Distinct roles of dopamine and acetylcholine in delay- and effort-based decision making in humans

Short title: Dopaminergic and cholinergic modulation of cost-benefit decision making

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Abstract

In everyday life, we encounter situations that require tradeoffs between potential rewards and associated costs, such as time and (physical) effort. The literature indicates a prominent role for dopamine in discounting of both delay and effort, with mixed findings for delay discounting in humans. Moreover, the reciprocal antagonistic interaction between dopaminergic and cholinergic transmission in the striatum suggests a potential opponent role of acetylcholine in these processes. We found opposing effects of dopamine D2 (haloperidol) and acetylcholine M1 receptor (biperiden) antagonism on specific components of effort-based decision making in healthy humans: haloperidol decreased, whereas biperiden increased the willingness to exert physical effort. In contrast, delay discounting was reduced under haloperidol, but not affected by biperiden. Together, our data suggest that dopamine, acting at D2 receptors, modulates both effort and delay discounting, while acetylcholine, acting at M1 receptors, appears to exert a more specific influence on effort discounting only.

Introduction

Consider the following scenarios: Would you prefer to order an average pizza that can be delivered within minutes or rather wait an extra hour for your most favourite pizza? Similarly, would you visit a highly-rated pizza place that requires climbing up a steep hill or opting for a conveniently accessible pizza place right in front of the next bus stop? In scenarios like this, decision making involves the balancing of potential rewards against distinct costs required to obtain them. The tendency to devalue rewards as a function of effort or delay costs are commonly described as effort and delay discounting, respectively (Bickel & Marsch, 2001; Hartmann et al., 2013).

Striatal dopamine has been suggested to play a central role in both effort and delay discounting. For effort-based decision making, studies in both humans and rodents indicate that diminished dopamine transmission makes individuals less willing to exert physical effort in exchange for larger rewards (Denk et al., 2005; Farrar et al., 2010; Le Heron et al., 2018; McGuigan et al., 2019; Salamone & Correa, 2012; Soder et al., 2020; Wardle et al., 2011). Pharmacological studies consistently demonstrate that agents that enhance dopaminergic transmission in humans increase reward sensitivity and decrease effort sensitivity, while studies directly investigating the effects of selective D2-receptor antagonism in healthy humans are rare (Bogdanov et al., 2022; Chong et al., 2023; Le Bouc et al., 2016). For delay discounting, the existing literature is somewhat more mixed. Some studies suggest that increased dopamine transmission decreases delay discounting (de Wit et al., 2002; Floresco et al., 2008; Kayser et al., 2012), whereas others have found either no effect (Acheson & de Wit, 2008; Hamidovic et al., 2008) or an increase in delay discounting (Pine et al., 2010). Notably, more recent evidence in humans indicates decreased delay discounting after blockade of D2 receptors (Soutschek & Tobler, 2023; Wagner et al., 2020). While

63 dopamine has received much attention in cost-benefit decision making, other
64 neuromodulators may also play an important role (Borderies et al., 2020; Meyniel et
65 al., 2016; Nunes et al., 2013). One modulator that has not received much attention in
66 this regard is acetylcholine, which is surprising given the literature on reciprocal
67 antagonistic interactions between acetylcholine and dopamine signalling in the
68 striatum (Chantranupong et al., 2023; Foster et al., 2016; Gerber et al., 2001;
69 Myslivecek, 2021; Threlfell et al., 2010). This suggests that pharmacological blockade
70 of M1 receptors will have effects on cost-benefit decision making that are opposite to
71 those of blocking dopamine D2 receptors. In line with this, animal studies indicate that
72 muscarinic agonists induce behavioural changes in effort-based choices that are
73 similar to those produced by dopamine antagonists (Hailwood et al., 2019; Nunes et
74 al., 2013), underscoring the potential interplay between dopamine and acetylcholine
75 in modulating cost-benefit decision making. Furthermore, research in animal models
76 points to a role for acetylcholine in modulating delay-based choices through both
77 muscarinic and nicotinic receptors, albeit with inconsistent findings (Dallery & Locey,
78 2005; Kolokotroni et al., 2011; Mendez et al., 2012; Ozga & Anderson, 2018).
79 Importantly, studies directly investigating these effects in human decision making are
80 lacking.

81 To our knowledge, there has been no study so far that tested the impact of
82 dopaminergic and cholinergic manipulations on both aspects of cost-benefit decision
83 making in one single experiment. To fill this gap, we investigated the effects of two
84 drugs, haloperidol and biperiden, that selectively block either dopamine D2-like or
85 muscarinic M1 acetylcholine receptors in human participants performing two decision-
86 making tasks involving effort- and delay-based decisions. The goal of our study was
87 threefold. First, we aimed to conceptually replicate the finding that dopamine D2

antagonists increase discounting of physical effort. Second, we aimed to assess the contribution of acetylcholine to cost-benefit decision making and conceptually contrast it with the effects of dopamine. In doing so, we investigated whether any effects of muscarinic or dopaminergic receptor antagonism would modulate the computation of both time and effort costs or have a more specific effect on one cost dimension. Third, we sought to contribute new evidence to the thus far conflicting literature on the role of dopamine in delay-based decision making using a large sample size and a within-subjects design. Based on previous findings, we hypothesized that the administration of haloperidol will (1) increase effort discounting and (2) reduce delay discounting. In contrast, we expected opposite effects of biperiden, in particular (3) a decrease in effort discounting and (4) an increase in delay discounting. In brief, we found opposing effects of haloperidol and biperiden only on specific components of effort-based choices. Specifically, haloperidol reduced the willingness to invest physical effort, whereas biperiden increased it. Results for delay discounting were less consistent. While haloperidol decreased delay discounting, there was no credible modulation by biperiden.

– insert Figure 1 here –

Results

62 healthy participants performed two cost-benefit decision-making tasks aimed to quantify the extent to which the subjective value of a monetary reward is discounted as a function of either effort or delay costs. Participants completed both tasks during three sessions under the influence of either the D2 receptor antagonist haloperidol (2 mg), the M1 acetylcholine receptor antagonist biperiden (4 mg), or a placebo in a

113 within-subjects design (Fig. 1a). The effort-based decision-making task (effort
114 discounting task, Fig. 1b) involved choices between options varying in reward
115 magnitude and effort requirement (using handgrip force), while the delay-based
116 decision-making task (delay discounting task, Fig. 1c) involved choices between one
117 option varying in reward magnitude and delay versus a fixed one. Thus, both tasks
118 required participants to choose between a high-reward/high-cost (high-cost option)
119 and a low-reward/low-cost (low-cost option) alternative.
120
121 *Drug Effects on Choice Behaviour*
122 Participants consistently exhibited a preference for the high-cost option over the low-
123 cost alternative in both tasks (effort discounting task: 78.50% ± 1.03; delay discounting
124 task: 71.31% ± 1.12; Fig. 2a). For each of the two tasks, we used a Logistic Bayesian
125 Generalized Linear Mixed Model (GLMM) to investigate the impact of drug
126 manipulation, changes in task parameters, and the interaction between both, on
127 choosing the high-cost option. Specifically, to regress participants' choices, we
128 included the following fixed-effect predictors: drug condition, reward magnitude, cost
129 level (i.e., effort or delay), and all possible interactions. In the effort discounting task,
130 we used the difference terms (high-cost option minus low-cost option) for both reward
131 and effort. For the delay discounting task, we used the absolute reward and delay
132 levels of the varying high-cost option. To account for within-subject variability, we
133 included random intercepts for each subject along with random slopes for all fixed-
134 effect predictors (see Materials and Methods). We first confirmed that participants
135 effectively discounted rewards based on costs and thereby adhered to the task
136 requirements: As expected, in both discounting tasks higher reward magnitudes
137 increased, while higher cost levels (effort or delay) decreased participants' likelihood

138 to select the high-cost option (reward effect on effort discounting: HDI_{Mean} = 3.44,
139 $HDI_{95\%}$ = [2.96; 3.95]; reward effect on delay discounting: HDI_{Mean} = 55.64, $HDI_{95\%}$ =
140 [41.76; 69.38], effort effect on effort discounting: HDI_{Mean} = -1.64, $HDI_{95\%}$ = [-1.87; -
141 1.40]; delay effect on delay discounting: HDI_{Mean} = -2.29, $HDI_{95\%}$ = [-3.30; -1.25], Fig.
142 2b-c).
143
144 – insert Figure 2 here –
145
146 Notably, and in line with our predictions, we found that the two drugs had opposite
147 effects on the tendency to choose high-effort options in the effort discounting task
148 relative to placebo. Haloperidol reduced the willingness to invest higher effort for
149 greater reward, while biperiden increased this willingness (placebo: 79.17% ± 1.76;
150 haloperidol: 74.34% ± 1.85; biperiden: 81.99% ± 1.64; Fig. 2a (left panel)). These
151 effects were confirmed by credible main effects of both haloperidol (HDI_{Mean} = -0.532,
152 $HDI_{95\%}$ = [-0.943; -0.136]) and biperiden (HDI_{Mean} = 0.620, $HDI_{95\%}$ = [0.230; 1.048]; Fig.
153 3a) on choosing the high-cost option relative to placebo. Moreover, this analysis
154 revealed that biperiden increased reward sensitivity, as evidenced by a credible
155 interaction effect between biperiden and reward (HDI_{Mean} = 0.802, $HDI_{95\%}$ = [0.256;
156 1.409]; Fig. 3b). See Supplementary Table 1 for the full results.
157 In contrast, in the delay discounting task, both drugs had no effect on the
158 average rate of choosing the high-cost option (placebo: 71.59% ± 2.25; haloperidol:
159 71.55% ± 1.73; biperiden: 70.79% ± 1.82; Fig. 2a (right panel)), as indicated by the
160 absence of credible main effects for haloperidol (HDI_{Mean} = -0.046, $HDI_{95\%}$ = [-2.648;
161 1.884]) and biperiden (HDI_{Mean} = -1.315, $HDI_{95\%}$ = [-4.147; 0.655]; Fig. 3d). Importantly,
162 however, the analysis revealed a reduced sensitivity to delays under haloperidol,

evidenced by a credible interaction effect between haloperidol and delay (HDI_{Mean} = 1.332, $HDI_{95\%}$ = [0.328; 2.440]; Fig. 3f), while the other drug interactions did not reach credibility (Fig. 3 and Supplementary Table 2). This indicates that diminished dopaminergic activity attenuates the impact of time costs on decision making.

– insert Figure 3 here –

Having established distinct task-specific drug effects on participants' choice behaviour, we next investigated potential confounding order and fatigue effects using separate GLMMs for effort- and delay-based decision making. These models mirrored the previously described GLMMs but included additional predictors to test for fatigue and session effects and their modulation by drugs.

To test for possible fatigue effects, we added trial number as well as the two-way interaction with drug as additional predictors. This analysis revealed a credible main effect of trial number for both the effort and delay discounting task (trial number effect on effort discounting: HDI_{Mean} = -0.60, $HDI_{95\%}$ = [-0.75; -0.46]; trial number effect on delay discounting: HDI_{Mean} = -0.20, $HDI_{95\%}$ = [-0.33; -0.08]), suggesting that the tendency to choose high-cost options, irrespective of cost type, decreased over the course of the experiment. Notably, we found a credible interaction effect between trial number and haloperidol in the effort discounting task (HDI_{Mean} = -0.43, $HDI_{95\%}$ = [-0.63; -0.23]), indicating that the fatigue effect was more pronounced under haloperidol compared to placebo. Importantly, even after accounting for these fatigue-related effects, the main effect of haloperidol on effort discounting remained credible (HDI_{Mean} = -0.48, $HDI_{95\%}$ = [-0.90; -0.05]) (Supplementary Table 12 and 13).

Next, to investigate session and drug-order effects, we included session and the two-way interactions between session and drug as additional predictors. These analyses confirmed a main effect of session only for effort-based choices (HDI_{Mean} = 0.49, $HDI_{95\%}$ = [0.13; 0.85]), suggesting increased preference for high-effort options in later sessions, likely reflecting task familiarity. Crucially, the interaction effects between either drug and session were not credible in both tasks (Supplementary Table 14 and 15). This indicates that neither dopaminergic nor cholinergic manipulations modulated learning effects across sessions. Moreover, this finding underscores that the observed drug-induced effects cannot be explained by drug order effects.

To summarize, regression-based results show that haloperidol reduced the overall propensity to choose the high-cost options in the effort domain. While haloperidol had no effect on the average rate of selecting the high-cost option in delay-based choices, it attenuated participants' sensitivity to delay costs. In contrast, biperiden increased the overall propensity of selecting the high-cost option in the effort discounting task, opposite to the effect of haloperidol. Consistent with this, biperiden also increased sensitivity to reward magnitudes during effort-based choices.

Drug Effects on Computational Parameters

To obtain a more detailed understanding of the mechanism underlying the drug effects on behaviour described above, we used hierarchical Bayesian modelling. To begin with, we determined the best-fitting discounting models for both effort and delay, comparing four commonly used models (linear, parabolic, hyperbolic, exponential). In line with previous findings (Green & Myerson, 2004; Hartmann et al., 2013; Kirby & Maraković, 1995; Klein-Flügge et al., 2015; Lockwood et al., 2017), model comparisons revealed that effort discounting was best described by a parabolic model,

suggesting a greater impact of changes in high rather than low effort levels. In contrast, delay discounting was best described by a hyperbolic model, indicating a greater impact of changes in low rather than high delay levels (Supplementary Table 3). For each model, we first calculated the subjective values of all choice options, based on participant-specific weighing of reward magnitude and associated costs (i.e., effort and delay levels). By introducing condition-specific shift parameters, we captured potential drug effects on the effort and delay discounting parameter κ (denoted as $s_{\kappa_{HAL}}$ for haloperidol and $s_{\kappa_{BIP}}$ for biperiden), with positive/negative shift parameter values indicating increased/decreased effort and delay discounting, respectively. We then used a softmax function to transform the option values into choice probabilities, with choice stochasticity being modelled by an inverse temperature parameter β. Again, condition-specific shift parameters for haloperidol and biperiden captured potential drug effects on choice stochasticity ($s_{\beta_{HAL}}$ for haloperidol and $s_{\beta_{BIP}}$ for biperiden), with positive/negative shift parameters indicating more deterministic/more stochastic decision making (see Materials and Methods and Supplementary Methods). Model validation and parameter recovery confirmed that both models accurately captured key features of the choice data (see Supplementary Results).

– insert Figure 4 here –

The results from the computational model of the effort discounting task align with and extend the regression-based results presented above. Specifically, again biperiden and haloperidol exerted opposing effects on both the discounting and inverse temperature parameter. Haloperidol increased effort discounting, while biperiden

diminished it. Similarly, haloperidol induced more stochastic choices, while biperiden led to more deterministic decisions (Table 1). For both drug-specific effects on the effort discounting parameter κ, we acknowledge that, strictly speaking, the 95% HDI of $s\kappa_{BIP}$ (HDI_{Mean} = -0.012,; $HDI_{95\%}$ = [-0.000; 0.027]) and $s\kappa_{HAL}$ (HDI_{Mean} = 0.013, $HDI_{95\%}$ = [-0.025; 0.000]) did overlap with zero, albeit to a very small extent (Fig. 4a). Notably, the density that did not overlap with zero still accounted for more than 94% of the posterior distribution (94.8% HDI > 0 for haloperidol and 94.4% HDI > 0 for biperiden). This provides strong evidence for a credible modulation of effort discounting by cholinergic M1 and dopaminergic D2 receptor manipulation, despite the slight overlap.

A similar pattern emerged in the analysis of the inverse temperature parameter, further supporting the partly opposing effects of these neurotransmitters. The HDIs for $s\beta_{HAL}$ (HDI_{Mean} = -0.089, $HDI_{95\%}$ = [-0.164; -0.010]) and $s\beta_{BIP}$ (HDI_{Mean} = 0.127, $HDI_{95\%}$ = [0.048; 0.219]) did not overlap with zero, supporting the modulatory effects of these drugs on choice stochasticity. Specifically, haloperidol increased choice stochasticity, while biperiden exhibited the opposite effect (Fig. 4b).

--insert Table 1 here--

For the delay discounting task, computational modelling revealed credible evidence only for a dopaminergic, but not cholinergic modulation of delay discounting (Fig. 4d and Table 2). In line with the diminished delay sensitivity reported above, haloperidol reduced delay discounting, making participants more willing to wait for greater financial rewards with increasing levels of delay ($s\kappa_{HAL}$: HDI_{Mean} = -0.630, $HDI_{95\%}$ = [-1.083; -0.237]). For biperiden, we did not observe any shift of the discounting parameter ($s\kappa_{BIP}$:

HDI_{Mean} = -0.125, $HDI_{95\%}$ = [-0.410; 0.148]). Next, we examined the effects of dopaminergic and muscarinic antagonism on choice stochasticity (Fig. 4e). Biperiden credibly increased the choice stochasticity ($s\beta_{BIP}$: HDI_{Mean} = -0.043, $HDI_{95\%}$ = [-0.085; -0.000]), while we did not find credible evidence for a modulatory effect of haloperidol, as the 95% HDI overlapped with zero ($s\beta_{HAL}$: HDI_{Mean} = -0.055, $HDI_{95\%}$ = [-0.114; 0.006]).

--insert Table 2 here--

Lastly, to test whether putatively confounding side effects of the pharmacological treatment account for our main effects of interest, we tested medication effects on several control measures, including mood (alertness, calmness, and contentedness) and basic physiological parameters (heart rate, systolic, and diastolic blood pressure), using Bayesian Linear Mixed Models. In short, biperiden administration induced reductions in systolic blood pressure and heart rate at T_1 and at T_2. Moreover, relative to placebo, both biperiden and haloperidol caused decreases in subjective alertness ratings at T_2 (all $HDI_{95\%} < 0$). T_1 represents the measurement taken before participants began the effort discounting task, and T_2 represents the measurement taken after they completed the delay discounting task. Importantly, neither the changes in blood pressure or heart rate, nor reductions in alertness showed credible correlations with any shift parameter that was credibly modulated by haloperidol or biperiden in both tasks. This implies that the drug-induced changes in behaviour were not linked to drug effects on alertness, heart rate, or blood pressure. More detailed information can be found in the Supplementary Results.

Taken together, the results derived from hierarchical Bayesian modelling are consistent with findings obtained from the GLMMs. Diminishing dopaminergic D2 receptor activity decreases the willingness to invest effort for rewards, possibly by amplifying effort discounting. Conversely, the administration of a cholinergic M1 receptor antagonist produces opposite effects. However, this pattern of opponent dopaminergic and cholinergic effects on specific components of effort discounting was not present in the delay discounting task. Instead, the findings suggest a reduced impact of delay on decision making under haloperidol, while biperiden affected only the choice stochasticity. This implies that contrasting effects of dopaminergic and cholinergic manipulations may reflect computationally-specific, rather than universal effects.

Across-Task Relationship of Discounting Behaviour

Lastly, as an exploratory analysis, we asked whether there was a relationship between discounting of delays versus efforts across individuals. In other words, we tested whether people showing steep discounting of physical efforts would also show steep delay-based discounting. In line with previous findings (Klein-Flügge et al., 2015; Seaman et al., 2018), we found no relationship between individuals' tendency to discount rewards based on efforts compared to delays (no credible correlation between the effort and delay discounting parameters κ under placebo; r = -0.17, $HDI_{95\%}$ = [-0.06; 0.39]).

Discussion

In this study, we investigated the effects of pharmacologically manipulating dopaminergic and cholinergic neurotransmission on cost-benefit decision making in

309 healthy young adults. Specifically, we administered haloperidol or biperiden, two drugs
310 that selectively block either dopamine D2-like or muscarinic M1 acetylcholine
311 receptors, respectively, and tested the effects on discounting a monetary reward as a
312 function of either effort or delay. In short, we found that reducing dopaminergic
313 transmission at D2-like receptors decreased participants' willingness to invest physical
314 effort for monetary rewards and attenuated the impact of delay on decision making. In
315 contrast, cholinergic M1 receptor manipulations promoted the preference for high-
316 effort options, without affecting delay-based choices.

317 The goal of our study was threefold. First, we sought to conceptually replicate
318 the boosting effects of dopamine on motivation. Second, we examined the contribution
319 of acetylcholine, acting at M1 receptors, on cost-benefit decision making, as the
320 influence of muscarinic acetylcholine receptors on human (value-based) decision
321 making has rarely been reported. Third, we aimed to address the conflicting literature
322 on dopamine's role in delay-based decision making by providing data from a large
323 sample using a within-subjects design.

324 Dopamine has been widely suggested to play a key role in various aspects of
325 reward processing and cost-benefit decision making (Jocham et al., 2011, 2014;
326 Webber et al., 2020). It modulates choices based on expected rewards and costs
327 associated with different options (Schultz, 2016a, 2016b; Tanaka et al., 2019).
328 However, the direction of dopaminergic manipulations on different aspects of costs
329 remains ambiguous. Traditionally, dopamine has been implicated in promoting
330 behaviour that maximizes reward outcomes, suggesting that increased dopaminergic
331 activity energizes behaviour to approach high-reward options despite associated costs
332 (Bailey et al., 2016; Berke, 2018; Phillips et al., 2007; Salamone & Correa, 2012).
333 According to this view, increasing dopaminergic transmission should bias decision

making toward high-reward options, even when they involve higher costs such as effort, delay, and risk. Conversely, decreasing dopaminergic transmission should have the opposite effect.

In line with this view, in our study, the administration of a D2-like receptor antagonist did in fact reduce the willingness to invest physical effort for reward. However, contrary to the notion that dopamine supports reward-maximizing behaviour, our findings in the delay discounting task did not confirm the expected pattern. We observed a decrease in delay discounting under haloperidol, rather than an increase. While there is indeed a substantial body of evidence suggesting enhancing effects of dopamine on motivation, as demonstrated by studies highlighting its involvement in promoting reward-seeking behaviour (Michely et al., 2020; Soder et al., 2020; Soutschek et al., 2020; Wardle et al., 2011), the impact of pharmacological manipulations targeting other cost-related factors, such as delay (de Wit et al., 2002; Hamidovic et al., 2008; Kayser et al., 2012; Petzold et al., 2019) and risk (Burke et al., 2018; Rutledge et al., 2015; Zack & Poulos, 2007), has produced rather inconsistent findings. These studies showed either contradicting results regarding dopaminergic manipulations or no effect at all. These inconsistencies challenge traditional views of dopamine and raise questions about the specific mechanisms through which dopamine modulates choices that incorporate time-dependent costs. A more recent theory proposes that dopamine, acting at D2-like receptors, biases action selection by increasing the preference for options with a proximity advantage over more distant alternatives (Soutschek et al., 2023; Westbrook & Frank, 2018). This theory is based on studies in rodents, where firing rates of neurons in the nucleus accumbens are increased by spatially proximal rewards, promoting a decision bias towards nearby low-reward options (Morrison & Nicola, 2014). This notion of proximity, originally

referring to spatial proximity, has been extended to the context of psychological proximity (Westbrook & Frank, 2018). According to this view, dopamine not only favours options that are physically closer in space, but also options that are psychologically closer, as in our case, rewards that are available sooner in time. Consequently, the administration of D2 receptor antagonists, which, according to this theory, are believed to reduce the proximity bias, have been shown in some studies to increase the preference for delayed and risky reward options, which lack the proximity advantage (Burke et al., 2018; Ojala et al., 2018; Soutschek & Tobler, 2023; Wagner et al., 2020). In other words, this theoretical framework proposes that dopamine may play a dual role in (i) promoting choices towards options with a psychological proximity advantage and (ii) weighing reward magnitudes against associated costs. Our findings of decreased delay discounting under haloperidol align with this theory, potentially suggesting a diminished preference for more proximal options when D2-receptor activity is reduced, resulting in increased endurance for higher (time) costs. On the other hand, the reduction of dopaminergic neurotransmission had the opposite effect on effort discounting, leading to a diminished willingness to bear higher (effort) costs. This apparently conflicting finding between effort and time costs may be explained by the fact that neither the low-effort nor the high-effort option had a pronounced psychological proximity advantage. Thus, in this specific context of cost-benefit decision making, the proximity factor appears to be less relevant, and dopamine instead may promote behaviour aimed at maximizing rewards simply by weighing rewards against associated costs. Importantly, our experimental paradigm did not directly manipulate psychological proximity, nor did it distinguish between proximity effects and the impact of delay. Therefore, specific effects of dopamine on psychological proximity in human delay discounting remain

highly speculative and warrant further investigation with experimental paradigms specifically tailored to this question.

Low doses of dopamine receptor antagonists may facilitate dopaminergic transmission by primarily blocking presynaptic autoreceptors, which may increase rather than decrease dopamine release (Frank & O'Reilly, 2006; Schoemaker et al., 1997). We would however argue that such a presynaptic mechanism of action is unlikely to explain our findings. First, a PET study found that the same dose of haloperidol as used here led to high levels of D2 receptor occupancy in the striatum (Kapur et al., 1996). Second, our pattern of results aligns with studies in rodents showing motivational deficits following ventral striatal dopamine depletion (Cousins et al., 1996; Mai et al., 2012; Salamone et al., 1994). Third, high doses of haloperidol have been shown to reduce alertness (Liem-Moolenaar et al., 2010), whereas drugs like methylphenidate that increase synaptic dopamine levels, enhance subjective ratings of alertness (Linssen et al., 2011; Swart et al., 2017). Consistent with this, we observed a reduction in alertness ratings following haloperidol administration. Together, this suggests that our results are best explained by a blockade of postsynaptic D2 receptors by haloperidol.

Notably, prior research has highlighted the contribution of other neurotransmitters such as serotonin (Meyniel et al., 2016; Miyazaki et al., 2020), adenosine (Randall et al., 2011; Salamone et al., 2018), and acetylcholine (Betts et al., 2021; Hailwood et al., 2019; Nunes et al., 2013), in the weighing of costs and rewards. However, the exact role of these neurotransmitters in reward processing and cost-benefit decision making in humans has been rarely investigated. Understanding the involvement of acetylcholine, due to its reciprocal activity with dopamine in the striatum, is of particular interest (Chantranupong et al., 2023; Gerber et al., 2001;

409 Moehle & Conn, 2019; Myslivecek, 2021). At the functional level, these mutual
410 interactions are evident from the fact that muscarinic receptor antagonist diminish the
411 extrapyramidal side effects of dopamine antagonists, and, vice versa, muscarinic
412 agonists display antipsychotic properties, resembling the action of D2 antagonists
413 (Brocks, 1999; Stanhope et al., 2001). Additionally, blocking M1 receptors has been
414 shown to reverse motivational impairments induced by dopaminergic antagonism,
415 further emphasizing its potential role in modulating dopamine-related processes
416 (Hailwood et al., 2019). At the cellular level, it has been shown that M1 receptor
417 activation inhibits D2-receptor-mediated effects in the striatum (Di Chiara et al., 1994).
418 These observations highlight an interplay between acetylcholine and dopamine
419 signalling. Therefore, in addition to testing dopaminergic D2-like receptor
420 manipulations, we also investigated the role of cholinergic M1 receptor
421 neurotransmission on decision making.

422 Indeed, we observed opposing effects of dopaminergic and cholinergic
423 manipulations within specific components of effort-, but not delay-based decision
424 making. Specifically, we found evidence for biperiden increasing the willingness to
425 invest effort for rewards and, in line with this, decreasing effort discounting. In contrast,
426 haloperidol reduced the general willingness to invest effort and increased effort
427 discounting. However, we also observed drug effects that were not in opposite
428 directions between biperiden and haloperidol. For example, biperiden increased
429 reward sensitivity, while haloperidol had no credible effect on the impact of rewards
430 on effort-based choices. Furthermore, haloperidol modulated decision times in both
431 experimental tasks, whereas biperiden did not affect them. These findings suggest
432 partially opposing effects between both neurotransmitters, mostly evident within
433 specific components of effort-based choices.

434 This partially opposing mechanistic relationship between dopaminergic and
435 cholinergic neurotransmission during the effort discounting task is further reflected in
436 changes in choice stochasticity. Previous studies have linked D2 receptor antagonism
437 with increased choice stochasticity (Eisenegger et al., 2014; Mikus et al., 2022).
438 Consistent with these findings, our results revealed that haloperidol administration
439 increased stochasticity and thereby reduced value dependency on choices, while
440 biperiden had the opposite effect. After lowering cholinergic M1 receptor activity,
441 participants were more likely to choose the option with the highest expected value
442 compared to placebo. However, it is important to note that biperiden had the opposite
443 effect in the delay discounting task, increasing, rather than reducing choice
444 stochasticity. This discrepancy indicates that the role of cholinergic neurotransmission
445 in balancing deterministic versus stochastic behaviour is more complex and needs
446 further investigation.

447 Some limitations should be noted. First, our focus was primarily on striatal D2
448 receptor activity, as haloperidol predominantly targets D2 receptors in the striatum
449 (Nordström et al., 1992). However, it is important to note that in the context of cost-
450 benefit decision making, dissociable roles of D1 versus D2 receptor activity have been
451 reported (Collins & Frank, 2014; Soutschek et al., 2023; Webber et al., 2020), and thus
452 the general role of dopamine beyond its selective activity on striatal D2 receptors
453 remains unclear. Conversely, biperiden primarily targets M1 receptors in the cortex
454 and striatum (Sudo et al., 1999), making it challenging to determine the precise
455 mechanisms underlying cortical and striatal cholinergic modulation and the reciprocal
456 effects on dopaminergic activity. Second, previous research has suggested a U-
457 shaped dose-response function for dopamine, indicating deleterious effects of both
458 extremely high and extremely low levels of dopamine (Cools & D'Esposito, 2011;

Goldman-Rakic et al., 2000). According to this idea, the same dopamine agent can produce opposing effects in different individuals. Therefore, it may be insightful to consider individual differences in baseline dopamine levels when studying the effects of dopaminergic manipulations. A recent study found evidence for the absence of a correlation between dopamine synthesis capacity and putative behavioural proxies of dopamine, such as working memory or trait impulsivity (van den Bosch et al., 2022). Consequently, investigating baseline dopamine levels require more costly and invasive techniques, such as positron emission tomography. Third, as participants were required to exert physical effort on each trial, fatigue effects could have developed in the effort discounting task. While our additional analysis confirmed a general fatigue effect and a dual role of haloperidol in both reducing the overall propensity to invest effort and in exacerbating the fatigue effect throughout the task, we acknowledge that recent studies revealed the existence of distinct states of fatigue (Matthews et al., 2023; Müller et al., 2021). Importantly, this was discovered by using task paradigms and computational models that were designed to distinguish between these different types of fatigue. Additionally, it is important to consider that potential motor effects, particularly in the context of dopaminergic manipulations, could also affect effort discounting behaviour. Future studies could extend our approach by incorporating measurements of force pulses to investigate potential motor-related effects and apply task designs and computational models specifically tailored to capture how drug manipulations might affect different forms of fatigue. Lastly, it is important to note that several factors preclude a direct quantitative comparison between the delay and effort discounting tasks. These include the distinct nature of rewards and costs (hypothetical vs. real), varying reward magnitudes in both tasks (large vs. small), and differences in task structure (fixed vs. variable alternative option).

Additionally, both tasks were consistently performed in a fixed order within and between participants (effort followed by delay). While this ensured consistent drug levels within each task, it is potentially introducing task order effects and possibly leading to differential drug concentrations between tasks. These methodological differences limit our ability to directly compare drug effects across the two cost domains. Future research would benefit from applying experimental paradigms that manipulate both delay and effort costs within the same task, allowing a more controlled and direct comparison of how pharmacological manipulations differentially influence sensitivity to these distinct cost types.

In conclusion, our findings support prior research indicating an invigorating effect of dopamine on motivation in an effort-based decision-making task. Moreover, our study contributed to understanding dopamine's involvement in temporal cost-benefit tradeoffs by revealing decreased delay discounting following dopaminergic D2-like receptor antagonism. Further, we demonstrate that the administration of biperiden, a muscarinic M1 receptor antagonist, had contrasting effects to those of dopaminergic D2 receptor antagonism in the general willingness to choose high-cost options and the effort discounting parameter. This suggests that in the context of human cost-benefit decision making, the previously reported reciprocal relationship between both neurotransmitters may be limited only to specific components of behaviour. Our findings indicate that, while D2 receptor activity plays a role in integrating both delay and effort costs, acetylcholine, acting at M1 receptors, may have a more specific role in effort processing.

507 **Materials and Methods**

508

509 **Ethics**

510 Ethical approval for the study (2021-1549) was obtained from the Ethics Committee of
511 the Medical Faculty of the University of Düsseldorf, Germany. Prior to participating, all
512 volunteers provided informed written consent.

513

514 **Participants**

515 Participants were recruited for the study via online advertisements and university
516 postings. They were initially screened via email interviews to verify compliance with
517 the inclusion and exclusion criteria. Inclusion criteria included an age range of 18 to
518 35 years, a body weight ranging from 60 to 90 kg, and a body mass index equal to or
519 greater than 18 and less than 28. Exclusion criteria included a history of psychiatric or
520 neurological illnesses, current intake of prescription medication (excluding oral
521 contraceptives), current pregnancy or breastfeeding, and the presence of any medical
522 conditions contraindicated for the drugs used in the study. Additionally, participants
523 with a history of drug use were excluded, with exceptions for alcohol, nicotine, and
524 cannabis, which were limited to consumption of less than 14 units of alcohol per week,
525 less than 5 cigarettes per day, and no cannabis consumption within the past month.

526 From an initial group of 96 individuals attending the medical screening on site,
527 33 candidates decided not to proceed, or they were excluded due to not meeting the
528 participation criteria (despite otherwise indicated in the prior interview). Eventually, a
529 total of 63 volunteers were enrolled in the study. One participant had to be excluded
530 due to experiencing side effects following the biperiden testing session, resulting in a
531 final sample size of 62 participants (32 female; Mean Age (SD): 22.79 (3.20); Age

532 Range: 18 - 35). The sample did not include any non-binary participants. All
533 participants received a fixed reimbursement of 240 € for their participation in all testing
534 sessions and were provided with a flexible payment based on their performance in the
535 tasks.
536
537 **Procedure**
538 A double-blind, randomized, within-subject design was employed. Participation
539 involved three testing sessions, each separated by a minimum of one week to ensure
540 complete drug washout. Prior to participation, on a separate day, participants
541 underwent a medical screening session to determine their eligibility. This screening
542 session consisted of a clinical interview, medical assessment, practice trials of both
543 tasks, and completion of several questionnaires assessing personality traits, including
544 Apathy Evaluation Scale (AES) (Lueken et al., 2006; Marin et al., 1991), Beck's
545 Depression Inventory (BDI) (Beck et al., 1996; Kühner et al., 2007), and Barratt
546 Impulsiveness Scale (BIS-15) (Meule et al., 2011; Spinella, 2007). The final decision
547 regarding participant suitability for the study was made by a physician at the end of
548 the screening session.
549 Each testing day followed the same procedure, with the only difference being
550 the administration of a placebo, biperiden (4 mg), or haloperidol (2 mg) in separate
551 sessions. Testing sessions were scheduled between 9 a.m. and 12 p.m., with efforts
552 made to assign participants to the same time slot consistently. Participants were
553 instructed to fast overnight and consume only water before the testing session.
554 Additionally, female participants completed a pregnancy test before the start of each
555 testing day. Upon arrival, participants underwent a screening conducted by a
556 physician, who restated the potential effects of the drug and provided a recap of the

557 testing day's procedures. Subsequently, participants received the assigned drug
558 treatment along with a standardized breakfast. Orally administered biperiden reaches
559 its peak concentration between 1 and 1.5 hours after administration (Brocks, 1999;
560 Grimaldi et al., 1986), while haloperidol reaches its peak concentration only between
561 2 and 6 hours after administration (Kudo & Ishizaki, 1999). In order to follow a double-
562 blind procedure while also accounting for variations in the drugs' peak times, a dummy
563 drug application was included. Thus, on each testing day, a second capsule was
564 administered 120 minutes after the first drug application, resulting in the planned delay
565 between drug and effort discounting task of approximately 180 minutes for haloperidol
566 (179.57 ± 2.61) and, on a separate day, approximately 60 minutes (59.65 ± 1.30) for
567 biperiden. The second task was performed 205.59 minutes (± 3.12) after haloperidol
568 and 86.24 minutes (± 6.09) after biperiden administration. Shortly before starting the
569 experimental task, participants further completed the trail-making test A (Tombaugh,
570 2004). Blood pressure and heart rate were measured three times throughout the
571 testing day: at T_0 (before drug administration), T_1 (before starting the effort discounting
572 task), and T_2 (after finishing the delay discounting task). These measurements
573 coincided with mood assessments using Visual Analogue Scales (Bond & Lader,
574 1974). Please refer to Fig. 1a for a detailed explanation of the procedure. The tasks
575 were presented in a fixed order during each session, starting with the effort discounting
576 task (Fig. 1b) and concluding with the delay discounting task (Fig. 1c). These
577 discounting paradigms were implemented using Visual Basic software and displayed
578 on a 15.6” laptop screen (Dell Latitude E5550). Participants used an external keypad
579 to indicate their choices, arranging the laptop and keypad in a manner that was most
580 comfortable for them.
581

Experimental Tasks

Effort Discounting Task

Participants engaged in a modified version of the Apple Tree Task, which has been previously utilized with both healthy volunteers and patients with neurological diseases (Bonnelle et al., 2015; Chong et al., 2018; Le Heron et al., 2018). Unlike the original task where participants accepted or rejected offers, in this modified task, they were presented with two alternative options on each trial. Prior to each experimental session, the participants' maximum voluntary contraction (MVC) was assessed by having them grip a handheld dynamometer (Vernier, Orlando, USA) with their dominant hand as forcefully as possible. The MVC was determined immediately before starting the task by measuring the highest force exerted over three contractions.

During each trial, they had to choose between a high-reward/high-effort (high-cost) and a low-reward/low-effort (low-cost) offer. Participants had unlimited time for their decision. Notably, both the reward levels and effort levels of each option were varied among five possible levels. The reward levels ranged from 2 to 16 (2, 4, 8, 12, and 16), and the effort levels ranged from no effort to 80% (0, 20, 40, 60, and 80%) of the individually determined MVC. After making a choice, participants were given a 5-second window to squeeze the handheld dynamometer and reach the required effort level. They had to maintain the required force for at least 1 second. Throughout this effort production period, a bar visually represented the force exerted, providing real-time feedback. Following successful trials, participants received feedback on the reward earned during the trial. If participants failed to reach the designated effort level, no apples were gathered. In cases where participants chose an offer that required no effort, they had to wait for the same duration without engaging in squeezing. At the end of the experiment, we asked participants to rate the perceived level of demand for

each effort level using a Likert scale ranging from 0 (“not demanding at all”) to 20 (“extremely demanding”). This subjective rating allowed us to examine whether the administration of the drugs had any effects on participants' perception of the demand associated with each effort level.

Each participant completed a total of 125 trials, divided into 5 blocks. The trial structure was full randomized for each participant and experimental session. To prevent strategic behaviour and mitigate delay discounting effects, all blocks and trials were the same length, regardless of previous choices made. Importantly, patients were required to squeeze the handheld dynamometer after every trial (if effort production was chosen), meaning that no hypothetical choices were made. Based on their task performance, participants received a flexible payment consisting of 1 cent for each apple they collected.

Delay Discounting Task

After completing the effort discounting task, participants proceeded to the delay-based decision-making task. In this task, they were presented with a similar choice paradigm, but this time between a high-reward/high-delay (high-cost) and a low-reward/low-delay (low-cost) option on each trial, again without any time limit. The tasks shared a common structure, with participants consistently facing decisions involving a tradeoff between a more favourable outcome with higher associated costs and a less favourable outcome with fewer costs. In contrast to the previous task, the low-cost option was fixed at 20 € and available immediately across all trials. The high-cost option varied between 20.20 € and 260 € (20.20, 20.40, 21, 22, 24, 30, 36, 40, 50, 60, 80, 100, 140, 200, 260 €), with associated delays ranging from 1 day to 60 days (1, 2, 3, 5, 8, 30, 60). This resulted in a total of 105 unique high-cost combinations.

632 Participants completed two blocks, with each block containing all unique
633 combinations, resulting in a total of 210 trials. We used a pseudorandomized trial
634 order, counterbalanced across experimental sessions but not across participants.
635 Consistent with previous studies, all choices in this task were hypothetical (Bickel et
636 al., 2009; Madden et al., 2003). However, participants were instructed to imagine that
637 one of their choices would be randomly selected and paid out.
638
639 **Statistical Analysis**
640 *Regression-Based Analysis*
641 To investigate the influence of drug administration (compared to placebo) and
642 experimental manipulations (i.e., reward magnitude, delay, and/or effort) on choice
643 behaviour, we employed Logistic Bayesian Generalized Linear Mixed Models, using
644 the brms package (Bürkner, 2017) in R (Version 4.1.3). In these models, we regressed
645 choices (choosing the high-cost option vs. choosing the low-cost option) on fixed-effect
646 predictors including drug, reward, cost (i.e., delay or effort), and all possible interaction
647 terms. Importantly, to test drug-specific effects on behaviour, we included the drug
648 condition (placebo, haloperidol, biperiden) as a 3-level categorical predictor with
649 placebo set as the reference. Thus, all drug-related main and interaction effects are
650 estimated in reference to the placebo. For the effort discounting task, as predictors we
651 used the difference term between both the reward magnitude and effort levels of the
652 two presented options (high-cost option – low-cost option). In the delay discounting
653 task, the reward and delay levels of the varying high-cost option were included as
654 regressors. To account for individual differences, all fixed-effect predictors were also
655 modelled as random slopes in addition to subject-specific random intercepts. To
656 ensure robust and informative analyses, we followed the approach suggested by

Gelman et al. (2008). Weakly informative priors were employed, with nonbinary variables scaled to have a mean of 0 and a standard deviation of 0.5. Posterior distributions of the parameter estimates were obtained by running four chains with 3000 samples (1000 samples for warmup). We present the 95% Highest Density Intervals (HDI) of the estimates to capture the uncertainty in the parameter estimates. The 95% HDI indicates that there is a 95% probability that the true parameter value falls within this interval. If the 95% HDI does not overlap with zero, it provides credible evidence that the respective model parameter is meaningful (Ahn et al., 2017; Kruschke, 2014). For detailed information on the models employed in this analysis, please refer to the Supplementary Methods.

Order and Fatigue Control Analysis

To further test for potential confounding effects on choice behaviour, we ran separate control regression analyses. For these models, we used the structure of the original GLMMs but included additional fixed-effect predictors to control for session and fatigue effects. Specifically, we included trial number as a predictor to account for potential systematic changes in choice behaviour throughout the task progress. In separate models, session was included as a fixed effect to control for potential learning or drug order effects across different experimental sessions. Importantly, to capture potential interactions between these control variables and the drug manipulations, we included the two-way interaction terms in the fixed-effects structure. This allows to investigate whether the effects of the drug manipulation on choice behaviour differed as a function of the task progress or experimental session. All other aspects of the model specification, including random-effects structure, priors, and estimation procedures, remained identical to the original regression models described above.

Hierarchical Bayesian Modelling

Next, to investigate the impact of dopaminergic and cholinergic manipulations on underlying cognitive processes, specifically how individuals integrate rewards and costs to discount subjective reward values, we employed hierarchical Bayesian modelling. This approach allowed us to estimate both group-level hyperparameters and individual subject-level estimates, leveraging the hierarchical structure of the experimental design. By incorporating information from each individual's estimates into the group estimates and vice versa, we obtained more robust and reliable parameter estimates compared to conventional methods like maximum likelihood estimation (Ahn et al., 2017).

To capture how changes in the subjective values are influenced by reward, effort, and delay, we employed a single-parameter discounting model to determine which discounting function best describes the observed behaviour. Initially, participants' responses from the placebo condition were fitted to four commonly used models for discounting: linear, parabolic, hyperbolic, and exponential (Białaszek et al., 2017; Chong et al., 2017; Hartmann et al., 2013; Klein-Flügge et al., 2015). Model fits were compared using the trial-based Leave-One-Out Information Criterion (LOOIC) from the loo package (Vehtari et al., 2017).

Consistent with previous findings, delay discounting was best described by a hyperbolic model (Green & Myerson, 2004; Kirby & Maraković, 1995), whereas effort discounting showed the best fit with a parabolic model (Hartmann et al., 2013; Klein-Flügge et al., 2015; Lockwood et al., 2017). See Supplementary Methods for more details. The discounting parameter in the delay discounting model was modelled in log space due to the skewed distribution of the values towards zero.

$$SV(HC_{(t)}) = \frac{R_{(t)}}{1+\exp(\kappa) * D_{(t)}} \quad (1)$$

$$SV(HC_{(t)}) = R_{HC_{(t)}} - \kappa * E_{HC_{(t)}}{}^{2} \quad (2)$$

$$SV(LC_{(t)}) = R_{LC_{(t)}} - \kappa * E_{LC_{(t)}}{}^{2} \quad (3)$$

In the delay discounting model (Eq. 1), R_t represents the reward magnitude and D_t represents the delay in days of the high-cost option (HC) on trial t, while the subjective value (SV) of the low-cost option (LC) was fixed at 20 for each trial. In contrast, the effort discounting models (Eq. 2 and 3) involve varying levels of both options. In this model, the SV of the HC option and the SV of the LC option are calculated separately. Once again, R_t denotes the corresponding reward magnitude, and E_t represents the associated effort in percentage on trial t.

$$\kappa = \kappa_{PLC} + I_{HAL_{(t)}} * s_{\kappa_{HAL}} + I_{BIP_{(t)}} * s_{\kappa_{BIP}} \quad (4)$$

Consistent with previous studies that examined drug effects on changes in discounting (Mathar et al., 2022; Peters & D'Esposito, 2020; Wagner et al., 2020), we extended the original single-parameter model by incorporating two additional free parameters (Eq. 4). In both cases, κ is the discounting parameter, either reflecting delay discounting or effort discounting. A higher κ value indicates a greater degree of discounting, whereas a lower κ value suggests less discounting. To capture potential drug effects (compared to placebo), two separate shift parameters ($s_{\kappa_{HAL}}$ for haloperidol

and $s_{\kappa_{BIP}}$ for biperiden) were included to model changes in the discounting rate. A positive shift parameter indicates that the corresponding drug increases discounting, while a negative shift parameter suggests that the drug decreases discounting. The condition for each trial is indicated by the dummy-coded variable I, which indicates the drug condition of the current trial.

$$P\left(HC_{(t)}\right) = \frac{\exp\left(SV(HC_{(t)}) * \beta\right)}{\exp\left(SV(HC_{(t)}) * \beta\right) + \exp\left(SV(LC_{(t)}) * \beta\right)} \quad (5)$$

$$\beta = \beta_{PLC} + I_{HAL_{(t)}} * s_{\beta_{HAL}} + I_{BIP_{(t)}} * s_{\beta_{BIP}} \quad (6)$$

We then used a softmax function to transform the option values to choice probabilities (Eq. 5). The choice stochasticity was modelled using the inverse temperature parameter β. A lower β value indicates more stochastic behaviour. Conversely, a higher β value suggests more deterministic choices.

Similar to the previous analysis, two additional shift parameters ($s_{\beta_{HAL}}$ for haloperidol and $s_{\beta_{BIP}}$ for biperiden) were introduced to capture potential drug effects on choice stochasticity (Eq. 6). A positive s_{β} parameter indicates that the corresponding drug decreases the level of stochasticity in choices, while a negative s_{β} parameter suggests that the drug increases stochasticity.

Model estimation was performed using MCMC sampling as implemented in STAN (Stan Development Team, 2020) via R and the rSTAN package (Version 2.21.0). We utilized separate group-level distributions for all parameters in the placebo condition (i.e., κ and β), as well as for the shift parameters (i.e., $s_{\kappa_{HAL}}$, $s_{\kappa_{BIP}}$, $s_{\beta_{HAL}}$, and s

754 β_{BIP}), which capture potential modulatory effects of the drugs. Prior distributions for the
755 parameter means and standard deviations were chosen within plausible ranges based
756 on previous findings (Knauth & Peters, 2022; Lockwood et al., 2021, 2022; Mathar et
757 al., 2022; Wagner et al., 2020). The sampling process involved running four chains
758 with 4000 iterations after a warmup period of 3000 iterations. Chain convergence was
759 assessed using the Gelman-Rubinstein convergence diagnostic r-hat, with values less
760 than 1.01 considered acceptable (Gelman & Rubin, 1992). We report the mean of the
761 posterior group distribution for all parameters, along with the associated 95% HDI.
762 Please refer to the Supplementary Methods for details of the prior distributions, model
763 comparison, and model estimation procedure.
764
765 *Model Validation & Parameter Recovery*
766 To assess the model's ability to capture and recover important characteristics of the
767 data, we conducted a model validation and parameter recovery analysis. This involved
768 generating 500 synthetic datasets per participant using the posterior distributions of
769 subject-level parameters obtained from the winning models. From these 500 datasets,
770 we randomly selected 10 datasets for each participant and conducted the same
771 analysis as described above, using the synthetic datasets instead of the actual data.
772 First, to validate that the simulated data accurately captures the key features of
773 the participants' behaviour, we simulated the relative choice rates and visualized how
774 behavioural patterns changed as a function of varying levels of costs and rewards.
775 Next, to evaluate the recovery of group-level parameters, we examined whether the
776 simulated group-level parameters fell within the 95% HDI of the actual group-level
777 parameter distribution. For the subject-level parameter estimates, we calculated the
778 correlation between the simulated (averaged across all 10 simulated datasets) and

true estimated subject-level parameters. The results of the model validation and parameter recovery are presented in the Supplementary Results.

Drug Effects on Vital Signs, Mood, Trail-Making Performance, MVC, and Effort Rating

The effects of the drugs on mood (alertness, calmness, and contentedness) and physiological measures (heart rate, systolic, and diastolic blood pressure) were analysed using Bayesian Linear Mixed Models. If credible drug interactions were found, we further explored the relationship between drug induced alterations in behaviour and potential explanatory factors, including changes in subjective mood ratings and/or physiological responses. Specifically, we calculated the absolute differences in mood ratings and physiological parameters between T_0 (before drug administration) and the time point where a credible drug effect was observed (either T_1 or T_2). These difference values were then correlated with the shift parameters that capture drug-induced changes in performance. The purpose of this Bayesian correlation analysis was to exclude that drug-induced changes in mood ratings or physiological measures could account for the observed drug-induced changes in behaviour. We further investigated potential confounding drug effects on trail-making response times, MVC, and subjective effort perception. These analyses did not reveal significant effects of drug manipulation on any of these measures (see Supplementary Results). More detailed descriptions of these analysis are presented in the Supplementary Methods.

Association between task- and drug-specific Computational Parameter Estimates

We investigated the association between discounting tendencies across different cost domains, specifically exploring whether participants who exhibit stronger effort

discounting also displayed stronger delay discounting. To examine this, we performed a Bayesian correlation analysis using the mean estimates of the κ parameters from the placebo conditions in both the effort and delay discounting task.

Computational parameter estimates, self-ratings scores, and demographics

In a supplementary analysis, we investigated potential associations between self-reported questionnaire scores, demographic data (including age and sex of the participants), and the estimated discounting parameters κ from the baseline (placebo) condition of both tasks. To this end, we performed robust linear regressions with the respective discounting parameter as the outcome variable (see Supplementary Methods and Supplementary Results).

Data availability

Anonymized participant's datasets analysed in the study are available from: https://osf.io/gx76t/

Code availability

The regression analysis and computational modelling code is available from: https://osf.io/gx76t/

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Competing interests

The authors declare no competing interests.

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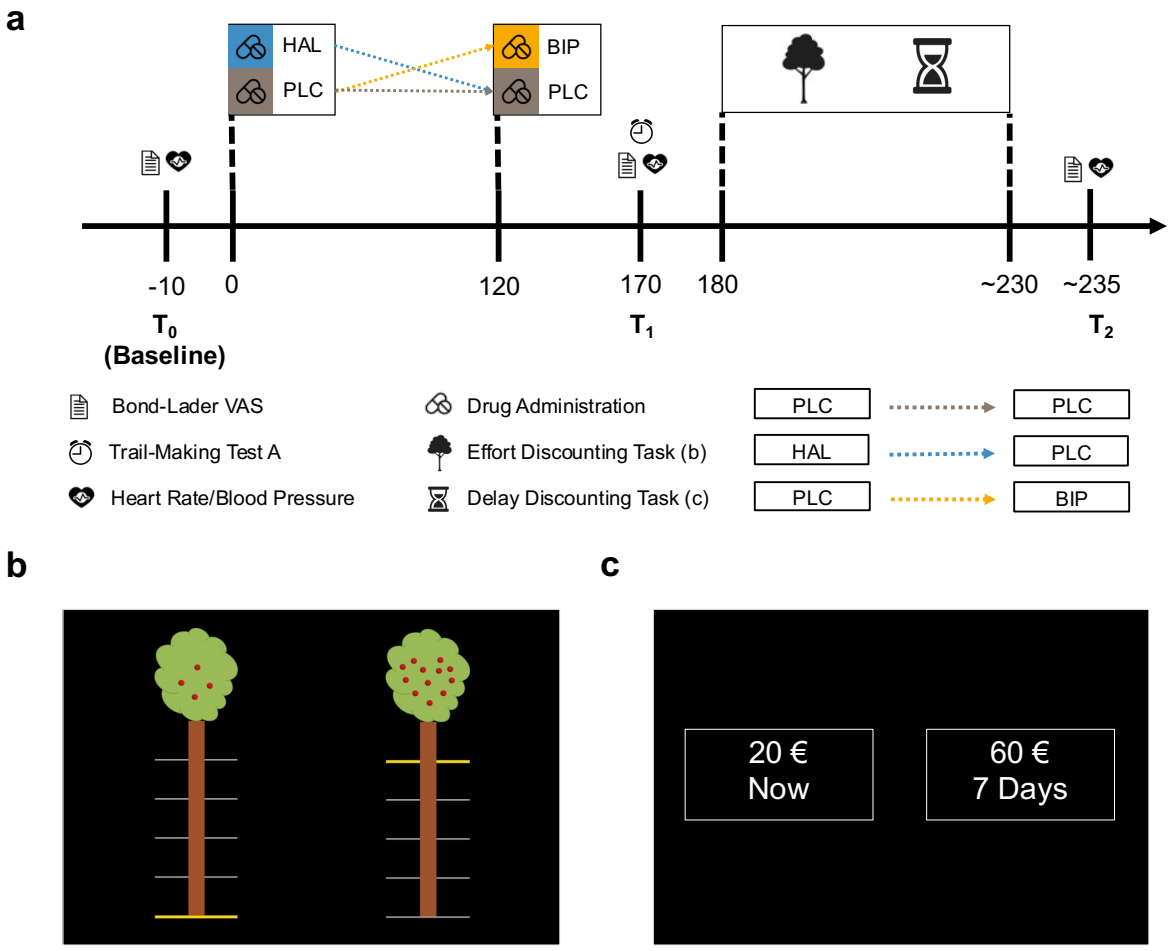

Fig. 1 Study procedure and experimental tasks. (**a**) The experimental sessions were standardized across all sessions except for the drug treatment, which was counterbalanced. To account for the different times of haloperidol and biperiden to reach peak plasma levels, a dummy drug application was introduced, ensuring that the maximum concentration of both drugs was aligned to task execution. Approximately 180 minutes after the first capsule and approximately 60 minutes after the second capsule, participants engaged in the effort discounting task (b), followed by the delay discounting task (c). Physiological measures (including heart rate and blood pressure) and mood ratings (using the Bond & Lader Visual Analogue Scales) were collected at three distinct time points. Additionally, participants completed the trail-making test part A before task execution (see Materials and Methods for more details). In both tasks, participants were presented with two alternative options, each providing information about a monetary reward in return for specific costs. (**b**) Effort Discounting Task. One option required less effort (indicated by the horizontal yellow line) and provided a smaller reward (indicated by the number of apples, low-cost option), while the other option required more effort and provided a higher reward (high-cost option). Participants then chose one option and exerted the required effort (adjusted to the maximum voluntary contraction, MVC) for at least 1 second. (**c**) Delay discounting task. Similarly, participants were presented with two offers: a smaller but immediately available reward (low-cost option) or a larger reward available after the delay indicated (high-cost option).

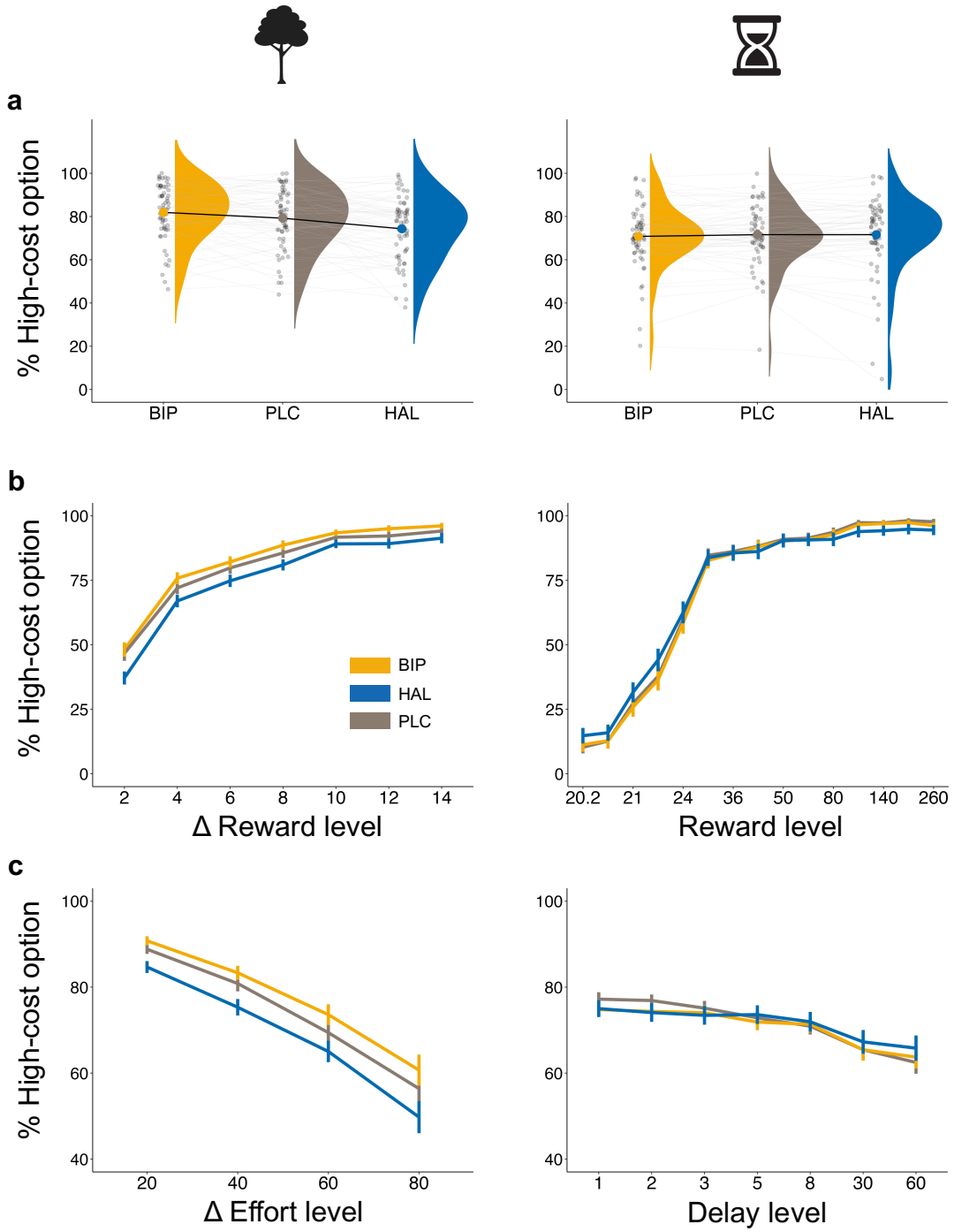

Fig. 2 Behavioural Performance in the Effort (left panel) and Delay (right panel) Discounting Task. (**a**) The overall proportions of high-cost choices were modulated by drug administration in the effort (left), but not in the delay discounting task (right). Biperiden increased and haloperidol decreased the willingness to invest physical effort in return for reward. (**b**) The probability of choosing the high-cost option increased as a function of increasing reward magnitude for both the effort and delay discounting tasks. In the effort discounting task (left), biperiden increased the impact of the reward level on choice. (**c**) Similarly, the tendency to choose the high-cost option decreased as a function of increasing levels of effort and delay. This effect is reduced by haloperidol in the delay discounting task (right). Values in **a** show group-level (single-subject) means represented by bold (light) dots. Values in **b** and **c** display averaged group-level means per reward and cost level, with error bars representing the standard error of the mean. In **b**, reward levels are presented as the difference in magnitude between the high- and low-cost option in the effort discontinuing task and as the absolute reward value of the high-cost option in the delay discounting task. Likewise in **c**, the effort level represents the difference between the proportions of the individually calibrated MVC of the high- versus low-cost option, while the delay levels indicate the delay of the high-cost option.

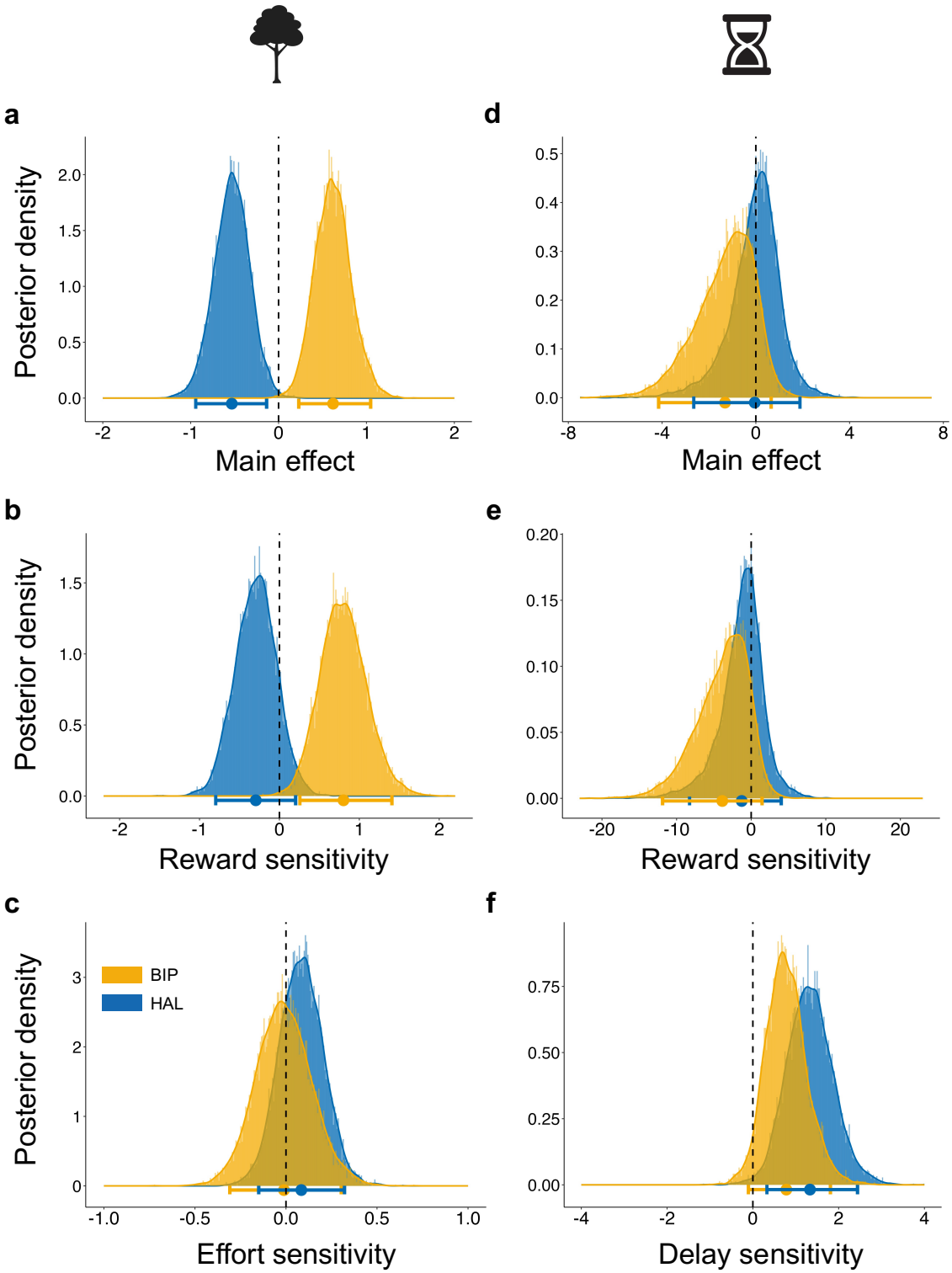

Fig. 3 Drug Effects on Choice Behaviour. Posterior distributions and 95% HDI of the Logistic Bayesian Generalized Linear Mixed Models depict the estimate of each effect on choosing the high-cost option. (**a**) Biperiden credibly increased the overall willingness to invest physical effort for a corresponding reward, while haloperidol had the opposite effect. (**b**) Biperiden increased reward sensitivity in the effort discounting task, as indicated by a biperiden-by-reward interaction, without a credible effect of haloperidol. (**c**) In contrast, neither drug affected effort sensitivity. (**d**) In the delay discounting task, the willingness to tolerate delays for rewards was not affected by either drug. (**e**) Likewise, neither drug modulated reward sensitivity in the delay discounting task. (**f**) However, haloperidol decreased delay sensitivity, with no credible effect of biperiden. Here, a positive estimate of the interaction effect between haloperidol and delay indicates a reduction of the negative parameter estimate associated with delay, suggesting an attenuation of the impact of delay on choice behaviour. Bold dots represent the mean group-level estimate of the posterior distribution. The horizontal bars represent the group-level 95% highest density interval.

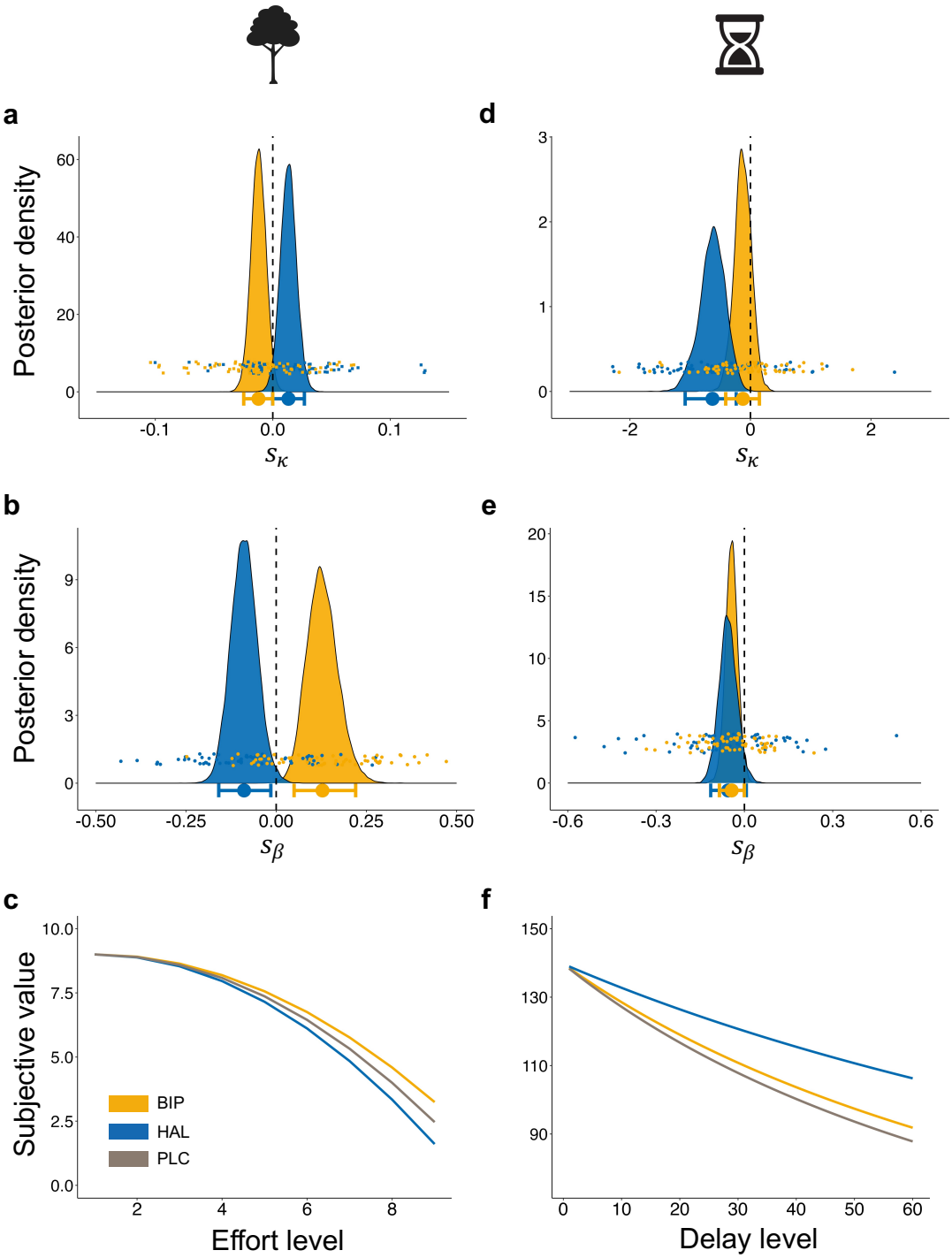

Fig. 4 Drug Effect on Computational Parameters. Posterior distributions and changes in the subjective value from the hierarchical Bayesian models. (**a**) In the effort discounting task, the discounting parameter κ is modulated in opposite directions by the drugs, with haloperidol increasing and biperiden decreasing effort discounting. (**b**) Similarly, these opposite effects are also present in the modulation of the softmax inverse temperature β, reflecting choice stochasticity. Biperiden administration led to more deterministic choices, while haloperidol induced more stochastic choices. (**c**) Modelled discounting functions show steeper discounting under haloperidol and flatter discounting under biperiden. (**d**) In the delay discounting task, the discounting parameter κ is reduced by haloperidol, with no credible modulatory effect of biperiden. (**e**) In contrast, the softmax inverse temperature β is reduced by biperiden, indicating more stochastic choices. (**f**) Overall, participants showed flatter discounting of future rewards under haloperidol compared to placebo. In **a**, **b**, **d**, and **e**, bold (light) dots represent the group-level (participant-level) mean estimate. The horizontal bars represent the group-level 95% highest density interval. In **c** and **f**, the subjective values are displayed as a discount function of effort and delay. Parabolic (effort discounting task) and hyperbolic (delay discounting task) functions are fitted on group-level mean estimates for each drug (see Materials and Methods).

Table 1. Summary of the Group-Level Parameter Estimates for the Effort Discounting Task, Including the Mean, Standard Deviation (SD), and the Lower and Upper Bounds of the 95% HDI Interval.

Parameter	Mean	SD	2.5%	97.5%
κ	0.102	0.008	0.086	0.118
β	0.667	0.032	0.605	0.732
$S\kappa_{HAL}$	0.013	0.007	-0.000	0.027
$S\kappa_{BIP}$	-0.012	0.006	-0.025	0.000
$S\beta_{HAL}$	-0.089	0.038	-0.164	-0.010
$S\beta_{BIP}$	0.127	0.043	0.048	0.219

Table 2. Summary of the Group-Level Parameter Estimates for the Delay Discounting Task, Including the Mean, Standard Deviation (SD), and the Lower and Upper Bounds of the 95% HDI Interval.

Parameter	Mean	SD	2.5%	97.5%
κ	-4.621	0.271	-5.176	-4.107
β	0.356	0.045	0.272	0.449
$S\kappa_{HAL}$	-0.630	0.214	-1.083	-0.237
$S\kappa_{BIP}$	-0.125	0.142	-0.410	0.148
$S\beta_{HAL}$	-0.055	0.030	-0.114	0.006
$S\beta_{BIP}$	-0.043	0.021	-0.085	-0.000