Pharmacological evidence for the implication of noradrenaline in effort

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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 (depression, 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. Enhancing noradrenaline levels with atomoxetine (0.5mg/kg) increased both engagement in the task and monkeys' compliance to task instructions, in line with an interpretation in terms of cognitive control. Altogether, our data strongly support noradrenaline's implication in effort processing.

I. 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 role in effort remains debated when effort can be dissociated from reward (Walton & Bouret, 2018). When executing simple actions involving force production, effort essentially refers to the amount of force produced. But effort also refers to the anticipated subjective cost of such force production, which is critical when selecting one of several possible courses of action based one their expected effort costs and reward benefits. In other words, effort corresponds to a computational variable capturing the amount of resources to mobilize, both when making a choice and performing the action. At the time of the decision, one tends to minimize this variable and to choose the least effortful option. However, at the time of the action, 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). Altogether, these results indicate that, as strong as the implication of dopamine in motivation is, its implication in effort remains limited when effort is dissociated from reward and force.

Recent work suggests that effort involves another major catecholamine: noradrenaline (Ventura et al., 2008; Bouret et al, 2012; Zénon et al., 2014). 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 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 such 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). *Second*, pharmacological manipulations of the NA system strongly affect performance in tasks requiring a high level of cognitive control (Chamberlain et al., 2006, 2009; Eagle et al., 2008) 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). Intuitively, these data could be interpreted in terms of 'mental effort', even though this idea has never been tested directly. *Third*, LC activity is closely associated with autonomic arousal and pupil dilation (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). Even, if we recently confirmed the strong correlation among LC activity, pupil dilation and force production, the relationship between LC, pupil dilation and effort remains unclear (Varazzani et al, 2015). *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 appear 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, even if no effort is involved). 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. Since we hypothesized that NA is involved in effort, we expected NA treatments 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 original insight into the role of NA in motivation and decision making.

II. 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 two 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). As a pro-noradrenergic drug, we used atomoxetine (a selective noradrenaline reuptake inhibitor) with a fixed dose of 0.5 mg/kg, and as an anti-noradrenergic drug, we used clonidine (a selective α2-agonist) 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 face 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 the same hour for all sessions of one monkey, 45 minutes before testing for atomoxetine, 30 minutes before testing for clonidine. For all monkeys, n=12 sessions were collected for active treatments and at least 12 sessions for control vehicle injections.

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 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 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. The options were composed of 2 attributes: reward size and required force level. 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). 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. 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.

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. 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 required force on the selected handgrip, the corresponding reward 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).

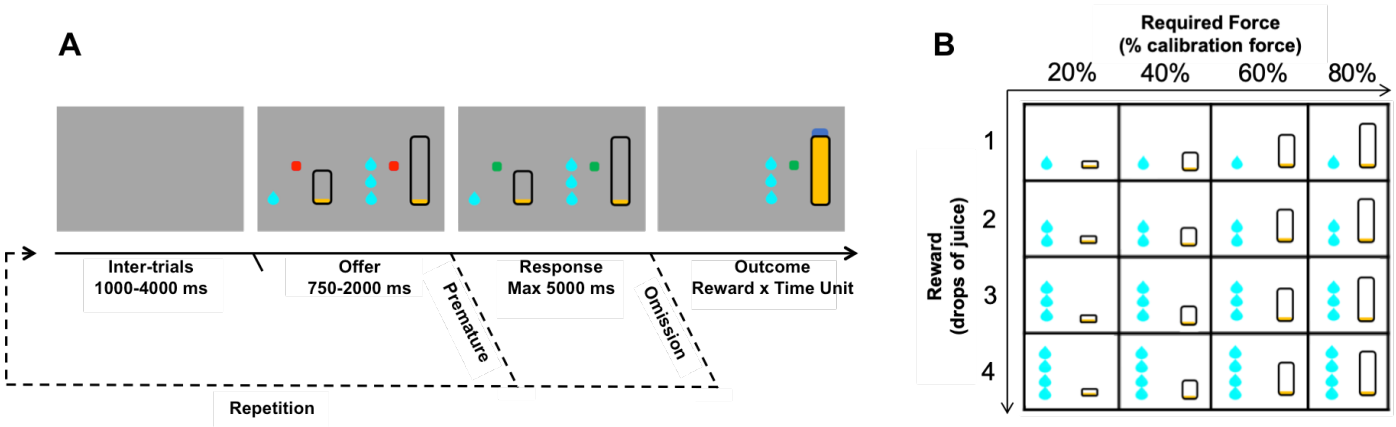

Figure 1. Behavioral task design

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, and therefore the visual feedback, 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). All 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). Note that effort costs 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. The model assumes that the behavior of the monkeys resulted from an effort cost-reward benefit stochastic optimization. Choices are predicted by a softmax decision function integrating the different option values whereas the peak force exerted is the one optimizing the value of the chosen option (*Equation 1*, *Equation 2*). The attributes of each option comprise a reward benefit term (modulated by the reward level), an effort cost term (modulated by the required force level) and a probability of success conditional to the exerted force (when the purpose of the valuation is to select the appropriate force). Each of these terms are parametrized by constants controlling the behavioral predictions given by the model; those constants can be divided into several categories: 1) sensitivities to action-outcome values ($K_{R:}$ reward sensitivity, $K_{E:}$ effort sensitivity) ; 2) behavioral response tendencies ($K_{0:}$ activation weight, $ó_{E:}$ 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). It should be noticed that 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) and 2) disentangling the behavioral signatures of effort cost-reward benefit valuations from potential behavioral by-products of alternative mechanisms (eg. behavioral excitation for K_0, subjective uncertainty or risk for $ó_E$).

Equation 1: Valuation

$$\begin{cases} V(F \mid option) = \kappa_0 F + (1+\kappa_S N) P(R_{option} \mid F) R - \kappa_E (1+\kappa_F N) F^2 \\ V(option) = V(F^* \mid option) \\ V(active) = \sum V(option) \\ P(R_{option} \mid F) = 1 - \mathrm{normcdf}(E_{option} \mid F, \sigma_E) \end{cases}$$

Equation 2: Selection

$$\begin{cases} P(participation = 1 \mid options_t) = \mathrm{logistic}(V(active) + b_P P(participation = 1 \mid options_{t-1})) \\ P(choice = R \mid options_t, participation_t = 1) = \mathrm{logistic}(V(option_R) - V(option_L) + b_P P(choice = R \mid options_{t-1}) + b_M) \\ E[F] = \arg\max_F (V(F \mid option_t)) + \varepsilon(\sigma_F) \end{cases}$$

Equation 3: Definitions

ε ? $N(0\,;\sigma_F)$

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

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

We describe in the following section the properties of this complete computational model. We begin with the required force selection mechanism that drives the exerted / peak force. The value components act in opposite directions: the reward benefit term (scaled by reward benefit sensitivity) enhances the exerted / peak force whereas the effort cost term (scaled by required force cost sensitivity) decreases the exerted / peak force in a non-linear fashion, because the required force goes directly to zero when the expected value of the action is negative (i.e. when action is less valuable than inaction). Obviously, these terms will control (in opposite direction) the effort cost/reward benefit trade-off governing the adaptation of force to experimental conditions (expected reward and effort) 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 effortcost term decreases the exerted / peak force for low rewards and high efforts (where the marginal cost of force has maximal impact on value). The activation component (scaled by the activation weight) acts as a benefit term independent from the expected reward, increasing exerted / 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 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.

In summary, the general intuition is that dynamic sensitivities control the allocation of force over time, in interaction with the value components for satiety and fatigue sensitivities. The nuisance terms were not included in the exerted? Peak ?force equation for the sake of simplicity. As a common practice, we included a noise term in the force prediction? which is scaled by the standard-deviation of the residuals. We continue by describing the effect of the different model components onto choices. 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 plays an opposite role decreasing participation for all conditions (without main dependence to the amount of expected rewards and demanded effort) 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 demanded effort). 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 doesn't 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).

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).

III. Results

Behavioral task

We designed a two-option 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. These options were 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).

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 participation, choices, and force production 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 2C***) and negatively modulated by the sum of offered required forces ($\beta = -0.51$, $t_{(147)} = -7.93$, $p = 4.99\times10^{-13}$) (***Figure 2D***), 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 (β = 2.39, $t_{(147)}$ = 9.44, p = 7.94×10^{-17}) (***Figure 2E***) and required force (β = -1.84, $t_{(147)}$ = -6.95, p = 1.09×10^{-10}) (***Figure 2F***). 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, β = -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.

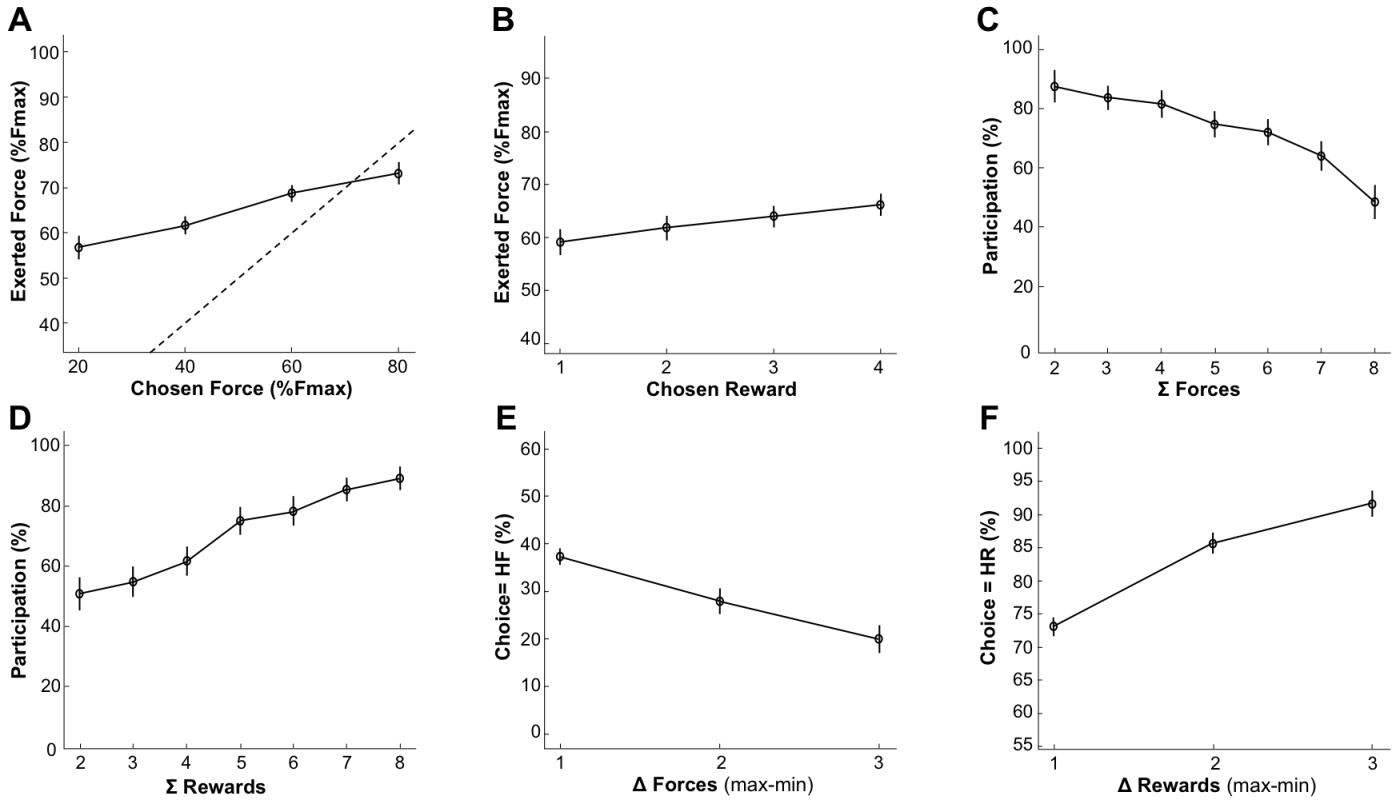

Figure 2. Behavior under placebo condition

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 (β = 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 (β = 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 (β = -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 (β = 0.49, $t_{(147)}$=6.62, p=7.36×10^{-5}) presented in an offer.

E. 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 (β = 2.39, $t_{(147)}$ = 9.44, p = 7.94×10^{-17})

F. 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 (β = -1.84, $t_{(147)}$ = -6.95, p = 1.09×10^{-10}).

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 that affects 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.

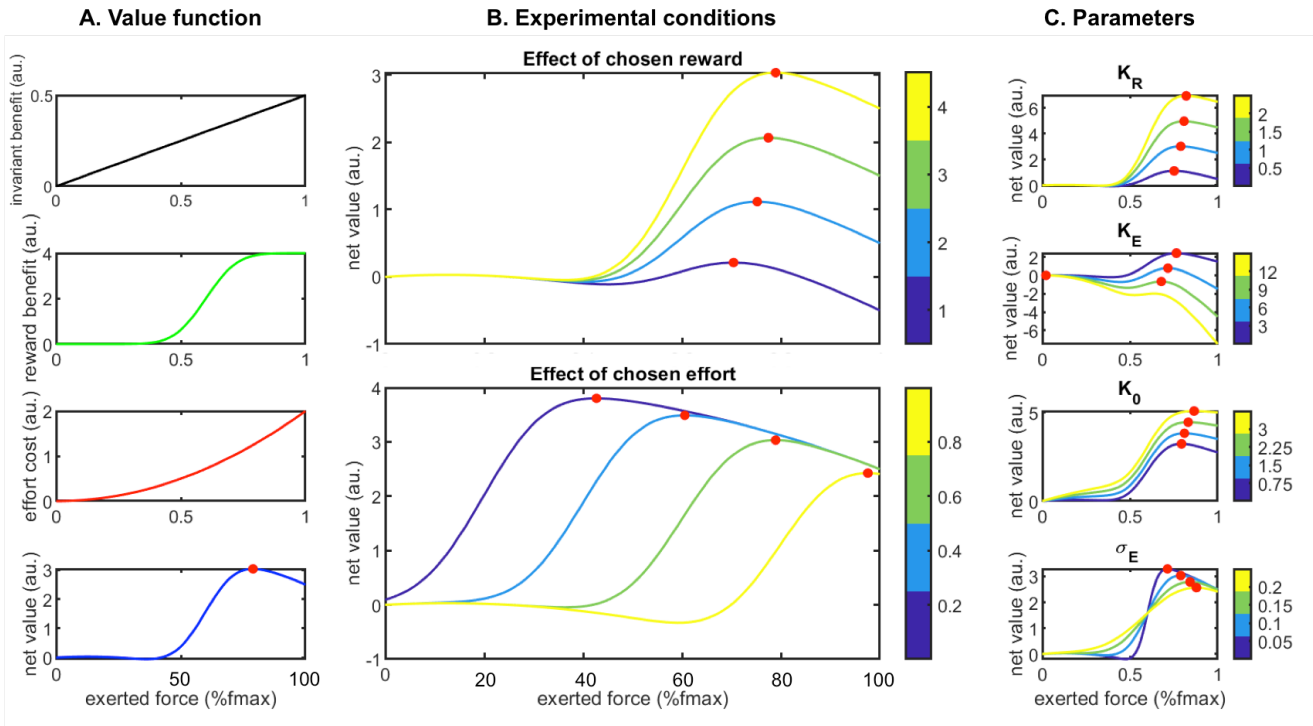

Figure 3. Properties of the optimal force selection model

A. Components of the value function depending on the expected 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 $\int_{E:}$ (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 $\{K_R = 1 ; K_S = -1 ; K_E = 2 ; K_F = 1 ; K_0 = 0.5 ; K_N = -1 ; \sigma_E = 0.1 ; b_M = 0 ; b_M = 0 ; \sigma_F = 0\}$ 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.

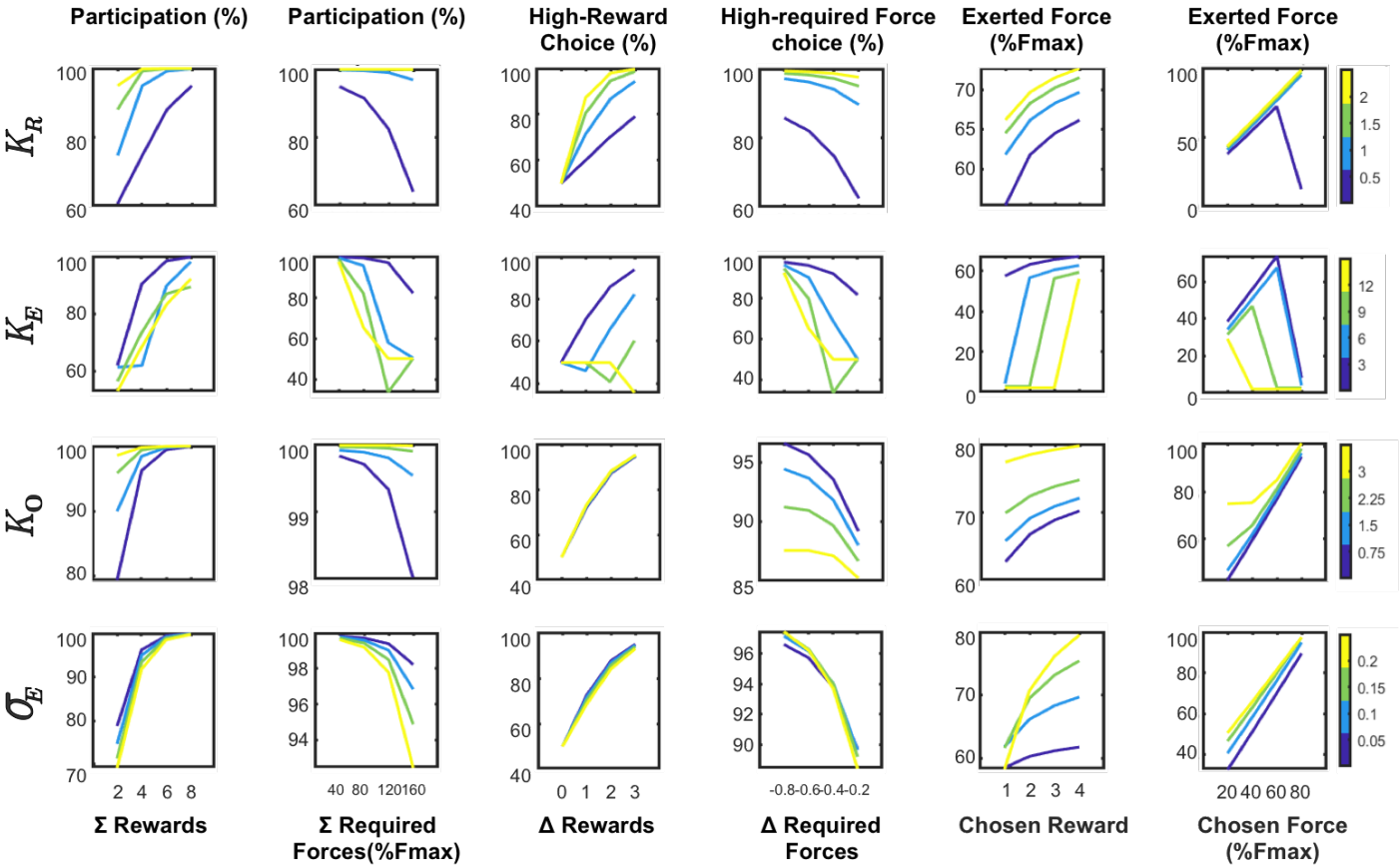

Figure 4. Predictions of the complete computational model for choice and force production

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 σ_E. Color-bars indicate parameter values. Simulations were performed with an initial parameters vector of $\{K_R = 1$; $K_S = -1$; $K_E = 2$; $K_F = 1$; $K_0 = 0.5$; $K_N = -1$; $\sigma_E = 0.1$; $b_M = 0$; $b_M = 0$; $\sigma_F = 0\}$ 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, there was a significant impact of clonidine on choices. In offers for which there was an option with both a higher reward and a higher force requirement, referred to as the high-reward/high-required-force option, the frequency of choosing the 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 the effort/reward trade-off underlying choices. To refine this observation and dissociate the sensitivity of choices to reward and to effort, respectively, 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)*** without any 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, a logistic regression of all choices 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 an increased bias in the logistic regression (*clonidine* = 1.33 +/- 0.30*, placebo* = 0.79 +/- 0.26*,* $F_{(1,145)}$ = 5.01, p = 0.02). Note that besides this effect on the weight of the participation bias, there was also a tendency for an increase in the 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. Furthermore, participation biases across clonidine sessions were negatively predicted by session-wise choice sensitivity to required force (β = -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 GLM performed on force peaks to decompose the influence of multiple factors showed that the drug only had a main effect on force production (*clonidine* = 0.55 +/- 0.05, *placebo* = 0.63 +/- 0.03, $F_{(1,145)}$ = 20.70, p = 1.12×10^{-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).

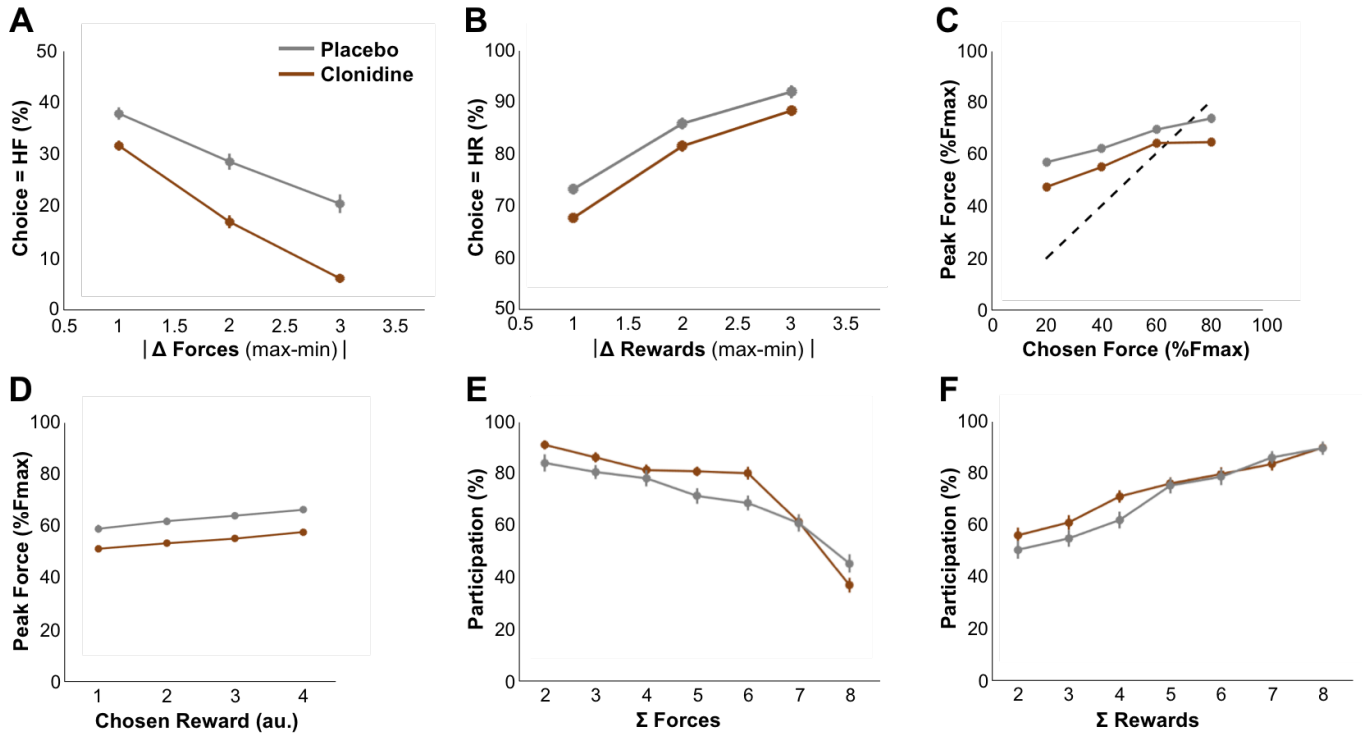

Figure 5. Clonidine affects choice and force production

Behavior of the monkeys under the placebo (grey) and clonidine (brown) conditions.

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 = 1.12×10^{-5}), without affecting the effects task factors (reward weights: *clonidine* = 0.02 +/- 8.3×10^{-3}, *placebo* = 0.02 +/- 5×10^{-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 hypothesis, there was a positive correlation between the parameters capturing these effects across clonidine sessions. The parameter βe capturing the influence of required force level on choices displayed a significant positive relationship with the intercept parameter (βo, bias) in the model capturing the influence of reward and effort on force production (β = 0.63+/- 0.10, $t_{(144)}$ = 6.48, p = 1.33×10^{-9}). Thus, across treatment sessions, there was a systematic 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.

We then used the computational model to capture the influence of the treatment. 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= 6.37×10^{-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 - 4.59×10^{-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.

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 assess the specificity of this effect of clonidine on motivational processes, we considered more generic effects on behavior. As mentioned above, 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 could not be described as a global decrease in behavioral reactivity, due to a decrease in vigilance or arousal. We also assessed a direct effect of clonidine on muscle effectors by measuring the efficiency of muscular contraction, and evaluate an interpretation of the effect of clonidine in terms of muscle contractility rather than in terms of motivation. We evaluated the muscular contractility 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, here, we considered effort as a computational variable affecting both choices and force production, but the influence of clonidine on choices could have been indirect. Under 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 (β = -9.73×10^{-5}+/- 9.13×10^{-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 (β = 0.04 +/- 0.06, $t_{(144)}$ = 0.70, p = 0.17) (***Figure 6D***). Finally, we also examined the possibility that success rate could be 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 = 2.93×10^{-5}). In sum, in line with our hypothesis, clonidine affected directly both components of effort: required force-based choices and force production, without any effect on reward processing.

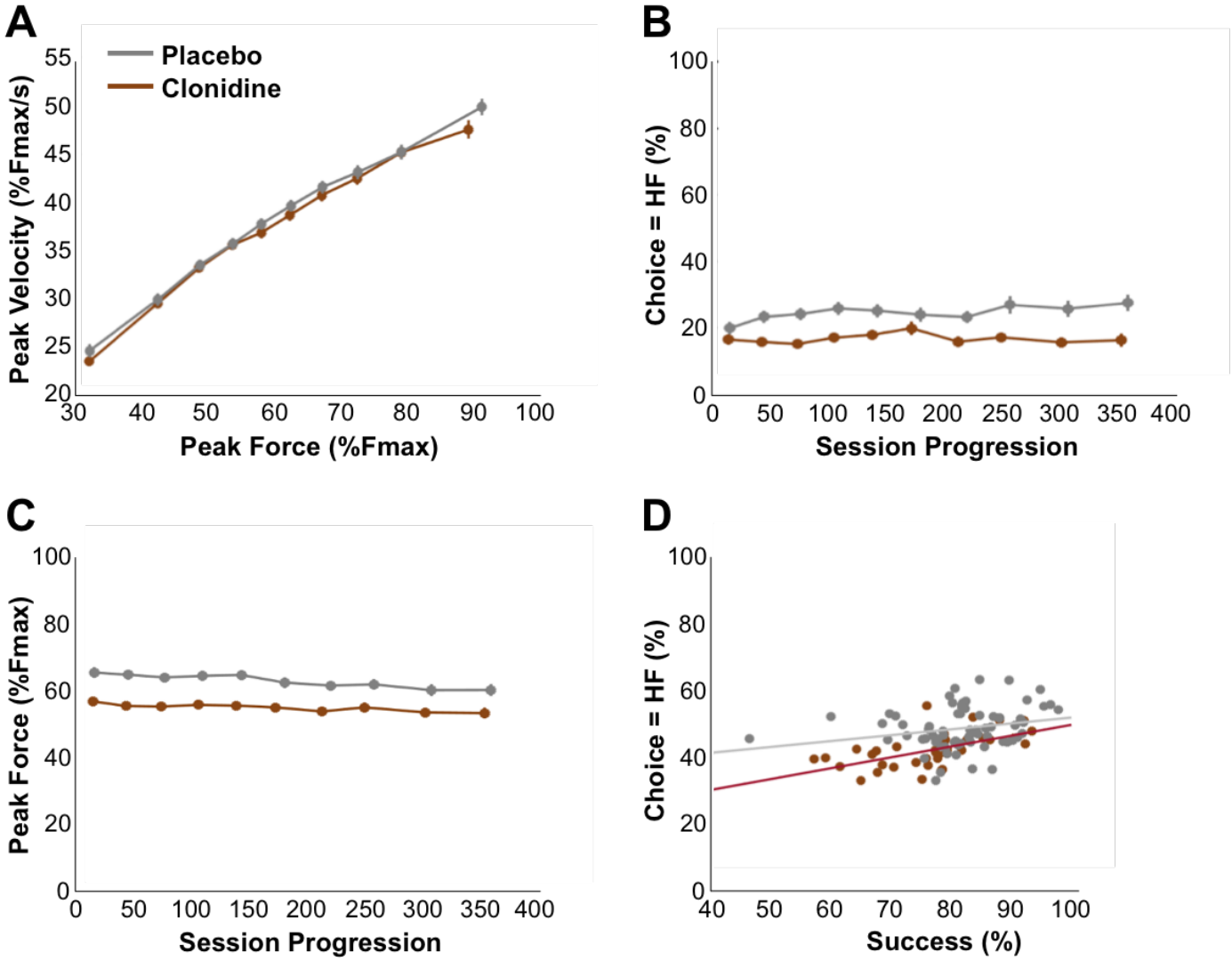

Figure 6. Specificity of the clonidine effect.

Behavior of the monkeys in the placebo (grey) and clonidine (brown) conditions.

A. Relationhip 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 ($\beta = 0.04 +/- 0.06$, $t_{(144)} = 0.70$, $p = 0.17$).

Atomoxetine does not affect force-based behavior but it enhances task execution

We conducted the same experimental procedure with atomoxetine, a drug that increases noradrenaline levels. In contrast to clonidine, atomoxetine did not affect the sensitivity of choices to the required force of options, with no effect on either the frequency of high-reward high-required force choices (*atomoxetine* = 0.61+/- 0.06, *placebo* = 0.63 +/- 0.03, $F_{(1,145)}$ = 0.28, p = 0.60), or the frequency of high-required force choices in the 1D-required force conditions (in which required force is the only distinct parameters between the options of the offer) (*atomoxetine* = 0.26+/- 0.05, *placebo* = 0.24 +/- 0.03, $F_{(1,145)}$ = 0.52, p = 0.47) (***Figure 7A***). Neither was there any effect on the frequency of high-reward choices in the 1-D-reward conditions (p>0.05) (***Figure 7B***). The logistic regression of choices confirmed the lack of effect of atomoxetine on choices (neither on the bias, the sensitivity to required force or of reward). The analysis of force production also yielded negative results: there was no significant difference in the average peak force exerted by the monkeys between the atomoxetine and the placebo condition (*atomoxetine* = 0.61+/- 0.05, *placebo* = 0.64 +/- 0.03, $F_{(1,145)}$ = 1.36, p = 0.24).

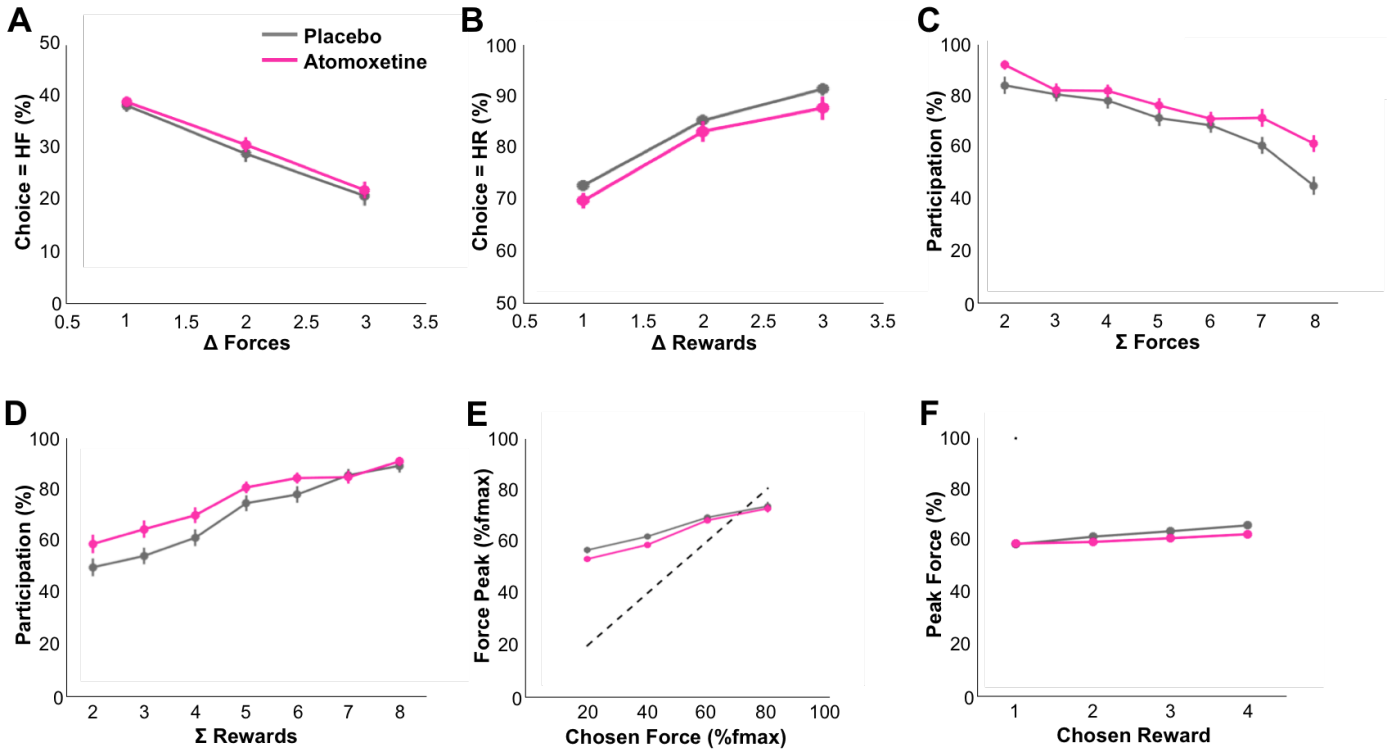

Figure 7. Monkeys' behavior under atomoxetine condition.

Summary of the behavior of the monkeys in the placebo (grey) and atomoxetine (pink) conditions.

A. Proportion of high-required force choices as a function of the difference between the offered required forces in the 1-D required force conditions. Atomoxetine had no effect on the modulation of the proportion of high required force choices by required force difference (*atomoxetine* = 0.26+/- 0.05, *placebo* = 0.24 +/- 0.03, $F_{(1,145)}$ = 0.52, p = 0.47).

B. Proportion of high-reward choices as a function of the difference between the offered rewards in the 1-D reward conditions. Atomoxetine had no effect on the modulation of the proportion of high reward choices by reward difference ($p>0.05$).

C-D. Modulation of participation by the sum of offered forces (**C**) and the sum of offered rewards (**D**). Atomoxetine did not alter the modulation of participation by the sum of rewards or sum of required forces.

E-F. Modulation of force peak (fraction of the calibration force) by the chosen required force (**E**) and chosen reward (**F**). The dotted line represents the optimal relation (identity) between exerted force and force difficulty (the minimum required force to complete the trial). Atomoxetine significantly increased the weight of the chosen force level on the peak force (*atomoxetine* = 0.07+/- 0.01, *placebo* = 0.06+/- 0.02, $F_{(1,145)} = 4.43$, $p = 0.04$) and had a negative influence on the weight the chosen reward that was close to significance (*atomoxetine* = 0.02+/- 0.01, *placebo* = 0.03 +/- 5×10^{-3}, $F_{(1,145)}) = 4.43$, $p = 0.04$).

We also used the computational model to better capture the influence of atomoxetine on effort-cost/reward-benefits assessment. As for clonidine, the model provided good fit for participation (balanced accuracy =75%), choice (balanced accuracy = 73%) and peak force ($R^2 = 22\%$) for atomoxetine sessions. When we tested whether the parameter sets were modified under the atomoxetine conditions, however, we could not detect any significant change in the multivariate analysis of variance (d=0, ë=0.93, p= 7.41×10^{-1}). Moreover, the classification procedure was not able to separate drug conditions (atomoxetine vs. placebo) consistently across monkeys (balanced accuracy = 50%, exceedance probability = 4.46×10^{-2}). This means that none of the parameters from the current computational model was able to reliably capture the influence of atomoxetine.

Other measures, however, indicate that atomoxetine enhances task performance. First, under atomoxetine, participation significantly increased, i.e. the monkeys squeezed the grips more often, successfully or not (*atomoxetine* = 0.71+/- 0.04, *placebo* = 0.62 +/- 0.03, $F_{(1,145)} = 11.09$, $p = 1.10\times10^{-3}$) (***Figure 7C-D***). This increased participation resulted in an increase in accumulated reward per session (*atomoxetine* = 355.70+/- 27.36, *placebo* = 272.11 +/- 35.25, $F_{(1,145)} = 8.87$, $p = 3.39\times10^{-3}$). Yet, the increased participation was not driven by an altered consideration of trial-by-trial factors (such as the reward and the required force, the session progression or the previous decision): when we modeled participation with a logistic regression including all these factors, atomoxetine only affected the intercept (*atomoxetine* = 1.52+/- 0.40, *placebo* = 0.79 +/- 0.26, $F_{(1,145)} = 8.28$, $p = 4.61\times10^{-3}$) (***Figure 7C-D***). Thus, atomoxetine only had a positive bias on the participation, without affecting its modulation by task parameters or session progression (which reflects fatigue and/or satiety).

Atomoxetine also had a significant influence on force production, but this influence was more subtle than that of clonidine. Even if, as mentioned above, atomoxetine had no main effect on force production, we evaluated its influence on the weight of distinct parameters determining force peak by running a GLM. Atomoxetine significantly increased

the weight of the chosen required force (*atomoxetine* = 0.07+/- 0.01*, placebo* = 0.06+/- 0.02*,* $F_{(1,145)}$ = 4.43, p = 0.04) (***Figure 7E***) and its negative influence on the weight the chosen reward approached significance (*atomoxetine* = 0.02+/- 0.01*, placebo* = 0.03 +/- 5×10^{-3}*,* $F_{(1,145)}$ = 3.26, p = 0.07) (***Figure 7F)***. In other words, under atomoxetine, the amount of force produced by the monkeys was more strongly influenced by the required force level and less strongly influenced by the reward size, which is not instrumental in this task. In other words, under atomoxetine, the forces produced by the monkeys became more sensitive to the task rule and tended to be less sensitive to the distracting effects of reward. As for clonidine, we considered the possibility that the effects of the drug could be reduced to a generic effect on behavioral reactivity, due to an increase in vigilance or arousal but this seemed quite unlikely: even if atomoxetine increased participation, it did not increase the exerted force and it did not decrease reaction time (*atomoxetine* = 0.57+/- 0.08*, placebo* = 0.52+/- 0.08*,* $F_{(1,145)}$ = 0.42, p = 0.51).

In summary, atomoxetine did not mirror the effect of clonidine on choices and force production, but it induced a direct increase in the participation to the task and an increased ability to follow task requirements and maybe ignore distractors. Since these effects were also associated with an increase in the total amount of reward earned, they can be described as an enhancement of task execution, and maybe interpreted in terms of in cognitive control.

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 drugs that decreased (clonidine) and increased (atomoxetine) brain noradrenergic 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 of the amount of force produced. This effect was relatively specific: clonidine did not affect reward processing and its effect could not be interpreted in terms of a global decrease in behavioral reactivity. The effect of atomoxetine was subtler: even if it did not seem to directly affect the effort/reward trade-off, it enhanced the execution of the task, as measured both by an increased participation and an increased executive control (better ability to follow the instructed force level and ignore the distracting incentive influence of reward). Altogether, this work strongly supports the role of noradrenaline in effort processing, which we defined as a computational variable corresponding to the resources mobilized for an action. In that frame, 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 (Dayan, 2012; Walton & Bouret, 2018). Here, 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). Moreover, by independently manipulating reward and force production, we could isolate the direct influence of effort from the incentive influence of reward on force production.

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 its numerous target structures, 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 each 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) and atomoxetine administration increases synaptic noradrenaline concentration (Bolden-Watson and Richelson, 1993; Bymaster et al., 2002; Wong et al., 1982). Still, regarding the secondary effects of clonidine, we cannot exclude the possibility that clonidine has a potential impact onto the hetero-inhibitory α_2 receptors located in the prefrontal cortex (Arnsten, 2015). However, the stimulation of prefrontal α_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.

Our initial hypotheses did not predict the asymmetrical response to the pro-noradrenergic and anti-noradrenergic modifications, as we had expected opposite patterns of response. We can list three scenarios to explain this asymmetry: 1) the two drugs probably did not lead to similar effective variations in the noradrenaline concentration (because of different absorption, distribution, mechanism of action and elimination (Goodman, 1996)), 2) A physiological non-linearity in the influence of the drugs on the noradrenergic system (e.g. flooring effect in the firing rate of locus coeruleus which cannot go negative, ceiling effect in the post-synaptic targets due to saturated receptors), 3) the two drugs might have effects in different anatomical regions because of the distribution of their respective targets (α2 receptors located in the LC and the prefrontal cortex for clonidine (Saunders and Limbird, 1999), noradrenaline transporter NET located in the cortex mainly for atomoxetine (Torres et al., 2003b)). Overall, the impact of sustained noradrenergic treatments on the fine dynamics of the interactions between LC neurons and the rest of the brain remains largely unknown, making the interpretation even more difficult. Despite all these limitations, we still assert that our results contain a commonality between the impact of clonidine and of atomoxetine: resource allocation, in line with the idea that noradrenergic manipulations can be interpreted under a single prism of function. Even if the underlying physiological mechanisms remain largely unexplored, we believe that such overarching function can guide future studies aimed at characterizing the underlying neural processes.

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 exerted less force. These effects cannot be accounted for by a global decrease in reactivity or by a motor impairment - as animals participated more in the task - implying that animals indeed displayed a specific alteration in the management of the effort/reward trade-off. Again, we could exclude interpretations in terms of risk because both choices and participation were better explained by effort than 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).

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.

Atomoxetine: an action on cognitive effort?

The effect of atomoxetine was subtler, since it only (and positively) affected participation, but not choices. Rather than producing a global change in force production, it increased the sensitivity to the instruction (required force) and tended to decrease the biasing influence of reward. By contrast with clonidine, we could not describe its effect using the computational model that captures the dual influence of effort on choices and actions. However, several elements suggest that noradrenaline might enhance the mobilization of resources in the cognitive domain, and thereby play a key role in cognitive control. Indeed, atomoxetine did not only increase participation in the task, but also increased the precision with which monkeys exerted their force on the grip, through both a better compliance to the instructed force level and a trend for a decreased influence of the reward (incentive). This could not be interpreted merely in terms of increased arousal state or behavioral reactivity, as response times were unaffected. Thus, we favor an interpretation in terms of cognitive effort, i.e. mobilization of mental resources to increase executive control and perform the task, which could explain both why monkeys worked more during the task and why they had a better control of their force (resulting in actions being closer to the instrumental force target and less dependent on non-instrumental reward expectation). Indeed, participation to trials and exerted force were the only constrained instrumental actions influencing the final reward (responding during a certain time interval for participation and above a certain effort threshold for exerted force), whereas the choice by itself was unconstrained. Note that this interpretation of the action of atomoxetine in terms of cognitive effort resonates with several studies demonstrating the positive effects of atomoxetine on executive functions (Chamberlain et al, 2006; Warner et al, 2018).

To some extent, the multiple influences of systemic manipulations of NA levels in this task 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, the effects of both treatments could be understood in a single theoretical framework in which noradrenaline levels control 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 interpretation is in line with previous pharmacological studies showing that manipulating NA levels directly affects several forms of cognitive effort such as inhibitory control (Chamberlain et al., 2006, 2009; Eagle et al., 2008) or attentional set-shifting (Dalley et al, 2001; Tait et al, 2007; McGaughy et al., 2008).

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 NA levels promote the mobilization of resources to face these challenges. 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, in line with our proposed interpretation of the effects of direct manipulations of NA levels. 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; Varazzani et al), 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.

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, either in the physical or in the cognitive domain. This interpretation

crystallizes several elements of the literature and hopefully paves the way for further research investigating the physiological mechanisms by which the *locus coeruleus* interacts with other brain regions to support effort.

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IV. Supplementary Materials

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.