Dopaminergic and Cholinergic Modulation of Human 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 effort discounting 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 point to a domain-general role of dopamine but a domain-specific role of acetylcholine in human cost-benefit decision making.

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, particularly at D2-like receptors, 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). For delay discounting, the existing literature is somewhat more mixed (de Wit et al., 2002; Denk et al., 2005; Floresco et al., 2008; Hamidovic et al., 2008; Kayser et al., 2012; Pine et al., 2010), with more recent evidence in humans indicating decreased delay discounting after blockade of D2 receptors (Soutschek & Tobler, 2023; Wagner et al., 2020). While dopamine has received much attention in cost-benefit decision making, other neuromodulators may also play an important role (Borderies et al., 2020; Meyniel et al., 2016; Nunes et al., 2013). One modulator that has not received much attention in this regard is acetylcholine, which is surprising given the literature on reciprocal antagonistic interactions between acetylcholine and dopamine signalling in the striatum (Chantranupong et al., 2023; Foster et al., 2016; Gerber et al., 2001; Myslivecek, 2021; Threlfell et al., 2010). This suggests that pharmacological blockade of M1 receptors will have effects on cost-benefit decision making that are opposite to those of blocking dopamine D2 receptors.

Although neural activity related to choices involving delay and effort shows some degree of overlap, there appears to be no clear relationship between individuals' sensitivity to both types of cost (Klein-Flügge et al., 2015; Prévost et al., 2010; Seaman et al., 2018). To our knowledge, there has been no study so far that tested the impact of dopaminergic and cholinergic manipulations on both aspects of cost-benefit

decision making in one single experiment. To fill this gap, we investigated the effects of two drugs, haloperidol and biperiden, that selectively block either dopamine D2-like or muscarinic M1 acetylcholine receptors in human participants performing two decision-making tasks involving effort- and delay-based decisions. The goal of our study was threefold. First, we aimed to conceptually replicate the finding that dopamine D2 antagonists increase discounting of physical effort. Second, we sought to further disambiguate the thus far inconsistent picture on the role of dopamine in delay-based decision making. Third, we aimed to assess the contribution of acetylcholine to cost-benefit decision making, and contrast it with the effects of dopamine. In doing so, we also addressed whether any effects of muscarinic or dopaminergic receptor antagonism would be domain-general, or specific to either time or effort costs. Based on previous findings, we hypothesized that the administration of haloperidol will (1) increase effort discounting and (2) reduce delay discounting. In contrast, we expect 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 effort discounting. 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.

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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 within-subjects design (Fig. 1a). The effort-based decision-making task (effort discounting task, Fig. 1b) involved choices between options varying in reward magnitude and effort requirement (using handgrip force), while the delay-based decision-making task (delay discounting task, Fig. 1c) involved choices between one option varying in reward magnitude and delay versus a fixed one. Thus, both tasks

required participants to choose between a high-reward/high-cost (high-cost option) and a low-reward/low-cost (low-cost option) alternative.

Drug Effects on Choice Behaviour

Participants consistently exhibited a preference for the high-cost option over the low-cost alternative in both tasks (effort discounting task: 78.50% ± 1.03; delay discounting task: 71.31% ± 1.12; Fig. 2a). For each of the two tasks, we used a Bayesian Generalized Linear Mixed Model (GLMM) to investigate the impact of drug manipulation, changes in task parameters, and the interaction between both, on choosing the high-cost option (see Methods). We first confirmed that participants effectively discounted rewards based on costs and thereby adhered to the task requirements: As expected, in both discounting tasks higher reward magnitudes increased, while higher cost levels (effort or delay) decreased participants likelihood to select the high-cost option (reward effect on effort discounting: HDI_{Mean} = 3.44, $HDI_{95\%}$ = [2.96; 3.95]; reward effect on delay discounting: HDI_{Mean} = 55.64, $HDI_{95\%}$ = [41.76; 69.38], effort effect on effort discounting: HDI_{Mean} = -1.64, $HDI_{95\%}$ = [-1.87; -1.40]; delay effect on delay discounting: HDI_{Mean} = -2.29, $HDI_{95\%}$ = [-3.30; -1.25], Fig. 2b-c).

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Notably, and in line with our predictions, we found that the two drugs had opposite effects on behaviour in the effort discounting task relative to placebo. Haloperidol reduced the willingness to invest higher effort for greater reward, while biperiden increased this willingness (placebo: 79.17% ± 1.76, haloperidol: 74.34% ± 1.85, biperiden: 81.99% ± 1.64, Fig. 2a (left panel)). These effects were confirmed by credible main effects of both haloperidol (HDI_{Mean} = -0.532, $HDI_{95\%}$ = [-0.943; -0.136]) and biperiden (HDI_{Mean} = 0.620, $HDI_{95\%}$ = [0.230; 1.048]; Fig. 3a) on choosing the high-cost option relative to placebo. Moreover, this analysis revealed that biperiden increased reward sensitivity, as evidenced by a credible interaction effect between biperiden and reward (HDI_{Mean} = 0.802; $HDI_{95\%}$ = [0.256; 1.409], Fig. 3b). See Supplementary Table 1 for the full results.

In contrast, in the delay discounting task, both drugs had no effect on the average rate of choosing the high-cost option (placebo: 71.59% ± 2.25, haloperidol: 71.55% ± 1.73, biperiden: 70.79% ± 1.82, Fig. 2a (right panel)), as indicated by the absence of credible main effects for haloperidol (HDI_{Mean} = -0.046, $HDI_{95\%}$ = [-2.648; 1.884]) and biperiden (HDI_{Mean} = -1.315, $HDI_{95\%}$ = [-4.147; 0.655]; Fig. 3c). Importantly, 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. 3d), while the other drug interactions did not reach credibility (Supplementary Table 2). This indicates that diminished dopaminergic activity attenuates the impact of time costs on decision making.

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.

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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. For this approach, we first calculated the subjective values of all choice options, based on participant-specific weighting 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 Methods and Supplementary Methods). Model validation and parameter recovery confirmed that both models accurately captured key features of the choice data (see Supplementary Results).

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The results from the computational model of the effort discounting task align with and extend the regression-based results presented above, which highlighted opposing effects of dopaminergic and cholinergic modulation on effort-based choices. 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 and dopaminergic manipulation, despite the slight overlap.

A similar pattern emerged in the analysis of the inverse temperature parameter, further supporting the contrasting 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).

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For the delay discounting task, computational modelling revealed credible evidence only for a dopaminergic, but not cholinergic modulation of delay discounting (Fig. 4c

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. 4d). Biperiden credibly reduced 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]).

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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). Significant effects were subsequently analysed using correlation analyses. In short, biperiden administration induced reductions in systolic blood pressure (p-values < 0.05) and heart rate (p-values < 0.001) compared to placebo at T_2 (after finishing the experimental tasks). Moreover, relative to placebo, both biperiden and haloperidol caused decreases in subjective alertness ratings (all p-values < 0.005) at T_2. Importantly, neither the changes in blood pressure or heart rate, nor reduction in alertness showed significant correlations with any shift parameter that was credibly modulated by haloperidol or biperiden in both tasks (all p-values > 0.1). 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. Both analyses consistently revealed opposing effects of dopaminergic and cholinergic manipulations on effort discounting. Diminishing dopaminergic activity decreases the willingness to invest effort for rewards by amplifying effort discounting. Conversely, the administration of a

muscarinic acetylcholine receptor antagonist produces opposite effects. However, this pattern of opponent dopaminergic and cholinergic effects observed in the effort discounting task was not found 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 the reciprocal interplay between dopaminergic and cholinergic systems may reflect a task-specific rather than domain-general influence.

Drug Effects on Decision Times

Having established distinct task-specific drug effects on participants' choice behaviour, we next asked how the drugs affected the dynamics of choice, as reflected in how response times were modulated by key decision variables. We investigated this with Bayesian Linear Mixed Models, using log-transformed response times on each trial as the dependent variable. In both tasks, higher reward magnitudes decreased, while higher cost levels (effort or delay) increased response times (reward effect on effort discounting: HDI_{Mean} = -0.183, $HDI_{95\%}$ = [-0.213; -0.154]; reward effect on delay discounting: HDI_{Mean} = -0.168, $HDI_{95\%}$ = [-0.190; -0.145]; effort effect on effort discounting: HDI_{Mean} = 0.084, $HDI_{95\%}$ = [0.063; 0.105]; delay effect on delay discounting: HDI_{Mean} = 0.036, $HDI_{95\%}$ = [0.020; 0.053], Fig. 5b-c). Notably, in both tasks, haloperidol attenuated this speeding effect of reward magnitude, indexed by a credible interaction effect between haloperidol and reward in both tasks (effort discounting: HDI_{Mean} = 0.036, $HDI_{95\%}$ = [0.009; 0.063]; delay discounting: HDI_{Mean} = 0.029, $HDI_{95\%}$ = [0.011; 0.046], Fig. 6b, 6e). Haloperidol further attenuated the decelerating effect of delay (HDI_{Mean} = -0.020, $HDI_{95\%}$ = [-0.036; -0.003], Fig. 6f), but not effort (HDI_{Mean} = -0.021, $HDI_{95\%}$ = [-0.047; 0.003], Fig. 6c). This aligns with the decreased delay sensitivity observed in the effort discounting task analysis. Moreover, haloperidol administration induced an overall increase in response times in the delay discounting task (HDI_{Mean} = -0.077, $HDI_{95\%}$ = [-0.123; -0.031], Fig. 6d), while this effect was not observed in the effort discounting task (HDI_{Mean} = 0.016, $HDI_{95\%}$ = [-0.047; 0.078], Fig. 6a). Unlike under haloperidol, none of the effects of task parameters on response speed were modulated by biperiden. See Supplementary Table 3 and 4 for full results.

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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 significant correlation between the effort and delay discounting parameters κ under placebo (r = 0.190, p = 0.140)). Additionally, the degree to which delay discounting was modulated by both drugs did not correlate with drug-induced changes in effort discounting (no correlations between $s_{\kappa_{HAL}}$ (r = -0.004, p = 0.970) and $s_{\kappa_{BIP}}$ (r = -0.018, p = 0.890) parameters derived from the effort and from the delay discounting task). This implies that individuals' sensitivity to costs is not modulated to the same extent across both cost domains by either haloperidol or biperiden.

Discussion

In this study, we investigated the effects of pharmacologically manipulating dopaminergic and cholinergic neurotransmission on cost-benefit decision making in healthy young adults. Specifically, we administered haloperidol or biperiden, two drugs that selectively block either dopamine D2-like or muscarinic M1 acetylcholine receptors, respectively, and tested the effects on discounting a monetary reward as a function of either effort or delay. In short, we found that reducing dopaminergic transmission decreased participants' willingness to invest physical effort for monetary rewards and attenuated the impact of delay on decision making. In contrast, cholinergic manipulations induced opposing effects only in the domain of effort, but not delay discounting.

The goal of our study was threefold. First, we sought to conceptually replicate the boosting effects of dopamine on motivation. Second, we aimed to further disambiguate the inconsistent picture regarding the role of dopamine in delay-based decision making. Third, we examined the contribution of acetylcholine on cost-benefit

decision making, as the influence of muscarinic acetylcholine receptors on human (value-based) decision making has rarely been reported.

Dopamine has been widely suggested to play a key role in various aspects of reward processing and cost-benefit decision making (Jocham et al., 2011, 2014; Webber et al., 2020). It modulates choices based on expected rewards and costs associated with different options (Schultz, 2016a, 2016b; Tanaka et al., 2019). However, the direction of dopaminergic manipulations on different aspects of costs remains ambiguous. Traditionally, dopamine has been implicated in promoting behaviour that maximizes reward outcomes, suggesting that increased dopaminergic activity energizes behaviour to approach high-reward options despite associated costs (Bailey et al., 2016; Berke, 2018; Phillips et al., 2007; Salamone & Correa, 2012). 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, administration of a D2 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 supported by 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). This suggests that dopamine may play a role in promoting choices towards options with a proximity advantage, taking into account not only the reward magnitude and associated costs but also the proximity of the available options. Our findings support this idea, as we showed that haloperidol decreased delay discounting, possibly by diminishing the preference for the more proximal options and thereby enduring higher (time) costs. On the other hand, the reduction of dopaminergic neurotransmission had the opposite effect on effort discounting, by diminishing the willingness to bear high (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 proximity advantage. Thus, in this specific context of cost-benefit decision making, the proximity factor is irrelevant, and dopamine instead appeared to promote behaviour that aimed at maximizing rewards simply by overcoming physical effort costs.

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

Indeed, we observed an antagonistic relationship between dopaminergic and cholinergic activity specifically in the context of effort-, but not delay-based decision making. Biperiden administration reduced effort discounting, whereas delay discounting was not affected. While dopamine is involved in processing both types of costs, our findings suggest that cholinergic transmission specifically modulates the impact of effort, but not delay, on choice. This opposing mechanistic relationship between dopaminergic and cholinergic neurotransmission during the effort discounting task is further reflected in changes in choice stochasticity. Previous studies have linked

D2 receptor antagonism with increased choice stochasticity (Eisenegger et al., 2014; Mikus et al., 2022), indicating that reductions in D2 receptor activity may lead to noisier representations of effort costs, inducing a shift from exploitative reward maximization to a more exploratory strategy (Beeler et al., 2010). Consistent with these findings, our results revealed that haloperidol administration increased stochasticity in choices and thereby reduced value dependency on choices, while biperiden had the opposite effect. After lowering cholinergic M1 receptor activity, participants were more likely to choose the option with the highest expected value compared to placebo. However, it is important to note that biperiden had the opposite effect in the delay discounting task, increasing, rather than reducing choice stochasticity. This discrepancy indicates that the role of cholinergic neurotransmission in balancing deterministic versus stochastic behaviour is more complex and needs further investigation.

Some limitations should be noted. First, our focus was primarily on striatal D2 receptor activity, as haloperidol predominantly targets D2 receptors in the striatum (Nordström et al., 1992). However, it is important to note that in the context of cost-benefit decision making, dissociable roles of D1 versus D2 receptor activity have been reported (Collins & Frank, 2014; Soutschek et al., 2023; Webber et al., 2020), and thus the general role of dopamine beyond its selective activity on striatal D2 receptors remains unclear. Conversely, biperiden primarily targets M1 receptors in the cortex and striatum (Sudo et al., 1999), making it challenging to determine the precise mechanisms underlying cortical and striatal cholinergic modulation and the reciprocal effects on dopaminergic activity. Second, previous research has suggested a U-shaped dose-response function for dopamine, indicating deleterious effects of both 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. Lastly, it is worth noting that both the nature and the size of the reward differed between both tasks, and

likewise, the nature of the cost. The delay discounting task involved (larger) hypothetical rewards and delays, while the effort discounting task offered (smaller) real rewards in return for a real physical effort. This decision was based on previous studies indicating no difference in delay discounting when comparing real and hypothetical rewards and delays (Kang et al., 2011; Madden et al., 2003). Since we are not aware of any studies investigating the effects of real versus hypothetical rewards and costs in the context of effort-based decision making, and to ensure ecological validity, we decided to use real rewards and costs in the effort discounting task. However, our results demonstrated that participants were consistently sensitive to changes in reward and cost levels in both tasks, regardless of whether they were hypothetical or real. This suggests that task-specific differences in rewards and costs did not influence participants' choice behaviour.

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 antagonism. Further, we demonstrated that the administration of biperiden, a muscarinic receptor antagonist, contrasted the effects of dopaminergic antagonism in effort-based choices without affecting delay discounting. This indicates a reciprocal relationship between cholinergic and dopaminergic activity only within this specific cost dimension, with dopamine playing a domain-general role in integrating proximity and effort costs, while acetylcholine may have a more task-specific role in effort processing.

Methods

Ethics

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

Participants

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

From an initial group of 96 individuals attending the medical screening on site, 33 candidates decided not to proceed, or they were excluded due to not meeting the participation criteria (despite otherwise indicated in the prior interview). Eventually, a total of 63 volunteers were enrolled in the study. One participant had to be excluded due to experiencing side effects following the biperiden testing session, resulting in a final sample size of 62 participants (32 female; Mean Age (SD): 22.79 (3.20); Age Range: 18 - 35). The sample did not include any non-binary participants. All participants received a fixed reimbursement of 240 € for their participation in all testing sessions and were provided with a flexible payment based on their performance in the tasks.

Procedure

A double-blind, randomized, within-subject design was employed. Participation involved three testing sessions, each separated by a minimum of one week to ensure complete drug washout. Prior to participation, on a separate day, participants

underwent a medical screening session to determine their eligibility. This screening session consisted of a clinical interview, medical assessment, practice trials of both task, and completion of several questionnaires assessing personality traits, including Apathy Evaluation Scale (AES) (Lueken et al., 2006; Marin et al., 1991), Beck's Depression Inventory (BDI) (Beck et al., 1996; Kühner et al., 2007), and Barratt Impulsiveness Scale (BIS-15) (Meule et al., 2011; Spinella, 2007). The final decision regarding participant suitability for the study was made by a physician at the end of the screening session.

Each testing day followed the same procedure, with the only difference being the administration of a placebo, biperiden (4 mg), or haloperidol (2 mg) in separate sessions. Testing sessions were scheduled between 9 a.m. and 12 p.m., with efforts made to assign participants to the same time slot consistently. Participants were instructed to fast overnight and consume only water before the testing session. Additionally, female participants completed a pregnancy test before the start of each testing day. Upon arrival, participants underwent a screening conducted by a physician, who restated the potential effects of the drug and provided a recap of the testing day's procedures. Subsequently, participants received the assigned drug treatment along with a standardized breakfast. Orally administered biperiden reaches its peak concentration between 1 and 1.5 hours after administration (Brocks, 1999; Grimaldi et al., 1986), while haloperidol reaches its peak concentration only between 2 and 6 hours after administration (Kudo & Ishizaki, 1999). In order to follow a double-blind procedure while also accounting for variations in the drugs' peak times, a dummy drug application was included. Thus, on each testing day, a second capsule was administered 120 minutes after the first drug application, resulting in the planned delay between drug and effort discounting task of approximately 180 minutes for haloperidol (179.57 ± 2.61) and, on a separate day, approximately 60 minutes (59.65 ± 1.30) for biperiden. The second task was performed 205.59 minutes (± 3.12) after haloperidol and 86.24 minutes (± 6.09) after biperiden administration. Shortly before starting the experimental task, participants further completed the trail-making test A (Tombaugh, 2004). Blood pressure and heart rate were measured three times throughout the testing day: at T_0 (before drug administration), T_1 (before starting the effort discounting task), and T_2 (after finishing the delay discounting task). These measurements coincided with mood assessments using Visual Analogue Scales (Bond & Lader,

1974). Please refer to Fig. 1a for a detailed explanation of the procedure. The tasks were presented in a fixed order during each session, starting with the effort discounting task (Fig. 1b) and concluding with the delay discounting task (Fig. 1c). These discounting paradigms were implemented using Visual Basic software and displayed on a 15.6” laptop screen (Dell Latitude E5550). Participants used an external keypad to indicate their choices, arranging the laptop and keypad in a manner that was most comfortable for them.

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. 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. 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. 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.

Participants completed two blocks, with each block containing all unique combinations, resulting in a total of 210 trials. Consistent with previous studies, all choices in this task were hypothetical (Bickel et al., 2009; Madden et al., 2003). However, participants were instructed to imagine that one of their choices would be randomly selected and paid out. The trial order was counterbalanced across sessions and participants to minimize any order effects.

Statistical Analysis

Regression-Based Analysis

To investigate the influence of drug administration (compared to placebo) and experimental manipulations (i.e., reward magnitude, delay, and/or effort) on choice behaviour, we employed Bayesian Generalized Linear Mixed Models, using the brms package (Bürkner, 2017) in R (Version 4.1.3). In these models, we regressed choices (choosing the high-cost option vs. choosing the low-cost option) on fixed-effect predictors including drug, reward, cost (i.e., delay or effort), and all possible interaction terms. For the effort discounting task, as predictors we used the difference term between both the reward magnitude and effort levels of the two presented options (high-cost option – low-cost option). In the delay discounting task, the reward and delay levels of the varying high-cost option were included as regressors. To account for individual differences, all fixed-effect predictors were also modelled as random slopes in addition to subject-specific random intercepts. To 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.

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 Results 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 $S\beta_{BIP}$), which capture potential modulatory effects of the drugs. Prior distributions for the parameter means and standard deviations were chosen within plausible ranges based on previous findings (Knauth & Peters, 2022; Lockwood et al., 2021, 2022; Mathar et al., 2022; Wagner et al., 2020). The sampling process involved running four chains with 4000 iterations after a warmup period of 3000 iterations. Chain convergence was assessed using the Gelman-Rubinstein convergence diagnostic r-hat, with values less than 1.01 considered acceptable (Gelman & Rubin, 1992). We report the mean of the posterior group distribution for all parameters, along with the associated 95% HDI. Please refer to the Supplementary Methods for details of the prior distributions, model comparison, and model estimation procedure.

Model Validation & Parameter Recovery

To assess the model's ability to capture and recover important characteristics of the data, we conducted a model validation and parameter recovery analysis. This involved generating 500 synthetic datasets per participant using the posterior distributions of subject-level parameters obtained from the winning models. From these 500 datasets, we randomly selected 10 datasets for each participant and conducted the same analysis as described above, using the synthetic datasets instead of the actual data.

First, to validate that the simulated data accurately captures the key features of the participants behaviour, we simulated the relative choice rates and visualized how behavioural patterns changed as a function of varying levels of costs and rewards. Next, to evaluate the recovery of group-level parameters, we examined whether the simulated group-level parameters fell within the 95% HDI of the actual group-level parameter distribution. For the subject-level parameter estimates, we calculated the 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.

Response Times Analysis

Similarly, to the model-agnostic analysis of the choice data discussed earlier, we performed a separate analysis focusing on participants' response times in both tasks using Bayesian Linear Mixed Models. In contrast to the previous analysis, with binary

choice data as the outcome variable with a Bernoulli response distribution and a logit link function, here, we used the log-transformed response times (in milliseconds) as the outcome variable with a Gaussian distribution function. We then regressed the response times to the same set of fixed-effect predictors, including drug, reward, cost (i.e., delay or effort), and their respective interaction terms.

However, in order to ensure full model convergence, we reduced the random-effects structure (the full random-effects structure led to convergence issues, indicated by r-hat values > 1.05). Specifically, we removed the three-way interaction effect (interaction between drug, reward, and cost type), including only main and two-way interaction effects in the random effects structure. As mentioned earlier, we applied weakly informative priors, scaling nonbinary variables to have a mean of 0 and a standard deviation of 0.5. Posterior distributions of parameter estimates were obtained by running four chains with 3000 samples, including 1000 samples for warmup.

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 linear mixed effects models. If significant 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 T_2, which is the final measurement after task completion. These difference values were then correlated with the shift parameters that capture drug-induced changes in performance. The purpose of this 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 testing whether participants who exhibit stronger effort discounting also displayed stronger delay discounting. To examine this, we computed the Pearson correlation coefficient using the mean estimates of the κ parameters from the placebo conditions in both the effort and delay discounting task.

Moreover, we tested whether drug-induced effects in one cost dimension were associated with participants' responses in the other cost dimension. In other words, we examined if participants who exhibited stronger responses to a drug in the effort discounting task also demonstrated stronger effects to the same drug in the delay discounting task. Again, we performed Pearson correlation analysis to investigate the potential association between the $s_{\kappa_{HAL}}$ parameter in the delay discounting task and the $s_{\kappa_{HAL}}$ parameter in the effort discounting task, as well as between the $s_{\kappa_{BIP}}$ parameter of the delay discounting task and the $s_{\kappa_{BIP}}$ parameter from the effort 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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Author contributions

M.E.A. and G.J. designed the experiments. M.E.A. and E.S. performed the experiments. M.E.A. and M.I.F. analysed the data. A.S. and G.J. contributed the materials and analysis tools. M.E.A., M.I.F., and G.J. wrote the manuscript. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

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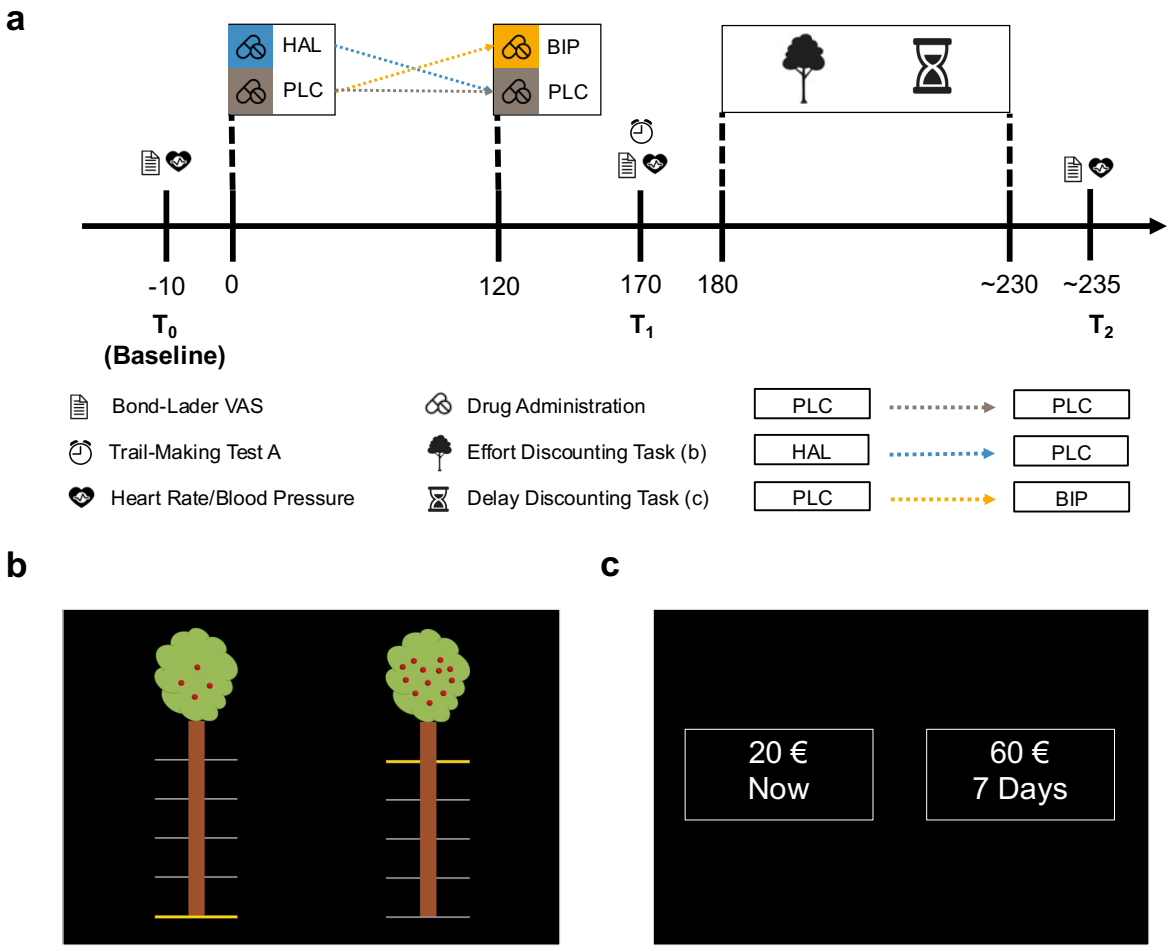

Fig. 1 Study procedure and experimental tasks. A The experimental sessions were standardized across all sessions except for the drug treatment, which was counterbalanced. To account for the different times of haloperidol and biperiden to reach peak plasma levels, a dummy drug application was introduced, 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 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).

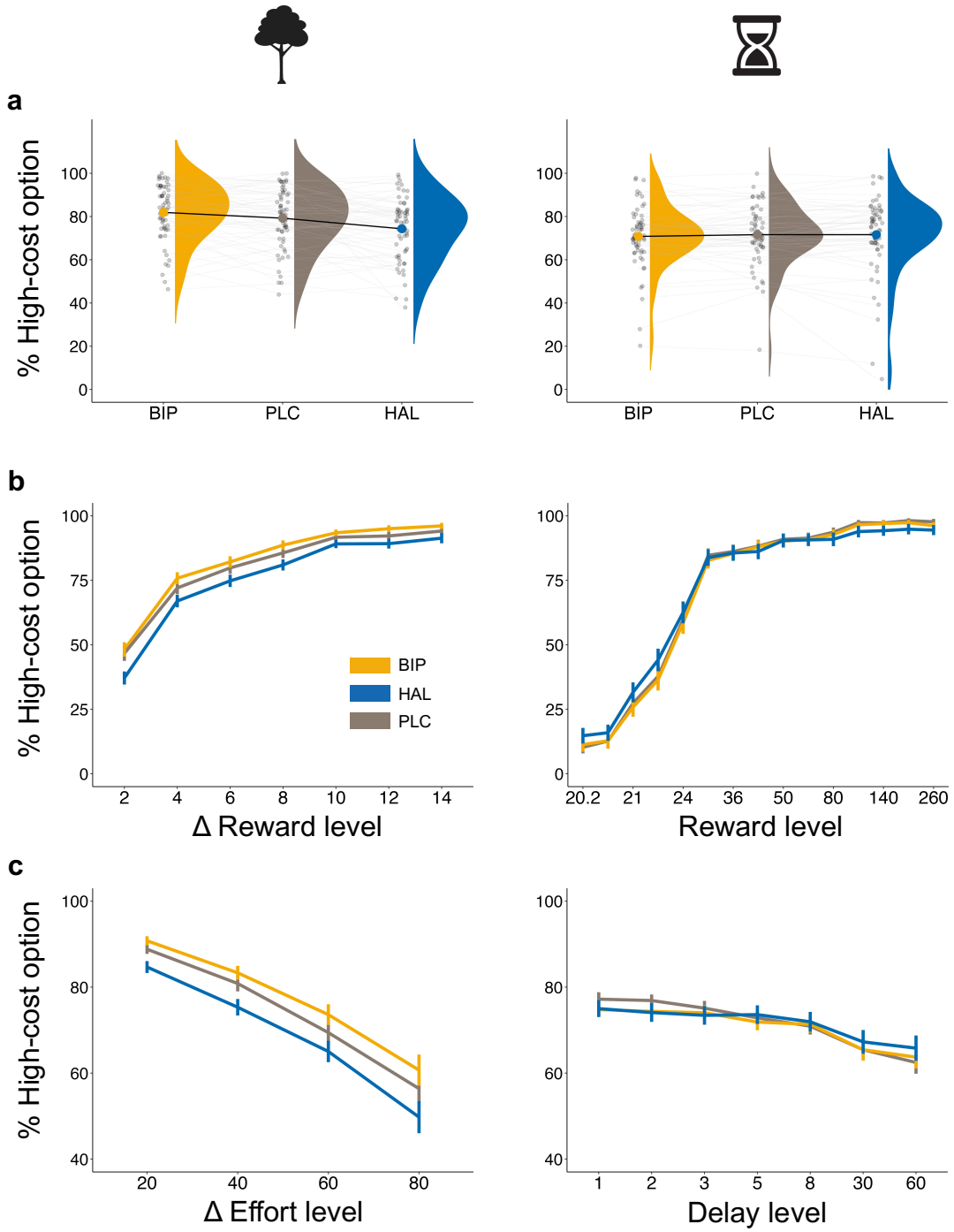

Fig. 2 Behavioural Performance in the Effort (left panel) and Delay (right panel) Discounting Task. **A** The overall proportions of high-cost choices are modulated by drug administration in the effort (left), but not in the delay discounting task (right). Biperiden increased and haloperidol decreased 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.

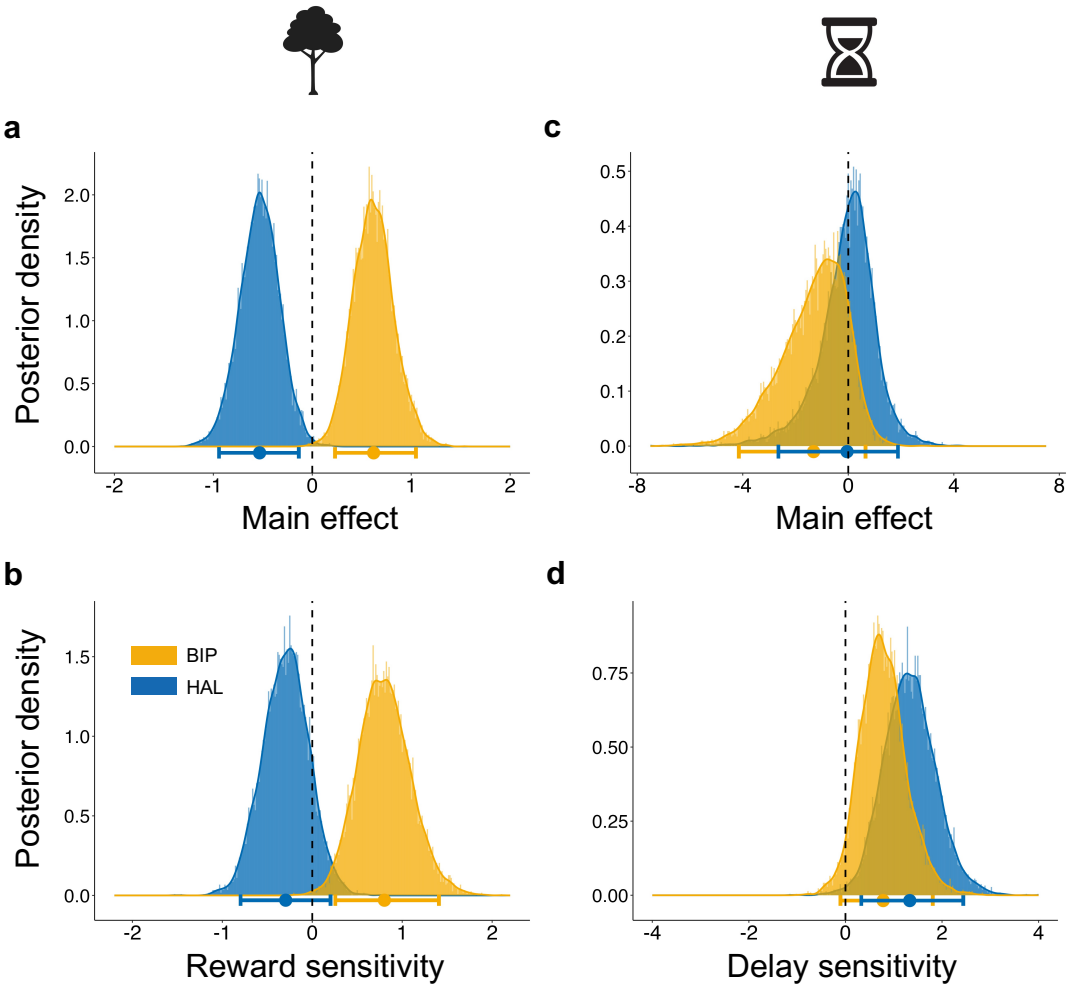

Fig. 3 Drug Effects on Choice Behaviour. Posterior distributions and 95% HDI of the Bayesian Generalized Linear Mixed Models depict the estimate of each effect on choosing the high-cost option. **A** Biperiden credibly increased the overall willingness to invest physical effort for a corresponding reward, 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, in the delay discounting task, the willingness to tolerate delays for rewards was not affected by either drug. **D** However, haloperidol decreased the 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.

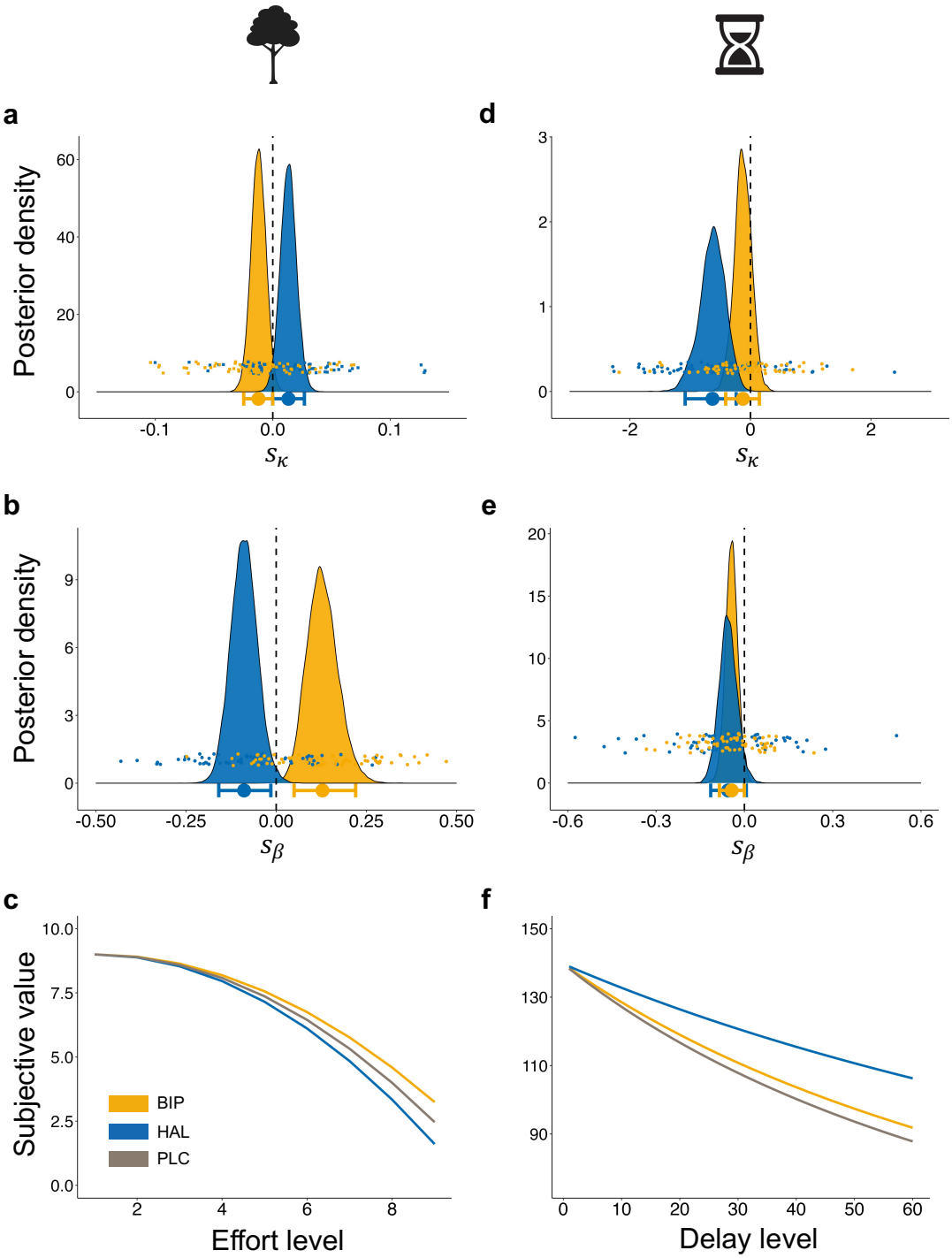

Fig. 4 Drug Effect on Computational Parameters. Posterior distributions and changes in the subjective value from the hierarchical Bayesian models. **A** In the effort discounting task, the discounting parameter κ is modulated in opposite directions by the drugs, with haloperidol increasing and biperiden 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 Methods).

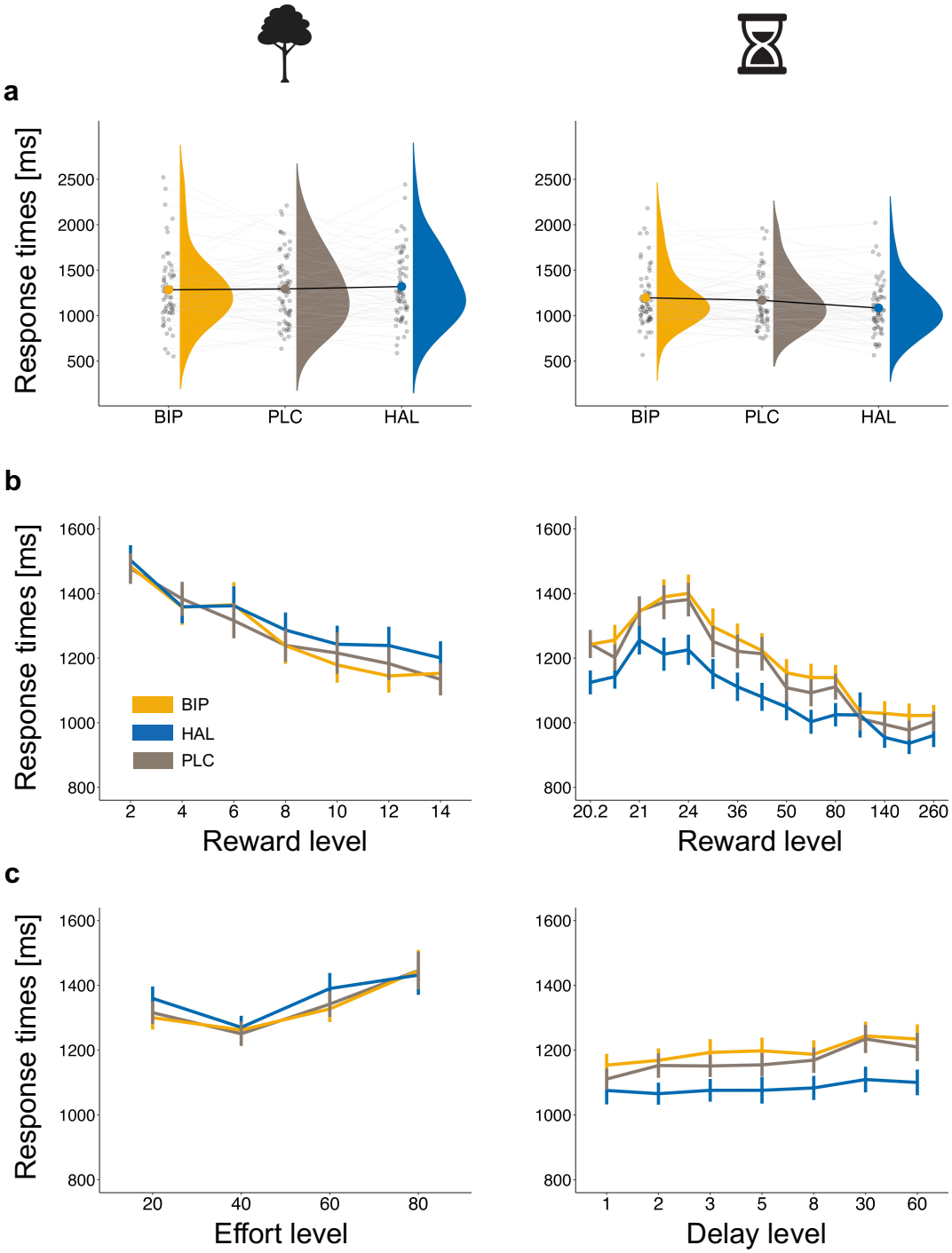

Fig. 5 Response Times in milliseconds (ms) in the Effort (left panel) and Delay (right panel) Discounting Tasks. **A** Overall response times in the effort discounting task (left) are not affected by haloperidol or biperiden. However, in the delay discounting task (right), haloperidol reduced the response times. **B** Response times decreased with larger rewards. Haloperidol reduced this speed-up effect in both the effort (left) and delay discounting task (right panel). **C** Conversely, response times increased with higher cost levels. This effect was not modulated by any drug in the effort discounting task (left). However, in the delay discounting task (right), haloperidol diminished the decelerating effect of increasing delay levels. **A** shows group-level (single-subject) means represented by bold (light) dots. **B** and **C** display averaged group-level means per reward and cost level, with error bars representing the standard error of the mean. 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, the effort level represents the difference between the proportions of the individually calibrated MVC of the high- and low-cost option, while the delay level indicates the delay of the high-cost option.

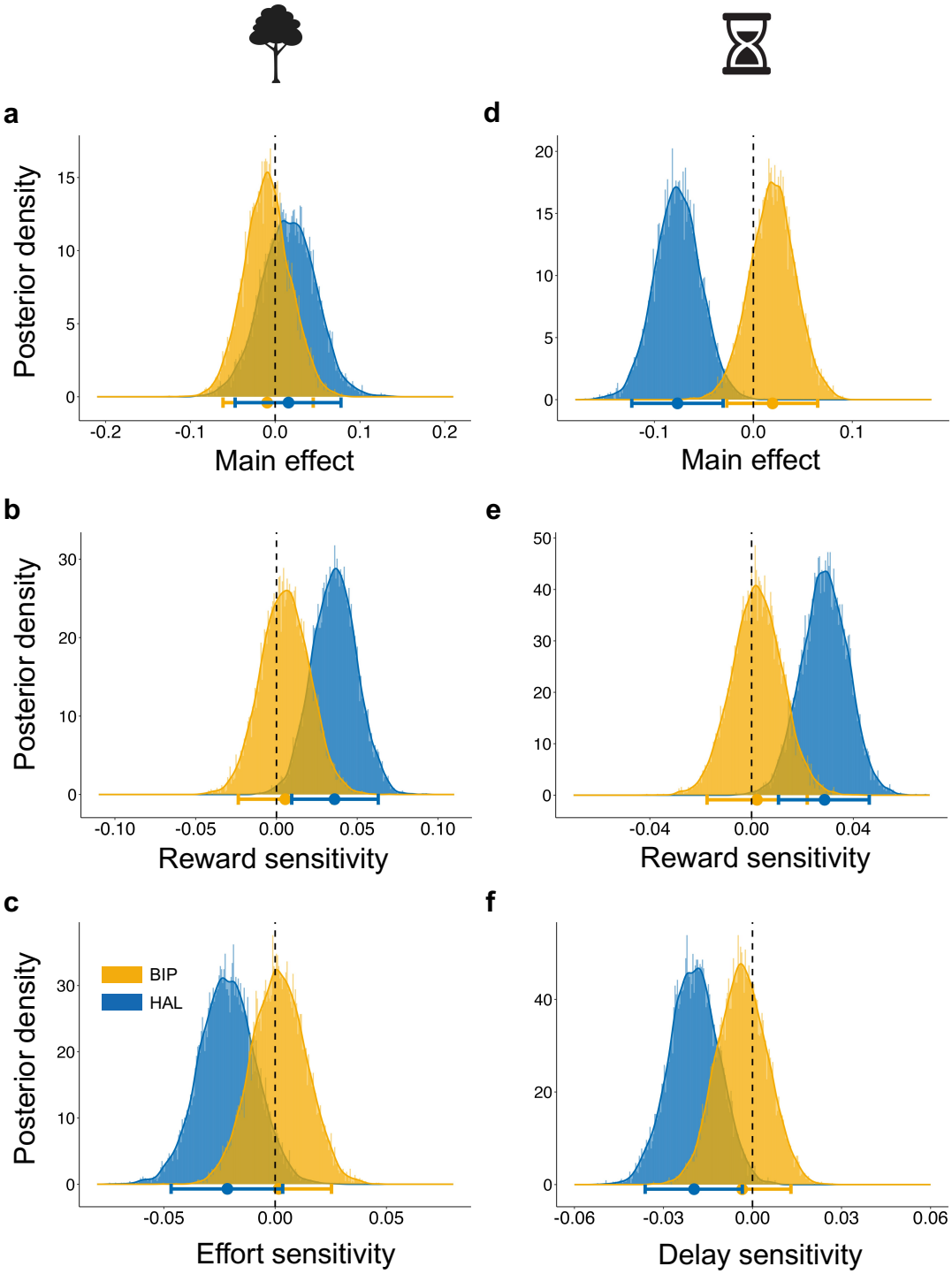

Fig. 6. Drug Effects on Decision Times. Posterior distributions and 95% HDI of the Bayesian Linear Mixed Models depict the estimate of each effect on decision times. **A** In the effort discounting task, overall decision times were not credibly influenced by either haloperidol or biperiden. **B** Notably, a haloperidol-by-reward interaction revealed a reduced reward sensitivity after haloperidol administration. **C** On the other hand, sensitivity towards increasing levels of effort is not affected by either drug. **D** In the delay discounting task, haloperidol credibly reduced overall response times, while biperiden did not show any credible effect. **E** Analogous to the effort discounting task, a credible haloperidol-by-reward interaction demonstrate reduced reward sensitivity following haloperidol administration. **F** Furthermore, haloperidol administration credibly reduced delay sensitivity, while biperiden had no effect on the impact of delay on response times. Bold dots represent the mean group-level estimate of the posterior distribution. The horizontal bars represent the group-level 95% highest density interval.

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