# Pharmacological evidence for the implication of noradrenaline in effort

Causal role of noradrenaline in effort

---

**Authors**

Nicolas Borderies (1), Julia Mattioni (1)*, Pauline Bornert (1)*, Sophie Gilardeau (2), Sébastien Bouret (1)

**Affiliations**

1. Motivation, Brain and Behavior team, Institut du Cerveau et de la Moelle épinière (ICM), INSERM UMRS 1127, CNRS UMR 7225, Pitié-Salpêtrière Hospital, Paris, France.

2. Phenoparc PRIM'R, Institut du Cerveau et de la Moelle épinière (ICM), INSERM UMRS 1127, CNRS UMR 7225, Pitié-Salpêtrière Hospital, Paris, France.

* Contributed equally to the work.

**Abstract**

The trade-off between effort and reward is one of the main determinants of behavior and its alteration is at the heart of major disorders such as depression or Parkinson's disease. Monoaminergic neuromodulators are thought to play a key role in this trade-off, but their relative contribution remains unclear. Rhesus monkeys (*Macaca mulatta*) performed a choice-task requiring a trade-off between the volume of fluid reward and the amount of force to be exerted on a grip. In line with a causal role of noradrenaline in effort, decreasing noradrenaline levels with systemic clonidine injections (0.01mg/kg) decreased exerted force and enhanced the weight of upcoming force on choices, without any effect on reward sensitivity. Computational modeling demonstrated that NA acted on a single hidden variable, which affected both choices (as a variable of decision) and force production (as a driving force). Thus, our data strongly support noradrenaline's implication in effort processing.

## Introduction

The balance between costs and benefits is crucial in many disciplines interested in behavior, and studies addressing the neurobiological processes underlying the arbitrage between effort costs and reward benefits provided a significant insight into this arbitrage (Berridge, 2004; Westbrook & Braver, 2016; Husain & Roissier, 2018; Salamone et al, 2018; Shenhav et al, 2017; Pessiglione et al, 2017; Walton & Bouret, 2018). Among the numerous structures potentially involved in the effort/reward trade-off, monoaminergic neuromodulatory systems play a central role. The 3 major monoaminergic neuromodulatory systems (dopaminergic, noradrenergic, and serotoninergic) are defined by the specific molecule that they are secreting, and their cell bodies are located in deep nuclei of the central nervous system (Briand et al, 2007; Doya, 2008; Dayan, 2012; Lee and Dan, 2012; Marder, 2012). These neuromodulatory systems are altered in several neurological and psychiatric diseases that include motivation disorders (major depressive disorders, schizophrenia , Parkinson's disease) (Albert and Benkelfat, 2013; Chaudhuri and Schapira, 2009; Kurian et al., 2011). Moreover, catecholamines are the target for the majority of pharmacological treatments for these diseases (Goodman, 1996; Torres et al., 2003a).

Among those neuromodulators, dopamine (DA) is thought to be particularly critical for motivation and the effort/ reward trade-off (Berridge, 2007; Schultz, 2015; Westbrook & Braver, 2016; Salamone et al, 2018). Indeed, dopaminergic activity is reliably related to the value of the upcoming reward (Fiorillo et al, 2003; Tobler et al, 2005; Roesch et al, 2007) but also to the vigor of the animal's response (Hamid et al., 2016; Niv et al., 2007; Ko & Wanat, 2016, Syied et al, 2016). Experimental manipulations of the dopaminergic system, using pharmacology (Beierholm et al., 2013) or optogenetics (Adamantidis et al., 2011; Hamid et al., 2016; Steinberg et al., 2013), demonstrated the causal role of dopamine in the production of motivated behaviors. But even if dopamine seems to be crucial for promoting resource mobilization based on the upcoming reward, its relation with effort (when separated from reward) remains debated. Effort generally refers to the amount of physical or mental energy needed to reach a goal. In situations where effort only refers to performance and scales with reward through incentive motivation, measuring it a specific process (distinct from reward and performance) is very difficult. Intuitively, however, effort can readily be separated from reward and incentive motivation, since we usually experience effort precisely when we need to perform a challenging task without the drive of an immediate reward. Based on this intuition, we propose to study effort as a motivational process affecting choices and performance based on the expected costs, independently of the incentive influence of rewards. Critically, our objective here is not to redefine the theoretical boundaries of effort. Rather, we aim at characterizing a motivational process centered on expected costs, independently form the expected benefits, both at a computational and at a neurobiological level.

In that frame, we refer to effort as a computational variable capturing the amount of resources necessary for action, both when making a choice (and using it as a decision variable) and when performing the action (and using it as a driving force for behavior). At the time of the decision, one tends to minimize this variable and to choose the least effortful option. At the time of the action, however performance increases with the amount of mobilized resources (Walton & Bouret, 2018). When using that definition of effort and when dissociating it from reward in experimental paradigms, the relation between DA and effort became tenuous. For example, in recent experiments measuring

dopaminergic activity using either single unit recordings or voltametry, it was much more sensitive to the amount of expected reward than to the level of effort (Wanat et al, 2010; Gan et al., 2010; Pasquereau and Turner, 2013; Hollon et al., 2014; Varazzani et al, 2015). Similarly, when effort, force and reward could be dissociated, dopaminergic manipulation had little effect on effort processing compared to its effect on reward processing, as measured using choices (Skvortsova et al, 2014; Le Bouc et al, 2016; Zenon et al, 2016; Chong et al, 2018). Again, we do not question the strong implication of dopamine in energizing behavior and cognition (Le Heron et al, 2018; McGuigan et al, 2019), but here our goal is to examine the possibility that energy for action can rely upon a complementary motivational process, which is critical when the action is not directly rewarded, and which we will refer to as effort.

Several recent studies suggested that effort (as defined here, i.e. as a source of energy for action complementary to incentive motivation) could rely upon the other major catecholamine: noradrenaline (NA, Ventura et al., 2008; Bouret et al, 2012; Zénon et al., 2014). The relation between NA and effort is indeed supported by a several lines of evidences: *First*, locus coeruleus (LC) noradrenergic neurons are systematically activated right before initiating a costly action (Rajkowski et al, 2004; Bouret & Sara, 2004; Kalwani et al, 2014) and the magnitude of this activation relates to the action's level of difficulty. Indeed, at that time, the firing of LC neurons scales positively with the costs and negatively with the reward levels, suggesting that LC activation is related to the mobilization of resources necessary for overcoming that difficulty (Bouret & Richmond, 2009, 2015; Varazzani et al, 2015). In line with an interpretation in terms of physical effort, we recently showed a strong effect of noradrenergic manipulation on the amount of exerted force in a task in which force was not instrumental (Jahn et al, 2018). What remains unclear, however, is the extent to which noradrenergic manipulations would affect effort, defined as a single computational variable affecting both choices and force production. Indeed, in Jahn et al (2018), noradrenergic manipulation did not affect choices when options were characterized by a trade-off between reward size and reward-schedule length. This might be taken as evidence against the role of NA in effort (assuming that schedule length involves effort), but since schedule length has a strong delay component, it might affect decision through a pure delay discounting process and therefore leave the relation between NA and effort open (see Minamimoto et al, 2012, and Walton & Bouret 2019 for a discussion on effort and delay). *Second*, pharmacological manipulations of the NA system strongly affect performance in tasks requiring a high level of executive control (Chamberlain et al., 2006, 2009; Eagle et al., 2008; Reynaud et al, 2019) or attentional set-shifting (Dalley et al, 2001; Tait et al, 2007; McGaughy et al., 2008). These data are directly in line with the key action of noradrenaline on executive functions and its neural substrate in the prefrontal cortex (Arnsten, 2000; Robbins & Arnsten, 2009; Spencer & Berridge, 2019). Intuitively, these data could be interpreted in terms of 'mental effort', with the intuition that here effort would affect the trade-off between difficulty and performance in the cognitive rather than physical domain. *Third*, LC activity is closely associated with autonomic arousal and pupil dilation (Abercrombie & Jacobs, 1987; Varazzani et al, 2015; Joshi et al, 2016), which is itself correlated with both physical and mental effort (Kahneman & Beatty, 1966; Wand et al, 2015; Kurzban et al, 2013, Alnæs et al., 2014; de Gee et al., 2017). *Fourth*, this relationship between LC/NA and effort also resonates with an extensive literature demonstrating the role of noradrenaline in vigilance and arousal, which constitute a basic form of resource mobilization and appears related to effort (Aston-Jones et al, 1996; Berridge & Waterhouse, 2003; Berridge & Arnsten, 2012). But since we defined effort as a computational variable affecting both decisions and action execution, it cannot be captured by a generic process such as vigilance and arousal, which are less specific and can be readily separated from both physical and cognitive effort (for instance, arousal can increase with reward alone or surprise, even if no effort is involved whatsoever). In short, several lines of evidence converge to support the hypothesis that noradrenaline plays a key role in effort, but there is no direct evidence.

The goal of the present study is to address this issue directly by manipulating NA levels in monkeys performing a task involving the effort/reward trade-off. We designed a behavioral task that differentiated completely effort costs (a force to produce) from benefits (the expected reward magnitude). Since this task involved both binary choices and action execution (monkeys choose the option by executing it), we could reliably measure effort as a process involved both in choices and force production, and separate it from confounding factors such as force itself, reward, or arousal. In order to establish a causal link between NA levels and effort, we used systemic pharmacological perturbations of noradrenergic transmission (clonidine). Since we hypothesized that NA was involved in effort, we expected clonidine to affect force production, and to have a stronger effect on effort-based compared to reward-based choices. Moreover, we expected the two effects (choice and force) to be related, through a single computational variable which we refer to as effort. For the most part, our results are compatible with this hypothesis and they provide a strong support to the emerging idea that noradrenaline plays a central role in motivation. Thus, even if energy for action and cognition can be modulated by the expected benefits through dopamine-dependent incentive processes, this study provides strong evidence that the specific influence of the expected costs on ressources mobilization and decision making relies upon a noradrenaline-dependent process which we refer to as effort.

## Materials and methods

### Monkeys

Three rhesus monkeys (Monkey A, male, 8 kg, 9 years old; Monkey B, male, 15 kg, 8 years old; Monkey E, female, 6 kg, 7 years old) were used as subjects for the experiments. All monkeys have been properly habituated to the lab environment and used in another behavioral experiment before this one. Experimental procedures were designed in association with veterinarians, approved by the Regional Ethical Committee for Animal Experiment (CREEA IDF no. 3) and performed in compliance with the European Community Council Directives (2010/63/UE) at the *Institut du Cerveau et de la Moelle Epinière* (Agreement number: A-75-13-19). Food was available *ad libitum*, and motivation was controlled by restricting access to fluid to experimental sessions, when water was delivered as a reward for performing the task. Animals received water supplementation whenever necessary (e.g. if they could not obtain enough water through work), and they had free access to water whenever testing was interrupted for more than a week.

### Experimental settings

#### Drugs

We selected a pharmacological agents that conformed to the following criteria: 1) selectivity for noradrenergic targets, 2) bibliographic references that could provide effective dose for the treatments and 3) compatibility with human pharmacology for translational purposes (Aghajanian et al, 1982; Eagle et al, 2008; Bouret & Richmond, 2009; Arnsten, 2015; Guedj et al, 2016; Jahn et al, 2018). We used clonidine, a selective α2-agonist known to decrease LC activity, with a fixed dose of 0.01mg/kg. Solutions were prepared freshly at the beginning of the week by dissolution into a fixed volume of saline per animal. The control vehicle was a saline solution (NaCl 0.9%) matched in volume. Systemic intra-muscular administrations were performed on the lateral side of the thigh. The pharmacological schedule followed a within-monkey, bloc-wise, multi-session procedure. Animals received an injection every day, there were blocks of active treatment administration (3 to 5 consecutive injection within a week) intermixed with blocks of inactive vehicle after a minimal washout period of 48h (Goodman, 1996). Solutions were administrated at 30 minutes before testing for all sessions. For all monkeys, n=12 sessions were collected for active treatments and at least 12 sessions for control vehicle injections. Two monkeys (A, B) were tested simultaneously (on the same day) with similar drug conditions and another monkey (E) was tested independently (after completion of the full schedule for the two previous monkeys).

#### Behavioral task

Monkeys performed the behavioral task while squatting in a restraining chair, in front of a computer screen (HP Compaq LA2405wg 24 inches, LCD technology, 1920x1200 pixels at 60Hz), with two homemade handgrips hooked on the chair. Handgrips were connected to pneumatic tubes converting the squeezing force of the animals into air pressure, which was transduced, amplified and digitalized at 1 kHz. A calibration procedure ensured every day that the sensitivity of the system was stable over time. The maximal overshoot was 151% of the calibration force. Average empirical maximal forces were 102.61 ± 1.25 % (mean ± sem) meaning that calibration were close to the empirical capacities of the monkeys. The monkeys were monitored in real time with a camera. Task execution and behavioral recordings were controlled by a single computer. The behavioral task was run under MATLAB 2013a (MathWorks)

with Psychtoolbox-3.0.11 (www.psychtoolbox.org). Reward delivery (water) was controlled by a custom-made automatic pump.

The behavioral paradigm was a binary choice task where monkeys chose between two options, each characterized by a trade-off between effort costs and reward benefits (***Figure 1***). The task was designed to evaluate the effort/reward trade-off both in terms of action selection (choice) and action execution (force production). In this task, monkeys had to choose between two options presented simultaneously on the left and right part of the screen by pressing the grip on the side of the chosen option. Each of the 2 options was composed of 2 attributes: reward size and required force level, which were manipulated independently and randomly across trials. Reward size corresponded to the amount of water delivered during the outcome period (4 levels, 1, 2, 3 and 4 'drops' of water) and required force level corresponded to the force threshold that had to be exceeded during the response period (20, 40, 60, 80% of maximal force). The experimental conditions differed between trials in their reward level (1, 2, 3 or 4 water drops) and required force (20, 40, 60, 80% of maximal force), assigned to each option (left or right). These conditions were assigned to a trial number with a random permutation of the 256 different conditions (4 reward levels and 4 required force levels for both left and right options), reinitialized at the end of each blocks of 256 trials and at the beginning of each new session (with an independent permutation). All monkeys had experience with tasks requiring exerting force on a grip before but they were gradually trained to perform this task, as well as with the principle of choosing between two grips. Monkeys were trained until they reached asymptotic performance in this task, implying that they could reliably estimate the amount of required force necessary for each action based on the corresponding visual cue. We used these training sessions to estimate a maximal force level for each grip and for each monkey. Since this maximal force was used as a calibration reference in all experimental sessions (forces are expressed a as percentage of this maximal force), it was kept constant for the reminder of the study (this prevented two artefacts: variations of success rate due to between-sessions variations of difficulty or strategic participation of the monkeys due to between-sessions variations of difficulty).

Each trial started with the presentations of an offer (combination of two options), which lasted for a random interval (ranging from 750 to 2000ms) during which the monkeys could inspect the options' attributes, but not respond. In case of premature response during this period, the exact same offer was repeated at the next trial until a correct response was made. This ensured that monkeys carefully considered that 2 options before responding, thereby emphasizing the distinction between option evaluation and action. The beginning of the response period was cued by a visual stimulus (go signal, colored square), indicating that the monkey could select one of the two options by squeezing the handgrip corresponding to the chosen option on the side of visual presentation of the corresponding cue. In case of omission (when the monkey did not respond during the response period), the exact same options were repeated at the next trial until a choice was made. If the monkey appropriately exerted the level of force associated with the selected option on the corresponding handgrip, the reward associated to that option was delivered. Otherwise the task simply skipped to the next trial. Trials were separated by a random interval of 1-4 seconds. Each session ended when the monkey stopped participating and responding to free reward delivery (~ 45 minutes on average, across animals, which was sufficient to sample the whole range of options).

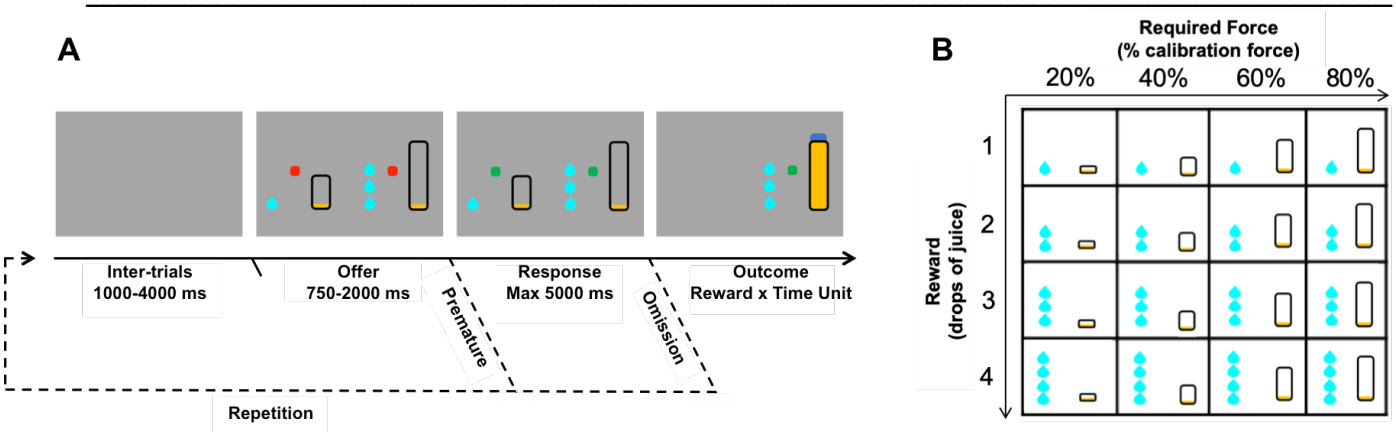


**Figure 1. Behavioral task design**

**A.** Schematic description of a trial sequence with successive screenshots displayed to the monkeys. A trial started with a grey screen (inter-trial phase) followed by the presentation of two red instruction dots, and two options, each of them composed of a reward cue and a required force cue (offer phase). When the instruction dots turned green (response phase), the monkeys could choose one option by pressing the corresponding handgrip (left or right). A continuous visual feedback was displayed to signal the online force exerted by the monkey (yellow filling of the required force cue). The announced reward (drops of juice) was delivered if and when the exerted force reached the target force (outcome phase). The same trial started again if the monkey responded before the end of the offer phase (premature error) or provided no response at all (omission).

**B.** Experimental design for the combinations of required force and reward size used to define options. Each option, regardless of its side of presentation, was defined by a combination of a given reward level (1, 2, 3 or 4 drops) and a given required force (20, 40, 60, 80% of the calibration force). The effort and reward components of each option were manipulated systematically and randomly, such that the influence of effort and reward on choices were orthogonalized by design. All possible combinations of pairwise options were sampled during the task.

## Data analysis

### Behavior

Effort was captured by assessing its effect on choices, (i.e. the weight of the costs associated to the required force level), and on action execution (i.e. the force exerted during action execution, estimated using force peaks). Again, given the task design, the influence of effort could be studied independently from that of reward, both on choices and on force production. The number of trials per session was sufficient to allow for a complete and homogenous sampling of all combinations of required force and reward levels in these experiments. Note that effort costs and reward levels affected not only the selection between the two options of an offer but also the willingness to perform the task at all, which we assessed using participation frequency as a function of the offered options. The dataset contained three levels of observations that were treated differently: 1) trial-wise observations, 2) session-wise observations and 3) monkey-wise observations. We summarized trial-wise observations with average scores (participation frequency, choice frequency, force peak) to assess aggregate effects, and with regression weights extracted from generalized linear models (logistic models for binomial data) to assess parametric effects. Only trials with an explicit choice

expressed (no omission or anticipation) were selected in the analysis of choices and force peaks. For session-wise observations, all sessions were considered independent; therefore, we computed behavioral metrics separately for each session and monkey. Next, the session-wise and monkey-wise analyses were modeled together into a mixed model, the random effect of monkey identity was a covariate of no interest and the fixed effects across sessions and monkeys were the effects of interest. Thereby, the experimental conditions of treatment type were modeled as a mixed effect. Inferences on active treatment effect were conducted with parametric two-sided two-samples t-test onto fixed effect of active treatment versus vehicle.

All analyses were done with MATLAB 2017a software. GLM and GLMM models were estimated with a maximum likelihood algorithm ("fitglm" and "fitglme" MATLAB functions). Computational model estimation was completed with an approximate maximum a posteriori algorithm. The procedure used a variational Bayesian technique under the Laplace assumption, implemented in a MATLAB toolbox (available at http://mbb-team.github.io/VBA- toolbox/).

**Computational modeling**

*Multi-source modeling of the modulation of behavior by effort cost/reward benefit trade-offs*

Lastly, we used a mathematical model derived from decision-theory principles to explain the variety of behavioral markers of interest in a unified framework. Further details regarding the model can be found in the supplementary material. The model assumes that the behavior of the monkeys resulted from an effort cost-reward benefit stochastic optimization (as in Lebouc et al, 2016). The exact implementation of the theoretical model for the present behavioral task had two main purposes: 1) integrating the various recorded behaviors into a unifying framework (enabling us to get a session-by-session estimate of the cognitive construct of interest, namely effort) and 2) disentangling the direct influence of effort cost-reward benefit valuations on behavior from potential confounding processes (eg. behavioral excitation (here captured with $K_0$) or subjective uncertainty (or risk, here captured by $\sigma_E$).

This model can be decomposed into two main components, valuation and selection, respectively captured in *equations 1 and 2*. The value of each option is computed by subtracting potential costs from potential benefits, based on the attributes of each options (*Equation 1.1*): the reward benefit term (modulated by the reward level, R), an effort cost term (a quadratic function of the force level F, see Hartmann et al., 2013; Klein-Flügge et al., 2015 for similar formulation) and a subjective probability of success conditional to the exerted force (see Manohar et al., 2015 for similar formulation), when the purpose of the valuation is to select the appropriate force, given the information about required force (Eoption) (*Equation 1.4*). Option value is computed with the assumption that the optimal force $F^*$ is applied (*Equation 1.2*), meaning that the best scenario is considered at the valuation stage. The influence of rewards and efforts decreases over time because of satiety and fatigue, respectively, which are captured by the corresponding variables and the number of trial in the session (N). Each of these terms are parametrized by constants controlling the behavioral predictions given by the model; those constants can be divided into 4 categories: 1) sensitivities to action-outcome values ($K_R$: reward sensitivity, $K_E$: effort sensitivity) ; 2) behavioral response tendencies ($K_0$: activation weight, $\sigma_E$: action-outcome uncertainty) ; 3) dynamic sensitivities ($K_S$: satiety sensitivity, $K_F$: fatigue sensitivity, $K_N$ ; activation-dynamic sensitivity) and 4) behavioral distraction tendencies ($b_M$: motor bias, $b_P$: perseveration bias). The second equation (*Equation 2*) captures 3 types of behavior: participation (whether monkeys are willing to engage in the task or not, at every trial), the choice itself (which of the two options is selected) and the exerted force (how much force the animal actually produces during action execution). Choices are predicted by a softmax decision function integrating the different option values whereas the exerted force is the one optimizing the value of the chosen option. Complex functions in these equations are specified in *equation 3*.

***Equation 1: Valuation Equations***

1. *Force valuation*

$$V\left(F\middle|option\right) = \kappa_0 F + \kappa_R\left(1+\kappa_S N\right)P\left(R_{option}\middle|F\right)R - \kappa_E\left(1+\kappa_F N\right)F^2$$

2. *Option valuation*

$$V(option) = V\left(F^*\middle|option\right)$$

3. *Offer valuation*

$$V(active) = \sum_{i=left,right} V(option_i)$$

4. *Subjective success rate evaluation*

$$P\left(R_{option} | F\right) = 1 - normcdf(E_{option} | F, \sigma_E)$$

***Equation 2: Selection Equations***

1. *Participation*

$$P\left(participation = 1 \middle| options_t\right) = logistic(V(active) + b_P P(participation = 1 | options_{t-1}))$$

2. *Choice*

$$P\left(choice = right \middle| options_t, participation_t = 1\right)$$

$$= logistic(V\left(option_{right}\right) - V\left(option_{left}\right) + b_P P\left(choice = right \middle| options_{t-1}\right) + b_M)$$

3. *Force*

$$F = \underset{F}{argmax}\left(V\left(F \middle| options_t\right)\right) + \varepsilon(\sigma_F)$$

***Equation 3: Definitions***

$\varepsilon = N(0, \sigma_F)$

$$\text{logistic}(x) = \frac{1}{1 + e^{-x}}$$

$$\text{normcdf}(x | \mu, \sigma) = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{x} e^{\frac{-(x-\mu)^2}{2\sigma^2}} dx$$

The model captures the influence of the cost/benefit trade off onto participation (*Equation 2.1)* and choice *(Equation 2.2*). These two behaviors are the results of a soft-max selection between the different options: participation rate was determined by the offer value (the value of the 2 options), choices were determined by the value difference between the right and left option. Intuitively, the reward benefit term increases the rate of participation (for options with a

maximal impact of the marginal benefit of participation on value) and biases choices towards more rewarding and effortful options (amplifying the effect of reward difference while blunting the effect of effort difference). The effort cost term has an opposite influence, decreasing participation for all conditions (without main dependence on the amount of expected rewards and required force) and biasing choices towards less rewarding and effortful options (blunting the effect of the reward difference while amplifying the effect of effort difference). The activation component simply increases participation in a similar pattern as the reward benefit component and biases choices towards less effortful options (because it automatically amplifies the global force anticipated for all levels of required force). The uncertainty component decreases participation by diluting the effect of the benefit component (therefore counter-acting its impact for low reward high effort options) but does not induce significant switch of the choice rate (because the model already assumes that the adaptation to reduce uncertainty of demanding effort occurs during the adjustment of exerted force).

One of the core features of this model is the selection of the exerted force, i.e how much force the animal will exert on the grip given the expected costs and benefits (*Equation 2.3*). The 2 components of value (reward and effort) act in opposite directions: the reward benefit term (scaled by reward benefit sensitivity) enhances the exerted force whereas the effort cost term (scaled by required force cost sensitivity) decreases the exerted force in a non-linear (quadratic) fashion (Lebouc et al, 2016). Note that since the force cannot take negative values, it goes directly to zero when the expected value of the action is negative (i.e. when action is less valuable than inaction). As a common practice (e.g. Lebouc et al, 2016), we included a noise term (ε), which is scaled by the standard-deviation of the residuals ($\sigma_F$). Obviously, the 2 components of value will control (in opposite direction) the adaptation of force to experimental conditions (expected reward and required force) such that the reward benefit term enhances the exerted force for low rewards (where the marginal benefit of force has maximal impact on value) and the effort cost term decreases the exerted force for low rewards and high required forces (where the marginal cost of force has maximal impact on value). The activation component (scaled by the activation weight, $K_0$) acts as a benefit term independent from the expected reward, increasing exerted force and blunting the effect of experimental conditions (this would lead to a maximal force exerted for all rewards and effort combinations at saturation). The uncertainty component ($\sigma_E$) does not have a clear effect on the direction of force modulation (because it depends on the dual impact of uncertainty on the marginal value of force and on the net value of force). By contrast, uncertainty has a straightforward effect on reward and its influence on behavior, including force production. The marginal expected success is directly weighted by the reward term in the equation. Note that the nuisance terms were not included in the exerted exerted force equation for the sake of simplicity. In summary, the dynamic sensitivities to reward benefits and effort costs control the allocation of force over time, in interaction with the value components for satiety and fatigue sensitivities.

*Bayesian model estimation*

The different models were inverted using a variational Bayesian approach under the Laplace approximation (Friston et al., 2007; Daunizeau et al., 2009), implemented in a Matlab toolbox (available at http://mbb-team.github.io/VBA-toolbox/; Daunizeau et al., 2014). This algorithm not only inverts nonlinear models with an efficient and robust parameter estimation (through a maximum a posteriori procedure), but also estimates the model posterior probability, which represents a trade-off between accuracy (goodness of fit) and complexity (degrees of freedom; Robert, 2001).

**Reporting**

The main text contains only major statistical results (group-level effects for variable of interest) whereas the supplementary materials contain tables reporting exhaustively the statistical results obtained in the analysis (subject-level effects and variable of no interest).

## Results

### Behavioral task

We designed a two-options reward-force choice task to evaluate the behavioral markers of effort-costs/reward-benefits arbitrages both in terms of choice and force production (***Figure 1***). At each trial, the monkey was required to make a choice between two options presented on the left and right part of the screen. Each of these options was characterized by two attributes: reward size and required force. Reward size corresponded to the volume of water delivered in correct trials and trials were considered as correct when monkeys produced a force that exceeded the threshold defined by the required force (in terms of percentage of the maximal force, as defined in the methods). As depicted in ***Figure 1***, options' attributes (force and reward) were visually cued: reward size was indicated by a number of drops and required force by the height of a rectangle. We refer to the offer as the pair of options presented at a given trial. The presentation of the offer lasted for a random interval (ranging from 750 to 2000ms) during which the monkey could inspect the options' attributes. Then, a visual go signal, indicated the beginning of the response initiation period, during which the monkey could choose one of the two options by squeezing the corresponding handgrip. Finally, if the monkey successfully exerted the required force i.e. exceeded the force threshold for the selected option, the corresponding reward was delivered. In case of failure to exert the required force, the task simply skipped to the next trial, which was selected randomly. In case of omission (no squeezing either grip), the exact same offer was repeated at the next trial, until a choice was made. Participation (squeezing any grip, successfully or not) and choices (selection of one of the 2 options by pressing on the corresponding side) were treated separately. The experimental conditions differed between trials in their reward level (1, 2, 3 or 4 water drops) and required force (20, 40, 60, 80% of maximal force), randomly and independently assigned to each option (left or right) (***Figure 1***). Only sessions that included more than 100 trials were included in the analysis. This corresponded to the average number of trials required to explore once each combination of reward and force options without taking into consideration the side of presentation ($(4+3+2+1)^2$). The analysis included 148 sessions (48 for monkey A, 52 for monkey B, 48 for monkey E) with a median length of n=361 trials (431 for monkey A, 278 for monkey B, 408 for monkey E) and an inter-quartile range of 219 trials (212 for monkey A, 104 for monkey B, 225 for monkey E).

**The task mobilizes an effort/reward trade-off**

We first assessed the validity of the task by evaluating the impact of task parameters on monkeys' behavior. We tested whether reward size and required force affected force production, participation and choices using generalized linear models (***Figure 2***).

First, the force exerted by the monkeys was a reliable indicator of the monkey's compliance to the task rule (***Figure 2A***): force peak increased systematically with the required force of the chosen option ($\beta$ = 0.06, $t_{(147)}$ = 4.45, $p$ = $1.69\times10^{-5}$), demonstrating that monkeys understood the relationship between visual cues and the amount of force to exert on the grip. Note that force exertion was also affected by the chosen reward ($\beta$ = 0.02, $t_{(147)}$ = 3.25, $p$ = $1.42\times10^{-3}$) (***Figure 2B***) and the interaction between reward and required force was significant ($\beta$ = 0.01, $t_{(147)}$ = 2.97, $p$ = $3.50\times10^{-3}$).

Participation reflects the monkeys willingness to perform the task and select one of the two options, given the offer. In the analysis of participation, we asked two questions: 1) whether offer attributes (required forces and rewards) influenced trial-by-trial participation and 2) whether this influence reflected an effort cost/reward benefit trade-off. To answer the first question, we imagined two scenarios for the influence of offer attributes on participation: (i) monkeys adjusted their participation based on the value of only one option in the offer - the best option, which is the optimal strategy - or (ii) participation was influenced by the relative value of the current offer (defined by the rewards and required forces of the 2 options) on the scale of what could be expected in this task, in terms of reward sizes and required force levels. In that frame, the relative value of each offer would simply scale with the sum of the value of the two options (sum of rewards – sum of forces). We tested these two hypotheses by comparing a model predicting participation based on the largest reward and the smallest required force to a model where participation depended on the sum of rewards and the sum of required forces. Compared to the latter, the former model was very unlikely (*freq* = 0.37, *ep* = $3.6\times10^{-3}$). Hence, monkey's participation more likely arose from an evaluation process involving both options (scenario (ii)). To address the second question, i.e. whether this process reflected an effort-cost/reward-benefit trade-off, we selected the best model (sum of option values) to test for a consistent effect of reward and required force attributes onto the participation. This confirmed that participation was positively modulated by the sum of rewards offered ($\beta$ = 0.49, $t_{(147)}$ = 6.62, $p$ = $7.36\times10^{-5}$) (***Figure 2D***) and negatively modulated by the sum of offered required forces ($\beta$ = -0.51, $t_{(147)}$ = -7.93, $p$ = $4.99\times10^{-13}$) (***Figure 2C***), in line with an effort cost-reward-benefit trade-off.

We also examined the monkeys' choices, which appeared reliably dependent upon the difference between option values (***Figure 2E-F***). There was indeed a significant contribution of the difference in both reward ($\beta$ = 2.39, $t_{(147)}$ = 9.44, $p$ = 7.94×10$^{-17}$) (***Figure 2F***) and required force ($\beta$ = -1.84, $t_{(147)}$ = -6.95, $p$ = 1.09×10$^{-10}$) (***Figure 2E***). Even if the previous analyses clearly demonstrates that monkeys adjusted their behavior based upon visual information about expected reward and required force, suggesting an effort-reward trade-off, the true nature of the cost as a decision variable influencing choices negatively might not have been effort but risk. Here, risk is defined as the probability of failing to complete a trial, knowing that the monkey participated. Indeed, monkeys tended to fail more often in trials with high required force (logistic regression of the success rate, $\beta$ = -3.24, $t_{(147)}$ = -3.98, $p$ = 1.05×10$^{-4}$), such that monkeys could have avoided options of high required force just because they were associated with higher risks (of not obtaining the reward) rather than with higher effort. To address this issue, we performed a model comparison between models predicting behavior using required force or success rate as predictor variables. Models integrating the required force level fit our data better than the other ones integrating risk for both participation (*freq* = 0.58, *ep* = 9.96×10$^{-1}$) and choices (*freq* = 0.98, *ep* = 1). Thus, behavior in this task provides reliable estimates of reward/effort trade-offs in monkeys.

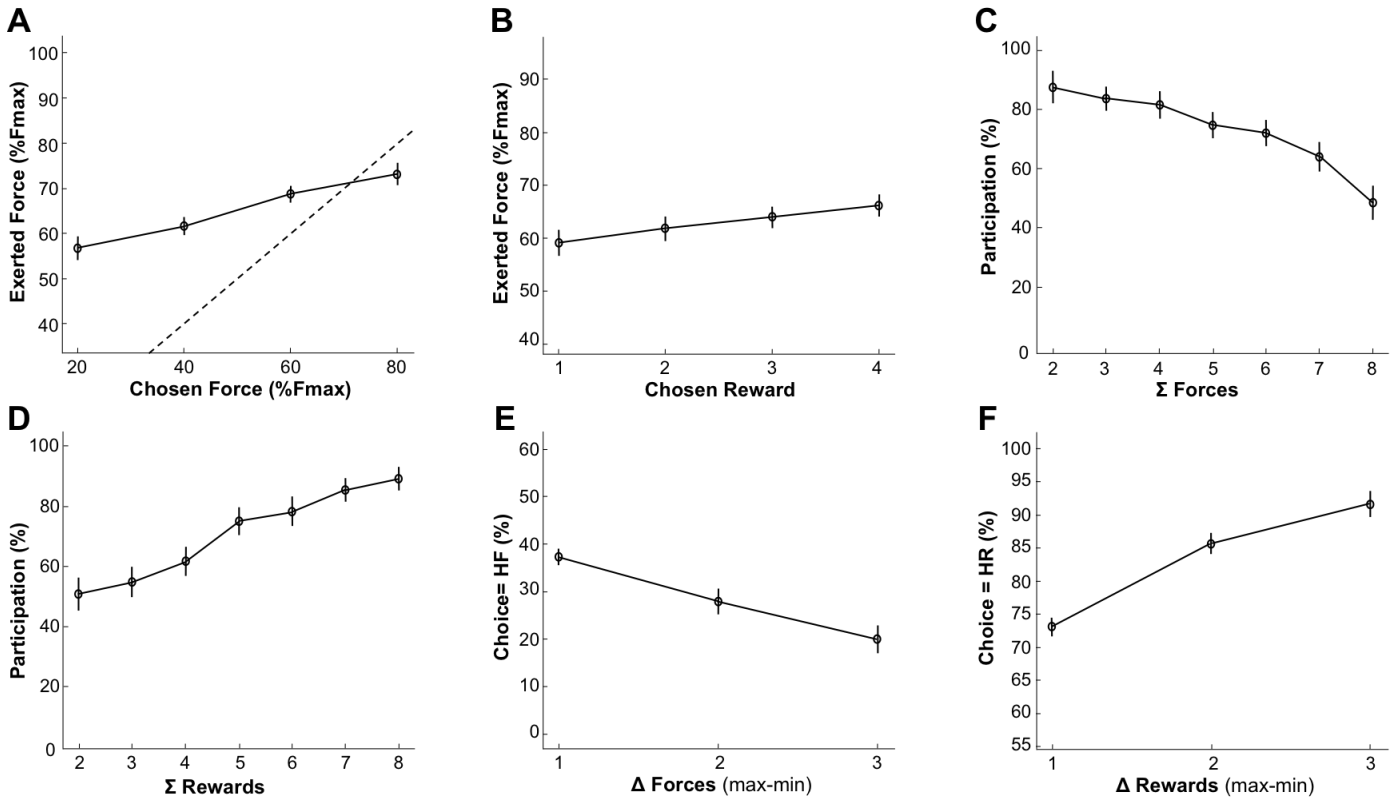


**Figure 2. Behavior under placebo condition**

Lines and dots represent group-level means (across monkeys) and error-bars represent SEM (across sessions). **A**. Relationship of exerted force with required force of the chosen option. The force exerted at the peak increased with the required force of the chosen option ($\beta$ = 0.06, $t_{(147)}$ = 4.45, $p$ = 1.69×10$^{-5}$). The dotted line represents the optimal relationship between exerted force and required force (the minimum required force to complete the trial i.e the position of the force threshold).

**B.** Relationship between exerted force and expected reward of the chosen option. Reward had a positive influence on the exerted force ($\beta$ = 0.02, $t_{(147)}$ = 3.25, $p$ = 1.42×10$^{-3}$)

**C-D.** Participation (%) to trials as a function of the sum of required forces (**C**) or reward (**D**). **C**. Participation was negatively modulated by the sum of required forces ($\beta$ = -0.51, $t_{(147)}$ = -7.93, $p$ = 4.99×10$^{-13}$) presented in an offer. **D.** Monkeys' participation was positively modulated by the sum of rewards ($\beta$ = 0.49, $t_{(147)}$=6.62, $p$=7.36×10$^{-5}$) presented in an offer.

**E**. Proportion of high-reward choices as a function of the difference in offered rewards between the 2 options (1d-reward conditions). There was a significant effect of the difference in required force on choices ($\beta$ = -1.84, $t_{(147)}$ = -6.95, $p$ = 1.09×10$^{-10}$).

**F.** Proportion of high-required force choices across difference in offered forces (1d-required force conditions). There was a significant contribution of the difference in reward in choices ($\beta$ = 2.39, $t_{(147)}$ = 9.44, $p$ = 7.94×10$^{-17}$).

Finally, we used a computational approach to capture the joint influence of the effort-costs/reward-benefits trade-off on choices and force production (see ***Figure 3*** and Methods for details of the model). In short, effort is defined as a single computational variable having a dual influence on behavior: a negative influence on choices (all other things being equal, monkeys minimize energy expenditure) and a positive influence on force production (monkeys exert more force and therefore spend more energy for high-force options). The model assumes that monkeys tried to optimize the ratio between effort-costs (the amount of resources needed to perform the task, modulated by fatigue accumulating during the task) and reward benefits (the expected reward, given the force produced, as well as the level of satiety that builds up over time. When compared to the behavioral data, the model exhibited a good fit of participation (balanced accuracy = 72%), choice (balanced accuracy = 73%) and peak force ($R^2$ = 16%). It was also able to remarkably reproduce the qualitative effect of experimental conditions (***Figure 4***). This computational approach confirms the interpretation of the behavioral data in terms of effort, defined as the amount of resources invested in the action and affecting both choices (as a variable of decision) and force production (as a driving force). Altogether, this analysis of the behavioral data indicates that monkeys did follow an effort/reward trade-off in this task, with effort influencing negatively the choice and positively action execution, and reward size modulating positively both of these processes.

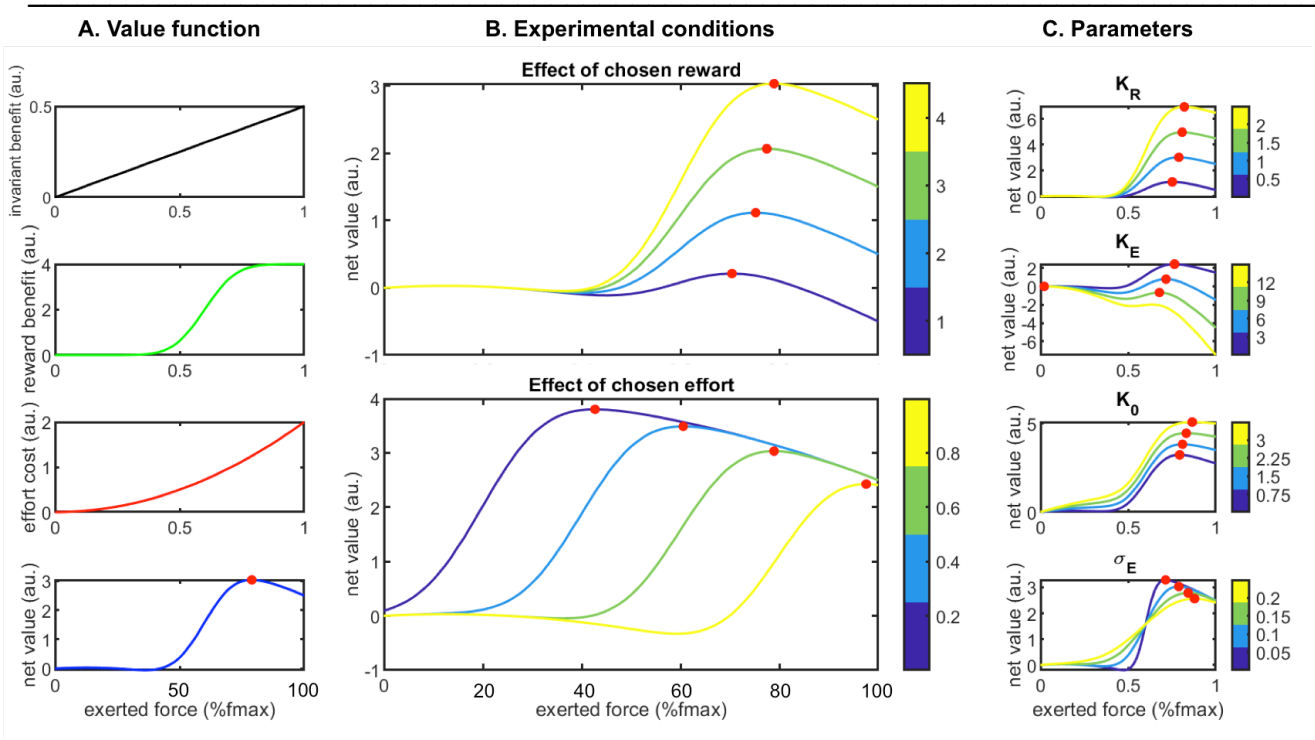


**Figure 3. Properties of the optimal force selection model**

**A**. Components of the value function depending on the exerted force. **A1**: the activation component is a linear invariant benefit, **A2**: the reward benefit component is a sigmoidal function with a slope scaled by the uncertainty component, **A3**: the effort cost component is a quadratic function. **A4**: the net value is the sum of three previously described components. **B**. Impact of main experimental conditions onto the value function: **B1**: chosen rewards increase the optimal expected value and slightly shift the optimal force. **B2**: chosen effort decreases the optimal expected value but increases the optimal force (bottom) **C**. Impact of main parameters onto the value function. **C1**: increase of $K_r$ (sensitivity to reward) leads to huge increase of optimal value and slight increase of optimal force. **C2**: increase of $K_e$ (sensitivity to effort) leads to decrease of optimal value and decrease of optimal force with a collapse to zero-force when the optimal value becomes negative. **C3**: increase of Ko (activation weight) leads to increase of optimal value and increase of optimal force. **C3**: increase of ∫E: (action-outcome uncertainty) leads to decrease of optimal value and increase of optimal force, shifting it away from the target force (bottom). Simulations were performed with an initial parameters vector of {= 1 ; = -1 ; = 2 ; = 1 ; = 0.5 ; = -1 ; = 0.1 ; = 0 ;= 0 ; =0} and an initial input vector of { R = 4 ; E = 0.6 ; N = 0 }. Red dots indicate the optimal force to exert when the net value function is represented. Color-bars indicate either input or parameter values when there are variations.

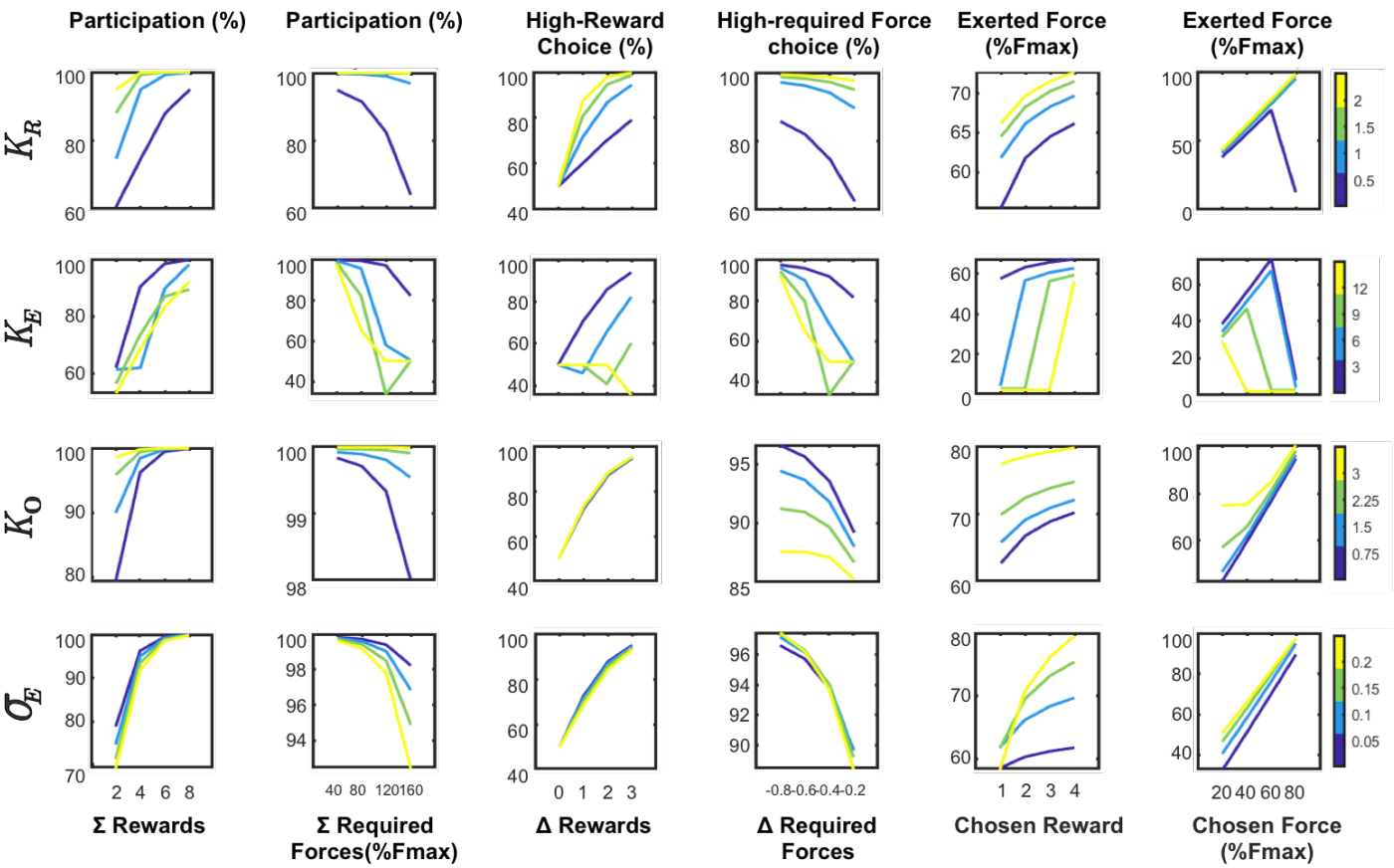


**Figure 4. Predictions of the complete computational model for choice and force production**

The graphs display major predicted dependencies between experimental conditions and measurements under changing parameter values. The columns display the relationship between: **A.** the participation rate and sum of offered rewards. **B.** the participation rate and sum of offered efforts. **C.** The proportion of high-reward choices and difference in offered rewards; **D.** The proportion of high-effort choices and difference in offered required forces; **E**. The exerted force and the chosen reward. **F.** the chosen effort. The rows display the impact of the 4 key parameters (top to bottom: $K_r$, $K_e$, $K_o$ and $\int_E$. Color-bars indicate parameter values. Simulations were performed with an initial parameters vector of {= 1 ; = -1 ; = 2 ; = 1 ; = 0.5 ; = -1 ; = 0.1 ; = 0 ;= 0 ; =0} and an initial input vector of { R = 4 ; E = 0.6 ; N = 0 }.

**Clonidine increases effort sensitivity without affecting reward sensitiviy**

To assess the role of noradrenaline in the effort/reward trade-off, we examined the influence of clonidine, a drug that decreases noradrenaline levels, on the previously described behavioral measures (Aghajanian et al, 1982; Bouret & Richmond, 2009) (***Figure 5***). First, clonidine had a significant influence on choices and the nature of that influence was particularly obvious in some task situations. For example, in offers for which one of the 2 options included both the highest level of force and the highest level of reward (referred to as the high-reward/high-required-force option), the frequency of choosing that high-reward high-required force option was decreased (*clonidine* = 0.47, *placebo* = *0.63*, $F_{(1,145)}$ = 43.54, $p$ = 7.28×10$^{-10}$), indicating a shift in sensitivity to expected effort and/ or to the expected reward. To evaluate the specific influence of the drug on reward-based vs effort-based choices, we selected conditions in which options differed only in reward levels (1D-reward conditions) and conditions in which options differed only in required force (1D-required force conditions). Practically, we computed the frequency of high-reward choices in the 1D-reward conditions and the frequency of high-required force choices in the 1D-required force conditions (***Figure 5A-B)***. There was a specific decrease in the proportion of high-required force choices in the 1D-required force conditions (*clonidine* = 0.14, *placebo* = *0.24*, $F_{(1,145)}$ = 14.81, $p$ = 1.78×10$^{-4}$) (***Figure 5A)*** but no significant effect on high-reward choices in the 1D-reward conditions (*clonidine* = 0.86, *placebo* = *0.86*, $F_{(1,145)}$ = 9.5×10$^{-3}$, $p$ = 0.92) (***Figure 5B)***. Finally, to evaluate the relative influence of reward and effort information on choices across all task conditions, we used a logistic regression to model choices in every single trial of the task, for both placebo and clonidine sessions. This analysis confirmed that the weight assigned to the difference in required force levels between options increased under clonidine (*clonidine* = -2.55 +/- 0.23 (mean and SEM), *placebo* = -1.65 +/- 0.28, $F_{(1,145)}$ = 14.81, $p$ = 1.78×10$^{-4}$) while the drug did not affect the weight assigned to the difference in reward sizes (*clonidine* = 2.29 +/- 0.21, *placebo* = 2.45 +/- 0.30, $F_{(1,145)}$ = 0.47, $p$ = 0.49).

After assessing the impact of clonidine on choices, we considered its influence on participation as a function of the required forces and reward sizes of the offers (sets of 2 conditions, ***Figure 5C-D***) using a mixed model in which monkey identity was treated as random effects and all other factors as fixed effects. Paradoxically, monkeys participated more under clonidine treatment (*clonidine* = 0.68, *placebo* = *0.62*, $F_{(1,145)}$ = 5.82, $p$ = 1.71×10$^{-2}$), a phenomenon characterized by a significant increase in participation bias (the constant term of the logistic regression; *clonidine* = 1.33 +/- 0.30, *placebo* = 0.79 +/- 0.26, $F_{(1,145)}$ = 5.01, $p$ = 0.02). Besides this increase in participation bias, there was also a tendency for an increase in the negative weight of the sum of required forces that did not reach significance in the fixed-effect component (*clonidine* = -0.75 +/- 0.18, *placebo* = -0.46 +/- 0.04, $F_{(1,145)}$ = 2.02, $p$ = 0.16) but was significant for 2 out of 3 monkeys (random effects, Monkey A, $F_{(1,145)}$ = 37.46, $p$ = 8.27×10$^{-9}$ ; Monkey B, $F_{(1,145)}$ = 15.92, $p$ = 1.04×10$^{-4}$ ; Monkey E, $F_{(1,145)}$ = 2.05, $p$ = 0.15). The positive effect of clonidine on the participation bias might be a side effect of the increased sensitivity to effort that reduces the average total reward per trial, and thus might induce a compensatory increase in participation to maintain the total amount of reward per session. Consistent with this explanation, there was no difference in the total reward earned between clonidine and placebo sessions (*clonidine* = 269.99 +/- 32.41 ml, *placebo* = 272.11 +/- 35.25 ml, $F_{(1,145)}$ = 6.4×10$^{-3}$, $p$ = 0.93), despite the decrease in high required force/high-reward choices (see above). Furthermore, participation biases across clonidine sessions were negatively predicted by session-wise choice sensitivity to required force ($\beta$ = -0.51 +/- 0.08, $t_{(145)}$ = -6.15, $p$ = 7.14×10$^{-9}$), supporting an interpretation in which the influence of clonidine on a single latent decision variable (effort costs) had both a negative influence on required force-dependent choices and a positive

influence on participation, through a compensatory mechanism to ensure sufficient water intake.

Clonidine also affected force production negatively, as measured by a significant decrease in the maximum exerted force (force peak) after clonidine compared to placebo injections (*clonidine* = 0.55 +/- 0.04, *placebo* = 0.64+/- 0.03, $F_{(1,145)}$ = 21.78, $p$ = 6.91×10$^{-6}$). The maximal force recorded within experimental sessions were significantly reduced under clonidine compared to placebo sessions (empirical Fmax(placebo)= 94.42 ± 3.86% ; empirical Fmax(clonidine)= 105.75 ± 1.91% ; F(1,145) = 10.4 , p = 1.55e-03 ). The GLM performed on force peaks to decompose the influence of multiple factors showed that the drug only had a negative effect on the constant term (the positive bias to exert force on the grip, *clonidine* = 0.55 +/- 0.05, *placebo* = 0.63 +/- 0.03, $F_{(1,145)}$ = 20.70, $p$ = 1.12×10$^{-5}$), but it did not affect the modulation of exerted force by either task factors (required force weight: *clonidine* = 0.06 +/- 0.01, *placebo* = 0.05 +/- 0.01, $F_{(1,145)}$ = 0.92, $p$ = 0.33, ***Figure 5E,*** reward weights: *clonidine* = 0.02 +/- 8.3×10$^{-3}$, *placebo* = 0.02 +/- 5×10$^{-3}$, $F_{(1,145)}$ = 0.93, $p$ = 0.33, ***Figure 5F***). Thus, clonidine biased force production negatively but it did not affect its modulation by task parameters (reward and required force).

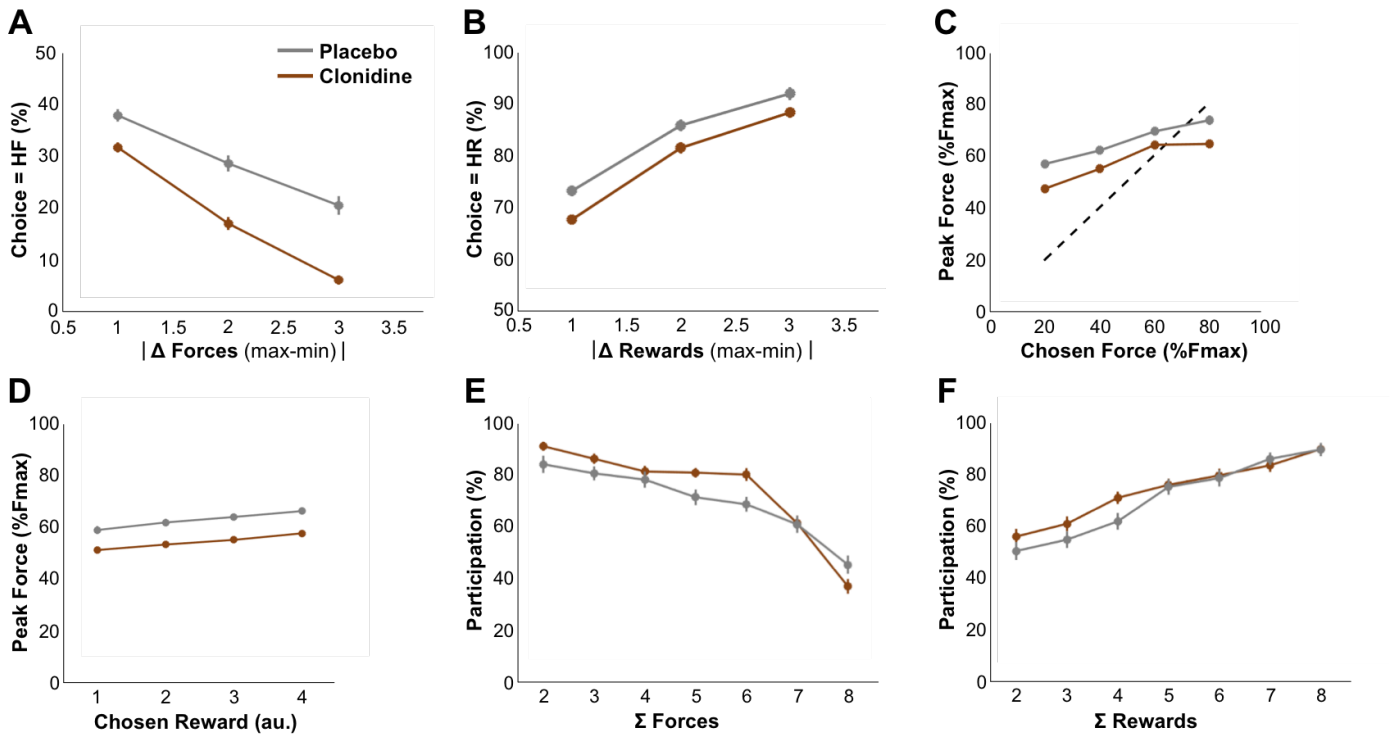


**Figure 5. Clonidine affects choice and force production**

Behavior of the monkeys under the placebo (grey) and clonidine (brown) conditions. Lines and dots represent group-level means (across monkeys) and error-bars represent SEM (across sessions).

**A.** Relationship between the percentage of high-required force choices and the difference in offered forces. The weight of the difference in required force increased under clonidine (clonidine = -2.55 +/- 0.23, placebo = -1.65 +/- 0.28, $F_{(1,145)}$ = 14.81, p = 1.78×10$^{-4}$).

**B.** Relationship between the percentage of high-reward choices and the difference in offered rewards. Under clonidine, the weight of the difference in reward sizes did not change (clonidine = 2.29 +/- 0.21, placebo = 2.45 +/- 0.30, $F_{(1,145)} = 0.47$, p = 0.49).

**C-D.** Relationship between exerted force relation and chosen force level (**C**) and chosen reward size (**D**). The dotted line represents the optimal relation (identity) between exerted force and force difficulty (the minimum required force to complete the trial). Clonidine had a main effect on force production (*clonidine* = 0.55 +/- 0.05, *placebo* = 0.63 +/- 0.03, $F_{(1,145)} = 20.70$, $p = 1.12\times10^{-5}$), without affecting the effects task factors (reward weights: *clonidine* = 0.02 +/- $8.3\times10^{-3}$, *placebo* = 0.02 +/- $5\times10^{-3}$, $F_{(1,145)} = 0.93$, $p = 0.33$; required force weight: *clonidine* = 0.06 +/- 0.01, *placebo* = 0.05 +/- 0.01, $F_{(1,145)} = 0.92$, $p = 0.33$).

**E-F.** Relationship between participation and the sum of offered forces (**E**) and sum of offered rewards (**F**). There was a tendency for an increase in the weight of the sum of required forces that did not reach significance (*clonidine* = -0.75 +/- 0.18, *placebo* = -0.46 +/- 0.04, $F_{(1,145)} = 2.02$, $p = 0.16$) (**E**) but no effect of clonidine on the modulation of participation by the sum of rewards (**F**).

Altogether, the effect of clonidine onto choices and force production could be subsumed under a common increase of the sensitivity to effort cost. As an empirical confirmation of this intuition, there was a positive correlation between the parameters capturing each of these two effects across clonidine sessions. The parameter $\beta e$ capturing the influence of required force level on choices and the intercept parameter ($\beta o$, bias) in the model capturing the modulation of force production displayed a significant positive relationship ($\beta$ = 0.63+/- 0.10, $t_{(144)} = 6.48$, $p = 1.33\times10^{-9}$). Thus, across treatment sessions, there was a systematic positive relationship between the influence of clonidine on required force-based choices and on force production, in line with the idea that clonidine acts on a single variable, effort, which affects these two behavioral measures.

To confirm that interpretation, we used the computational model to capture the influence of the treatment on the effort variable. The first step was to check that the model provided a good fit for all 3 key variables: participation (balanced accuracy =76%), choice (balanced accuracy = 76%) and peak force ($R^2$ = 21%) for clonidine sessions. Given the quality of the fit, we were justified in extracting the 10 parameters calculated on a session-by-session basis. We started by testing whether the set of parameters belonging to the placebo conditions were different from the clonidine session with a multivariate analysis of variance (predicting the parameter set with the treatment condition), enabling us to estimate the number of relevant dimensions separating the two treatment conditions. Only one dimension was sufficient to separate the two treatment conditions (d=1, ë=0.69, p= $6.37\times10^{-5}$), which means that a single hyperplane in the parameter space can provide a reasonable classification of treatment conditions. To further characterize the effect of clonidine on the computational parameters, we conducted a classification analysis (predicting the treatment condition with the parameter set) under sparsity assumption (a lower number of predictive parameters is more likely) to infer whether a specific parameter of the model was modified under the clonidine condition (and therefore could be a good predictor of the clonidine condition in the classification). We could reliably predict the treatment condition based on the computational parameters (balanced accuracy = 72%, exceedance probability = 1 - $4.59\times10^{-4}$). We found three non-zero parameters that predicted the clonidine condition: an increase of the force cost sensitivity $K_E$ (+1.14 sd.), an increase of the laterality bias $b_M$ (right-oriented) (+0.76 sd.) and a decrease of the perseveration bias $b_P$ (-0.69 sd.). The modification of the side bias, a behavioral nuisance parameter, could be due to the physical implementation

of the required force (reflecting the fact that monkeys perceived the right handgrip as less difficult and thus selected it more often, all others things being equal). But more importantly, the force sensitivity that drives the three behavioral measures (participation, choice and force production), was the single parameter of interest being impacted, and there was no effect on reward sensitivity, behavioral activation weight or subjective uncertainty. In other words, the computational analysis confirmed that clonidine influenced a single variable, 'effort', affects both choices and force production as a function of expected costs but independently of expected benefits.

Altogether, this analysis demonstrates that clonidine administration increased the sensitivity to effort costs, i.e. increases the negative effect of required force on choices and decreased the amount of force produced. To further assess the specificity of this effect of clonidine on motivational processes, we considered more generic effects on behavior. *First*, we considered a global negative effect on behavioral reactivity (related to arousal or vigilance), rather than a specific effect on effort. As mentioned above, however, participation rate was increased under clonidine and response time was unaffected (*clonidine* = 0.53 +/- 0.06, *placebo* = 0.52 +/- 0.08, $F_{(1,145)}$ = 0.10, $p$ = 0.75). Thus, the influence of clonidine on behavior in this task could not be captured solely as a global decrease in behavioral reactivity. We also examined the influence of clonidine on response times (RT). A simple regression analysis of RT could not retrieve any significant effect of clonidine, neither at the beginning of the session (RT(placebo)= 0.505 ± 0.087 s.; RT(clonidine)= 0.539 ± 0.069 s.; F(1,145) = 1.366 , p =0.244) nor on linear variations across the session (ΔRT/Δtime(placebo)= 0.045± 0.042 s. ; ΔRT/Δtime (clonidine)= -0.011 ± 0.031 s.; F(1,145) =1.385, p =0.241). This does not exclude the possibility that clonidine affected vigilance of monkeys because the trend is toward a slowing down of monkey responses. However, it could totally be a motivational effect that impact decision uncertainty, a major factor in the determination of response time (see supplements). *Second*, we considered a direct effect of clonidine on muscle effectors, rather than on a decision variable computed in the brain. We measured the efficiency of muscular contraction through the known linear relationship between maximal force contraction and maximal velocity of contraction, also called Fitts law (see LeBouc et al, 2016 for more details). The muscular contractility index (i.e. the regression coefficient between the velocity peak and the force peak) was not affected by clonidine treatment (*clonidine* = 4.32 +/- 0.43, *placebo* = 4.14 +/- 0.40, $F_{(1,145)}$ = 1.19, $p$ = 0.27) (***Figure 6A***). Thus, clonidine did not impact the monkeys' capacity to execute the actions, and its influence on behavior was more likely due to an impact on motivation, more precisely on the effort processing. *Finally*, we considered a scenario where clonidine only had a direct effect of performance, but an indirect effect on choices (via the resulting decrease in reward probability). Under such an 'indirect' scenario, clonidine only affected force production and consequently decreased the success rate of monkeys, making options requiring higher forces appear more risky (higher probability of failing). In other words, the influence of clonidine on choices would have been mediated by its effect on success rate. However, we observed no progressive change of the high-required force choices during the course of clonidine sessions, as would be expected with a progressive adaptation to a decrease in success rate ($\beta$ = $-9.73\times10^{-5}$+/- $9.13\times10^{-5}$, $t_{(145)}$ = -1.06, $p$ = 0.28) (***Figure 6B***). The effect of clonidine on force was stable across trials (no main effect of trial number on peak force, ***Figure 6C***). Furthermore, we did not observe any significant relationship between the success rate and the proportion of high-required force choices across sessions ($\beta$ = 0.04 +/- 0.06, $t_{(144)}$ = 0.70, $p$ = 0.17) (***Figure 6D***). Finally, we directly examined the possibility that success rate was a better predictor of choices than required force by adding it as a covariate in the logistic regression model describing the influence of task parameters on choices, as well as the effect of clonidine. This did not affect the model fit, indicating that success rate had no significant role in mediating the influence of clonidine on required force-based choices ($F_{(1,145)}$ = 18.63, $p$ = $2.93\times10^{-5}$). In sum, the influence of clonidine on behavior is unlikely to result from a global decrease in behavioral reactivity, as expected for an

interpretation in terms of vigilance or arousal. It is also unlikely to result from a direct effect on muscular effectors, and an indirect influence on choices though success rate. Rather, in line with our hypothesis, clonidine affects a single decision variable, which we refer to as 'effort' and which affects both choices and force production.

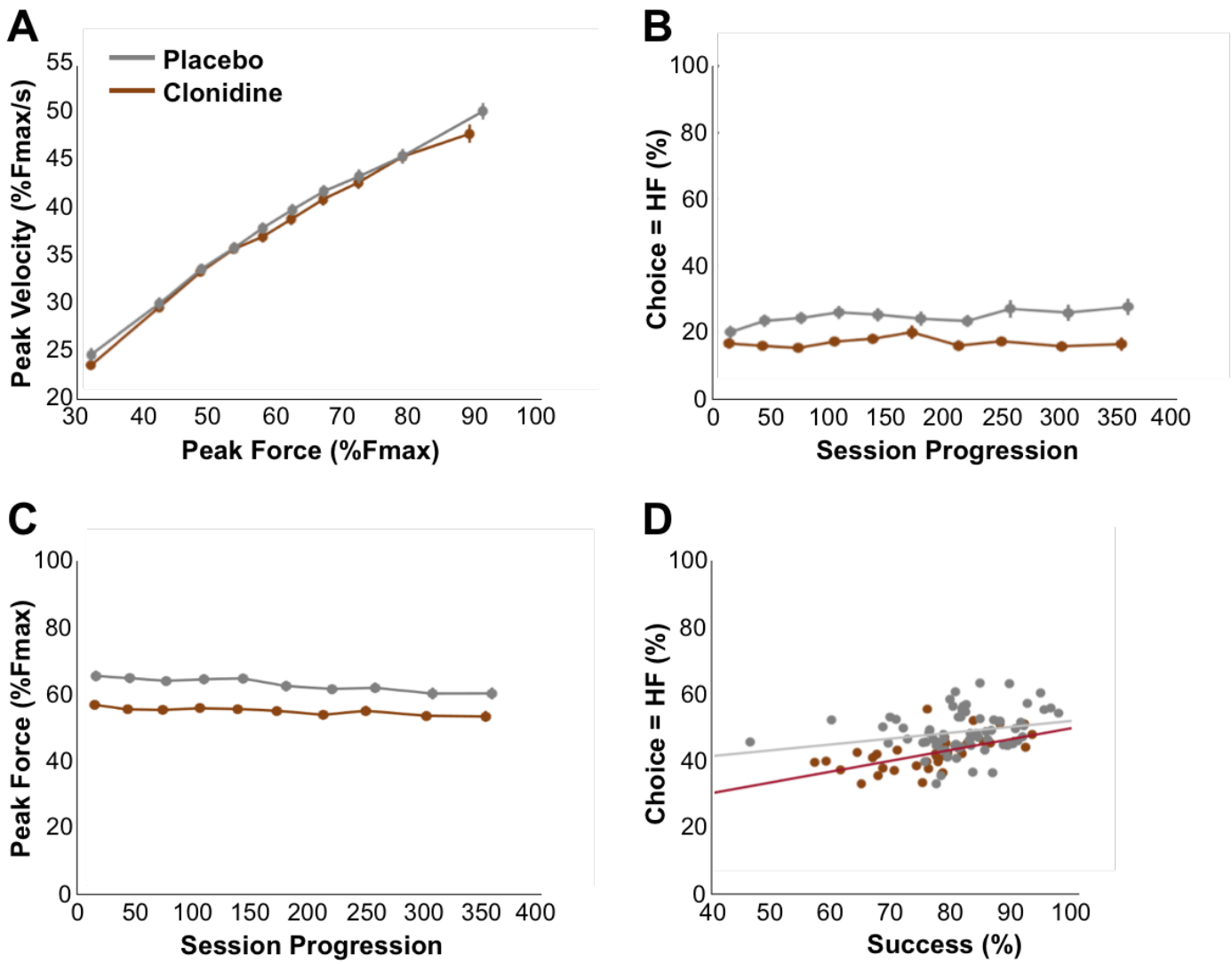


**Figure 6. Specificity of the clonidine effect.**

Behavior of the monkeys in the placebo (grey) and clonidine (brown) conditions. Lines and dots represent group-level means (across monkeys) and error-bars represent SEM (across sessions).

**A**. Relation between peak velocity and peak of the exerted force (commonly known as Fitts law). Clonidine did not affect this proxy for muscular contractility (*clonidine* = 4.32 +/- 0.43, *placebo* = 4.14 +/- 0.40, $F_{(1,145)} = 1.19$, $p = 0.27$). **B.** Influence of session progression (trial number) on the percentage of high-required force choices. Monkeys made less high-required force choices overall but the effect was constant over the session ($\beta = -9.73\times10^{-5}$+/- $9.13\times10^{-5}$, $t_{(145)} = -1.06$, $p = 0.28$).

**C.** Influence of session progression (trial number) on exerted force. Exerted force was decreased under clonidine but the effect of the drug was constant over the session (p>0.05).

**D.** Proportion of high-required force choices as a function of success (proportion of correctly executed actions in the session, across sessions). There was no significant relationship between success rate and the proportion of high-force choices ($\beta$ = 0.04 +/- 0.06, $t_{(144)}$ = 0.70, $p$ = 0.17).

## Discussion

**Summary**

In the present study, we investigated the causal implication of noradrenaline in the effort/reward trade-off in monkeys performing a novel task where 1) the influence of effort and reward could be dissociated and 2) this trade-off affected two distinct motivational processes: choice and force production. We examined the causal role of noradrenaline using systemic injections of clonidine, which decreased brain noradrenaline levels, and we used saline injections in control sessions. Clonidine amplified effort costs, as measured both by a reduced fraction of high-force choices and by a reduction in the amount of force produced. This effect was relatively specific: clonidine did not affect reward-based choices and its effect could not be interpreted in terms of a global decrease in behavioral reactivity or in terms of motor impairment. Altogether, this work strongly supports the role of noradrenaline in effort, which we defined as a computational process adjusting the amount of resources mobilized for action. In that frame, the noradrenaline dependent variable (« effort ») affects not only choices, as resource expenditure tends to be avoided, but also action production, as this increase in resources at the time of action drives performance.

**Technical considerations:**

This novel behavioral task enabled us to clarify the role of noradrenaline in effort by eliminating confounding factors. Here, we defined effort as a computational process reflecting the dual influence of resource mobilization on choices and force production. We believe that it is critical to clarify the definition of effort and avoid confusion with other variables such as mere exerted force, risk, or reward, in order to assess the relative contribution of distinct neuromodulatory systems to the distinct components of decision making (Doya, 2008; Dayan, 2012; Walton & Bouret, 2018). First and foremost, by independently manipulating reward and required force, we could isolate the direct influence of expected effort costs (required force) from the incentive influence of reward on force production. In addition, although monkeys had unequal performances across force levels, we verified that the effects of required force on behavior were more likely to be accounted for by effort than by risk (probability of failing) or muscular efficacy.

We used a systemic pharmacological approach to modulate noradrenergic levels in the brain and assess the causal role of noradrenaline in effort processing. Indeed, our goal here was to evaluate the functional role of noradrenaline through its global impact on the brain, without restricting our study to one of the numerous targets of the *locus coeruleus*. Even though the functional heterogeneity of the noradrenergic system has been emphasized in recent studies, our study aims at characterizing the noradrenergic system as a single functional entity (Chandler et al., 2014; Schwarz et al., 2015, Uematsu et al, 2017). Given its widespread impact on global brain functions, we believe that a global manipulation of NA levels provides critical information regarding its functional role (Eldar et al., 2013; Guedj et al., 2016; Sara and Bouret, 2012; Warren et al., 2016). Another limitation of such pharmacological modifications is our limited knowledge of the actual impact of those treatments onto the noradrenergic system (*locus coeruleus* firing rate, synaptic cleft noradrenaline concentration, post-synaptic potentials). Here, we take for granted that our observations result from the primary effects of the drug, as it remains the most parsimonious explanation for any observed pharmacological effect, and we therefore neglect the secondary effects. An important body of literature has demonstrated that clonidine leads to decreased *locus coeruleus* activity (Abercrombie and Jacobs, 1987; Aghajanian and VanderMaelen, 1982; Bouret & Richmond, 2009). Still, regarding its secondary effects, we cannot exclude the

possibility that clonidine has a potential impact onto the hetero-inhibitory $\alpha_2$ receptors located in the prefrontal cortex (Arnsten, 2015). However, the stimulation of prefrontal $\alpha_2$ receptors was shown to facilitate persistent activity in the prefrontal cortex and working memory performances (Arnsten and Goldman-Rakic, 1985; Li et al., 1999), which is hard to reconcile with our findings regarding the effect of clonidine. In spite of these limitations, we hope that this study, by providing a clear insight into the role of noradrenaline in decision-making, will inspire future studies to dissect its underlying neurobiological mechanisms.

**Dual impact of clonidine on effort-based choices and force production**

Clonidine had a strong and specific effect on effort processing, as monkeys tended to avoid options requiring more force and globally, they exerted less force. These effects are unlikely to be accounted for by a global decrease in reactivity or by a motor impairment: animals participated more in the task under clonidine and our measure of motor functions displayed no significant effect of the treatment. We could also exclude an interpretations in terms of risk (through a motor impairment) because both choices and participation were better explained by the level of required force than by success rate. Noticeably, the strong effect of clonidine on effort-based choices in this task contrasts with the lack of effect of clonidine on cost sensitivity in a task where monkeys chose between sequences of different lengths to obtain their reward, and cost was interpreted in terms of delay rather than effort (Jahn et al, 2018). Altogether, our work shows that clonidine specifically affects the processing of effort costs without affecting decisions based on reward availability. This provides neurobiological support to the idea that effort differs from other types of costs such as delay or risk, which both relate to the distribution of reward in time and rely more critically upon dopamine (Varazzani et al, 2015; Klein-Fugge et al, 2015; Roesh et al, 2007; Kobayashi & Schultz, 2008; Fiorillo et al, 2003; Soares et al, 2016; Walton & Bouret, 2018). More generally speaking, this work points to a very complementary role of NA and DA in effort, defined more generally as a mobilization of resources for action: the NA system would be involved in mobilizing energy based on expected costs (what, here, were referred to as 'effort') whereas DA would be more critical in mobilizing energy based on expected benefits (reward).

Besides affecting effort-based decision-making, clonidine also decreased the amount of force produced, irrespectively of the instruction. This confirms and extends previous observations where clonidine decreased the amount of force produced in a task where force was not instrumental (Jahn et al, 2018). Interestingly, in this task, the influence of clonidine on force production across sessions was directly related to its influence on decision making, in line with the idea that it affects a common process, effort, which affects both choices and action execution. Critically, computational modeling confirmed that such a computational variable could reliably capture the monkeys' behavior in control conditions as well as the influence of clonidine. Altogether, these data are compatible with the idea that by decreasing NA levels, clonidine disrupts the monkeys' ability to mobilize resources to face the challenge at hand.

**Relation with LC neurophysiology**

This interpretation is in line with our recent neurophysiological studies demonstrating a strong relationship between the activation of LC neurons and the triggering of demanding actions. Indeed, it is now firmly established that a transient LC activation occurs when animals trigger a goal-directed behavioral response (Rajkowski et al, 2004; Bouret & Sara, 2004; Bouret & Richmond, 2009; Kalwani et al, 2014). Quantitative analyses of this activity revealed that the magnitude of the LC activation associated with the triggering of an action increased when the action value

decreased, because its magnitude increased with lower reward and/or higher cost (Bouret et al, 2012 Bouret & Richmond, 2015; Varazzani et al, 2015). Note that the LC activation related to the difficulty to trigger the action (just before action onset) could readily be dissociated from the activation related to the execution of the effortful action itself (Varazzani et al, 2015). In sum, the fact that effortful events are associated with a transient activation of LC neurons is in line with the present findings suggesting that a minimum NA level is necessary to cope with effort. To some extent, this relationship between LC activation and effort is related to an emerging literature showing a strong link between cognitive load and pupil dilation, since pupil is sometimes interpreted as a proxy for central noradrenergic tone (Kahneman & Beatty, 1966; Wand et al, 2015.; Kurzban et al, 2013, Alnæs et al., 2014; de Gee et al., 2017; Nassar et al., 2012; Van der Wel & Steenbergen, 2018 for review). Interestingly, Zenon et al (2014) already proposed to use pupil dilation as a physiological measure of effort to overcome either physical or mental challenges. Note, however, that even if the relationship between pupil diameter and LC activity has been demonstrated both at rest and in relation to task performance (Joshi et al, 2016; Varazzani et al, 2015), it is far from being specific. Indeed, pupil dilation is essentially a measure of autonomic arousal and as such it is associated with numerous other autonomic and neuronal responses (Joshi et al, 2016; Reimer et al, 2016). Thus, even if physiological, imaging and pharmacological data coherently support an interpretation of NA function in terms of effort, the physiological processes underlying this function require further investigation, in particular to understand how the activation of the central noradrenergic system interacts with the rest of the brain to support behavioral and cognitive processes underlying effort.

**NA and effort: beyond the physical domain?**

Even if this study focused on physical effort, other studies have demonstrated the strong implication of noradrenaline in various forms of attention or executive control, which could be interpreted in terms of cognitive effort (Chamberlain et al., 2006, 2009; Eagle et al., 2008; Dalley et al, 2001; Tait et al, 2007; McGaughy et al., 2008; Warner et al, 2018; Reynaud et al, 2019). Even though this would require further testing, we believe that the physical and mental effort are actually two facets of the same core 'effort' function in which NA plays a crucial role: to some extent, the influence of systemic manipulations of NA levels could all be interpreted in terms of allocation of cognitive resources. Indeed, even if clonidine affected physical effort, it affected the control of behavior (how much force the animals were willing to exert) rather than directly changing the reactivity of muscular effectors. In other words, our data are compatible with a theoretical frame where noradrenaline levels define the amount of cognitive control available to overcome the challenges at hand, irrespectively of the nature of the challenge and the resources to be mobilized. Again, this is very speculative and assessing the extent to which the role of NA in effort could be understood in terms of cognitive control would require extensive work, both at the computational and at the experimental level.

**Clinical relevance**

These findings may provide an important neurobiological addition to recent frameworks for pathological deficits in motivation such as apathy, observed in neurological disorders such as Parkinson's disease and psychiatric disorders such as depression (Kurian et al., 2011; Torres et al., 2003a; Pessiglione et al, 2017; Le Heron et al, 2019). Indeed, a deficit in motivation could be related both to an alteration of the incentive system (which enhances energy based on expected benefits, and relies upon dopamine) and an alteration of an 'effort' system that enhances energy based on

expected costs (as we propose here to rely upon noradrenaline). Being able to evaluate the relative impact of the disease upon each of these systems and/or to assess the efficacy of complementary strategies based upon DA vs NA may, in the long run, be beneficial to patients suffering from apathy.

## Conclusion

In sum, the current study demonstrates the causal role of noradrenaline in effort, defined as a process that mobilizes resources in order to face challenges at hand. We do not claim that this work provides a definitive description of effort, neither at a theoretical not at a neurobiological level. But since this interpretation crystallizes several elements of the literature on noradrenaline and complements the huge literature on the incentive effect of dopamine, we hope that it will pave the way for further research investigating the physiological mechanisms by which the *locus coeruleus* interacts with other brain regions to support effort.

## Bibliography


Abercrombie ED, Jacobs BL. Microinjected clonidine inhibits noradrenergic neurons of the locus coeruleus in freely moving cats. Neuroscience Letters. 1987 May 6;76(2):203–8.

Adamantidis AR, Tsai H-C, Boutrel B, Zhang F, Stuber GD, Budygin EA, et al. Optogenetic Interrogation of Dopaminergic Modulation of the Multiple Phases of Reward-Seeking Behavior. J Neurosci. 2011 Jul 27;31(30):10829–35.

Aghajanian GK, VanderMaelen CP. alpha 2-adrenoceptor-mediated hyperpolarization of locus coeruleus neurons: intracellular studies in vivo. Science. 1982 Mar 12;215(4538):1394–6.

Albert PR, Benkelfat C. The neurobiology of depression--revisiting the serotonin hypothesis. II. Genetic, epigenetic and clinical studies. Philos Trans R Soc Lond, B, Biol Sci. 2013;368(1615):20120535.

Alnæs D, Markus Handal Sneve, Espeseth T, Endestad T, Pavert SHP van de, Laeng B. Pupil size signals mental effort deployed during multiple object tracking and predicts brain activity in the dorsal attention network and the locus coeruleus. Journal of Vision. 2014 Apr 1;14(4):1–1.

Arnsten AFT. Stress weakens prefrontal networks: molecular insults to higher cognition. Nat Neurosci. 2015 Oct;18(10):1376–85.

Arnsten AFT, Goldman-Rakic PS. Alpha 2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. Science. 1985 Dec 13;230:1273–7.

Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci. 2005;28:403–50.

Beierholm U, Guitart-Masip M, Economides M, Chowdhury R, Düzel E, Dolan R, et al. Dopamine modulates reward-related vigor. Neuropsychopharmacology. 2013;38(8):1495–1503.

Berridge CW, Waterhouse BD. The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Research Reviews. 2003 Apr 1;42(1):33–84.

Berridge CW. Noradrenergic modulation of arousal. Brain Research Reviews. 2008 Jun 1;58(1):1–17.

Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. Life Sci. 1993;52(12):1023–9.

Bouret S, Richmond BJ. Relation of Locus Coeruleus Neurons in Monkeys to Pavlovian and Operant Behaviors. J Neurophysiol. 2009 Feb;101(2):898–911.

Bouret S, Sara SJ. Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci. 2005 Nov;28(11):574–82.

Chamberlain SR, Hampshire A, Müller U, Rubia K, Del Campo N, Craig K, et al. Atomoxetine modulates right inferior frontal activation during inhibitory control: a pharmacological functional magnetic resonance imaging study. Biol Psychiatry. 2009 Apr 1;65(7):550–5.

Chamberlain SR, Müller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. Neurochemical modulation of response inhibition and probabilistic learning in humans. Science. 2006 Feb 10;311(5762):861–3.

Chandler DJ, Gao W-J, Waterhouse BD. Heterogeneous organization of the locus coeruleus projections to prefrontal and motor cortices. Proc Natl Acad Sci USA. 2014 May 6;111(18):6816–21.

Chaudhuri KR, Schapira AHV. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol. 2009 May;8(5):464–74.

Cools R, Nakamura K, Daw ND. Serotonin and dopamine: unifying affective, activational, and decision functions. Neuropsychopharmacology. 2011 Jan;36(1):98–113.

Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. Neuron. 2008 May 8;58(3):306–24.

Dayan P. Twenty-five lessons from computational neuromodulation. Neuron. 2012;76(1):240–56.

de Gee JW, Colizoli O, Kloosterman NA, Knapen T, Nieuwenhuis S, Donner TH. Dynamic modulation of decision biases by brainstem arousal systems. Elife. 2017 Apr 11;6.

Dienel GA, Cruz NF. Aerobic glycolysis during brain activation: adrenergic regulation and influence of norepinephrine on astrocytic metabolism. J Neurochem. 2016 Jul;138(1):14–52.

Dragone A, Lasaponara S, Pinto M, Rotondaro F, De Luca M, Doricchi F. Expectancy modulates pupil size during endogenous orienting of spatial attention. Cortex. 2017 Oct 3;

Doya K. Modulators of decision making. Nat Neurosci. 2008 Apr;11(4):410-6.

Eagle DM, Bari A, Robbins TW. The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. Psychopharmacology. 2008 Aug 1;199(3):439–56.

Eldar E, Cohen JD, Niv Y. The effects of neural gain on attention and learning. Nat Neurosci. 2013 Aug;16(8):1146–53.

Fiorillo CD, Tobler PN, Schultz W. Discrete coding of reward probability and uncertainty by dopamine neurons. Science. 2003;299(5614):1898–902.

Fooden J. Systematic review of the rhesus macaque, Macaca mulatta (Zimmermann, 1780) [Internet]. Chicago, Ill. : Field Museum of Natural History; 2000 [cited 2018 Sep 14]. 196 p. Available from: http://archive.org/details/systematicreview96foode

Gan JO, Walton ME, Phillips PEM. Dissociable cost and benefit encoding of future rewards by mesolimbic dopamine. Nature Neuroscience. 2010 Jan;13(1):25–7.

Goodman LS. Goodman and Gilman's the pharmacological basis of therapeutics. Vol. 1549. McGraw-Hill New York; 1996.

Guedj C, Monfardini E, Reynaud AJ, Farnè A, Meunier M, Hadj-Bouziane F. Boosting Norepinephrine Transmission Triggers Flexible Reconfiguration of Brain Networks at Rest. Cereb Cortex. 2016 Sep 6;

Hamid AA, Pettibone JR, Mabrouk OS, Hetrick VL, Schmidt R, Vander Weele CM, et al. Mesolimbic dopamine signals the value of work. Nature neuroscience. 2016;19(1):117.

Hollon NG, Arnold MM, Gan JO, Walton ME, Phillips PEM. Dopamine-associated cached values are not sufficient as the basis for action selection. Proc Natl Acad Sci USA. 2014 Dec 23;111(51):18357–62.

Joshi S, Li Y, Kalwani RM, Gold JI. Relationships between Pupil Diameter and Neuronal Activity in the Locus Coeruleus, Colliculi, and Cingulate Cortex. Neuron. 2016 Jan 6;89(1):221–34.

Keele SW. Movement control in skilled motor performance. Psychological Bulletin. 1968;70(6, Pt.1):387–403.

Klein-Flügge MC, Kennerley SW, Saraiva AC, Penny WD, Bestmann S. Behavioral Modeling of Human Choices Reveals Dissociable Effects of Physical Effort and Temporal Delay on Reward Devaluation. PLOS Computational Biology. 2015 Mar 27;11(3):e1004116.

Kobayashi S, Schultz W. Influence of reward delays on responses of dopamine neurons. Journal of neuroscience. 2008;28(31):7837–46.

Kurian MA, Gissen P, Smith M, Heales SJ, Clayton PT. The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. The Lancet Neurology. 2011 Aug 1;10(8):721–33.

Le Bouc R, Rigoux L, Schmidt L, Degos B, Welter M-L, Vidailhet M, et al. Computational Dissection of Dopamine Motor and Motivational Functions in Humans. J Neurosci. 2016 22;36(25):6623–33.

Le Heron, C., Plant, O., Manohar, S., Ang, Y. S., Jackson, M., Lennox, G., . . . Husain, M. Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson's disease. Brain. 2018. 141(5), 1455-1469.

Lee S-H, Dan Y. Neuromodulation of Brain States. Neuron. 2012 Oct 4;76(1):209–22.

Li B-M, Mao Z-M, Wang M, Mei Z-T. Alpha-2 Adrenergic Modulation of Prefrontal Cortical Neuronal Activity Related to Spatial Working Memory in Monkeys. Neuropsychopharmacology. 1999 Nov;21(5):601–

Manohar, S. G., & Husain, M. Reduced pupillary reward sensitivity in Parkinson's disease. npj Parkinson's Disease, 2015. 1, 15026.

Marder E. Neuromodulation of Neuronal Circuits: Back to the Future. Neuron. 2012 Oct 4;76(1):1–11.

McGaughy J, Ross RS, Eichenbaum H. Noradrenergic, but not cholinergic, deafferentation of prefrontal cortex impairs attentional set-shifting. Neuroscience. 2008 Apr 22;153(1):63–71.

McGuigan, S., Zhou, S. H., Brosnan, M. B., Thyagarajan, D., Bellgrove, M. A., & Chong, T. T. (2019). Dopamine restores cognitive motivation in Parkinson's disease. *Brain, 142*(3), 719-732.

Nassar MR, Rumsey KM, Wilson RC, Parikh K, Heasly B, Gold JI. Rational regulation of learning dynamics by pupil-linked arousal systems. Nature Neuroscience. 2012 Jun 3;15(7):nn.3130.

Niv Y, Daw ND, Joel D, Dayan P. Tonic dopamine: opportunity costs and the control of response vigor. Psychopharmacology (Berl). 2007 Apr;191(3):507–20.

Partan SR. SINGLE AND MULTICHANNEL SIGNAL COMPOSITION: FACIAL EXPRESSIONS AND VOCALIZATIONS OF RHESUS MACAQUES (MACACA MULATTA). Behaviour. 2002 Aug 1;139(8):993–1027.

Pasquereau B, Turner RS. Limited Encoding of Effort by Dopamine Neurons in a Cost–Benefit Trade-off Task. J Neurosci. 2013 May 8;33(19):8288–300.

Paukert M, Agarwal A, Cha J, Doze VA, Kang JU, Bergles DE. Norepinephrine Controls Astroglial Responsiveness to Local Circuit Activity. Neuron. 2014 Jun 18;82(6):1263–70.

Pessiglione M, Vinckier F, Bouret S, Daunizeau J, Le Bouc R. Why not try harder? Computational approach to motivation deficits in neuro-psychiatric diseases. Brain. 2017 Nov 29;

Reynaud AJ, Froesel M, Guedj C, Ben Hadj Hassen S, Cléry J, Meunier M, Ben Hamed S, Hadj-Bouziane F. Atomoxetine improves attentional orienting in a predictive context. Neuropharmacology. 2019 May 15;150:59-69.

Roesch MR, Calu DJ, Schoenbaum G. Dopamine neurons encode the better option in rats deciding between differently delayed or sized rewards. Nature Neuroscience. 2007 Dec;10(12):1615–24.

Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology. 2007 Apr 1;191(3):461–82.

Sara SJ. The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci. 2009 Mar;10(3):211–23.

Sara SJ, Bouret S. Orienting and reorienting: the locus coeruleus mediates cognition through arousal. Neuron. 2012;76(1):130–141.

Saunders C, Limbird LE. Localization and trafficking of alpha2-adrenergic receptor subtypes in cells and tissues. Pharmacol Ther. 1999 Nov;84(2):193–205.

Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997;275(5306):1593–9.

Schwarz LA, Miyamichi K, Gao XJ, Beier KT, Weissbourd B, DeLoach KE, et al. Viral-genetic tracing of the input-output organization of a central noradrenaline circuit. Nature. 2015 Aug 6;524(7563):88–92.

Soares S, Atallah BV, Paton JJ. Midbrain dopamine neurons control judgment of time. Science. 2016 Dec 9;354(6317):1273–7.

Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. A causal link between prediction errors, dopamine neurons and learning. Nature neuroscience. 2013;16(7):966.

Spencer RC, Berridge CW. Receptor and circuit mechanisms underlying differential procognitive actions of psychostimulants. Neuropsychopharmacology. 2019; 44(10):1820-1827

Syed ECJ, Grima LL, Magill PJ, Bogacz R, Brown P, Walton ME. Action initiation shapes mesolimbic dopamine encoding of future rewards. Nat Neurosci. 2016 Jan;19(1):34–6.

Torres GE, Gainetdinov RR, Caron MG. Plasma membrane monoamine transporters: structure, regulation and function. Nat Rev Neurosci. 2003 Jan;4(1):13–25.

Toussay X, Basu K, Lacoste B, Hamel E. Locus coeruleus stimulation recruits a broad cortical neuronal network and increases cortical perfusion. J Neurosci. 2013 Feb 20;33(8):3390–401.

Uematsu A, Tan BZ, Ycu EA, Cuevas JS, Koivumaa J, Junyent F, et al. Modular organization of the brainstem noradrenaline system coordinates opposing learning states. Nature Neuroscience. 2017 Nov;20(11):1602–11.

Varazzani C, San-Galli A, Gilardeau S, Bouret S. Noradrenaline and dopamine neurons in the reward/effort trade-off: a direct electrophysiological comparison in behaving monkeys. Journal of Neuroscience. 2015;35(20):7866–77.

Ventura R, Latagliata EC, Morrone C, La Mela I, Puglisi-Allegra S. Prefrontal Norepinephrine Determines Attribution of “High” Motivational Salience. PLoS One [Internet]. 2008 Aug 22 [cited 2018 Sep 14];3(8). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2516177/

Walton ME, Bouret S. What Is the Relationship between Dopamine and Effort? Trends in Neurosciences. 2019 Feb 1;42(2):79–91.

Wang C-A, McInnis H, Brien DC, Pari G, Munoz DP. Disruption of pupil size modulation correlates with voluntary motor preparation deficits in Parkinson’s disease. Neuropsychologia. 2016;80:176–84.

Wang X, Piñol RA, Byrne P, Mendelowitz D. Optogenetic Stimulation of Locus Ceruleus Neurons Augments Inhibitory Transmission to Parasympathetic Cardiac Vagal Neurons via Activation of Brainstem α1 and β1 Receptors. J Neurosci. 2014 Apr 30;34(18):6182–9.

Warner CB, Ottman AA, Brown JN. The Role of Atomoxetine for Parkinson Disease–Related Executive Dysfunction: A Systematic Review. Journal of clinical psychopharmacology. 2018;38(6):627–31.

Warren CM, Wilson RC, van der Wee NJ, Giltay EJ, van Noorden MS, Cohen JD, et al. The effect of atomoxetine on random and directed exploration in humans. PloS one. 2017;12(4):e0176034.

Wong DT, Threlkeld PG, Best KL, Bymaster FP. A new inhibitor of norepinephrine uptake devoid of affinity for receptors in rat brain. J Pharmacol Exp Ther. 1982 Jul;222(1):61–5.

Yakovleff A, Roby-Brami A, Guezard B, Mansour H, Bussel B, Privat A. Locomotion in rats transplanted with noradrenergic neurons. Brain Research Bulletin. 1989 Jan 1;22(1):115–21.

Yao ST, Finkelstein DI, Lawrence AJ. Nitrergic stimulation of the locus coeruleus modulates blood pressure and heart rate in the anaesthetized rat. Neuroscience. 1999;91(2):621–9.

Yu AJ, Dayan P. Uncertainty, neuromodulation, and attention. Neuron. 2005 May 19;46(4):681–92.

Zénon A, Devesse S, Olivier E. Dopamine manipulation affects response vigor independently of opportunity cost. Journal of Neuroscience. 2016;36(37):9516–25.

Zénon A, Sidibé M, Olivier E. Pupil size variations correlate with physical effort perception. Front Behav Neurosci [Internet]. 2014 Aug 25 [cited 2018 Sep 14];8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4142600/

**Acknowledgements:**

The authors would like to thank Caroline Jahn for providing critical preliminary data and valuable input regarding the experimental design and the project as a whole. We also would like to thank the ICM Phenoparc Core Facility, especially Estelle Chavret-Reculon and Morgane Weissenburger for continuous assistance ranging from animal care to precious advices regarding these experiments. This project was supported by CNRS, ICM and by a grant from Fondation de France to SB.

# Supplementary Materials

## Description of the computational model

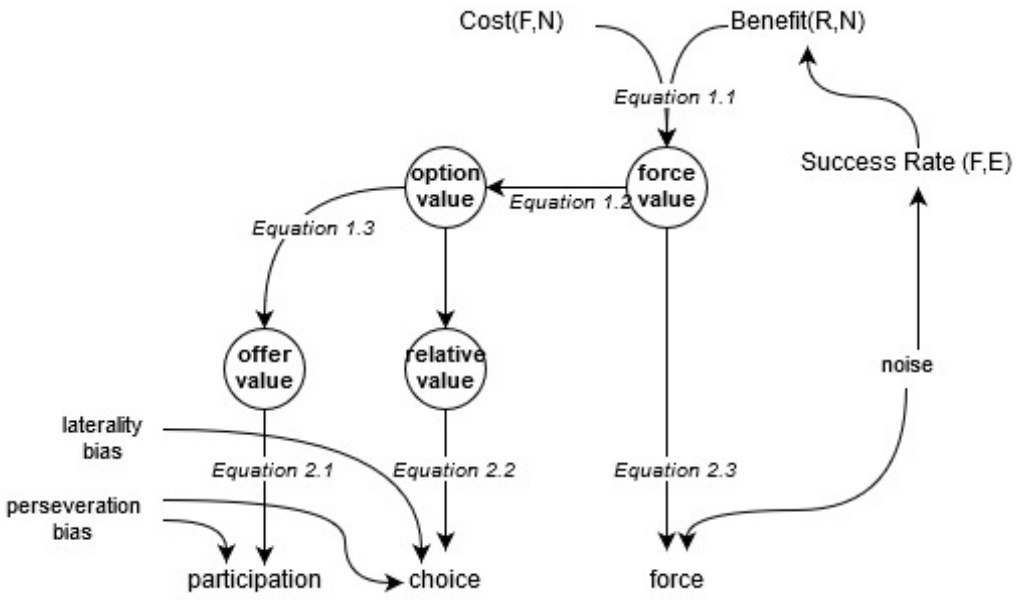


*Figure S1. Graphical structure of the computational model*

| Input | Description | Latent variable |
|---|---|---|
| R | Expected reward | ↑ Benefit |
| E | Required force | ↓ Success Rate |
| F | Exerted force | ↑ Success Rate<br>↑ Cost |
| N | Trial number | ↓ Benefit<br>↑Cost |
| **Output** | **Description** | |
| participation | Active (1) or Passive (0) | |
| choice | Left (0) or Right (1) | |
| Force | Percentage of maximal force exerted (0-100%) | |
| **Parameter** | **Description** | **Effect** |
| $\kappa_R$ | Reward sensitivity | ↑ participation $\propto R$<br>choice → High R<br>↑ force $\propto R$ |
| $\kappa_E$ | Effort sensitivity | ↓ participation $\propto E$<br>choice→ Low E<br>↓ force |
| $\kappa_0$ | Activation rate | ↑ participation<br>choice → High E<br>↑ force |
| $\kappa_S$ | Satiety sensitivity | ↓ participation $\propto R, N$<br>choice → Low R<br>↓ force $\propto R, N$ |
| $\kappa_F$ | Fatigue sensitivity | ↓ participation $\propto E, N$<br>choice→ Low E<br>↓ force $\propto E, N$ |
| $\sigma_E$ | Force execution noise | ↓ participation<br>↑ force |

| | | |
|---|---|---|
| $b_P$ | Perseveration bias | participation→ previous participation<br><br>choice→ previous choice |
| $b_M$ | Laterality bias | choice→ Right option |

**Analysis of response-time in the reward-effort choice task**

In the first examination of the behavioral data, we inspected how the response time (RT) of the monkeys related to the experimental conditions. In order to be consistent with the former approach, only behavioral markers demonstrating a consistent effect of the cost and benefit manipulations were kept for further analysis in the drug conditions. Unfortunately, this was not the case in the exploratory analysis that we conducted. In principle, response time during this task aggregated several processes: option valuations, option comparisons and action preparation. We started with the initial assumption that option valuation was the dominant determinant of monkey's latencies (similarly to the participation rate which usually follow the opposite pattern of response times). Therefore, we tested an effect of the sum of rewards and the sum of efforts offered on response time but neither reached significance. To relax the initial assumption, we considered alternative scenarios for the determination of response time in this task and compared them in a formal model comparison approach. We formulated four possibilities: 1) response-times reflect offer valuation and is impacted by the sum of options values (our initial hypothesis), 2) response-times reflect option comparison before attribute integration and is impacted by the difference of option values, 3) response-times reflect action preparation after the option is selected and is impacted by the chosen option value or 4) response-times reflect option comparison after attribute integration and is impacted by a global choice uncertainty metric. For the last formulation, we chose to represent the choice uncertainty with the entropy of the joint participation and choice probabilities derived from the logistic regressions, which can be understood as the wavering between the three implicit options of the task (participating on the left, right or not participating). The result of the model comparison showed a clear winning model ($freq = 0.91$, $ep > 0.999$), the choice uncertainty model (the last one). This demonstrates a commonality in the determinant of response-time across monkeys and sessions but was insufficient to qualify as a valid behavioral marker of cost-benefit computations. Indeed, the best model doesn't allow us to identify separately influences of the reward and effort on response-time and the estimation of behavioral parameters depends upon the other pre-defined behavioral markers (participation and choice) which makes this marker redundant and less robust.

## Supplementary figures

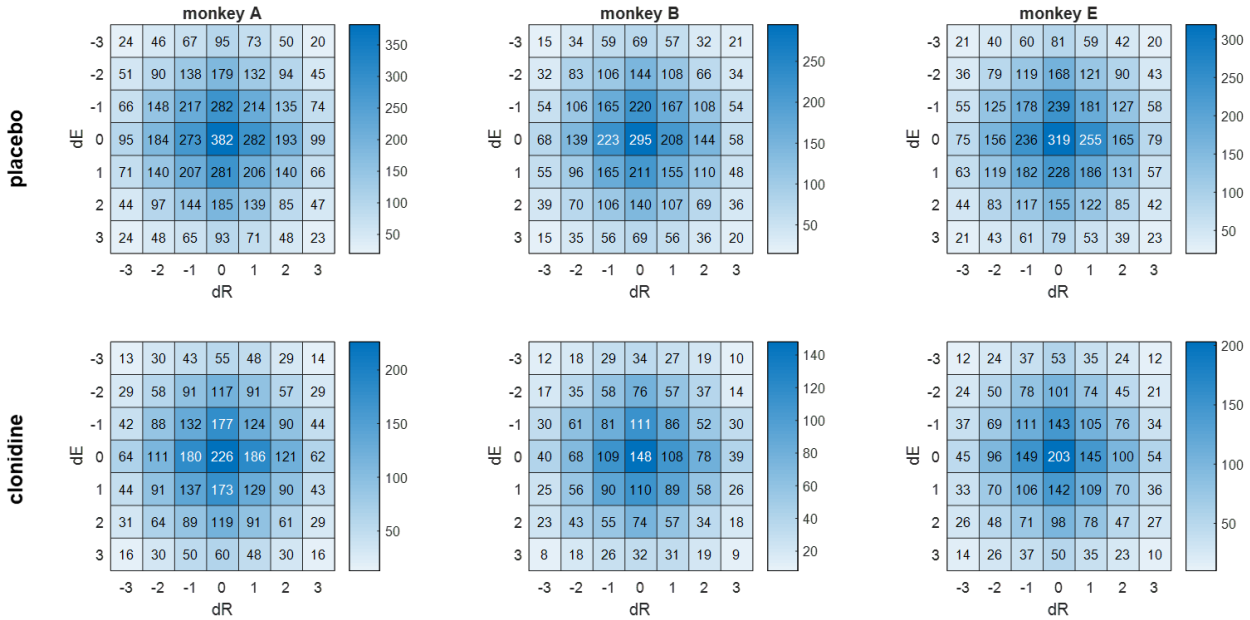


***Figure S1. Distribution of experimental conditions across placebo and drug sessions for all monkeys.***

*dR = difference of reward levels between the two options. dE = difference of force levels between the two options. Absolute numbers of trials are indicated inside each box. Note that there is a difference between the placebo and drug session in the absolute numbers (because there were more placebo sessions included) but no difference in the relative proportions. Figure 1. Distribution of experimental conditions across placebo and drug sessions for all monkeys. dR = difference of reward levels between the two options. dE = difference of force levels between the two options. Absolute numbers of trials are indicated inside each box. Note that there is a difference between the placebo and drug session in the absolute numbers (because there were more placebo sessions included) but no difference in the relative proportions.*

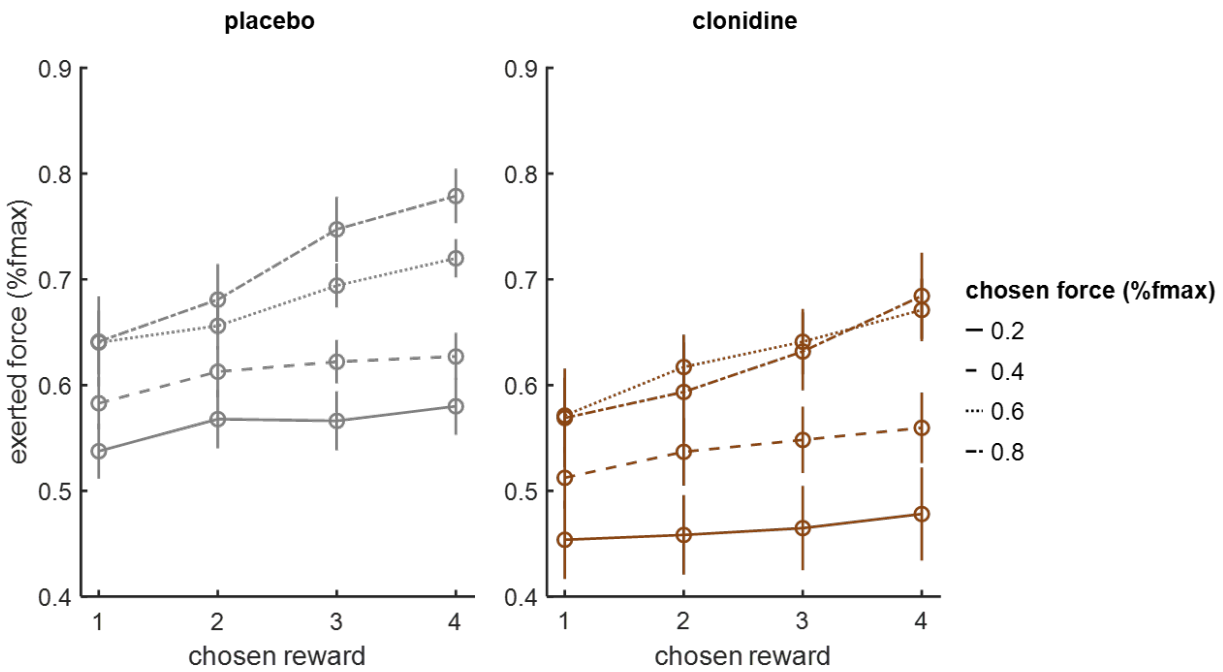

**Figure S 2.** ***Exerted force depicted as a function of the chosen reward (in abscises) and the required force level (with different line styles), for the placebo (in grey) and the clonidine sessions (in brown).***

## Supplementary tables

### Table S 1. Summary of treatments impact on main behavioral metrics

| subject | treatment | N(session) | participation rate (%) | | high-reward high-effort choice rate (%) | | peak force (%) | | response time (s.) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | mean | sem | mean | sem | mean | sem | mean | sem |
| A | clonidine | 13 | 0,68 | 0,02 | 0,45 | 0,02 | 0,48 | 0,01 | 0,64 | 0,02 |
| A | placebo | 21 | 0,67 | 0,02 | 0,64 | 0,03 | 0,59 | 0,01 | 0,72 | 0,02 |
| B | clonidine | 12 | 0,76 | 0,02 | 0,40 | 0,02 | 0,52 | 0,01 | 0,40 | 0,01 |
| B | placebo | 26 | 0,64 | 0,03 | 0,55 | 0,02 | 0,61 | 0,01 | 0,35 | 0,01 |
| E | clonidine | 12 | 0,63 | 0,04 | 0,57 | 0,03 | 0,66 | 0,03 | 0,56 | 0,03 |
| E | placebo | 23 | 0,56 | 0,04 | 0,70 | 0,02 | 0,72 | 0,02 | 0,50 | 0,01 |

### Table S 2. Summary of treatments impact on ethological metric

| subject | treatment | N_session | behavioral diversity (#) | | behavioral activity (%) | | Affiliation | Aggression | Alertness | Avoidance | Food consumption | Food search | Object manipulation | Stereotypies | Rest | Self-injury | Self-protection | Submission |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | mean | sem | mean | sem | frequencies (%) | | | | | | | | | | | |
| A | clonidine | 13 | 4,88 | 0,52 | 0,69 | 0,05 | 0,05 | 0,01 | 0,06 | 0,00 | 0,08 | 0,09 | 0,01 | 0,28 | 0,31 | 0,04 | 0,08 | 0,00 |
| A | placebo | 21 | 5,86 | 0,46 | 0,76 | 0,05 | 0,06 | 0,01 | 0,05 | 0,00 | 0,21 | 0,22 | 0,02 | 0,06 | 0,24 | 0,01 | 0,12 | 0,00 |
| B | clonidine | 12 | 2,63 | 0,42 | 0,60 | 0,07 | 0,02 | 0,00 | 0,00 | 0,00 | 0,11 | 0,02 | 0,00 | 0,00 | 0,40 | 0,00 | 0,45 | 0,00 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B | placebo | 26 | 4,14 | 0,40 | 0,64 | 0,05 | 0,00 | 0,00 | 0,05 | 0,00 | 0,15 | 0,17 | 0,00 | 0,01 | 0,36 | 0,00 | 0,26 | 0,00 |
| E | clonidine | 12 | 4,38 | 0,68 | 0,60 | 0,04 | 0,26 | 0,00 | 0,05 | 0,00 | 0,08 | 0,10 | 0,00 | 0,08 | 0,40 | 0,00 | 0,02 | 0,01 |
| E | placebo | 23 | 4,91 | 0,37 | 0,71 | 0,05 | 0,10 | 0,00 | 0,17 | 0,00 | 0,10 | 0,10 | 0,00 | 0,19 | 0,29 | 0,00 | 0,02 | 0,02 |

| subject | treatment | Affiliation | Aggression | Alertness | Avoidance | Food consumption | Food search | Object manipulation | Stereotypies | Rest | Self-injury | Self-protection | Submission |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | frequencies (%) | | | | | | | |
| A | clonidine | 0,05 | 0,01 | 0,06 | 0,00 | 0,08 | 0,09 | 0,01 | 0,28 | 0,31 | 0,04 | 0,08 | 0,00 |
| A | placebo | 0,06 | 0,01 | 0,05 | 0,00 | 0,21 | 0,22 | 0,02 | 0,06 | 0,24 | 0,01 | 0,12 | 0,00 |
| B | clonidine | 0,02 | 0,00 | 0,00 | 0,00 | 0,11 | 0,02 | 0,00 | 0,00 | 0,40 | 0,00 | 0,45 | 0,00 |
| B | placebo | 0,00 | 0,00 | 0,05 | 0,00 | 0,15 | 0,17 | 0,00 | 0,01 | 0,36 | 0,00 | 0,26 | 0,00 |
| E | clonidine | 0,26 | 0,00 | 0,05 | 0,00 | 0,08 | 0,10 | 0,00 | 0,08 | 0,40 | 0,00 | 0,02 | 0,01 |
| E | placebo | 0,10 | 0,00 | 0,17 | 0,00 | 0,10 | 0,10 | 0,00 | 0,19 | 0,29 | 0,00 | 0,02 | 0,02 |

**Table S 3. Summary of the logistic regression coefficients for participation rate**

| Level | Subject | Regressor | Treatment | Estimate | SE | tStat | pValue |
|---|---|---|---|---|---|---|---|
| group | | beta_0 | clonidine | 1,33 | 0,30 | 4,44 | 1,77E-05 |
| group | | beta_0 | placebo | 0,79 | 0,26 | 3,02 | 3,03E-03 |
| group | | sumR | clonidine | 0,45 | 0,12 | 3,87 | 1,65E-04 |
| group | | sumR | placebo | 0,54 | 0,06 | 9,08 | 6,66E-16 |
| group | | sumE | clonidine | -0,76 | 0,19 | -4,07 | 7,65E-05 |
| group | | sumE | placebo | -0,46 | 0,05 | -9,99 | 0,00E+00 |
| group | | ntrial | clonidine | -0,59 | 0,12 | -4,93 | 2,26E-06 |
| group | | ntrial | placebo | -0,89 | 0,21 | -4,25 | 3,77E-05 |
| group | | part_t | clonidine | 0,93 | 0,17 | 5,37 | 3,00E-07 |
| group | | part_t | placebo | 0,92 | 0,19 | 4,99 | 1,69E-06 |
| subject | A | beta_0 | clonidine | 0,17 | 0,25 | 0,69 | 4,94E-01 |
| subject | A | beta_0 | placebo | 0,17 | 0,25 | 0,69 | 4,94E-01 |
| subject | B | beta_0 | clonidine | 0,34 | 0,25 | 1,36 | 1,76E-01 |
| subject | B | beta_0 | placebo | 0,34 | 0,25 | 1,36 | 1,76E-01 |
| subject | E | beta_0 | clonidine | -0,52 | 0,25 | -2,04 | 4,32E-02 |
| subject | E | beta_0 | placebo | -0,51 | 0,25 | -2,04 | 4,32E-02 |
| subject | A | sumR | clonidine | 0,23 | 0,11 | 1,98 | 4,99E-02 |
| subject | A | sumR | placebo | 0,10 | 0,05 | 1,98 | 4,99E-02 |
| subject | B | sumR | clonidine | -0,20 | 0,11 | -1,73 | 8,57E-02 |
| subject | B | sumR | placebo | -0,09 | 0,05 | -1,73 | 8,57E-02 |
| subject | E | sumR | clonidine | -0,03 | 0,11 | -0,25 | 8,05E-01 |
| subject | E | sumR | placebo | -0,01 | 0,05 | -0,25 | 8,05E-01 |
| subject | A | sumE | clonidine | -0,28 | 0,19 | -1,48 | 1,40E-01 |
| subject | A | sumE | placebo | 0,04 | 0,03 | 1,59 | 1,13E-01 |
| subject | B | sumE | clonidine | -0,12 | 0,19 | -0,65 | 5,19E-01 |
| subject | B | sumE | placebo | -0,01 | 0,03 | -0,20 | 8,43E-01 |
| subject | E | sumE | clonidine | 0,40 | 0,19 | 2,13 | 3,52E-02 |
| subject | E | sumE | placebo | -0,04 | 0,03 | -1,39 | 1,65E-01 |
| subject | A | ntrial | clonidine | 0,07 | 0,06 | 1,10 | 2,71E-01 |
| subject | A | ntrial | placebo | 0,24 | 0,22 | 1,10 | 2,71E-01 |
| subject | B | ntrial | clonidine | -0,13 | 0,06 | -2,05 | 4,20E-02 |
| subject | B | ntrial | placebo | -0,45 | 0,22 | -2,05 | 4,20E-02 |
| subject | E | ntrial | clonidine | 0,06 | 0,06 | 0,93 | 3,52E-01 |
| subject | E | ntrial | placebo | 0,20 | 0,22 | 0,93 | 3,52E-01 |
| subject | A | part_t | clonidine | -0,29 | 0,17 | -1,73 | 8,52E-02 |
| subject | A | part_t | placebo | -0,36 | 0,19 | -1,94 | 5,40E-02 |
| subject | B | part_t | clonidine | -0,07 | 0,17 | -0,43 | 6,68E-01 |
| subject | B | part_t | placebo | -0,03 | 0,19 | -0,16 | 8,73E-01 |
| subject | E | part_t | clonidine | 0,37 | 0,17 | 2,16 | 3,22E-02 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| subject | E | part_t | placebo | 0,39 | 0,19 | 2,10 | 3,72E-02 |

**Table S 4. Summary of the logistic regression coefficients for choice rate**

| Level | Subject | Regressor | Treatment | Estimate | SE | tStat | pValue |
|---|---|---|---|---|---|---|---|
| group | | b_right | clonidine | 0,46 | 0,16 | 2,90 | 4,34E-03 |
| group | | b_right | placebo | 0,04 | 0,28 | 0,14 | 8,86E-01 |
| group | | dR | clonidine | 2,29 | 0,21 | 10,84 | 0,00E+00 |
| group | | dR | placebo | 2,45 | 0,30 | 8,25 | 8,88E-14 |
| group | | dE | clonidine | -2,55 | 0,23 | -10,87 | 0,00E+00 |
| group | | dE | placebo | -1,65 | 0,28 | -5,89 | 2,59E-08 |
| group | | choice_t | clonidine | 0,24 | 0,08 | 2,99 | 3,31E-03 |
| group | | choice_t | placebo | 0,25 | 0,09 | 2,85 | 5,04E-03 |
| group | | dRxntrial | clonidine | 0,00 | 0,09 | 0,04 | 9,70E-01 |
| group | | dRxntrial | placebo | -0,12 | 0,08 | -1,43 | 1,54E-01 |
| group | | dExntrial | clonidine | -0,03 | 0,09 | -0,32 | 7,48E-01 |
| group | | dExntrial | placebo | 0,16 | 0,06 | 2,68 | 8,20E-03 |
| subject | A | b_right | clonidine | 0,02 | 0,02 | 1,28 | 2,04E-01 |
| subject | A | b_right | placebo | 0,35 | 0,27 | 1,28 | 2,04E-01 |
| subject | B | b_right | clonidine | 0,01 | 0,02 | 0,96 | 3,36E-01 |
| subject | B | b_right | placebo | 0,26 | 0,27 | 0,96 | 3,36E-01 |
| subject | E | b_right | clonidine | -0,03 | 0,02 | -2,24 | 2,67E-02 |
| subject | E | b_right | placebo | -0,61 | 0,27 | -2,24 | 2,67E-02 |
| subject | A | dR | clonidine | -0,30 | 0,15 | -1,98 | 4,99E-02 |
| subject | A | dR | placebo | -0,59 | 0,30 | -1,98 | 4,99E-02 |
| subject | B | dR | clonidine | 0,04 | 0,15 | 0,28 | 7,82E-01 |
| subject | B | dR | placebo | 0,08 | 0,30 | 0,28 | 7,82E-01 |
| subject | E | dR | clonidine | 0,26 | 0,15 | 1,70 | 9,07E-02 |
| subject | E | dR | placebo | 0,51 | 0,30 | 1,70 | 9,07E-02 |
| subject | A | dE | clonidine | 0,20 | 0,21 | 0,97 | 3,34E-01 |
| subject | A | dE | placebo | 0,54 | 0,29 | 1,87 | 6,32E-02 |
| subject | B | dE | clonidine | -0,47 | 0,21 | -2,25 | 2,59E-02 |
| subject | B | dE | placebo | -0,52 | 0,29 | -1,81 | 7,29E-02 |
| subject | E | dE | clonidine | 0,27 | 0,21 | 1,28 | 2,03E-01 |
| subject | E | dE | placebo | -0,02 | 0,29 | -0,08 | 9,38E-01 |
| subject | A | choice_t | clonidine | 0,06 | 0,07 | 0,79 | 4,32E-01 |
| subject | A | choice_t | placebo | -0,12 | 0,09 | -1,42 | 1,57E-01 |
| subject | B | choice_t | clonidine | 0,03 | 0,07 | 0,43 | 6,68E-01 |
| subject | B | choice_t | placebo | 0,16 | 0,09 | 1,92 | 5,70E-02 |
| subject | E | choice_t | clonidine | -0,09 | 0,07 | -1,22 | 2,26E-01 |
| subject | E | choice_t | placebo | -0,04 | 0,09 | -0,49 | 6,27E-01 |
| subject | A | dRxntrial | clonidine | -0,07 | 0,05 | -1,41 | 1,60E-01 |
| subject | A | dRxntrial | placebo | -0,10 | 0,07 | -1,41 | 1,60E-01 |
| subject | B | dRxntrial | clonidine | 0,01 | 0,05 | 0,26 | 7,96E-01 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| subject | B | dRxntrial | placebo | 0,02 | 0,07 | 0,26 | 7,96E-01 |
| subject | E | dRxntrial | clonidine | 0,05 | 0,05 | 1,15 | 2,50E-01 |
| subject | E | dRxntrial | placebo | 0,08 | 0,07 | 1,15 | 2,50E-01 |
| subject | A | dExntrial | clonidine | 0,05 | 0,07 | 0,74 | 4,59E-01 |
| subject | A | dExntrial | placebo | -0,03 | 0,04 | -0,74 | 4,59E-01 |
| subject | B | dExntrial | clonidine | -0,11 | 0,07 | -1,61 | 1,09E-01 |
| subject | B | dExntrial | placebo | 0,06 | 0,04 | 1,61 | 1,09E-01 |
| subject | E | dExntrial | clonidine | 0,06 | 0,07 | 0,87 | 3,88E-01 |
| subject | E | dExntrial | placebo | -0,03 | 0,04 | -0,87 | 3,88E-01 |

**Table S 5. Summary of the regression coefficients for peak force**

| Level | Subject | Regressor | Treatment | Estimate | SE | tStat | pValue |
|---|---|---|---|---|---|---|---|
| group | | k_0 | clonidine | 0,551 | 0,047 | 11,74 | 0,00E+00 |
| group | | k_0 | placebo | 0,637 | 0,033 | 19,38 | 0,00E+00 |
| group | | rchoice | clonidine | 0,022 | 0,008 | 2,63 | 9,44E-03 |
| group | | rchoice | placebo | 0,026 | 0,005 | 5,22 | 6,21E-07 |
| group | | echoice | clonidine | 0,062 | 0,012 | 5,15 | 8,32E-07 |
| group | | echoice | placebo | 0,056 | 0,016 | 3,64 | 3,83E-04 |
| group | | side | clonidine | 0,006 | 0,011 | 0,54 | 5,92E-01 |
| group | | side | placebo | -0,009 | 0,020 | -0,46 | 6,47E-01 |
| group | | ntrial | clonidine | -0,012 | 0,004 | -3,25 | 1,42E-03 |
| group | | ntrial | placebo | -0,014 | 0,003 | -5,06 | 1,22E-06 |
| group | | rchoicexechoice | clonidine | 0,011 | 0,004 | 2,96 | 3,56E-03 |
| group | | rchoicexechoice | placebo | 0,014 | 0,005 | 3,04 | 2,83E-03 |
| group | | echoicexside | clonidine | 0,000 | 0,008 | -0,05 | 9,64E-01 |
| group | | echoicexside | placebo | 0,001 | 0,006 | 0,10 | 9,19E-01 |
| subject | A | k_0 | clonidine | -0,063 | 0,046 | -1,35 | 1,80E-01 |
| subject | A | k_0 | placebo | -0,044 | 0,032 | -1,35 | 1,80E-01 |
| subject | B | k_0 | clonidine | -0,048 | 0,046 | -1,04 | 3,01E-01 |
| subject | B | k_0 | placebo | -0,034 | 0,032 | -1,04 | 3,01E-01 |
| subject | E | k_0 | clonidine | 0,111 | 0,046 | 2,38 | 1,84E-02 |
| subject | E | k_0 | placebo | 0,077 | 0,032 | 2,38 | 1,84E-02 |
| subject | A | rchoice | clonidine | 0,007 | 0,008 | 0,83 | 4,10E-01 |
| subject | A | rchoice | placebo | 0,004 | 0,005 | 0,83 | 4,10E-01 |
| subject | B | rchoice | clonidine | -0,019 | 0,008 | -2,33 | 2,10E-02 |
| subject | B | rchoice | placebo | -0,011 | 0,005 | -2,33 | 2,10E-02 |
| subject | E | rchoice | clonidine | 0,012 | 0,008 | 1,51 | 1,34E-01 |
| subject | E | rchoice | placebo | 0,007 | 0,005 | 1,51 | 1,34E-01 |
| subject | A | echoice | clonidine | 0,027 | 0,012 | 2,31 | 2,20E-02 |
| subject | A | echoice | placebo | 0,036 | 0,016 | 2,31 | 2,20E-02 |
| subject | B | echoice | clonidine | -0,007 | 0,012 | -0,64 | 5,23E-01 |
| subject | B | echoice | placebo | -0,010 | 0,016 | -0,64 | 5,25E-01 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| subject | E | echoice | clonidine | -0,020 | 0,012 | -1,68 | 9,60E-02 |
| subject | E | echoice | placebo | -0,026 | 0,016 | -1,68 | 9,53E-02 |
| subject | A | side | clonidine | 0,001 | 0,009 | 0,12 | 9,08E-01 |
| subject | A | side | placebo | 0,002 | 0,020 | 0,08 | 9,36E-01 |
| subject | B | side | clonidine | 0,017 | 0,009 | 1,94 | 5,38E-02 |
| subject | B | side | placebo | 0,039 | 0,020 | 1,95 | 5,27E-02 |
| subject | E | side | clonidine | -0,018 | 0,009 | -2,06 | 4,15E-02 |
| subject | E | side | placebo | -0,040 | 0,020 | -2,03 | 4,41E-02 |
| subject | A | ntrial | clonidine | 0,001 | 0,001 | 0,84 | 4,00E-01 |
| subject | A | ntrial | placebo | 0,001 | 0,002 | 0,84 | 4,00E-01 |
| subject | B | ntrial | clonidine | -0,001 | 0,001 | -1,00 | 3,21E-01 |
| subject | B | ntrial | placebo | -0,002 | 0,002 | -1,00 | 3,21E-01 |
| subject | E | ntrial | clonidine | 0,000 | 0,001 | 0,15 | 8,81E-01 |
| subject | E | ntrial | placebo | 0,000 | 0,002 | 0,15 | 8,81E-01 |
| subject | A | rchoicexechoice | clonidine | 0,005 | 0,003 | 1,72 | 8,80E-02 |
| subject | A | rchoicexechoice | placebo | 0,008 | 0,005 | 1,72 | 8,80E-02 |
| subject | B | rchoicexechoice | clonidine | 0,001 | 0,003 | 0,40 | 6,93E-01 |
| subject | B | rchoicexechoice | placebo | 0,002 | 0,005 | 0,40 | 6,93E-01 |
| subject | E | rchoicexechoice | clonidine | -0,006 | 0,003 | -2,11 | 3,63E-02 |
| subject | E | rchoicexechoice | placebo | -0,010 | 0,005 | -2,11 | 3,63E-02 |
| subject | A | echoicexside | clonidine | -0,004 | 0,008 | -0,51 | 6,13E-01 |
| subject | A | echoicexside | placebo | -0,003 | 0,006 | -0,51 | 6,13E-01 |
| subject | B | echoicexside | clonidine | 0,017 | 0,008 | 2,26 | 2,54E-02 |
| subject | B | echoicexside | placebo | 0,014 | 0,006 | 2,26 | 2,54E-02 |
| subject | E | echoicexside | clonidine | -0,013 | 0,008 | -1,75 | 8,21E-02 |
| subject | E | echoicexside | placebo | -0,010 | 0,006 | -1,75 | 8,21E-02 |

**Table S 6. Summary of treatments impact on computational metrics**

| subject | treatment | N(session) | Kr | | Ks | | Ke | | Kf | | K0 | | Kn | | Bm | | Bp | | € | | € | | log-model-evidence | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | mean | sem | mean | sem | mean | sem | mean | sem | mean | sem | mean | sem | mean | sem | mean | sem | mean | sem | mean | sem | mean | sem |
| A | clonidine | 13 | 0,53 | 0,05 | -0,40 | 0,13 | 2,16 | 0,11 | 0,22 | 0,15 | 1,23 | 0,15 | -0,04 | 0,06 | 0,07 | 0,06 | 0,72 | 0,07 | 0,01 | 0,00 | 0,35 | 0,18 | -318,54 | 75,71 |
| A | placebo | 21 | 0,56 | 0,06 | -1,13 | 0,24 | 1,36 | 0,18 | -0,15 | 0,16 | 0,80 | 0,27 | -0,46 | 0,16 | 0,22 | 0,08 | 0,48 | 0,08 | 0,01 | 0,00 | 0,25 | 0,06 | -442,98 | 63,19 |
| B | clonidine | 12 | 0,43 | 0,01 | 0,17 | 0,13 | 2,25 | 0,10 | 0,20 | 0,11 | 2,04 | 0,13 | -0,18 | 0,21 | 0,08 | 0,04 | 0,76 | 0,07 | 0,00 | 0,00 | 0,19 | 0,01 | -176,62 | 10,36 |
| B | placebo | 26 | 0,67 | 0,09 | -0,32 | 0,16 | 1,93 | 0,11 | 0,06 | 0,10 | 1,58 | 0,18 | -0,52 | 0,14 | -0,26 | 0,08 | 1,11 | 0,08 | 0,06 | 0,02 | 0,22 | 0,01 | -241,34 | 22,78 |
| E | clonidine | 12 | 0,63 | 0,09 | -0,15 | 0,17 | 1,97 | 0,26 | 0,26 | 0,22 | 1,70 | 0,34 | -0,06 | 0,14 | -0,20 | 0,17 | 1,12 | 0,12 | 0,18 | 0,08 | 0,18 | 0,01 | -333,48 | 50,85 |
| E | placebo | 23 | 0,68 | 0,09 | -0,24 | 0,20 | 1,62 | 0,21 | 0,14 | 0,14 | 1,42 | 0,27 | -0,25 | 0,10 | -0,59 | 0,09 | 1,32 | 0,14 | 0,17 | 0,06 | 0,20 | 0,01 | -352,90 | 54,61 |