1 **Independent contributions of noradrenaline to behavioural flexibility and**

2 **motivation**

3

4 Caroline Jahn[1-4], Sophie Gilardeau[5], Chiara Varazzani[1-2], Bastien Blain[1,6], Jerome

5 Sallet[3-4], Mark Walton[3-4], Sebastien Bouret[1]

6

7 [1]Motivation, Brain and Behavior Team, Institut du Cerveau et de la Moelle Epinière,

8 75013 Paris, France

9 [2]Frontières du Vivant, Université Sorbonne Paris Cité, Paris, France

10 [3]Department of Experimental Psychology, Oxford, OX1 3UD, United Kingdom

11 [4]Wellcome Centre for Integrative Neuroimaging, University of Oxford, UK

12 [5]Institute for Translational Neuroscience of Paris IHU-A-ICM, 75013 Paris, France

13 [6]Centre d'Economie de la Sorbonne, Université Paris 1, 75013 Paris, France

14

Abstract

Among neuromodulatory systems, the noradrenergic system remains one of the least understood. Several theories have pointed out its implication in behavioural flexibility and more recently in motivation, with a strong role in effort processing. Here, we designed a sequential cost/benefit decision task to test the causal role of noradrenaline in these two functions. We manipulated noradrenaline using clonidine, an alpha-2 noradrenergic receptor agonist, which reduces central noradrenaline levels. Clonidine had two distinct effects: it decreased choice volatility (without affecting the cost/benefit trade off) and reduced force production. Because the effects were independent, they cannot be accounted for by a non-specific effect on arousal. Altogether, these results support the global implication of noradrenaline in facing challenging situations in two complementary ways: by modulating behavioural volatility, which would facilitate adaptation depending on the lability of the environment, and by modulating the mobilization of resources to face immediate challenges.

Introduction

Noradrenaline is among the most widespread neuromodulator in the brain and it has been involved in many cognitive processes, but its specific function remains unclear. The noradrenergic system was initially associated with vigilance and arousal (Kety, 1972; Harley, 1987; Aston-Jones et al., 1991; Berridge, 1991; Waterhouse et al., 1998; Berridge and Waterhouse, 2003), but several authors suggested that this role could extend to cognitive functions such as attention or learning and memory (Usher et al., 1999; Arnsten, 2000; Harley, 2007; Arnsten et al., 2012; Sara and Bouret, 2012; Sara, 2015). In particular, noradrenaline has been associated with various forms of cognitive flexibility (Deveauges and Sara, 1990; Bouret and Sara, 2004; Chamberlain et al., 2006; Tait et al., 2007; McGaugy et al., 2008; Guedj et al., 2016). Based on this work, several authors proposed original theories to capture the implication of the noradrenergic system in behavioural or cognitive flexibility (Yu and Dayan, 2005; Aston-Jones and Cohen, 2005; Bouret and Sara, 2005). More recently, we and others have also emphasized the potential role of noradrenaline in motivation, with a strong role in effort processing (Ventura et al., 2008; Bouret and Richmond, 2009; Zenon et al., 2014; Varazzani et al., 2015).

While aspects of these theories overlap, it has nonetheless been difficult to determine how to reconcile these different ideas as they have seldom been directly tested in the same experiment. Moreover, several recent studies have emphasized the strong relation between autonomic arousal and cognitive functions classically attributed to the noradrenergic system (Einhauser et al., 2008; Preuschoff et al., 2011; Nassar et al., 2012; Gee et al., 2017). This is based on the strong correlation

53 between locus coeruleus (LC) firing and measures of autonomic arousal such as

54 heart rate or pupil diameter, but this relation is far from being specific (Abercrombie &

55 Jacobs, 1987; Joshi et al., 2016; Gee et al., 2017). Thus, one hypothesis would be

56 that noradrenaline is simply associated with autonomic arousal and contributes to all

57 processes linked with arousal in a highly non-specific fashion. In that frame, the

58 various functions classically attributed to the LC (behavioural flexibility and

59 motivation) could all be captured by a non-specific role in arousal and vigilance.

60 Alternatively, noradrenaline would be involved in a set of specific and independent

61 processes, which could not be captured by a generic function such as vigilance or

62 arousal.

63   Therefore, the goal of these experiments is to test the causal role of

64 noradrenaline in behavioural flexibility and motivation using a quantitative approach.

65 To do this, we developed an original sequential decision making task, used

66 computational modelling to identify precisely the cognitive processes of interest and

67 then examined the consequences of manipulating central noradrenergic level using

68 systemic injection of clonidine, an alpha-2 noradrenergic receptor agonist which

69 decreases the firing of LC neurons and reduces central noradrenaline levels

70 (Abercrombie and Jacobs 1987; Abercrombie et al., 1988; Grant et al., 1988; Berridge

71 and Abercrombie, 1999; Bouret and Richmond, 2009). To obtain a reward, a monkey

72 should repeatedly squeeze a grip on a differing number of occasions to obtain

73 rewards. The amount of force exerted on the grip was virtually not relevant for the

74 task, since animals could complete a trial by exerting even a very small amount of

75 force. The number of squeezes and the amount of reward that could be obtained on

76 a given trial were instructed to the animal by the stimulus displayed on the screen. In

4

77   most trials, after a number of responses on a given sequence, the animals were

78   offered a choice to either complete the original sequence or change to execute a

79   different one, with a different sequence length and reward size. This enabled us to

80   look at the effect of clonidine on the cost/benefit trade-off during the choice about

81   whether to persist or switch. In this setting, behavioural flexibility was assessed by

82   measuring the variability in the choices. Motivation was assessed by measuring the

83   willingness to work and the amount of force exerted on the grip, which was not a
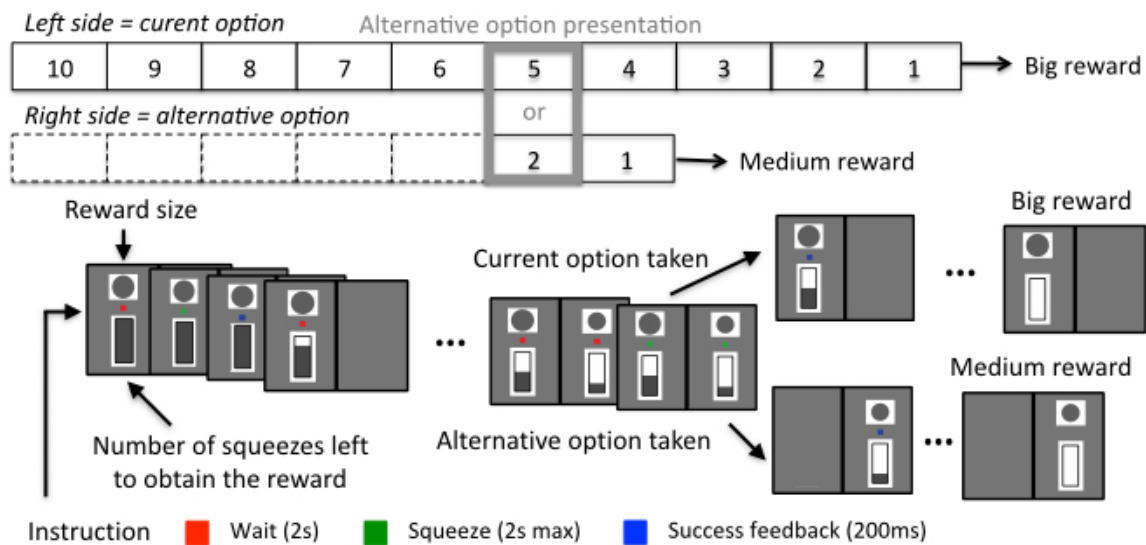
84   requirement for this task.

85   Clonidine had two distinct effects. First, in line with the role of noradrenaline in

86   behavioural flexibility, clonidine dose-dependently decreased choice volatility:

87   monkeys' choices were more consistent under clonidine, but there was no effect on

88   the cost-benefit trade-off. Second, in line with the role of noradrenaline in motivation

89   and effort, clonidine dose-dependently reduced force production during the task.

90   Because the effects on behavioural flexibility and motivation were statistically

91   independent, they cannot be accounted for by a common confounding factor or a

92   non-specific effect on arousal and vigilance. Altogether, these results support the

93   global implication of noradrenaline in facing challenging situations in two

94   complementary ways: i) by enhancing the mobilization of resources to face

95   immediate challenges and ii) by increasing behavioural volatility, which would

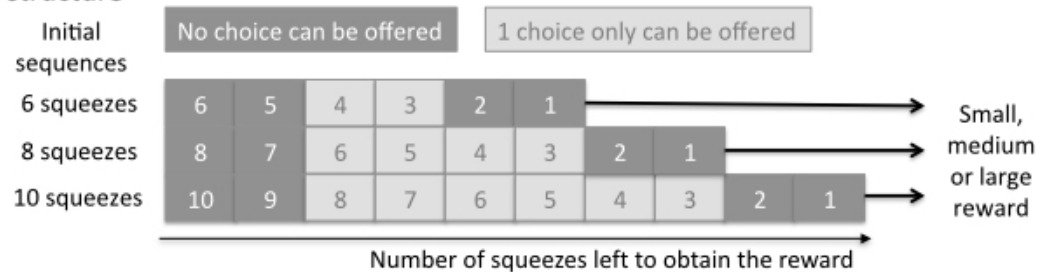96   facilitate adaptation in a labile environment.

5

97 **Results**

98 *Overview of the task*

99 We trained three monkeys to perform the task depicted in figure 1. In each trial,

100 monkeys performed series of actions (squeezing a grip 6, 8 or 10 times) to get a

101 small, medium or large fluid reward (fig 1A). Note that the amount of force required to

102 complete the trial was minimal and monkeys always succeeded to complete a

103 squeeze when they tried. In 70% of trials, we introduced a choice by presenting an

104 alternative option before monkeys could complete the trial. This alternative option,

105 presented on the opposite side of the monitor compared to the current option, was

106 also characterized by a given number of squeezes and a given reward size. Thus,

107 monkeys could either choose to continue with the current option by squeezing the

108 same grip as before, or switch to the other grip to start completing the alternative

109 option and obtain the corresponding reward. As expected, the monkeys behavioural

110 responses were affected both by the expected costs (number of remaining squeezes)

111 and benefits (reward size), with no overall choice bias toward a specific side (left vs.

112 right) or a specific option (current vs. alternative) (T-tests, $p > 0.05$, see below). To

113 capture the role of noradrenaline in behavioural flexibility and motivation, we then

114 examined the influence of clonidine on corresponding behavioural measures in this

115 task.

A Example choice trial

Left side = curent option   Alternative option presentation

| 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | → Big reward |

Right side = alternative option   or

| | | | | | 2 | 1 | → Medium reward |

Reward size

Number of squeezes left to obtain the reward

Current option taken   Big reward

Alternative option taken   Medium reward

Instruction ■ Wait (2s)   ■ Squeeze (2s max)   ■ Success feedback (200ms)

B Task structure

Initial sequences   No choice can be offered   1 choice only can be offered

6 squeezes	6	5	4	3	2	1				→ Small,
8 squeezes	8	7	6	5	4	3	2	1		medium or large
10 squeezes	10	9	8	7	6	5	4	3	2	1	→ reward

Number of squeezes left to obtain the reward

116
117 **Figure 1: task**

118

119 *Effects of clonidine on behavioural flexibility: choices*

120 We first measured the influence of clonidine on the average chosen number of

121 squeezes and chosen reward size (fig 2A), which provides a global estimate of the

122 animals' relative sensitivity to costs and benefits. This measure was also not reliably

123 affected by the treatment (linear regression taking into account subject variability,

124 $t(10)=1.85$, $p=0.09$ and $t(10)=0.65$, $p=0.53$, respectively).

125 We next examined the influence of clonidine on the choice bias towards the

126 current versus alternative option, over and above the influence of expected costs

127 (number of squeezes) and benefits (reward sizes). Because all options were offered

7

128   in equal proportions as current and alternative options, any departure of the

129   probability to take the alternative option from 50% would represent a bias toward

130   staying or switching. At the group level, there was no significant bias toward staying

131   or switching across all treatment conditions (linear regression taking into account

132   subject variability, t(10)=0.52, p=0.52), and the bias was not different from zero in

133   any condition (T-test, p>0.47, for all doses) (fig 2B).

134   We then looked the stability in choices across doses. As shown on figure 2C,

135   there was a clear linear increase in stability across doses of clonidine, which means

136   that with increasing doses of clonidine, the monkeys became increasingly likely to

137   make the *same* decisions when faced with the *same* type of choice (linear regression

138   taking into account variability across subjects, β=0.559±0.183, t(10)=3.06, p=0.01).

139
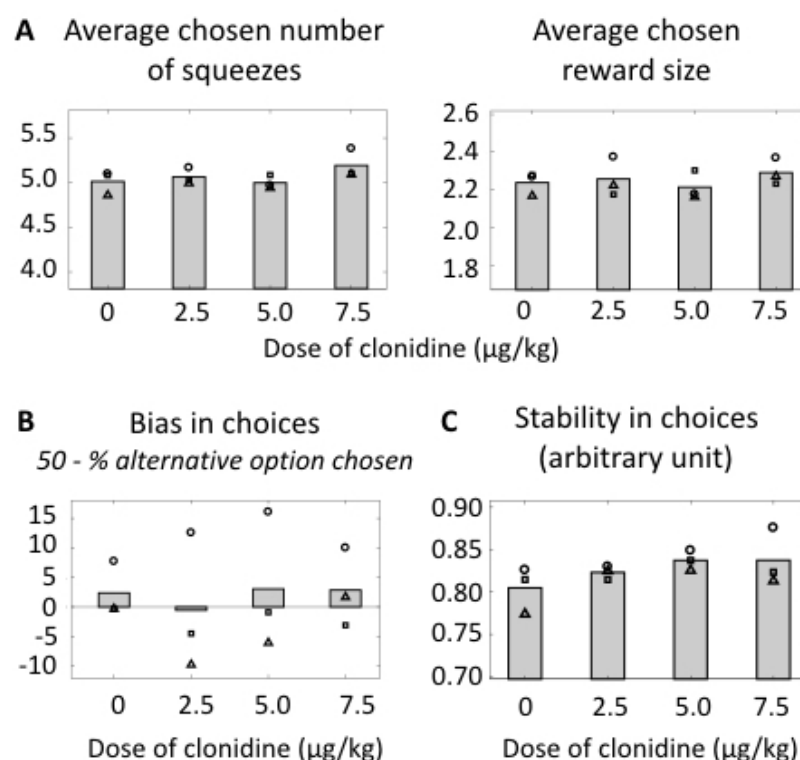
140   **Figure 2: Effect of clonidine on decision-making**

141   To capture the specific influence of clonidine on distinct components of

142   decision-making, we built a simple choice model depicted in equations 1 and 2 in

143   *Material and Methods*. In this model the value of each option corresponds to a trade-

144   off between reward at stake and sequence length, controlled by a parameter

145   k(sequence length). The probability to select a given option depends on (i) the value

146   difference with the alternative and (ii) a fixed bias, e.g. a preference for either staying

147   with the current option or taking the alternative, as well as (iii) the choice consistency,

148   which determines the degree to which choices are consistent with the evaluation.

149   As shown on figure 3, we looked at the effect of the treatment on the three

150   parameters of the choice model (k(sequence length), bias and consistency). The

151   parameter k(sequence length) describing the relative sensitivity to reward and

152   sequence length was significantly different from zero, indicating that monkeys readily

153   integrated these two factors to guide their behaviour (all p<0.01). Had either the

154   sensitivity to sequence length or reward size changed following administration of

155   clonidine, this parameter would have varied For example an increase in effort

156   sensitivity would have be translated in an increase in k(sequence length). But as

157   shown on figure 3A, this parameter estimate was again not affected by the treatment

158   (linear regression taking into account variability across subjects, t(10)=-0.10, p=0.92),

159   indicating a lack of effect of clonidine on the cost-benefit analysis. In line with the

160   previously described model-free analysis (fig 2B), there was no systematic bias to

161   stay with the current option or switch to the alternative at the group level (bias

162   parameter not significantly different from zero, all p>0.55) and no effect of treatment

163   on this bias parameter (linear regression taking into account variability across

164   subjects, t(10)=-0.10, p=0.92) (fig 3B). By contrast, clonidine induced a dose

165   dependent increase in choice consistency (fig 3C). To analyse this formally, we ran a

166   linear regression taking into account the variability across subjects. This revealed a

167   significant linear effect of dose on the consistency parameter's estimates

168   ($\beta=0.248\pm0.070$, (10)=3.54, p<0.01).

169   Figure 3D-G illustrates the influence of the highest dose of clonidine on

170   choices. The colour maps represent the proportion of alternative option chosen for

171   different values of the current and the alternative options. Most stable choices are

172   represented in white (subjects always choose the alternative option) and black (they

173   always choose the current option). Grey colours represent less stable choices, with

174   the maximum of randomness in along the diagonal, where the values of the two

175   options are close. The more consistent the choices are, the smaller the area of this

176   grey colours zone is. Figures 3C and D were generated using the estimated

177   consistency parameter of the choice model under saline (fig 3C) and clonidine (fig

178   3E). Figures E and F with subjects' actual choices. For both, under clonidine, the

179   area occupied by stable choices expend at the expense of less stable choices,

180   reflecting the increase in choice consistency following the pharmacological

181   manipulation of noradrenaline.

182

**Figure 3: Clonidine specifically affects consistency in choice**

185
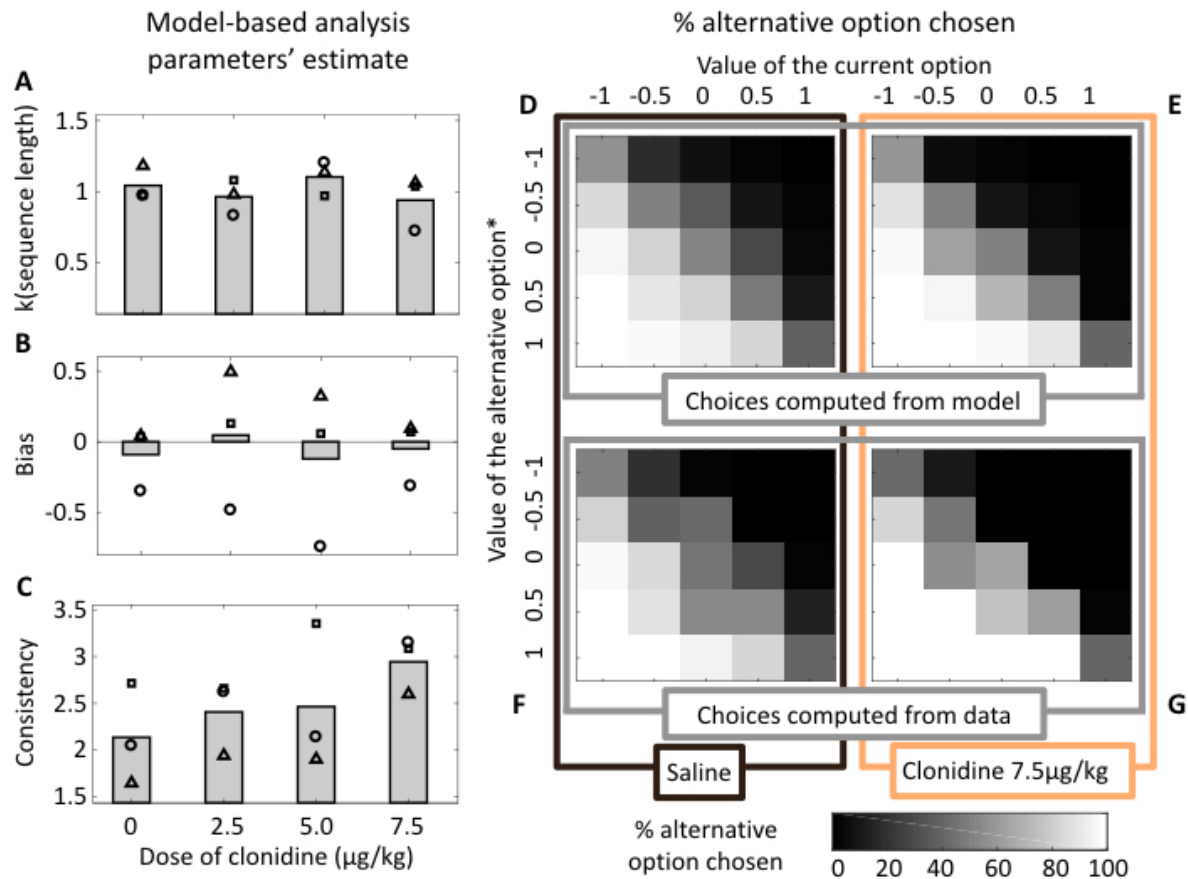
Effect of clonidine on reaction times

We next evaluated the effects of clonidine on reaction time across task conditions. We separated conditions where monkeys had to make a choice between two options from conditions where they only squeezed the grip to progress through the trial. As frequently observed, monkeys were slower to respond in choice than no-choice trials (fig 4A). We examined the influence of clonidine on reaction times in these two types of trials and a multi-level linear regression taking into account variability across

193   subjects revealed a significant linear effect of choice ($\beta=0.641\pm0.022$, $t(17)=6.30$,

194    $p<0.001$) and dose ($\beta=0.070\pm0.007$, $t(17)=2.90$, $p<0.01$), but no significant interaction

195   ($t(16)=0.13$, $p=0.89$). Hence, clonidine significantly slowed down reaction times, but

196   its effects were undistinguishable between choice and non-choice conditions. We

197   also separated choice reaction times according to two levels of choice difficulty

198   (depending on whether the dimensions to integrate to make the choice were

199   congruent or not: *hard* and *easy choices*, respectively) and found a significant linear

200   effect of choice difficulty ($\beta=0.258\pm0.013$, $t(33)=7.52$, $p<0.001$) and dose

201   ($\beta=0.083\pm0.008$, $t(33)=2.75$, $p<0.001$), but once again no interaction ($t(32)=-0.44$,

202    $p=0.66$). Both clonidine and choice difficulty increase reaction time but their effects

203   are additive, indicating that clonidine does not interfere with the influence of difficulty

204   on reactions times. Overall, monkeys' reaction times were clearly modulated across

205   conditions: animals slowed down when they had to make a choice, especially if it was

206   difficult. High doses of clonidine also slowed down the monkeys but because its

207   effects were equivalent across conditions (no interaction), it did not affect the

208   behavioural effect of difficulty.

209   Together, our analyses therefore revealed two effects of clonidine on

210   behaviour: it dose-dependently increased choice consistency and decreased choice

211   reaction times. We examined the relation between these two effects across

212   treatments and animals. We found a positive correlation (linear regression taking into

213   account variability across subjects, $\beta=0.321\pm0.095$, $t(10)=3.47$, $p<0.01$) between the

214   estimated consistency parameter and the choice reaction time (fig 4B). This

215   correlation between the effect of treatments on reaction time and choice consistency

216   suggests that clonidine affects a single functional entity, which we could refer to as

12

217   "speed-consistency trade-off". Altogether, this analysis provides a clear

218   computational characterization of the contribution of the noradrenergic to behavioural

219   flexibility in this task.

220

221   **Figure 4: Effects of clonidine on reaction times**

222
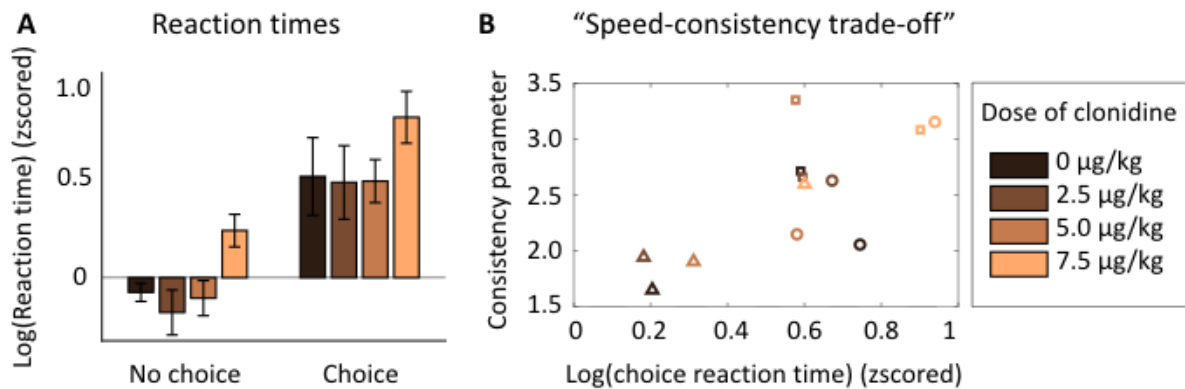
223   *Effect of clonidine on motivation: willingness to work*

224   After assessing the implication of noradrenaline in behavioural flexibility, we

225   examined the causal role of noradrenaline in motivation in this task. For that, we

226   examined the influence of clonidine on two behavioural measures that are classically

227   used to assess motivation, willingness to work and physical force production (fig 5).

228   We measured monkeys' willingness to work by counting the proportion of accepted

229   squeezes. Since the action is very easy, monkeys never failed to complete a

230   squeeze if they tried to, the number of squeezes that they accept to perform directly

231   reflects their motivation to complete the trial. First, the willingness to work during 1-

232   hour-long sessions was not significantly affected by dose (linear regression taking

233   into account the variability across subjects, t(10)=-0.36, p=0.73) (fig 5A). Thus,

234   clonidine did not have a global effect on the monkeys' engagement in the task.

235   We also examined the effect of clonidine on the animals' ability to adjust their

236   behaviour across levels of progression through the sequences. We first examined

237   willingness to work for the first squeeze of all sequences. We included every trial,

238   since there was no way for monkeys to predict at the start of a sequence if a choice

239   was going to be offered later in that sequence. We again examined the influence of

240   reward size and sequence length on the willingness to perform the first squeeze

241   using a linear regression taking into account the variability across subjects. This

242   analysis revealed a significant negative effect of sequence length (i.e., the animals

243   were less willing to engage on long sequences: β=-18.81±2.44, t(104)=-7.71,

244   p<0.001) and a marginally significant positive effect of reward size (animals were

245   more willing to engage for greater reward: β=-4.79±2.44, t(104)=1.96, p=0.052), but

246   no effect of dose of clonidine (t(104)=1.43, p = 0.16) and no interaction with

247   sequence length (t(102)=0.20, p=0.84) or reward (t(102)=-0.65, p=0.52).

248   In a subsequent analysis, we examined the influence of clonidine on the

249   adjustments of willingness to work across the steps of a trial, as a function of the

250   upcoming sequence length and reward size (fig 5B). Indeed, monkeys displayed a

251   sharp increase in their willingness to work after the first squeeze, which can be

252   related to the engagement in the sequence. We fitted the curves depicted in figure 5B

253   with equation 3 for all trials during which no choice was offered. In this model,

254   k(intercept) controls the intercept (initial willingness to work) and k(slope) the slope of

255   the rise of the willingness to work across the sequence. We then examined the

14

256 influence of reward and sequence length on each of these parameter estimates using

257 a multi-level linear regression taking into account the variability across monkeys. The

258 parameter k(intercept) displayed a significant positive linear effect of sequence length

259 (β=0.160±0.019, t(104)=8.09, p<0.001) and a negative effect of reward size (β=-

260 0.048±0.019, t(104)=-2.44p<0.05), but again there was no significant linear effect of

261 dose (t(103)=-1.85, p=0.07), and no interaction with either the sequence length

262 (t(101)=0.32, p=0.75) or the reward size(t(101)=-0.12, p=0.91). By contrast, neither

263 the task factors (reward and sequence length) nor the dose of clonidine and its

264 interaction with the tasks factors affected the parameter k(slope), which captured the

265 slope of the change in willingness to work across the sequence (all p > 0.30).

266   In short, monkeys displayed robust adjustments of their willingness to produce

267 the action across conditions, defined by the distance to reward and the amount of

268 expected reward at the end of the sequence, but this was unaffected by clonidine.

269 This implies that clonidine did not affect the monkeys' general willingness to work,

270 ruling out a non-specific effect on arousal.

271

272 *Effect of clonidine on motivation: Force production*

273 Lastly, we examined the effect of clonidine on another key component of motivation:

274 force production. As shown on figure 4C, force peak was significantly decreased

275 under clonidine treatment (linear regression, t(10)=-3.24, p<0.01). Moreover, as

276 described in an earlier section, clonidine increased overall the reaction times (linear

277 regression, t(10)=2.63, p=0.02). Hence we considered the possibility that clonidine

278 had a global, non-specific effect on arousal or vigilance, which would be responsible

15

279 for both longer reaction times and smaller force peaks. Such a scenario implies a

280 strong relation between the effects of clonidine on force peak and reaction time. We

281 first compared the effect on force peak and reaction time in a 2-way ANOVA with

282 factors dose and measure (force peak vs. reaction time). We found a significant main

283 effect of dose ($F_{(3, 16)}=5.25$, $p=0.01$), measure ($F_{(1,16)}=4.72$, $p=0.04$), but

284 importantly also a significant interaction between the two ($F_{(3, 16)}=8.59$, $p=0.001$),

285 indicating that the effect of clonidine differs significantly between the two measures.

286 We furthered this analysis using a linear regression (fig 4D): there was no reliable

287 correlation between the two measures ($r=-0.4$, $p=0.19$). Moreover, we ran separate

288 linear regressions without the highest dose, we found that the effect on force peak

289 was still significant ($t(7)=-3.93$, $p=0.005$) whereas it was not the case for reaction

290 times ($t(7)=0.16$, $p=0.88$), implying that the linear effect was mostly due to the last

291 dose. We also found a greater linear effect of dose on ($\beta=-0.222\pm0.068$) than on

292 reaction times ($\beta=0.106\pm0.040$). Overall, the analyses imply that clonidine had a

293 greater impact of effort production than willingness to work and reaction times.

294 Finally we found no significant correlation between the consistency parameter

295 and the force peak, ($t(10)=-1.39$, $p=0.15$). This shows that the effect of clonidine on

296 force production and decision-making ("speed-consistency trade-off") are

297 independent and probably not due to a global effect on arousal/vigilance.
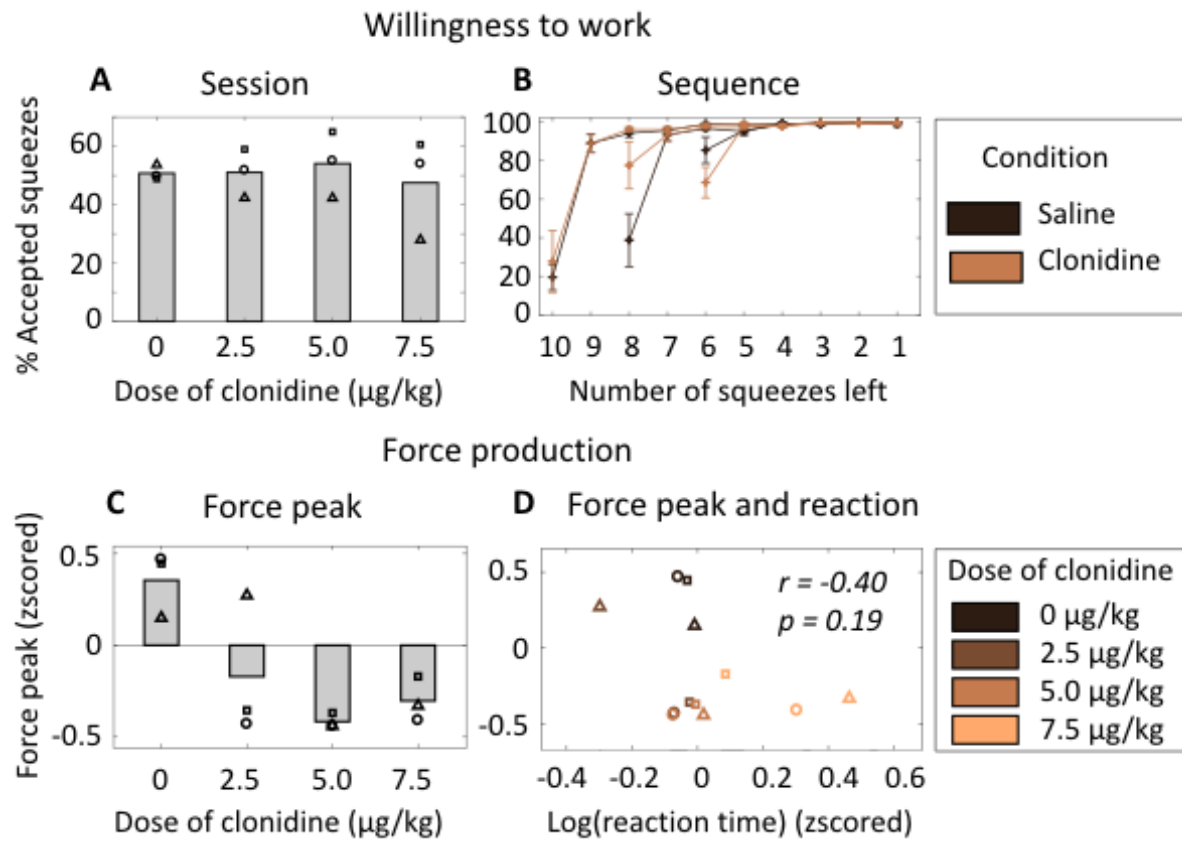
Figure 5: Effects of clonidine on motivation

Discussion

300

301 In the present work, we used a novel decision-making task, which required monkeys

302 to make sequential actions for reward and, on a majority of trials, to choose whether

303 to stick with the current sequence or to switch to an alternative based on the costs

304 and benefits of the options. This task allowed us to independently evaluate two

305 classes of functions thought to involve noradrenaline: behavioural flexibility and

306 motivation. Using systemic injections of clonidine, at doses that specifically decrease

307 the level of noradrenaline in the brain (Kawahara et al., 1999; Fernandez-Pastor et

308 al., 2005), we showed that noradrenaline was causally involved both in specific

309 aspects of behavioural flexibility (speed consistency trade-off) and also in motivation

310 (willingness to work and force production). Importantly, the effects on force were

311 specific to this parameter and did not relate to other measures of motivation such as

312 response speed or willingness to work, negating any general changes in arousal or

313 vigilance.

314

315 *Noradrenaline regulates behavioural flexibility: speed/consistency trade-off*

316 The first major effect of clonidine treatment was on choice consistency, thus

317 extending the causal role of noradrenaline to value-based decision-making. Model-

318 free analysis showed that clonidine induced a decrease in choice variability. In other

319 words, when given clonidine, the monkeys became more likely to repeat the same

320 choice when presented with particular pairs of choice options. This was also backed

321 up by our model-based analysis, where we separated the evaluation from the option

322 selection components in a simple "value-first" model (Padoa-Schiopa, 2011). These

18

323   two processes were controlled by 3 distinct parameters: *k(sequence length)* for the

324   cost-benefit evaluation, a *bias* and *consistency* for the option selection. This model-

325   based approach linked the behavioural change induced by clonidine specifically with

326   an increase of the consistency parameter, independent of the valuation process and

327   the bias parameter. Hence this effect was due to a decrease in choice variability

328   rather than to a systematic biasing of the choices in any direction (such as by reward,

329   cost, side or current vs. alternative option).

330   Variability in choices is assumed in many models of decision-making, but its

331   functional role remains debated. It has been proposed that it arises from random

332   noise driven by internal neural variability (Wang, 2002; Faisal et al., 2008;

333   Drugowitsch et al., 2016) and in that case, noradrenaline would control the amount of

334   noise that is allowed in the computation (Aston-Jones and Cohen, 2005). Along those

335   lines, it has recently been proposed that noradrenaline controls the precision of

336   sensory cortical representation (Warren et al., 2015).

337   Optimal economic theory stipulates that the behaviour is optimal when there is

338   no noise, meaning that the choices follow exactly the values of the options. In that

339   sense, clonidine would seem to make monkeys more optimal since it increases

340   choice consistency. But this absence of noise is only optimal in a constant

341   environment. In a more uncertain and dynamic environment, however, noise in

342   choices is thought to facilitate adaptation (Aston-Jones and Cohen, 2005; Yu and

343   Dayan 2005; Nassar et al., 2012; Wilson et al., 2014). Thus, an increase in choice

344   consistency under clonidine might also be interpreted as a decrease in efficacy if

345   placed in a labile and/or uncertain environment. Importantly, our experiment shows

346 that an effect of noradrenaline manipulation on choice variability can be observed

347 even without a change in reward rate. This implies that the action of noradrenaline on

348 choice consistency is systematic and generic, rather than dependent upon the

349 specific task contingency. As such, these results are consistent with two recent

350 studies. The first showed that specifically enhancing LC inputs to rat anterior

351 cingulate cortex triggers behavioural variation (Tervo et al., 2014). The second

352 showed that systemic clonidine increases decisiveness in rats by reducing the

353 deliberative search process and representation of the unchosen path in the

354 hippocampus in a spatial decision-making task (Amemiya and Redish, 2016).

355 Our work also indicates that the effect of clonidine on choice consistency was

356 associated with a slowing of choice reaction times, in line with the idea that

357 noradrenaline affects an internal decision variable, a specific function that affects

358 both consistency and speed. The effect on speed consistency trade-off resonates

359 with the idea that efficient deliberation takes time, such that slow decisions are also

360 more reliable because they are based on a more thorough evaluation of subjective

361 costs and benefits (Jocham et al., 2014).

362 Thus, not only is our work further supporting the implication of the

363 noradrenergic system in behavioural flexibility, but it provides a clear computational

364 characterization of its role. Noradrenaline promotes behavioural volatility by favouring

365 faster and less reliable choices, thereby inducing a more noisy behaviour, and

366 without affecting the cost-benefit trade-off.

367

368 *Noradrenaline regulates motivation: force production*

20

369   In line with the conclusions of our recent electrophysiological studies (Varazzani et

370   al., 2015), these experiments using direct manipulation of the noradrenergic system

371   demonstrated its causal implication in motivation. Clonidine dose-dependently and

372   specifically reduced the amount of force produced, and this effect on force was

373   independent of the effects on reaction time, ruling out a simple interpretation in terms

374   global motor impairment. It is also unlikely to be caused by a global effect on arousal

375   or vigilance, as clonidine had no impact on either the animals' willingness to work or

376   on their ability to switch from the current to the alternative option. The influence of

377   clonidine on force production was independent of task conditions, including reward.

378   Indeed, the amount of force produced was not contingent in this task and the effect of

379   clonidine was equivalent across reward conditions. Hence clonidine did not affect

380   incentive processes, as it is often the case with dopaminergic treatments (Denk et al.,

381   2005; Lebouc et al., 2016; Yohn et al., 2016; Zenon et al., 2016).

382   Thus, the effect of clonidine causing reduced force production seems to be

383   relatively specific to the action requirements, but did not affect the overall cost-benefit

384   analysis. Indeed, neither the initial choice to engage with the sequence, nor the

385   binary choice in the middle of the sequence to stick with the initial option or to switch

386   to the novel alternative were affected by the treatment as shown in the model-based

387   analysis. At first, this might appear surprising since squeezing the grip multiple times

388   could be taken as an effort. But since the minimal force to validate a squeeze was

389   very small and monkeys always succeeded to reach it if they initiated the action,

390   physical effort is unlikely to be a major component of the cost in this task. Moreover,

391   previous studies using a similar task suggest that some monkeys could treat

392   sequences as delay, and neglect the motor cost relative to the temporal discounting

393   effect of the sequence (Minamimoto et al., 2012). Given the small number of animals

394   in monkey studies, this effect remains difficult to evaluate. Finally, this is in line with

395   recent electrophysiological data in an effort-reward trade-off task (Varazzani et al.,

396   2015) showing an activation of LC neurons correlated with the amount of force

397   produced on a grip at the time of executed action, but not when evaluating this

398   option. In other words, the LC neurons only encoded the effort component at the time

399   of when monkeys needed to actually mobilize energy to produce the action and not

400   when choosing whether to act in the first place. This reinforces the idea that

401   noradrenaline plays a specific role in actually producing the effort – mobilizing energy

402   to face a challenge – as we suggested earlier (Bouret and Richmond, 2015;

403   Varrazani et al., 2015). It is intriguing that such a role is complementary yet distinct

404   from the influence of the other major catecholamine, dopamine, which is known to be

405   key for assessing the value of working through sequences of actions for reward but is

406   perhaps not required to overcome force constraints (Ishiwari et al., 2004; Gan et al.,

407   2010; Pasquereau and Turner, 2013; Varazzani et al., 2015; Salamone et al., 2016).

408   A key question for future studies will be to directly contrast the precise roles these

409   neurotransmitters play in effort-based decision-making.

410   Last, we found that the effects on force production were not correlated with

411   choice consistency. Hence the two effects were independent, further ruling out an

412   interpretation in terms of global, low level process such as arousal or vigilance. This

413   is probably due to the action of clonidine on different networks. It has recently been

414   shown different populations of LC neurons project to the prefrontal cortex and the

415   motor cortex (Chandler et al., 2014). These two distinct networks could underlie the

416   effects on choice consistency and force production respectively. But irrespectively of

22

417 the underlying neurobiological mechanisms, this work demonstrates that these two

418 facets of noradrenergic functions are relatively independent, and specific. In other

419 words, the implication of noradrenaline in cognition and behavior cannot be reduced

420 to arousal or vigilance, even if LC activity strongly correlates with autonomic arousal.

421 One of the upcoming challenges will be to understand the neuronal mechanisms

422 underlying these specific operations, and how they articulate with functions of other

423 neuromodulatory systems such as dopamine and serotonine.

424

425 *Conclusion*

426 To conclude, these results delineate the causal implication of noradrenaline in

427 behavioural flexibility and motivation. As only particular behavioural functions were

428 altered by clonidine, we can go beyond an interpretation based on a global arousing

429 effect of noradrenaline. Instead, our results are compatible with the idea that

430 noradrenaline is involved in facing challenges through two specific and

431 complementary actions: i) an increase in behavioural volatility and ii) the mobilization

432 of physical resources to face immediate challenges. This proposal relies on the

433 assumption that these two processes are adaptive to solve most challenges. While

434 the former would facilitate adaptation in an uncertain or changing environment, the

435 later is clearly advantageous in an environment where you must compete for

436 resources and achieve the goals that are set. Key challenges remain to understand

437 how this system articulates with other neuromodulators in adaptive behaviours and

438 what is its precise action on its target networks.

Materials and Methods

Monkeys

Two male rhesus monkeys (Monkey A, 15 kg, 5 years old; Monkey D, 15 kg, 6 years old) and one female (Monkey E, 4.5 kg, 3 years old) were used for the experiment. Their access to water was restricted and during testing days (Monday to Friday), they received water as reward. All experimental procedures were designed in association with the Institut du Cerveau et de la Moelle Epiniere (ICM) veterinarians, approved by the Regional Ethical Committee for Animal Experiment (CREEA IDF no. 3) and performed in compliance with the European Community Council Directives (86/609/EEC).

Task

Each monkey sat in a primate chair positioned in front of a monitor on which visual stimuli were displayed. Two electronic grips (M2E Unimecanique, Paris, France) were mounted on the chair at the level of the monkey's hands. Monkeys were not constrained to use one hand or the other to squeeze the grips. Each grip corresponded to one side of the screen. Water rewards were delivered from a tube positioned between the monkey's lips. Behavioural paradigm was controlled using the REX system (NIH, MD, USA) and Presentation software (Neurobehavioral systems, Inc, CA, USA).

The task consisted of performing sequences of squeezes on a grip to obtain rewards. At the beginning of each trial, the length of the sequence (number of

461   squeezes) and the size of the reward were indicated by two different cues that

462   appeared simultaneously with a red dot on either the left or right side of the screen

463   (counterbalanced across trials) (Fig 1). There were nine initial options defined by

464   three initial sequence lengths (6, 8 and 10 squeezes) and three reward sizes (small,

465   medium and big). After a fixed delay of 2s, the red dot turned green and to initiate a

466   trial, monkeys had 2s to perform a squeeze above the minimum force threshold with

467   the grip corresponding to the side of the screen where stimuli were displayed. The

468   threshold was manually calibrated during the training phase, so that monkeys would

469   always reach it if they squeezed the grip (bell-shaped force profile). After a correct

470   squeeze, the dot turned blue for 200ms. Then, the dot turned red again and the cue

471   corresponding the sequence length changed to show the number of remaining

472   squeezes to complete the sequence. After an incorrect squeeze, the stimuli

473   disappear and the same trial restarted from the beginning of the sequence after 1 -

474   1.5s of inter-trial interval delay. A squeeze was incorrect if monkeys squeezed the

475   wrong grip, squeezed any grip when the dot was red or did not reach the minimum

476   force threshold 2s after the dot turned green. After the last correct squeeze of the

477   sequence, the dot disappeared, the cue indicating the number of remaining squeezes

478   was at zero and monkeys received the size of the reward corresponding to the

479   reward cue. At the end of the reward delivery, a new trial started after 1 - 1.5s of

480   inter-trial interval delay.

481   In 30% of trials, monkeys had no option other than to complete the initial

482   sequence. However, in 70% of trials, monkeys were given the choice during the

483   sequence to take an alternative option (Fig 1A). The alternative option was presented

484   on the opposite side of the screen and occurred at least three squeezes after the

485   beginning the initial sequence and at most three squeezes before the end of it (fig

486   1B). To choose this option, monkeys had to switch to squeezing the corresponding

487   grip when the dot turned green. Only one alternative option was offered per trial and

488   it was presented only once during the sequence. In 10% of trials, the alternative

489   option was the *same* as the current option (i.e., same reward size and same

490   remaining sequence length). In 20% of trials, the two dimensions of the choice were

491   *congruent*: the alternative option had either a longer / same sequence length and a

492   smaller / same reward size or a shorter / same sequence length and a larger / same

493   reward. In the remaining 40% of trials, the two dimensions of the choice were

494   *incongruent*: the alternative option either had a longer sequence length but a bigger

495   reward size or a shorter sequence length but a smaller reward. The sequence length

496   and reward size of the alternative option were drawn so that: i) if option A was offered

497   as a current option and B as alternative on one trial, it was equally probable that A

498   would be offered as a alternative and B as a current option on another trial, ii) all

499   sequence lengths (3 to 8 squeezes) were equally probable for the current and the

500   alternative options, and iii) before the choice, the numbers of squeezes performed

501   were counterbalanced across sequences. As a consequence, starting with a long

502   sequence was more probable (11 out of 18 trials) than a medium (5 out of 11 trials)

503   and a short (2 out of 11 trials) sequence. All reward sizes and sides were equally

504   probable.

505

506   *Pharmacological procedure*

507   We used three doses of clonidine - 2.5, 5.0 and 7.5µg/kg - which is a selective

508   alpha-2 noradrenergic receptor agonist that suppresses LC firing and consequently

509   noradrenaline release at the doses that we used (Kawahara et al., 1999; Fernandez-

510   Pastor et al., 2005). The doses that we used were below the sedative effect threshold

511   determined in rats (Sara et al., 1995; Lapiz and Morilak, 2006) and monkeys (Bouret

512   and Richmond, 2009), but elicited a subjective feeling of sedation humans (Jäläkä et

513   al., 1999). Clonidine hydrochloride (C7897, Sigma-Aldrich, St. Louis, MO, USA)

514   solutions were prepared freshly each day by dissolution in 1mL saline for monkey A

515   and D, and 0.5mL for monkey E. The same volume of saline solution was given in

516   saline condition. Drug or saline solution was injected intramuscularly 20min before

517   testing in monkeys' home cages. Each dose or vehicle was given for five consecutive

518   days (Monday to Friday). Order of drug and saline weeks (one drug week per dose

519   and 2 saline weeks) was randomly assigned for each animal.

520

521   *Data analysis*

522   Data were analysed with Matlab software (MathWorks). To assess changes in the

523   decision process, we looked at three variables: (i) the proportion of alternative

524   options chosen per session, (ii) average chosen number of squeezes, (iii) the

525   average chosen reward size and (iv) the stability in choices. The stability was

526   computed by assessing for each possible combination of differences in reward size

527   (5 possibilities: -2, -1, 0, +1, +2) and sequence length (5 possibilities: -4, -2, 0, +2,

528   +4) between the current and the alternative option if the same choice (taking the

529   alternative or the current option) was made. We then took the average for these 25

530   possibilities. The stability is therefore maximal if monkeys are perfectly stable in there

531   choices and minimal if there are completely random.

532   We also built a simple decision model where the value of each option (the

533   current and the alternative) is computed as:

$$V(option) = R(option) - k(sequence\ length) * SL(option) \qquad (1)$$

534   where V(option) is the value, R(option) the reward size and SL(option) the sequence

535   length of the considered option. Sequence Length corresponds to the remaining

536   number of squeezes to perform to obtain the reward. The values of the two options

537   are compared to determine the probability to take the alternative option as follows:

$$P(AO) = \frac{100}{1 + exp(-(V(AO) - V(CO) + bias) * consistency)} \qquad (2)$$

538   where P(AO) is the probability to take the alternative option, V(AO) and V(CO) the

539   values of the alternative and current options respectively computed with equation 1.

540   The three parameters k(sequence length), bias and consistency in equations 1 and 2

541   were estimated by inverting the model so as to minimize the free energy, using a

542   variational Bayes approach under Laplace approximation (Friston et al., 2007;

543   Daunizeau et al., 2009), implemented in a Matlab toolbox (available at http://mbb-

544   team.github.io/VBA-toolbox/; Daunizeau et al., 2014).

545   Reaction time corresponds to the time between the display of the green dot

546   and the crossing of the minimum force threshold for correct squeezes. Reaction time

547   distributions for each grip and each monkey log-transformed and z-scored (mean set

548   to zero and variance to one). We compared reaction times across different squeeze

549   types. When comparing *Choice* and *No Choice* reaction times, No Choice reaction

550 time corresponds to trials where no choice was offered but in principle could have

551 been (fig 1B) and Choice reaction time corresponds to points in the sequence where

552 monkeys were presented with an alternative option but stayed with the original

553 option. When looking at the effect of difficulty on choice reaction times, *Easy* choices

554 correspond to ones where the two dimensions of the choice are strictly congruent

555 and monkeys do not change grip. *Hard* choice squeezes correspond to squeezes

556 where the two dimensions of the choice are strictly incongruent and monkeys do not

557 change grip.

558 Motivational changes with treatment were assessed by two variables: force

559 peak and willingness to work.

560 To calculate force peak, force time series for both grips were low-pass filtered

561 at 15 Hz (zero-phase second-order Butterworth filter) and we took the maximal value

562 of the force signal between two crossings of the minimal force threshold.

563 Willingness to work corresponds to the proportion of accepted squeezes per

564 session. Willingness to work at the beginning of each sequence was computed by

565 taking the first squeeze of all trials. Willingness to work across sequences of given

566 length and reward size were estimated by taking all trials where no choice was

567 offered in a given drug condition for each monkey and fitted using the following

568 model:

$$\%correct\ squeezes(n) = \big(1 - k(intercept) * exp(-k(slope) * n)\big) * 100 \quad (3)$$

569 Where n is the number of squeezes done in the sequence. Parameters k(intercept)

570 and k(slope) were estimated for each dose and each monkey using the same

571   procedure as for the parameters of equations 1 and 2.

572

573   *Statistical Analysis*

574   Data are plotted as mean +/- standard error to the mean. Statistics used are indicated

575   in the *Results* sections. Comparisons between means were performed using

576   parametric tests (ANOVA and T-test). We performed linear regression on z-scored

577   distributions (reaction times and force peaks) using the function glmfit in Matlab. In

578   cases when distributions were not z-scored, we fitted an intercept for each subject

579   hence taking into account the variability in mean across subjects using the function

580   fitlme in Matlab. The general equation was:

$$y = \beta_0 + \beta_0(subject) + \sum \beta_i . x_i \quad (4)$$

581   where y is the data, β_0 a constant, $\beta_0(subject)$ a constant fitted for each subject, x_i

582   the experimental factors and β_i their weights in the linear regression. T-tests were

583   performed on weights distributions. In all cases t-values and degrees of freedom are

584   given according to statistical analysis reports of glmfit and fitlme. All statistical tests

585   were two-sided. *P* > 0.05 was considered to be not statistically significant. We

586   evaluated the quality of our models' fit using balanced accuracy (between 0 and 1)

587   computed as:

$Balanced\ accuracy$

$$= \frac{1}{2} \cdot \left(\frac{true\ positives}{true\ positives + false\ negatives} \right.$$

$$\left. + \frac{true\ negatives}{true\ negatives + false\ positives} \right) \quad (5)$$

588   which was between 0.80 and 0.86 for all fits (Brodersen et al., 2010).

Acknowledgments

Competing interests

The authors declare no competing interests.

References

Abercrombie, E. D., and B. L. Jacobs. "Microinjected Clonidine Inhibits Noradrenergic Neurons of the Locus Coeruleus in Freely Moving Cats." *Neuroscience Letters* 76, no. 2 (May 6, 1987): 203–8.

Abercrombie, E. D., R. W. Keller, and M. J. Zigmond. "Characterization of Hippocampal Norepinephrine Release as Measured by Microdialysis Perfusion: Pharmacological and Behavioral Studies." *Neuroscience* 27, no. 3 (December 1988): 897–904.

Amemiya, Seiichiro, and A. David Redish. "Manipulating Decisiveness in Decision Making: Effects of Clonidine on Hippocampal Search Strategies." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 36, no. 3 (January 20, 2016): 814–27. doi:10.1523/JNEUROSCI.2595-15.2016.

Arnsten, A. F. "Through the Looking Glass: Differential Noradenergic Modulation of Prefrontal Cortical Function." *Neural Plasticity* 7, no. 1–2 (2000): 133–46. doi:10.1155/NP.2000.133.

Arnsten, Amy F. T., Min J. Wang, and Constantinos D. Paspalas. "Neuromodulation of Thought: Flexibilities and Vulnerabilities in Prefrontal Cortical Network Synapses." *Neuron* 76, no. 1 (October 4, 2012): 223–39. doi:10.1016/j.neuron.2012.08.038.

Aston-Jones, G., C. Chiang, and T. Alexinsky. "Discharge of Noradrenergic Locus Coeruleus Neurons in Behaving Rats and Monkeys Suggests a Role in Vigilance." *Progress in Brain Research* 88 (1991): 501–20.

Aston-Jones, Gary, and Jonathan D. Cohen. "An Integrative Theory of Locus Coeruleus-Norepinephrine Function: Adaptive Gain and Optimal Performance." *Annual Review of Neuroscience* 28 (2005): 403–50. doi:10.1146/annurev.neuro.28.061604.135709.

Aston-Jones, G., and B. Waterhouse. "Locus Coeruleus: From Global Projection

33

625   System to Adaptive Regulation of Behavior." *Brain Research* 1645 (August 15,
626   2016): 75–78. doi:10.1016/j.brainres.2016.03.001.

627   Berridge, C. W., and E. D. Abercrombie. "Relationship between Locus Coeruleus
628   Discharge Rates and Rates of Norepinephrine Release within Neocortex as
629   Assessed by in Vivo Microdialysis." *Neuroscience* 93, no. 4 (1999): 1263–70.

630   Berridge, C. W., M. E. Page, R. J. Valentino, and S. L. Foote. "Effects of Locus
631   Coeruleus Inactivation on Electroencephalographic Activity in Neocortex and
632   Hippocampus." *Neuroscience* 55, no. 2 (July 1993): 381–93.

633   Berridge, Craig W., and Barry D. Waterhouse. "The Locus Coeruleus-Noradrenergic
634   System: Modulation of Behavioral State and State-Dependent Cognitive
635   Processes." *Brain Research. Brain Research Reviews* 42, no. 1 (April 2003):
636   33–84.

637   Bouret, Sebastien, and Barry J. Richmond. "Relation of Locus Coeruleus Neurons in
638   Monkeys to Pavlovian and Operant Behaviors." *Journal of Neurophysiology*
639   101, no. 2 (February 2009): 898–911. doi:10.1152/jn.91048.2008.

640   Bouret, Sebastien, and Barry J. Richmond. "Sensitivity of Locus Ceruleus Neurons to
641   Reward Value for Goal-Directed Actions." *The Journal of Neuroscience: The*
642   *Official Journal of the Society for Neuroscience* 35, no. 9 (March 4, 2015):
643   4005–14. doi:10.1523/JNEUROSCI.4553-14.2015.

644   Bouret, Sebastien, and Susan J. Sara. "Network Reset: A Simplified Overarching
645   Theory of Locus Coeruleus Noradrenaline Function." *Trends in Neurosciences*
646   28, no. 11 (November 2005): 574–82. doi:10.1016/j.tins.2005.09.002.

647   Bouret, Sebastien, and Susan J. Sara. "Reward Expectation, Orientation of Attention
648   and Locus Coeruleus-Medial Frontal Cortex Interplay during Learning." *The*
649   *European Journal of Neuroscience* 20, no. 3 (August 2004): 791–802.
650   doi:10.1111/j.1460-9568.2004.03526.x.

651   Brodersen, K. H., C. S. Ong, K. E. Stephan, and J. M. Buhmann. "The Balanced
652   Accuracy and Its Posterior Distribution." In *2010 20th International Conference*

653   *on Pattern Recognition*, 3121–24, 2010. doi:10.1109/ICPR.2010.764.

654   Chamberlain, Samuel R., Ulrich Müller, Andrew D. Blackwell, Luke Clark, Trevor W.
655   Robbins, and Barbara J. Sahakian. "Neurochemical Modulation of Response
656   Inhibition and Probabilistic Learning in Humans." *Science (New York, N.Y.)*
657   311, no. 5762 (February 10, 2006): 861–63. doi:10.1126/science.1121218.

658   Chandler, Daniel J., Wen-Jun Gao, and Barry D. Waterhouse. "Heterogeneous
659   Organization of the Locus Coeruleus Projections to Prefrontal and Motor
660   Cortices." *Proceedings of the National Academy of Sciences of the United*
661   *States of America* 111, no. 18 (May 6, 2014): 6816–21.
662   doi:10.1073/pnas.1320827111.

663   Daunizeau, J., K. J. Friston, and S. J. Kiebel. "Variational Bayesian Identification and
664   Prediction of Stochastic Nonlinear Dynamic Causal Models." *Physica D.*
665   *Nonlinear Phenomena* 238, no. 21 (November 1, 2009): 2089–2118.
666   doi:10.1016/j.physd.2009.08.002.

667   Daunizeau, Jean, Vincent Adam, and Lionel Rigoux. "VBA: A Probabilistic Treatment
668   of Nonlinear Models for Neurobiological and Behavioural Data." *PLoS*
669   *Computational Biology* 10, no. 1 (January 2014): e1003441.
670   doi:10.1371/journal.pcbi.1003441.

671   Denk, F., M. E. Walton, K. A. Jennings, T. Sharp, M. F. S. Rushworth, and D. M.
672   Bannerman. "Differential Involvement of Serotonin and Dopamine Systems in
673   Cost-Benefit Decisions about Delay or Effort." *Psychopharmacology* 179, no. 3
674   (May 2005): 587–96. doi:10.1007/s00213-004-2059-4.

675   Devauges, V., and S. J. Sara. "Activation of the Noradrenergic System Facilitates an
676   Attentional Shift in the Rat." *Behavioural Brain Research* 39, no. 1 (June 18,
677   1990): 19–28.

678   Drugowitsch, Jan, Valentin Wyart, Anne-Dominique Devauchelle, and Etienne
679   Koechlin. "Computational Precision of Mental Inference as Critical Source of
680   Human Choice Suboptimality." *Neuron* 92, no. 6 (December 21, 2016): 1398–

681   1411. doi:10.1016/j.neuron.2016.11.005.

682   Einhäuser, Wolfgang, James Stout, Christof Koch, and Olivia Carter. "Pupil Dilation
683   Reflects Perceptual Selection and Predicts Subsequent Stability in Perceptual
684   Rivalry." *Proceedings of the National Academy of Sciences of the United*
685   *States of America* 105, no. 5 (February 5, 2008): 1704–9.
686   doi:10.1073/pnas.0707727105.

687   Faisal, A. Aldo, Luc P. J. Selen, and Daniel M. Wolpert. "Noise in the Nervous
688   System." *Nature Reviews. Neuroscience* 9, no. 4 (April 2008): 292–303.
689   doi:10.1038/nrn2258.

690   Fernández-Pastor, Begoña, Yolanda Mateo, Sonia Gómez-Urquijo, and J. Javier
691   Meana. "Characterization of Noradrenaline Release in the Locus Coeruleus of
692   Freely Moving Awake Rats by in Vivo Microdialysis." *Psychopharmacology*
693   180, no. 3 (July 2005): 570–79. doi:10.1007/s00213-005-2181-y.

694   Friston, Karl, Jérémie Mattout, Nelson Trujillo-Barreto, John Ashburner, and Will
695   Penny. "Variational Free Energy and the Laplace Approximation." *NeuroImage*
696   34, no. 1 (January 1, 2007): 220–34. doi:10.1016/j.neuroimage.2006.08.035.

697   Gan, Jerylin O., Mark E. Walton, and Paul E. M. Phillips. "Dissociable Cost and
698   Benefit Encoding of Future Rewards by Mesolimbic Dopamine." *Nature*
699   *Neuroscience* 13, no. 1 (January 2010): 25–27. doi:10.1038/nn.2460.

700   Gee, Jan Willem de, Olympia Colizoli, Niels A. Kloosterman, Tomas Knapen, Sander
701   Nieuwenhuis, and Tobias H. Donner. "Dynamic Modulation of Decision Biases
702   by Brainstem Arousal Systems." *eLife* 6 (April 6, 2017): e23232.
703   doi:10.7554/eLife.23232.

704   Grant, S. J., G. Aston-Jones, and D. E. Redmond. "Responses of Primate Locus
705   Coeruleus Neurons to Simple and Complex Sensory Stimuli." *Brain Research*
706   *Bulletin* 21, no. 3 (September 1988): 401–10.

707   Guedj, Carole, Elisabetta Monfardini, Amélie J. Reynaud, Alessandro Farnè, Martine
708   Meunier, and Fadila Hadj-Bouziane. "Boosting Norepinephrine Transmission

709 Triggers Flexible Reconfiguration of Brain Networks at Rest." *Cerebral Cortex*
710 *(New York, N.Y.: 1991)*, September 6, 2016. doi:10.1093/cercor/bhw262.

711 Harley, C. W. "A Role for Norepinephrine in Arousal, Emotion and Learning?: Limbic
712 Modulation by Norepinephrine and the Kety Hypothesis." *Progress in Neuro-*
713 *Psychopharmacology & Biological Psychiatry* 11, no. 4 (1987): 419–58.

714 Harley, Carolyn W. "Norepinephrine and the Dentate Gyrus." *Progress in Brain*
715 *Research* 163 (2007): 299–318. doi:10.1016/S0079-6123(07)63018-0.

716 Ishiwari, Keita, Suzanne M. Weber, Susana Mingote, Mercè Correa, and John D.
717 Salamone. "Accumbens Dopamine and the Regulation of Effort in Food-
718 Seeking Behavior: Modulation of Work Output by Different Ratio or Force
719 Requirements." *Behavioural Brain Research* 151, no. 1–2 (May 5, 2004): 83–
720 91. doi:10.1016/j.bbr.2003.08.007.

721 Jäkälä, P., M. Riekkinen, J. Sirviö, E. Koivisto, and P. Riekkinen. "Clonidine, but Not
722 Guanfacine, Impairs Choice Reaction Time Performance in Young Healthy
723 Volunteers." *Neuropsychopharmacology: Official Publication of the American*
724 *College of Neuropsychopharmacology* 21, no. 4 (October 1999): 495–502.
725 doi:10.1016/S0893-133X(99)00048-2.

726 Jocham, Gerhard, P. Michael Furlong, Inga L. Kröger, Martin C. Kahn, Laurence T.
727 Hunt, and Tim E. J. Behrens. "Dissociable Contributions of Ventromedial
728 Prefrontal and Posterior Parietal Cortex to Value-Guided Choice." *NeuroImage*
729 100 (October 15, 2014): 498–506. doi:10.1016/j.neuroimage.2014.06.005.

730 Joshi, Siddhartha, Yin Li, Rishi M. Kalwani, and Joshua I. Gold. "Relationships
731 between Pupil Diameter and Neuronal Activity in the Locus Coeruleus,
732 Colliculi, and Cingulate Cortex." *Neuron* 89, no. 1 (January 6, 2016): 221–34.
733 doi:10.1016/j.neuron.2015.11.028.

734 Kawahara, Y., H. Kawahara, and B. H. Westerink. "Tonic Regulation of the Activity of
735 Noradrenergic Neurons in the Locus Coeruleus of the Conscious Rat Studied
736 by Dual-Probe Microdialysis." *Brain Research* 823, no. 1–2 (March 27, 1999):

737   42–48.

738 Kety, S. S. "The Possible Role of the Adrenergic Systems of the Cortex in Learning."
739   *Research Publications - Association for Research in Nervous and Mental*
740   *Disease* 50 (1972): 376–89.

741 Lapiz, M. D. S., and D. A. Morilak. "Noradrenergic Modulation of Cognitive Function
742   in Rat Medial Prefrontal Cortex as Measured by Attentional Set Shifting
743   Capability." *Neuroscience* 137, no. 3 (February 2006): 1039–49.
744   doi:10.1016/j.neuroscience.2005.09.031.

745 Le Bouc, Raphaël, Lionel Rigoux, Liane Schmidt, Bertrand Degos, Marie-Laure
746   Welter, Marie Vidailhet, Jean Daunizeau, and Mathias Pessiglione.
747   "Computational Dissection of Dopamine Motor and Motivational Functions in
748   Humans." *The Journal of Neuroscience: The Official Journal of the Society for*
749   *Neuroscience* 36, no. 25 (June 22, 2016): 6623–33.
750   doi:10.1523/JNEUROSCI.3078-15.2016.

751 Mather, Mara, David Clewett, Michiko Sakaki, and Carolyn W. Harley.
752   "Norepinephrine Ignites Local Hotspots of Neuronal Excitation: How Arousal
753   Amplifies Selectivity in Perception and Memory." *Behavioral and Brain*
754   *Sciences*, January 2016. /core/journals/behavioral-and-brain-
755   sciences/article/norepinephrine-ignites-local-hotspots-of-neuronal-excitation-
756   how-arousal-amplifies-selectivity-in-perception-and-
757   memory/A1750B4C91812D0CC7F6D42872DC05AD.

758 McGaughy, J., R. S. Ross, and H. Eichenbaum. "Noradrenergic, but Not Cholinergic,
759   Deafferentation of Prefrontal Cortex Impairs Attentional Set-Shifting."
760   *Neuroscience* 153, no. 1 (April 22, 2008): 63–71.
761   doi:10.1016/j.neuroscience.2008.01.064.

762 Minamimoto, Takafumi, Yukiko Hori, and Barry J. Richmond. "Is Working More Costly
763   than Waiting in Monkeys?" *PloS One* 7, no. 11 (2012): e48434.
764   doi:10.1371/journal.pone.0048434.

765   Nassar, Matthew R., Katherine M. Rumsey, Robert C. Wilson, Kinjan Parikh,
766   Benjamin Heasly, and Joshua I. Gold. "Rational Regulation of Learning
767   Dynamics by Pupil-Linked Arousal Systems." *Nature Neuroscience* 15, no. 7
768   (June 3, 2012): 1040–46. doi:10.1038/nn.3130.

769   Padoa-Schioppa, Camillo. "Neurobiology of Economic Choice: A Good-Based
770   Model." *Annual Review of Neuroscience* 34 (2011): 333–59.
771   doi:10.1146/annurev-neuro-061010-113648.

772   Pasquereau, Benjamin, and Robert S. Turner. "Limited Encoding of Effort by
773   Dopamine Neurons in a Cost-Benefit Trade-off Task." *The Journal of
774   Neuroscience: The Official Journal of the Society for Neuroscience* 33, no. 19
775   (May 8, 2013): 8288–8300. doi:10.1523/JNEUROSCI.4619-12.2013.

776   Preuschoff, Kerstin, Bernard Marius 't Hart, and Wolfgang Einhäuser. "Pupil Dilation
777   Signals Surprise: Evidence for Noradrenaline's Role in Decision Making."
778   *Frontiers in Neuroscience* 5 (2011): 115. doi:10.3389/fnins.2011.00115.

779   Salamone, John D., Samantha E. Yohn, Laura López-Cruz, Noemí San Miguel, and
780   Mercè Correa. "Activational and Effort-Related Aspects of Motivation: Neural
781   Mechanisms and Implications for Psychopathology." *Brain: A Journal of
782   Neurology* 139, no. Pt 5 (May 2016): 1325–47. doi:10.1093/brain/aww050.

783   Sara, S. J., C. Dyon-Laurent, and A. Hervé. "Novelty Seeking Behavior in the Rat Is
784   Dependent upon the Integrity of the Noradrenergic System." *Brain Research.
785   Cognitive Brain Research* 2, no. 3 (July 1995): 181–87.

786   Sara, Susan J. "Locus Coeruleus in Time with the Making of Memories." *Current
787   Opinion in Neurobiology* 35 (December 2015): 87–94.
788   doi:10.1016/j.conb.2015.07.004.

789   Sara, Susan J., and Sebastien Bouret. "Orienting and Reorienting: The Locus
790   Coeruleus Mediates Cognition through Arousal." *Neuron* 76, no. 1 (October 4,
791   2012): 130–41. doi:10.1016/j.neuron.2012.09.011.

792   Tait, David S., Verity J. Brown, Anja Farovik, David E. Theobald, Jeffrey W. Dalley,

793   and Trevor W. Robbins. "Lesions of the Dorsal Noradrenergic Bundle Impair
794   Attentional Set-Shifting in the Rat." *The European Journal of Neuroscience* 25,
795   no. 12 (June 2007): 3719–24. doi:10.1111/j.1460-9568.2007.05612.x.

796 Tervo, Dougal G. R., Mikhail Proskurin, Maxim Manakov, Mayank Kabra, Alison
797   Vollmer, Kristin Branson, and Alla Y. Karpova. "Behavioral Variability through
798   Stochastic Choice and Its Gating by Anterior Cingulate Cortex." *Cell* 159, no. 1
799   (September 25, 2014): 21–32. doi:10.1016/j.cell.2014.08.037.

800 Usher, M., J. D. Cohen, D. Servan-Schreiber, J. Rajkowski, and G. Aston-Jones.
801   "The Role of Locus Coeruleus in the Regulation of Cognitive Performance."
802   *Science (New York, N.Y.)* 283, no. 5401 (January 22, 1999): 549–54.

803 Varazzani, Chiara, Aurore San-Galli, Sophie Gilardeau, and Sebastien Bouret.
804   "Noradrenaline and Dopamine Neurons in the Reward/Effort Trade-off: A
805   Direct Electrophysiological Comparison in Behaving Monkeys." *The Journal of*
806   *Neuroscience: The Official Journal of the Society for Neuroscience* 35, no. 20
807   (May 20, 2015): 7866–77. doi:10.1523/JNEUROSCI.0454-15.2015.

808 Ventura, Rossella, Emanuele Claudio Latagliata, Cristina Morrone, Immacolata La
809   Mela, and Stefano Puglisi-Allegra. "Prefrontal Norepinephrine Determines
810   Attribution Of 'high' motivational Salience." *PloS One* 3, no. 8 (August 22,
811   2008): e3044. doi:10.1371/journal.pone.0003044.

812 Wang, Xiao-Jing. "Probabilistic Decision Making by Slow Reverberation in Cortical
813   Circuits." *Neuron* 36, no. 5 (December 5, 2002): 955–68.

814 Warren, Christopher M., Eran Eldar, Ruud L. van den Brink, Klodianna-Daphne Tona,
815   Nic J. van der Wee, Eric J. Giltay, Martijn S. van Noorden, et al.
816   "Catecholamine-Mediated Increases in Gain Enhance the Precision of Cortical
817   Representations." *The Journal of Neuroscience: The Official Journal of the*
818   *Society for Neuroscience* 36, no. 21 (May 25, 2016): 5699–5708.
819   doi:10.1523/JNEUROSCI.3475-15.2016.

820 Waterhouse, B. D., H. C. Moises, and D. J. Woodward. "Phasic Activation of the

821   Locus Coeruleus Enhances Responses of Primary Sensory Cortical Neurons
822   to Peripheral Receptive Field Stimulation." *Brain Research* 790, no. 1–2 (April
823   20, 1998): 33–44.

824 Wilson, Robert C., Andra Geana, John M. White, Elliot A. Ludvig, and Jonathan D.
825   Cohen. "Humans Use Directed and Random Exploration to Solve the Explore-
826   Exploit Dilemma." *Journal of Experimental Psychology. General* 143, no. 6
827   (December 2014): 2074–81. doi:10.1037/a0038199.

828 Yohn, Samantha E., Emily E. Errante, Aaron Rosenbloom-Snow, Matthew
829   Somerville, Margaret Rowland, Kristin Tokarski, Nadia Zafar, Merce Correa,
830   and John D. Salamone. "Blockade of Uptake for Dopamine, but Not
831   Norepinephrine or 5-HT, Increases Selection of High Effort Instrumental
832   Activity: Implications for Treatment of Effort-Related Motivational Symptoms in
833   Psychopathology." *Neuropharmacology* 109 (October 2016): 270–80.
834   doi:10.1016/j.neuropharm.2016.06.018.

835 Yu, Angela J., and Peter Dayan. "Uncertainty, Neuromodulation, and Attention."
836   *Neuron* 46, no. 4 (May 19, 2005): 681–92. doi:10.1016/j.neuron.2005.04.026.

837 Zénon, Alexandre, Sophie Devesse, and Etienne Olivier. "Dopamine Manipulation
838   Affects Response Vigor Independently of Opportunity Cost." *The Journal of
839   Neuroscience: The Official Journal of the Society for Neuroscience* 36, no. 37
840   (September 14, 2016): 9516–25. doi:10.1523/JNEUROSCI.4467-15.2016.

841 Zénon, Alexandre, Mariam Sidibé, and Etienne Olivier. "Pupil Size Variations
842   Correlate with Physical Effort Perception." *Frontiers in Behavioral
843   Neuroscience* 8 (2014). doi:10.3389/fnbeh.2014.00286.

844 **Figures**

845 *Figure 1: task*

846 Monkeys performed an operant task where they have to exert a certain number

847 (sequence) of squeezes on a grip to obtain fluid reward. They were sitting in a chair

848 with two grips (right and left) facing a screen. The principle of the task is use the grip

849 corresponding to the side where stimuli are displayed, wait when the dot is red,

850 squeeze when it is green and a blue dot indicates a correct squeeze. All squeezes of

851 a sequence must be performed correctly to obtain the reward. A squeeze is incorrect

852 if monkeys do not squeeze above the minimum force threshold when the green dot is

853 displayed, squeeze when the red dot is displayed, or use the wrong grip. After an

854 incorrect squeeze, the same trial restarts. After all squeezes of a sequence are

855 performed correctly, monkeys receive the fluid reward and a new trial starts. In 70%

856 of trials, monkeys have the choice to continue with their current sequence by using

857 the same grip or changing grip and perform an alternative sequence for an alternative

858 reward size.

859 *A) Example of a choice trial (70% of trials).* The trial starts with the presentation of

860 the option, which is defined by a side (here left), an initial sequence length (10

861 squeezes here, bottom cue) and a reward size (medium here, top cue). At each

862 squeeze, the bottom cue indicates the remaining number of squeezes to perform

863 (bottom cue). 5 squeezes before the end of the current, an alternative option is

864 offered. Here, by squeezing the left grip, monkeys choose the current option and

865 must perform the 5 remaining squeeze to obtain the megrim reward (top). By

866 squeezing the right grip, monkeys choose the alternative option and must perform 2

867   squeezes to obtain the small reward (bottom). After all squeezes of a sequence are

868   performed correctly, the gauge indicating the remaining number of squeezes in the

869   sequence appears as empty and monkeys receive the fluid reward. After an inter-trial

870   interval of 1 to 1.5s, another trial starts.

871   B) *Task structure.* Initial sequences start with 6, 8 to 10 squeezes and lead to 3 sizes

872   of reward (small, medium and big).   In 30% of trials, no choice is offered and

873   monkeys must perform the initial sequence to be rewarded. In 70% of trials one

874   choice is offered during one of the squeeze in light grey (at least 3 trials after the

875   beginning of a sequence and 3 trials before the end) on the figure.

876   *Figure 2: Effect of clonidine on decision-making*

877   *A) Average chosen number of squeezes and reward size.* Average number of

878   squeezes chosen to be performed at the choice point in each treatment condition.

879   There was no effect of treatment condition. Size of average reward chosen (1 for

880   small, 2 for medium and 3 for big) in each treatment condition. Same as A. There

881   was no effect of treatment condition. Symbols correspond to each subject (circle:

882   monkey A, square: monkey D, triangle: monkey E). There was no significant bias

883   toward staying or switching across all treatment conditions..

884   *B) Overall bias for alternative or current option.* 50 - Mean across monkeys of the

885   percentage of alternative option chosen for each treatment condition. Same as A.

886   C*) Choices stability. Arbitrary unit.* Mean across monkeys and treatment condition.

887   Same as A. Linear regression taking into account the variability across individuals

888   revealed a significant positive linear effect of treatment condition ($p<0.05$).

889   *Figure 3: Clonidine specifically affects consistency in choice*

890   *Mode-based analysis: parameters' estimate. A) k(sequence length) parameter*

891   *estimates.* Mean across monkeys of the k(sequence length) parameter estimates for

892   each treatment condition in the choice model: Probability to take the alternative

893   option = 1/(1+exp(-(Value(alternative option)–Value(current

894   option)+bias).consistency)) with Value(option) = Reward size – k(sequence

895   length).Sequence Length, where sequence length is the remaining number of

896   squeezes to perform to obtain the reward. Symbols correspond to each subject

897   (circle: monkey A, square: monkey D, triangle: monkey E). There was no effect of

898   treatment condition at the group level. *B) Bias parameter estimates.* Same as A.

899   There was no effect of treatment condition at the group level. *C)* Same as A. Multi-

900   level regression on estimated beta parameters taking into account the variability

901   across subjects revealed a significant effect of treatment condition (p<0.01).

902   *% alternative option chosen.* Mean across monkeys of the percentage of alternative

903   option chosen depending on the value of the current option and the corrected value

904   of the alternative option (V(alternative option)* = V(alternative option) + bias). D*)*

905   *Model under saline.* Plot of the mean percentage of alternative option chosen

906   computed with the choice model (estimates of the beta parameter). E*) Model under*

907   *the higher dose of clonidine.* Same as D. F*) Data under saline.* Plot of the actual

908   choices for the estimated values. G) *Data under the higher dose of clonidine.* Same

909   as F.

910   *Figure 4: Effects of clonidine on reaction times*

911   *A) Reaction times for no choice and choice.* Reaction times in 2 squeeze types (no

912   choice and choice) for each treatment condition. No choice squeezes are matched to

913   choice squeeze for position in the sequence and compared to choices in which

914   subject did not change grip. Reaction time distributions for each grip and each

915   monkey are logged z-scored (mean sets to zero and variance to one). Mean across

916   monkeys, error bars represent standard errors to the mean. Colour code corresponds

917   to treatment condition. Linear regression on log-transformed reaction times revealed

918   a significant positive linear effect of choice ($p<0.001$) and treatment condition

919   ($p<0.01$).

920   *B) Correlation between choice reaction times and consistency parameter estimates.*

921   Reaction times corresponds to the time between the display of the green dot and the

922   crossing of the minimum force threshold for correct squeezes where monkeys had to

923   make a choice and did not change grip. The consistency parameter was computed

924   by fitting the choice model. They were computed for each subject and treatment

925   condition. Same as A. The correlation between these two parameters was significant

926   ($p<0.01$).

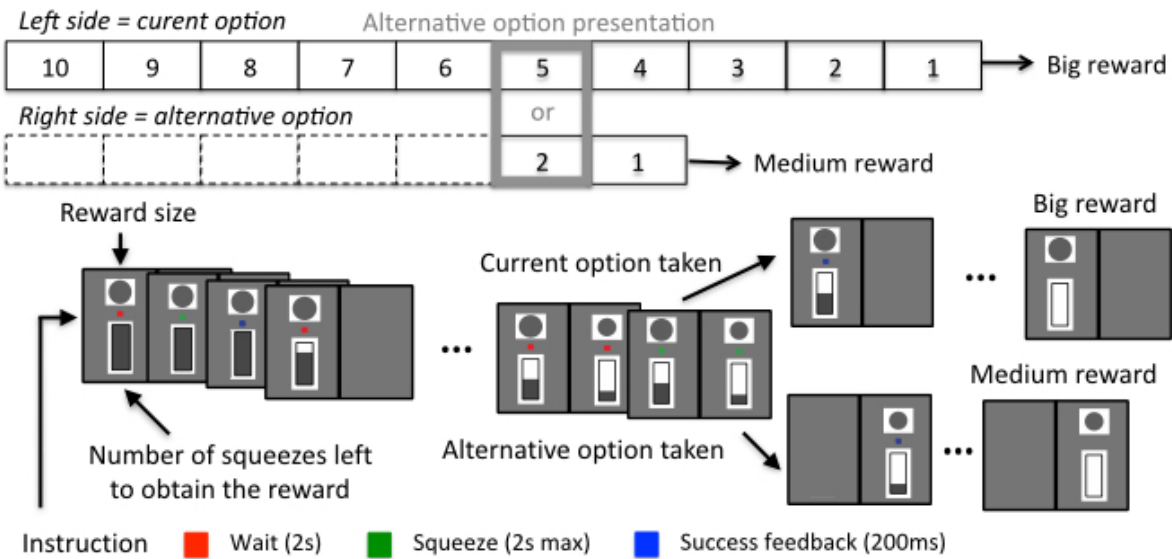927   *Figure 5: Effect of clonidine on motivation*

928   *Willingness to work. A) Willingness to work during the session.* Number of accepted

929   squeezes / total number of squeeze during the session (1 hour) for each treatment

930   condition (in %). Mean across monkeys. Symbols correspond to each subject (circle:

931   monkey A, square: monkey D, triangle: monkey E). There was no significant effect of

932   treatment condition. *B) Willingness to work across the sequence.* Number of correct

933   squeezes / total number of squeezes depending on the number of remaining

934   squeezes to complete the sequence in trials where no choice was offered (in %). For

935   simplicity, only the effect of treatment (colour code: saline vs. clonidine, all doses

936   pooled) and sequence length are shown here. Mean across monkeys, error bars

937   represent standard errors to the mean.

938   *Force production. C) Force peak.* Maximal value of the force signal between two

939   crossings of the minimal force threshold for correct squeezes. Force peak

940   distributions for each grip and each monkey are z-scored (mean sets to zero and

941   variance to one). Mean across monkeys. Same as A. Linear regression showed a

942   negative effect of doses on peak force (p<0.01). *B) Peak force and reaction time.*

943   Peak force is the same as in C. Reaction time corresponds to the time between the

944   display of the green dot and the crossing of the minimum force threshold for correct

945   squeezes for each treatment condition. Reaction time distributions for each grip and

946   each monkey are logged and z-scored (mean sets to zero and variance to one).

947   Symbols correspond to each subject (same as A). Colour code corresponds to
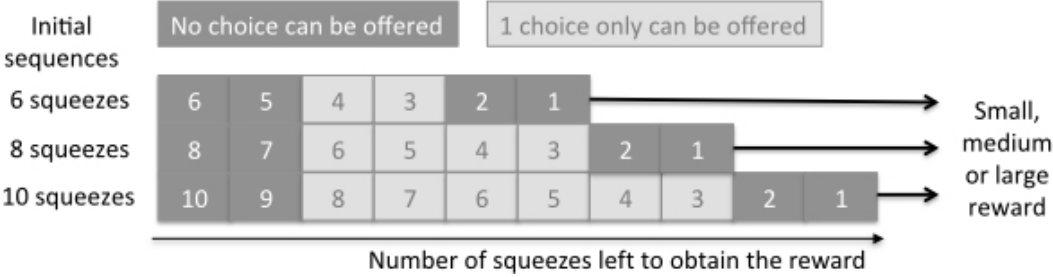
948   treatment condition.

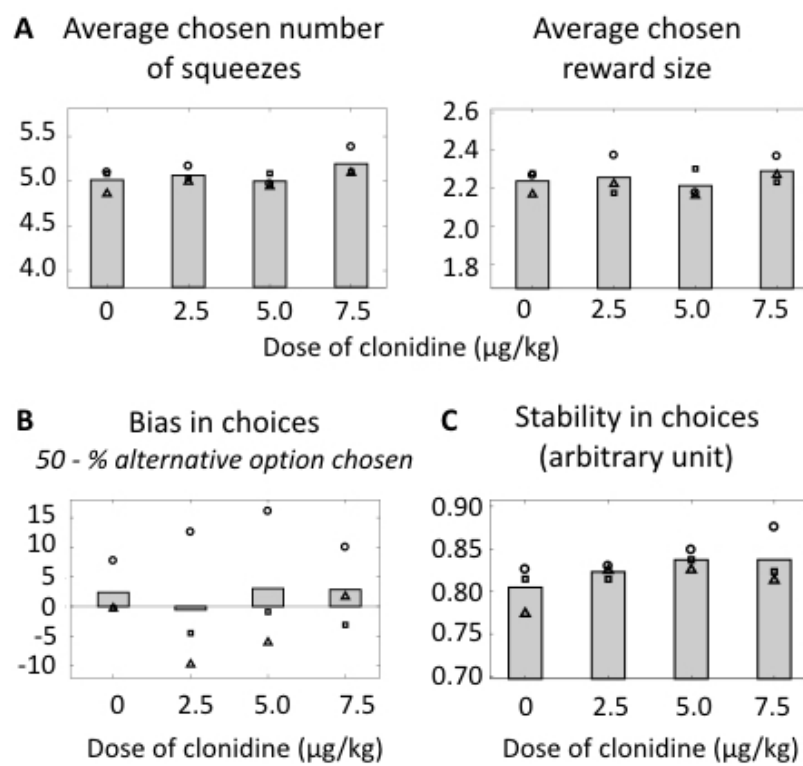47

949 **Figure 1: task**
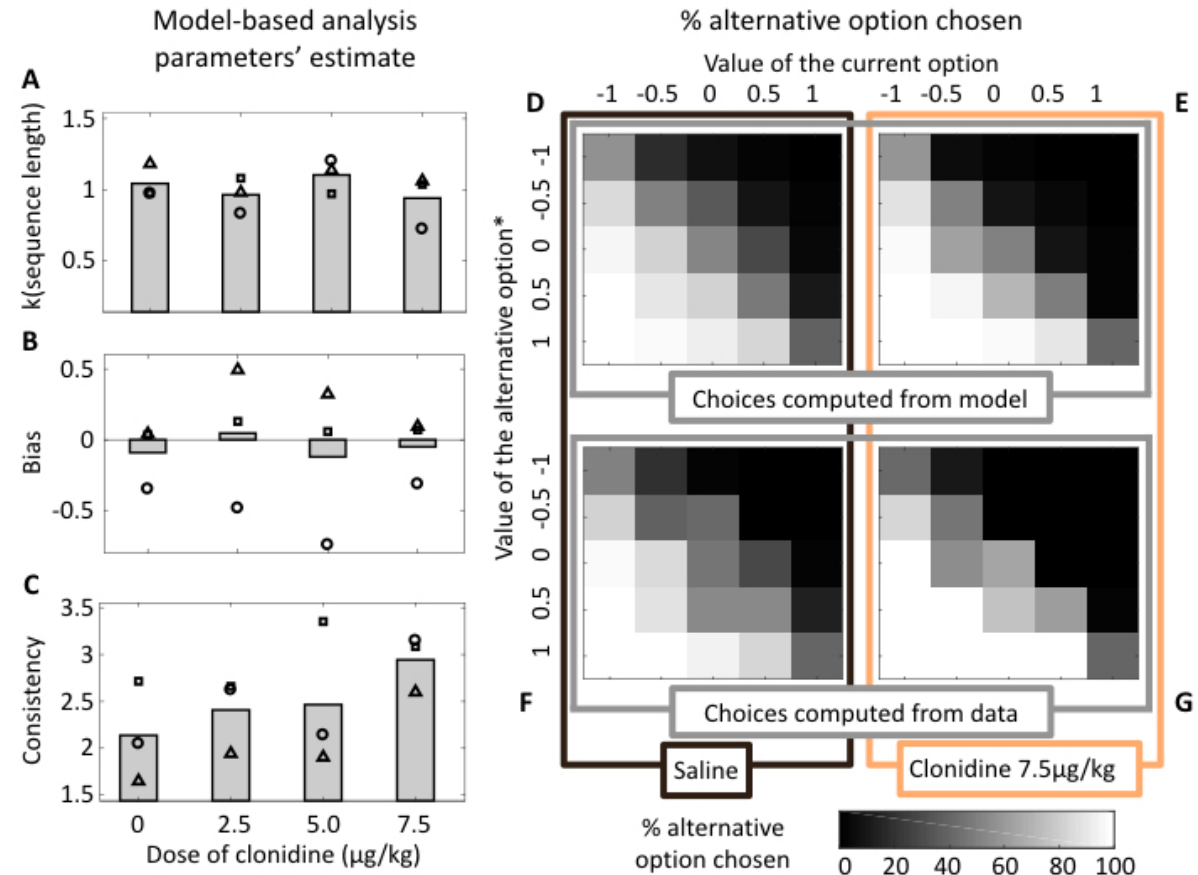
950

A Example choice trial

B Task structure

951 **Figure 2: Effect of clonidine on decision-making**
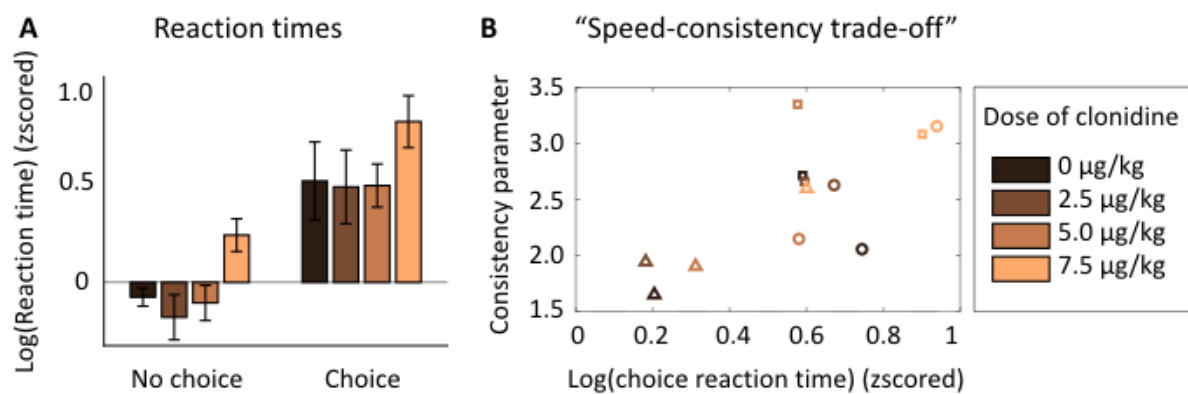
952

953   **Figure 3: Clonidine specifically affects consistency in choice**

954

955 **Figure 4: Effects of clonidine on reaction times**

956

957   **Figure 5: Effect of clonidine on motivation**