



HAL
open science

Atomoxetine and Reward size equally improve task engagement and perceptual decisions but differently affect movement execution

Kristin Kaduk, Tiphaine Henry, Jerome Guitton, Martine Meunier, David Thura, Fadila Hadj-Bouziane

► **To cite this version:**

Kristin Kaduk, Tiphaine Henry, Jerome Guitton, Martine Meunier, David Thura, et al.. Atomoxetine and Reward size equally improve task engagement and perceptual decisions but differently affect movement execution. *Neuropharmacology*, 2023, 241, pp.109736. 10.1016/j.neuropharm.2023.109736 . hal-04286752

HAL Id: hal-04286752

<https://cnrs.hal.science/hal-04286752v1>

Submitted on 15 Nov 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Atomoxetine and Reward size equally improve task engagement and perceptual decisions but differently affect movement execution

Running title: Impact of ATX and reward size on decision and action

Kristin Kaduk^{1,2,4}, Tiphaine Henry^{1,2}, Jerome Guitton³, Martine Meunier^{1,2},
David Thura^{1,2}, Fadila Hadj-Bouziane^{1,2}

¹ University UCBL Lyon 1, F-69000, France

² INSERM, U1028, CNRS UMR5292, Lyon Neuroscience Research Center,
ImpAct Team, Lyon, F-69000, France;

³ Biochemistry and Pharmacology-Toxicology Laboratory, Lyon-Sud Hospital, Hospices
Civils de Lyon, F-69495 Pierre Bénite, France

⁴ Decision and Awareness Group, Cognitive Neuroscience Laboratory, German Primate
Center, Leibniz Institute for Primate Research, Kellnerweg 4, Goettingen, 37077,
Germany

Corresponding authors: Kristin Kaduk, kkaduk@dpz.eu and Fadila Hadj-Bouziane,
fadila.hadj-bouziane@inserm.fr

Highlights:

- ATX and reward size improve task engagement and perceptual decision
- ATX (but not reward size) increases movement duration
- Reward size energizes both decision and action
- ATX might guide the allocation of energetical resources during goal-directed actions

Keywords: noradrenaline, reward, monkey, perceptual decision-making, effort

Author contributions

FHB was responsible for the study concept and design. TH, MM & KK collected data under FHB's supervision. KK processed the data and performed the data analysis. JG processed and performed the analyses of the blood samples. KK & FHB wrote the manuscript, and DT and MM provided critical comments on interpreting the results. All authors provided feedback on the manuscript and approved the final version for publication.

Acknowledgments: We thank Gislène Gardechaux, Frédéric Volland, Roméo Saleme, Eric Koun for technical and engineering assistance and Igor Kagan for his support. This work was funded by the French National Research Agency (ANR) ANR-14-CE13-0005-1 grant.

Conflict of Interest: The authors declare no competing financial interests.

Abstract

Our ability to engage and perform daily activities relies on balancing the associated benefits and costs. Rewards, as benefits, act as powerful motivators that help us stay focused for longer durations. The noradrenergic (NA) system is thought to play a significant role in optimizing our performance. Yet, the interplay between reward and the NA system in shaping performance remains unclear, particularly when actions are driven by external incentives (reward). To explore this interaction, we tested four female rhesus monkeys performing a sustained Go/NoGo task under two reward sizes (low/high) and three pharmacological conditions (saline and two doses of atomoxetine, a NA reuptake inhibitor: ATX-0.5 mg/kg and ATX-1 mg/kg).

We found that increasing either reward or NA levels equally enhanced the animal's engagement in the task compared to low reward saline; the animals also responded faster and more consistently under these circumstances. Notably, we identified differences between reward size and ATX. When combined with ATX, high reward further reduced the occurrence of false alarms (i.e., incorrect go trials on distractors), implying that it helped further suppress impulsive reactions. In addition, ATX (but not reward size) consistently increased movement duration dose-dependently, while high reward did not affect movement duration but decreased its variability. We conclude that noradrenaline and reward modulate performance, but their effects are not identical, suggesting underlying differential mechanisms. The high reward might energize/invigorate decisions and action, while ATX might help regulate energy expenditure, depending on the context, through the NA system.

Introduction

Most of us have experienced situations where we know exactly what to do and how to do it, but we lack the motivation to engage or stay focused on the task. Yet, with a little help, one can improve. For instance, the perspective of earning a reward increases our engagement in a task for a prolonged period of time (Esterman et al., 2014; Massar et al., 2016). It also leads to more efficient behavior. In the sensorimotor domain, for instance, studies show that reward simultaneously increases the velocity and the precision of motor control and can reduce reaction times and error rates in decisions involving cognitive control (Manohar et al., 2015; Opris et al., 2011; Revol et al., 2019; Salamone et al., 2018; Takikawa et al., 2002). Considerable evidence points toward the role of the neuromodulator, dopamine (DA), in mediating reward-induced effects on both decision-making and motor control (Bourgeois et al., 2016; Coddington & Dudman, 2019; da Silva et al., 2018; Lee et al., 2012; Niv et al., 2006, 2007; Salamone et al., 2018).

An increasing number of studies suggest that another neuromodulator, noradrenaline (NA), is also significantly modulated by expected reward (Jahn et al., 2020; Varazzani et al., 2015) and participates in the optimization of performance (Aston-Jones & Cohen, 2005; Robbins & Arnsten, 2009). NA facilitates behavioral response by improving the signal-to-noise ratio within sensory cortices (Berridge & Waterhouse, 2003; Foote et al., 1980; Mizuyama et al., 2016). Recent theories suggest that NA affects task engagement by mobilizing energetical resources (Bouret & Richmond, 2015; Raizada, 2008; Varazzani et al., 2015). For instance, pharmacologically increasing NA-availability in the brain improves perceptual decision-making abilities (Gelbard-Sagiv et al., 2018; Guedj et al., 2019) while reducing its availability decreased the production of physical effort to overcome challenges in upcoming choices (Borderies et al., 2020; Jahn et al., 2018).

Although recent studies have advanced our understanding of the convergence and interaction of the dopamine and noradrenaline signaling pathways (overview in (Ranjbar-Slamloo & Fazlali, 2020)), as well as their impact on attention and reward processing (see review, (Zhang et al., 2023)) and on memory linking (Chowdhury et al., 2022), the complex influence of NA on performance, mainly when behavior depends on external incentives (reward) remains unclear. More precisely, pressing questions remain about how NA, relative to reward, shapes behavior and whether they interact to influence task engagement, perceptual decision-making abilities, and movement execution.

To close this gap, we assessed the interaction between noradrenaline and reward by investigating the effect of atomoxetine (ATX) administration, an NA reuptake inhibitor, in four monkeys performing a sustained Go/NoGo discrimination task with varying rewards (low and high). Guedj et al. (2019) found that ATX helped monkeys optimize their response strategy in a Go/NoGo task by fine-tuning perceptual and decisional processes and reducing reaction time variability. We sought to determine if increasing the reward level similarly impacts animals' performance. We also examined the animals' engagement in the task under both reward and ATX conditions by measuring the number of completed trials and breaks. Additionally, we probed the impact of ATX and high reward on decision and movement durations. We predicted that high reward and ATX would each improve task engagement, perceptual decision-making abilities, and movement execution. We also anticipated that animals maintained on a controlled food regimen might perform better under higher reward compared to ATX and that combining high reward and ATX would further improve behavior, considering the strong interaction between DA and NA in goal-directed behavior (Jahn et al., 2020; Varazzani et al., 2015).

Method

Subjects

Four adult female monkeys participated in the study (macaca mulatta; monkey 1, 5.5 kg, 16 years old; monkey 2, 5.8 kg, 12 years old; monkey 3, 8.4 kg, 9 years old; monkey 4, 6.3 kg, 9 years old). The animals had free access to water. They were maintained on a food regulation schedule with primate food supplemented by fruits and vegetables, individually tailored to maintain a stable level of performance. Prior to the current experiment, positive reinforcement training was used to accustom monkeys to intramuscular injections and blood samplings from the saphenous vein.

This study was conducted in strict accordance with Directive 2010/63/UE. The project was authorized by the French Ministry for Higher Education and Research (project no. 20-12-0401-005) after evaluation by the French Committee on the Ethics of Experiments in Animals (C2EA) CELYNE registered at the national level as C2EA number 42.

Behavioral Task

Monkeys were seated in a primate chair, facing a 19-inch high-resolution touch screen (distance: 18 cm). The whole experiment, i.e., the presentation of the stimuli, reward delivery (apple sauce), and behavioral data acquisition, was implemented in Presentation® software (<https://www.neurobs.com/>).

The task was a Go/NoGo Continuous Performance Task (Decamp et al., 2011) designed to assess the ability to discriminate a target among nine different distractors (**Figure 1A**), following the criteria of the (Rosvold et al., 1956) paradigm (for a review see, page 10: “the task had to involve the presentation of constantly changing stimuli with some clearly defined “target” stimulus or pattern that occurred at a low frequency relative to the number of stimuli presented over the duration of the task”). The stimuli consisted of ten white

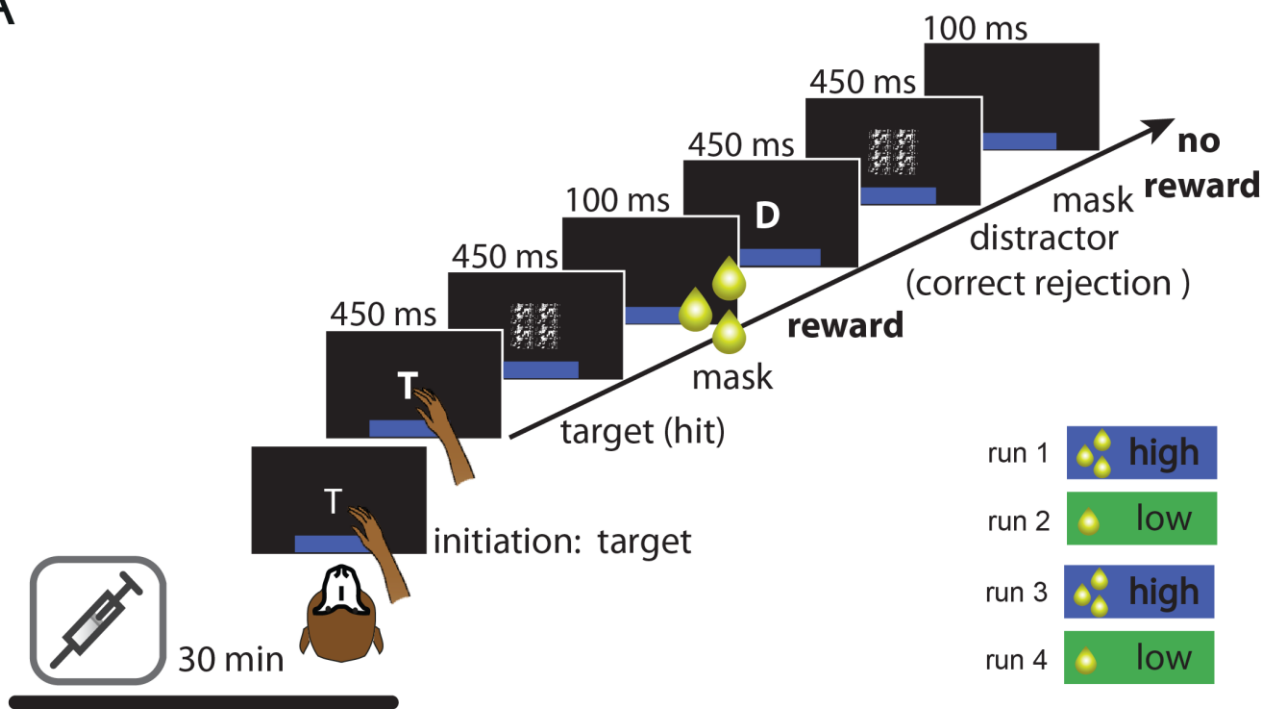
Latin letters (size: 3.2°, except for monkey 4: the size was 6.4°) on a black background. The letters were sequentially presented on the center of the screen at a 1Hz frequency. Each letter appeared for 450 ms followed by a mask and an inter-trial interval for 450 ms and 100 ms, respectively.

A daily session lasted 60 min and was divided into four runs of equal duration (15 min). The reward level (low or high) for a correct response varied across runs and was signaled by a green or blue bar (for low and high reward, respectively) on the bottom of the screen throughout the run. The low and high reward levels corresponded to 50 ms and 150 ms valve opening duration, respectively, such that the reward amount was three times higher in the high compared to the low reward condition. All the sessions included the same fixed sequence of 4 runs, alternating high and low reward levels and always starting with a high reward level. Given that the duration of each run was fixed and set to a limit of 15 min, we could measure the animals' task engagement by computing the number of trials they completed and its counterpart, i.e., breaks in seconds.

In each run, monkeys initiated the task by putting their right hand on a lever, affixed to the chair. The first letter that appeared on the screen corresponded to the target letter for the upcoming run. The monkey had to touch the target letter to start the run. Then, during 15 min, ten different letters were sequentially presented pseudo-randomly. The target letter appeared in 30% of the cases and when it was present, monkeys were required to release the lever and reach to the target on the touch screen within an imparted time of 900 ms (correct Go response). By contrast, when a distractor appeared on the screen, the animals had to refrain from responding, i.e., to keep the hand on the lever (correct NoGo response). The animals received a reward for correct Go responses while correct NoGo responses were not rewarded. Every incorrect response – either Go or NoGo - was followed by a penalty time of 3500 ms (monkey 4: 3000 ms) and no reward delivery.

For each run, a different target letter was selected among 10 possible letters (i.e., the target letter in one run would become a distractor in the following run). The letters randomly assigned to the four runs were the same over five consecutive sessions. This schema was repeated in the following weeks to equate the difficulty level across pharmacological conditions (see below). Before the testing sessions, the animals were familiarized with the task, the session's structure, and the limited time they would be exposed to the different runs (high and low levels of reward) under the different pharmacological conditions. The pharmacological testing started after a difference in performance between the high and low reward levels emerged.

A



B



Figure 1. A) Experimental design: Go/NoGo Continuous Performance Task. The monkey initiated the task by touching a lever that triggered the appearance of the target letter on the screen. The animals were then sequentially presented with letters that could either be the target or distractors (frequency: 1Hz). The letter was presented for 450 ms, followed by a 450 ms mask to eliminate after-image effects and an inter-trial interval combined with reward delivery (100 ms). Monkeys needed to discriminate the target among the nine distractors. When a target was presented, the monkey was required to touch the screen to receive a reward (correct Go response). When a distractor was presented, the monkey was required to keep its hand on the lever (correct NoGo response) and no reward was provided. A 3000-3500 ms time followed each error (incorrect Go- and NoGo-responses). On each testing day, the animals performed 4 runs, each lasting 15 minutes, alternating between high and low levels of reward, signaled respectively by a blue or green bar at the bottom of the screen. **B) Drug administration schedule.** The animals were tested under three pharmacological conditions over three separate weeks and 5 consecutive days per week. Specifically, in the first week, each monkey was tested for five consecutive days after intramuscular saline (control) injections, the second week, after ATX injections at the dose of 0.5 mg/kg, the third week, after ATX injections at the dose of 1.0 mg/kg in the third week. The intramuscular injections were performed 30 min before starting the task and the same dose was administered every day over one week.

Drug administration

The pharmacological testing followed the schema represented in **Figure 1B**. The animals were tested under three pharmacological conditions in separate weeks: saline solution (control, 0.5 ml) and two doses of atomoxetine, a noradrenaline reuptake inhibitor (ATX, Tocris Bioscience, Ellisville, MO) at two doses: 0.5 and 1 mg/kg diluted into saline solution (total volume injected: 0.3 - 2 ml). Every injection was administered intramuscularly 30 min prior to testing. The same dose was administered every day over five consecutive days. For each animal, we collected data from 5 sessions of saline (control condition), 5 sessions of ATX at 0.5 mg/kg, 5 sessions of ATX at 1 mg/kg.

Quantification of atomoxetine in blood samples

We measured ATX concentration in the blood plasma (**Table 1**) at the end of behavioral testing, approximately 100 min after the intramuscular injections. Blood samples were withdrawn from the saphenous vein (min. 0.5 ml – max. 1.3 ml) and centrifuged.

Liquid chromatography was performed on an Accucore RP-MS (ThermoFisher) column 2.6 μm (100 mm x 2.1 mm i.d.) maintained at 30°C. For atomoxetine, the elution was achieved isocratically with a mobile phase containing water and formic acid 0.1% for 30 % and acetonitrile and formic acid 0.1% for 70% at a flow rate of 300 $\mu\text{L}/\text{min}$ (retention time: 2.4 min). The used Detector was a high-resolution mass spectrometer (HRMS) (Q-Exactive Plus, ThermoFisher, San Jose, USA) equipped with an electrospray (ESI) source. Data were acquired with target SIM mode with a resolution set at 70 000 and in positive ion mode. The $[\text{M}+\text{H}]^+$ ion for atomoxetine and D5-atomoxetine (used as internal standard) were detected at m/z 256.16959 and m/z 261.20061, respectively. The sample preparation was for atomoxetine: a volume of 50 μL of a solution containing 200 ng/mL of D5-atomoxetine was added to 50 μL of plasma samples. After protein precipitation by 300 μL of cold acetonitrile for both compounds, the sample was mixed and centrifuged for 5 min at 13 000 g. The supernatant was removed and evaporated to dryness at 37°C under a stream of nitrogen. The residues were re-suspended in 200 μL in the mobile phase and 10 μL were injected. The methods were validated in plasma and were linear and sensitive in the 10 to 600 ng/mL range for atomoxetine.

Table 1. ATX concentration (in ng/ml) directly after behavioral testing (approximately 100 min after intramuscular injections).

Monkey	Daily injection of ATX 0.5mg/kg					Daily injection of ATX 1 mg/kg					Saline injections	
	Day1	Day2	Day3	Day4	Day5	Day1	Day2	Day3	Day4	Day5	Day1	Day2
M1	201	---	193	216	241	431	368	---	541	483	< 5	< 5

M2	25	114	225	201	---	504	---	473	489	380	< 5	< 5
M3	123	243	219	171	---	369	---	376	496	389	< 5	< 5
M4	---	---	---	233	293	---	---	---	549	320	< 5	< 5

ATX concentration (in ng/ml) measured from blood samples withdrawn from the animal's saphenous vein after behavioral testing (approximately 100 min after intramuscular injections). The data are presented for each monkey during the second and third weeks of testing under ATX (0.5 and 1 mg/kg). The data confirm that ATX concentration was detectable in the animals' blood after intramuscular administration of ATX and that this concentration depended on the administered dose (higher after 1 mg/kg compared to 0.5 mg/kg). After two consecutive weeks of testing under ATX, no significant trace of ATX in the animals' blood was found during the saline (control) condition (last column on the right).

Data analysis

Data were analyzed using the R software (version 3.2.4, R Core Team, 2016). Across the four animals, we analyzed 20 sessions of saline (control condition) which we compared to 20 sessions of ATX 0.5 mg/kg and 20 sessions of ATX 1 mg/kg. Each dependent variable described below was computed across runs for the high *versus* low reward for each session (saline or ATX) and each monkey separately.

We first assessed the engagement of the animals in the task under different conditions (low and high rewards under saline or ATX). As dependent variables, for each run, we measured the total number of completed trials and the time monkeys spent taking breaks, expressed in seconds per run. Importantly, each run lasted a maximum of 15 min once the animal initiated the task. During the imparted time, a completed trial corresponded to either a correct or incorrect touch on the screen (Go responses) or a correct or incorrect press on the lever (NoGo responses). Breaks denoted a lack of response (Go or NoGo responses) to either a target or a distractor stimulus, demonstrating that the animal was not engaged in the task, such that the animal did not press the lever to perform the task.

Second, we analyzed the animals' perceptual decision-making abilities for each condition (low and high reward in saline and ATX conditions). We measured accuracy (the percentage of correct Go and NoGo responses from all completed trials), the percentage of misses (incorrect Go responses/ all completed target trials) and false alarms (incorrect

NoGo responses/ all completed distractor trials). Using the signal detection theory, we then examined how well the animals discriminated target stimuli from distractors (Stanislaw & Todorov, 1999). We computed a perceptual sensitivity index (d' or d' , Eq. (1)), the sensitivity to discriminate the target stimulus among distractors, and the response bias (c , Eq. (2)), the extent to which one response is more probable than another. The averaged response bias for each subject was classified into the following categories with one sample t-tests comparing to zero: (1) positive values denoted a bias toward NoGo responses, (2) no significant difference denoted no directional bias or a neutral bias, (3) negative values denoted a bias toward Go responses. In addition, we investigated the functional relationship between d' and response bias that can be mathematically described as the “Line of optimal response” (LOR) (Lynn et al., 2015; Lynn & Barrett, 2014). The LOR is based on a model estimation considering the response bias in relation to a given d' to maximize utility or reward rate depending on the context (i.e., $c_{optimal}$, Eq.3; more details in Guedj et al., 2019). As such, the Line of optimal response” considers the target frequency (α) and j and h as payoff values and a and m as penalties for each outcome. Specifically, the target frequency was 30% in our task design, only hits (correct Go response) were rewarded, and a time out followed any incorrect response. In that context, the following parameters were set to compute the LOR depending on the context: hits had a payoff value of 150 in high rewarded runs and 50 in low rewarded runs; correct rejection (correct NoGo response) had 0; false alarm (incorrect Go responses) had a penalty outcome value of -10; and a miss (incorrect NoGo response) in high rewarded runs of -150 and a miss in low rewarded runs of -50. The d' and the response bias (c) were computed as follow:

$$d' = z(\text{Hit rate}) - z(\text{False alarm rate}) \quad (1)$$

$$c = -0.5 * (z(\text{Hit rate}) + z(\text{False alarm rate})) \quad (2)$$

The optimal bias was defined as follow:

$$c_{optimal} = \frac{\log\left(\left(\frac{1-\alpha}{\alpha}\right) * \frac{j-a}{h-m}\right)}{d'} \quad (3)$$

where α represents the target frequency and j and h are the payoff value for hits and for correct rejection and a and m , as penalties for either a miss or false alarm.

Finally, we computed for correct and incorrect Go-trials, the average and standard deviation of decision duration (time from stimulus onset to lever release) and movement duration (time from releasing the level until the touch of the monitor).

Statistical analysis

To analyze the effect of ATX and reward size on each dependent variable, we used *Linear Mixed Models* (lme4 package for R) to account for the hierarchical structure of our data (observations nested within sessions and individual monkeys). Mixed-effect models are specifically designed to handle such dependencies by including random effects, which allow the intercept and/or slopes to vary across sessions or monkeys (e.g. Baayen et al., 2008).

To test our hypothesis as to whether the combination of reward and ATX would further influence the dependent variables, we performed comparisons between models testing for two types of interactions between reward and pharmacological conditions: additive *versus* multiplicative. The multiplicative model (10 parameters) included three fixed effects; ATX, reward and their interaction, the random intercepts for (1) monkey, (2) sessions, and (3) sessions that are nested in subjects, the intercept, the residual error, and degree of freedom for the error term. The additive model (8 parameters) was identical, except it did not include the interaction term for reward and ATX. The equations of the additive and multiplicative models were as follows:

- Additive Model: Dependent variable = $\beta_0 + \beta_1 * ATX + \beta_2 * Reward + b_1(Monkey) + b_2(Session) + b_3(Monkey.Session) + \epsilon$

- Multiplicative Model: Dependent variable = $\beta_0 + \beta_1 * ATX + \beta_2 * Reward + \beta_3 * ATX * Reward + b_1(Monkey) + b_2(Session) + b_3(Monkey.Session) + \epsilon$

in which β_0 is the intercept, β_1 and β_2 are the fixed effect coefficients for ATX and Reward, respectively, and $b_1(Monkey)$, $b_2(Session)$, and $b_3(Monkey.Session)$ are the random effects for the intercepts for Monkey, Session and their interaction, respectively. The multiplicative model has an additional fixed effect, β_3 , representing the interaction between ATX and Reward. The last two parameters are the residual error and degrees of freedom for the error term.

As both models are theoretically plausible, we evaluated the residuals of both models. The one with significantly lower deviance, as assessed by a chi-squared test, was selected as the best model explaining the data.

The result of this model comparisons shows that the multiplicative model with reward (high, low) and pharmacological condition (saline, ATX 0.5, ATX 1) is significantly better compared to the model with additive terms for the following dependent variables: number of trials, breaks, accuracy, d' , response bias (c), Euclidean distance to the LOR, percentage of misses, decision duration, the standard deviation of decision duration (see different indices for model fits and the chi-square test results in **Table 2**). No difference was found between the two models for movement duration mean and standard deviation and percentage of false alarms (see different indices for model fits and the chi-square test results in **Table 2**).

To analyze how ATX interacted with reward size, we computed posthoc tests with false discovery rate corrections for multiple comparisons (emmeans package for R). FDR-adjusted P values were set to the pre-specified significance level $\alpha=0.05$.

Table 2. Comparison of the model with additive and multiplicative term

	Variable	Type of model	Number of parameters	AIC	BIC	LogLik	deviance	Chi-square statistic (X ²)	df	p-value
Task engagement	Number of trials	additive	8	1677	1699	-831	1661			
		multiplicative	10	1654	1682	-817	1634	27.32	2	<.001
	Breaks	additive	8	1689	1711	-836	1673			
		multiplicative	10	1669	1697	-825	1649	23.74	2	<.001
Perceptual decision-making	Accuracy	additive	8	799	821	-391	783			
		multiplicative	10	782	810	-381	762	20.69	2	<.001
	Percentage of Misses	additive	8	994	1016	-489	978			
		multiplicative	10	976	1004	-478	956	21.7	2	<.001
	Percentage of False Alarms	additive	8	764	786	-374	748	5.09	2	.079
		multiplicative	10	763	790	-371	743			
	Perceptual sensitivity	additive	8	264	287	-124	248			
		multiplicative	10	249	277	-114	229	19.51	2	<.001
	response bias	additive	8	64	86	-24	48			
		multiplicative	10	49	77	-14	29	19.32	2	<.001
Euclidean distance to LOR	additive	8	279	301	-131	263				
	multiplicative	10	264	292	-122	244	18.85	2	<.001	
Response execution	Decision duration	additive	8	1035	1058	-510	1019			
		multiplicative	10	1032	1060	-506	1012	7.22	2	.027
	Movement duration	additive	8	1002	1024	-493	986			
		multiplicative	10	1004	1032	-492	984	1.77	2	.414
	Standard deviation of decision duration	additive	8	1160	1183	-572	1144			
		multiplicative	10	1150	1178	-565	1130	14.51	2	.001
Standard deviation of movement duration	additive	8	823	845	-403	807				
	multiplicative	10	826	854	-403	806	1.19	2	.553	

Note. Results from the comparison between the model with the multiplicative terms (ATX * reward, including 10 parameters) and additive terms (ATX + reward, including 8 parameters) for all dependent variables. Here, several indices are stated for the model fit: The Akaike information criterion (AIC, lower AIC provides better model fit to the data using the fewest possible independent variables), the Bayesian information criterion (BIC, lower BIC provides better model fit to the data also considering the number of observations), the log-likelihood (higher log-likelihood provides better model fit to the data) and deviance (lower deviance provides better model fit to the data) for each model. The chi-square test (X², the difference in degree of freedom between the models, df and p-value) states which model has significantly lower deviance (in bold).

Results

We analyzed the behavior of four rhesus monkeys performing a Go/NoGo task where we manipulated the size of reward (low/high) and the level of noradrenaline using atomoxetine (ATX) injection. The animals were tested in three subsequent weeks following a fixed sequence: saline, ATX 0.5mg/kg, and ATX 1mg/kg. We assessed the effect of reward size and its interaction with ATX on different cognitive and motor processes: 1) task engagement or motivation (with the number of completed trials and breaks), perceptual decisions over time, and response execution (decision duration, movement duration and trial-by-trial variability in decision and movement durations throughout runs). All the related statistical analyses are provided in **Tables 3** and **4** for these two comparisons, respectively (for more detailed results of the multiplicative model, see Supplementary Information, **Table S1**).

Reward size strongly affects task engagement and perceptual decision processes.

The animals were tested under two reward size conditions following saline injection during the first week. First, the animals were significantly more engaged in the task in high compared to low reward conditions (**Figure 2**). They completed significantly more trials (about twice as much) in high *versus* low reward saline (LRW_{saline}_vs_HRW_{saline}: $\beta = 595$, $t(57) = 8.83$, $p_{FDR} < .001$) and made significantly fewer breaks (i.e., the time during which they did not press the lever to engage in the task, LRW_{saline}_vs_HRW_{saline}: $\beta = -524$, $t(57) = -7.13$, $p_{FDR} < .001$). Second, the animals were significantly more accurate in performing the task under high *versus* low reward (**Figure 2**, LRW_{saline}_vs_HRW_{saline}: $\beta = 12.6$, $t(57) = 7.76$, $p_{FDR} < .001$). Both types of errors, misses (of rewarded targets) and false alarms (on distractors), were significantly reduced under high relative to low reward saline (all P values $p < .05$, details in **Table 3**). To further characterize the impact of reward size on perceptual decision-

making processes, we analyzed the data in the framework of the signal detection theory and computed the perceptual sensitivity to detect a target among distractors (d') and response bias (c). Compared to low reward saline, high reward significantly improved d' (LRW_{saline_vs_HRWsaline}: $\beta = 1.4$, $t(57) = 7.7$, $p_{FDR} < .001$) and reduced the response bias (LRW_{saline_vs_HRWsaline}: $\beta = -0.3$, $t(57) = -4.9$, $p_{FDR} < .001$). We then evaluated the distance of the animals' performance to the "Line of optimal response" (LOR, see methods for details), representing the functional relationship between d' and response bias (Figure 2). We found that high reward significantly reduced the distance to the LOR relative to low reward saline (LRW_{saline_vs_HRWsaline}: $\beta = 0.9$, $t(57) = -6.4$, $p_{FDR} < .001$). Finally, under high reward, the animals' decision duration was significantly reduced and less variable relative to low reward saline (Figure 2, all P values < 0.01 , details in **Table 3**). The mean duration of movements was not affected by reward size but was less variable under high compared to low reward saline (LRW_{saline_vs_HRWsaline}: $\beta = -5.4$, $t(57) = -2.98$, $p_{FDR} < .031$).

Together, these results demonstrate the strong effect of reward size on the animals' motivation to engage in the task and their efficiency in performing the task in terms of accuracy and decision speed. The only parameter that was not modulated by reward size was movement duration.

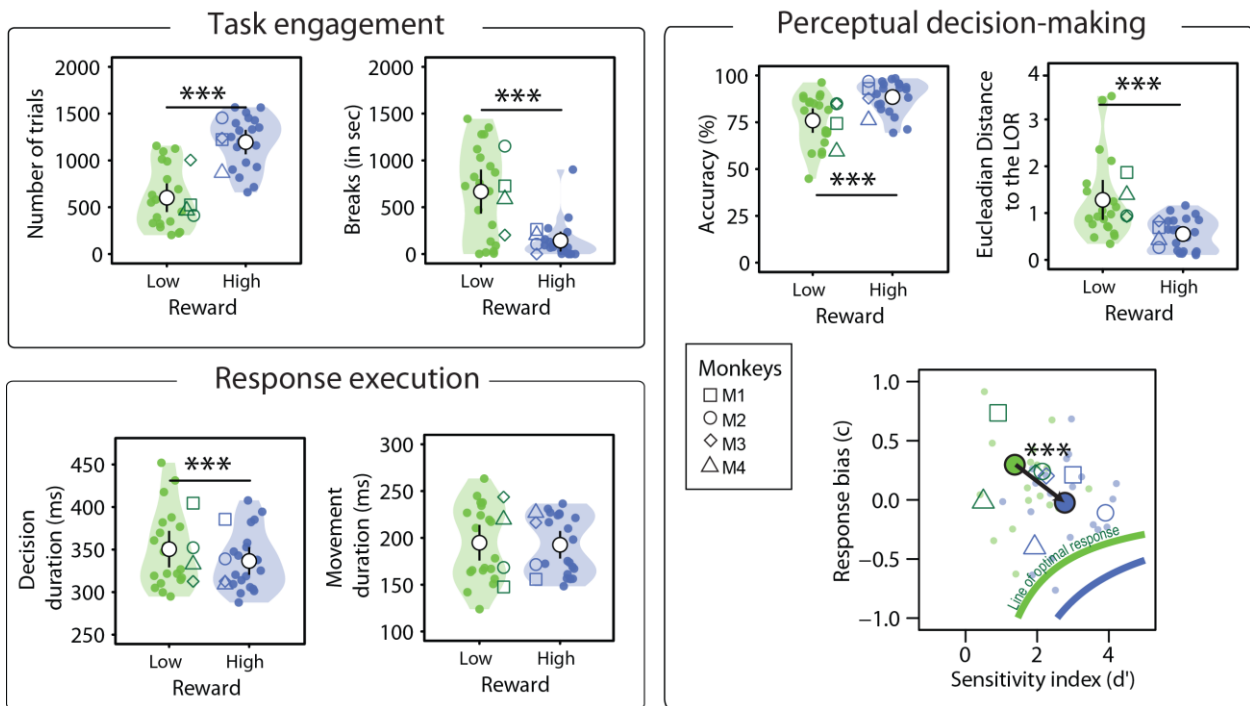


Figure 2. Effect of reward size on task engagement, perceptual decision-making and response execution. High reward (in blue vs. low reward in green) increased task engagement, improved perceptual decision-making, decreases decision duration but did not affect movement duration (mixed effect models followed by FDR-corrected posthoc tests, *** p_{FDR} value ≤ 0.001 , ** p_{FDR} value ≤ 0.01 , * p_{FDR} value ≤ 0.05). Small colored dots represent the average value for each reward size, while the large white dots represent the mean of these averages (with 95% confidence interval around the mean). Distributions of average values are illustrated by violin plots for high and low reward. Each monkey's average value is further differentiated by distinct shapes. In the panel of perceptual decision-making, the Line of Optimal Response (LOR) describes the relationship between response bias and perceptual sensitivity for low (green) and high reward (blue), respectively, based on the contingencies of the task (target frequency and outcome values, as explained in the method section). As for the other plots, small colored dots represent the average value for each reward size, with the large dots indicating the mean of these averages. Each monkey's average value is further differentiated by distinct shapes.

Effect of ATX and Interaction between reward size and ATX

During weeks 2 and 3, the animals were tested under the same reward schedule (low and high) following ATX injection, subsequently increasing dosage (0.5 and 1 mg/kg). The first question we ask is, how ATX affected the animals' motivation and performance relative to reward size? We directly compared the animals' performance under low reward ATX condition to high reward saline. All the results are presented in **Figure 3**, and the statistical results are shown in **Table 3**. We found that low reward ATX and high reward saline equally boosted task engagement, significantly increasing the number of completed trials per 15-min runs and reducing the duration of the breaks. Both conditions also equally improved

accuracy, adjusting the animals' sensitivity to detect the target and their bias closer to the LOR. Finally, the animals made faster decisions (**Figure 3C**) with lower variability in both conditions. No significant difference was identified between high reward saline and low reward ATX. These results held for either dose of ATX tested (0.5 and 1 mg/kg).

The only significant difference between high reward saline and low reward ATX was found for movement duration (HRW_{saline_vs_LR}ATX0.5: $\beta = 14.10$, $t(32) = 3.25$, $p_{FDR} = .006$; HRW_{saline_vs_LR}ATX1: $\beta = 28.04$, $t(32) = 6.50$, $p_{FDR} < .001$). Therein, only ATX (but not high reward) slowed down movement in a dose-dependent manner (LRW_{saline_vs_HR}ATX0.5: $\beta = 11.91$, $t(32) = -2.74$, $p_{FDR} = .016$; LRW_{saline_vs_HR}ATX1: $\beta = 25.86$, $t(32) = 5.96$, $p_{FDR} < .001$) (**Figure 3C**).

To understand the interplay between reward size and ATX, we then asked, how the combination of high reward and ATX affected performance? As shown in **Table 2**, we found that the multiplicative model (ATX*Reward size) outperformed the additive model (ATX+Reward size) for almost all variables tested, except for movement duration (mean and variance) and the percentage of false alarms on distractors. This result suggests a strong interplay between ATX and reward size on the animals' performance. The effect of ATX on animal's performance – such as task engagement, accuracy, perceptual sensitivity (d'), Euclidean distance to the LOR, percentage of misses and decision duration – is amplified with an increase in reward size, indicating a multiplicative interaction that results in performance boots beyond what would be expected if their influence were merely additive.

There was no difference between both models (additive *versus* interactive) for movement duration and false alarms. We observed non-significant interaction effects for movement duration (**Table S1**), indicating that the impact of reward on movement duration remains consistent across different levels of ATX. A marginal additive effect between reward size and ATX was observed for the percentage of false alarms, indicating that the impact

varied depending on the specific dose of ATX and reward size. Consistently, high reward and ATX generally decrease the percentage of false alarms. The significant interaction effect for ATX1 (**Table S1**) reflected a decrease in the percentage of false alarms for the combination of high reward and ATX compared to low reward, ATX.

The posthoc tests reveal that compared to high reward saline, combining high reward and the higher dose of ATX (1mg/kg) further increased the animals' engagement in the task (number of trials: HRW_{saline}_vs_HRW_{ATX1}: $\beta = 179.00$, $t(40) = 2.7$, $p_{FDR} = .021$) and reduced the movement duration. Comparatively, relative to low reward ATX, combining ATX and high reward had a more important impact, especially with the lowest dose of ATX (0.5 mg/kg), where it further improved the animals' engagement in the task (number of trials: LRW_{ATX0.5}_vs_HRW_{ATX0.5}: $\beta = 190.45$, $t(57) = 2.8$, $p_{FDR} = .014$) and their perceptual sensitivity (LRW_{ATX0.5}_vs_HRW_{ATX0.5}: $\beta = 0.45$, $t(57) = 2.5$, $p_{FDR} = .034$) with in particular less false alarms (LRW_{ATX0.5}_vs_HRW_{ATX0.5}: $\beta = -0.04$, $t(57) = -3.10$, $p_{FDR} = .008$) and a marginal reduction of movement duration (LRW_{ATX0.5}_vs_HRW_{ATX0.5}: $\beta = -8.22$, $t(57) = -2.10$, $p_{FDR} = .061$). With the highest dose of ATX (1 mg/kg) in combination with high reward, the animals also made significantly fewer false alarms relative to low reward under the same dose of ATX (LRW_{ATX1}_vs_HRW_{ATX1}: $\beta = -0.03$, $t(57) = -2.60$, $p_{FDR} = .025$) and their average movement duration was also significantly reduced (LRW_{ATX1}_vs_HRW_{ATX1}: $\beta = -8.89$, $t(57) = -2.20$, $p_{FDR} = .046$).

In sum, relative to low reward ATX or high reward saline, combining ATX and high reward further improved the animals' engagement in the task interactively for most variables. It also further boosted the animals' accuracy by reducing the percentage of false alarms on distractors. This effect was only visible between low reward ATX and high reward ATX, suggesting that reward size contributed to further reducing impulsive choice (additive effect). Finally, the movement duration presented a peculiar picture depending on the conditions:

ATX injections (but not reward size) systematically and specifically slowed down the animals' movement duration in a dose dependent manner, and the combination of ATX and high reward only partly counteracted this effect. These results highlight the specificity of each modulator (reward size *versus* ATX) on performance.

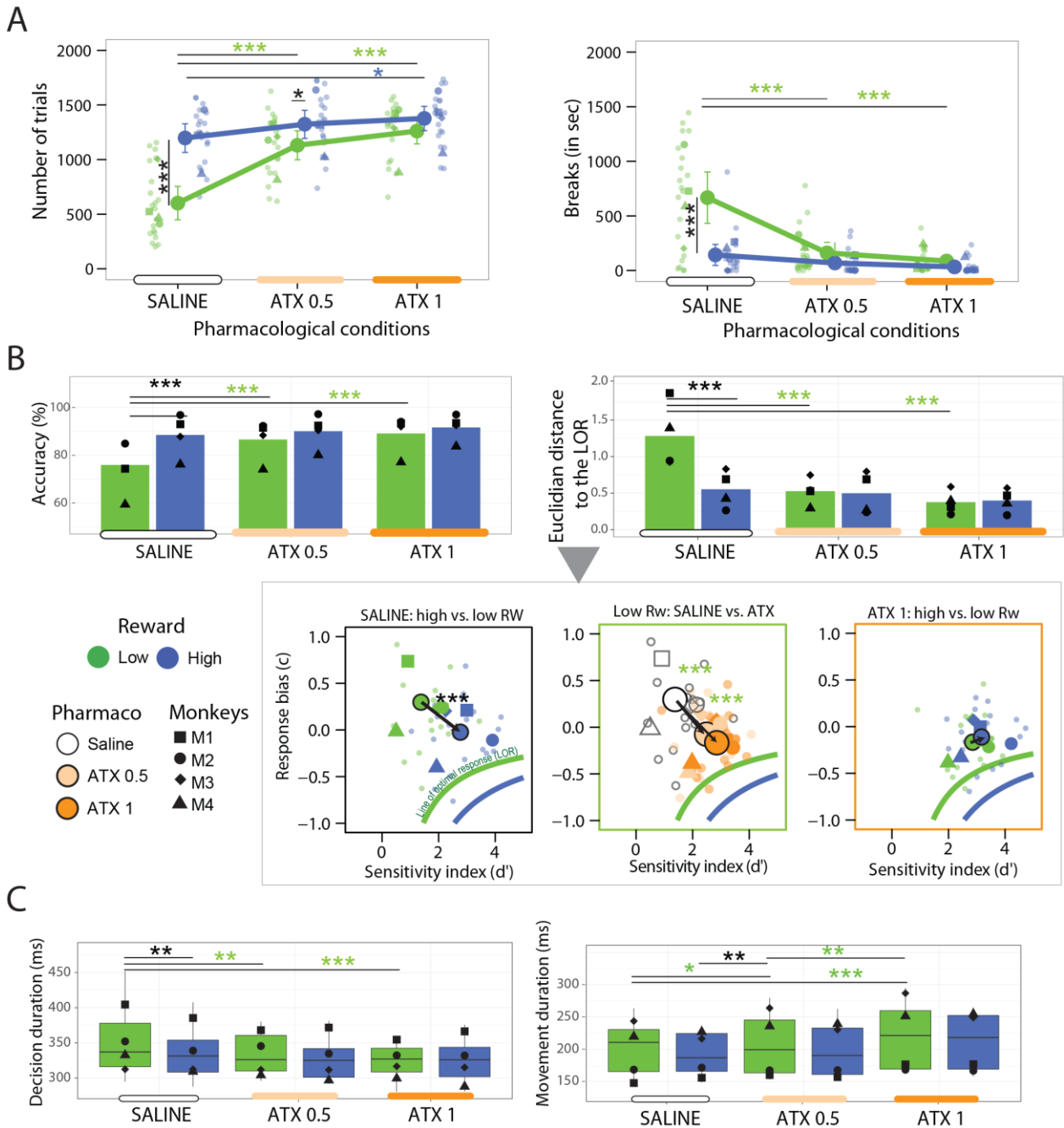


Figure 3. Effect of ATX and Interaction between reward size and ATX on task engagement, perceptual decision-making processes and response execution. A) Task engagement. ATX and high reward increased the average number of trials and decreased the duration of breaks throughout runs, compared to low reward saline. Small colored dots indicate the individual values for each reward size (low in green vs. high

in blue) and pharmacological conditions across the x-axis: saline, ATX 0.5 mg/kg, and ATX 1.0 mg/kg. The large colored dots represent the mean, with 95% confidence interval of the mean. Each monkey's average value is further differentiated by distinct shapes. The star's significance level is based on FDR-corrected posthoc tests from mixed effect models ($*** \leq 0.001$, $** \leq 0.01$, $* \leq 0.05$). Green and blue stars illustrate significant differences between pharmacological conditions in the low and high reward conditions, respectively, while black stars illustrate significant differences for low *versus* high reward. **B) Perceptual decision-making processes.** The bar graphs show the accuracy (on the left) and the Euclidean distance to the "Line of optimal response" (LOR) (on the right) for the different pharmacological conditions as in A. The graphs below display how reward and ATX modify the functional relationship between perceptual sensitivity (d') and response bias (c) by reducing the Euclidean distance to the LOR. The LOR is displayed for low reward (green) and high reward (blue), respectively, based on the contingencies of the task (target frequency and outcome values, as explained in the method section). The shift between the two lines is due to the different outcome values of high and low reward, which impact the relationship between d' and response bias. From left to right, Panel 1 illustrates the significant reduction of the distance to the LOR in the high *versus* low reward saline condition; Panel 2 displays the significant reduction of the distance to the LOR after ATX injections (0.5 and 1 mg/kg) compared to saline in the low reward conditions; Panel 3 show no significant effect of reward size for ATX 1 condition. **C) Response execution.** The boxplots display the mean and variance of the decision and movement durations in the different pharmacological conditions as in A and B. The results show that high reward and/or ATX (ATX 0.5 mg/kg and ATX 1.0 mg/kg) significantly reduced decision duration compared to the low reward saline condition. By contrast, movement duration was differently affected by ATX and high reward. Only ATX (but not high reward) slowed down movement duration compared to the saline condition.

Discussion

Multiple neurotransmitter systems interact to support and shape behavior. While previous studies have primarily examined the interaction of the noradrenaline and dopamine systems on memory and reward processing, their combined influence on cognitive and motor performance remains largely unexplored. Investigating the interaction between reward and noradrenaline levels to provide insight into the extent to which the influence of the former involves the latter was the central focus of this study. We compared monkeys' performance in a Go/NoGo task after either increasing the amount of reward and/or the level of extracellular noradrenaline using ATX injections. We found that reward size and ATX significantly promoted task engagement and improved perceptual decision-making abilities. Importantly, ATX and high reward differently affected movement execution. While both conditions speeded the decision duration and reduced its variability, only ATX systematically increased movement duration dose-dependently. At the same time, high reward did not affect movement duration but decreased its variability. When combined with ATX, high reward further reduced the occurrence of false alarms (i.e., incorrect go on distractors) while only partly counteracting the ATX-induced increase of movement duration.

Reward size and ATX equally improved perceptual decision-making abilities and task engagement.

Regarding perceptual decision-making abilities, the current findings are consistent with previous results manipulating the levels of NA (Arnsten, 2009; Bari & Robbins, 2013; Chamberlain et al., 2009; Gelbard-Sagiv et al., 2018; Reynaud et al., 2019, 2021). Compared to low reward saline, under ATX, the animals were more accurate. They missed fewer targets and were better at inhibiting responses toward distractors, echoing the idea that ATX contributed to improving both sensory discrimination (Gelbard-Sagiv et al., 2018; Loughnane et al., 2019) and cognitive control (Chamberlain et al., 2009; Ye et al., 2021). This translated into an improved perceptual sensitivity (d') and reduced response bias (c), leading to performance optimization in the form of a closer distance to the “Line of optimal response” (Lynn et al., 2015). The LOR was computed based on each outcome's target frequency and payoff values. In the present task, only correct responses to the target (hit) were rewarded and appeared in 30% of the cases, and incorrect responses (false alarms and misses) were followed by a 3-sec penalty time, hampering reward delivery. In accordance with Guedj et al. (2019), we found that ATX significantly decreased the distance to the LOR, demonstrating an optimization of the response strategy to maximize the overall reward rate.

Another way to increase the reward rate within a fixed imparted time is to stay engaged in the task. We thus measured the animals' engagement in the task by computing the number of trials and breaks they performed during the 15-min runs. We found that the four monkeys doubled their number of trials and made fewer breaks in runs with ATX compared to low reward saline. Electrophysiological studies show that the activity of NA neurons reflects the engagement in discrimination tasks (Kruk & Millar, 1979; Rajkowski et

al., 1994) and the initiation of a costly action (Bouret & Sara, 2005; Rajkowski et al., 2004), suggesting that LC activity might reflect the mobilization of resources necessary to cope with challenging environments. Finally, we also found that under ATX, animals took their decision faster, with more consistency (less variability in decision duration; see more details for an additional analysis investigating performance fluctuations over a run in the Supplementary Information, i.e., the Variance Time Course Analysis).

How does increasing reward size affect perceptual decision-making abilities relative to ATX injection? We found that it had a similar effect: it did increase accuracy and perceptual sensitivity the same way ATX did. It also shifted the animals' response bias and reduced the distance to the LOR. The effect of reward on perceptual abilities is coherent with the vast literature demonstrating the strong boosting effect of reward in different contexts involving perceptual discrimination abilities (Hübner & Schlösser, 2010; Pessoa, 2015). Finally, previous studies have shown that the reward context in which behavior is performed strongly modulates response vigor during decision (Dudman & Krakauer, 2016; Revol et al., 2019; Shadmehr et al., 2019; Thura, 2020; Thura et al., 2014). Our results also align with those findings, demonstrating that three out of four monkeys reacted faster and were less variable in releasing the lever in the high compared to the low reward condition.

One novelty of the present results lies in the direct comparison between the effect of reward size and ATX. Contrary to our prediction that reward size would boost performance over ATX, we found no statistical difference between the two conditions regarding perceptual decision-making abilities despite the difference in reward volume (benefits) delivered to the animals. Either increase the size of the reward or the level of NA using ATX injections optimized task engagement and perceptual decision-making abilities without any speed-accuracy trade-off during the decision process. One possible explanation is that both ATX and reward size similarly and non-specifically affect catecholamine transmission (DA

and NA), leading to improvement in task engagement and perceptual decision-making abilities (Chowdhury et al., 2022; Zhang et al., 2023). ATX might also moderate the effect of reward - in the form of an increase - on behavior by influencing DA signaling. Yet, while reward modulates the activity of both NA and DA neurons (Jahn et al., 2018; Varazzani et al., 2015), previous studies also indicate that a moderate dose of ATX (0.5 mg/kg, the dose used in our second week of testing) stimulates twice as much NA transmission in the prefrontal cortex, relative to DA transmission (Bymaster, 2002) and that it improves the signal-to-noise ratio within the main source of NA in the brain, the locus coeruleus (LC) (Bari & Aston-Jones, 2013; Warren et al., 2017). The influence of ATX on DA and NA signaling should be tested in future studies to understand their interplay and the underlying mechanisms of motivation, decision and action. Another possibility, not mutually exclusive, is that NA and reward act on similar processes (Ranjbar-Slamloo & Fazlali, 2020), affecting both reward sensitivity and effort-oriented behavior, leading to improved task engagement and perceptual decision abilities. The prospect of earning a high reward may have increased the willingness to exert an effort (Westbrook et al., 2020) by biasing the ratio toward benefits over costs. This effect might reflect the target's enhanced motivational value among distractors under both high reward and ATX (Aston-Jones et al., 1999; Ventura et al., 2007) or the reduced subjective perception of effort associated with the increased number of trials and improved performance (Borderies et al., 2020), the outcome leading to an equal net value between ATX and high reward.

Interestingly, combining high reward with ATX further improved task engagement and perceptual sensitivity (accuracy and d') in an interactive manner, compared to the high reward saline or low reward ATX condition. We found more pronounced interactive effects between ATX and high reward during week 2 (under ATX 0.5 mg/kg), in which presumably the imbalance between the impact on NA and DA transmission within the prefrontal cortex

might be more important (see above, Bymaster, 2002), compared to the higher dose used in week 3 (ATX 1 mg/kg). The interaction between reward size and ATX points towards common processes shared by both modulators onto motivation (measured as task engagement) and perceptual sensitivity (Zhang et al., 2023). In the next paragraph, we further discuss these effects, considering specificities related to the impact of ATX and reward size on performance.

Specificities related to the impact of ATX and reward size on performance

Beyond the interactive effect of reward size and ATX, we also found specificities related to each of these modulators on performance. First, regarding errors, and as discussed above, our results show that the animals made fewer errors under high reward or ATX and missed fewer targets (Go trials), and were better at inhibiting responses toward distractors (noGo trials), consistent with accumulating evidence demonstrating the impact of these modulators on perceptual discrimination abilities (e.g. Gelbard-Sagiv et al., 2018; Pessoa, 2015) and cognitive control (e.g. Chamberlain et al., 2009; Krebs et al., 2010). Yet, when combined with ATX, high reward further reduced false alarms on distractors relative to low reward ATX. No such difference was found for the other type of error (misses of target). This could indicate that reward, compared to ATX, more effectively contributed to reducing impulsive choices and improving cognitive control (Burton et al., 2021) while equally improving perceptual discrimination abilities. The structure of our task required inhibiting responses in 70 % of the cases when a distractor was presented, and only correct responses towards targets (in 30% of the cases) were rewarded. It is thus possible that this led to a higher probability of detecting differences for distractors than targets, given this imbalance. Alternatively, this result could indicate a more specific effect of ATX during rewarded decisions requiring a directed movement. This result fits with the findings of

Kalwani and colleagues (2014), who demonstrated that LC neurons responded to cues instructing the execution of an action (but not to cues instructing to withhold a response). This property might confer the LC/NA system a more specific role in decisions involving goal-directed movements. Reward size, instead, might energize both decision and action indistinctively, invigorating behavior involving or not a directed action, an effect likely mediated through the dopaminergic system (Carland et al., 2019; Niv et al., 2007; Walton & Bouret, 2019).

Second, we found that ATX, but not reward size, selectively and systematically affected movement duration, i.e., the time it took the animals to reach the screen after releasing the lever. ATX slowed down the animals' mean movement duration in a dose-dependent manner while combining ATX with high reward partly counteracted this effect. The ATX-induced increase in movement duration aligns with prior studies in rats using ATX or guanfacine injections, an NA agonist (Redding et al., 2019). By contrast, we did not find any effect of reward size on movement duration compared to previous studies reporting a reduction of movement duration with reward (Dudman & Krakauer, 2016; Shadmehr et al., 2019), though our results showed that high reward reduced variability in movement duration (Summerside et al., 2018). Note that the increase in movement duration under ATX did not prevent the animals' improvement in task engagement, sensitivity, and decision duration to the same level as that achieved under high reward. In fact, this increment in movement duration had virtually no consequence on the reward rate, given the imparted time to respond set to 900 ms.

What does this tell us about the impact of ATX and reward on movement control? Why would the animals perform slower reaching movements under ATX? Especially

movements that do not require a particular degree of precision (reaching for a 10° window around a target, about twice smaller)? ATX might induce physical or motor fatigue (Blondeau & Dellu-Hagedorn, 2007). However, this idea does not align with the fact that the animals completed more trials and maintained high performance under ATX compared to the saline control condition. Alternatively, it is possible that under ATX, the animals slowed down their movement to ensure more controlled action to avoid errors. This interpretation is supported by the reduction of false alarms under ATX and is consistent with previous findings as discussed above (Chamberlain et al. 2019), even though the effect of reward size seemed stronger than that of ATX in reducing impulsive responses. Another, not mutually exclusive, interpretation is that the increase in movement duration under ATX reflects a strategy to minimize the effort (costs) associated with the higher level of task engagement and response optimization, given that speeding up decision time and improving accuracy is effortful (Manohar et al., 2015; Morel et al., 2017). ATX, by increasing more so NA availability, might render the system more “sensitive” to the effort invested and slow down movements to compensate for the more demanding physical and cognitive effort invested in increasing what matters the most for subjects engaged in successive decisions between actions, the rate of reward (Balci et al., 2011; Reynaud et al., 2020; Saleri Lunazzi et al., 2021). Under ATX, animals made twice as many trials and improved their performance. It is thus possible that to achieve this more demanding goal involving repetitive movements, slowing down movement might help minimize costs (Shadmehr et al., 2016; Tanaka et al., 2006). The significant relationship we found between the increase in movement duration and the increase in the number of trials after ATX 1 injection (relative to saline) further supports this claim (Figure S1).

Could this strategy help avoid fatigue, as energy resources are limited? This resonates with recent recordings from the locus coeruleus (LC), the primary source of NA

in the brain, suggesting that NA encodes the amount of energetical resources necessary for the execution of a given action (Bornert & Bouret, 2021). Such coding might help guide the allocation of energy resources expenditure. While ATX also interferes with DA functioning (Bymaster, 2002; Upadhyaya et al., 2013), future studies selectively targeting each neuromodulator will also help directly test for any specificity regarding their role in weighing benefits and costs.

While our study's outcomes are promising, certain limitations are worth noting. First, investigating NA's specific function in cognition and behavior using systemic injections of drugs like ATX is challenging due to their distributed effects, including non-specific effects such as sedation, especially with high doses (Blondeau & Dellu-Hagedorn, 2007). Future studies will benefit from comparing the impact of selective interventions to uncover shared and distinct contributions of neurotransmitter systems (as in (Fitzpatrick et al., 2019)). Second, we tested saline and ATX conditions sequentially across weeks, focusing mainly on the interaction between ATX and reward within each week (weeks 2 and 3). While we cannot rule out potential learning or habituation effects across weeks, these effects do not affect our conclusions regarding the interactive effects between ATX and reward size, tested within each week (weeks 2 and 3). Finally, the animals' performance was already high in the first week of testing. Even though the shape of the interaction could be related to potential ceiling or floor effects in performance, we could identify both additive and multiplicative effects between reward size and ATX.

In conclusion, our results demonstrate that reward size and ATX influenced decisional parameters similarly and strongly interacted to facilitate behavior. Both modulators strongly boosted motivation, measured in task engagement and reduced distractibility during prolonged periods. We suggested they might act on similar processes

(reward and effort processing) to facilitate behavior. Our results also suggest a differential role of these behavioral modulators on decision and action that might rely on the interplay between catecholaminergic signaling systems, i.e., NA and DA, to account for the management of energetical resources depending on the balance between perceived costs and benefits. As exemplified here with the ATX-induced increase of movement duration, this balance can lead to different types of adjustments between task engagement, decision and action. Considering these different processes is critical for understanding the mechanisms by which modulators affect the different facets of behavior. Overall, our results highlight the versatility of modulators on behavior, demonstrating how they affect motivation and perceptual decisions by working in different but complementary ways.

References

- Arnsten, A. F. T. (2009). Toward a New Understanding of Attention-Deficit Hyperactivity Disorder Pathophysiology: An Important Role for Prefrontal Cortex Dysfunction. *CNS Drugs*, 23(Supplement 1), 33–41. <https://doi.org/10.2165/00023210-200923000-00005>
- Aston-Jones, G., & Cohen, J. D. (2005). Adaptive gain and the role of the locus coeruleus-norepinephrine system in optimal performance. *The Journal of Comparative Neurology*, 493(1), 99–110. <https://doi.org/10.1002/cne.20723>
- Aston-Jones, G., Rajkowski, J., & Cohen, J. (1999). Role of locus coeruleus in attention and behavioral flexibility. *Biological Psychiatry*, 46(9), 1309–1320. [https://doi.org/10.1016/S0006-3223\(99\)00140-7](https://doi.org/10.1016/S0006-3223(99)00140-7)
- Baayen, R. H., Davidson, D. J., & Bates, D. M. (2008). Mixed-effects modeling with crossed random effects for subjects and items. *Journal of Memory and Language*, 59(4), 390–412. <https://doi.org/10.1016/j.jml.2007.12.005>
- Balci, F., Simen, P., Niyogi, R., Saxe, A., Hughes, J. A., Holmes, P., & Cohen, J. D. (2011). Acquisition of decision making criteria: Reward rate ultimately beats accuracy. *Attention, Perception, & Psychophysics*, 73(2), 640–657. <https://doi.org/10.3758/s13414-010-0049-7>
- Bari, A., & Aston-Jones, G. (2013). Atomoxetine modulates spontaneous and sensory-evoked discharge of locus coeruleus noradrenergic neurons. *Neuropharmacology*, 64, 53–64. <https://doi.org/10.1016/j.neuropharm.2012.07.020>
- Bari, A., & Robbins, T. W. (2013). Noradrenergic versus dopaminergic modulation of impulsivity, attention and monitoring behaviour in rats performing the stop-signal task: Possible relevance to ADHD. *Psychopharmacology*, 230(1), 89–111. <https://doi.org/10.1007/s00213-013-3141-6>

- Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus–noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, *42*(1), 33–84. [https://doi.org/10.1016/S0165-0173\(03\)00143-7](https://doi.org/10.1016/S0165-0173(03)00143-7)
- Blondeau, C., & Dellu-Hagedorn, F. (2007). Dimensional Analysis of ADHD Subtypes in Rats. *Biological Psychiatry*, *61*(12), 1340–1350. <https://doi.org/10.1016/j.biopsych.2006.06.030>
- Borderies, N., Bornert, P., Gilardeau, S., & Bouret, S. (2020). Pharmacological evidence for the implication of noradrenaline in effort. *PLOS Biology*, *18*(10), e3000793. <https://doi.org/10.1371/journal.pbio.3000793>
- Bornert, P., & Bouret, S. (2021). Locus coeruleus neurons encode the subjective difficulty of triggering and executing actions. *PLOS Biology*, *19*(12), e3001487. <https://doi.org/10.1371/journal.pbio.3001487>
- Bouret, S., & Richmond, B. J. (2015). Sensitivity of Locus Ceruleus Neurons to Reward Value for Goal-Directed Actions. *Journal of Neuroscience*, *35*(9), 4005–4014. <https://doi.org/10.1523/JNEUROSCI.4553-14.2015>
- Bouret, S., & Sara, S. J. (2005). Network reset: A simplified overarching theory of locus coeruleus noradrenaline function. *Trends in Neurosciences*, *28*(11), 574–582. <https://doi.org/10.1016/j.tins.2005.09.002>
- Bourgeois, A., Chelazzi, L., & Vuilleumier, P. (2016). How motivation and reward learning modulate selective attention. In *Progress in Brain Research* (Vol. 229, pp. 325–342). Elsevier. <https://doi.org/10.1016/bs.pbr.2016.06.004>
- Burton, S., Knibb, G., & Jones, A. (2021). A meta-analytic investigation of the role of reward on inhibitory control. *Quarterly Journal of Experimental Psychology*, *74*(10), 1818–1828. <https://doi.org/10.1177/17470218211008895>
- Bymaster, F. (2002). Atomoxetine Increases Extracellular Levels of Norepinephrine and Dopamine in Prefrontal Cortex of Rat A Potential Mechanism for Efficacy in Attention

Deficit/Hyperactivity Disorder. *Neuropsychopharmacology*, 27(5), 699–711.

[https://doi.org/10.1016/S0893-133X\(02\)00346-9](https://doi.org/10.1016/S0893-133X(02)00346-9)

Carland, M. A., Thura, D., & Cisek, P. (2019). The Urge to Decide and Act: Implications for Brain Function and Dysfunction. *The Neuroscientist*, 25(5), 491–511.

<https://doi.org/10.1177/1073858419841553>

Chamberlain, S. R., Hampshire, A., Müller, U., Rubia, K., del Campo, N., Craig, K., Regenthal, R., Suckling, J., Roiser, J. P., Grant, J. E., Bullmore, E. T., Robbins, T. W., & Sahakian, B. J. (2009). Atomoxetine Modulates Right Inferior Frontal Activation During Inhibitory Control: A Pharmacological Functional Magnetic Resonance Imaging Study. *Biological Psychiatry*, 65(7), 550–555. <https://doi.org/10.1016/j.biopsych.2008.10.014>

Chowdhury, A., Luchetti, A., Fernandes, G., Filho, D. A., Kastellakis, G., Tzilivaki, A., Ramirez, E. M., Tran, M. Y., Poirazi, P., & Silva, A. J. (2022). A locus coeruleus-dorsal CA1 dopaminergic circuit modulates memory linking. *Neuron*, 110(20), 3374–3388.e8.

<https://doi.org/10.1016/j.neuron.2022.08.001>

Coddington, L. T., & Dudman, J. T. (2019). Learning from Action: Reconsidering Movement Signaling in Midbrain Dopamine Neuron Activity. *Neuron*, 104(1), 63–77.

<https://doi.org/10.1016/j.neuron.2019.08.036>

da Silva, J. A., Tecuapetla, F., Paixão, V., & Costa, R. M. (2018). Dopamine neuron activity before action initiation gates and invigorates future movements. *Nature*, 554(7691), 244–248.

<https://doi.org/10.1038/nature25457>

Decamp, E., Clark, K., & Schneider, J. S. (2011). Effects of the alpha-2 adrenoceptor agonist guanfacine on attention and working memory in aged non-human primates: Guanfacine effects on cognition in aged primates. *European Journal of Neuroscience*, 34(6), 1018–

1022. <https://doi.org/10.1111/j.1460-9568.2011.07815.x>

- Dudman, J. T., & Krakauer, J. W. (2016). The basal ganglia: From motor commands to the control of vigor. *Current Opinion in Neurobiology*, *37*, 158–166.
<https://doi.org/10.1016/j.conb.2016.02.005>
- Esterman, M., Reagan, A., Liu, G., Turner, C., & DeGutis, J. (2014). Reward reveals dissociable aspects of sustained attention. *Journal of Experimental Psychology: General*, *143*(6), 2287–2295. <https://doi.org/10.1037/xge0000019>
- Fitzpatrick, C. M., Runegaard, A. H., Christiansen, S. H., Hansen, N. W., Jørgensen, S. H., McGirr, J. C., De Diego Ajenjo, A., Sørensen, A. T., Perrier, J.-F., Petersen, A., Gether, U., Woldbye, D. P. D., & Andreasen, J. T. (2019). Differential effects of chemogenetic inhibition of dopamine and norepinephrine neurons in the mouse 5-choice serial reaction time task. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *90*, 264–276.
<https://doi.org/10.1016/j.pnpbp.2018.12.004>
- Foote, S. L., Aston-Jones, G., & Bloom, F. E. (1980). Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. *Proceedings of the National Academy of Sciences*, *77*(5), 3033–3037.
<https://doi.org/10.1073/pnas.77.5.3033>
- Gelbard-Sagiv, H., Magidov, E., Sharon, H., Hendler, T., & Nir, Y. (2018). Noradrenaline Modulates Visual Perception and Late Visually Evoked Activity. *Current Biology*, *28*(14), 2239–2249.e6. <https://doi.org/10.1016/j.cub.2018.05.051>
- Guedj, C., Reynaud, A., Monfardini, E., Salemme, R., Farnè, A., Meunier, M., & Hadj-Bouziane, F. (2019). Atomoxetine modulates the relationship between perceptual abilities and response bias. *Psychopharmacology*, *236*(12), 3641–3653. <https://doi.org/10.1007/s00213-019-05336-7>
- Hübner, R., & Schlösser, J. (2010). Monetary reward increases attentional effort in the flanker task. *Psychonomic Bulletin & Review*, *17*(6), 821–826. <https://doi.org/10.3758/PBR.17.6.821>

- Jahn, C. I., Gilardeau, S., Varazzani, C., Blain, B., Sallet, J., Walton, M. E., & Bouret, S. (2018). Correction to: Dual contributions of noradrenaline to behavioural flexibility and motivation. *Psychopharmacology*, *235*(10), 3081–3081. <https://doi.org/10.1007/s00213-018-5018-1>
- Jahn, C. I., Varazzani, C., Sallet, J., Walton, M. E., & Bouret, S. (2020). Noradrenergic But Not Dopaminergic Neurons Signal Task State Changes and Predict Reengagement After a Failure. *Cerebral Cortex*, *30*(9), 4979–4994. <https://doi.org/10.1093/cercor/bhaa089>
- Kalwani, R. M., Joshi, S., & Gold, J. I. (2014). Phasic Activation of Individual Neurons in the Locus Ceruleus/Subceruleus Complex of Monkeys Reflects Rewarded Decisions to Go But Not Stop. *The Journal of Neuroscience*, *34*(41), 13656–13669. <https://doi.org/10.1523/JNEUROSCI.2566-14.2014>
- Krebs, R. M., Boehler, C. N., & Woldorff, M. G. (2010). The influence of reward associations on conflict processing in the Stroop task. *Cognition*, *117*(3), 341–347. <https://doi.org/10.1016/j.cognition.2010.08.018>
- Kruk, Z. L., & Millar, J. (1979). The effect of bilateral ventral noradrenaline bundle lesions on lever pressing for food in rats. *Psychopharmacology*, *64*(1), 41–43. <https://doi.org/10.1007/BF00427343>
- Lee, D., Seo, H., & Jung, M. W. (2012). Neural Basis of Reinforcement Learning and Decision Making. *Annual Review of Neuroscience*, *35*(1), 287–308. <https://doi.org/10.1146/annurev-neuro-062111-150512>
- Loughnane, G. M., Brosnan, M. B., Barnes, J. J. M., Dean, A., Nandam, S. L., O’Connell, R. G., & Bellgrove, M. A. (2019). Catecholamine Modulation of Evidence Accumulation during Perceptual Decision Formation: A Randomized Trial. *Journal of Cognitive Neuroscience*, *31*(7), 1044–1053. https://doi.org/10.1162/jocn_a_01393
- Lynn, S. K., & Barrett, L. F. (2014). “Utilizing” Signal Detection Theory. *Psychological Science*, *25*(9), 1663–1673. <https://doi.org/10.1177/0956797614541991>

- Lynn, S. K., Wormwood, J. B., Barrett, L. F., & Quigley, K. S. (2015). Decision making from economic and signal detection perspectives: Development of an integrated framework. *Frontiers in Psychology*, 6. <https://doi.org/10.3389/fpsyg.2015.00952>
- Manohar, S. G., Chong, T. T.-J., Apps, M. A. J., Batla, A., Stamelou, M., Jarman, P. R., Bhatia, K. P., & Husain, M. (2015). Reward Pays the Cost of Noise Reduction in Motor and Cognitive Control. *Current Biology*, 25(13), 1707–1716. <https://doi.org/10.1016/j.cub.2015.05.038>
- Massar, S. A. A., Lim, J., Sasmita, K., & Chee, M. W. L. (2016). Rewards boost sustained attention through higher effort: A value-based decision making approach. *Biological Psychology*, 120, 21–27. <https://doi.org/10.1016/j.biopsycho.2016.07.019>
- Mizuyama, R., Soma, S., Suemastu, N., & Shimegi, S. (2016). Noradrenaline Improves Behavioral Contrast Sensitivity via the β -Adrenergic Receptor. *PLOS ONE*, 11(12), e0168455. <https://doi.org/10.1371/journal.pone.0168455>
- Niv, Y., Daw, N. D., Joel, D., & Dayan, P. (2007). Tonic dopamine: Opportunity costs and the control of response vigor. *Psychopharmacology*, 191(3), 507–520. <https://doi.org/10.1007/s00213-006-0502-4>
- Niv, Y., Joel, D., & Dayan, P. (2006). A normative perspective on motivation. *Trends in Cognitive Sciences*, 10(8), 375–381. <https://doi.org/10.1016/j.tics.2006.06.010>
- Opris, I., Lebedev, M., & Nelson, R. J. (2011). Motor Planning under Unpredictable Reward: Modulations of Movement Vigor and Primate Striatum Activity. *Frontiers in Neuroscience*, 5. <https://doi.org/10.3389/fnins.2011.00061>
- Pessoa, L. (2015). Multiple influences of reward on perception and attention. *Visual Cognition*, 23(1–2), 272–290. <https://doi.org/10.1080/13506285.2014.974729>
- Raizada, R. D. S. (2008). Challenge-driven attention: Interacting frontal and brainstem systems. *Frontiers in Human Neuroscience*, 1. <https://doi.org/10.3389/neuro.09.003.2007>

- Rajkowski, J., Kubiak, P., & Aston-Jones, G. (1994). Locus coeruleus activity in monkey: Phasic and tonic changes are associated with altered vigilance. *Brain Research Bulletin*, *35*(5–6), 607–616. [https://doi.org/10.1016/0361-9230\(94\)90175-9](https://doi.org/10.1016/0361-9230(94)90175-9)
- Rajkowski, J., Majczynski, H., Clayton, E., & Aston-Jones, G. (2004). Activation of Monkey Locus Coeruleus Neurons Varies With Difficulty and Performance in a Target Detection Task. *Journal of Neurophysiology*, *92*(1), 361–371. <https://doi.org/10.1152/jn.00673.2003>
- Ranjbar-Slamloo, Y., & Fazlali, Z. (2020). Dopamine and Noradrenaline in the Brain; Overlapping or Dissociate Functions? *Frontiers in Molecular Neuroscience*, *12*, 334. <https://doi.org/10.3389/fnmol.2019.00334>
- Redding, Z. V., Chawla, P., & Sabol, K. E. (2019). The use of reaction time distributions to study attention in male rats: The effects of atomoxetine and guanfacine. *Psychopharmacology*, *236*(12), 3579–3592. <https://doi.org/10.1007/s00213-019-05329-6>
- Revol, P., Collette, S., Boulot, Z., Foncelle, A., Niki, C., Thura, D., Imai, A., Jacquin-Courtois, S., Cabanac, M., Osiurak, F., & Rossetti, Y. (2019). Thirst for Intention? Grasping a Glass Is a Thirst-Controlled Action. *Frontiers in Psychology*, *10*, 1248. <https://doi.org/10.3389/fpsyg.2019.01248>
- Reynaud, A. J., Blini, E., Koun, E., Macaluso, E., Meunier, M., & Hadj-Bouziane, F. (2021). Atomoxetine modulates the contribution of low-level signals during free viewing of natural images in rhesus monkeys. *Neuropharmacology*, *182*, 108377. <https://doi.org/10.1016/j.neuropharm.2020.108377>
- Reynaud, A. J., Froesel, M., Guedj, C., Ben Hadj Hassen, S., Cléry, J., Meunier, M., Ben Hamed, S., & Hadj-Bouziane, F. (2019). Atomoxetine improves attentional orienting in a predictive context. *Neuropharmacology*, *150*, 59–69. <https://doi.org/10.1016/j.neuropharm.2019.03.012>

- Reynaud, A. J., Saleri Lunazzi, C., & Thura, D. (2020). Humans sacrifice decision-making for action execution when a demanding control of movement is required. *Journal of Neurophysiology*, *124*(2), 497–509. <https://doi.org/10.1152/jn.00220.2020>
- Robbins, T. W., & Arnsten, A. F. T. (2009). The Neuropsychopharmacology of Fronto-Executive Function: Monoaminergic Modulation. *Annual Review of Neuroscience*, *32*(1), 267–287. <https://doi.org/10.1146/annurev.neuro.051508.135535>
- Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome, E. D., & Beck, L. H. (1956). A continuous performance test of brain damage. *Journal of Consulting Psychology*, *20*(5), 343–350. <https://doi.org/10.1037/h0043220>
- Salamone, J. D., Correa, M., Yang, J.-H., Rotolo, R., & Presby, R. (2018). Dopamine, Effort-Based Choice, and Behavioral Economics: Basic and Translational Research. *Frontiers in Behavioral Neuroscience*, *12*, 52. <https://doi.org/10.3389/fnbeh.2018.00052>
- Salieri Lunazzi, C., Reynaud, A. J., & Thura, D. (2021). Dissociating the Impact of Movement Time and Energy Costs on Decision-Making and Action Initiation in Humans. *Frontiers in Human Neuroscience*, *15*, 715212. <https://doi.org/10.3389/fnhum.2021.715212>
- Shadmehr, R., Huang, H. J., & Ahmed, A. A. (2016). A Representation of Effort in Decision-Making and Motor Control. *Current Biology*, *26*(14), 1929–1934. <https://doi.org/10.1016/j.cub.2016.05.065>
- Shadmehr, R., Reppert, T. R., Summerside, E. M., Yoon, T., & Ahmed, A. A. (2019). Movement Vigor as a Reflection of Subjective Economic Utility. *Trends in Neurosciences*, *42*(5), 323–336. <https://doi.org/10.1016/j.tins.2019.02.003>
- Summerside, E. M., Shadmehr, R., & Ahmed, A. A. (2018). Vigor of reaching movements: Reward discounts the cost of effort. *Journal of Neurophysiology*, *119*(6), 2347–2357. <https://doi.org/10.1152/jn.00872.2017>

- Takikawa, Y., Kawagoe, R., Itoh, H., Nakahara, H., & Hikosaka, O. (2002). Modulation of saccadic eye movements by predicted reward outcome. *Experimental Brain Research*, *142*(2), 284–291. <https://doi.org/10.1007/s00221-001-0928-1>
- Tanaka, H., Krakauer, J. W., & Qian, N. (2006). An Optimization Principle for Determining Movement Duration. *Journal of Neurophysiology*, *95*(6), 3875–3886. <https://doi.org/10.1152/jn.00751.2005>
- Thura, D. (2020). Decision urgency invigorates movement in humans. *Behavioural Brain Research*, *382*, 112477. <https://doi.org/10.1016/j.bbr.2020.112477>
- Thura, D., Cos, I., Trung, J., & Cisek, P. (2014). Context-Dependent Urgency Influences Speed–Accuracy Trade-Offs in Decision-Making and Movement Execution. *The Journal of Neuroscience*, *34*(49), 16442–16454. <https://doi.org/10.1523/JNEUROSCI.0162-14.2014>
- Upadhyaya, H. P., Desaiyah, D., Schuh, K. J., Bymaster, F. P., Kallman, M. J., Clarke, D. O., Durell, T. M., Trzepacz, P. T., Calligaro, D. O., Nisenbaum, E. S., Emmerson, P. J., Schuh, L. M., Bickel, W. K., & Allen, A. J. (2013). A review of the abuse potential assessment of atomoxetine: A nonstimulant medication for attention-deficit/hyperactivity disorder. *Psychopharmacology*, *226*(2), 189–200. <https://doi.org/10.1007/s00213-013-2986-z>
- Varazzani, C., San-Galli, A., Gilardeau, S., & Bouret, S. (2015). Noradrenaline and Dopamine Neurons in the Reward/Effort Trade-Off: A Direct Electrophysiological Comparison in Behaving Monkeys. *Journal of Neuroscience*, *35*(20), 7866–7877. <https://doi.org/10.1523/JNEUROSCI.0454-15.2015>
- Ventura, R., Morrone, C., & Puglisi-Allegra, S. (2007). Prefrontal/accumbal catecholamine system determines motivational salience attribution to both reward- and aversion-related stimuli. *Proceedings of the National Academy of Sciences*, *104*(12), 5181–5186. <https://doi.org/10.1073/pnas.0610178104>

- Walton, M. E., & Bouret, S. (2019). What Is the Relationship between Dopamine and Effort? *Trends in Neurosciences*, 42(2), 79–91. <https://doi.org/10.1016/j.tins.2018.10.001>
- Warren, C. M., Wilson, R. C., Van Der Wee, N. J., Giltay, E. J., Van Noorden, M. S., Cohen, J. D., & Nieuwenhuis, S. (2017). The effect of atomoxetine on random and directed exploration in humans. *PLOS ONE*, 12(4), e0176034. <https://doi.org/10.1371/journal.pone.0176034>
- Westbrook, A., van den Bosch, R., Määttä, J. I., Hofmans, L., Papadopetraki, D., Cools, R., & Frank, M. J. (2020). Dopamine promotes cognitive effort by biasing the benefits versus costs of cognitive work. *Science*, 367(6484), 1362–1366. <https://doi.org/10.1126/science.aaz5891>
- Ye, R., Rua, C., O’Callaghan, C., Jones, P. S., Hezemans, F. H., Kaalund, S. S., Tsvetanov, K. A., Rodgers, C. T., Williams, G., Passamonti, L., & Rowe, J. B. (2021). An in vivo probabilistic atlas of the human locus coeruleus at ultra-high field. *NeuroImage*, 225, 117487. <https://doi.org/10.1016/j.neuroimage.2020.117487>
- Zhang, Y., Chen, Y., Xin, Y., Peng, B., & Liu, S. (2023). Norepinephrine system at the interface of attention and reward. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 125, 110751. <https://doi.org/10.1016/j.pnpbp.2023.110751>

Table 3. Results from the posthoc tests for all dependent variables.

Dependent variables		low reward, saline <i>versus</i>			ATX 0.5 <i>versus</i> ATX 1		High reward <i>versus</i> ATX	
		high reward, saline t-values (FDR corrected p-values)	low reward, ATX		low reward	high reward	0.5 mg/kg	1 mg/kg
			0.5 mg/kg	1 mg/kg				
Task engagement	Number of trials	8.8 (< .001)	7.9 (< .001)	9.8 (< .001)	1.9 (.1)	0.8 (.433)	-1.0 (.394)	1.0 (.394)
	Breaks	-7.1 (< .001)	-6.9 (< .001)	-7.9 (< .001)	-1.0 (.482)	-0.5 (.722)	0.3 (.812)	-0.8 (.584)
Perceptual decision-making	Accuracy	7.8 (< .001)	5.4 (< .001)	6.7 (< .001)	1.3 (.314)	0.8 (.501)	-1.0 (.472)	0.3 (.745)
	Percentage of Misses	-6.6 (< .001)	-5.1 (< .001)	-5.9 (< .001)	-0.8 (.707)	-0.7 (.707)	0.1 (.958)	-0.7 (.707)
	Percentage of False Alarms	-5.6 (< .001)	-2.4 (.051)	-3.4 (.008)	-1.1 (.394)	-0.7 (.527)	1.3 (.299)	0.3 (.785)
	Perceptual sensitivity (d')	7.7 (< .001)	4.8 (< .001)	6.3 (< .001)	1.5 (.209)	0.9 (.440)	-1.2 (.340)	0.3 (.730)
	Response bias (c)	-4.9 (< .001)	-3.6 (.008)	-4.5 (.002)	-0.9 (.584)	-0.8 (.584)	-0.5 (.725)	-1.4 (.420)
	Euclidean distance to LOR	-6.4 (< .001)	-4.7 (< .001)	-5.6 (< .001)	-0.9 (.683)	-0.6 (.742)	-0.2 (.870)	-1.1 (.683)
Decision and movement durations	Decision duration	-3.8 (.002)	-3.3 (.010)	-4.6 (.001)	-1.2 (.351)	-0.6 (.624)	-0.8 (.573)	-2.0 (.131)
	Standard deviation of decision duration	-5.6 (< .001)	-4.3 (.001)	-4.8 (< .001)	-0.5 (.796)	0.1 (.974)	-0.2 (.941)	-0.7 (.739)
	Movement duration	-0.5 (.590)	2.7 (.016)	6.0 (< .001)	3.2 (.006)	3.1 (.008)	3.3 (.006)	6.5 (< .001)
	Standard deviation of movement duration	-3.0 (.031)	-1.4 (.308)	-0.6 (.620)	0.8 (.541)	1.5 (.284)	1.0 (.472)	1.8 (.230)

Note. Significant differences are indicated in Bold.

Table 4. Results from the posthoc tests for all dependent variables for comparing high reward combined with ATX to high reward, saline and low reward, ATX.

Dependent variables		Combining high reward AND ATX			
		ATX 0.5 mg/kg (week 2)	ATX 1 mg/kg (week 3)	ATX 0.5 mg/kg	ATX 1 mg/kg
		<i>versus</i> high reward, saline (week 1)		<i>versus</i> low reward, <u>ATX*</u>	
Task engagement	Number of trials	1.9 (.104)	2.7 (.021)	2.8 (.014)	1.7 (.132)
	Breaks	-1.0 (.482)	-1.5 (.306)	-1.3 (.400)	-0.7 (.584)
Perceptual decision-making	Accuracy	0.8 (.501)	1.6 (.202)	2.2 (.076)	1.6 (.202)
	Percentage of Misses	-0.4 (.782)	-1.1 (.59)	-0.6 (.778)	-0.5 (.778)
	Percentage of False Alarms	-0.8 (.527)	-1.5 (.269)	-3.1 (.008)	-2.6 (.025)
	Perceptual sensitivity	0.7 (.536)	1.7 (.173)	2.5 (.034)	1.7 (.164)
	Response bias (c)	0.1 (.975)	-0.8 (.584)	0.7 (.584)	0.9 (.584)
	Euclidean distance to LOR	-0.3 (.87)	-1.0 (.683)	-0.2 (.87)	0.2 (.87)
Decision and movement durations	Decision duration	-1.4 (.312)	-2.1 (.131)	-1.0 (.444)	-0.1 (.915)
	Standard deviation of decision duration	-1.0 (.604)	4.4 (.604)	-2.1 (.604)	-2.2 (.796)
	Movement duration	1.4 (.232)	-1.0 (.001)	-2.1 (.061)	-2.2 (.046)
	Standard deviation of movement duration	-0.8 (.541)	0.6 (.612)	-2.3 (.086)	-1.5 (.284)

Note. Displayed are t-values and in parenthesis the *p*-values. * Indicates that the comparisons have been performed within the same week. Significant differences are indicated in Bold.

Supplementary Information

Atomoxetine and Reward size equally improve task engagement and perceptual decisions but differently affect movement execution

Kristin Kaduk^{1,2,4}, Tiphaine Henry^{1,2}, Jerome Guitton³, Martine Meunier^{1,2},
David Thura^{1,2}, Fadila Hadj-Bouziane^{1,2}

¹ University UCBL Lyon 1, F-69000, France

² INSERM, U1028, CNRS UMR5292, Lyon Neuroscience Research Center,
ImpAct Team, Lyon, F-69000, France;

³ Biochemistry and Pharmacology-Toxicology Laboratory, Lyon-Sud Hospital,
Hospices Civils de Lyon, F-69495 Pierre Bénite, France

⁴ Decision and Awareness Group, Cognitive Neuroscience Laboratory, German
Primate Center, Leibniz Institute for Primate Research, Kellnerweg 4, Goettingen,
37077, Germany

Table S1. Effect of reward size and ATX on task engagement, perceptual decision-making processes and response execution. Statistical results of the linear mixed-effect model: main effects and interactions of reward with both levels of ATX for all dependent variables tested.

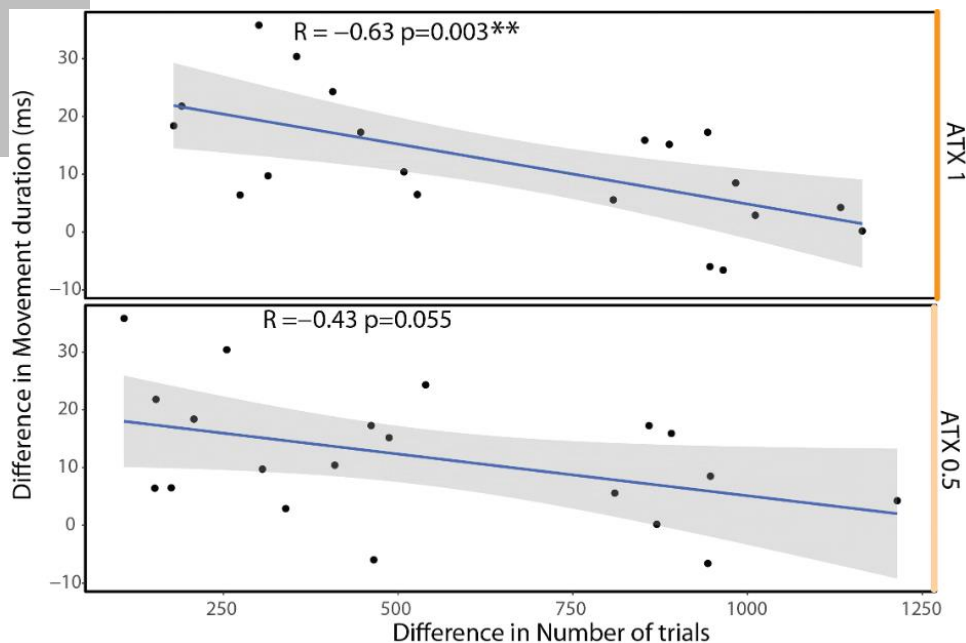
	DV	term	estimate	std. error	t-value	df	p-value
Task engagement	Number of trials	ATX.5	529,65	65,82	8,05	116	<0.001
		ATX_1	659,8	65,82	10,02	116	<0.001
		RewardHigh	594,4	65,82	9,03	116	<0.001
		ATX.5:RewardHigh	-403,95	93,08	-4,34	116	<0.001
		ATX_1:RewardHigh	-480,8	93,08	-5,17	116	<0.001
	Breaks	ATX.5	-505,55	71,96	-7,03	116	<0.001
		ATX_1	-580,45	71,96	-8,07	116	<0.001
		RewardHigh	-524,25	71,96	-7,29	116	<0.001
		ATX.5:RewardHigh	431,7	101,76	4,24	116	<0.001
		ATX_1:RewardHigh	470,45	101,76	4,62	116	<0.001
Perceptual decision-making	Accuracy	ATX.5	10,65	1,87	5,69	31,6	<0.001
		ATX_1	13,21	1,87	7,06	31,6	<0.001
		RewardHigh	12,56	1,58	7,96	60	<0.001
		ATX.5:RewardHigh	-9,07	2,23	-4,07	60	<0.001
		ATX_1:RewardHigh	-10,01	2,23	-4,49	60	<0.001
	Percentage of Misses	ATX.5	-24,5	4,49	-5,45	30,8	<0.001
		ATX_1	-28,3	4,49	-6,3	30,8	<0.001
		RewardHigh	-24,76	3,64	-6,81	60	<0.001
		ATX.5:RewardHigh	22,64	5,14	4,4	60	<0.001
		ATX_1:RewardHigh	22,91	5,14	4,45	60	<0.001
	Percentage of False Alarms	ATX.5	-4,54	1,78	-2,55	23,7	.018
		ATX_1	-6,54	1,78	-3,67	23,7	.001
		RewardHigh	-7,07	1,24	-5,72	60	<0.001
		ATX.5:RewardHigh	3,1	1,75	1,78	60	.081

		ATX_1:RewardHigh	3,77	1,75	2,16	60	.035	
	Perceptual sensitivity (d')	ATX.5	1,12	0,22	5,07	29,1	<0.001	
		ATX_1	1,48	0,22	6,7	29,1	<0.001	
		RewardHigh	1,4	0,18	7,89	60	<0.001	
		ATX.5:RewardHigh	-0,94	0,25	-3,77	60	<0.001	
		ATX_1:RewardHigh	-1,08	0,25	-4,32	60	<0.001	
		Response bias (c)	ATX.5	-0,37	0,1	-3,84	22,8	.001
	ATX_1		-0,46	0,1	-4,78	22,8	<0.001	
	RewardHigh		-0,32	0,06	-5,03	60	<0.001	
	ATX.5:RewardHigh		0,37	0,09	4,09	60	<0.001	
	ATX_1:RewardHigh		0,38	0,09	4,18	60	<0.001	
	Euclidean distance to the LOR	ATX.5	-0,76	0,15	-5,05	27	<0.001	
		ATX_1	-0,91	0,15	-6,05	27	<0.001	
		RewardHigh	-0,73	0,11	-6,55	60	<0.001	
		ATX.5:RewardHigh	0,7	0,16	4,45	60	<0.001	
		ATX_1:RewardHigh	0,75	0,16	4,77	60	<0.001	
	Response execution	Decision duration	ATX.5	-18	5,29	-3,4	87,5	.001
			ATX_1	-24,62	5,29	-4,66	87,5	<0.001
			RewardHigh	-13,92	3,6	-3,86	60	<0.001
			ATX.5:RewardHigh	10,25	5,09	2,01	60	.049
ATX_1:RewardHigh			13,52	5,09	2,65	60	.010	
Movement duration		ATX.5	11,91	4,24	2,81	112,1	.006	
		ATX_1	25,86	4,24	6,09	112,1	<0.001	
		RewardHigh	-2,18	3,91	-0,56	60	.578	
		ATX.5:RewardHigh	-6,04	5,52	-1,09	60	.278	
		ATX_1:RewardHigh	-6,71	5,52	-1,22	60	.229	
		ATX.5	-41,84	9,17	-4,56	27	<0.001	

	SD of decision duration	ATX_1	-47,15	9,17	-5,14	27	<0.001
		RewardHigh	-40,32	6,99	-5,77	60	<0.001
		ATX.5:RewardHigh	31,92	9,89	3,23	60	.002
		ATX_1:RewardHigh	36,92	9,89	3,73	60	<0.001
	SD of the movement duration	ATX.5	-3,1	2,14	-1,45	30,5	.158
		ATX_1	-1,29	2,14	-0,6	30,5	.552
		RewardHigh	-5,42	1,77	-3,07	60	.003
		ATX.5:RewardHigh	1,18	2,5	0,47	60	.638
		ATX_1:RewardHigh	2,73	2,5	1,09	60	.279

Note. For each dependant variable, the statistical values are provided in the following order: 1) main effect of ATX 0.5 mg/kg, 2) main effect of ATX 1 mg/kg, 3) main effect of reward size, 4) interaction between reward size and ATX 0.5 mg/kg and 5) interaction between reward size and ATX 1 mg/kg.

Figure S1. Relationship between changes in movement duration and task engagement in ATX relative to Saline



An increase in movement duration under ATX (relative to Saline) was associated with increased task engagement. For the low reward condition, the changes in movement duration (low values indicate the monkey responded slower relative to Saline) and the changes in the number of trials (higher values

indicate the monkey completed more trials relative to Saline) are displayed for both ATX doses (0.5 and 1 mg/kg). A linear correlation line showing the relationship between the movement duration and number of trials surrounded by the 95% confidence interval (gray). At the top of each plot, the Pearson Correlation Coefficient is provided together with its associated P value. The results reveal a significant negative linear relationship between the increase in movement duration after the injection of ATX 1 (relative to Saline) and the increase in the number of trials and a trend toward the same direction in the ATX 0.5 condition.

Variance Time Course (VTC) Analysis

Methods. To further examine the performance fluctuations over a run, we computed trial-by-trial variability in decision time across trials using the Variance Time Course analysis (Esterman et al., 2014). Accordingly, the decision times were z-transformed within the subject and session to normalize the scale to compute the absolute deviation of each trial's RT from the mean RT of the session. A Gaussian kernel of 5 trials with full width at half-maximum was used to smooth the variance time courses. Finally, a median split on the smoothed decision time data per session was applied, categorizing each trial into epochs with high-variability in decision time (OUT Zone) and epochs with low-variability in decision time epochs (IN Zone). This resulted in the following dependent variable: frequency of OUT Zone trials (number of trials in OUT Zone / (trials in OUT Zone + trials in IN Zone)). The Variance Time Course analysis identified periods of low and high variability in reaction time (RT), referred to as IN Zone and OUT Zone, respectively.

Results. We then examined the performance fluctuations over time using the Variance Time Course analysis to identify epochs of low- (IN Zone) and high variability in RT (OUT Zone). Compared to low reward saline, high-variability decision duration epochs (OUT Zone) were significantly reduced after high reward saline (LRW_{saline}_VS_HRW_{saline}: $\beta = -23$, $t(1,57) = -7.29$, $p_{FDR} < .001$), or ATX (LRW_{saline}_VS_LRW_{ATX0.5}: $\beta = -19$, $t(1,40) = -6.3$, $p_{FDR} < 0.001$; LRW_{saline}_VS_LRW_{ATX1}: $\beta = -25$, $t(1,40) = -8.2$, $p_{FDR} < .001$). No significant difference was found between high reward and ATX nor between the two doses of ATX for the variable derived from the Variance Time Course analysis (all P values > 0.05 , details in Table S1). In summary, high-variability decision duration periods (OUT Zone) were significantly reduced after the high reward saline compared to the low reward saline and after low reward ATX, indicating that larger rewards and ATX can enhance focus and consistency during task performance.

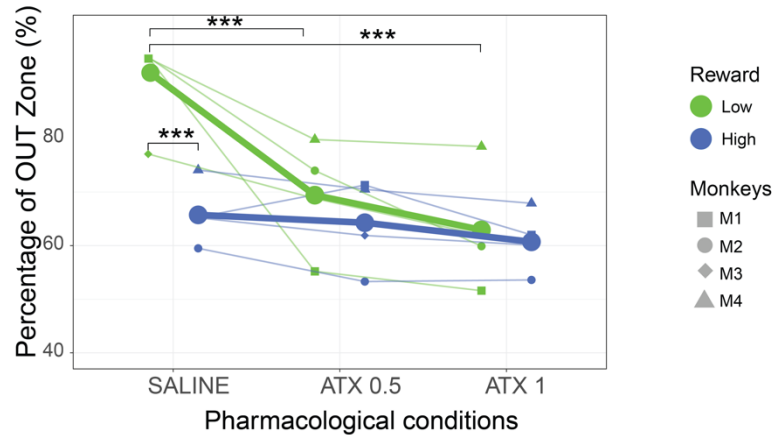


Figure S2. High reward, Saline and ATX, low reward decreases the percentage of OUT Zones. The percentage of OUT Zones displayed here was derived from trial-by-trial variability in decision duration across trials using the Variance Time Course analysis (see methods). It reflects the occurrence of epochs with high-variability in RTs across the whole runs (percentage of OUT Zone). The thick lines represent the averaged values across the four animals for low and high reward (in green and blue, respectively) in the different pharmacological conditions across the x-axis: saline, ATX 0.5 mg/kg, and ATX 1.0 mg/kg. The data from each animal are depicted by the thin lines overlaying the four symbols (square, circle, diamond, triangle). The stars show the level of significance derived from the mixed effect models followed by FDR-corrected posthoc tests (***) p_{FDR} value ≤ 0.001 , ** p_{FDR} value ≤ 0.01 , * p_{FDR} value ≤ 0.05). The results show that ATX and high reward significantly decreased the percentage of OUT Zones.

Table S2. VTC analysis: Results of the Posthoc tests for all contrasts

	low reward, saline versus			ATX 0.5 versus ATX 1		high reward versus ATX	
	high reward, saline t-values (FDR corrected p-values)	low reward, ATX		low reward	high reward	0.5 mg/kg	1 mg/kg
		0.5 mg/kg	1 mg/kg				
Percentage of OUT Zone	-7.3 <.001	-6.3 (<.001)	-8.2 (<.001)	-1.9 (.136)	-1 (.428)	1 (.428)	-0.9 (.473)
Combining high reward AND ATX							
	ATX 0.5 mg/kg (week 2)		ATX 1 mg/kg (week 3)		ATX 0.5 mg/kg	ATX 1 mg/kg	
	versus high reward, saline (week 1)				versus low reward, <u>ATX</u> *		
Percentage of OUT Zone					-1.5 (.25)	-0.6 (.641)	

Note. Displayed are t-values and in parenthesis, the p-values. (.25) indicates that the comparisons have been performed within the same week. Significant differences are indicated in Bold.

Table S3. VTC analysis: Model comparison

Variable	Type of model	Number of parameters	AIC	BIC	LogLik	deviance	Chi-square statistic (X^2)	df	p-value
Percentage of OUT Zone	additive	8	932	954	-458	916			
	interaction	10	911	939	-446	891	24.85	2	< .001

Note. multiplicative term (ATX * reward) and additive terms (ATX + reward, AIC = Akaike information criterion, BIC = Bayesian information criterion

References

Esterman, M., Reagan, A., Liu, G., Turner, C., & DeGutis, J. (2014). Reward reveals dissociable aspects of sustained attention. *Journal of Experimental Psychology: General*, 143(6), 2287–2295. <https://doi.org/10.1037/xge0000019>