTA stimulation was switched off resulting in a 3- way interaction (previous-win x stick x stim x$p = .017$). (D) This graph reflects the difference in strategic betting on vs off stimulation. A positive value indicates that betting strategy was greater when on than off, hence reflecting the interaction term seen in Fig 2C (on vs off). Each point represents one patient. The inset at the top right shows the on-off difference for the same datapoints displayed in the main plot i.e., the density of the effect of stimulation. The positive shift on this histogram therefore demonstrates that the strategy was significantly stronger when stimulation was on compared to off ($p = .0017$).

Figure 3 Computational modelling of reversal learning task. (A) There was no significant difference in the learning rate between on and off stimulation, nor between the patients and the controls. (B) The degree to which participants used the learned knowledge, represented by inverse temperature (β) , was lower in patients when compared to healthy controls (HC) (*p = .039). Stimulation did not have a significant effect. (C) The model was more confident (mean deviance of model) in predicting the choices of healthy controls than those of patients. (D) The amount bet was dependent on the modelled value (Q) of the chosen option (**$p < .001$). The higher the value the higher the bet placed. This effect was stronger in patients on stimulation (and overall stronger in HC when compared to the patient cohort). The patients' bets were overall higher. (x$p < .001$) (E) The effect shown in D was subsequently factored out using linear regression and plotted split according to the bet level on the previous trial. Healthy controls showed a significant previous bet bias. When looking at the patients there was an interaction with stimulation settings. Patients with stimulation on showed a reduced previous bet bias, hence, a more rational betting strategy (x$p < .001$).

Table 1 Patient cohort: Demographic details, stimulation settings and clinical response of the 10 included patients

ID	Gender	Age	Frequency and PW	Amplitude	Stimulation arrays	Responder
1	Female	31	185 Hz; 60 ms	2.7 V	0N, 1N	Yes
2	Female	57	185 Hz; 60 ms	4.0 V	0N	Yes
3	Male	47	185 Hz; 60 ms	3.7 V (left), 0 V (right)	0N, 1N	Yes
4	Female	39	185 Hz; 60 ms	Right: 1.8 V, Left: 1.8 V	Right: 0N, Left: 8N, 9N	Yes
5	Male	47	185 Hz; 60 ms	3.3 V	0N	Yes
6	Male	57	185 Hz; 60 ms	3.6 V	1N	Yes
7	Female	79	185 Hz; 60 ms	1.2 V (left), 1.2 V (right)	Right:0N, 1N, Left: 8N, 9N	Yes
8	Male	67	185 Hz; 60 ms	Right: 1.3 V, Left: 3.0 V	Right: 0N, 1N, Left: 8N, 9N	Yes
9	Female	30	185 Hz; 60 ms	3.3 V	0N	Yes
10	Female	40	185 Hz; 60 ms	Right: 2.9 V, Left: 0.7 V	Right: 0N, 1N, Left: 8N	Yes

PW = pulse width; Stimulation arrays: refers to the number of the electrode in use and its programmed polarity; N= negative.

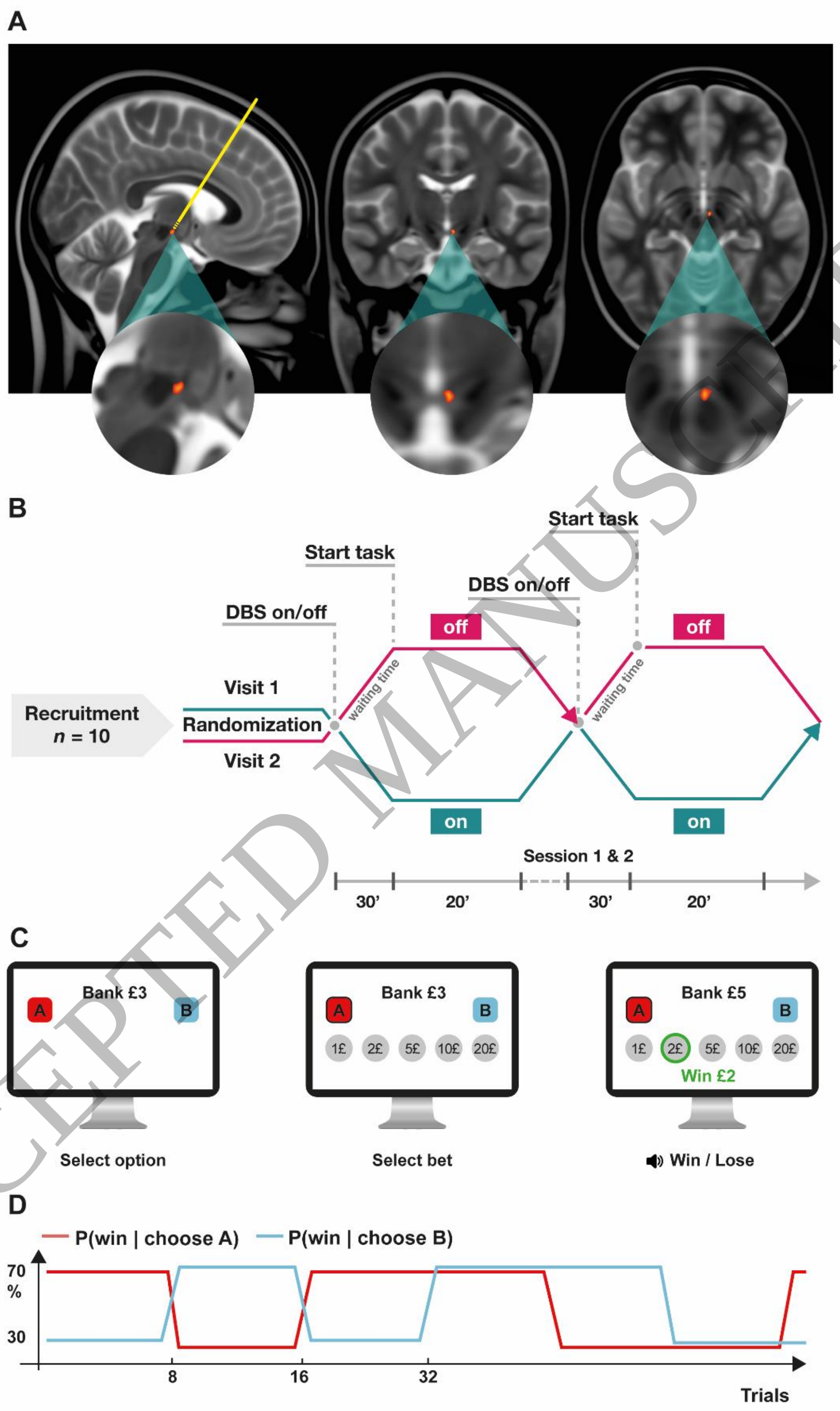

Figure 1
185x310 mm (x DPI)

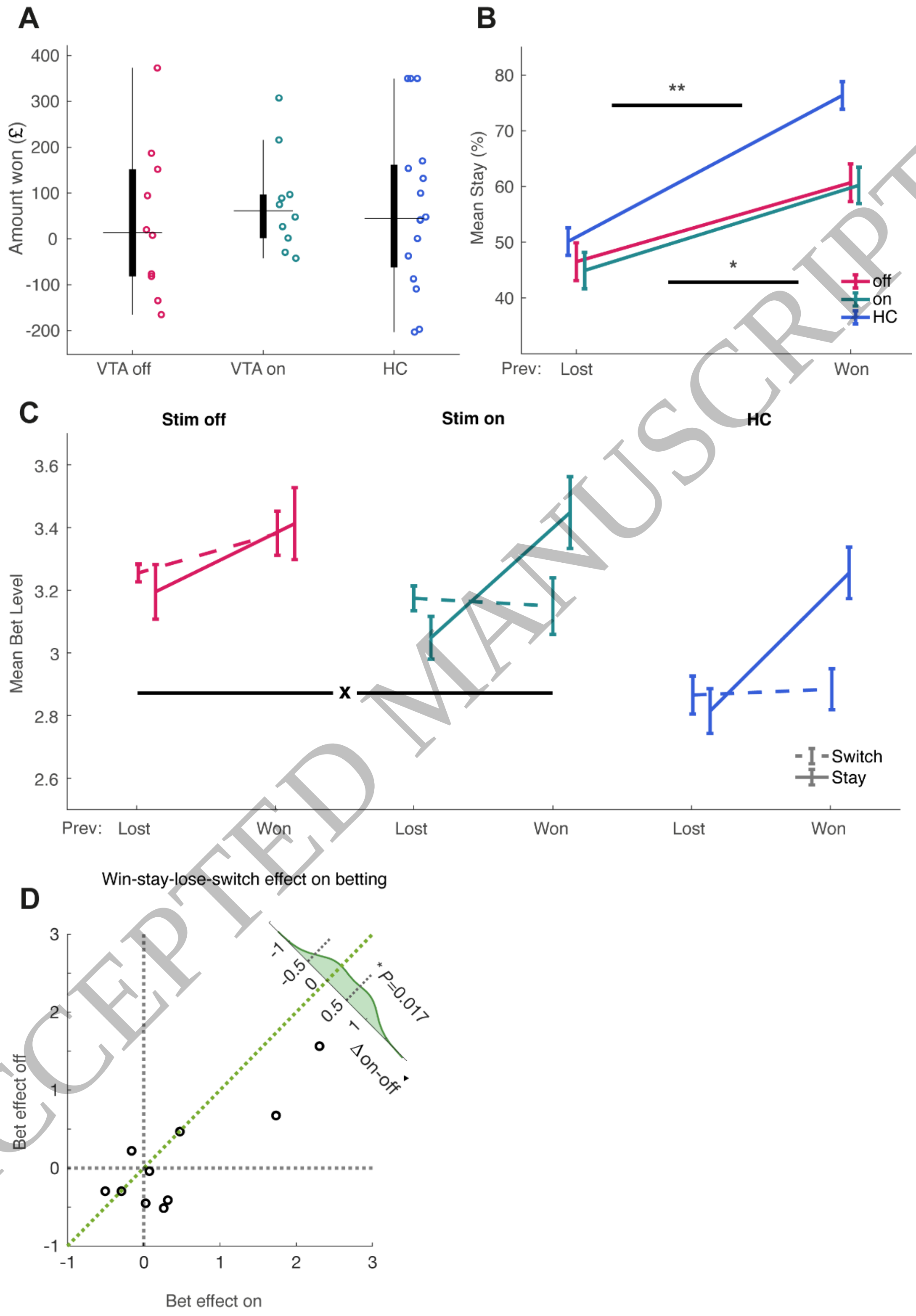

Figure 2

185x271 mm (x DPI)

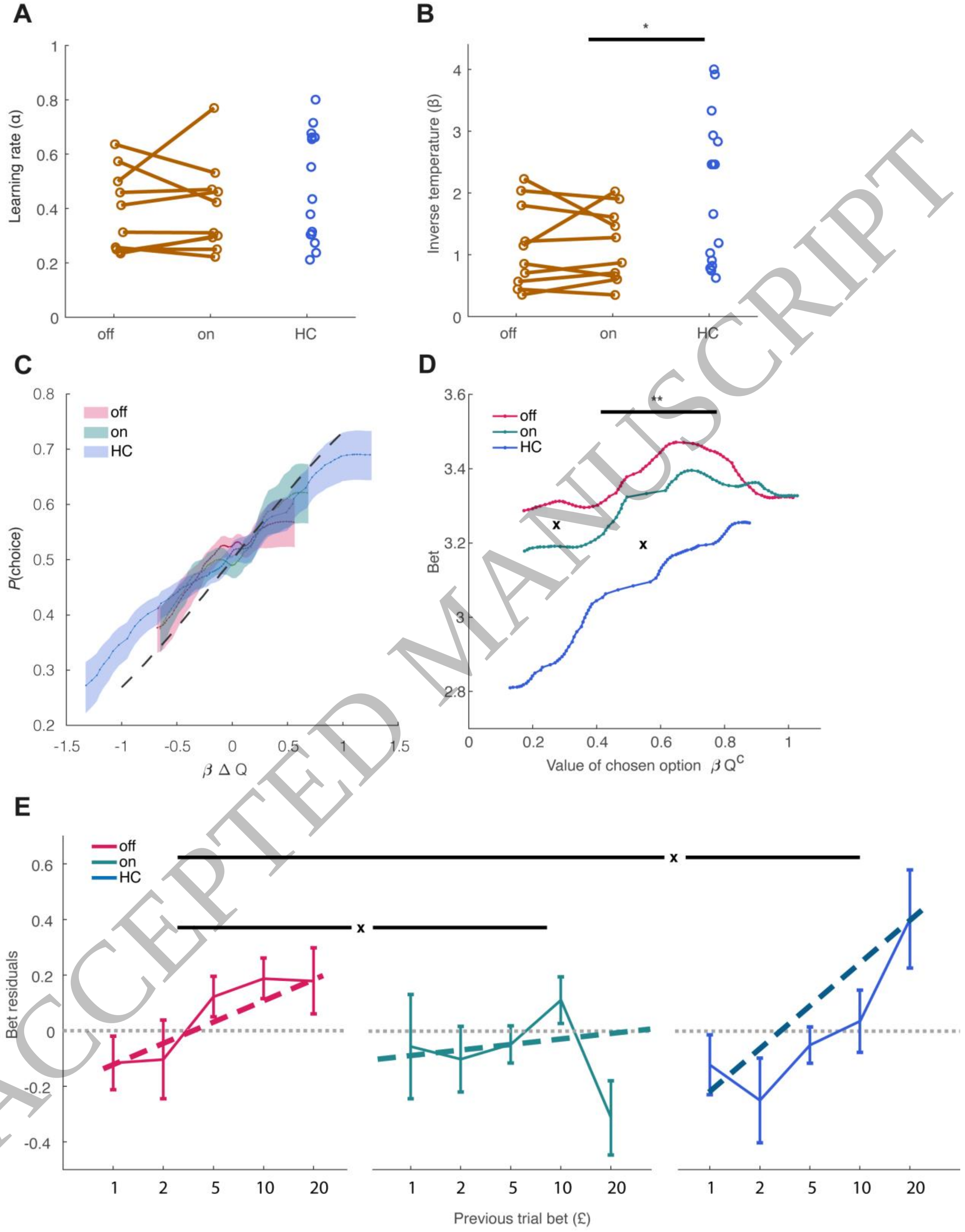

Figure 3

186x243 mm (x DPI)

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†Comparable PK, PD, efficacy, and safety profile of SC to IV except for injection site pain.[1,2]

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*As of April 2024, TYSABRI SC can be administered outside a clinical setting (e.g. at home) by a HCP for patients who have tolerated at least 6 doses of TYSABRI well in a clinical setting. Please refer to section 4.2 of the SmPC.[1]

TYSABRI is indicated as single DMT in adults with highly active RRMS for the following patient groups:[1,2]

- **Patients with highly active disease despite a full and adequate course of treatment with at least one DMT**
- **Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gd+ lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI**

Very common AEs include nasopharyngitis and urinary tract infection. Please refer to the SmPC for further safety information, including the risk of the uncommon but serious AE, PML.[1,2]

Abbreviations: AE: Adverse Event; **DMT:** Disease-Modifying Therapy; **Gd+:** Gadolinium-Enhancing; **HCP:** Healthcare Professional; **IV:** Intravenous; **JCV:** John Cunningham Virus; **MRI:** Magnetic Resonance Imaging; **PD:** Pharmacodynamic; **PK:** Pharmacokinetic; **PML:** Progressive Multifocal Leukoencephalopathy; **RRMS:** Relapsing-Remitting Multiple Sclerosis; **SC:** Subcutaneous.

References: 1. TYSABRI SC (natalizumab) Summary of Product Characteristics. **2.** TYSABRI IV (natalizumab) Summary of Product Characteristics.

Adverse events should be reported. For Ireland, reporting forms and information can be found at www.hpra.ie. For the UK, reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store. Adverse events should also be reported to Biogen Idec on MedInfoUKI@biogen.com 1800 812 719 in Ireland and 0800 008 7401 in the UK.

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