Neurobiology of Cost-Benefit Decision Making

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Zusammenfassung

Menschen stehen täglich vor Entscheidungen, bei denen sie zwischen verschiedenen Optionen wählen, die unterschiedliche Konsequenzen haben können. Wenn Individuen solche Entscheidungen treffen, berücksichtigen sie nicht nur den Nutzen der Option, sondern auch die Kosten, die mit dieser Wahl verknüpft sind. Diese Dissertation trägt dazu bei, das Verständnis über die Mechanismen, die diesen Kosten-Nutzen-Entscheidungen zugrunde liegen, zu vertiefen.

Die vorliegende Arbeit setzt einen Schwerpunkt auf die Neurobiologie von Entscheidungen, die den Abwägungsprozess zwischen Belohnungen und korrespondierenden Kosten beinhalten. Speziell wurde der Einfluss zwei verschiedener Neurotransmitter untersucht: Dopamin und Acetylcholin. Während eine Vielzahl von Studien zeigen, dass Dopamin eine wichtige Rolle bei Kosten-Nutzen-Entscheidungen spielt, ist die Rolle des Acetylcholins in diesen Prozessen weniger klar. Um die unterschiedlichen Rollen der beiden Neurotransmitter zu untersuchen, wurde das Entscheidungsverhalten gesunder Menschen in einer psychopharmakologischen, Placebo-kontrollierten Studie mit Messwiederholung untersucht. Dopaminerge und cholinerge Transmission wurden mit Haloperidol, einem Dopaminantagonisten, wirksam an den Rezeptoren der D2-Familie, und Biperiden, einem cholinergen Muskarinantagonisten, wirksam am M1 Rezeptor, manipuliert. Zwei Verhaltensparadigmen wurden verwendet, um getrennt den Einfluss zeitlicher Verzögerungskosten und physikalischer Aufwandskosten auf belohnungsbasiertes Entscheidungsverhalten zu erfassen. Regressionsanalysen und computationale Modellierungen wurden verwendet, um die Auswirkungen der pharmakologischen Manipulationen auf Kosten-Nutzen-Entscheidungen zu messen. Dabei konnten unterschiedliche Effekte beider Neuromodulatoren aufgezeigt werden. Haloperidol verringerte die Bereitschaft, eine körperliche Anstrengung aufzubringen um eine Belohnung zu erhalten, während Biperiden diese erhöhte. Zusätzlich reduzierte Haloperidol den Einfluss zeitlicher Verzögerungen auf das Entscheidungsverhalten, während Biperiden in diesem Bereich keine Auswirkungen zeigte.

Darüber hinaus untersucht die vorliegende Arbeit ein klinisches Beispiel für die aufwandsbasierte Entscheidungsfindung. Hierzu wurden Unterschiede in aufwandsbasierten Entscheidungsfindungsprozessen zwischen Schlaganfallpatient*innen, die während täglicher Rehabilitationsmaßnahmen Motivationsdefizite vorwiesen, und Kontroll-Schlaganfallpatient*innen, deren Verhalten unauffällig war, analysiert. Diese Studie zeigte einen komplexen Zusammenhang zwischen der Entscheidung, eine bestimmte Handlung zu vollziehen, und der tatsächlichen Ausführung dieser Handlung. Die beobachteten Motivationsdefizite konnten weder durch klinische Fragebogen, noch durch das

Entscheidungsverhalten im Rahmen des Verhaltensparadigmas erfasst werden. Vielmehr zeigen die Ergebnisse, dass Patient*innen mit Motivationsdefiziten nach der Entscheidung darüber, einen bestimmten körperlichen Aufwand zu erbringen, häufiger daran scheiterten, diesen Aufwand auch erfolgreich auszuführen.

Insgesamt liefert die vorliegende Arbeit Hinweise für eine kostenübergreifende Rolle von Dopamin und eine kosten-spezifische Rolle von Acetylcholin in der Modulation von Kosten-Nutzen-Entscheidungen. Zusätzlich wurde in einem spezifischen klinischen Beispiel gezeigt, dass Motivationsdefizite während rehabilitativer Maßnahmen bei Schlaganfallpatient*innen nicht durch eine verringerte Bereitschaft zur Aufbringung körperlichen Aufwands erklärt werden konnte, sondern durch eine verminderte Ausdauerfähigkeit, um die anstrengenden Handlungen auszuführen.

Abstract

Humans constantly face decisions where they have to choose between different options involving varying possible outcomes. When individuals make these decisions, they not only take into account the reward of the option, but also the corresponding costs that are associated with the option. This thesis contributes to a better understanding of the mechanisms underlying these cost-benefit decision-making processes.

The present work focuses on the neurobiology of choices that involve trade-offs between rewards and corresponding costs. Specifically, we investigated the role of two distinct neurotransmitters: dopamine and acetylcholine. While a wide range of studies suggest a crucial role of dopamine on cost-benefit decisions, the role of acetylcholine in these choices is rather unclear. To study these distinct roles, we examined choice behaviour in healthy human participants in a psychopharmacological, placebo-controlled, within-subjects design. Dopaminergic and cholinergic transmission was manipulated using haloperidol, a D2-like dopamine receptor antagonist, and biperiden, an M1 muscarinic receptor antagonist. The experimental paradigm included two tasks that separately measured the impact of temporal delay and physical effort costs on reward-based choices. We used regression-based methods and computational modelling to investigate the effects of the pharmacological manipulations on cost-benefit decision making. We found distinct effects of both neuromodulators on choices that involve physical effort, with haloperidol decreasing and biperiden increasing the willingness to invest effort in return for reward. In addition to that, haloperidol reduced the impact of delays on choices, while biperiden had no effect on this aspect.

Additionally, this work investigates a clinical case of effort-based decision making. Particularly, we analysed differences in effort-based decision making between stroke patients that showed motivational deficits during rehabilitation training and control stroke patients that were unaffected. This revealed a rather complex relationship between the decision to perform an action and the actual performance of that action. Observed motivational deficits in stroke patients could not be captured by clinical questionnaires, nor by choice behaviour in the decision-making paradigm. Rather, after choosing to engage in an effortful trial, patients with motivational deficits were more likely to fail performing the physical effort.

Taken together, the present work provides evidence for a cost-general role of dopamine and a cost-specific role of acetylcholine in modulating cost-benefit decision making. Moreover, in a specific clinical case, we show that reduced motivation during rehabilitative therapy in post-stroke patients is not explained by a reduced willingness to invest physical effort, but rather by a reduced persistence with effortful behaviour.

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1. Introduction

Imagine you are at home, in the mood for pizza, living in a bustling city filled with numerous pizzerias. The decision of which pizzeria to visit involves comparing and weighing the restaurant's different factors against each other: the quality of the food, the cost of the meal, the distance to the restaurant, the size of the pizza, as well as the atmosphere of the place. This seemingly simple decision illustrates the fundamental process of cost-benefit decision making, where individuals must balance potential rewards or benefits against associated costs.

Individuals highly differ in their valuations of costs against benefits, and these individual differences can be linked to specific personality traits (Bonnelle et al., 2015; Holt et al., 2003). Moreover, neurological and psychiatric disorders, such as addiction and mood disorders, have been shown to alter cost-benefit decision making. This suggests that changes in brain structures or neurochemical processes may influence how costs and rewards impact choices (Amlung et al., 2017; Bickel & Marsch, 2001; Le Heron et al., 2018a; Pessiglione et al., 2018; Peters & Büchel, 2011).

This thesis focuses on the neurobiological mechanisms underlying two distinct cost factors involved in decision-making processes: delay costs (i.e., the time one must wait to receive a reward) and physical effort costs (i.e., the physical energy expenditure that is required to obtain a reward). While years of research have contributed to a better understanding of these processes, important aspects of the underlying mechanisms, including the role of non-dopaminergic neurotransmitters, remain elusive. To fill this gap, in Experiment I, we investigated the neurochemical dynamics that govern delay- and effort-based decisions by pharmacologically manipulating dopaminergic and cholinergic neurotransmitter systems in healthy participants.

In Experiment II, we set the perspective to a clinical context, focusing on stroke patients. Impaired goal-directed behaviour and motivational deficits can ultimately reduce participation in rehabilitation training and have wide-ranging impacts on recovery (Knecht et al., 2016; Kwakkel et al., 2004; Luker et al., 2015). Thus, in a second study, we examined the neurocognitive mechanisms of effort-based decision making in stroke patients with motivational impairments, aiming to provide insights into how these deficits manifest in a specific clinical group.

This work links the neurobiological understanding of cost-benefit decision-making processes to the practical challenges faced by a clinical population, emphasizing the translational potential of this research. This introduction provides a broad overview of the decision-making processes related to effort and delay. Furthermore, this work will offer a more detailed explanation of the reciprocal interplay between dopamine and acetylcholine.

1.1. Effort-Based Decision Making

Effort-based decision making involves evaluating whether the value of a particular goal is worth the physical (or cognitive) effort required to obtain it. Such trade-offs play a critical role in everyday life decisions. As illustrated in the example before, the decision to visit your favourite pizzeria is influenced not only by the potential reward that you assign to the pizza but also by the effort required to reach the location, such as the convenience of transportation. Driving an easy route with a car may be appropriate, but what if you have to ride a bike up a steep hill? Individuals tend to maximize rewards while minimizing effort (Rigoux & Guigon, 2012; Salamone et al., 2018; Walton et al., 2007). As the associated effort level increases, the value of the reward decreases, a phenomenon that is commonly described as effort discounting (Chong et al., 2016; Hartmann et al., 2013).

Effort-based decision making is traditionally assessed through paradigms in which participants must choose between a high-reward option that requires more effort and a low-reward alternative with a smaller effort demand (Cousins et al., 1996; Font et al., 2008; Randall et al., 2012; Salamone et al., 1991). In this context, motivation can be characterized as a series of cost-benefit decisions, where individuals weigh the physical effort they are willing to invest in return for an associated reward (Chong et al., 2016). Research in animal models has highlighted the crucial role of striatal dopamine in behavioural activation and the exertion of effort (Denk et al., 2005; Salamone et al., 1991, 1994). Studies in rodents show that nucleus accumbens dopamine depletion or the administration of dopamine antagonists consistently affect effort-based decision making, inducing a low-effort bias that shifts choices away from high-effort options towards low-effort alternatives (Correa et al., 2016; Pardo et al., 2012; Yang et al., 2020; Yohn et al., 2015). Conversely, pharmacological enhancements of dopaminergic neurotransmission in rodents increase the willingness to choose high-effort options (Bardgett et al., 2009; Cagniard et al., 2006). These findings suggest that high levels of dopamine are associated with an enhanced willingness to invest physical effort in exchange for a reward, while low levels of dopamine have the opposite effect. Importantly, similar findings have been observed in human studies. For instance, agents that enhance dopaminergic transmission increase the tendency to exert effort for a reward in both healthy humans and clinical populations (Bogdanov et al., 2022; Chong et al., 2023; Le Bouc et al., 2016; Le Heron, et al., 2018c; Soder et al., 2020; Wardle et al., 2011). On the other hand, dopamine antagonists produce opposing effects, reducing the willingness to invest effort for rewards (Korb et al., 2020; Ohmann et al., 2020).

While the role of dopamine as a critical neuromodulator of effort-based decision making is well-established, in recent years, many laboratories have begun to explore the contribution of non-dopaminergic neurotransmitters. Electrophysiological recordings in primates revealed

a positive correlation between effort initiation and the firing rate of neurons in the locus coeruleus, suggesting a potential role of noradrenaline in modulating effort-based decision making (Varazzani et al., 2015). Furthermore, pharmacological studies conducted in healthy humans indicate a potential involvement of serotonin in these processes, as increasing serotonin levels through selective serotonin reuptake inhibitor administration has been shown to decrease the impact of costs on effort-related choices (Meyniel et al., 2016). Studies conducted in rats further suggest that the stimulation of GABA receptors in the ventral pallidum induces a low-effort bias (Farrar et al., 2008), while the administration of adenosine receptor antagonists produces the opposite effect by reversing a drug-induced low-effort bias (Correa et al., 2016; Nunes et al., 2013; Pardo et al., 2012; Randall et al., 2011, 2012).

Recently, acetylcholine emerged as a potential neuromodulator in effort-based decision making, as studies report interactions between dopaminergic and cholinergic neurons at both functional and cellular levels (Di Chiara et al., 1994; Gerber et al., 2001; Myslivecek, 2021). In line with that, injections of cholinergic agonists acting at muscarinic receptors in rats induce behavioural changes similar to those produced by dopamine antagonists (Hailwood et al., 2019; Nunes et al., 2013), underscoring the potential interplay between dopamine and acetylcholine in modulating cost-benefit decision making. The reciprocal relationship between dopamine and acetylcholine will be explored more extensively in the next chapters. Notably, to the best of our knowledge, the effects of cholinergic manipulations on effort-based decision making have not been investigated in humans yet.

Effort-based decision making is a process that involves various neural structures and neurotransmitters, and changes in these systems can have profound implications on motivational function across several neurological and psychiatric disorders. Conditions such as Parkinson's disease, schizophrenia, Alzheimer’s disease, and major depressive disorder are known to exhibit motivational dysfunctions in patients (Blouzard et al., 2023; Gold et al., 2013; Le Heron, et al., 2018c; Saleh, et al., 2021b; Treadway et al., 2012), potentially caused by shifted reward and effort trade-offs. Similarly, stroke patients have also been observed to exhibit deficits in motivation (Nicholson et al., 2013; Tay et al., 2021; West & Bernhardt, 2012), but despite significant consequences for the patients, this phenomenon has received less attention. In clinical practice, diminished motivation can directly affect patients’ outcomes by influencing engagement in rehabilitative therapy. Thus, reductions in activity and participation can further impede patients' recovery process, making it a particularly detrimental aspect of post-stroke rehabilitation (Knecht et al., 2016; Kwakkel et al., 2004). Despite the prevalence of motivational deficits in clinical practice, quantitative research on the underlying behavioural mechanisms of these impairments is limited. Gaining a deeper understanding of these deficits is critical for enhancing rehabilitation strategies and optimizing outcomes for stroke patients.

1.2. Delay-Based Decision Making

Returning to the previous pizza example, the decision of which pizzeria to visit is influenced not only by the required effort but also by the associated time delay until receiving the reward. Imagine a highly recommended pizzeria that tests your patience with an hour-long wait. In this scenario, the decision to visit this restaurant and endure the larger waiting costs, rather than opting for a less tasty pizza with a shorter waiting time, requires individuals to balance the benefit of a more recommended pizza against the desire for immediate gratification. Delay discounting refers to the devaluation of rewards as a function of their delayed delivery, a phenomenon common among both humans and animals (Kalenscher & Pennartz, 2008; Mazur, 1987; Peters & Büchel, 2011). Similar to effort discounting, the extent of delay discounting can be quantified through experimental decision-making tasks, where participants choose between a high reward option delivered later in time and a smaller, more immediate reward. Selecting the smaller, immediate reward can be described as impulsive behaviour, while choosing the later, larger reward reflects patience and self-control (Bevilacqua & Goldman, 2013; Madden et al., 2003).

Neuroimaging studies in humans have identified a crucial role of the ventral striatum in impulsive choices, implicating an involvement of dopamine in delay-based decision making (Hariri et al., 2006; Peters & Büchel, 2010, 2011; Smith et al., 2016). However, unlike the relatively coherent picture of the role of dopamine in effort valuation and motivation, the modulatory effects of dopamine on delay discounting are less clear, and it remains uncertain whether dopamine's effect on effort discounting generalizes to the temporal dimension.

Studies in rodents have reported mixed results, with some indicating increased impulsivity under dopamine antagonists (Denk et al., 2005; Wade et al., 2000), while others showed no effect after administration of agonistic or antagonistic agents (Koffarnus et al., 2011; van Gaalen et al., 2006). Discrepancies regarding the modulatory effects of dopaminergic manipulations on delay-based choices also appear in human studies. For instance, the finding that acute administration of D-amphetamine, a drug that mainly increases dopamine levels, decreases delay discounting (de Wit et al., 2002), could not be replicated in later studies (Acheson & de Wit, 2008; Hamidovic et al., 2008). Additionally, two different agents that both increase dopaminergic transmission through different mechanisms – levodopa and tolcapone – had opposite effects on delay-based decision making in separate studies, with levodopa increasing and tolcapone decreasing delay discounting (Kayser et al., 2012; Pine et al., 2010). This lack of consistent findings might be attributed to differences in baseline dopamine levels, the use of different pharmacological agents with distinct mechanisms, or different effects of D1 versus D2 receptor manipulations (Soutschek et al., 2023). These inconsistencies highlight the need for further research on the role of dopamine in delay discounting to understand its

underlying neurobiological mechanisms. Notably, emerging evidence suggests that selectively reducing dopaminergic neurotransmission at the D2 receptor consistently decreases delay discounting (Soutschek & Tobler, 2023; Wagner et al., 2020; Weber et al., 2016).

Research on the neurobiology of delay-based decision making further indicates a crucial role of non-dopaminergic neurotransmitters in weighing rewards versus delays, suggesting a broader neurobiological basis for delay discounting. Studies with rodents have shown that the administration of selective serotonin reuptake inhibitors increase the selection of high-reward/high-delay options (Bizot et al., 1988), while substances that reduce serotonergic levels induce the opposite effect (Bizot et al., 1999; Denk et al., 2005; Winstanley et al., 2004). Similarly, pharmacological elevations of noradrenaline levels reduce delay discounting, implicating the involvement of noradrenergic mechanisms in impulsive decision making (Bizot et al., 2011; Robinson et al., 2008). While the influence of cholinergic modulation on delay-based decision making has not been explored extensively, existing research in animal models suggests a modulating role of acetylcholine through both muscarinic and nicotinic receptors, while the findings remain inconclusive (Dallery & Locey, 2005; Kolokotroni et al., 2011; Ozga & Anderson, 2018). This emphasizes the need for further research in this area to investigate the role of acetylcholine in delay discounting.

Lastly, it is important to note that pathological levels of delay discounting are characteristics of a range of different clinical conditions, including attention-deficit/hyperactivity disorder, gambling and substance use disorders (Bickel et al., 2007; Jackson & MacKillop, 2016; Peters & Büchel, 2011; Petry, 2001). This underlines the potential role of delay discounting to serve as a trans-diagnostic marker, providing insights into various psychopathologies (Amlung et al., 2019; Chen et al., 2021). A deeper understanding of the neurobiological basis of delay discounting could enable clinicians and researchers to better predict treatment outcomes, optimize interventions, and develop preventative strategies based on an individual's discounting behaviour.

1.3. Interplay between Dopamine and Acetylcholine

There is an extensive body of literature investigating the effects of dopamine transmission on effort- and delay-based decision making. As mentioned in the preceding chapters, prior research has consistently demonstrated a critical role of striatal dopamine in promoting motivation and shifting behaviour towards high-effort choices in both rodents and humans. Specifically, reducing dopaminergic transmission via dopamine blockade has been shown to reduce the tendency to choose high-effort options, whereas enhancements of dopamine levels have produced the opposite effect (Denk et al., 2005; Le Bouc et al., 2016; Michely et al., 2020; Salamone et al., 1991; Soder et al., 2020; Soutschek et al., 2020). While the interplay between

dopamine and effort-based decision making is relatively coherent, the relationship between dopamine and delay-based choices is more complex. However, recent evidence suggests that D2 receptor blockade diminishes delay discounting (Soutschek & Tobler, 2023; Wagner et al., 2020; Weber et al., 2016). Considering the evidence implicating the involvement of striatal dopamine in both processes, examining other neuromodulators that influence dopaminergic transmission may provide additional insights into both effort- and delay-based decision making.

The striatum does not only contain the highest concentration of dopamine receptors but also the highest density of acetylcholine, primarily released by cholinergic interneurons (Holt et al., 1997; Jones et al., 2001; Lavoie et al., 1989; Macintosh, 1941). In clinical contexts, the treatment of Parkinson's disease involves opposing manipulations of both dopaminergic and cholinergic transmission. This is accomplished either by increasing the extracellular levels of dopamine or by decreasing the levels of acetylcholine in the striatum (Brocks, 1999; Goetz et al., 2002; Pisani et al., 2003). In line with that, on a cellular level, studies have shown that rewards and reward-predicting stimuli elicit a phasic increase in striatal dopamine transmission, which is accompanied by a corresponding phasic decrease in acetylcholine (Chantranupong et al., 2023; Cohen et al., 2012; Morris et al., 2004; Schultz et al., 1997). This mechanism is thought to facilitate motor activity and act as a learning signal (Krok et al., 2023). Consistently, activation of muscarinic M1 receptors inhibits dopaminergic D2 receptor-mediated effects in the striatum (Di Chiara et al., 1994; Threlfell et al., 2010). Moreover, deletion of muscarinic M1 receptors in rats leads to an elevated dopamine transmission in the striatum, while enhancing acetylcholine concentrations via acetylcholinesterase inhibition reduces stimulus-induced dopamine release (Gerber et al., 2001; Kudernatsch & Sutor, 1994). Beyond these cellular interconnections, a functional interplay between both neurotransmitter systems has been demonstrated. For instance, the administration of a muscarinic receptor agonist has been shown to reverse amphetamine-induced effects on rodents (Woolley et al., 2009). Similarly, muscarinic antagonists reduce the side effects of dopamine antagonists, while muscarinic agonists display antipsychotic properties, similar to the actions of D2 receptor antagonists (Brocks, 1999; Stanhope et al., 2001). Based on this, the idea of a dopamine/acetylcholine balance postulates that both transmitters act antagonistically, thereby directly influencing each other's release.

This interaction between acetylcholine and dopamine in the striatum, along with the evidence of dopamine's involvement in impulsive and motivational decision making, suggests that acetylcholine may act as a potential modulator of such behaviours. Nevertheless, we still lack an understanding of how these two neuromodulators interact in humans to influence cost-benefit trade-offs during decision making, as studies investigating this are missing. However, studies in rodents indicate that inhibiting muscarinic M1 receptors can enhance performance and reverse the detrimental effects of dopamine antagonists in effort-based decision-making

tasks (Hailwood et al., 2019; Nunes et al., 2013), supporting the idea of a reciprocal relationship between dopamine and acetylcholine. Notably, the association between acetylcholine and delay discounting is less clear. The effects of nicotine receptor stimulation on delay-based decision making are mixed, with some studies reporting a decrease in impulsivity, while others report an increase (Dallery & Locey, 2005; Kolokotroni et al., 2011; Ozga & Anderson, 2018). Another study that investigated how manipulations of cholinergic transmission affect delay discounting showed that muscarinic receptor antagonists increase delay discounting (Mendez et al., 2012), further supporting the idea of an antagonistic relationship between dopamine and acetylcholine in cost-benefit decision making.

1.4. Objectives and Hypotheses

Given the well-documented modulatory role of dopamine in cost-benefit decision making and the bidirectional relationship between dopamine and acetylcholine in the striatum, in Experiment I, we examined the effects of dopaminergic and cholinergic manipulations on delay- and effort-based decision making. Specifically, we performed a placebo-controlled psychopharmacological study involving healthy participants with a within-subjects design. We administered two drugs that selectively manipulate dopaminergic and cholinergic neurotransmission: haloperidol, a dopaminergic D2-like receptor antagonist, and biperiden, a muscarinic M1 receptor antagonist.

To the best of our knowledge, no prior research has studied the acute effects of cholinergic M1 receptor manipulations on different dimensions of cost-benefit decision making in humans. Further, no human studies have investigated the effects of dopaminergic D2-like receptor manipulations on both effort and delay discounting within the same participants. Based on previous findings, we postulated that dopaminergic and cholinergic manipulations would exert opposing effects on choice behaviour (Di Chiara et al., 1994; Krok et al., 2023; Morris et al., 2004; Threlfell et al., 2010). Specifically, we aimed to conceptually replicate the effects of D2 blockade on delay- and effort-based decision making, hypothesizing an increase in effort discounting and, consistent with recent findings, a decrease in delay discounting (Ohmann et al., 2020; Soder et al., 2020; Soutschek & Tobler, 2023; Wagner et al., 2020). Conversely, we expected opposing effects of biperiden. Based on the reciprocal relationship within the striatum, we predicted that reducing cholinergic activity at the M1 receptor would decrease effort discounting and increase delay discounting.

The significance of understanding the principles of cost-benefit decision making extends beyond daily choices and has profound clinical implications. For instance, motivational deficits, characterized by aberrant effort-based decision making, are observed in various neurological and psychiatric disorders (Le Heron et al., 2018a, 2018c; Saleh, et al., 2021b;

Treadway et al., 2012). In light of the clinical significance of this issue, in Experiment II, we specifically focused on stroke patients, a group that has been understudied in the context of motivational deficits and cost-benefit decision making. To this end, we assessed effort-based decision making and questionnaire scores of stroke patients exhibiting motivational deficits during neurorehabilitation training and compared them with a matched control group of stroke patients without such deficits. We hypothesised that stroke patients with motivational deficits would display higher levels of effort discounting compared to stroke patients without motivational deficits, in accordance with findings from similar experimental tasks in other clinical populations (Le Heron et al., 2018b, 2018c; Saleh, et al., 2021b). Additionally, we expected those patients to show more severe apathy symptoms. Experiment II aimed to enhance our understanding of the neurocognitive mechanisms governing effort-based decision making among stroke patients, with the goal of providing insights to strengthen neurorehabilitative therapies and ultimately improve functional recovery.

2. Methods

This section provides a brief overview of the experimental paradigms and primary analytical methods employed in the current work. Both experiments used decision-making scenarios that presented participants with binary choice options, varying in reward magnitude and associated cost requirements.

2.1. Effort Discounting Paradigm

In Experiments I and II, two distinct versions of a physical effort-based decision-making paradigm were employed. Both involved binary choices assessing participants' willingness to invest physical effort in exchange for a monetary reward.

In Experiment I, we used a two-alternative choice paradigm. Participants chose between two simultaneously available options, both varying in physical effort and monetary reward level (Fig. 1a). Notably, one option consistently required a lower effort and offered a lower reward than the alternative, creating a consistent choice scenario between a low-reward/low-effort and a high-reward/high-effort offer. After selecting an option, participants had to perform the corresponding physical effort by squeezing a hand dynamometer and maintaining the force for at least one second to receive the associated reward.

In Experiment II, we adapted the experimental paradigm to be more suitable for clinical populations. To this end, the amount of sensory information was reduced by showing only a single option that combined reward and effort information (Fig. 1b). Patients could either accept the offer, resulting in a performance phase akin to Experiment I, or reject the offer, leading to a fixed resting period.

In both experiments, participants had to evaluate whether the offered monetary reward was worth the required physical effort by weighing reward and effort information. Physical effort was operationalized as the amount of force that was exerted on a handheld dynamometer. The effort requirement was based on each individual’s maximum voluntary contraction, calibrated before starting the task. The effort level per trial was then adapted to their individual force capacity. To account for any order effects, each reward and effort combination was sampled in a randomized order across trials for each participant.

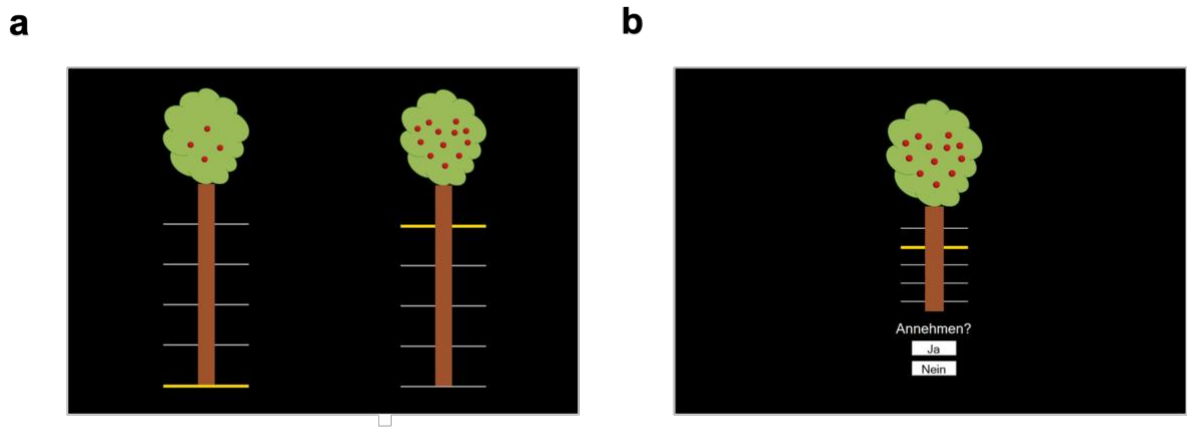

Figure 1. Effort Discounting Paradigm in Experiments I and II. (**a**) In Experiment I, the low-reward/low-effort option required less effort (indicated by the horizontal yellow line) and offered a smaller reward (indicated by the number of apples). Conversely, the high-effort/high-reward option required more effort and provided a larger reward. Participants had to choose one option and exert the required effort (adjusted to the maximum voluntary contraction) for at least one second. (**b**) In Experiment II, sensory information was reduced and participants were presented only with a single image of an apple tree. Again, the tree depicted information regarding a monetary reward available in exchange for a physical effort. Patients could either accept ("Ja") or reject ("Nein") the offer. After accepting, participants had to perform the physical effort and maintain the force for at least one second. Rejecting an offer led to a short break.

In Experiment I, the primary outcome variable was the selection of the high-reward/high-effort option (versus the low-reward/low-effort alternative). We analysed this choice behaviour using a logistic mixed-effects regression analysis and computational modelling. In addition, we investigated decision times using a linear mixed-effects regression model. In Experiment II, the primary outcome variables included choice behaviour (accepting versus rejecting an offer) and the subsequent performance phase, investigating whether participants successfully met the effort demand (success versus failure). We also analysed two essential criteria for successful effort performance, namely *produced force* (i.e., were participants able to exceed the required effort) and *persistence* (i.e., were participants able to maintain the effort for the necessary duration). All variables in Experiment II were analysed using logistic mixed-effects regression models.

2.2. Delay Discounting Paradigm

In Experiment I, we extended our analysis of the impact of costs on decision making by evaluating the influence of temporal delays on choices. Similar to the two-alternative effort-based decision-making task from the same experiment, in the delay-based decision-making task, participants chose between a high-reward/high-delay and a low-reward/low-delay option on each trial. We operationalized delay as the number of days participants had to wait to receive a monetary reward (Fig. 2).

Figure 2. Delay Discounting Paradigm in Experiment I. Similar to the effort discounting task in Experiment I, in the delay discounting task, participants had to choose between a varying high-reward/high-delay offer and a fixed low-reward/low-delay alternative. The low-reward/low-delay option always offered 20 € available immediately.

Unlike the effort discounting task, the delay discounting task consistently involved a fixed low-reward/low-delay option (i.e., 20 € available immediately), in line with the majority of studies in this field (Ballard & Knutson, 2009; Madden et al., 2003; Petry, 2001). On the other hand, the reward and delay levels of the high-reward/high-delay option were parametrically manipulated across trials in a pseudorandomized order. Consequently, the delay discounting paradigm required participants to consider a trade-off between a larger reward with longer associated delay costs and a smaller reward with no delay costs. In accordance with prior research, the choices made in this task were hypothetical (Bickel et al., 2009; Kang et al., 2011; Madden et al., 2003).

The primary outcome measure of interest was the selection of the high-reward/high-delay option (versus the fixed low-reward/low-delay alternative), which was analysed using a logistic mixed-effects model and computational modelling. Similar to the effort discounting task, decision times were analysed using linear mixed-effects models.

2.3. Pharmacological Manipulations in Healthy Participants

In Experiment I, we investigated the effects of dopaminergic and cholinergic manipulations on decision making in healthy participants (N = 62, 32 women), using a psychopharmacological intervention in a double-blinded, placebo-controlled, within-subject design. To modulate dopaminergic transmission, we administered 2 mg haloperidol, a dopaminergic D2-like receptor antagonist. In contrast, cholinergic neurotransmission was manipulated with 4 mg biperiden, a muscarinic M1 receptor antagonist. To account for variations in the drugs' peak times, we implemented a dummy drug application. After the initial drug administration, each participant received a second capsule 120 minutes later. Importantly, at least one of these capsules contained a placebo. This design ensured that the start of the experimental tasks

coincided with the drugs' peak concentration – approximately 180 minutes after haloperidol and 60 minutes after biperiden administration (Brocks, 1999; Grimaldi et al., 1986; Kudo & Ishizaki, 1999). Eventually, participants engaged first in the effort- and then delay-based decision-making task under three different conditions, enabling the evaluation of their choice behaviour under the influence of each pharmacological manipulation in comparison to their baseline performance.

2.4. Patient Groups

In Experiment II, we recruited participants undergoing inpatient neurorehabilitation. We compared stroke patients (N = 30, 13 women) with motivational deficits to a control stroke group (N = 30, 12 women) who did not display any apparent motivational impairment during their inpatient treatment. Motivational impairments were defined as exhibiting reduced (or no) drive, initiation, and endurance during both rehabilitative training and various activities of daily living.

The behavioural deficits were routinely and repeatedly evaluated by treating physical and occupational therapists, as well as nurses, during standard clinical practice using Likert scales and further cross-validated through weekly interdisciplinary team discussions. Physical and occupational therapists rated patients' drive, initiation, and active participation in rehabilitative training using a six-level Likert scale (ranging from 0 to 5). On the other hand, nurses evaluated patients' drive and participation during activities of daily living and self-care training using a three-level Likert scale (ranging from 0 to 2). Patients were assigned to the *drive-impaired* group when they scored two or less on the six-level Likert scale used by physical and occupational therapists and/or when they scored one or less on the nurse-assessed three-level Likert scale. Control patients were matched to the drive-impaired patients on age, gender, and degree of impairment, quantified by the Barthel Index (Lübke et al., 2004; Mahoney & Barthel, 1965). They were included in the study if their scores on both rating scales were higher than the cut-off levels.

During the experimental task, patients completed different depression and apathy self-report questionnaires. These questionnaires included the depression subscale of the Hospital Anxiety and Depression Scale (Petermann, 2011; Zigmond & Snaith, 1983), the depression subscale of the 21-item version of the Depression Anxiety Stress Scales (Antony et al., 1998; Lovibond & Lovibond, 1995), the German version of the Apathy Evaluation Scale (Lueken et al., 2006; Marin et al., 1991), and a German translation of the Apathy Motivation Index (Ang et al., 2017). The severity of depression and apathy was compared between both groups using unpaired t-tests, corrected for multiple comparisons.

2.5. Statistical Analyses

We used different statistical methods to investigate the underlying mechanisms of cost-benefit decision making. This section outlines the two primary analytical techniques that were applied: regression-based analysis and computational modelling. The former assessed the direct effects of experimental task parameter manipulations on the participants' choice behaviour (i.e., reward and cost sensitivity), offering a straightforward interpretation of the behavioural outcomes. The latter aimed to reveal the latent decision mechanisms underlying these decision-making processes.

2.5.1. Regression-Based Analysis

We employed logistic mixed-effects regression models to analyse the effects of experimental task manipulations on choice behaviour as a function of pharmacological interventions (Experiment I) and patients' drive states (Experiment II). In all choice models, we regressed binary choices (choosing the high-reward/high-cost option versus choosing the low-reward/low-cost option for Experiment I; accepting versus rejecting the offer for Experiment II) on several predictors, including reward magnitude, cost levels (i.e., delay and effort), and their interactions. To investigate how drug manipulations modulated choice behaviour in Experiment I, we included the drug administration, as well as all possible two- and three-way interaction terms between drug administration, reward, and cost levels as additional predictors. Similarly, in Experiment II, we analysed group effects on the evaluation of varying levels of reward and cost on choices. To do this, we included the group status (drive-impaired versus control group) and all possible two- and three-way interaction effects between group and both task parameters as additional predictors in the analysis.

Moreover, in Experiment I, choice decision times were analysed for both tasks using linear mixed-effects regression models with the same set of predictors and log-transformed decision times as outcome variables. In Experiment II, in an explorative analysis, performance during the effort production phase (success versus failure to reach the effort demand) was analysed using the same logistic mixed-effects regression model, with performance outcome rather than choice as the dependent variable. Additionally, we analysed persistence and produced force using similar regression models.

2.5.2. Computational Modelling

While regression-based analyses offer straightforward computable methods that provide valuable insights into choice behaviour, they lack a theoretical foundation of the underlying neurocomputational processes. To better understand the latent decision processes that govern

delay- and effort-based decision making and to reveal the distinct effects of pharmacological manipulations on these aspects, in Experiment I, we employed computational modelling to quantify participants' choice behaviour. Computational models aim to capture and define human information processing using mathematical equations. This approach enables us to generate precise predictions of behaviour and quantitatively test competing hypotheses (Ahn et al., 2017; Farrell & Lewandowsky, 2018; Wilson & Collins, 2019). Our motivation to employ the computational modelling was twofold: first, we sought to identify the mathematical model that most accurately describes participants' choice behaviour, and second, we aimed to estimate parameter values that quantify the impact of both drug administrations on decision making.

Traditionally, computational modelling is accomplished using the maximum-likelihood approach, which estimates parameters at the subject level (Myung, 2003; Wilson & Collins, 2019). However, in the current work, we adopted a hierarchical Bayesian estimation method combined with a Markov Chain Monte Carlo sampling scheme, which involves continuously updating prior parameter distributions to posterior distributions based on the observed data, using Bayes' theorem (Lee & Wagenmakers, 2014). This method offers an advantage over maximum-likelihood estimations as it simultaneously generates subject- and group-level distributions for a given parameter instead of point estimates (Vincent, 2016). This range of "true" values represents the degree of belief/certainty associated with each parameter estimate, a feature that point estimates, traditionally derived from maximum likelihood methods, cannot provide (Benjamin et al., 2018; Wagenmakers et al., 2018). This Bayesian approach of interpreting probability as a degree of belief enables us to interpret parameters and quantify their associated uncertainties directly from the posterior distribution (Kruschke, 2010, 2014). Moreover, Bayesian techniques have demonstrated more reliable parameter estimations compared to alternative approaches, and they are particularly effective at capturing variability between and within individuals, making the method well-suited for our within-subjects design (Ahn et al., 2017; Rouder & Lu, 2005; Vandekerckhove et al., 2011).

In our study, we initially fitted four distinct classes of effort and delay discounting models to identify the mathematical equation that best describes the observed choice behaviours, using data from the placebo condition. These candidate models propose different mathematical explanations for how rewards are discounted as a function of changing costs. In other words, all models share the principle that they describe how the subjective value (*SV*) of a reward (*R*) for each option is devalued as a function of costs (*C*) on trial *t*. However, they differ in the shape of the discounting curve. In the effort discounting task, *C* represents the effort level, and in the delay discounting task, *C* represents the delay level of the high-cost option. The impact of the costs on the subjective value is weighed by a condition-specific free discounting parameter κ, with higher κ values indicating greater discounting and lower κ values

suggesting less discounting. In line with previous studies, the models we investigated included hyperbolic (Eq. 1), parabolic (Eq. 2), linear (Eq. 3), and exponential (Eq. 4) discounting functions (Białaszek et al., 2017; Chong et al., 2017; Hartmann et al., 2013; Klein-Flügge et al., 2015). In the hyperbolic model, due to the skewed distribution of the free discounting parameter towards zero, κ was modelled in log space.

$$SV(t) = \frac{R(t)}{1+\exp(\kappa)* C(t)} \quad (1)$$

$$SV(t) = R(t) - \kappa * C(t)^2 \quad (2)$$

$$SV(t) = R(t) - \kappa * C(t) \quad (3)$$

$$SV(t) = R(t) * e^{-\kappa * C(t)} \quad (4)$$

In the effort discounting task, the subjective value of the high- (*HC*) and low-cost (*LC*) option is calculated separately. In contrast, in the delay discounting task, the subjective value of the low-cost option is a fixed variable at 20. This is because the low-reward/low-delay option consistently offers 20 € immediately. In the next step, we used a softmax function to transform option values into choice probabilities (Eq. 5). Here, *P* represents the probability of choosing the high-cost option over the low-cost alternative on trial *t*. We used the inverse temperature parameter β to model choice stochasticity, with lower β values indicating more stochastic behaviour. Conversely, higher β values suggest more deterministic choices.

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

Model fits were compared post hoc using the Leave-One-Out Information Criterion, which provides an estimate of the predictive accuracy (Vehtari et al., 2017). Lower values indicate better model fit, analogous to conventional information criteria such as Akaike's information criterion and Bayesian information criterion (Akaike, 1974; Schwarz, 1978). Consistent with prior studies (Green & Myerson, 2004; Hartmann et al., 2013; Kirby & Maraković, 1995; Klein-Flügge et al., 2015; Lockwood et al., 2017), model comparisons showed that effort discounting was best described by a parabolic/concave model, which suggests steeper discounting of larger rather than smaller physical effort levels. On the other hand, delay discounting was best described by a hyperbolic/convex model, which assumes steeper discounting for smaller rather than larger delays.

After identifying the best-fitting discounting functions separately for each task, we aimed to quantify how different drug manipulations modulated cost-benefit decision making. To capture potential drug effects on the discounting parameter κ and the inverse temperature parameter β, we extended the single-parameter discounting model and softmax function by introducing separate shift parameters for haloperidol and biperiden (Eq. 6 and Eq. 7). A positive shift parameter value indicates a drug-induced increase, while a negative value indicates a drug-induced decrease of the associated parameter. Importantly, this shift is always relative to the baseline behaviour from the placebo condition. The drug manipulation is indicated by the dummy-coded variable *I*, which refers to the drug condition of the current trial *t*.

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

$$\beta = \beta_{PLC} + I_{HAL_{(t)}} * s_{\beta_{HAL}} + I_{BIP_{(t)}} * s_{\beta_{BIP}} \quad (7)$$

For a more detailed description of the model selection and fitting procedure, please refer to the original publication (Erfanian Abdoust et al., 2023).

3. Results

3.1. Experiment I: Distinct roles of dopamine and acetylcholine in delay- and effort-based decision making in humans

The following chapter is based on our submitted manuscript, which is currently under review at *PLOS Biology* (see attachments):

Erfanian Abdoust, M., Froböse, M. I., Schnitzler, A., Schreivogel, E., Jocham, G. Dopaminergic and Cholinergic Modulation of Human Cost-Benefit Decision Making. Preprint at bioRxiv (2023), doi: 10.1101/2023.11.20.566558v2

Previous studies have demonstrated the crucial role of dopamine in discounting rewards based on increasing levels of effort and delay (Denk et al., 2005; Floresco et al., 2008; Pine et al., 2010; Salamone & Correa, 2012; Soder et al., 2020; Webber et al., 2020). Moreover, studies at the cellular and functional level suggest a reciprocal interplay between dopamine and acetylcholine in the striatum (Di Chiara et al., 1994; Morris et al., 2004; Myslivecek, 2021; Threlfell et al., 2010). However, to the best of our knowledge, the effects of acute cholinergic manipulations on human effort or delay discounting have not been investigated yet. Additionally, while the association between dopamine and effort-based decision making is relatively well-established, evidence regarding the role of dopamine in delay-based choices is more complex and inconsistent (de Wit et al., 2002; Denk et al., 2005; Hamidovic et al., 2008; Kayser et al., 2012; Soder et al., 2020; Wardle et al., 2011).

In Experiment I, we sought to investigate the effects of dopaminergic and cholinergic manipulations on effort and delay discounting in healthy volunteers (N = 62) who performed two decision-making tasks, each designed to measure the degree of effort and delay discounting. We modulated dopaminergic and cholinergic neurotransmission by administrating haloperidol, a D2-like dopamine receptor antagonist, and biperiden, a M1 muscarinic receptor antagonist. Based on previous findings, we hypothesized that reducing dopaminergic activity via D2 antagonism would elevate effort discounting and, in line with more recent findings, reduce delay discounting (Soder et al., 2020; Soutschek & Tobler, 2023; Wagner et al., 2020; Wardle et al., 2011; Weber et al., 2016). Additionally, consistent with the reciprocal activity in the striatum, we further postulated that inhibiting cholinergic activity via muscarinic antagonism would yield contrasting effects, namely a decrease in effort and an increase in delay discounting.

In the effort-based decision-making task, participants were presented with two options varying in reward magnitude and the physical effort required to obtain the reward. As expected,

regression-based analysis confirmed that participants discounted rewards based on increasing levels of effort. Further, and in line with our hypothesis, the analysis showed opposing effects of the drugs on specific features of choice behaviour. Reducing dopaminergic D2 receptor activity via haloperidol decreased participants' willingness to invest more effort for greater rewards. In contrast, administration of the muscarinic M1 receptor antagonist biperiden increased this general willingness. In addition to that, biperiden increased the reward sensitivity, indicating that reduced levels of cholinergic transmission amplify the impact of rewards on choices, while haloperidol did not affect reward sensitivity. Computational modelling of behaviour further supported these findings. We introduced condition-specific shift parameters to capture drug effects on the discounting parameter κ, with positive/negative shift parameter values reflecting increased/decreased discounting under the influence of either haloperidol or biperiden in comparison to placebo. In line with the regression-based results, biperiden and haloperidol again exerted opposing effects on the effort discounting parameter. Specifically, haloperidol increased effort discounting, while biperiden diminished it. These contrasting mechanisms were further reflected in the effects of the drugs on the choice stochasticity parameter β, supporting the idea of a reciprocal relationship between both transmitters in cost-benefit decision making. Again, condition-specific parameters captured potential drug effects. This analysis revealed an increase under haloperidol, while biperiden decreased choice stochasticity.

In the delay discounting task, participants had to choose between two options, one that offered a fixed low reward available immediately versus a varying alternative offer with a larger reward delivered after a temporal delay. Again, a regression-based analysis showed that participants discounted rewards based on delay, indicating their adherence to the task structure. However, in contrast to the effort discounting task, neither drug affected the general tendency to choose the high-reward/high-delay option. However, regression-based analysis revealed an attenuated delay sensitivity under haloperidol, suggesting that reduced dopaminergic activity diminishes the influence of time costs on choice behaviour. In line with this reduction in delay sensitivity, the computational modelling revealed evidence for a reduced delay discounting parameter under haloperidol. We did not observe any effect of biperiden on the discounting parameter. However, while haloperidol had no modulatory effect on choice stochasticity, biperiden administration increased it.

In additional analyses, we further investigated how the drug manipulations affected choice dynamics, reflected by the decision times. In both experimental tasks, higher reward magnitudes decreased, while higher cost levels increased decision times. Moreover, haloperidol induced an overall decrease in decision times in the delay discounting task, but not in the effort task. Importantly, haloperidol reduced the speeding effect of reward magnitude in

both tasks, suggesting a general reduction in sensitivity towards rewards. Furthermore, haloperidol attenuated the decelerating effect of delay, but not effort, on decision times. This indicates that haloperidol reduced sensitivity specifically towards delay costs, consistent with the analysis of delay-based choice behaviour, which similarly revealed decreased delay sensitivity and delay discounting under haloperidol. Notably, biperiden did not modulate any aspect of the decision times. This lack of biperiden-induced changes in decision dynamics contrasts with the partly opposing effect patterns of biperiden and haloperidol observed in the primary analysis of choice behaviour.

In summary, our findings support the hypothesis of opposing effects of dopaminergic and cholinergic manipulations on decision making only within specific components of effort-based decision making. While dopaminergic antagonism reduced the general willingness to invest effort, increased effort discounting, and decreased delay sensitivity and delay discounting, cholinergic antagonism had the opposite effect only in the context of effort-based choices. Importantly, these opposing mechanisms were not present in all effort-related processes, such as the sensitivity towards rewards or decision times. These findings suggest a cost-general role of dopamine and a rather cost-specific role of acetylcholine in mediating specific features of cost-benefit decision making.

3.2. Experiment II: Effort-based decision making and motivational deficits in stroke patients

The following chapter is based on our manuscript published in *Brain and Cognition* (see attachments):

Erfanian Abdoust, M., Knecht, S., Husain, M., Le Heron, C., Jocham, G., & Studer, B. (2024). Effort-based decision making and motivational deficits in stroke patients. *Brain and cognition, 175,* https://doi.org/10.1016/j.bandc.2023.106123

In Experiment I, we demonstrated the involvement of dopaminergic and cholinergic neurotransmission in modulating different components of effort-based decision making. Notably, alterations in effort discounting have been observed in clinical diseases such as Parkinson's disease or major depressive disorder. However, the specific behavioural mechanisms underlying these aberrant cost-benefit choices across different clinical conditions remain elusive (Le Heron, et al., 2018a, 2018c; Saleh, 2021a; Treadway et al., 2012). To elucidate these mechanisms, in Experiment II, we shifted our focus to a relatively understudied clinical group: stroke patients. Specifically, we investigated whether stroke inpatients who exhibit reduced drive, initiation, and endurance during functional rehabilitative training display

systematic changes in effort-based decisions compared to matched stroke patients with intact motivation.

We recruited stroke patients who showed motivational deficits (N = 30), as assessed by their treating specialist, and compared them to an age-, sex- and severity-matched control group (N = 30). Patients performed a well-established effort-based decision-making task similar to the paradigm used in Experiment I (Chong et al., 2018; Le Heron, 2018b, 2018c; Saleh, et al., 2021b). Importantly, we adapted the task to suit the clinical population. We minimised sensory overload by adopting a simplified accept/reject paradigm rather than a two-alternative choice design. Patients were presented with a single offer on each trial, combining information on a monetary reward associated with a physical effort requirement. Patients then decided to accept or reject the offer, leading either to a corresponding performance phase (if accepted) or a short break (if rejected). Further, to evaluate whether clinical measures of apathy or depression could explain differences in motivational states, patients completed different questionnaires assessing the severity of these constructs. We hypothesised that patients with drive impairment would exhibit higher levels of apathy and a reduced willingness to invest physical effort in exchange for a reward. We initially focused on choice behaviour, i.e., accepting or rejecting an offer. However, contrary to our prediction and previous findings in clinical populations with other disorders (Le Heron, et al., 2018b; 2018c; Saleh, et al., 2021b), a substantial proportion of participants from both groups (N = 18) did not show any discounting behaviour at all; i.e., they accepted all offers regardless of effort or reward level. Specifically, this behaviour was observed in 10 patients from the drive-impairment group and 8 patients from the control groups, without a significant difference between both groups in this regard. To address this unexpected behavioural pattern, we further explored a second dependent variable: performance outcome. In other words, we examined whether participants successfully completed the physical effort after choosing to engage in the trial.

A regression-based analysis did not reveal significant group differences in accepting or rejecting the high-effort option. However, after choosing to engage in a trial, patients with apparent drive impairment were less likely to successfully complete the required effort compared to control patients. To analyse the underlying mechanisms of this performance discrepancy, we examined whether participants could successfully (i) produce the necessary effort demand and (ii) maintain the force for the required duration of one second to earn the reward. This analysis showed that patients with drive impairment failed more often due to reduced persistence. While they could generate the required force level, they failed to maintain the force over the required duration, indicating a lack of short-time persistence with physical effort compared to control patients.

Notably, we did not find significant group differences in questionnaire scores, indicating that variations in clinical severity of depression or apathy could not explain the (observed)

reduced drive during neurorehabilitation training and reduced persistence during the performance phase.

In conclusion, stroke patients with diminished drive during neurorehabilitative therapy did not differ from matched control patients in their general willingness to engage in effortful behaviour. However, after choosing to perform an action, they failed more frequently to complete the trial successfully due to deficits in maintaining the effort force over the required duration. This reduced ability to maintain physical effort, rather than a general unwillingness to invest effort, could explain the apparent observations of reduced drive during rehabilitative therapy. Notably, this altered behavioural dimension of goal-directed activity was not captured by apathy or depression questionnaires but only through clinical observation.

4. General Discussion

This work investigated the neurobiological and cognitive mechanisms underlying cost-benefit decision making. Previous studies have consistently demonstrated dopamine's crucial role in amplifying motivation in choices involving physical effort (Michely et al., 2020; Soder et al., 2020; Wardle et al., 2011). However, as previous studies reported rather inconsistent findings, the exact contribution of dopamine to decisions that involve rewards and an associated temporal delay remains unclear (de Wit et al., 2002; Hamidovic et al., 2008; Kayser et al., 2012; Petzold et al., 2019; Pine et al., 2010). Furthermore, the modulatory influence of neurotransmitters beyond dopamine, particularly acetylcholine, has received less attention despite the established functional interplay between cholinergic and dopaminergic neurons in the striatum (Chantranupong et al., 2023; Di Chiara et al., 1994; Gerber et al., 2001; Myslivecek, 2021). Moreover, alterations in effort-based decision making and motivational deficits are prevalent among different clinical conditions, including stroke patients. In these patients, motivational impairments typically manifest as diminished drive during daily activities and training, challenging successful rehabilitation and long-term recovery (Knecht et al., 2016; Kwakkel et al., 2004; Van Peppen et al., 2004). However, the cognitive mechanisms underlying these behavioural deficits are less clear.

This work comprises two experiments to address these research questions. In the first experiment, we investigated the roles of dopamine and acetylcholine in cost-benefit decision making in healthy individuals, using choice scenarios that involve temporal delay and physical effort costs. In the second experiment, we examined effort-based decision making in stroke patients with motivational deficits during rehabilitation, aiming to elucidate the mechanisms behind these impairments. We present evidence of a cost-general role for dopamine and a novel cost-specific role for acetylcholine in modulating human decision-making processes that involve the evaluation of rewards and associated costs, encompassing physical effort and temporal delay costs. Additionally, we demonstrate that stroke inpatients exhibiting clinically diminished drive during neurorehabilitation training are not characterized by alterations in effort-based decisions, i.e., they do not show a reduced willingness to engage in effortful actions. Instead, their motivational impairments manifest as a deficit in maintaining effortful behaviour over an extended period.

In Experiment I, we conceptually replicated previous studies on the relationship between dopamine and effort-based decision making by demonstrating that haloperidol, a dopaminergic D2-like receptor antagonist, reduced participants' willingness to invest physical effort in exchange for a monetary reward (Soder et al., 2020; Soutschek et al., 2020; Wardle et al., 2011). Moreover, we showed that haloperidol not only enhanced effort discounting but also attenuated delay discounting, aligning with more recent findings in this domain (Soutschek

& Tobler, 2023; Wagner et al., 2020; Weber et al., 2016). These findings are in line with a theoretical framework proposing that dopamine, acting at D2-like receptors, influences decision making not only by modulating the impact of reward amount and associated costs on choices but also by integrating the psychological proximity of the available options (Soutschek et al., 2023; Westbrook & Frank, 2018). In other words, this theory suggests that dopamine plays a dual role in decision-making processes. On the one hand, it biases choices towards options with the highest reward by computing the acceptability of costs associated with obtaining a reward. This is the traditional view positing that dopaminergic activity energizes behaviour to pursue high-reward options despite associated costs (Bailey et al., 2016; Berke, 2018; Salamone & Correa, 2012). On the other hand, according to this theory, dopamine also biases actions towards options that have a psychological proximity advantage over more distant alternatives, for instance, as in our experimental paradigm, rewards that are available sooner in time. This would explain why dopamine antagonists, such as haloperidol, have been shown to reduce delay discounting (Soutschek & Tobler, 2023; Wagner et al., 2020; Weber et al., 2016). They potentially diminish the preference for the option with a psychological proximity advantage (i.e., the immediately available low-reward option), thereby leading to an increased tendency to endure higher temporal costs. In contrast, in the context of effort-based decisions, neither option holds a distinct proximity advantage. Therefore, the administration of a dopaminergic D2 receptor antagonist simply modulates the impact of reward and cost on choices, resulting in a higher devaluation of rewards as effort levels increase.

Building upon prior research and based on the cellular and functional interplay between dopamine and acetylcholine in the striatum (Brocks, 1999; Di Chiara et al., 1994; Stanhope et al., 2001), we hypothesized that biperiden, a muscarinic acetylcholine receptor antagonist, would elicit effects contrary to those of haloperidol. Regarding effort-based decisions, we partly observed contrasting effects between biperiden and haloperidol, particularly on the general willingness to invest effort and the effort discounting parameter from the computational model. This aligns with our hypothesis about the opposing roles of dopamine and acetylcholine in cost-benefit decision making. However, it is important to note that this opposing relationship was not evident across all components of effort-based decision making. For instance, biperiden increased reward sensitivity, while haloperidol had no effect. Conversely, haloperidol affected decision times, while biperiden did not. Regarding delay-based decision making, we did not observe an effect of biperiden on delay discounting, whereas haloperidol attenuated it. Together, these findings indicate that dopamine likely plays a role in integrating both types of costs, while acetylcholine appears to exert a more specific influence on some components of effort-based decision making.

In a clinical case, we demonstrated that stroke patients who exhibit clinically diminished motivation during neurorehabilitation training, as assessed by their treating specialists, did not

display differences from unaffected control stroke patients in their willingness to engage in physical effort. However, after choosing an effort-demanding option, they were more prone to failing the required effort demand. This failure was not attributed to an inability to achieve the required effort threshold. Instead, the patients demonstrated a deficit in maintaining effortful behaviour for the necessary time duration. This distinction between the choice to act and the subsequent performance of that action aligns with a recently proposed neurocognitive framework for cost-benefit decision making (Le Heron, et al., 2018a). This framework defines three distinct phases of goal-directed behaviour: (a) choosing whether to act or not, (b) performing and persisting with the chosen action, and (c) evaluating the outcome and learning from the consequences. Our findings suggest that stroke patients with drive impairment appear to be affected specifically in the performance phase of effort-based decision making. This could potentially be explained by a discrepancy between the patient's expectation of their ability to perform and their actual capabilities. Such performance deficits might contribute to the clinical observations of reduced motivation during functional neurorehabilitative training.

Notably, our finding that drive-impaired stroke patients showed no differences in the decision but differed in the subsequent performance phase contrasts with previous studies in Parkinson's disease and cerebral small vessel disease patients. In those clinical populations, studies showed a reduced willingness to accept effortful offers compared to controls, with no reported difference in performance once they engaged in the effortful task (Le Heron, et al., 2018b, 2018c; Saleh, et al., 2021b). This suggests potential differences in the underlying cognitive mechanisms of motivational deficits across various neurological conditions and states.

Individuals routinely encounter cost-benefit decision-making scenarios requiring a trade-off between potential benefits against associated costs, such as time and effort. Carefully weighing these rewards and costs is essential for intact decision making across various domains. Alterations in these decision processes can lead to impulsive behaviour, diminished motivation, and maladaptive decision-making patterns (Amlung et al., 2019; Chen et al., 2021; Le Heron, et al., 2018a). For instance, motivational impairments in the context of neurorehabilitation can substantially reduce recovery and long-term success (Oyake, et al., 2020a, 2020b). Therefore, understanding the neurochemical and behavioural underpinnings of these choice processes is crucial for developing therapeutic interventions and enhancing functional rehabilitation outcomes. Our findings provide evidence for a cost-general role of dopamine in modulating decisions that involve physical effort and delay. Furthermore, we demonstrate that acetylcholine plays a specialized role in specific features of effort-based decision making. Moreover, our results suggest that motivational deficits in stroke patients are not primarily characterized by alterations in their willingness to perform effortful acts or not but rather by deficits in persisting with the required effortful behaviour, indicating a need for

specialized rehabilitation strategies focusing on aiding patients in sustaining effort during physically demanding therapy sessions.

5. Future Research

In Experiment I, we provided evidence for distinct roles of dopamine and acetylcholine in shaping cost-benefit decision making. While dopamine modulates the integration of rewards and both types of costs on choices, acetylcholine appears to exert a more specialized effect on some components of effort-based decision making. This work, however, focused solely on physical effort and delay as cost factors. Therefore, the potential roles of both neurotransmitters in integrating other cost dimensions, such as cognitive effort or probability, remain unclear. While the role of dopamine in these types of cost-benefit decisions has been reported in the literature (Froböse et al., 2020; McGuigan et al., 2019; Ojala et al., 2018; Petzold et al., 2019; Westbrook et al., 2020), studies on the modulatory effects of acetylcholine on these aspects in humans are missing. Thus, to gain a more comprehensive understanding of acetylcholine's role in cost-benefit decision making, future research could employ behavioural paradigms that encompass these additional cost dimensions, allowing for a more general exploration of the relationship between cholinergic activity and other types of cost-benefit choices. Similarly, we measured effort and delay discounting in separate tasks at different time points, making a direct comparison of these two constructs complicated. Therefore, to gain a more comprehensive understanding of the neuropharmacology in cost-benefit decision making across different dimensions of costs, future studies could apply paradigms that measure the impact of different costs within the same task, enabling a more precise analysis of how different neurotransmitters influence distinct cost-benefit computations.

Prior research studies indicate the potential for a U-shaped dose-response function of dopamine, suggesting that both extremely high and extremely low levels of dopamine can have adverse effects on behaviour (Cools & D'Esposito, 2011; Goldman-Rakic et al., 2000). This pattern implies that the impact of dopamine-modulating drugs may vary depending on the individual's baseline dopamine levels. Given the functional interplay between dopamine and acetylcholine, it is plausible that a similar U-shaped dose-response function may also exist for acetylcholine. Consequently, future investigations could consider individual differences in baseline levels of these neurotransmitters when evaluating the effects of cholinergic and dopaminergic manipulations on decision making, using neuroimaging techniques such as positron emission tomography or single photon emission computed tomography.

Furthermore, combining these neuroimaging techniques with pharmacological manipulations could provide additional valuable insights. Investigating whether alterations of different neurotransmitter systems affect similar or distinct brain regions would further elucidate the neural mechanisms underlying their roles in cost-benefit decision making.

Experiment II revealed that motivational deficits observed during neurorehabilitation training were not characterized by aberrant choices in an effort-based decision-making paradigm but rather by the inability to perform the required effort. However, the identification of patients with diminished drive was based solely on subjective ratings provided by their treating clinicians. While this approach offers insights into patients' behaviour during everyday clinical life, it is susceptible to potential biases introduced by subjective assessments. To improve reliability and validity, future research should develop and incorporate a validated construct of motivational deficits during training, specifically designed to identify patients who meet validated criteria for drive impairment. This would eventually lead to more robust and generalizable findings directly applicable to clinical practice.

Lastly, as a clinical translation of Experiment I and II, a pharmacological intervention study might be considered for patients showing motivational deficits during rehabilitation training. Administrating drugs that either increase dopaminergic activity or act as antagonists at the cholinergic M1 receptor could provide insights into whether the reported neuropharmacological effects in Experiment I translate to clinically relevant improvements in patients with motivational deficits during rehabilitation training. It could also help to assess whether the modulatory effects of these neurotransmitters influence not only decisions to engage in an effortful option but also in performing the corresponding act.

6. Conclusion

The present work investigated two distinct dimensions of cost-benefit decision making: effort and delay discounting. We examined the neurobiological underpinnings of delay- and effort-based decisions in humans, specifically the impact of dopamine and acetylcholine. In a clinical case, we further explored alterations in effort-based decision-making processes among post-stroke patients exhibiting motivational deficits during training. To the best of our knowledge, this is the first study to investigate the effects of both dopaminergic and cholinergic manipulations on cost-benefit decisions in humans. Furthermore, studies directly investigating the processes underlying reduced drive during neurorehabilitation training in post-stroke patients are scarce. Therefore, we aimed to examine the latent neurocognitive mechanisms contributing to these motivational deficits.

Cost-benefit decision making involves the evaluation of potential rewards against associated costs, which include different dimensions such as time or effort. A careful weighing of these two aspects is critical across diverse domains and alterations in these processes can contribute to maladaptive behaviours observed in various clinical conditions and syndromes, such as apathy, major depressive disorder, and substance use disorder (Le Heron, et al., 2018a; Madden et al., 2003; Petry, 2001; Treadway et al., 2012). For instance, in the clinical setting, alterations in effort-based decision making can have detrimental consequences, particularly in scenarios where active participation and endurance are required. Therefore, understanding the influence of distinct neurotransmitter systems and the underlying neurocognitive mechanisms guiding these cost-benefit decision-making processes, may not only identify the causes of maladaptive decision making, but also enable possible interventions that improve these issues.

Our study supports prior findings, providing a conceptual replication of dopamine's invigorating effect on motivation, and we contributed to understanding its role in delay discounting. Furthermore, we revealed partly opposing effects of dopamine and acetylcholine in human effort-based decision making, a phenomenon previously observed exclusively in animal studies. Moreover, our findings indicate that post-stroke patients exhibiting diminished drive during neurorehabilitative training display similar choice patterns to unaffected control participants in an effort-based decision-making task. However, these patients showed deficits in sustaining physical effort over a prescribed duration, a behavioural characteristic which was not captured by clinical questionnaires but rather through observations by clinical specialists.

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Eidesstattliche Erklärung

Ich versichere an Eides statt, dass die Dissertation von mir selbstständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist.

Erklärung über bisherige Promotionsversuche

Die Dissertation wurde in der vorliegenden oder in ähnlicher Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den 02.05.2024

List of Publications

The following section lists the publications and manuscripts submitted to peer-reviewed journals that form the basis of this thesis. It further details the contributions of each author to the respective articles.

I.) Erfanian Abdoust, M., Froböse, M. I., Schnitzler, A., Schreivogel, E., Jocham, G. (under review at *PLOS Biology*) Dopaminergic and Cholinergic Modulation of Human Cost-Benefit Decision Making. Preprint at bioRxiv (2023), doi: 10.1101/2023.11.20.566558v2

Mani Erfanian Abdoust: Conceptualization, Formal Analysis, Investigation, Methodology, Visualization, Writing – original draft. Monja Isabel Froböse: Formal Analysis, Investigation, Writing – Review & Editing. Alfons Schnitzler: Resources, Writing – Review & Editing. Elisabeth Schreivogel: Investigation, Writing – Review & Editing. Gerhard Jocham: Funding Acquisition, Project Administration, Resources, Supervision, Writing – Review & Editing.

II.) Erfanian Abdoust, M., Erfanian Abdoust, M., Knecht, S., Husain, M., Le Heron, C., Jocham, G., & Studer, B. (2024). Effort-based decision making and motivational deficits in stroke patients. *Brain and cognition, 175,* https://doi.org/10.1016/j.bandc.2023.106123

Mani Erfanian Abdoust: Formal analysis, Investigation, Visualization, Writing – original draft. Stefan Knecht: Conceptualization, Methodology, Project administration, Writing – review & editing. Masud Husain: Resources, Writing – review & editing. Campbell Le Heron: Resources, Writing – review & editing. Gerhard Jocham: Investigation, Writing – review & editing. Bettina Studer: Data curation, Funding acquisition, Project administration, Software, Supervision, Writing – review & editing.

Attachments

Published and submitted manuscripts under review

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

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. In line with this, animal studies indicate that muscarinic agonists induce behavioural changes in effort-based choices that are similar to those produced by dopamine antagonists (Hailwood et al., 2019; Nunes et al., 2013), underscoring the potential interplay between dopamine and acetylcholine in modulating cost-benefit decision making. Furthermore, research in animal models points to a role for acetylcholine in modulating delay-based choices through both muscarinic and nicotinic receptors, albeit with inconsistent findings (Dallery & Locey, 2005; Kolokotroni et al., 2011; Mendez et al., 2012; Ozga & Anderson, 2018). Importantly, studies directly investigating these effects in human decision making are lacking.

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 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

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 Logistic 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. Specifically, to regress participants' choices, we included the following fixed-effect predictors: drug condition, reward magnitude, cost level (i.e., effort or delay), and all possible interactions. In the effort discounting task, we used the difference terms (high-cost option minus low-cost option) for both reward and effort. For the delay discounting task, we used the absolute reward and delay levels of the varying high-cost option. To account for within-subject variability, we included random intercepts for each subject along with random slopes for all fixed-effect predictors (see Materials and 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).

– insert Figure 2 here –

Notably, and in line with our predictions, we found that the two drugs had opposite effects on the tendency to choose high-effort options 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. 3d). 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. 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

359 referring to spatial proximity, has been extended to the context of psychological
360 proximity (Westbrook & Frank, 2018). According to this view, dopamine not only
361 favours options that are physically closer in space, but also options that are
362 psychologically closer, as in our case, rewards that are available sooner in time.
363 Consequently, the administration of D2 receptor antagonists, which, according to this
364 theory, are believed to reduce the proximity bias, have been shown in some studies
365 to increase the preference for delayed and risky reward options, which lack the
366 proximity advantage (Burke et al., 2018; Ojala et al., 2018; Soutschek & Tobler, 2023;
367 Wagner et al., 2020). In other words, this theoretical framework proposes that
368 dopamine may play a dual role in (i) promoting choices towards options with a
369 psychological proximity advantage and (ii) weighing reward magnitudes against
370 associated costs. Our findings of decreased delay discounting under haloperidol align
371 with this theory, potentially suggesting a diminished preference for more proximal
372 options when D2-receptor activity is reduced, resulting in increased endurance for
373 higher (time) costs. On the other hand, the reduction of dopaminergic
374 neurotransmission had the opposite effect on effort discounting, leading to a
375 diminished willingness to bear higher (effort) costs. This apparently conflicting finding
376 between effort and time costs may be explained by the fact that neither the low-effort
377 nor the high-effort option had a pronounced psychological proximity advantage. Thus,
378 in this specific context of cost-benefit decision making, the proximity factor appears to
379 be less relevant, and dopamine instead may promote behaviour aimed at maximizing
380 rewards simply by weighing rewards against associated costs. Importantly, our
381 experimental paradigm did not directly manipulate psychological proximity, nor did it
382 distinguish between proximity effects and the impact of delay. Therefore, specific
383 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;

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 D2-like receptor manipulations, we also investigated the role of cholinergic M1 receptor neurotransmission on decision making.

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

This partially 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). Consistent with these findings, our results revealed that haloperidol administration increased stochasticity 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. 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.

Materials and 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 tasks, 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. 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.

Participants completed two blocks, with each block containing all unique combinations, resulting in a total of 210 trials. We used a pseudorandomized trial order, counterbalanced across experimental sessions but not across participants. 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.

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 Logistic 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. Importantly, to test drug-specific effects on behaviour, we included the drug condition (placebo, haloperidol, biperiden) as a 3-level categorical predictor with placebo set as the reference. Thus, all drug-related main and interaction effects are estimated in reference to the placebo. 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.

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.

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

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

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

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

β_{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

779 true estimated subject-level parameters. The results of the model validation and
780 parameter recovery are presented in the Supplementary Results.
781
782 *Drug Effects on Vital Signs, Mood, Trail-Making Performance, MVC, and Effort Rating*
783 The effects of the drugs on mood (alertness, calmness, and contentedness) and
784 physiological measures (heart rate, systolic, and diastolic blood pressure) were
785 analysed using Bayesian Linear Mixed Models. If credible drug interactions were
786 found, we further explored the relationship between drug induced alterations in
787 behaviour and potential explanatory factors, including changes in subjective mood
788 ratings and/or physiological responses. Specifically, we calculated the absolute
789 differences in mood ratings and physiological parameters between T_0 (before drug
790 administration) and the time point where a credible drug effect was observed (either
791 T_1 or T_2). These difference values were then correlated with the shift parameters that
792 capture drug-induced changes in performance. The purpose of this Bayesian
793 correlation analysis was to exclude that drug-induced changes in mood ratings or
794 physiological measures could account for the observed drug-induced changes in
795 behaviour. We further investigated potential confounding drug effects on trail-making
796 response times, MVC, and subjective effort perception. These analyses did not reveal
797 significant effects of drug manipulation on any of these measures (see Supplementary
798 Results). More detailed descriptions of these analysis are presented in the
799 Supplementary Methods.
800
801 *Association between task- and drug-specific Computational Parameter Estimates*
802 We investigated the association between discounting tendencies across different cost
803 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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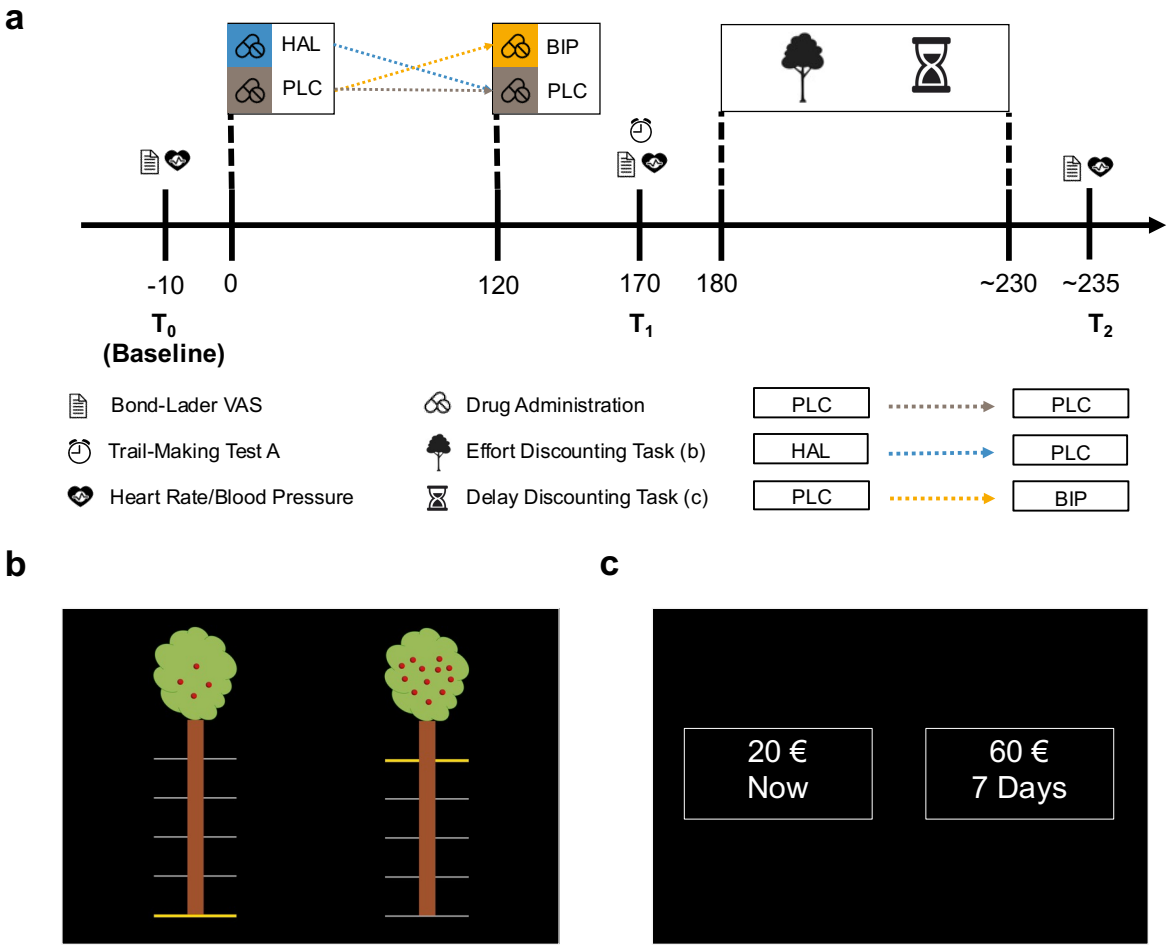

Fig. 1 Study procedure and experimental tasks. (**a**) The experimental sessions were standardized across all sessions except for the drug treatment, which was counterbalanced. To account for the different times of haloperidol and biperiden to reach peak plasma levels, a dummy drug application was introduced,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

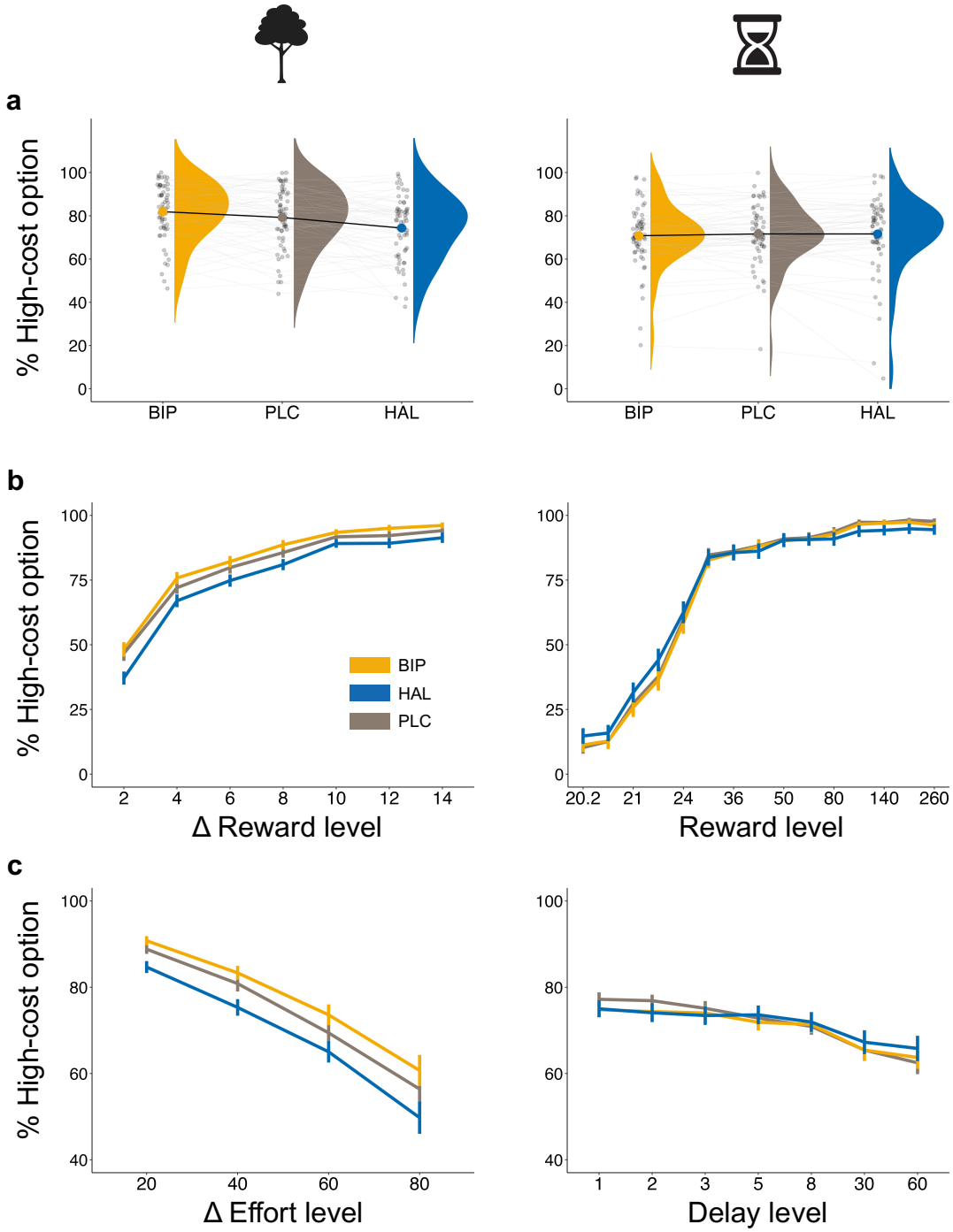

Fig. 2 Behavioural Performance in the Effort (left panel) and Delay (right panel) Discounting Task. (**a**) The overall proportions of high-cost choices were modulated by drug administration in the effort (left), but not in the delay discounting task (right). Biperiden increased and haloperidol decreased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

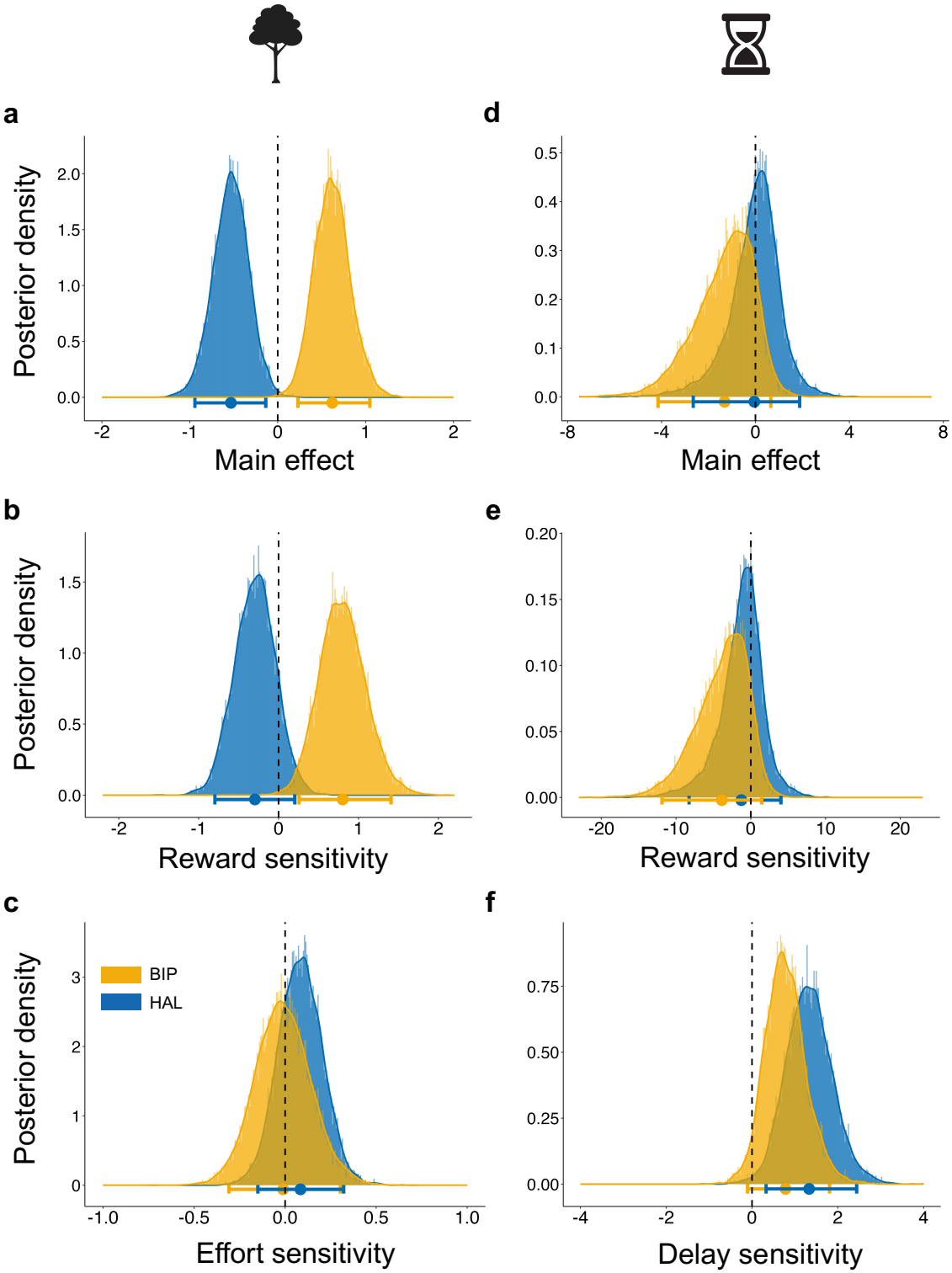

Fig. 3 Drug Effects on Choice Behaviour. Posterior distributions and 95% HDI of the Logistic Bayesian Generalized Linear Mixed Models depict the estimate of each effect on choosing the high-cost option. (**a**) Biperiden credibly increased the overall willingness to invest physical effort for a corresponding 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.

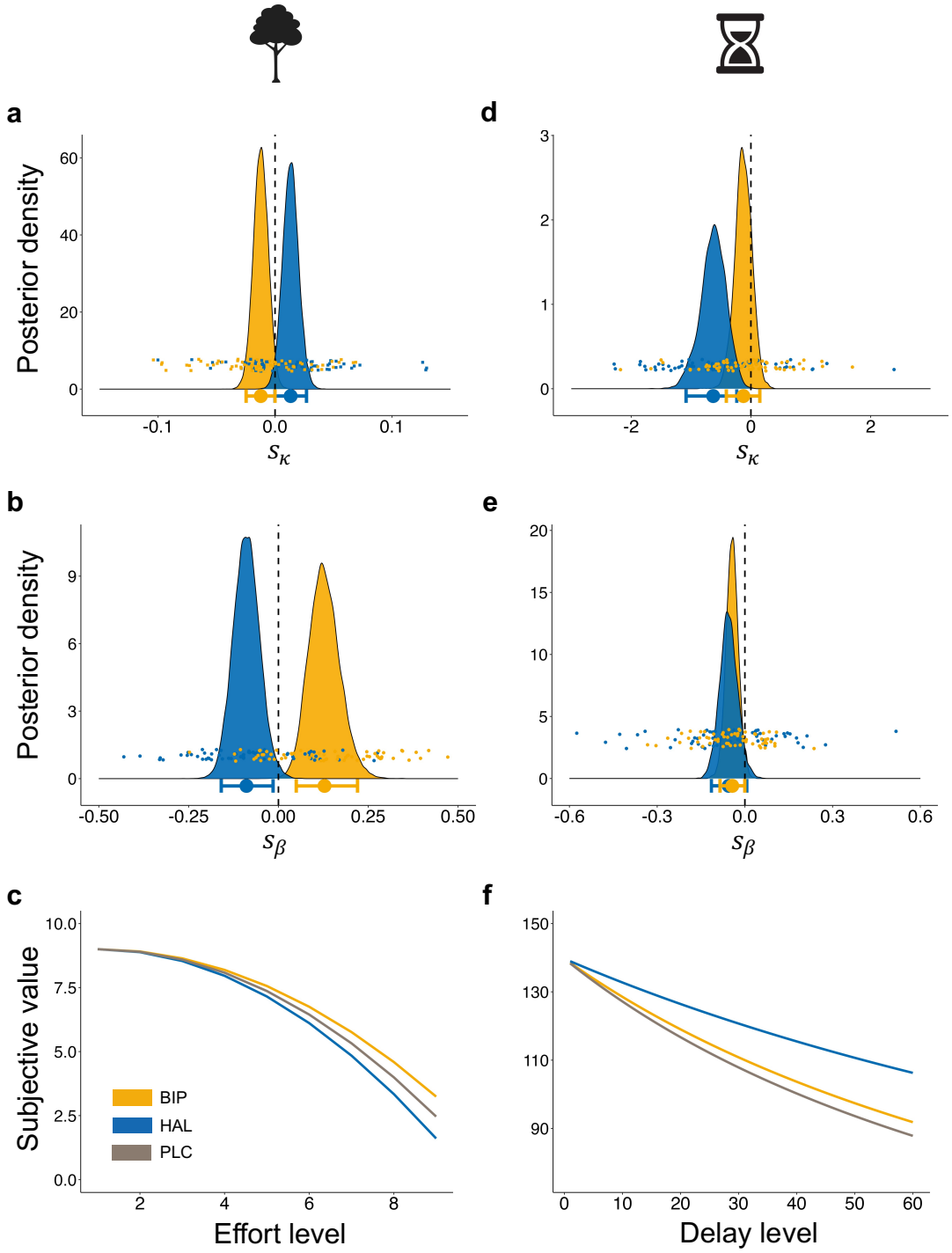

Fig. 4 Drug Effect on Computational Parameters. Posterior distributions and changes in the subjective value from the hierarchical Bayesian models. (**a**) In the effort discounting task, the discounting parameter κ is modulated in opposite directions by the drugs, with haloperidol increasing and biperiden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

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Supplementary Results

1. Baseline Session Analysis

To analyse choice behaviour in the absence of drug manipulations, we conducted Logistic Bayesian Generalized Linear Mixed Models exclusively focusing on the data from the placebo (baseline) session. This analysis confirmed robust main effects of each task parameters on choice behaviour, demonstrating the expected patterns of reward and cost sensitivity across both tasks. Specifically, in both tasks, increased reward magnitudes were associated with a higher likelihood of choosing the high-cost option, while increased effort or delay levels decreased this likelihood (Supplementary Fig. 1 and Supplementary Table 4 and 5).

2. Model Validation and Parameter Recovery

The simulated datasets mirror the original data reasonably well, confirming the model's ability to capture essential behavioural patterns observed in the actual data (Supplementary Fig. 2). Moreover, the parameter recovery revealed successful recovery of all group-level parameters, such that the mean of the simulated group-level parameters fell within the 95% HDI of the true parameter distribution (Supplementary Fig. 3). Similarly, averaged simulated and actual subject-level parameters were strongly correlated (all $r > 0.8$), indicating reliable estimation at the individual subject level (Supplementary Fig. 4).

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

Bayesian Linear Mixed Models revealed that biperiden administration led to a reduction in heart rate and systolic blood pressure at both T_1 (heart rate: HDI_{Mean} = -6.82, $HDI_{95\%}$ = [-10.74; - 2.97]; systolic blood pressure: HDI_{Mean} = -3.91, $HDI_{95\%}$ = [-7.74; -0.13]) and T_2 (heart rate: HDI_{Mean} = -7.88, $HDI_{95\%}$ = [-11.83; -3.89]; systolic blood pressure: HDI_{Mean} = -4.80, $HDI_{95\%}$ = [-8.74; -0.95]), with no credible impact on diastolic blood pressure (Supplementary Fig. 5). Moreover, subjective ratings of alertness were credibly lower under both haloperidol and biperiden at T_2 (biperiden: HDI_{Mean} = -0.15, $HDI_{95\%}$ = [-0.26; - 0.05]; haloperidol: HDI_{Mean} = -0.15, $HDI_{95\%}$ = [-0.25; -0.04]; Supplementary Fig. 6). Notably, we did not find credible drug effects on the response times in the

trail-making test A, the subjective rating of effort demand, and the MVC in the effort discounting task (Supplementary Fig. 7).

To investigate whether changes in physiological measures and mood ratings could be attributed to drug-induced changes in behaviour, we performed Bayesian correlation tests between each shift parameter that was credibly modulated by drug administration (i.e., $\mathcal{S}\kappa_{HAL}$ and $\mathcal{S}\beta_{BIP}$ in the delay discounting task and $\mathcal{S}\kappa_{HAL}$, $\mathcal{S}\kappa_{BIP}$, $\mathcal{S}\beta_{HAL}$, and $\mathcal{S}\beta_{BIP}$ in the effort discounting task) and the relative change in each control measure that credibly altered by drug intake (i.e., heart rate, systolic blood pressure, alertness ratings under biperiden and alertness ratings under haloperidol).

We found no credible correlation between any computational parameter that was modulated by biperiden and changes in systolic blood pressure at T1 in the effort (r = 0.10, $HDI_{95\%}$ = [-0.14; 0.33] for $\mathcal{S}\kappa_{BIP}$; r = -0.16, $HDI_{95\%}$ = [-0.39; 0.07] for $\mathcal{S}\beta_{BIP}$) and delay (r = 0.06, $HDI_{95\%}$ = [-0.19; 0.29] for $\mathcal{S}\beta_{BIP}$) discounting task. Similarly, we did not find any credible correlation between the computational parameters and biperiden-induced changes in systolic blood pressure at T2 (r = -0.04, $HDI_{95\%}$ = [-0.27; 0.20] for $\mathcal{S}\kappa_{BIP}$ (effort); r = -0.08, $HDI_{95\%}$ = [-0.31; 0.17] for $\mathcal{S}\beta_{BIP}$ (effort); r = 0.13, $HDI_{95\%}$ = [-0.10; 0.35] for $\mathcal{S}\kappa_{BIP}$ (delay)). The same applies for biperiden-induced reductions in heart rate at T1 (r = 0.05, $HDI_{95\%}$ = [-0.18; 0.28] for $\mathcal{S}\kappa_{BIP}$ (effort); r = 0.06, $HDI_{95\%}$ = [-0.18; 0.28] for $\mathcal{S}\beta_{BIP}$ (effort); r = -0.06, $HDI_{95\%}$ = [-0.29; 0.18] for $\mathcal{S}\kappa_{BIP}$ (delay)) and at T2 (r = 0.23, $HDI_{95\%}$ = [-0.00; 0.45] for $\mathcal{S}\kappa_{BIP}$ (effort); r = -0.09, $HDI_{95\%}$ = [-0.32; 0.16] for $\mathcal{S}\beta_{BIP}$ (effort); r = -0.18, $HDI_{95\%}$ = [-0.40; 0.07] for $\mathcal{S}\kappa_{BIP}$ (delay)) for both experimental paradigms. Alertness, which was affected by both drugs at T2, also did not show any credible correlations with biperiden- (r = 0.14, $HDI_{95\%}$ = [-0.10; 0.37] for $\mathcal{S}\kappa_{BIP}$ (effort); r = 0.77, $HDI_{95\%}$ = [-0.16; 0.30] for $\mathcal{S}\beta_{BIP}$ (effort), r = -0.16, $HDI_{95\%}$ = [-0.38; 0.08] for $\mathcal{S}\beta_{BIP}$ (delay)) as well as haloperidol-induced changes (r = -0.05, $HDI_{95\%}$ = [-0.28; 0.19] for $\mathcal{S}\kappa_{HAL}$ (effort); r = -0.09, $HDI_{95\%}$ = [-0.33; 0.16] for $\mathcal{S}\beta_{HAL}$ (effort); r = 0.05, $HDI_{95\%}$ = [-0.20; 0.29] for $\mathcal{S}\kappa_{HAL}$ (delay)).

4. 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 decision times were modulated by key decision variables. We investigated this with Bayesian Linear Mixed Models, using log-transformed decision times on each trial as the dependent variable. In both tasks, higher reward magnitudes decreased, while higher cost levels (effort or delay) increased decision 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]; Supplementary Fig. 8b-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]: Supplementary Fig. 9b, 9e). Haloperidol further attenuated the decelerating effect of delay (HDI_{Mean} = -0.020, $HDI_{95\%}$ = [-0.036; -0.003]; Fig. 9f), but not effort (HDI_{Mean} = -0.021, $HDI_{95\%}$ = [-0.047; 0.003]; Supplementary Fig. 9c). This aligns with the decreased delay sensitivity observed in the delay discounting task analysis. Moreover, haloperidol administration induced an overall increase in decision times in the delay discounting task (HDI_{Mean} = -0.077, $HDI_{95\%}$ = [-0.123; -0.031]; Supplementary Fig. 9d), while this effect was not observed in the effort discounting task (HDI_{Mean} = 0.016, $HDI_{95\%}$ = [-0.047; 0.078]; Supplementary Fig. 9a). Unlike under haloperidol, none of the effects of task parameters on response speed were modulated by biperiden. See Supplementary Table 6 and 7 for full results.

5. Computational Model Parameters & Self Ratings

Robust linear regression models did not reveal any significant associations between sex, self-reported questionnaire ratings (total scores and subscales), and both effort and delay baseline (placebo-condition) discounting parameters (Supplementary Tables 8 – 11). However, the analysis did reveal a significant main effect of individuals age on the effort discounting parameter, indicating

a higher tendency to discount rewards in older compared to younger participants (*beta* = 0.007, *p* = 0.008).

Supplementary Methods

6. Fitting Procedure Bayesian Regression

To examine the impact of varying levels of reward and/or costs, as well as the administered drug, on choosing the high-reward/high-cost option, we employed Logistic Bayesian Generalized Linear Mixed Models. For the effort discounting task, the fixed effects included reward (difference between reward magnitudes of the high-cost versus low-cost option), effort (difference between effort requirement of the high-cost versus low-cost option), the administered drug (with placebo set as the reference category), and their interactions. For the delay discounting task, we followed a similar approach, but instead of using difference values, we used the absolute reward and delay levels of the high-cost option, given that the low-cost option remains fixed to a constant value throughout the task. Furthermore, to mitigate the risk of false positive results, all models contained a full random-effects structure (Barr et al., 2013). This approach allowed us to account for individual variability, leading to more robust and reliable findings.

To control for potential confounding effects of fatigue and session, we ran additional separate GLMMs, extending the fixed-effects structures. Specifically, to test for fatigue, we included trial number and its two-way interactions with drug as additional predictors. In separate models, we controlled for session effects by adding session, as well as the two-way interactions between session and drug.

Further, to gain insights into choice behaviour in the absence of any pharmacological manipulations, we conducted additional GLMMs exclusively analysing data from the placebo sessions. These models were identical to the previously described regression analyses, including the full random-effects structure, but excluded the *drug* predictor. This analysis provided estimates of the main effects of task manipulations (i.e., reward and cost sensitivity) under the baseline condition.

To ensure robust and informative Bayesian parameter estimation and avoid issues of unstable parameter estimation that could appear with noninformative and flat priors, we followed the approach recommended by Gelman et al. and implemented weakly informative priors (2008). First, we standardized all nonbinary variables to have a mean of 0 and a standard deviation of 0.5. Then, we used the following priors in our analyses:

Regression Coefficient	$\beta \sim Cauchy(0, 2.5)$
Intercept	$\beta_0 \sim Cauchy(0, 10)$
Correlation Matrix	$\Sigma \sim LKJcorr(1)$
Standard Deviation	$\sigma \sim Student(3, 0, 2.5)$

7. Fitting Procedure Hierarchical Bayesian Model

7.1. Model Fitting and Comparison

To identify the model that best describes how rewards are devalued by increasing levels of effort and delay, we employed four commonly used discounting models on participants' choice data from both tasks (Białaszek et al., 2017; Chong et al., 2017; Hartmann et al., 2013; Klein-Flügge et al., 2015): linear (Supplementary Eq. 1), parabolic (Supplementary Eq. 2), hyperbolic (Supplementary Eq. 3), and exponential (Supplementary Eq. 4). To minimize the potential impact of drug administration on the discounting function, we restricted the model fitting to choice data from the (baseline) placebo condition.

$$SV(t) = R(t) - \kappa * C(t) \quad (1)$$

$$SV(t) = R(t) - \kappa * C(t)^2 \quad (2)$$

$$SV(t) = \frac{R(t)}{1+\exp(\kappa)*C(t)} \quad (3)$$

$$SV(t) = R(t) * e^{-\kappa*C(t)} \quad (4)$$

All discounting models assume that the subjective value (SV) of an offer is calculated by taking into account the reward (R) and the cost (C) level on trial (t). In the effort discounting task, the cost

level is represented by the effort level, which is scaled to the proportion of the maximum voluntary contraction. In the delay discounting task, the cost level is represented by the delay of the high-cost option, indicating the number of days necessary to wait to obtain the reward. The degree to which rewards are discounted by increasing levels of costs is modelled by a subject-specific discounting parameter (κ), which quantifies the steepness of each individual's devaluation of rewards as costs increase. Higher values of κ represent higher steepness in devaluation, indicating stronger sensitivity to increasing costs, while lower values represent lower steepness, indicating less sensitivity to increasing costs. Importantly, in the effort discounting task, two options with varying levels of reward and effort are presented on each trial, leading to the calculation of two different SVs. In contrast, in the delay discounting task, one option varies in reward and delay, while the other SV is fixed at 20, resulting in the calculation of a single SV for that option per trial. Additionally, note that the κ values for the delay discounting task were modelled in log space to prevent numerical instability caused by highly skewed κ values. SVs for the high-reward/high-cost (HC) and the low-reward/low-cost (LC) were then transformed to choice probabilities, using a softmax function (Eq. 5).

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

The choice consistency was modelled using the inverse temperature parameter β.

To determine the best fitting models for describing participants' behaviour in each task, we employed the leave-one-out information criterion (LOOIC), which estimates out-of-sample prediction accuracy by utilizing the log-likelihood. The LOOIC was assessed using the loo package in R (Vehtari et al., 2017). Lower LOOIC values indicate better model fit, similar to traditional information criteria such as AIC and BIC (see Supplementary Table 3).

7.2. Model Parametrization and Priors

For all hierarchical models, we assume that the subject-level parameters are drawn from group-level normal distributions. We use Uniform and half-Cauchy distributions for the group-level mean (μ) and standard deviations (σ) of the (baseline) placebo-condition discounting parameters κ and inverse temperature β, respectively. For all shift parameters, which indicate drug-specific effects on κ and β, Gaussian prior distributions were used for the means, and half-Cauchy distributions were used for the standard deviations. Based on previous findings, the standard deviations of all half-Cauchy distributions were set with a location of 0 and a scale of 2.5. Additionally, more restrictive priors were set for the Gaussian distribution of all group-level shift hyperparameters with a location of 0 and a scale of 2 (Knauth & Peters, 2022; Mathar et al., 2022; Wagner et al., 2020). To account for the different degrees of discounting depending on the cost type and the logarithmic transformation of κ in delay discounting, we used distinct ranges for the Uniform distribution of the group-level means in both tasks. These ranges were based on numerically plausible values and previous findings (Knauth & Peters, 2022; Lockwood et al., 2021, 2022; Mathar et al., 2022; Wagner et al., 2020).

In summary, the prior distributions for our hierarchical models are as follows:

$$\mu_{\kappa(Effort)} \sim Uniform(0, 5)$$

$$\mu_{\kappa(Delay)} \sim Uniform(-20, 3)$$

$$\sigma_{\kappa} \sim HalfCauchy(0, 2.5)$$

$$\mu_{\beta} \sim Uniform(0, 10)$$

$$\sigma_{\beta} \sim HalfCauchy(0, 2.5)$$

$$\mu_{S_x} \sim Normal(0, 2)$$

$$\sigma_{S_x} \sim HalfCauchy(0, 2.5)$$

8. Physiological Measures and Bond-Lader Visual Analogue Scale

Participants completed subjective mood ratings using the German version of the Bond and Lader visual analogue scale (Bond & Lader, 1974) at three different time points (T_0, T_1, and T_2). Additionally, blood pressure and heart rate measurements were taken at the same time points using a digital blood pressure monitor (OMRON model M500, Healthcare Europe B.V., The Netherlands). These manipulation checks were conducted at T_0 (before drug administration), T_1 (before starting the task, approximately 170 min after haloperidol or 50 min after biperiden intake), and T_2 (after finishing the task, approximately 230 min after haloperidol or 110 min after biperiden intake). These assessments allowed us to examine potential effects of the administered drugs on subjective mood states and physiological parameters. Subjective mood rating scales involved 16 binary items presented on a horizontal line on a sheet of paper. Each item consisted of two words describing opposing mood states (e.g., “happy versus sad”), and participants indicated their mood by marking the line closer to one of the two words. Based on a factor analysis using a principal component solution and orthogonal rotation of the factor matrix, three separate factor scores were extracted: alertness, contentedness, and calmness. Self-ratings were analysed by measuring the distance in millimetres from the end of the line to the subject's mark. These measurements were then log-transformed to correct for skewness (Bond & Lader, 1974). In addition, once per session, participants completed an effort rating, in which they were required to rate each effort level they encountered during the tasks. Furthermore, prior to beginning the effort discounting task, participants completed the trail-making test A, and we measured participants’ maximum voluntary contraction (MVC).

To analyse the effects of the drugs on mood ratings, physiological measures, trail-making test response times, MVC, and subjective effort perception ratings, we applied Bayesian Linear Mixed Effects Models. For mood ratings and physiological measures, the models included the factors time (T_0, T_1, and T_2), drug (PLC, HAL, BIP), and their interaction as fixed effects, with subject-specific intercepts. Similarly, for the trail-making test, MVC, and effort ratings, which were measured once per session, the models included drug (PLC, HAL, BIP), session (Session 1, Session 2, Session 3), and their interaction as fixed effects, with subject-specific intercepts. For analysing effort ratings, we additionally included effort levels as fixed effects in the model. For

parameter estimation, we used non-informative priors (the brms default) and ran four chains with 3000 samples (1000 samples for warmup).

Importantly, to test whether credible changes in physiological parameters or mood ratings induced by drug administration could explain changes in behaviour, we used Bayesian correlation tests to examine possible associations. We correlated difference values (T_0 vs. timepoints with credible drug-induced influences; i.e., T_2 for mood ratings, T_1 and T_2 for physiological parameters) with the mean estimates of all shift parameters that were credibly modulated by either haloperidol or biperiden.

9. Decision Times Analysis

Similarly, to the model-agnostic analysis of the choice data, we performed a separate analysis focusing on participants' decision 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 decision times (in milliseconds) as the outcome variable with a Gaussian distribution function. We then regressed the decision 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.

10. Computational Parameter Estimates, Self-Rating Scores, and Demographics

As a last step of our analysis, we examined potential associations between the discounting parameters κ and self-reported questionnaire ratings, including the Apathy Evaluation Scale (AES)

and Barratt Impulsiveness Scale-15 (BIS-15), with all subscales, and Beck Depression Inventory (BDI). We also investigated the relationship of both model parameters with demographic variables (sex and age). To this aim, we conducted four separate robust linear regressions, using the mean estimates of the discounting parameter κ from the placebo condition of both tasks, serving as a baseline value for each participants' discounting behaviour. We chose robust regression models because they have been shown to be less sensitive to the influence of outliers (Yu & Yao, 2017). We regressed this outcome against predictors of age, sex, and the z-scored total scores of all questionnaire scores. Further, to gain insights into the effects of each subscale of the apathy and impulsivity questionnaires, we again performed separate robust regression models, this time using the z-scored subscale scores of both questionnaires as predictors.

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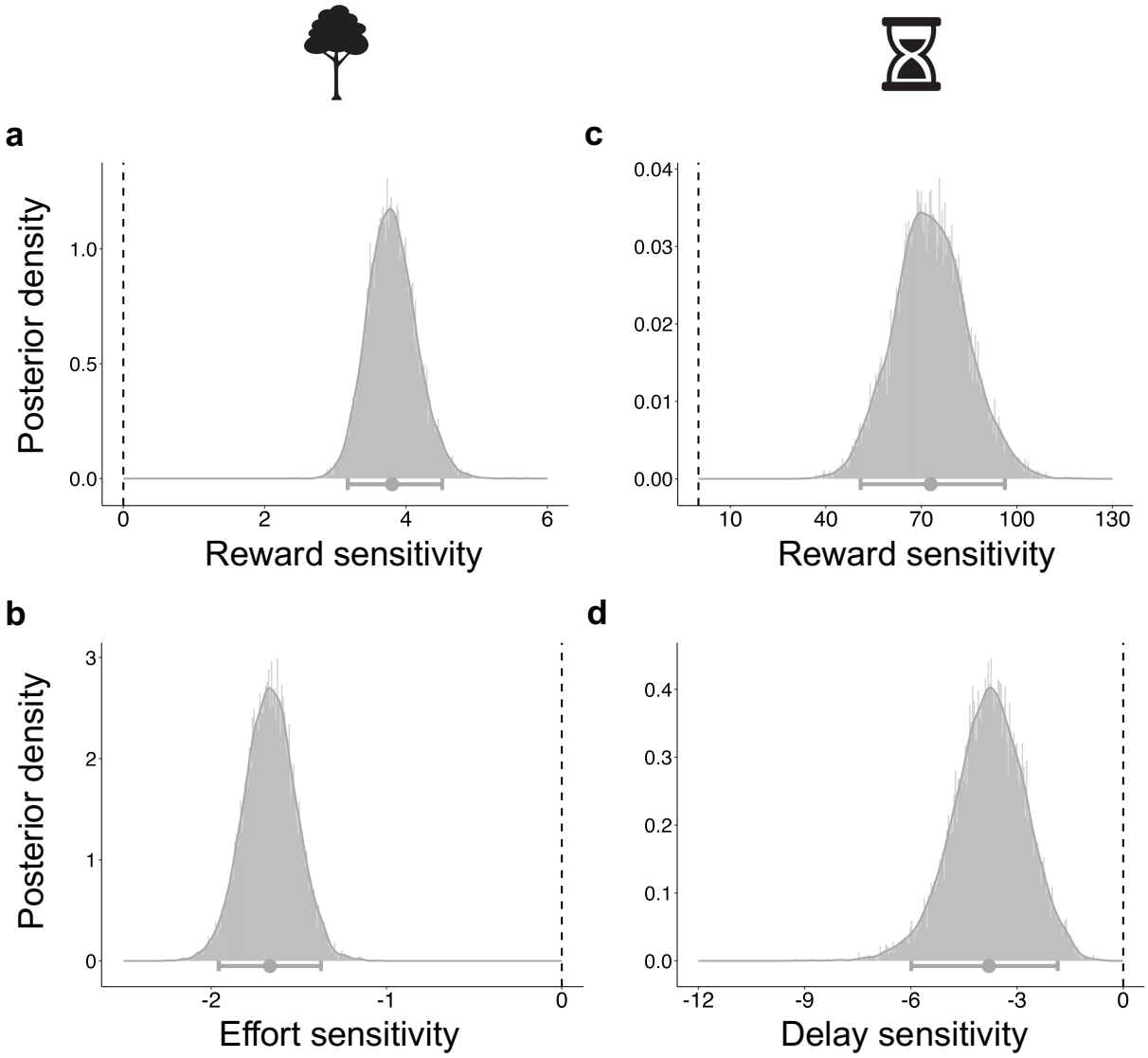
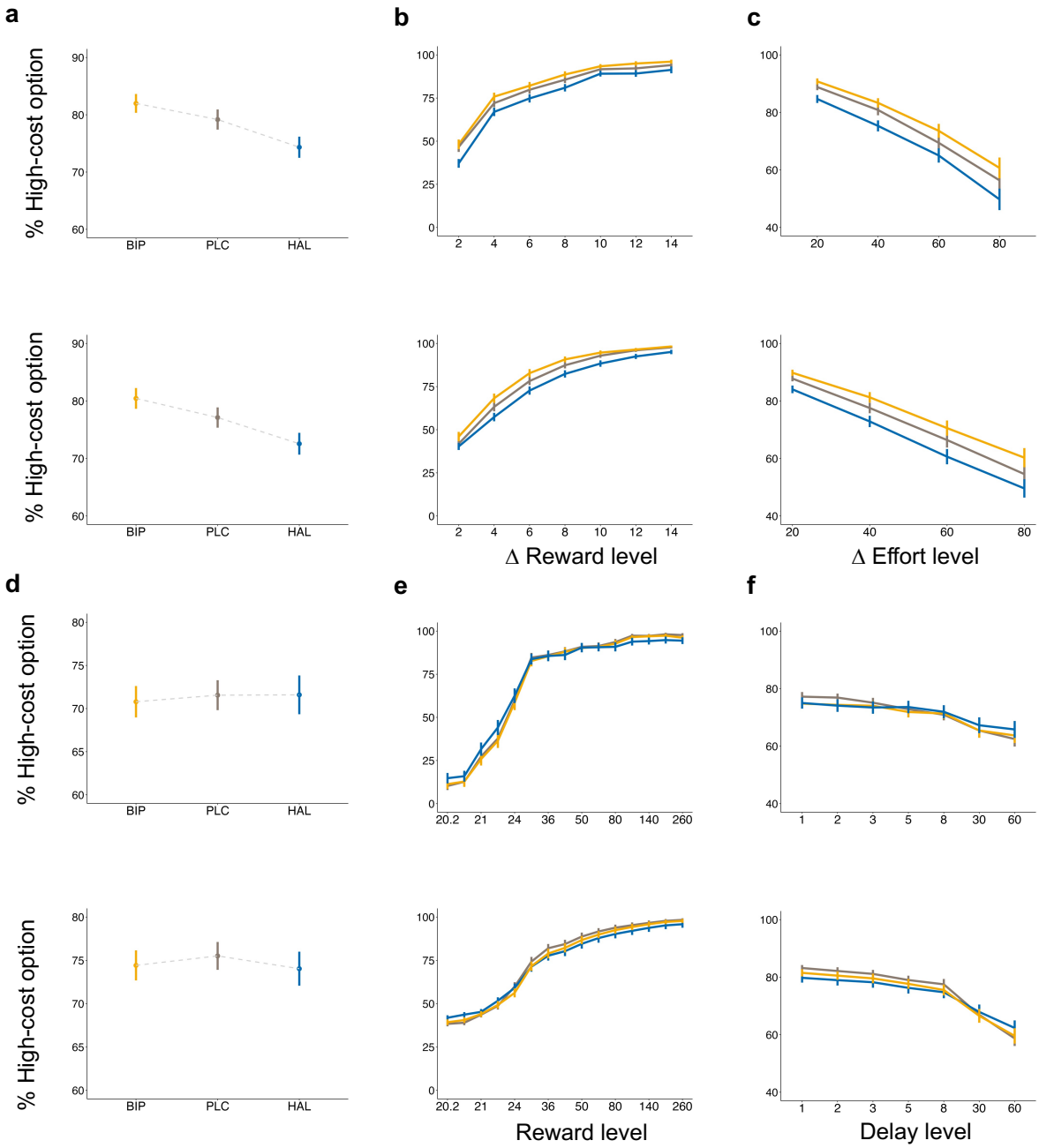
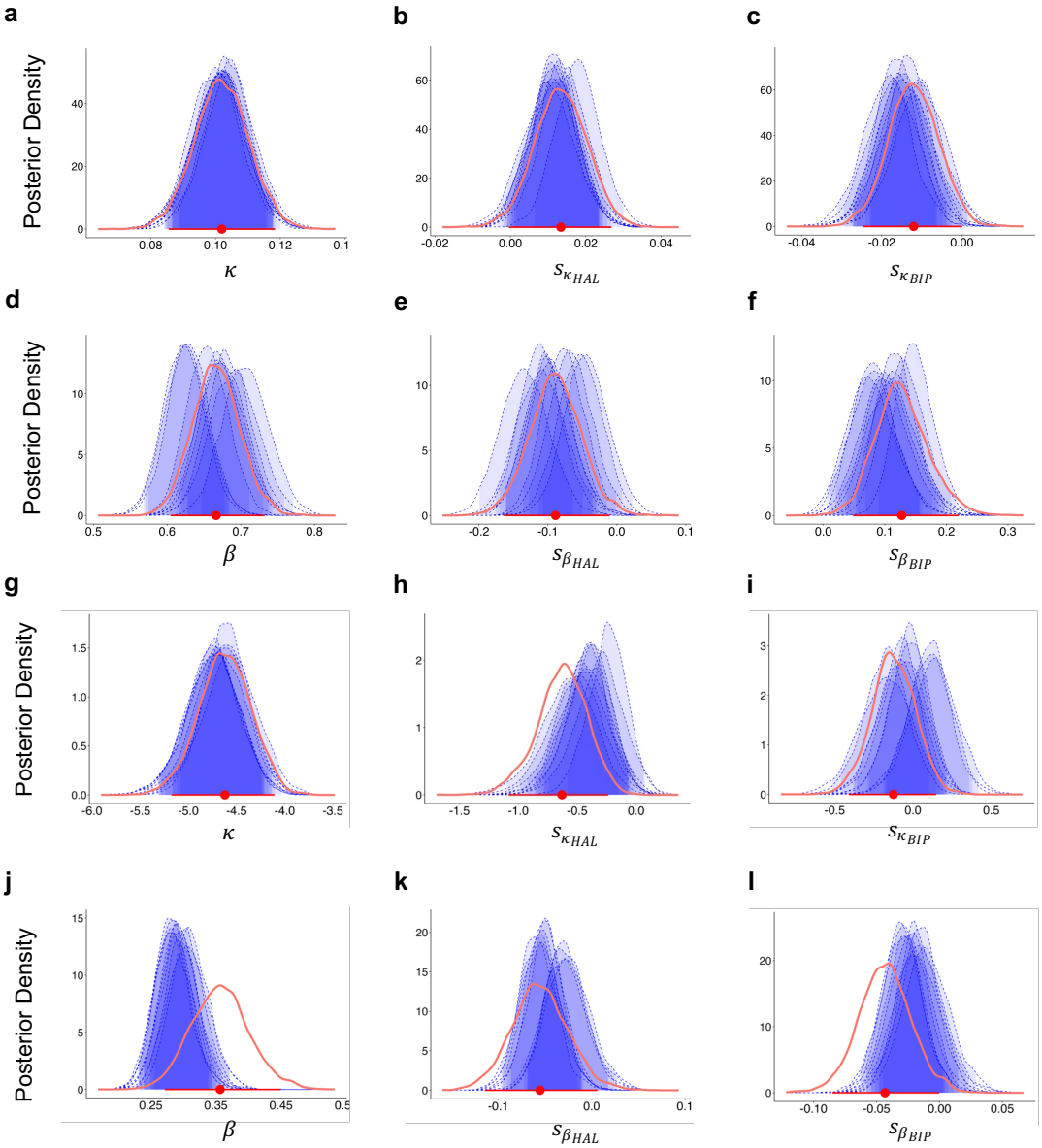
Supplementary Figures



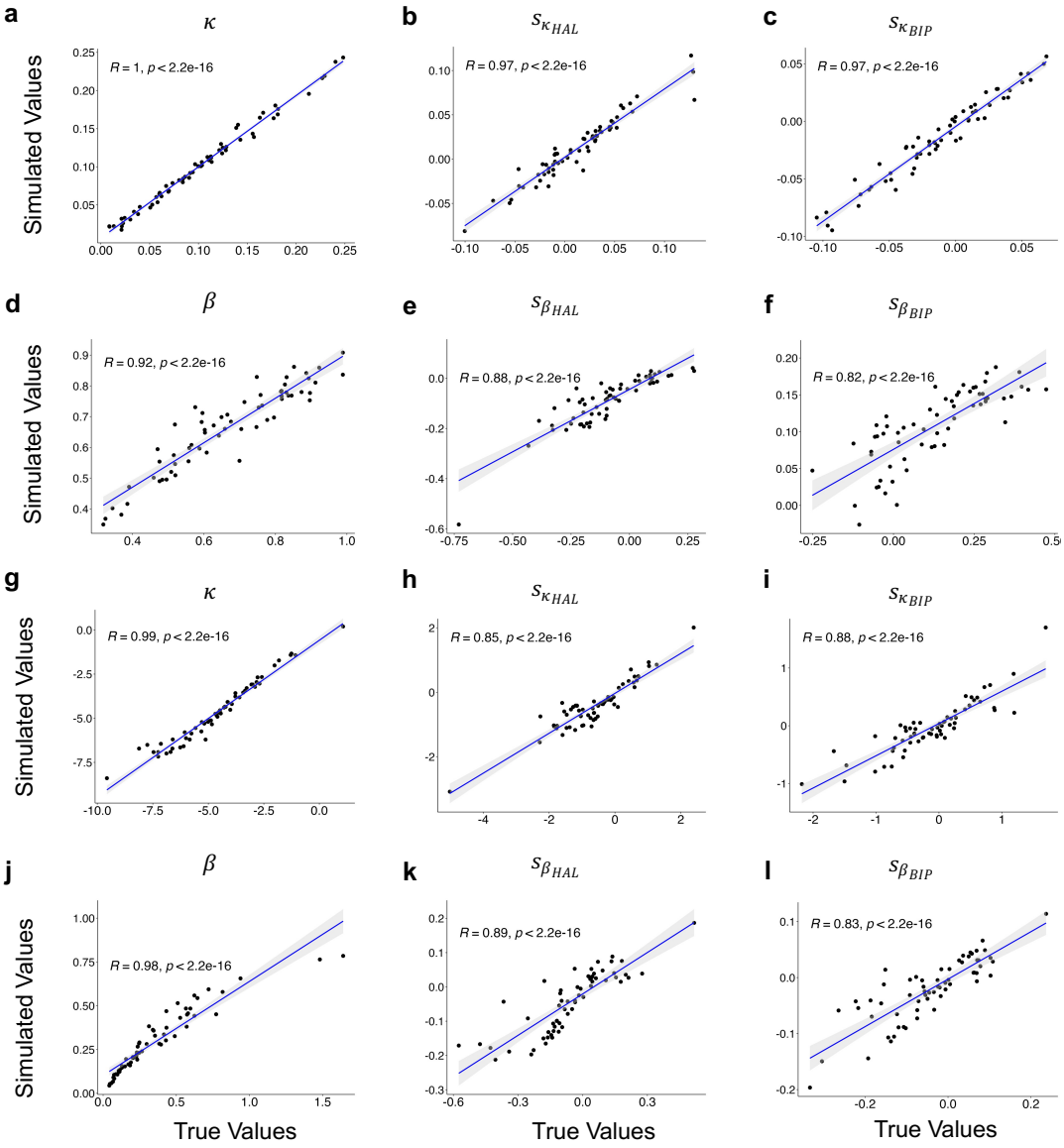
Supplementary Fig. 1. Choice Behaviour in the placebo (baseline) condition. Posterior distributions and 95% HDI of the Logistic Bayesian Generalized Linear Mixed Models depict the estimate of each task parameter on choosing the high-cost option. (**a**) Higher reward magnitudes increased the overall willingness to invest physical effort for a corresponding reward in the effort discounting task. (**b**) Higher levels of effort had the opposite effect. (**c**) Similarly, higher reward magnitudes increased the likelihood to choose the high-cost option in the delay discounting task. (**d**) In contrast, higher levels of delay decreased the willingness to choose the high-reward/high-delay option. Bold dots represent the mean group-level estimate of the posterior distribution. The horizontal bars represent the group-level 95% highest density interval.



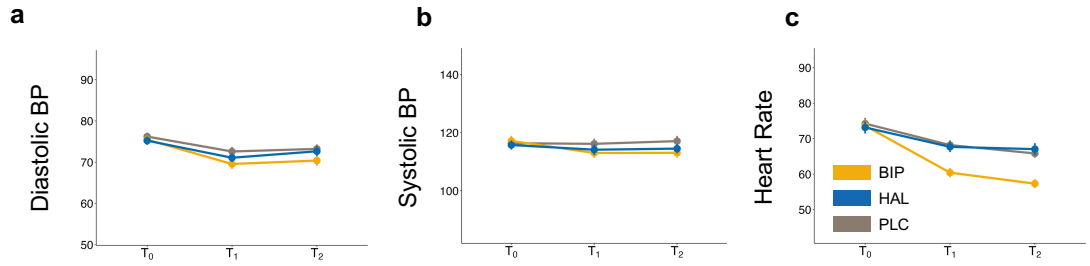
Supplementary Fig. 2. Model Validation for the Effort (a-c) and Delay Discounting Task (d-f). Plots depict the averaged overall proportion of choosing the high-cost option as a function of reward and cost for both the effort (**a, b, c**) and the delay (**d, e, f**) discounting task. The upper panels display the actual data and the lower panels present the simulated data for comparison. Group-level means are indicated by dots, with error bars representing the standard error of the mean. In the effort discounting task, reward levels are presented as the difference in magnitude between the high- and low-cost option, and in the delay discounting task, reward levels are shown as the reward value of the high-cost option. Likewise, the effort level corresponds to the difference between the proportions of the individually calibrated MVC of the high and low-cost option, while the delay levels indicate the delay of the high-cost option.



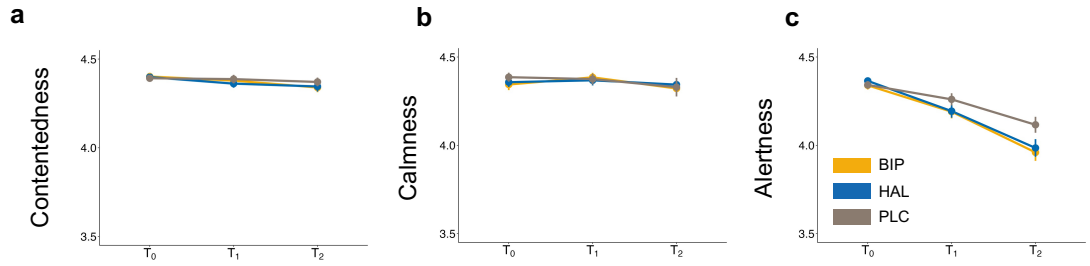
Supplementary Fig. 3. Parameter Recovery of the Group-Level Posterior Distributions for the Effort (a-f) and Delay Discounting Task (g-l). We tested the ability of our models to recover parameters using simulated datasets. Each panel displays the actual distribution (red) of each parameter of interest alongside ten corresponding simulated datasets (blue). Horizontal bars, depicted in red, represent the group-level 95% HDI of the actual parameter estimate, with dots indicating the mean of the distribution. The shaded area in blue depicts the 95% HDI of the simulated parameter estimates. We evaluated whether the mean estimates of the simulated group-level parameter values fell within the 95% HDI of the true parameter distribution. The parameter recovery analysis of the group-level distribution demonstrated positive results, as all mean parameter estimates of the simulated data are located within the 95% HDI of the actual dataset.



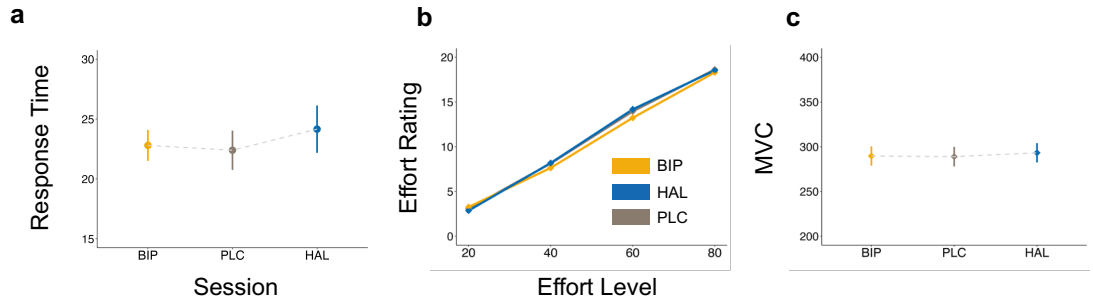
Supplementary Fig. 4. Parameter Recovery of the Subject-Level Parameters for the Effort (a-f) and Delay Discounting Task (g-l). We calculated the Pearson correlation coefficients between the mean subject-level posterior distribution of the simulated and actual data. For the simulated data, subject-level means were averaged across each dataset. The correlation coefficients demonstrate strong to excellent correlations (all $r > 0.8$), further confirming that the models are able to accurately to recover the actual task parameter values.



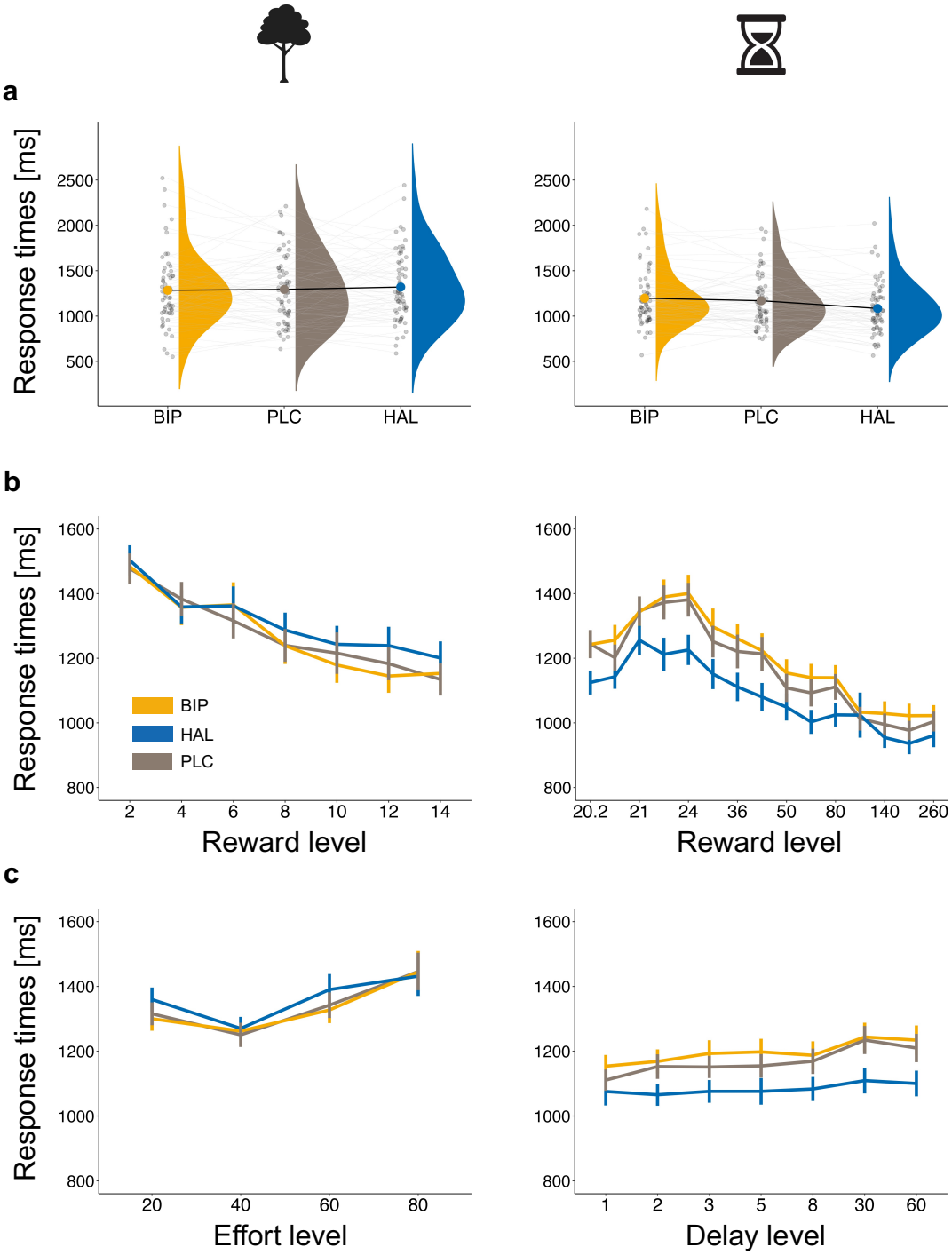
Supplementary Fig. 5. Physiological Effects of Drug Administration. Plots depict the change in each physiological parameter following drug administration. (**a**) Diastolic BP decreased at T1 (HDI_{Mean} = -3.75, $HDI_{95\%}$ = [-5.71; -1.85]) and T2 (HDI_{Mean} = -2.99, $HDI_{95\%}$ = [-4.96; -1.07]) compared to T0. However, we did not find a credible main or interaction effect of drug, implying that diastolic BP decreases as the task progresses irrespective of drug administration. (**b**) Systolic BP reflected notable two-way biperiden interactions at T1 and T2 (Biperiden x T1: HDI_{Mean} = -3.91, $HDI_{95\%}$ = [-7.74; -1.07]; Biperiden x T2: HDI_{Mean} = -4.80, $HDI_{95\%}$ = [-8.74; -0.95]), suggesting a more pronounced decrease in systolic BP following Biperiden application. (**c**) Heart rate was reduced at T1 (HDI_{Mean} = -6.82, $HDI_{95\%}$ = [-10.74; -2.97]) and T2 (HDI_{Mean} = -7.88, $HDI_{95\%}$ = [-11.83; -3.89]) relative to T0. A credible two-way interaction was found between Biperiden at T1 and T2 (Biperiden x T1: HDI_{Mean} = -6.82, $HDI_{95\%}$ = [-10.74; -2.97]; Biperiden x T2: HDI_{Mean} = -7.88, $HDI_{95\%}$ = [-11.83; -3.89]), indicating that, analogously to the drop in systolic BP, the drop in heart rate at T1 and T2 is more pronounced following biperiden administration compared to placebo. Dots represent the group-level mean, error bars depict the standard error of the mean.



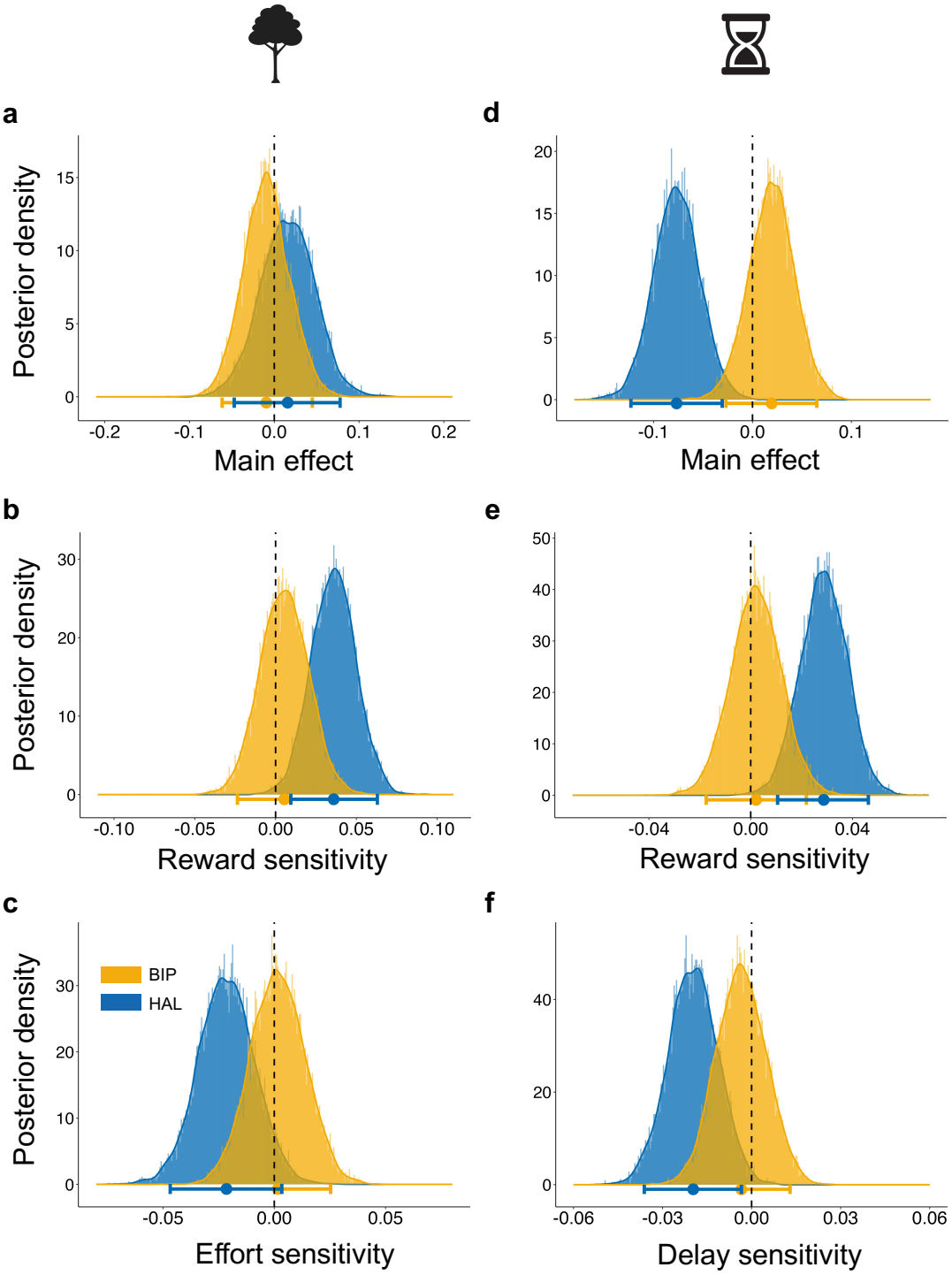
Supplementary Fig. 6. Subjective Mood Rating Effects of Drug Administration. Plots show alterations in subjective mood ratings following drug administration. No credible effects of time or drug were found for (**a**) contentedness and (**b**) calmness ratings. However, (**c**) alertness ratings notably decreased over time, exhibiting a credible drop at both T1 (HDI_{Mean} = -0.08, $HDI_{95\%}$ = [-0.16; -0.01]) and T2 (HDI_{Mean} = -0.23, $HDI_{95\%}$ = [-0.30; -0.15]) compared to T0. Importantly, at T2, credible two-way interaction effects were found for biperiden and haloperidol (Biperiden x T2: HDI_{Mean} = -0.15, $HDI_{95\%}$ = [-0.26; -0.05]; Haloperidol x T2: HDI_{Mean} = -0.15, $HDI_{95\%}$ = [-0.25; -0.04]), suggesting that both drugs led to more pronounced reductions in alertness ratings towards the end of the experiment, compared to placebo. Dots represent the group-level mean, error bars depict the standard error of the mean.



Supplementary Fig. 7. Drug Effects on Trail-Making Test Performance, Subjective Effort Ratings, and MVC. (**a**) No credible drug effects were observed for response times during trail-making test A. However, credible main effects of session were found (Session 2: HDI_{Mean} = -4.77, $HDI_{95\%}$ = [-8.41; -1.17]; Session 3: HDI_{Mean} = -6.40, $HDI_{95\%}$ = [-10.14; -2.66]), suggesting that participants became faster after the first session, possibly due to familiarity with the task. (**b**) Effort ratings were modulated only by increasing effort levels (HDI_{Mean} = 5.15, $HDI_{95\%}$ = [4.81; 5.49]), suggesting no drug effects on the subjective experience of effort demand. (**c**) MVC was not credibly modulated by drug administration, indicating that participant's ability to exert effort was not modulated by drug either. Dots represent the group-level mean and error bars represent standard error of the mean.



Supplementary Fig. 8. Decision Times in milliseconds (ms) in the Effort (left panel) and Delay (right panel) Discounting Tasks. (**a**) Overall decision times in the effort discounting task (left) were not affected by haloperidol or biperiden. However, in the delay discounting task (right), haloperidol reduced the decision times. (**b**) Decision times decreased with larger rewards. Haloperidol reduced this speed-up effect in both the effort (left) and delay discounting task (right panel). (**c**) Conversely, decision 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.



Supplementary Fig. 9. 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 decision 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 decision times. Bold dots represent the mean group-level estimate of the posterior distribution. The horizontal bars represent the group-level 95% highest density interval.

Supplementary Tables

Supplementary Table 1. Bayesian Generalized Linear Mixed Models of the Effort Discounting Task, Regressing Choices (High-Cost vs. Low-Cost Option) on Predictors for Drug, Reward (Difference between High-Cost vs. Low-Cost Reward Level), Effort (Difference between High-Cost vs. Low-Cost Effort Level), and their Interaction Terms.

Parameter	Estimate	Est. Error	2.5%	97.5%
(Intercept)	2.544	0.219	2.116	2.988
Biperiden	0.620	0.207	0.230	1.048
Haloperidol	-0.532	0.203	-0.943	-0.136
Reward	3.436	0.251	2.961	3.945
Effort	-1.638	0.122	-1.874	-1.402
Biperiden x Reward	0.802	0.292	0.256	1.409
Haloperidol x Reward	-0.296	0.257	-0.797	0.203
Biperiden x Effort	-0.011	0.153	-0.309	0.303
Haloperidol x Effort	0.084	0.121	-0.150	0.321
Reward x Effort	0.150	0.183	-0.212	0.509
Biperiden x Reward x Effort	0.104	0.295	-0.476	0.675
Haloperidol x Reward x Effort	-0.223	0.238	-0.682	0.256

Supplementary Table 2. Bayesian Generalized Linear Mixed Models of the Delay Discounting Task, Regressing Choices (High-Cost vs. Low-Cost Option) on Predictors for Drug, Reward (High-Cost Option Reward), Delay (High-Cost Option Delay), and their Interaction Terms.

Parameter	Estimate	Est. Error	2.5%	97.5%
(Intercept)	19.555	2.629	14.436	24.643
Biperiden	-1.315	1.263	-4.147	0.655
Haloperidol	-0.046	1.095	-2.648	1.884
Reward	55.637	7.095	41.762	69.382
Delay	-2.291	0.522	-3.303	-1.250
Biperiden x Reward	-3.871	3.478	-11.873	1.453
Haloperidol x Reward	-1.271	2.952	-8.257	4.037
Biperiden x Delay	0.781	0.481	-0.104	1.807
Haloperidol x Delay	1.332	0.540	0.328	2.440
Reward x Delay	-2.804	1.382	-5.521	-0.142
Biperiden x Reward x Delay	1.054	1.333	-1.361	4.003
Haloperidol x Reward x Delay	2.383	1.525	-0.465	5.514

Supplementary Table 3. Model comparison for the effort and delay discounting task. To compare the validity of each model, we used the leave-one-out cross-validation information criterion (LOOIC) procedure. A lower LOOIC score indicates a better-fitting model.

Model	***Effort***	***Delay***
	LOOIC	**LOOIC**
Parabolic	15109.7*	27279.6
Linear	17337.5	26041.5
Hyperbolic	18477.9	25662.4*
Exponential	17961.2	26217.5

Supplementary Table 4. Bayesian Generalized Linear Mixed Models of the Effort Discounting Task – Baseline Session; Regressing Choices (High-Cost vs. Low-Cost Option) on Predictors for Reward (Difference between High-Cost vs. Low-Cost Reward Level), Effort (Difference between High-Cost vs. Low-Cost Effort Level), and their Interaction Terms.

Parameter	Estimate	Est. Error	2.5%	97.5%
(Intercept)	2.747	0.288	2.199	3.331
Reward	3.802	0.342	3.174	4.512
Effort	-1.664	0.148	-1.957	-1.373
Reward x Effort	0.120	0.235	-0.345	0.587

Supplementary Table 5. Bayesian Generalized Linear Mixed Models of the Delay Discounting Task – Baseline Session; Regressing Choices (High-Cost vs. Low-Cost Option) on Predictors for Reward (High-Cost Option Reward), Delay (High-Cost Option Delay), and their Interaction Terms.

Parameter	Estimate	Est. Error	2.5%	97.5%
(Intercept)	25.867	4.242	17.793	34.506
Reward	72.914	11.447	50.953	96.234
Delay	-3.793	1.036	-5.985	-1.853
Reward x Delay	-6.699	2.927	-12.868	-1.206

Supplementary Table 6. Bayesian Linear Mixed Models of the Effort Discounting Task, Regressing Decision Times on Predictors for Drug, Reward (Difference between High-Cost vs. Low-Cost Reward Level), Effort (Difference between High-Cost vs. Low-Cost Effort Level), and their Interaction Terms.

Parameter	Estimate	Est. Error	2.5%	97.5%
(Intercept)	7.047	0.038	6.973	7.124
Biperiden	-0.009	0.027	-0.062	0.045
Haloperidol	0.016	0.032	-0.047	0.078
Reward	-0.183	0.015	-0.213	-0.154
Effort	0.084	0.011	0.063	0.105
Biperiden x Reward	0.005	0.015	-0.024	0.035
Haloperidol x Reward	0.036	0.014	0.009	0.063
Biperiden x Effort	0.002	0.012	-0.022	0.025
Haloperidol x Effort	-0.021	0.013	-0.047	0.003
Reward x Effort	0.083	0.016	0.051	0.116
Biperiden x Reward x Effort	-0.020	0.023	-0.067	0.026
Haloperidol x Reward x Effort	0.000	0.023	-0.045	0.047

Supplementary Table 7. Bayesian Linear Mixed Models of the Delay Discounting Task, Regressing Decision Times on Predictors for Drug, Reward (High-Cost Option Reward), Delay (High-Cost Option Delay), and their Interaction Terms.

Parameter	Estimate	Est. Error	2.5%	97.5%
(Intercept)	6.974	0.028	6.922	7.032
Biperiden	0.019	0.023	-0.027	0.065
Haloperidol	-0.077	0.023	-0.123	-0.031
Reward	-0.168	0.011	-0.190	-0.145
Delay	0.036	0.008	0.020	0.053
Biperiden x Reward	0.002	0.010	-0.017	0.022
Haloperidol x Reward	0.029	0.009	0.011	0.046
Biperiden x Delay	-0.003	0.008	-0.020	0.013
Haloperidol x Delay	-0.020	0.008	-0.036	-0.003
Reward x Delay	0.005	0.011	-0.017	0.027
Biperiden x Reward x Delay	0.013	0.016	-0.019	0.044
Haloperidol x Reward x Delay	-0.002	0.016	-0.033	0.030

Supplementary Table 8. Fixed effects from robust linear regression model with κ as dependent variable and questionnaire total scores, sex, and age as independent variable for the effort discounting task.

Variables	Parameter Estimates	Standard Error	*z*	*p*
(Intercept)	-0.059	0.051	-1.157	0.252
Sex	0.010	0.016	0.661	0.511
Age	0.007	0.002	2.770	**0.008**
BIS-15	-0.006	0.008	-0.828	0.411
AES	0.006	0.009	0.709	0.481
BDI	-0.006	0.011	-0.584	0.562

Supplementary Table 9. Fixed effects from robust linear regression model with κ as dependent variable and questionnaire total scores, sex, and age as independent variable for the delay discounting task.

Variables	Parameter Estimates	Standard Error	*z*	*p*
(Intercept)	-4.621	1.645	-2.808	**0.007**
Sex	-0.510	0.531	-0.962	0.340
Age	0.011	0.076	0.146	0.885
BIS-15	-0.197	0.282	-0.700	0.487
AES	0.458	0.312	1.471	0.147
BDI	-0.023	0.217	-0.108	0.915

Supplementary Table 10. Fixed effects from robust linear regression model with κ as dependent variable and questionnaire subscales as independent variable for the effort discounting task.

Variables	Parameter Estimates	Standard Error	*z*	*p*
(Intercept)	0.098	0.007	13.088	**< 0.001**
BIS-15 attentional	0.005	0.011	0.497	0.6212
BIS-15 motor	-0.025	0.013	-1.863	0.0678
BIS-15 non-planning	0.010	0.007	1.475	0.1459
AES - Apathy	0.016	0.009	1.781	0.0804
AES - Disinterest	-0.008	0.007	-1.083	0.2835
AES – Social Withdrawal	0.007	0.011	0.579	0.5650

Supplementary Table 11. Fixed effects from robust linear regression model with κ as dependent variable and questionnaire subscales as independent variable for the delay discounting task.

Variables	Parameter Estimates	Standard Error	*z*	*p*
(Intercept)	-4.728	0.228	-20.717	**< 0.001**
BIS-15 attentional	-0.605	0.336	-1.801	0.0771
BIS-15 motor	0.039	0.345	0.114	0.9100
BIS-15 non-planning	0.224	0.286	0.783	0.4372
AES - Apathy	0.311	0.294	1.056	0.2957
AES - Disinterest	0.432	0.262	1.647	0.1054
AES – Social Withdrawal	-0.252	0.232	-1.086	0.2824

Supplementary Table 12. Bayesian Generalized Linear Mixed Models of the Effort Discounting Task – Fatigue Effects; Regressing Choices (High-Cost vs. Low-Cost Option) on Predictors for Drug, Reward (Difference between High-Cost vs. Low-Cost Reward Level), Effort (Difference between High-Cost vs. Low-Cost Effort Level), and their Interaction Terms, as well as Trial Number and two-way Trial number x Drug interactions.

Parameter	Estimate	Est. Error	2.5%	97.5%
(Intercept)	2.602	0.224	2.169	3.056
Biperiden	0.606	0.210	0.206	1.030
Haloperidol	-0.475	0.216	-0.903	-0.045
Reward	3.516	0.256	3.037	4.049
Delay	-1.682	0.122	-1.919	-1.438
Trial Number	-0.605	0.073	-0.747	-0.462
Biperiden x Reward	0.792	0.299	0.218	1.398
Haloperidol x Reward	-0.196	0.272	-0.718	0.348
Biperiden x Delay	0.012	0.157	-0.294	0.328
Haloperidol x Delay	0.024	0.124	-0.221	0.274
Biperiden x Trial Number	0.142	0.107	-0.068	0.350
Haloperidol x Trial Number	-0.431	0.101	-0.632	-0.232
Reward x Delay	0.132	0.186	-0.241	0.490
Biperiden x Reward x Delay	0.117	0.298	-0.480	0.676
Haloperidol x Reward x Delay	-0.262	0.248	-0.740	0.238

Supplementary Table 13. Bayesian Generalized Linear Mixed Models of the Delay Discounting Task – Fatigue Effects; Regressing Choices (High-Cost vs. Low-Cost Option) on Predictors for Drug, Reward (High-Cost Option Reward), Delay (High-Cost Option Delay), and their Interaction Terms, as well as Trial Number and two-way Trial number x Drug interactions.

Parameter	Estimate	Est. Error	2.5%	97.5%
(Intercept)	20.230	2.637	15.137	25.461
Biperiden	-1.318	1.235	-4.043	0.695
Haloperidol	-0.019	1.080	-2.477	1.921
Reward	57.451	7.123	43.829	71.553
Delay	-2.295	0.537	-3.341	-1.240
Trial Number	-0.204	0.064	-0.326	-0.079
Biperiden x Reward	-3.878	3.407	-11.446	1.564
Haloperidol x Reward	-1.219	2.927	-7.948	4.017
Biperiden x Delay	0.792	0.490	-0.106	1.843
Haloperidol x Delay	1.338	0.557	0.243	2.481
Biperiden x Trial Number	0.146	0.088	-0.028	0.320
Haloperidol x Trial Number	-0.003	0.087	-0.173	0.163
Reward x Delay	-2.808	1.409	-5.618	-0.059
Biperiden x Reward x Delay	1.086	1.363	-1.365	4.061
Haloperidol x Reward x Delay	2.369	1.554	-0.687	5.574

Supplementary Table 14. Bayesian Generalized Linear Mixed Models of the Effort Discounting Task – Session Effects; Regressing Choices (High-Cost vs. Low-Cost Option) on Predictors for Drug, Reward (Difference between High-Cost vs. Low-Cost Reward Level), Effort (Difference between High-Cost vs. Low-Cost Effort Level), and their Interaction Terms, as well as Session and two-way Session x Drug interactions.

Parameter	Estimate	Est. Error	2.5%	97.5%
(Intercept)	2.542	0.213	2.133	2.966
Biperiden	0.594	0.199	0.217	1.007
Haloperidol	-0.542	0.193	-0.924	-0.176
Reward	3.411	0.247	2.944	3.916
Delay	-1.648	0.120	-1.883	-1.409
Session	0.488	0.183	0.125	0.852
Biperiden x Reward	0.783	0.288	0.253	1.373
Haloperidol x Reward	-0.284	0.250	-0.776	0.207
Biperiden x Delay	-0.018	0.149	-0.308	0.279
Haloperidol x Delay	0.092	0.121	-0.142	0.326
Biperiden x Session	-0.158	0.305	-0.758	0.445
Haloperidol x Session	-0.426	0.293	-1.018	0.132
Reward x Delay	0.148	0.182	-0.216	0.499
Biperiden x Reward x Delay	0.090	0.290	-0.486	0.642
Haloperidol x Reward x Delay	-0.222	0.237	-0.685	0.241

Supplementary Table 15. Bayesian Generalized Linear Mixed Models of the Delay Discounting Task – Session Effects; Regressing Choices (High-Cost vs. Low-Cost Option) on Predictors for Drug, Reward (High-Cost Option Reward), Delay (High-Cost Option Delay), and their Interaction Terms, as well as Session and two-way Session x Drug interactions.

Parameter	Estimate	Est. Error	2.5%	97.5%
(Intercept)	20.491	2.751	15.007	25.963
Biperiden	-1.355	1.260	-4.100	0.616
Haloperidol	0.024	1.121	-2.543	2.007
Reward	58.132	7.390	43.331	72.868
Delay	-2.286	0.539	-3.353	-1.230
Session	0.400	0.242	-0.062	0.871
Biperiden x Reward	-3.924	3.464	-11.646	1.420
Haloperidol x Reward	-1.081	3.032	-8.141	4.302
Biperiden x Delay	0.787	0.487	-0.087	1.843
Haloperidol x Delay	1.347	0.567	0.219	2.495
Biperiden x Session	-0.064	0.375	-0.807	0.657
Haloperidol x Session	-0.315	0.370	-1.044	0.392
Reward x Delay	1.088	1.349	-1.314	4.003
Biperiden x Reward x Delay	2.430	1.585	-0.660	5.601
Haloperidol x Reward x Delay	-2.809	1.429	-5.678	0.008

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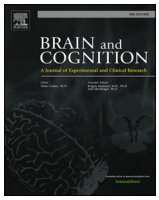

Effort-based decision making and motivational deficits in stroke patients

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ABSTRACT

Motivational deficits in patients recovering from stroke are common and can reduce active participation in rehabilitation and thereby impede functional recovery. We investigated whether stroke patients with clinically reduced drive, initiation, and endurance during functional rehabilitative training (n = 30) display systematic alterations in effort-based decision making compared to age, sex, and severity-matched stroke patients (n = 30) whose drive appeared unaffected. Notably, the two groups did not differ in self-reported ratings of apathy and depression. However, on an effort-based decision-making task, stroke patients with clinically apparent drive impairment showed intact willingness to accept effort for reward, but were more likely to fail to execute the required effort compared to patients without apparent drive impairments. In other words, the decision behavioural assessment revealed that stroke patients that displayed reduced drive, initiation, and endurance during inpatient neurorehabilitation failed to persist in goal-directed effort production, even over very short periods. These findings indicate that reduced drive during rehabilitative therapy in post-stroke patients is not due to a diminished motivation to invest physical effort, but instead is related to a reduced persistence with effortful behaviour.

1. Introduction

Stroke remains a leading cause of death and long-term disability worldwide (Feigin et al., 2022). Recovery of lost physical functions, cognitive abilities, and quality of life after a stroke can be achieved through neurorehabilitative training (Platz, 2019). Such neurorehabilitative therapy is characterized by effortful training of physical and cognitive abilities and requires active, effortful participation and a high level of motivation and perseverance (Studer & Knecht, 2016; Studer et al., 2021; Yoshida et al., 2021). Rehabilitation specialists apply multiple motivational strategies to encourage their patients to perform rehabilitative training actively and persistently (Danzl et al., 2012; Oyake et al., 2020a, 2020b). Yet, despite therapists' best efforts, reductions in motivation, drive, and persistence are well documented in stroke patients (Nicholson et al., 2013; West & Bernhardt, 2012). Potential reasons for some stroke patients failing to fully and enduringly engage in rehabilitative training have been discussed in the extant literature. These reasons include social and environmental factors (Maclean & Pound, 2000), patients' beliefs and attitudes (Morris et al., 2017), dissatisfaction due to boredom or feelings of disempowerment (Luker et al., 2015), as well as neuropsychiatric conditions such as depression and apathy (Gaete & Bogousslavsky, 2008; Mayo et al., 2009).

Since functional recovery after stroke is dose-dependent on the amount of neurorehabilitative training performed (Knecht et al., 2016; Kwakkel et al., 2004; Van Peppen et al., 2004), any reduction in therapy engagement and persistence is likely to reduce patients' outcomes. Yet, quantitative research on the motivational impairments after stroke

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remains sparse, and to the best of our knowledge, no objective measures that allow characterising individual patients' motivational impairments observed during clinical practice have been developed to date.

In the current study, we tested whether stroke patients that demonstrated low drive and persistence during post-acute inpatient neurorehabilitation, as identified by their treating rehabilitation specialists, showed systematic shifts in effort-based decision making assessed with an objective behavioural probe. Effort-based decision making is characterised by a trade-off between a rewarding outcome and the required physical and/or mental effort to obtain this reward (e.g., Chong et al., 2016), and is supported by mesolimbic and nigrostriatal dopamine pathways and medial frontal brain areas, including ventromedial prefrontal cortex and anterior cingulate cortex (see e.g., reviews by Bailey et al., 2016; Le Heron et al., 2019; Lopez-Gamundi et al., 2021; Salamone et al., 2018; Walton & Bouret, 2019).

Since neurorehabilitation requires engaging in effortful training for the prospect of a long-term reward (successful recovery), we reasoned that effort-based decision-making paradigms are well suited for identifying and characterising potential systematic and generalised motivational impairments after stroke that can manifest in reduced drive and endurance during neurorehabilitation. Indeed, previous research in other neurological (Le Heron et al., 2018a; Muhammed et al., 2016) and psychiatric conditions (Saleh et al., 2021a; Treadway et al., 2012) affecting dopaminergic and prefrontal networks have linked diminished motivation and goal-directed behaviour to systematic alterations in effort-based decision making. In stroke patients, some neuropsychological investigations were able to link (the risk of) apathy and depression to basal ganglia and frontal lesions (Carnes-Vendrell et al., 2019; Douven et al., 2017; Hama et al., 2011; Nickel & Thomalla, 2017 but see also Aubignat et al., 2023; Douven et al., 2020), broadly consistent with the idea that diminished motivation in stroke patients might be linked to neuropathological changes in networks supporting effort-based decision making.

We compared, for the first time, stroke patients with and without observed motivational impairments during neurorehabilitative training (matched in age, gender, and stroke severity) on a previously validated effort-based decision-making paradigm (Chong et al., 2016). In this task, patients were repeatedly presented with a monetary offer and a physical effort required to obtain it. Effort and reward magnitudes were parametrically varied from trial to trial, and on each trial, patients decided whether to accept or reject the offer. If they chose to accept a given offer, they next had to perform the physical effort indicated to obtain the reward. The design of the task allows to assess individuals' general willingness to exert physical efforts for rewards, as well as to dissect how much their motivation is affected by effort requirements ("effort sensitivity") versus by the magnitude of rewards ("reward sensitivity") (see also Bonnelle et al., 2015). We hypothesised that stroke patients with diminished drive during rehabilitative training would display a lower effort willingness than control patients, indicating that the motivational problems observed during rehabilitative training in some stroke patients are a manifestation of a situation-unspecific disbalance in the valuation trade-off between effort and reward. We also aimed to identify whether this expected reduced willingness to exert effort for reward in the patients displaying reduced drive and endurance during rehabilitative training was linked to an increased effort sensitivity or decreased reward sensitivity, in order to inform further development of therapeutic strategies during post-stroke rehabilitation.

The patients assessed in the current study were identified by their rehabilitation specialists as showing diminished drive, initiative, and perseverance during rehabilitative training, despite having the physical capacity and abilities to perform at higher levels. They required constant external motivational prompting to initiate and sustain with therapist-guided functional exercises and nurse-assisted self-care activities. These behavioural observations align with the manifestation of reduced goal-directed behaviour in the neuropsychiatric syndrome of apathy (Marin, 1990). Apathy, characterised by diminished goal-directed behaviour, emotion, and cognition (Robert et al., 2009), is prevalent in a third of stroke survivors (van Dalen et al., 2013) and impedes physical and cognitive recovery post stroke (Mikami et al., 2013). Two recent effort-based decision-making studies in Parkinson's disease and cerebral small vessel disease found that patients with apathy demonstrated a reduced willingness to exert effort for rewards, driven by a reduced reward sensitivity (Le Heron et al., 2018a, 2018b). We therefore also administered an apathy self-report questionnaire to our stroke patients and tested whether the differences in effort-based decision making observed between our two clinical groups were explained by apathy. Finally, as depression has also been found to affect effort-based decision-making behaviour (Hartmann et al., 2013; Treadway et al., 2012), and post-stroke depression has been linked to lesions in the neural networks supporting effort-based decision making, specifically basal ganglia and frontal cortex (Douven et al., 2017), we additionally assessed patients' depression status through questionnaire measures.

2. Material and methods

2.1. Patients

The study was conducted at the Mauritius Neurorehabilitation Hospital in Meerbusch, Germany. Two groups of adult German-speaking stroke patients in the sub-acute stage of recovery took part in this study during inpatient neurorehabilitation: 1) patients who showed reduced (or no) drive, initiation, and endurance during rehabilitative training according to their treating rehabilitation specialists (n = 30, 13 women) and 2) patients who did not display any apparent motivational impairments during rehabilitative treatment. Throughout the methods and results section, we refer to group 1 as "drive-impaired stroke patients" (*DI* group) and group 2 as "not drive-impaired stroke patients" (*control* group). Drive is a distinct feature of goal-directed behaviour that refers to both energization and persistence towards a goal over time (Hebb, 1955; Kringelbach & Berridge, 2016; Wise, 1987). These two dimensions appeared to be lacking during rehabilitative treatment in the stroke patients within our target group.

Patients' drive during rehabilitative treatment was repeatedly rated by treating physical and occupational therapists and nurses during standard clinical practice using Likert scales, and were cross-validated through weekly interdisciplinary team discussions. We verified the clinical validity of these observations and ratings through a retrospective analysis of prospectively collected longitudinal data from an independent sample of 586 stroke patients which revealed that therapists' drive ratings in the first week of inpatient rehabilitative treatment predicted their achieved functional recovery five weeks later, independently of the degree of physical impairment (see Supplementary Material for further details of the Methods and Results). This validation analysis thus confirmed that the drive ratings used for classification in the current study were clinically meaningful.

Exclusion criteria for both groups included severe cognitive impairment, aphasia, and isolation due to colonization with multidrug-resistant organisms. Furthermore, we matched DI and control patients for age, gender, and degree of impairment in activities of daily living (i.e., severity) quantified by the Barthel-Index (Lübke et al., 2004; Mahoney & Barthel, 1965). In total, out of the 465 patients that were screened for eligibility, n = 77 fulfilled the inclusion criteria for the DI group (i.e., showed no or little drive during therapy and daily life activities), and n = 388 fulfilled the inclusion criteria for the control group (i.e., were matched to DI individuals for age, gender, and Barthel-Index score). Eventually, 30 patients from each group completed the follow-up (see Supplementary Fig. S1 for a detailed description of the screening and recruitment process). All patients provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty of the Heinrich Heine University of Düsseldorf (protocol no 2017014131).

2.2. Procedure

Patients were tested in a single behavioural testing session. Each session lasted approximately 60 min. The patients completed an effort-based decision-making task and self-report questionnaires assessing symptoms of depression and apathy.

2.3. Effort-based decision-making task

To investigate the willingness to exert effort in return for rewards, patients performed a task which was previously used in healthy volunteers and patients with neurological diseases (Bonnelle et al., 2015; Chong et al., 2018; Le Heron et al., 2018b; Saleh et al., 2021b). At the beginning of each experimental session, each participant's individual maximum voluntary contraction (MVC) was assessed by asking the subjects to grip a handheld dynamometer (Vernier, Orlando, USA) as strongly as possible with their preferred (non-affected) hand. The MVC was calculated by measuring the highest force exerted over three contractions. Then, patients performed a training session to be familiarized with the force required to reach each effort level. On each trial, patients were presented with an image of an apple tree (Fig. 1) that combined information about the obtainable reward (number of apples) and the required physical effort (vertical position of a bar on the trunk of the tree). Patients could either accept or reject the offer and indicated their choice by pressing a "yes" or "no" key of an external computer keyboard.

Accepting an offer resulted in a 5 s window to squeeze a handheld dynamometer to reach the required effort level and maintain the required force for at least 1 s. During this effort production period, a bar that filled the trunk as patients squeezed gave on-line visual force feedback. Successful trials were followed by a feedback phase visualizing the reward earned during the trial. If subjects failed to reach the denoted level or did not maintain the required force continuously for at least 1 s, no apples were gathered. In contrast, rejecting an offer led to a 5 s pause announcing the upcoming trial. To prevent strategic behaviour and temporal discounting effects, all blocks and trials lasted for the same duration, regardless of the previous choice. Importantly, patients had to squeeze after every accepted trial, thus no hypothetical choices were made. Five possible reward levels (2, 4, 8, 12, or 16 apples on the tree), and five possible effort levels (10 %, 27.5 %, 45 %, 62.5 %, or 80 % of the individually determined MVC) were used. Each reward and effort combination (5 x 5 = 25) was sampled a total of four times in a randomized order, adding up to a total of 100 trials split into four blocks consisting of 25 trials each. Patients were instructed to "collect" as many apples as possible by trading off the reward (number of apples) against the cost (the required effort level).

Based on task performance, they received a flexible payment consisting of 0.5 cents for each apple collected. We chose to use real instead of hypothetical payouts due to differences between choices made in hypothetical versus real settings (Camerer & Mobbs, 2017; Galotti, 2007). To reduce fatigue effects, a break of three to five minutes was introduced after each block. These breaks were used to fill out the questionnaires. For each trial, choice (accept/reject), success in performing the required effort (success/fail), decision latency, duration of force, and accomplished force (in Newton), as well as deviations from the effort demand (in Newton and percent), were recorded. To assess participants' subjective effort perception, we asked them to rate the perceived physical demand of each effort level on a 21-point visual rating scale at the end of the experiment, ranging from 0 (*not demanding at all*) to 20 (*extremely demanding*).

2.4. Questionnaires

Patients were administered two depression and apathy questionnaires: the depression subscale of the Hospital Anxiety and Depression Scale (*HADS*) (Petermann, 2011; Zigmond & Snaith, 1983) and the depression subscale of the 21-item version of the Depression Anxiety Stress Scales (*DASS*) (Antony et al., 1998; Lovibond & Lovibond, 1995). Patients were also asked to complete the German versions of the Apathy Evaluation Scale (*AES*) (Lueken et al., 2006; Marin et al., 1991) as well as a German translation of the Apathy Motivation Index (*AMI*) (Ang et al., 2017). These questionnaires have been extensively validated in clinical cohorts in previous research, with good internal consistency, reliability, specificity, and sensitivity results (Ang et al., 2017; Lueken et al., 2006, 2007; Osman et al., 2012). The questionnaires were completed during the breaks between the experimental blocks. Cronbach's alphas for the total scales of AES, AMI, HADS, and DASS were determined $\alpha = 0.87$, $\alpha = 0.71$, $\alpha = 0.67$, and $\alpha = 0.88$ respectively.

2.5. Analyses of behaviour and questionnaires

As a general measure of task performance, we calculated the proportion of accepted (acceptance rate) and successfully completed accepted trials (success rate) and compared them between groups using non-parametric Mann–Whitney *U* test (due to non-Gaussian distribution of the data: Shapiro-Wilk, $p < 0.05$ for acceptance and success rate). To test whether the patient groups differed in terms of how their choices and success were governed by reward and effort levels, we conducted two generalized linear mixed effects models with a logistic link function (to account for the binomial distribution of the data), using the *glmer* function from the *lme4* package in R (*lme4* Version 1.1.26; Bates et al.,

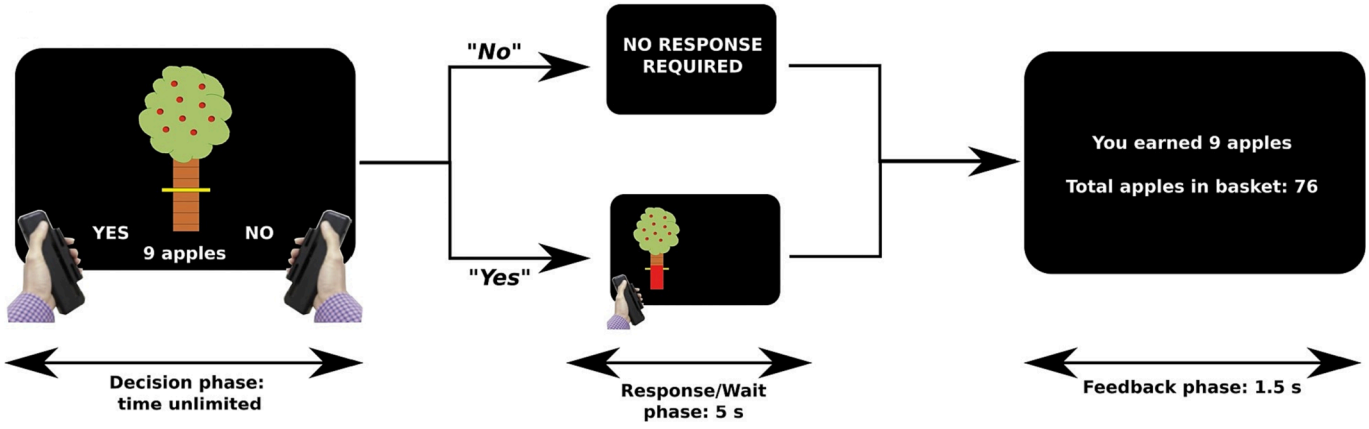

Fig. 1. On each trial, participants were presented with an image of an apple tree that combined information about a monetary reward available (number of apples) in return for physical effort required to exert (vertical position of a bar). Patients could either accept ("Yes") or reject ("No") each offer. After accepting an offer, participants had to perform the required effort (adjusted to the maximum force) and maintain the force for at least 1 s, while rejecting an offer led to a short pause. From Le Heron et al. (2018).

2015). These functions included either choice (accept versus reject) or success in performing the required effort (success versus fail) as a binary outcome variable, and fixed effects of effort level, reward level (both continuous), group (categorical), and their interactions.

Additionally, the models contained a random effects structure of subjects and both task-associated variables (i.e., reward and effort level). Categorical responses were coded as binary values and continuous variables were grand mean-centered. To disentangle the dissociable effects of reward and effort sensitivity, i.e., to which degree the choices were affected by variations in reward and effort levels, respectively, we specifically evaluated the following interaction effects: (i) Effort x Group, (ii) Reward x Group, and (iii) Effort x Reward x Group.

In addition, to test whether variations in effort-based decision making can be explained by differences in apathy or depression severity, we repeated the exact same analysis as above twice, but now, instead of categorizing patients as drive-impaired or non-impaired, we grouped them according to (a) apathy and (b) depression state based on questionnaires. Assignment to the apathetic/non-apathetic or depressed/non-depressed group was performed according to clinical cut-off values. Patients were determined as *apathetic* when either of the two self-rating scores reached the cut-off value (n apathetic = 31 vs. n non-apathetic = 29). The same logic was applied to identify *depressed* individuals (n depressed = 13 vs. n non-depressed = 47). Comparisons of questionnaire results were performed with a two-sample unpaired t-test, or Mann–Whitney U test, depending on the variable type. Questionnaire scores were entered as continuous variables. Bonferroni correction was applied to correct for multiple comparisons. Self-reported ratings of the perceived effort demand were analysed using a mixed-model ANOVA with rating as dependent variable, group as a between-subject variable, and effort level as a within-subject variable.

Finally, in a supplementary analysis, we explored whether behaviour on the effort-based decision-making task, as quantified by acceptance and success rates, was associated with a specific pattern of brain damage using voxel-based lesion-behaviour mapping (VBML; see Supplementary Material for an extended description of the applied methodology).

3. Results

3.1. Patient characteristics and questionnaire results

The two groups were matched on gender, age, type of stroke, and Barthel-Index. Demographics, clinical background variables, and descriptive statistics are presented as means and standard deviations in Table 1. Notably, there were no significant differences between DI and control individuals in apathy scores (as measured on AES and AMI) or depression scores (as measured on DASS and HADS).

3.2. Drive impaired patients differ in effort performance, but not in accept/reject choices

We first compared patients' willingness to engage in effortful trials, indexed by the overall percentage of trials accepted (acceptance rate). This did not reveal any significant differences between DI and control individuals (82.9 % ± 2.97 and 81.4 % ± 3.74 for DI and control patients, respectively, z = -0.517, p = 0.605). Next, we used logistic regression to assess how patients' trial-by-trial choices depended on reward and effort level, and whether this differed between patient groups. This analysis showed a significant effect of reward (b = 0.519, z = 5.121, $p < 0.001$) and effort (b = -5.763, z = -4.029, $p < 0.001$), but neither a significant main or interaction effect of group (Group: b = 0.057, z = 0.882, p = 0.949; Group × Effort: b = 2.649, z = 1.603, p = 0.109; Group x Reward: b = -0.085, z = − 0.648, p = 0.517; Group x Reward x Effort: b = -0.198, z = -0.931, p = 0.352, Fig. 2). This indicates that patients' choices were sensitive to both reward and effort levels, but also that these effects did not differ between groups.

Contrary to our expectations, and unlike findings of previous studies using the same paradigm but in patients with Parkinson's disease and small vessel cerebrovascular disease (Le Heron et al., 2018a, 2018b; Saleh et al., 2021b), a substantial proportion of our sample did not show any effort discounting at all. In other words, they accepted all offers irrespective of effort and/or reward level (10 subjects (33.3 %) in the DI group and 8 subjects (26.6 %) in the control group). A post-hoc chi-square test comparing the number of such individuals did not show any significant group difference (χ^2 = 0.318, p = 0.573). Hence, this behaviour does not appear to be associated with drive state. To ascertain that our pattern of results did not depend on this particular behaviour, we re-ran the same analyses as described above, while excluding individuals that accepted all offers. This analysis yielded the same pattern (no significant differences between groups in terms of choice behaviour, Supplementary Tables S1 and S2).

Next, we repeated the same analyses as above, but now using success (reward attained or not) instead of choice as the dependent variable of interest. On average, patients performed the required force and therefore obtained the reward in 83.9 % of accepted trials. There was a significant group difference, with the DI group achieving the required effort on lower percentage of accepted trials compared to controls (79.8 ± 3.09 and 88.0 % ± 2.43, mean ± SEM for DI and controls, respectively, z = -2.004, p = 0.045). These results show that despite accepting effort-requiring offers as often as control patients, DI patients actually performed the required instrumental effort less consistently. The results of the logistic regression further corroborated these findings. Success rates were related to effort, but not reward level (Reward: b = 0.029, z = 1.259, p = 0.208; Effort: b = -6.442, z = -7.925, $p < 0.001$). Notably, there was no interaction effect of group (Group × Effort: b = -0.172, z = -0.161, p = 0.872; Group x Reward: b = 0.014, z = 0.495, p = 0.620; Group x Effort x Reward: b = -0.143, z = -1.350, p = 0.177), but a main effect of group (b = -0.885, z = -2.095, p = 0.036; Fig. 2). Together, this indicates that reduced success rates in DI subjects are not due to an increased sensitivity for efforts or a decreased sensitivity for rewards; but rather due to a lack of execution of the willingness to engage in effortful activities and short-term perseverance with effortful activities. This lack of effort execution and perseverance is observed across all levels of effort and is not limited to high efforts alone.

Voxel-based lesion-behaviour mapping did not find any statistically significant associations between lesion location and acceptance rate or success rate across both groups.

Table 1
Demographics, clinical background data, and questionnaire scores.

	DI group (n = 30)	Control group (n = 30)	Group comparison χ^2/T	p
Gender (*n, %*)				
Female	13 (46.7)	12 (46.7)	0.07	0.793
Male	17 (53.3)	18 (53.3)		
Age (*M, SEM*)	71.76 (1.54)	74.07 (1.57)	−0.84	0.407
Barthel-Index (*M, SEM*)	50.17 (1.26)	59.50 (1.38)	−1.59	0.117
Age (*M, SEM*)	71.76 (1.54)	74.07 (1.57)	−0.84	0.407
Days since stroke (*M, SEM*)	40.57 (4.44)	41.56 (3.56)	0.18	0.861
Diagnosis (*n, %*)				
Ischemic stroke	28 (93.33)	26 (86.67)	0.74	0.389
Hemorrhagic stroke	2 (6.67)	4 (13.33)		
Questionnaires (*M, SEM*)				
DASS-21	5.17 (0.36)	4.03 (0.32)	0.96	0.339
HADS-D	7.10 (0.46)	4.97 (0.39)	2.34	0.061
AES	14.50 (0.65)	12.90 (0.62)	0.74	0.461
AMI				
Total Score	24.55 (0.89)	23.40 (0.88)	0.526	0.601
Behavioural	5.38 (0.39)	5.57 (0.39)	−0.20	0.839
Social	11.10 (0.59)	10.73 (0.59)	0.30	0.766
Emotional	8.07 (0.51)	7.10 (0.47)	1.08	0.281

Note. DASS-21 = depression subscale of the Depression Anxiety Stress Scales (clinical cut-off ≥ 10), HADS-D = depression subscale of the Hospital Anxiety and Depression Scale (clinical cut-off ≥ 8), AES = Apathy Evaluation Scale (clinical cut-off ≥ 18), AMI = Apathy Motivation Index.

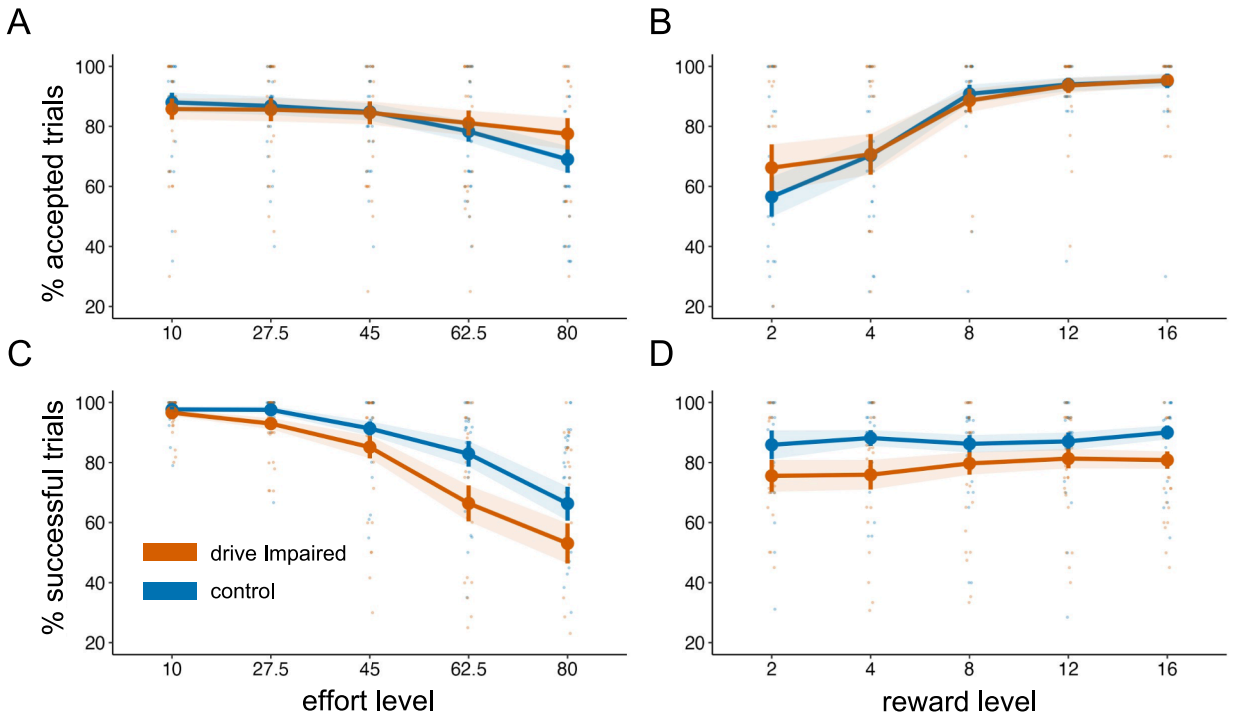

Fig. 2. Averaged acceptance and success rates are plotted as functions of effort (A, C) and reward (B, D). Acceptance rates decrease as a function of effort (A) and increase as a function of reward (B), with no significant group difference. However, after accepting an offer, DI individuals fail significantly more often, compared to their unaffected counterparts (C, D). Effort levels are presented as proportions of the individually calibrated MVC. Bold (light) dots represent the group (single-subject) mean, error bars and shaded areas represent standard error of the mean.

3.3. DI individuals appear to lack perseverance, not strength

The finding that DI patients are more likely than controls to fail to perform the required instrumental effort may be caused by two factors. To successfully complete a trial after accepting an offer, patients have to pass two binary criteria: First, they must exceed the required effort (produced force; e.g., 80 % of MVC). Second, they have to maintain this force for at least 1 s (persistence). We therefore applied the same logistic regression model as above, with *produced force* and *persistence* as binary dependent variables. Fig. 3 illustrates the proportion of participants who successfully achieved either of the two criteria across varying levels of effort. There were no significant effects of group on produced force (Group: $b = -0.416$, $z = -0.822$, $p = 0.411$; Group x Reward: $b = 0.031$, $z = 0.830$, $p = 0.406$; Group x Effort: $b = -1.303$, $z = -0.825$, $p = 0.409$; Group x Effort x Reward: $b = -0.167$, $z = -1.162$, $p = 0.245$). In contrast, however, we found a significant main effect of group on persistence ($b = -0.937$, $z = -2.250$, $p = 0.025$), without any significant interactions (Group x Reward: $b = -0.013$, $z = -0.069$, $p = 0.945$; Group x Effort: $b = 0.151$, $z = 0.689$, $p = 0.491$; Group x Effort x Reward: $b = -0.035$, $z = -0.208$, $p = 0.835$). Notably, both variables were modulated by effort

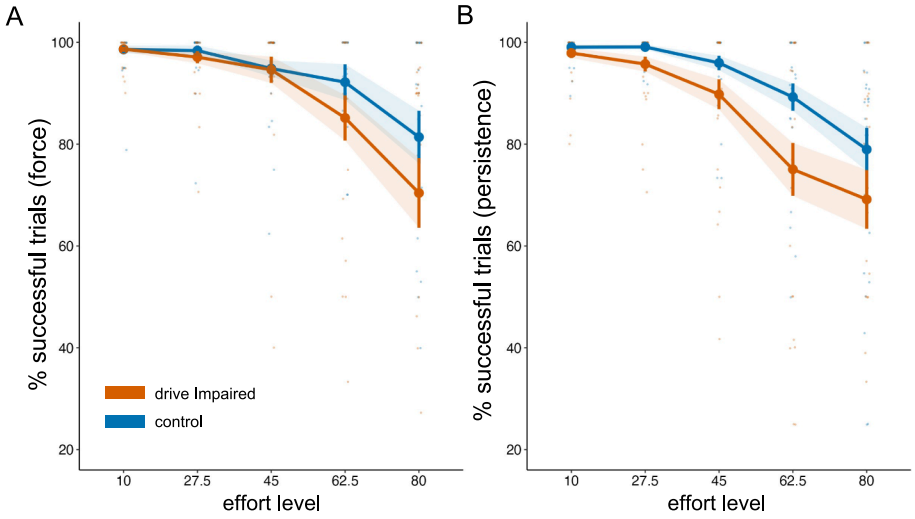

Fig. 3. Patient's performance in the physical effort task, illustrated by the averaged proportion of participants who met each criterion. (A) Across groups, individuals did not differ in their ability to achieve the necessary effort threshold. (B) However, we found a significant group difference in the capability to maintain the force over the target level for at least one second. Effort levels are presented as proportions of the individually calibrated MVC. Bold (light) dots represent the group (single-subject) mean, error bars and shaded areas represent standard error of the mean.

(Effort [produced force]: b = -4.673, z = -4.119, $p < 0.001$; Effort [persistence]: b = -1.510, z = -9.063, $p < 0.001$), but not by reward (Reward [produced force]: $b = 0.010$, $z = 0.388$, $p = 0.698$; Reward [persistence]: $b = 0.259$, $z = 1.677$, $p = 0.094$). Together, these results indicate that both groups did not differ in their ability to reach the required force demand. Instead, after reaching the force level, DI patients failed to hold and maintain the effort production more often than control patients, indicating a lack of short-time perseverance with effort. This lack of perseverance in force production occurred across all effort levels.

This finding raises questions about their understanding of the task requirements, specifically the need to sustain the effort for more than 1 s. To address this concern, an additional analysis was conducted, including block and the interaction between block and group as predictors. A Group x Block interaction would indicate that the two groups differed in their initial understanding of the task and potentially showed different patterns of performing the task over time (i.e., learning to maintain effort production for a certain duration). However, the interaction effect did not reach statistical significance (Group x Block: $b = 0.023$, $z = 0.190$, $p = 0.850$), suggesting that the groups did not differ in their understanding of the task requirements or in their learning patterns throughout the task. More detailed information on this analysis, along with supplementary analyses of task performance, are presented in the supplementary material (Supplementary Table S3 and Supplementary Figure S2 and S3). Notably, voxel-based lesion-behaviour mapping did not reveal statistically significant associations between lesion location and perseveration across both groups.

Finally, we asked patients to rate their subjective perception of effort. While both groups reported increased subjective perception with increasing effort levels, this did not differ between groups (Supplementary Figure S4).

3.4. Effects of depression and apathy on behavioural responses

While we did not find any significant effects of the depression state on behavioural responses, differences in the apathy state (i.e., an apathy score in the clinical range) were associated with changes in terms of choice behaviour. Our analyses revealed a significant two-way interaction between reward and apathy state upon accept/reject choices (b = -0.340, z = -2.750, p = 0.006), that was primarily driven by apathic patients accepting more offers with low rewards than non-apathic patients. These findings indicate altered processing of reward magnitude on decisions about engaging or not in effortful actions. In other words, patients that were less motivated according to self-reported apathy questionnaires displayed a reduced sensitivity to changing rewards (Fig. 4). There were no differences in performance between either depressed vs. non-depressed or apathetic vs. non-apathetic patients. A full table of these analyses and the corresponding results is presented in the Supplementary Material (Supplementary Table S4 – S7).

4. Discussion

Functional recovery after stroke requires motivation to engage in physically demanding rehabilitative training. Unfortunately, reductions in motivation and drive during rehabilitative training are not uncommon post stroke, with mechanisms underlying reduced persistence in effortful training still being elusive. Gaining a deeper understanding of deficits is crucial for enhancing functional rehabilitation strategies and optimizing outcomes for stroke patients.

Therefore, we aimed to investigate decision-making mechanisms underlying effort-based choices in stroke patients, comparing those with and without reduced drive, initiation, and endurance during rehabilitation training, according to their treating rehabilitation specialists. To this end, we used a behavioural probe of effort-based decision making outside of the direct therapy context. We found that stroke patients that demonstrated low drive and persistence during rehabilitative training did not differ from control patients in terms of their willingness to accept or reject an effortful offer. Instead, after choosing to engage in an effort-requiring option, those patients were more likely to fail the physical effort demand – not because of an inability to achieve their target, but because of a lack of persistence in effort production.

Taken together, stroke patients with apparent drive impairments during rehabilitative therapy were just as willing as patients without motivational impairments to commit to effort production for a certain

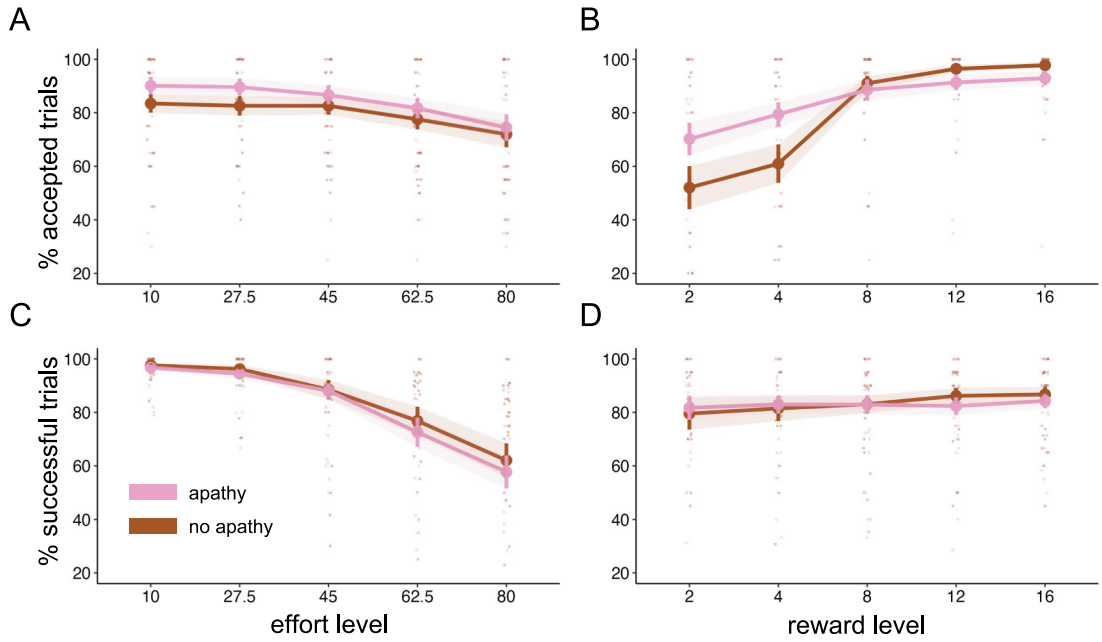

Fig. 4. Averaged acceptance and success rates as functions of effort (A, C) and reward (B, D) for apathetic and non-apathetic patients. Success rates (C, D) did not differ between the two groups, whereas choice rates in the apathy group reveal a reduced sensitivity to changing reward levels. Effort levels are presented as proportions of the individually calibrated MVC. Bold (light) dots represent the group (single-subject) mean, error bars and shaded areas represent standard error of the mean.

reward during the choice phase. However, after choosing an effort-requiring prospective reward, they did not maintain the required effort challenge to actually reap the reward during the action phase, suggesting a discrepancy between expectation and performance. Consequently, motivation and goal-directed decision making can be conceptualized as behaviour that does not solely involve the decision about engaging in a physical act or not, but also the performance resulting from the decision. Indeed, motivation is defined as a force or energy that activates, directs, and sustains a given behaviour (Hebb, 1955; Kleinginna & Kleinginna, 1981; Studer & Knecht, 2016). In line with that, a recent neurocognitive framework of cost-benefit decision making defines three different phases of goal-directed motivation: (a) choosing whether to act or not, (b) persisting with the chosen behaviour, and (c) learning about the outcome (Le Heron et al., 2018c).

Intriguingly, our results suggest that these different dimensions of goal-directed motivation and behaviour can be affected selectively. Functional neuroimaging studies in healthy individuals indicate that all three phases are supported by the ventral striatum and the anterior cingulate cortex, and deficits in goal-directed behaviour observed across different brain disorders appear to be linked to disruptions of functional networks involving these two core regions (Le Heron et al., 2018c). In our stroke sample, voxel-based lesion-behaviour mapping did not reveal a specific localised neural correlate for the failure to execute effort-based choices, as operationalised in the success rate. This null finding may suggest that the behaviour is driven by a functional network rather than a single localised area that can be detected using VBLM (see e.g., Karnath et al., 2018). Alternatively, it could be due to the lesion overlap in our sample size being on the lower end of the threshold required to obtain reliable statistical results (Lorca-Puls et al., 2018). Future research may aim to elucidate the neurocomputational mechanisms underlying the observed selective change in effort execution.

Drive-impaired stroke patients appear to be affected uniquely in the persisting phase of effortful behaviour, even on the very short time scale of the trials of our paradigm. Such a reduced ability to maintain physical effort, even after choosing to produce this effort, could be a possible explanation for clinical observations of reduced drive, initiation, and endurance during functional rehabilitative therapy and training of activities of daily living. As perseverance in training programs is a crucial part of successful rehabilitation after stroke, a reduced ability to maintain goal-directed effort could ultimately limit patients' functional recovery and – in the long term – the quality of life (Danzl et al., 2012; Paolucci et al., 2012). Moreover, patients showing this type of behaviour may be falsely diagnosed as being depressed, since impaired drive and reduced persistence in completing tasks or activities are common symptoms of depression (Tay et al., 2021). We found no systematic differences in self-reported depression symptoms between our two patient groups.

In contrast to our hypothesis, patients who were identified by their rehabilitation specialists as showing diminished drive, initiative, and perseverance did not differ from unaffected control patients in terms of self-reported ratings of apathy. These results suggest a potential distinction between behavioural patterns that are captured by questionnaires versus those perceived by clinical professionals, and indicate that self-report apathy questionnaires might be unsuitable to identify all individuals that are at risk of reduced participation and persistence with rehabilitative training. It is plausible that the deficits observed in those patients, which primarily manifest during the persistence phase of goal-directed behaviour, may not be fully captured by the self-report questionnaires and their sub-scales used in our study. These questionnaires primarily assess global apathy levels and may not detect specific deficits in maintaining certain effortful behaviours over time. Additionally, as the questionnaires rely on self-reporting, there is a possibility of a lack of insight into one's own motivational impairments. Patients with impaired drive might exhibit reduced awareness or insight into their own deficits, leading to potential underestimation of their condition when relying solely on self-reported measures. Future research may test if deficits in persisting with a certain behaviour may be a latent dimension of apathy that prevails independently and requires new questionnaires and instruments to be captured.

Self-reported apathy ratings were also not associated with any systematic changes in effort persistence on our task in our samples. However, apathy scores (measured with the AES and AMI) were linked to a reduced reward sensitivity when deciding about acting or not, such that patients with higher levels of apathy showed a reduced sensitivity for changing reward levels and a higher propensity to accept low reward options compared to non-apathetic patients. This result contrasts with previous work who found an apathy-related *decrease* in acceptance of low reward offer in Parkinson's and cerebral small vessel disease (Le Heron et al., 2018a, 2018b; Saleh et al., 2021b). Given that this is the first study in stroke patients, further research will be needed to determine if our result is coincidental or reflects a true, potentially disease-driven difference.

Some limitations of the current study should be noted. First, as mentioned above, a considerable number of patients in both groups did not show any effort discounting at all. These patients accepted each offer that was presented, regardless of reward or effort level. Interestingly, the same behavioural pattern was also reported in a recent study investigating effort discounting in healthy controls and people with schizophrenia and major depressive disorder (Cathomas et al., 2021). In that study, a lack of effort discounting was present in both clinical groups, but not in control participants. Like the current study, these clinical groups were tested during in-patient treatment. Thus, one conceivable explanation is that the lack of effort discounting was driven by a social desirability effect driven by the treatment environment. Our patients may have unconsciously considered the experiment as a part of their treatment, given that it took part during and in direct relationship to their rehabilitation program. Therefore, the tendency to accept all presented offers could be seen as a result of a behavioural approach that aims to meet hypothetical requirements of participation and commitment. As we did not directly measure impulsive behaviour in our sample, it also remains possible that this choice pattern is based on alterations in impulse control and/or response inhibition. This potential link warrants further exploration in future studies. Another limitation of our study is related to the definition of *drive-impaired* stroke patients, as it is not a validated construct but rather based on subjective evaluations provided by clinicians. However, it is worth noting that these observations are robust due to the extensive experience, interdisciplinary exchange, and expertise of the clinical staff who made them. By regularly monitoring and evaluating patients' behaviour, clinical staff can provide a comprehensive and nuanced understanding of their deficits. Moreover, our independent validation study confirmed that these ratings had clinical validity by demonstrating that they predicted the functional recovery achieved by patients through rehabilitative training. Further, our task design included money, a secondary and extrinsic reward, as an incentive. Hence, the generalizability of the results to intrinsic benefits (such as positive feelings experienced through successful participation) may be limited. Finally, a supplementary voxel-based lesion-behaviour mapping on the structural brain scans acquired as part of clinical routine did not reveal the neural substrates of impaired drive after stroke. In samples similar to ours, functional neuroimaging during an effort-based decision-making task may provide more insights into the precise neurocomputational underpinnings.

To our knowledge, this is the first study to characterize behavioural mechanisms that underlie perceived disruptions in drive, initiation, and persistence during rehabilitative training among stroke patients. Through use of value-based and effort-based decision-making paradigms, doctors and therapists may be able to reveal, classify, and quantify different domains of motivation that cannot be captured by self-report questionnaires, diagnostic manuals, and judgments alone, and develop new and individualised motivational approaches to be employed by neurorehabilitative specialists. Revealing the processes and phases that underlie aberrant goal-directed behaviour could

therefore serve as a novel and promising new approach to eventually customize individual therapies for rehabilitation patients.

5. Conclusions

Stroke patients that show reduced drive, initiation, and endurance during neurorehabilitative therapy do not differ from control patients in terms of committing to effortful behaviour. Instead, they are characterized by deficits in maintaining the physical effort force for the required time, even after accepting to perform that action. Notably, this altered behavioural dimension of goal-directed activity was not captured by apathy questionnaires, but clinical observation only. These findings underscore the clinical significance of assessing and addressing persistence deficits in stroke patients, as they may provide valuable insights for optimizing neurorehabilitative therapies and enhancing functional recovery.

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CRediT authorship contribution statement

Mani Erfanian Abdoust: Formal analysis, Investigation, Visualization, Writing – original draft. **Stefan Knecht:** Conceptualization, Methodology, Project administration, Writing – review & editing. **Masud Husain:** Resources, Writing – review & editing. **Campbell Le Heron:** Resources, Writing – review & editing. **Gerhard Jocham:** Investigation, Writing – review & editing. **Bettina Studer:** Data curation, Funding acquisition, Project administration, Software, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bandc.2023.106123.

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Supplementary material

for

“Effort-based decision making and motivational deficits in stroke patients”

1. Assessments of patients' drive during rehabilitative training

Patients' drive, initiation and endurance during rehabilitative training, including self-care training, were observed continuously by the treating clinicians, and rated weekly by two different professional groups: physical/occupational therapists and nurses. Two separate rating scales were developed to account for the different interactions and situations of each professional group with the patients.

Physical/occupational therapists rated patients' drive, initiation and active participation in rehabilitative training on the following six-level scale, ranging from 0 to 5 (original in German):
0 – the patient does not respond to encouragement, shows no interest in therapy, and is difficult to motivate
1 – the patient sometimes responds to encouragement, begins exercising after encouragement, but does not finish short exercises
2 – the patient waits for encouragement, needs frequent external motivational stimulation and finishes exercises only when supported continuously
3 – the patient sometimes waits for encouragement, performs some exercises without continuous support
4 – the patient initiates and executes exercises independently, is interested in new things, but sometimes fails to perform agreed self-directed training
5 – the patient demands shaping of his exercise program to his developing skills, stays motivated throughout therapy sessions, performs self-directed training consistently and reliably

Nurses evaluated patients' drive and participation during activities of daily living and self-care training, using a 3-level Likert scale, with options ranging from 0 ("patient usually shows no drive and does not actively participate in self-care"), to 1 ("patient usually shows little drive of their own"), to 2 ("patient actively participates in activities of daily living.").

Patients were assigned to the DI group when they scored 2 or lower on the 6-level Likert scale used by physical and occupational therapists and/or when they scored 1 or lower on the nurse-assessed 3-level Likert scale. Patients were recruited for the control group when their scores were higher than the cut-off levels on both rating scales.

2. Validation of the drive assessments: Impaired drive predicts weaker rehabilitation outcome

To confirm the clinical validity of the drive assessment, a retrospective analysis of prospectively collected anonymised data from a large set of other stroke patients (n = 518) undergoing inpatient rehabilitation at the same hospital as our main sample was conducted, in collaboration with Gregor Maier and Heidrun Pickenbrock. The dataset was collected as part of a large project on predictors of recovery in stroke, which was approved by the independent Ethics Committee of the Medical Faculty of the Heinrich Heine University Düsseldorf (registration ID: 2018034633) and for which written consent was collected from each patient or, in case of inability to consent, from their representative. The dataset included data on the proportional recovery of gait (n=400), transfers (n=361) and stairs climbing (n=394) abilities achieved over five weeks of inpatient specialized high-intensive rehabilitation following acute stroke care. This treatment is thus administered in the subacute phase, with the precise time of onset post stroke varying between patients as a function of individual acute care needs. Gait, transfer, and stair-climbing abilities were assessed for each patient at the beginning and within week 6 of their inpatient treatment using the "Scores of Independence for Neurologic

and Geriatric Rehabilitation (SINGER)" (Gerdes et al., 2012). Proportional recovery was then calculated as the archived percentage of the maximum possible recovery (Veerbeek et al., 2018). Patients' drive, initiation, and endurance during rehabilitative training at the start of the treatment were assessed using the 6-level Likert scale explained above.

Multiple linear regressions were used to test whether proportional recovery in patients' gait, transfer, and stair-climbing abilities achieved over five weeks of inpatient rehabilitative treatment were systematically predicted by their drive ratings at treatment onset. The models also included the following predictors: i) initial level of gait/transfers/stairs climbing abilities, ii) overall level of impairment at treatment onset [indicated in the German rehabilitation system by the "phase of rehabilitation" (B,C,D)].

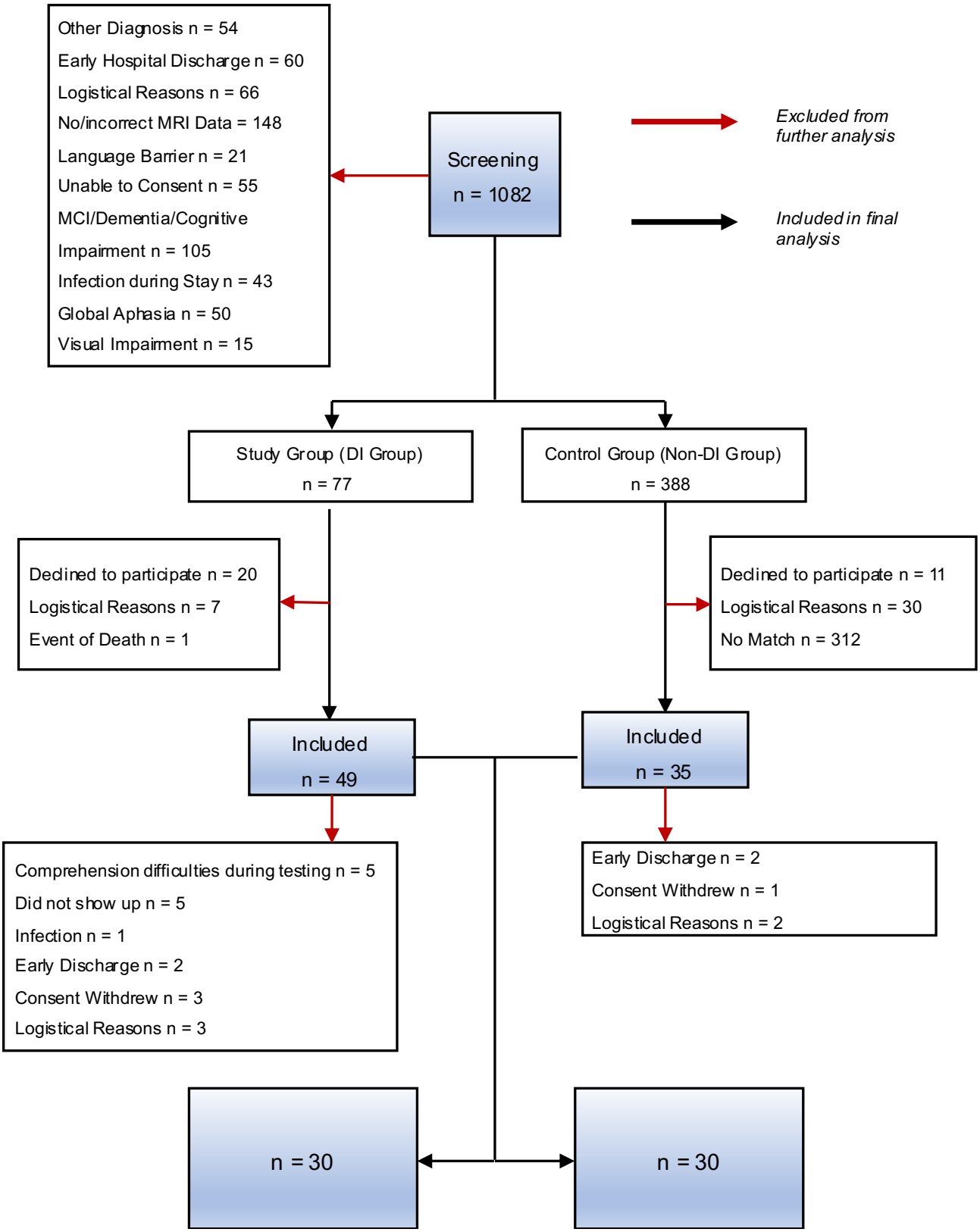
Patients' drive ratings at the start of the treatment significantly predicted proportional recovery achieved after five weeks of inpatient treatment in all three assessed physical abilities (gait: $b = 0.09$, $t(394) = 2.01$, $p = 0.046$; transfers: $b = 0.14$, $t(355) = 2.61$, $p = 0.009$; stairs climbing: $b = 0.19$, $t(388) = 3.76$, $p < 0.001$). In the case of proportional recovery of gait, a significant interaction between initial drive and initial gait abilities was furthermore found ($b = -0.19$, $t(394) = -3.47$, $p < 0.001$), with higher drive having a stronger positive impact in the more impaired patients. For all three assessed physical abilities, initial functional level had a positive effect (gait: $b = 0.32$, $p < 0.001$; transfers: $b = 0.27$, $p < 0.001$; stairs climbing: $b = 0.27$, $p = 0.005$) and overall degree of impairment had a negative effect on achieved functional recovery.

In summary, this large dataset analysis in an independent sample to the one recruited for our main study confirmed that patients' drive, initiation, and endurance during rehabilitative training, assessed by their treating clinicians, predicted the subsequently achieved rehabilitation outcome.

3. Voxel-based lesion-behaviour mapping

To test whether behavioral patterns in effort-based decision-making were associated with specific brain lesions, MRI images (T1, T2, and flair sequences) taken as part of clinical routine during acute care treatment or during subacute neurorehabilitation were extracted from electronic patient records. Lesion tracing was conducted with MRIcron (Rorden & Brett, 2000), and normalization of structural images and lesion masks were normalized with the Clinical Toolbox (Rorden et al., 2012) in SPM 12. A voxel-based whole-brain lesion-behavior mapping analysis was performed with NiiStat (https://github.com/neurolabusc/NiiStat), implemented in MATLAB 2018b.

A general linear model (pooled-variance t-test, linear regression) tested whether the acceptance rate, the success rate, and the proportion of trials with successful maintenance of force for at least 1 second on our effort-based decision-making task (were related to localized brain damage. Only voxels that were damaged in at least 6 subjects (~10% of patients across both groups) were included in each analysis. The alpha level was set to 0.025 and a Bonferroni correction was applied. Anatomical regions with significant lesion-behavior associations were labeled by using the Automated Anatomical Labeling (AAL) atlas. Due to missing/damaged data for one participant of the control and three patients of the DI group, the sample size for this analysis was 56.



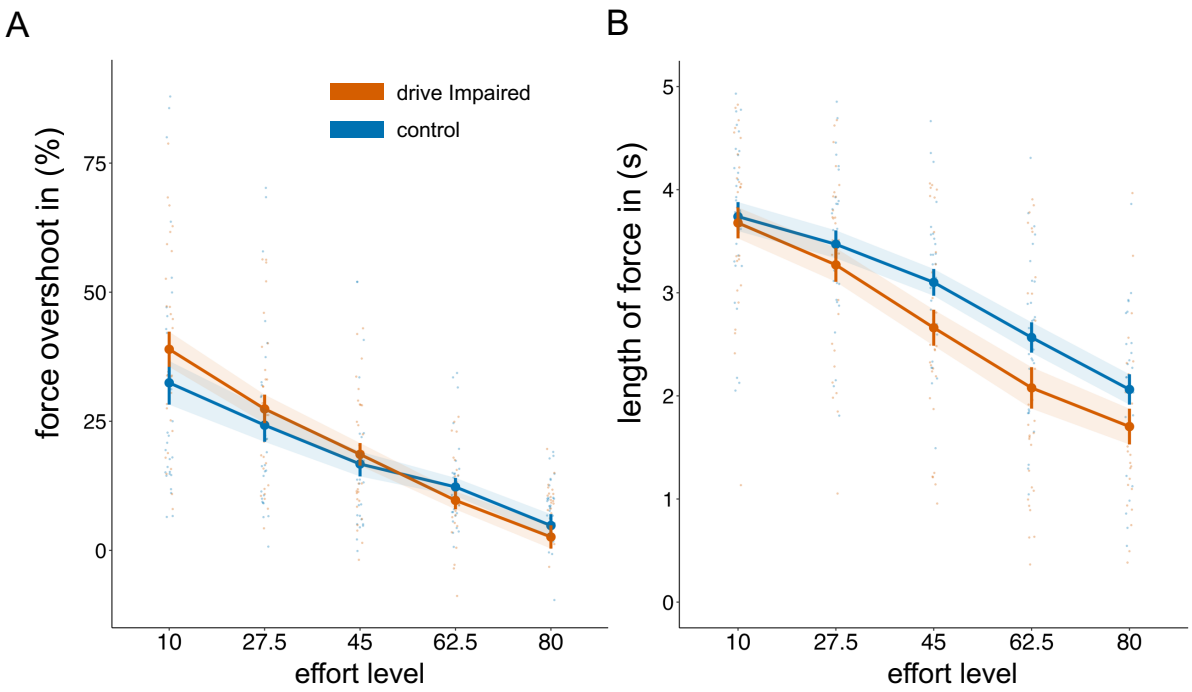
Supplementary Fig. S1. Flow-chart of screening and recruitment process. The classification of participants as drive impaired/not impaired was determined through repeated observations made by two professional groups: physical and occupational therapists during rehabilitative training, and nurses during activities of daily living. These observations were further cross-validated through weekly interdisciplinary team discussions.

Supplementary Table S1. Mixed effects from logistic regression model after excluding participants that accepted all offers; 'choice' as dependent variable.

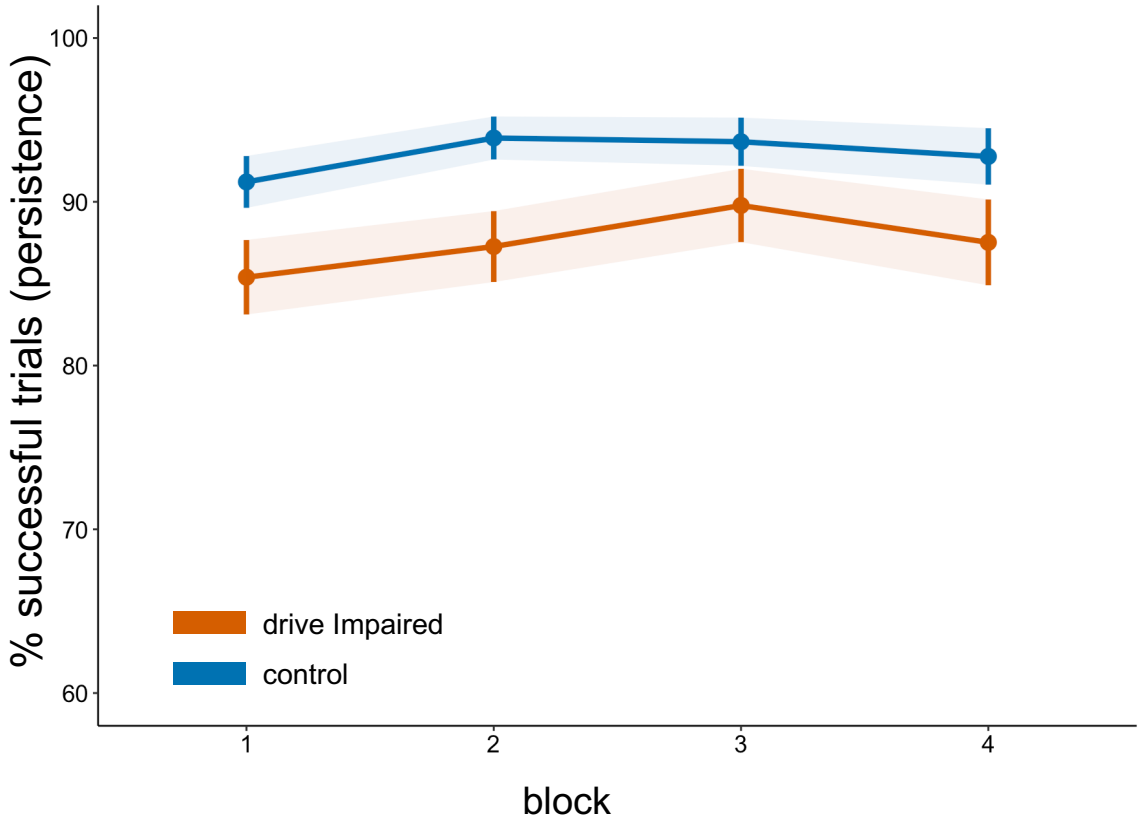
Variables	***Parameter Estimates***	***Standard Error***	***z***	***p***
(Intercept)	3.38	0.45	7.46	**> 0.001**
Reward	0.61	0.10	6.04	**> 0.001**
Effort	-6.10	1.25	-4.88	**> 0.001**
Group	-0.48	0.62	-0.76	0.445
Reward x Effort	-0.29	0.17	-1.74	0.082
Reward x Group	-0.07	0.14	-0.52	0.600
Effort x Group	2.74	1.66	1.65	0.099
Reward x Effort x Group	-0.20	0.20	-0.97	0.334

Supplementary Table S2. Mixed effects from logistic regression model after excluding participants that accepted all offers; 'success' as dependent variable

Variables	***Parameter Estimates***	***Standard Error***	***z***	***p***
(Intercept)	3.47	0.40	8.59	**> 0.001**
Reward	0.07	0.03	2.59	**0.009**
Effort	-6.70	1.04	-6.45	**> 0.001**
Group	-1.20	0.54	-2.22	**0.027**
Reward x Effort	0.16	0.11	1.48	0.139
Reward x Group	-0.02	0.03	-0.67	0.501
Effort x Group	0.62	1.30	0.48	0.635
Reward x Effort x Group	-0.19	0.14	-1.36	0.175



Supplementary Fig. S2. Illustration of the *force overshoot* (A), indicating the extent of effort produced beyond the required level in percent , and *length of force* (B), indicating the duration where force exceeded the required effort level in seconds, as a function of effort. On average, DI patients exceeded the required effort level by 19.5% (± 1.94), while controls surpassed the effort level by 18.1% (± 2.41). In contrast, DI patients maintained the necessary force for an average duration of 2.70 seconds (± 0.14), whereas controls sustained force for an average of 3.00 seconds (± 0.12). To further test the homogeneity of variance, we used Levene's test on participant-wise averages in force overshoot and length of force. This test showed no significant difference between both groups for both measures (force overshoot: $F(1,58) = 0.058$, $p = 0.811$, length of force: $F(1,58) = 1.830$, $p = 0.181$), implying that force variability did not vary across both groups.



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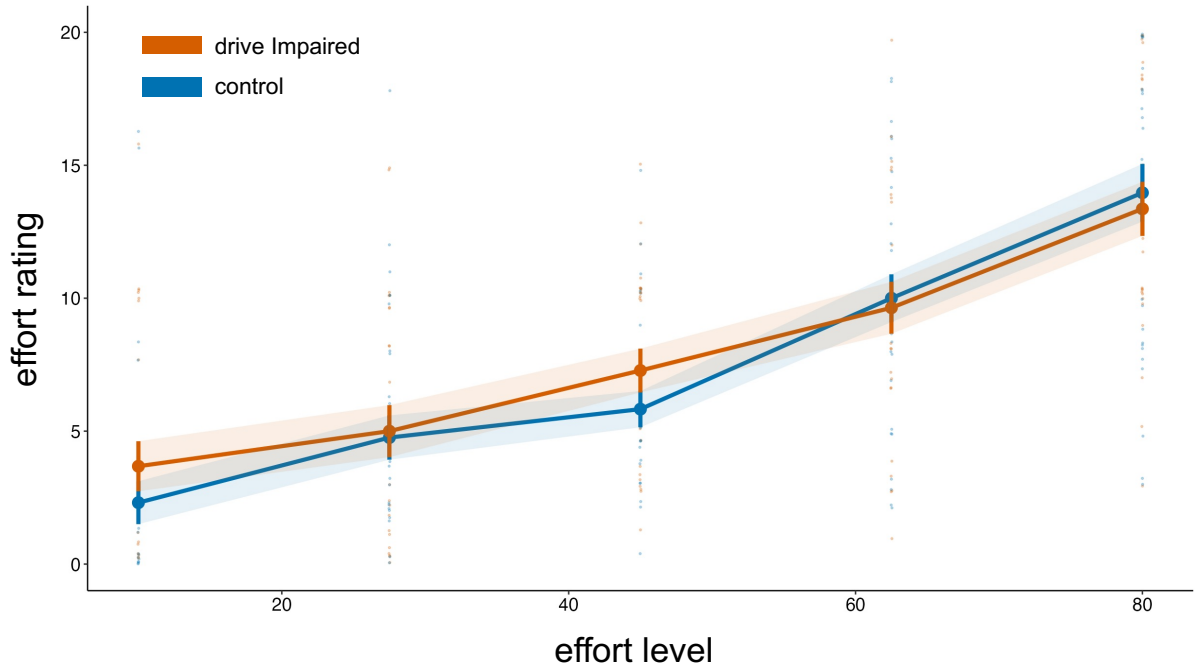
148 **Supplementary Fig. S3.** Patient's performance in the physical effort task, illustrated by the
149 averaged proportion of participants who met each criterion per block. We investigated whether
150 patients learned the task requirements differently, reflected in their ability to achieve the effort
151 requirement with an increasing number of blocks. Across groups, individuals did not differ in
152 their learning patterns throughout the task.
153

154

Supplementary Table S3. Mixed effects from logistic regression model with 'persistence' as dependent variable and 'block' included as independent variable.

Variables	***Parameter Estimates***	***Standard Error***	***z***	***p***
(Intercept)	3.82	0.30	12.49	**> 0.001**
Reward	0.25	0.15	1.65	0.099
Effort	-1.50	0.17	-9.07	**> 0.001**
Group	-0.89	0.41	-2.15	**0.032**
Block	0.17	0.09	1.97	**0.049**
Reward x Effort	-0.09	0.13	-0.72	0.474
Reward x Group	-0.02	0.19	-0.11	0.912
Effort x Group	0.13	0.22	0.61	0.544
Group x Block	0.02	0.12	0.19	0.850
Reward x Effort x Apathy	-0.03	0.17	-0.16	0.876



Supplementary Fig. S4. Post-task effort ratings. To investigate patients' subjective perception of increasing effort levels, we asked them to rate each of the five effort levels on a 21-point rating scale at the end of each experiment. An ordinal regression analysis was conducted with effort rating as dependent variable. The results revealed that there was no significant difference in perceived physical effort between the DI subjects and non-impaired controls (Group: $b = 0.163$, $z = 0.752$, $p = 0.452$; Group x Effort: $b = -0.013$, $z = 0.009$, $p = 0.150$). As expected, increasing effort levels were associated with a greater level of perceived demand (Effort: $b = 0.065$, $z = -9.071$, $p < 0.001$). These findings indicate that although both groups perceived increasing effort levels as more demanding, they did not differ in their subjective evaluation of the effort requirements. Effort levels are presented as proportions of the individually calibrated MVC. Bold (light) dots represent the group (single-subject) mean, error bars and shaded areas represent standard error of the mean.

Supplementary Table S4. Mixed effects from logistic regression model with 'choice' as dependent variable and 'apathy' as independent variable.

Variables	***Parameter Estimates***	***Standard Error***	***z***	***p***
(Intercept)	4.94	0.68	7.24	**> 0.001**
Reward	0.65	0.10	6.64	**> 0.001**
Effort	-4.57	1.49	-3.07	**0.002**
Apathy	-0.10	0.89	-0.13	0.910
Reward x Effort	-0.54	0.21	-2.57	**0.010**
Reward x Apathy	-0.34	0.12	-2.75	**0.006**
Effort x Apathy	0.18	1.70	0.11	0.913
Reward x Effort x Apathy	0.40	0.22	1.83	0.067

Supplementary Table S5. Mixed effects from logistic regression model with 'success' as dependent variable and 'apathy' as independent variable.

Variables	***Parameter Estimates***	***Standard Error***	***z***	***p***
(Intercept)	2.81	0.32	8.71	**> 0.001**
Reward	0.05	0.02	2.40	**0.017**
Effort	-6.79	0.80	-8.44	**> 0.001**
Apathy	-0.16	0.44	-0.37	0.710
Reward x Effort	-0.05	0.08	-0.57	0.568
Reward x Apathy	-0.03	0.03	-1.24	0.216
Effort x Apathy	0.56	1.07	0.52	0.601
Reward x Effort x Apathy	0.03	0.11	0.32	0.752

Supplementary Table S6. Mixed effects from logistic regression model with 'choice' as dependent variable and 'depression' as independent variable.

Variables	*Parameter Estimates*	*Standard Error*	*z*	*p*
(Intercept)	4.74	0.57	8.33	**> 0.001**
Reward	0.53	0.09	6.26	**> 0.001**
Effort	-5.40	1.28	-4.22	**> 0.001**
Depression	0.95	1.10	0.86	0.388
Reward x Effort	-0.37	0.19	-1.94	0.052
Reward x Depression	-0.24	0.16	-1.53	0.126
Effort x Depression	3.01	2.03	1.48	0.138
Reward x Effort x Depression	0.10	0.26	0.37	0.711

Supplementary Table S7. Mixed effects from logistic regression model with 'success' as dependent variable and 'depression' as independent variable.

Variables	*Parameter Estimates*	*Standard Error*	*z*	*p*
(Intercept)	2.82	0.26	10.93	**> 0.001**
Reward	0.03	0.01	1.76	0.078
Effort	-6.52	0.66	-9.90	**> 0.001**
Depression	-0.26	0.53	-0.48	0.630
Reward x Effort	0.01	0.06	0.08	0.938
Reward x Depression	0.06	0.03	2.05	**0.041**
Effort x Depression	-0.48	1.30	-0.37	0.710
Reward x Effort x Depression	-0.21	0.12	-1.75	0.078

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