

1 **Noradrenergic but not dopaminergic neurons signal task state changes and**
2 **predict re-engagement after a failure**

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16 **Abstract**

17 The two catecholamines, noradrenaline and dopamine, have been shown to play
18 comparable roles in behaviour. Both noradrenergic and dopaminergic neurons
19 respond to salient cues predicting reward availability and to stimulus novelty, and
20 shape action selection strategies. However, their roles in motivation have seldom been
21 directly compared. We therefore examined the activity of noradrenergic neurons in the
22 *locus coeruleus* and putative midbrain dopaminergic neurons in monkeys cued to
23 perform effortful actions for rewards. The activity in both regions correlated with the
24 likelihood of engaging with a presented option. By contrast, only noradrenaline neurons
25 were also (i) predictive of engagement in a subsequent trial following a failure to
26 engage and (ii) sensitive to the task state change, the discovery of the new task
27 condition in unrepeated trials. This indicates that while dopamine is primarily important
28 for the promotion of actions directed towards currently available rewards,
29 noradrenergic neurons play a crucial complementary role in mobilizing resources to
30 promote future engagement.

31 **Introduction**

32 Catecholaminergic neuromodulation is thought to be critical for numerous aspects of
33 behaviour, including motivation, learning, decision-making and behavioural flexibility
34 (Robbins & Roberts 2007; Doya 2008; Sara 2009; Robbins & Arnsten 2009; Sara &
35 Bouret 2012). Both noradrenaline and dopamine neurons respond to novel and salient
36 stimuli and signal predictions of future reward (Schultz 1998; Bouret & Sara 2004;
37 Ravel & Richmond 2006; Berridge 2007; Ventura et al. 2007; Matsumoto & Hikosaka
38 2009; Bromberg-Martin et al. 2010) and both systems have been implicated in
39 motivating action (Robbins & Everitt 2007; Nicola 2010; Bouret et al. 2012; Varazzani
40 et al. 2015; Jahn et al, 2018; Walton & Bouret, 2019). Nonetheless, the specific
41 contributions of dopamine and noradrenaline to these functions remain unclear, in part
42 as their roles have seldom been compared in the same task (but see Bouret et al. 2012
43 and Varazzani et al. 2015).

44 *Locus coeruleus* (LC) noradrenergic-containing neurons have a long-stated role in
45 signalling new information about the state of the world, specifically a change in
46 predictability of the environment (Swick et al, 1994; Vankov et al, 1995; Dalley et al,
47 2001; Aston-Jones & Cohen, 2005; Bouret & Sara, 2005; Yu & Dayan, 2005). LC
48 neurons are particularly sensitive to unexpected and/or novel stimuli (Kety 1972; Foote
49 et al. 1980; Aston-Jones & Bloom 1981; Grant et al, 1988; Sara & Segal, 1991; Vankov
50 et al, 1995; Bouret & Sara, 2004; Bouret et al, 2012), and the transient activation of LC
51 neurons in response to unexpected stimuli is often thought to facilitate adaptation
52 through an increase in behavioural flexibility (Bouret & Sara, 2005; Dayan & Yu, 2006,
53 Einhauser et al, 2008; Nassar et al, 2012, Urai et al. 2017; Muller et al. 2019). In that

54 frame, the magnitude of LC responses to sensory stimuli increases when these stimuli
55 are unexpected, and therefore provide information about the state of the world that
56 may be useful to guide subsequent behaviour. By contrast, perfectly expected stimuli
57 provide little information, and so their presentation should not require the updating of
58 behaviour. In other words, such a function could allow the activation of LC neurons to
59 promote the adaptation of behaviour in response to a change in the state of the world
60 (Aston-Jones & Cohen, 2005; Bouret & Sara, 2005; Yu & Dayan, 2005). Such a role
61 for noradrenaline in behavioural flexibility has received strong support from
62 pharmacological studies (Devauges & Sara, 1990; Tait et al, 2007; McGaughy et al,
63 2008; Jahn et al, 2018; Jepma et al, 2018).

64 More recently, noradrenaline function has been extended to include the promotion of
65 effortful actions (Ventura et al. 2008; Bouret & Richmond 2009; Zénon et al. 2014;
66 Varazzani et al. 2015). Indeed, LC neurons are reliably activated when animals initiate
67 an action (Bouret & Sara, 2004; Rajkowski et al, 2004; Kalwani et al 2014). Critically,
68 the magnitude of this activation seems to be related to the amount of effort necessary
69 to trigger the action (Bouret & Richmond, 2015; Varazzani et al, 2015). In line with this
70 interpretation, we recently used a pharmacological manipulation to demonstrate
71 directly that, on top of its role in behavioural flexibility, noradrenaline was also causally
72 involved in motivation (Jahn et al, 2018). One interpretation of the dual role of
73 noradrenergic LC neurons in behavioural flexibility and motivation is that flexibility
74 relies upon their response to unexpected stimuli whereas their role in motivation relies
75 upon their activation at the triggering of effortful actions. Alternatively, the response of
76 LC neurons to unexpected stimuli could be directly related to motivation.

77 Since the tripartite relationship among LC activity, processing of expected vs
78 unexpected stimuli, and motivation remain unexplored, we re-analysed a data set of
79 noradrenergic neurons in the LC recorded in monkeys presented with cues signalling
80 how much effort they would need to expend to gain rewards of various sizes (Varazzani
81 et al. 2015). The task was designed such that rejecting an offer caused it to be re-
82 presented on the subsequent trial, and the analyses reported by Varazzani et al. (2015)
83 deliberately excluded such repeated trials. Here, by including those trials, we could
84 investigate separately (i) the sensitivity to task state changes in unrepeated vs.
85 repeated trials and (ii) the encoding of motivational processes, by examining the
86 modulation of LC activity by willingness to perform the presented option (engagement)
87 in the current or in the future trials.

88 Moreover, to gain further insight on the specific role of noradrenaline as compared to
89 dopamine neurons, we compared the activity of LC neurons to that of putative DA
90 neurons recorded from *substantia nigra pars compacta* and *ventral tegmental area*
91 (SNc/VTA) in the same paradigm. Indeed, dopamine is also implicated in novelty and
92 information seeking (Horvitz et al. 1997; Schultz 1998; Costa et al. 2014; Bromberg-
93 Martin & Hikosaka, 2009; Naudé et al. 2016), as well as playing a prominent role in
94 motivation and action initiation (Walton & Bouret, 2019). As for LC noradrenergic
95 neurons, we could examine separately the relation between dopaminergic neurons
96 and sensitivity to task state changes and willingness to perform the presented option.

97 We found that that although the magnitude of the neuronal response at the cue
98 predicted the engagement in effortful actions similarly in the two catecholaminergic
99 systems, only noradrenaline neurons were sensitive to changes in task state, i.e. to
100 the difference between repeated (and therefore perfectly expected) and unrepeated

101 (and therefore informative) stimuli. Moreover, while dopamine neurons only reflected
102 the engagement at the cue onset, noradrenaline cells were also activated by erroneous
103 fixation breaks, in a manner that predicted the likelihood of future engagement after
104 erroneous trials. Taken together, our analyses demonstrate complementary but
105 distinct roles for noradrenaline and dopamine in signalling new states of the world and
106 in motivating current or future engagement with effortful actions.

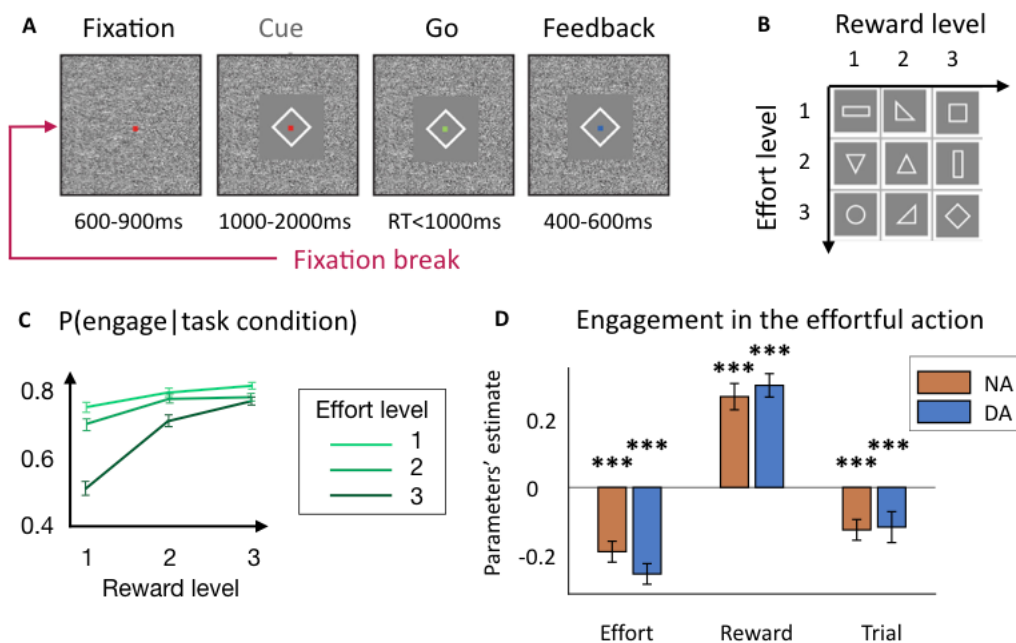
107 **Results**

108 *Behaviour*

109 Three monkeys were trained to perform a task in which visual cues indicated the
110 amount of effort (3 effort levels) that was required to obtain a reward (3 reward levels)
111 (fig 1A and B). Effort and reward levels were manipulated independently across the 9
112 task conditions. On a given trial, monkeys could either engage in the effortful action
113 (whether action is correct or not) or fail to engage by breaking fixation (the proportion
114 of trials where monkeys maintained fixation and omitted the response was negligible).
115 Importantly, unsuccessful trials, which effectively represent a failure, were repeated
116 (see Material and Methods and figure 1 for details).

117 The monkeys' willingness to engage in the task – measured as the attempt to squeeze
118 the clamp after seeing the cue – was clearly affected by the information about the
119 upcoming effort and reward levels (task condition) of the trial (fig 1C-D). In both
120 sessions when noradrenergic (NA) or dopaminergic (DA) neurons were recorded from,
121 the likelihood of engagement in the effortful action was negatively affected by the effort
122 level (NA: $\beta=-0.19\pm0.03$, $t(91)=-6.19$, $p<0.001$; DA: $\beta=-0.26\pm0.03$, $t(83)=-8.43$,
123 $p<0.001$) and positively modulated by the reward level (NA: $\beta=0.27\pm0.04$, $t(91)=6.93$,
124 $p<0.001$; DA: $\beta=0.31\pm0.04$, $t(83)=8.78$, $p<0.001$). Moreover, monkeys' engagement
125 was negatively modulated by the trial number (NA: $\beta=-0.13\pm0.03$, $t(91)=-4.11$,
126 $p<0.001$; DA: $\beta=-0.12\pm0.05$, $t(83)=-2.58$, $p<0.001$) (fig 1D). Note that there was no
127 significant difference between effort level, reward level and trial number weights in
128 engagement across for NA and DA recording sessions ($p=0.13$, $p=0.52$ and $p=0.88$
129 respectively). This was confirmed by a 2-way ANOVA measuring the effect of task

130 factor (effort and reward) and recording type (NA or DA) onto $-\beta(\text{effort})$ and $\beta(\text{reward})$:
 131 main effect of task factor $F(1,348)=3.35$, $p=0.07$) but no main effect of recording
 132 session type ($F(1,348)=2.14$, $p=0.15$) and no interaction ($F(2,348)=0.23$, $p=0.63$),
 133 meaning that engagement was affected in the same way by the two task factors in both
 134 types of recordings.
 135



136

137 *Figure 1: Task and behaviour*

138 *A) Task structure. Monkeys had to squeeze a clamp with a certain minimum intensity to obtain reward*
 139 *of a certain magnitude. During the whole trial, monkeys had to maintain fixation on a dot at the centre*
 140 *of the screen. If they broke the fixation, the trial restarted from the start after an inter-trial interval delay.*
 141 *A trial started with monkeys fixating the red dot, then a cue appeared indicating the effort and reward*
 142 *levels for the current trial. The dot turned green (Go signal) and monkeys had to squeeze the clamp to*
 143 *the minimum force threshold indicated by the cue. Upon reaching this threshold, the dot turned blue*
 144 *(Feedback) and remained blue as long as monkeys had to keep on squeezing. If monkeys maintain the*
 145 *effort long enough, they received the amount of reward indicated by the cue.*
 146 *B) Task design. Each trial corresponded to one of nine experimental conditions, defined by three levels*
 147 *of effort and three levels of reward.*
 148 *C) Probability to engage with the action as a function of effort and reward levels. Computed for all NA*
 149 *and DA sessions together.*

150 *D) Weights of the task parameters in the decision to engage with the effortful action. Multi-level logistic*
151 *regression of the decision to initiate the action by the three experimental task parameters: effort level,*
152 *reward level and trial number. Significant negative effect of effort level ($p<0.001$) and trial number*
153 *($p<0.001$) and significant positive effect of reward level ($p<0.001$) in both NA and DA session (no*
154 *difference between NA and DA sessions for all three parameters ($p<0.05$)). *** $p \leq 0.001$.*

155

156 *Noradrenergic and dopaminergic neurons' activity reflects monkeys' engagement in*
157 *the task*

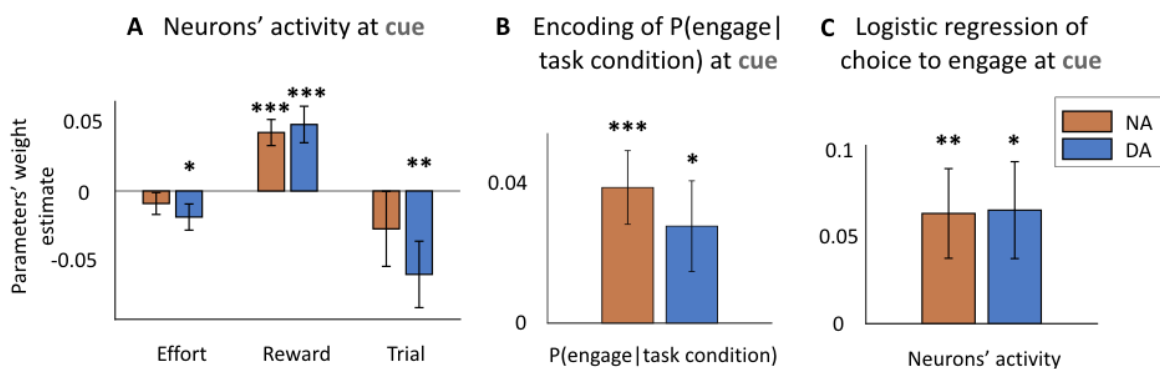
158 We have seen previously that the task factors (i.e. effort level, reward level and trial
159 number) influenced the probability of monkeys to engage with the effortful action.
160 Therefore, we first measured the influence of these task factors on neurons' activity at
161 the time of cue. Dopaminergic neurons' activity was significantly positively modulated
162 by reward level ($\beta=0.05\pm 0.01$, $t(83)=3.67$, $p<0.001$) and negatively modulated by the
163 effort level ($\beta=-0.02\pm 0.001$, $t(83)=-2.01$, $p=0.05$), as well as by trial number ($\beta=-$
164 0.06 ± 0.03 , $t(83)=-2.53$, $p=0.01$) (fig. 2A). Noradrenergic neurons' activity was only
165 significantly modulated by the reward size ($\beta=0.04\pm 0.001$, $t(91)=4.05$, $p<0.001$) but not
166 reliably modulated by either the effort level ($\beta=-0.01\pm 0.01$, $t(91)=-1.15$, $p=0.25$) nor trial
167 number ($\beta=-0.03\pm 0.03$, $t(91)=-1.02$, $p=0.31$) (fig 2A). However, we found no significant
168 difference between the encoding of the effort level and the trial number between
169 dopaminergic and noradrenergic neurons ($p=0.42$ and $p=0.37$ respectively). Critically,
170 there was a significant difference between the weights of effort and reward in the firing
171 rates of both noradrenergic and dopaminergic neurons (2-way ANOVA measuring the
172 effect of task factor (effort and reward) and recording type (NA or DA) onto $-\beta(\text{effort})$
173 and $\beta(\text{reward})$: main effect of task factor $F(1,348)=9.71$, $p=0.02$) but no main effect of
174 recording session type ($F(1,348)=0.61$, $p=0.4$) and no interaction ($F(2,348)=0.04$,

175 $p=0.8$). This means that the relative sensitivity of noradrenergic and dopaminergic
176 neurons to the task factors was similar, with a greater sensitivity for reward than effort
177 (post-hoc T-test on the distribution of $-\beta(\text{effort})$ and $\beta(\text{reward})$: $t(350)=-3.13$, $p=0.002$).

178 After having considered the relation between neuronal activity and task factors, we
179 looked at the relationship between neuronal activity and the engagement in the effortful
180 action. First, we did it across the nine task conditions (defined by a combination of
181 effort and reward levels) by using an aggregate measure of the engagement for each
182 condition (the probability to engage given the task condition). This tested whether
183 neuronal activity directly reflected the probability for the monkeys to engage in a
184 particular task condition. For each recording, we regressed this z-scored probability of
185 engagement on neurons' activity and found a significant positive effect at the
186 population level, for both noradrenergic and dopaminergic neurons (NA: $\beta=0.04\pm 0.01$,
187 $t(91)=3.70$, $p<0.001$, DA: $\beta=0.03\pm 0.01$, $t(83)=2.16$, $p=0.03$) (fig 2B). Again, there was
188 no difference in the strength of this signal encoding between populations ($p=0.50$).
189 Moreover, this activity was specific to the onset of the cue as there was no significant
190 encoding of this probability before the cue onset (pre-cue period) even in repeated
191 trials, in which monkeys already knew which cue was coming (500ms window before
192 cue onset: NA: $p=0.17$, DA: $p=0.71$). We also examined the relation between neuronal
193 activity and engagement on a trial by trial basis. We found that both noradrenergic and
194 dopaminergic responses were predictive of engagement on a trial by trial basis (NA:
195 $\beta=0.06\pm 0.03$, $t(91)=2.47$, $p=0.01$; DA: $\beta=0.06\pm 0.03$, $t(83)=2.36$, $p=0.02$) (fig 2C). Here
196 again, there was no difference in the strength of this signal encoding between
197 dopaminergic and noradrenergic neurons ($p=0.96$). Moreover, the activity was specific

198 to the onset of the cue, with no encoding of engagement in the pre-cue period (NA:
 199 $p=0.08$, DA: $p=0.88$).

200 Overall, we found that even if, contrary to behaviour, the activity of the noradrenergic
 201 and dopaminergic systems is biased toward the encoding of reward compared to effort
 202 the firing of these neurons reflected the engagement in the effortful action in a similar
 203 fashion at the time of the cue.



204
 205 *Figure 2: noradrenergic and dopaminergic neurons encoding of the task parameters and engagement*
 206 *at the time of cue*

207 *A) Encoding of task parameters at the time of cue (0-500ms from cue onset). Dopaminergic neurons*
 208 *were sensitive to all three task parameters (effort level: $p=0.05$; reward level: $p<0.001$; trial number:*
 209 *$p=0.01$). Noradrenergic neurons were only significantly sensitive to the reward level ($p<0.001$). No*
 210 *significant difference between the encoding of effort level and trial number in noradrenergic and*
 211 *dopaminergic neurons ($p>0.05$). * $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.*

212 *B) Noradrenergic and dopaminergic neurons reflect the engagement in a task condition. Linear*
 213 *regression of the probability to engage in a given task condition (effort and reward levels) for each*
 214 *session. Both populations encode significantly the probability to engage ($p<0.05$), no difference between*
 215 *the strength of encoding across populations ($p>0.05$). * $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.*

216 *C) Noradrenergic and dopaminergic neurons' activity reflects the engagement on a trial-by-trial basis*
 217 *throughout the session. Logistic regression of Noradrenergic and dopaminergic neurons' activity on*
 218 *engagement in the action. Both populations predict the engagement in the action ($p<0.05$). * $p < 0.05$;*
 219 *** $p \leq 0.01$; *** $p \leq 0.001$.*

220

221 *Both noradrenergic and dopaminergic neurons encode monkeys' engagement, but*
222 *only noradrenergic neurons are sensitive to changes in task state*

223 In order to understand if catecholaminergic neurons also encode changes in task
224 states (i.e. when their responses to cues differed between repeated and non-repeated
225 trials) and to determine the relationship between this factor and motivation
226 (engagement), we compared the encoding of these two variables at the time of cue.
227 To examine the effect of changes in task states, we compared cue-evoked activity in
228 repeated ('non-informative cue') versus non-repeated ('informative cue') trials. Since
229 erroneous trials were repeated, and monkeys knew the structure of the task, they could
230 predict following an error that the same condition (with the same visual cue) would be
231 presented again, such that the visual cue provided no information about the task state.
232 By contrast, after a correct trial, any of the nine task conditions could be pseudo-
233 randomly presented to the monkey, such that visual cues now provided information
234 about the upcoming reward and effort levels (task state). Erroneous trials were mainly
235 of two types: (i) monkeys broke the fixation (no engagement) and (ii) monkeys engaged
236 (tried to squeeze the clamp) but did not execute the action correctly. Therefore, as not
237 all trials in which monkeys engaged were successful, we were able to look conjointly
238 at the effect of engagement and the information being presented on neuronal activity.

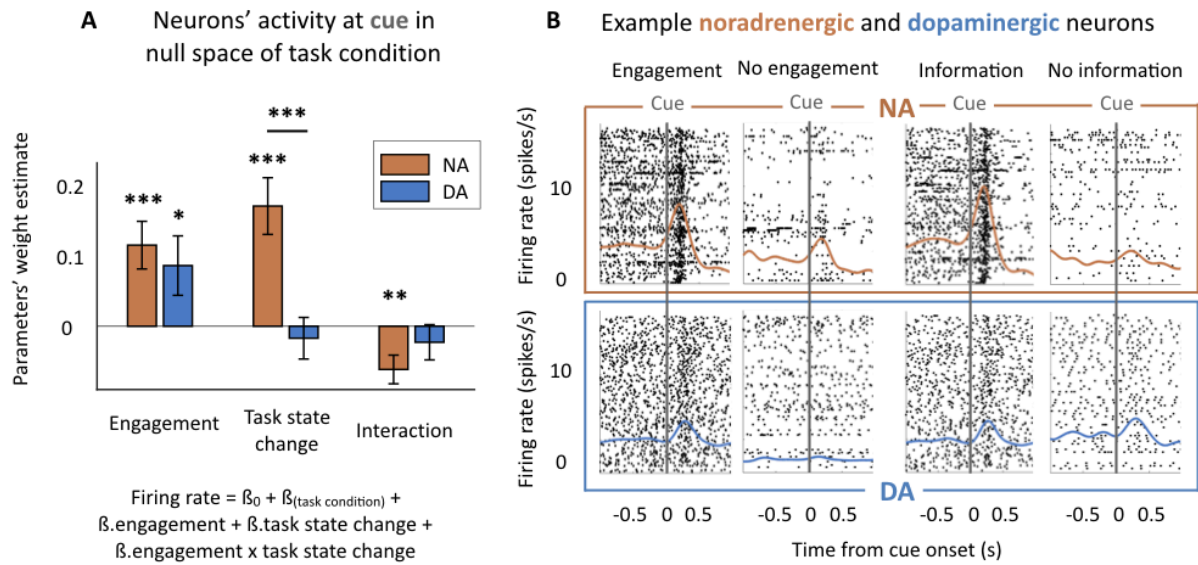
239 First, we found no interaction between the linear encoding of the effort, reward levels
240 and trial number with whether the trial was repeated or not in either noradrenergic
241 neurons or dopaminergic neurons (see Materials and Methods, NA: $p=0.24$, $p=0.26$
242 and $p=0.58$ respectively; DA: $p=0.26$, $p=0.27$ and $p=0.10$ respectively). This means

243 that the task condition was encoded in a similar fashion whether the cue was
244 informative or not.

245 To examine the effect of engagement and task state change above and beyond the
246 effect of a particular task condition (effort and reward levels), we regressed out the
247 effect of the task condition on the firing rate of neurons and looked at the effect of
248 engagement and task state change (unrepeated vs. repeated trials) on the remaining
249 neuronal activity (see Material and Methods). Here, we found an important dissociation
250 between the activity of noradrenergic and dopaminergic neurons (fig 3). For a given
251 trial condition, noradrenergic neurons were more active either when the action was
252 initiated (vs not) *or* when the cue provided information about the new task condition (in
253 unrepeated vs repeated trials) in a given experimental condition
254 ($\beta(\text{engagement})=0.11\pm 0.03$, $t(91)=3.40$, $p<0.001$; $\beta(\text{task state change})=0.16\pm 0.04$,
255 $t(91)=4.23$, $p<0.001$). We also found a significant negative interaction ($\beta(\text{interaction})=-$
256 0.06 ± 0.02 , $t(91)=-3.02$, $p=0.003$), which indicates that engagement and information
257 effects were not perfectly additive: when both factors were combined, the firing rate
258 increased less than by the sum of the two separate effects. On the other hand, while
259 dopaminergic neurons were on average more active when monkeys engaged in a
260 given condition ($\beta=0.08\pm 0.04$, $t(83)=2.05$, $p=0.04$), they were *not* sensitive to the task
261 state change ($p=0.56$). There was also no significant interaction between the two
262 effects ($p=0.36$), and the main effects were similar when we removed the interaction.
263 A direct comparison of these effects between noradrenergic and dopaminergic
264 neurons confirmed that, while there was no difference in the strength of their encoding
265 of engagement in the task ($p=0.59$) noradrenergic neurons encoded significantly more
266 task state change than dopaminergic neurons ($p<0.001$).

267 Here again, this effect was specific of the onset of the cue as when we examined the
268 500ms pre-cue period, there was neither an effect of engagement (NA: $p=0.17$, DA:
269 $p=0.77$) nor an effect of task state change (NA: $p=0.96$, DA: $p=0.07$). There was also
270 no effect of engagement in the pre-cue period if we only examined repeated trials
271 where monkeys already knew the task condition (NA: $p=0.31$, DA: $p=0.47$). In short,
272 when comparing the encoding of engagement and task state change (unrepeated vs.
273 repeated trials) variables over and above the task variables, both noradrenergic and
274 dopaminergic neurons encoded the engagement in the task, but only noradrenergic
275 neurons encoded the task state change (whether the cue was informative or not). In
276 addition, these effects were unaffected by the addition of trial number to the analyses,
277 which captures the influence of fatigue and satiety (main effects of engagement and
278 task state change remained as described before; main effect of trial number: NA:
279 $p=0.47$, DA: $p=0.02$; interaction of engagement and task state change with trial number
280 did not reach significance in either noradrenergic or dopaminergic neurons, NA:
281 $p(\text{engagement})=0.84$, $p(\text{task state change})=0.97$, DA: $p(\text{engagement})=0.91$, $p(\text{task}$
282 $\text{state change})=0.19$) (see supplemental figure 1A). Thus, engagement and task state
283 change had specific effects on neurons' firing rates, which in turn were independent of
284 the progression in the session.

285



286

287 *Figure 3: Change in task condition is encoded by noradrenergic but not dopaminergic neurons*

288 *A) Encoding of engagement and trial repetition in null space of task condition at cue (0-500ms from cue*
 289 *onset). Noradrenergic neurons encoded significantly the change in trial condition, the engagement and*
 290 *the interaction (all $p < 0.01$). Dopaminergic neurons encoded only significantly the engagement ($p < 0.05$).*
 291 ** $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$*

292 *B) Example noradrenergic and dopaminergic neurons. Neuronal activity of two representative neurons*
 293 *around the cue onset (grey vertical line). Top: spike activity (raster and spike density function) of a*
 294 *noradrenergic neuron showing a strong activation at cue. The activation is stronger in engaged vs. non-*
 295 *engaged trials (all experimental conditions pooled together) and for informative vs. non-informative*
 296 *cues. Bottom: same but for a dopaminergic neuron showing an intermediate activation at cue onset. Its*
 297 *activity was greater for engaged than non-engaged trials but was not modulated by the task state change*
 298 *of the cue. Note, even though the baseline firing appears different in these example neurons, there was*
 299 *no reliable effect of engagement before cue onset. Each panel corresponds to a different number of*
 300 *trials (each trial is a line in the raster plot).*

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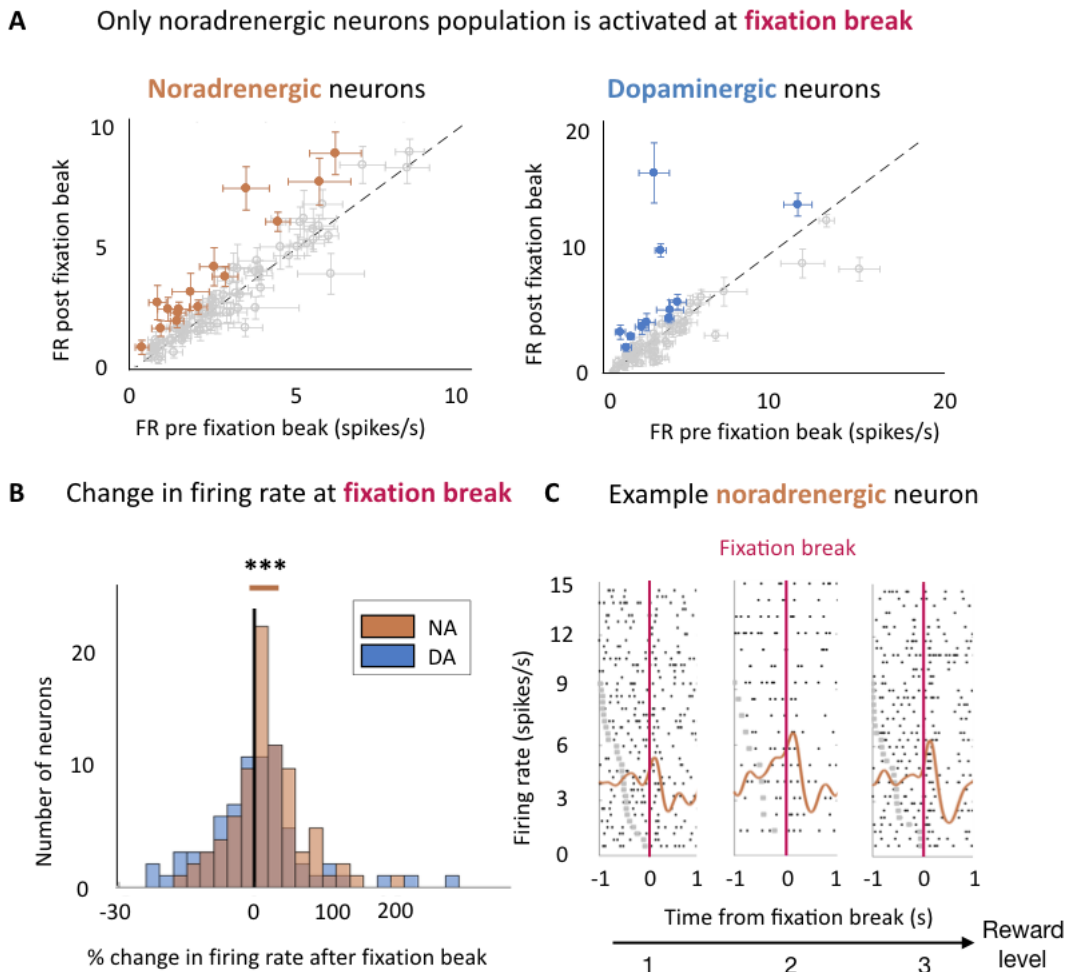
302 *Only noradrenergic neurons were activated after a failure to engage and are sensitive*
 303 *to the task condition*

304 We next examined the activity of dopaminergic and noradrenergic neurons time-locked
 305 to fixation break, which resulted in trial abortion. We focused our analysis on three
 306 epochs: a baseline epoch from -600 to -300ms prior to fixation; a pre-fixation break

307 epoch corresponding to the 300ms prior to fixation break, and post fixation break epoch
308 corresponding to the 300ms following fixation break. There was neither a significant
309 activation of dopaminergic neurons before fixation break ($p=0.62$) nor after the fixation
310 break ($p=0.49$). By contrast, noradrenergic neurons were significantly activated after
311 (mean difference= 0.30 ± 0.09 spikes/s, $t(83)=3.31$, $p=0.001$), but not before ($p=0.81$)
312 the fixation break had occurred. This activation corresponds to an average change of
313 $16.5\%\pm 0.04$ of activity between before (average firing rate = 2.83 spikes/s) and after
314 (average firing rate = 3.12 spikes/s) the fixation break (fig 4A). At the single neuron
315 level, 18.1% noradrenergic neurons were activated at the fixation break (one-tailed T-
316 test: firing rate(pre fixation break) < firing rate(post fixation break), $p<0.05$ were
317 considered as significant). Note that all results hold true if we removed fixation break
318 events that occurred less than 500ms after the cue onset.

319 We then looked at the modulation of fixation-break related activity across task
320 conditions. The firing of dopaminergic neurons did not show any significant modulation
321 across task conditions (probability to engage with the task condition: $p=0.97$) or
322 behavioural responses (engagement in the next trial: $p=0.45$) and it will not be
323 described further. By contrast, noradrenergic neurons' evoked activity was positively
324 modulated by the reward size ($\beta=0.06\pm 0.02$, $t(83)=3.64$, $p<0.001$) but neither by the
325 effort level nor by the trial number ($\beta(\text{effort level})=-0.01\pm 0.02$, $t(83)=-0.91$, $p=0.37$;
326 $\beta(\text{trial number})=-0.04\pm 0.03$, $t(83)=-1.31$, $p=0.20$) (fig 4B). Note however, that the
327 difference between the sensitivity to effort and reward did not reach significance (t-test
328 on $-\beta(\text{effort})$ and $\beta(\text{reward})$: $t(166)=1.88$, $p=0.06$). This activity was specific to the
329 onset of the fixation break as there was no modulation of the activity by these task

330 factors in the 300ms before the fixation break (effort level: $p=0.50$; reward level:
 331 $p=0.15$; trial number: $p=0.9$).



332

333

334 *Figure 4: Noradrenergic but not dopaminergic neurons were activated after the fixation break*

335 *A) Only noradrenergic neurons population is activated at fixation break. Firing rate pre (-300 – 0ms) and*
 336 *post (0 – 300s) fixation break for both noradrenergic (left) and dopaminergic neurons (right). Points and*
 337 *error bars are mean \pm SEM. Solid points indicate a significant activation (One-tailed T-test, $p<0.05$). For*
 338 *illustration purposes only, we have removed two dopaminergic neurons (with a non-significant activation*
 339 *at fixation break), whose firing rates were above 20 spikes/s from the display.*

340 *B) Noradrenergic and Dopaminergic neurons' change in firing rate evoked by activity after fixation break*
 341 *(0-300ms from fixation break). The distributions are represented on a log-scale. Noradrenergic neurons*
 342 *population was significantly activated after the fixation break ($p=0.001$) but not dopaminergic neurons*
 343 *population ($p=0.49$). *** $p \leq 0.001$.*

344 *C) Example noradrenergic neurons at fixation break for each reward level. Neuronal activity*
 345 *representative of noradrenergic neuron around fixation break (pink vertical line). Trials are sorted by*
 346 *decreasing latency between cue onset (grey dots) and fixation break. Cue onset is only visible for bottom*

347 *trials, with latencies shorter than the displayed 1 sec. Spike activity (raster and spike density function)*
348 *of a noradrenergic neuron showing an increase after the fixation break. In addition, its activity is*
349 *modulated by the reward level ($p < 0.001$).*

350

351 *Noradrenergic neurons activity predicted the engagement on the next trial*

352 Finally, we examined the relationship between fixation-break evoked activity and the
353 probability, across sessions, that the monkeys engaged on the next trial. Here again,
354 we only looked at fixation break events that occurred after cue onset, meaning that the
355 monkeys always knew the task condition at the time of the fixation break.

356 We found a significant positive effect of the probability to engage given the task
357 condition on LC activity at the time of the fixation break ($\beta = 0.05 \pm 0.02$, $t(83) = 2.79$,
358 $p = 0.007$). In other words, the more monkeys tended to engage in a specific task
359 condition, the more noradrenergic neurons would be active if a fixation break occurred
360 in this task condition. This effect was also present in the pre-fixation break activity (-
361 300-0ms to fixation break) ($\beta = 0.15 \pm 0.06$, $t(83) = 2.55$, $p = 0.01$), suggesting that it
362 appeared after cue onset, in line with the fact that noradrenergic neurons also
363 displayed a positive relation with task engagement at the time of the cue onset (fig 2B).
364 Indeed, we found a significant positive correlation ($r = 0.33$, $p = 0.002$) between the
365 strength of the encoding of the probability to engage at the time of cue and at the time
366 of the post-fixation break (fig 5B). In short, noradrenergic neurons were activated both
367 at cue onset and at the fixation break when it occurred. They tended to be more active
368 in conditions associated with a greater probability of engagement, both at the cue onset
369 and at the time of fixation break, and these two responses were correlated across the
370 population of LC neurons.

371 Given this strong relation between LC activity and probability of engagement in the
372 current trial when monkeys erroneously break fixation, we were interested to examine
373 whether this activity could also predict monkeys' likelihood of engagement in the
374 following trial. After a fixation break, two things could happen on the next trial (and
375 therefore in the same task condition): monkeys could now choose to engage with the
376 same task condition or could again reject the offer (fig 5A). We therefore examined if
377 LC activity at the time of fixation break could provide information about engagement in
378 the next trial, over and above task condition.

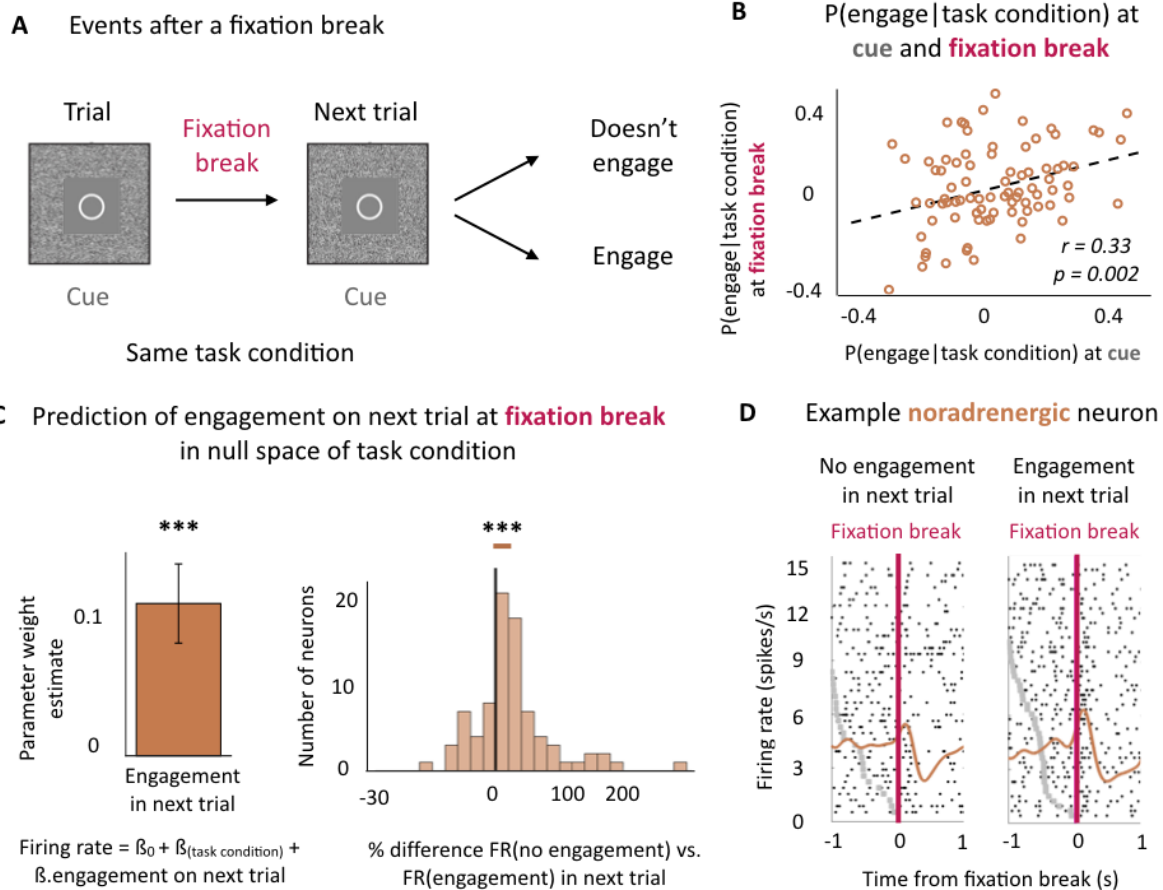
379 In fact, the magnitude of the fixation-break activation of noradrenergic neurons
380 (controlled for task condition) was predictive of subsequent engagement in the next
381 trial ($\beta=0.12\pm0.003$, $t(83)=3.84$, $p<0.001$; effect calculated on the z-scored distributions
382 of firing rates and translating to an average difference of $25.1\%\pm0.1$ of activity between
383 non-engage and engage on the next trial conditions) (fig 5C). At the single neuron
384 level, only 6.5% of neurons showed a significant effect (compared to 7.6% of neurons
385 showing a significant sensitivity to reward at fixation break and 20.6% at cue). Hence,
386 although the effects seen at the fixation break are relatively weak at the single neuron
387 level, they are very consistent across the population, such that at the population level
388 the effect clearly reaches significance. In fact 66.3% of neurons showed small but
389 consistently greater activation in trials in which monkeys engage on the next trial, which
390 is comparable to the proportion of neuron displaying a positive relation with reward at
391 the fixation break (63%) or at the cue (66.3%). We controlled for potential interactions
392 with confounding factors such as task state change (whether the erroneous trial was
393 itself a repeated or not), trial number and their interactions with the effect of the
394 engagement in the next trial, but none of them were significant (main effects:

395 $p(\text{information})=0.18$, $p(\text{trial number})=0.15$; interactions with engagement with next trial:
396 $p(\text{information})=0.27$, $p(\text{trial number})=0.81$). As previously mentioned, this activity was
397 specific of noradrenergic neurons as dopaminergic neurons were not activated post-
398 fixation break and did not signal the engagement in the next trial ($p=0.45$) (see
399 supplemental figure 1B).

400 Finally, we looked whether the effect of the engagement in the next trial could be found
401 before the cue of the next trials. In other words, we looked if we could predict the
402 engagement before the cue (-500 – 0ms) for trials where a fixation break occurred. We
403 found that it was not the case ($p=0.25$) and could therefore only conclude that
404 noradrenergic neurons predict the engagement on a trial-by-trial basis.

405 In summary, we found that noradrenergic but not dopaminergic neurons' activity at
406 fixation break reflected the probability to engage both in the current and in the
407 subsequent trial, over and above cost-benefit task conditions.

408



409

410

411 *Figure 5: Noradrenergic neurons' activity predicts the engagement on the next trial*

412 *A) Task structure after a fixation break.*

413 *B) Correlation between noradrenergic neurons' encoding of the probability to engage for each task*
 414 *condition at the cue onset and the fixation break across sessions. Significant correlation ($r=0.33$,*
 415 *$p<0.01$).*

416 *C) Noradrenergic neurons' activity at fixation break is predictive of engagement in the next trial above*
 417 *and beyond the task condition. Linear regression, significant effect ($p<0.001$). % difference between the*
 418 *firing rate distribution for no engagement in next trial and engagement in next trial in the null space of*
 419 *task conditions (mixed effect linear regressions on non-z-scored distributions). The distribution is*
 420 *represented on a log-scale. Significant difference ($p<0.001$). *** $p \leq 0.001$.*

421 *D) Example noradrenergic neurons at fixation break for no engagement (left) and engagement (right) in*
 422 *the next trial. Neuronal activity (raster and spike density function) is displayed around fixation break ($t=0$,*
 423 *pink vertical line). Trials are sorted by decreasing latency between cue onset (grey dots) and fixation*
 424 *break. Cue onset is only visible for bottom trials, with latencies shorter than the displayed 1 sec. As a*
 425 *majority of LC neurons, this one shows a stronger activation when monkeys engaged on the next trial*
 426 *($p<0.001$).*

427 **Discussion**

428 In this task, monkeys were presented with informative (non-repeated) and non-
429 informative (repeated) cues instructing them to produce actions of different intensities
430 to gain rewards of different magnitudes. The probability that monkeys would try to
431 produce the action (engagement) depended on the task condition (effort and reward
432 levels) but failing to engage would only lead to the repetition of the same task condition.
433 Repeated trials constituted series of actions towards the same goal: the reward. This
434 goal directed behaviour ended when the goal was reached. From that perspective,
435 there is a clear transition in behaviour after a correct trial, as animals get started on
436 another trial, another goal directed behaviour (Bouret & Richmond 2009). Hence, given
437 the structure of the task, unrepeated trials are more likely to constitute a task state
438 changes than repeated ones from a goal-directed behaviour perspective. We used this
439 task structure to reveal the precise roles of noradrenergic and dopaminergic neurons
440 in encoding motivation to engage in the task and in signalling task state changes. We
441 used the engagement in a task condition on a specific trial as a measure of motivation
442 and found that both noradrenergic and dopaminergic neurons' activities were
443 predictive of the engagement. Their activities were not only correlated with the session-
444 average probability to engage in a particular task condition, but also with the trial-by-
445 trial engagement. Furthermore, their activities were correlated with engagement over
446 and above the specific task condition. This strengthens the role of both
447 catecholaminergic systems in motivating effortful, reward directed actions.

448 However, the activity of noradrenergic and dopaminergic neurons differed significantly
449 when it came to signalling task state changes. First, only noradrenergic neurons'

450 activity was sensitive to whether or not the visual cue was providing information about
451 the new task state (which was the case only in non-repeated trials), over and above its
452 relation with upcoming reward and effort levels. Moreover, noradrenergic, but not
453 dopaminergic, neurons displayed activity after a fixation break, which ended the trial
454 and represented a failure to engage. This activity scaled with the probability of
455 engagement given the task condition and it was positively correlated with the
456 engagement in the next trial. Hence, noradrenaline, contrary to dopamine, plays a role
457 both in signalling information about task state and in promoting current and future
458 effortful actions given this information.

459 *Similarities and dissimilarities of the role of the catecholaminergic systems in*
460 *motivation*

461 This study builds on experiments presented in Varazzani et al (2015), but here includes
462 both repeated and non-repeated, and correct and incorrect trials, rather than just the
463 non-repeated correct trials reported in Varazzani et al (2015). This allowed us to
464 examine the influence of information about task state changes and motivation to
465 engage, and not just the cost-benefit parameters of the presented cues, on neural
466 activity. The inclusion of these additional trials did lead to slight differences in the
467 strength of encoding of task parameters to those reported previously. However,
468 importantly the overall pattern of effects was comparable, and any differences were
469 negligible compared to the difference in terms of sensitivity in noradrenaline and
470 dopamine neurons to changes in task state.

471 Both noradrenergic and dopaminergic neurons' activity was related to the engagement
472 in the effortful actions. Dopaminergic neurons' activity was tightly linked with the

473 engagement in the rewarded course of action independently of whether the trial was
474 repeated or not. Dopaminergic neurons were also activated at the time of producing
475 the action, but contrary to noradrenergic neurons, they did not correlate with the actual
476 force produced (Varazzani et al. 2015). The causal role of dopamine in incentive
477 processes has been shown in different species, with an emphasis on its role in
478 controlling reward sensitivity (Denk et al. 2005; Hoskins et al. 2014; Le Bouc et al.
479 2016; Yohn et al. 2016; Zénon et al. 2016; Noritake et al, 2018). Moreover, our results
480 are in line with studies demonstrating that dopamine release is strongly driven by the
481 initiation of a purposeful action for reward (Phillips et al. 2003; Roitman et al., 2004;
482 Syed et al. 2016).

483 Noradrenergic neurons' activity was also linked to the engagement in the effortful
484 course of action as well as to the actual production of the action (Varazzani et al.,
485 2015). This is in line with previous demonstrations that LC neurons respond to stimuli
486 predicting future rewards and action initiation responses (Bouret & Sara, 2004; Bouret
487 & Richmond 2009, 2015; Kalwani et al. 2014). Contrary to dopamine, causal
488 manipulation of the noradrenergic system does not seem to affect incentive processes
489 (Hoskins et al. 2014; Jahn et al. 2018). Indeed, our recent study showed that the
490 noradrenergic system controls the amount of force produced during the action, but not
491 the selection nor the initiation of the action (Jahn et al. 2018). Hence, the noradrenergic
492 system might be critical to ensure that the effortful action is appropriately performed
493 once a decision to engage has been taken (Bouret & Richmond 2015; Varazzani et al.
494 2015), whereas dopamine is instead key for signalling the subjective future reward to
495 be gained by performing an action and promoting that response (Ishiwari et al., 2004;

496 Gan et al. 2010; Pasquereau & Turner 2013; Varazzani et al. 2015; Papageorgiou et
497 al., 2016; Salamone et al. 2016).

498 *Why are dopaminergic neurons not sensitive to the information about task state*
499 *change in our task?*

500 Dopamine neurons have long been reported to respond to salient novel stimuli
501 (Strecker & Jacobs 1985; Ljunberg et al. 1992; Horvitz et al. 1997; Menegas et al.
502 2017) and to be implicated in novelty seeking (Costa et al. 2014). Therefore, it may
503 initially seem surprising that in our task, dopaminergic neurons were not sensitive to
504 the novelty of the presented task condition information. However, there are a number
505 of important differences between these experiments and the current one. For instance,
506 in previous experiments examining novelty seeking, it is unclear whether dopaminergic
507 neurons are encoding new information based on the change in uncertainty about the
508 world, independent of choice, or as a variable driving the behaviour. While Bromberg-
509 Martin and Hikosaka showed that dopaminergic neurons were sensitive to the
510 advanced information about the size of the reward, importantly in their study, monkeys
511 showed a preference for obtaining this information, implying that it was therefore
512 relevant for guiding the behaviour (Bromberg-Martin & Hikosaka 2009; Charpentier et
513 al. 2018). In another experiment, Naudé and colleagues showed that mice preferred a
514 probabilistic outcome to a deterministic outcome, and that this preference was
515 controlled by the dopaminergic system (Naudé et al. 2016). These two studies show
516 that dopaminergic neurons are sensitive to information as a variable that can influence
517 choices through preferences, since it acted as a reward (Charpentier et al. 2018). In
518 our task, as the cost-benefit cues were all well known, information (as provided by the

519 cues in non-repeated, but not in repeated trials) would neither cause sensory surprise
520 (as cues themselves were not novel) nor be relevant for modulating future choices.
521 Therefore, although we cannot rule out that some individual dopamine neurons do
522 code for this factor, it seems that dopamine neurons as a population do not encode
523 the information about task state changes when this is not relevant to guide the
524 behaviour.

525 *Noradrenergic neurons' activity reflects the role of noradrenaline in information*
526 *processing and engagement after a failure*

527 The crucial difference between dopaminergic and noradrenergic neurons was that
528 noradrenergic neurons were sensitive to the repetition of a trial at cue. Because task
529 state changes only occur after a successful trial, lower activation of LC neurons at cue
530 on repeated trials could reflect the fact that an error just occurred. However, we found
531 no significant effect of error on the previous trial in baseline activity before the cue.
532 Therefore, it is unlikely that there is a carry-over effect of error on the next trial. This
533 lower activation in repeated trials could also be simply due to the repetition of a visual
534 cue. However, there was no significant difference in the sensitivity to the task factors
535 (effort and reward levels) in repeated and non-repeated trials. Hence, there is no
536 evidence in our data for a simple stimulus repetition suppression effect. Moreover, from
537 a goal directed behavior perspective, there is much more likely to be a state transition
538 after a sequence ended with a reward, which would argue against a simple cue
539 repetition response. Therefore, we attributed this lower activation to the fact that the
540 monkeys already knew the task condition in repeated trials. Noradrenergic neurons
541 would be sensitive to the information about task state changes, which corresponds to

542 the discovery of a new state of the world either at the time of cue (i.e., which task
543 condition has been selected for the current trial) but also at fixation break (an error
544 means that the trial is terminated and that the same task condition is coming next). This
545 is in line with the long-stated, if underspecified, role of noradrenaline in signalling
546 important events in the environment (Kety 1972; Foote et al. 1980; Aston-Jones &
547 Bloom 1981; Abercrombie & Jacobs 1987; Berridge & Waterhouse 2003; Vazey et al.
548 2018). Noradrenaline has been implicated in signalling a need to provoke or facilitate
549 a cognitive shift to adapt to the environment (Bouret & Sara 2005; Yu & Dayan 2005;
550 Glennon et al. 2019). Here, noradrenergic neurons' sensitivity to change in task state
551 at the time of cue could reflect a need to process the information about the current task
552 condition.

553 Crucially, only noradrenergic neurons were activated following a break in fixation,
554 which represents a failure to engage in the effortful action. Similar patterns of activity
555 at the break of fixation have also been observed in mid-cingulate cortex (MCC), here
556 modulated by how close to reward delivery the error occurred or how much effort was
557 already invested in the task (Amiez et al. 2005). Given the connections between LC
558 and MCC, this suggests that MCC and LC might well interact when required to signal
559 salient events. A break of fixation was an important event not only as it signalled the
560 end of the trial, but also the re-occurrence of same task condition in the next one. This
561 post-fixation break activity was tightly linked to firing rates at the time of cue, which in
562 turn reflected the probability of engagement in the effortful action. A potential scenario
563 is that if the activity at the cue was too small to enable maintenance of the fixation and
564 the engagement in the trial, then activity at the fixation break reflects a prospective
565 update to enable performance of the action on the subsequent trial. Indeed, we found

566 that when we controlled for task condition, noradrenaline neurons were more active
567 after fixation break when monkeys then engaged in the subsequent trial. Finally, as we
568 were never able to predict the engagement in the trial from the baseline activity at the
569 cue, even for repeated trials and even for trials following a fixation break, we only
570 conclude that noradrenergic neurons predict the engagement on a trial-by-trial basis
571 but have no evidence that they do so through a slow fluctuation of activity that lasts
572 beyond the range of a trial.

573 Together, these results are compatible with the idea that noradrenergic neurons signal
574 and potentially facilitate the need to engage resources to undertake and complete
575 effortful actions (Bouret et al. 2012; Walton & Bouret 2019). In both cases, they do it
576 as a function of new information about the state of the world: about the start of a new
577 and unpredictable experimental condition that will bring a reward at the cue, and about
578 the failure to complete a trial that might have been worth it, since they re-engage
579 immediately at fixation break.

580 To conclude, our data show the specific and complementary roles of dopamine and
581 noradrenaline in motivation and behavioural flexibility. The former would promote
582 actions directed towards currently available rewards, while the latter could play a
583 critical role in facing challenging situations by mobilizing resources based on new
584 information about the environment.

585 **Materials and Methods**

586 *Monkeys*

587 Three male rhesus monkeys (Monkey D, 11 kg, 5 years old; Monkey E, 7.5 kg, 4 years
588 old; Monkey A, 10 kg, 4 years old) were used as subjects for the experiments. During
589 testing days (Monday to Friday), they received all their water as reward on testing days
590 and they received water according to their physiological needs on non-testing days. All
591 experimental procedures were designed in association with the Institut du Cerveau et
592 de la Moelle Epiniere (ICM) veterinarians, approved by the Regional Ethical Committee
593 for Animal Experiment (CREEA IDF no. 3) and performed in compliance with the
594 European Community Council Directives (86/609/EEC).

595 *Task*

596 The behavioural paradigm has previously been described in detail in Varazzani et al.
597 (2015). In brief, each monkey sat in a primate chair positioned in front of a monitor on
598 which visual stimuli were displayed. A pneumatic grip (M2E Unimecanique, Paris,
599 France) was mounted on the chair at the level of the monkey's hands. Water rewards
600 were delivered from a tube positioned between the monkey's lips. Behavioural
601 paradigm was controlled using the REX system (NIH, MD, USA) and Presentation
602 software (Neurobehavioral systems, Inc, CA, USA).

603 The task consisted of squeezing the grip to a minimum imposed force threshold to
604 obtain rewards, delivered at the end of each successful squeeze (fig 1A and B). At the
605 beginning of each trial, subject had to fixate a red dot at the centre of the screen before
606 a cue appeared. The cue indicated the minimum amount of force to produce to obtain

607 the reward (3 force levels) and the amount of reward at stake (3 reward levels: 1, 2
608 and 4 drops of water). After a variable delay (1500±500ms from cue display), the dot
609 at the centre of the cue turned green (Go signal) and subject had 1000ms to initiate
610 the action, meaning squeezing the clamp very little (threshold set to detect any attempt
611 to perform the action). If the monkey reached the minimum force threshold indicated
612 by the cue, the dot turned blue and remained blue if the effort was sustained for
613 500±100ms. At the end of this period, if at least the minimum required effort had been
614 maintained, the water reward was delivered.

615 Fixation of the central dot had to be maintained through the different phases of the
616 task. A trial was incorrect if: (i) the monkey broke fixation before the reward delivery,
617 (ii) he squeezed the clamp before the go signal, (iii) he failed to squeeze the clamp at
618 all or (iv) at the minimum force threshold or (v) didn't maintain the effort long enough.
619 After an error the same trial was repeated until it was successfully completed. Within
620 a session, the nine combinations of effort and reward conditions were selected with
621 equal probability and presented in a random order. As erroneous trials were repeated,
622 the policy with the highest reward rate was to always engage until satiety.

623 Monkeys were trained for several months on this task. They first learned to distinguish
624 and perform two different force levels and the difficulty of the task was progressively
625 increased until they were could do so with the nine experimental conditions. Finally,
626 they learned that they had to fixate the central dot to go through a trial.

627 *Electrophysiological recordings*

628 Single unit recording using vertically movable single electrodes was carried out using
629 conventional techniques. The electrophysiological signals were acquired, amplified

630 (x10,000), digitized, and band-pass filtered (100 Hz to 2 kHz) using the OmniPlex
631 system (Plexon). Precise description of the recording procedures can be found in the
632 article where LC and SNc/VTA data used here were originally reported (Varazzani et
633 al. 2015). Noradrenergic neurons recordings were performed on monkey A (29
634 neurons in 15 sessions) and monkey D (63 neurons in 38 sessions), midbrain
635 dopaminergic neurons recordings were performed on monkey D (56 neurons in 38
636 sessions, sometimes simultaneously as noradrenergic neurons recordings) and
637 monkey E (28 neurons in 19 sessions).

638 *Data analysis*

639 Data were analysed with Matlab software (MathWorks). Figures represent data \pm
640 standard deviation to the mean.

641 In all our analyses we only considered trials (correct and incorrect) in which monkeys
642 did not break the fixation before the onset of the cue (NA: 324 trials on average for
643 monkey A and 281 for monkey D, DA: 314 trials on average for monkey D and 274 for
644 monkey E). We took all those trials and computed the probability that for a given effort
645 and reward level (or a given task condition), subjects would engage with the trial. We
646 considered that monkeys engaged if they maintained fixation throughout the trial and
647 initiated the action even if it occurred before the Go signal, (5% of trials in both
648 noradrenergic (NA) and dopaminergic (DA) neurons recording sessions), not strongly
649 (0% and 0.1% of trials in NA and DA sessions respectively) or long enough (8% and
650 10% of trials in NA and DA sessions respectively). Although it was possible to fail to
651 engage with a trial by maintaining fixation but not squeezing the clamp, this type of
652 mistake was rare (2% and 1% of trials in NA and DA sessions respectively) and

653 monkeys mostly rejected a trial by breaking fixation (20% of all trials in both NA and
654 DA sessions). Erroneous trials were therefore mainly of two types: i) monkeys broke
655 the fixation and failed to engage with the trial (*no engagement* and *no new information*
656 as the same trial type is presented again: 20% of all trials in both NA and DA sessions)
657 and ii) monkeys engaged (tried to squeeze the clamp) but did not complete the correct
658 action (*engagement* but *no new information*: 17% and 20% of engaged trials, which
659 corresponds to 13% and 15% of all trials in NA and DA sessions respectively).

660 We examined the effects of effort, reward and trial number on the engagement in the
661 action using a multi-level logistic regression for each session. The three variables were
662 z-scored so that we could compare their weights across sessions. We then went on to
663 examine task conditions influenced neuronal activity. To assess the effect of task
664 conditions on neurons' activity at the time of cue onset, we used a window from 0 to
665 500ms from cue onset. When we looked at these effects in the pre-cue period, we
666 used a window from -500 to 0ms from cue onset. Neurons' activity was measured in
667 firing rates (spikes per second) and were z-scored for each session to compare
668 the activity across neurons. First, the effects of the task factors: effort, reward and trial
669 number in a session on neurons' activity were estimated using a multi-level linear
670 regression for each neuron. Second, we assessed the relationship between neurons'
671 firing rates and engagement in a given trial by running a logistic regression of neurons'
672 firing rates on engagement. Finally, we looked at the linear encoding of the z-scored
673 probability to engage given the task condition on neurons' firing rates using a linear
674 regression.

675 When we looked at the effect of the novelty of the trial state (here referred to as "task
676 state change") on neuronal activity, we first looked at whether the fact that a cue was

677 informative ($I=1$) or not ($I=0$) changed the sensitivity of neurons for the task factor (E,
678 R, N) at the time cue by regressing the task factors and the interaction between the
679 task factors and the informativity ($I=0$ or 1) onto the trial-by-trial neurons' activity. A
680 significant interaction would mean that an informative cue (signalling the new task
681 state) would increase or decrease the sensitivity for the task factor. We then wanted to
682 assess the conjoint effect of engagement and task state change on neurons' firing
683 rates above and beyond the effect of effort and reward levels. To do so, we ran a multi-
684 level linear regression taking into account the task condition variability. In other words,
685 we removed from neurons' firing rates the effect of the task condition using a mixed
686 model:

$$687 \quad \text{Neurons' firing rates} = \beta_0 + \beta_0(\text{task condition}) + \sum_i \beta_i \cdot x_i$$

688 where β_0 a constant, $\beta_0(\text{task condition})$ a constant fitted for each combination of effort
689 and reward level (9 possibilities), x_i the experimental factors and β_i their weights in the
690 linear regression (e.g. engagement, task state change, interaction). When looking at
691 the effect of engagement and task state change at cue, we tested the following
692 experimental factors: engagement, task state change and interaction between effect.
693 We then added to the regression the following confounds: trial number, interaction
694 between trial number and engagement and interaction between trial number and task
695 state change. All results hold when adding the confounds.

696 We then moved on to assess whether noradrenergic and dopaminergic neurons were
697 activated before the fixation break. We only considered fixation breaks that occurred
698 after the display of the cue. We compared firing rates from 600ms before the fixation
699 break to 300ms after (in 300ms windows). For all analyses at fixation break, we only

700 included sessions during which there were more than 20 fixation break events after
701 the onset of the cue (91 % of NA sessions and 89 % of DA sessions). Delays between
702 the onset of the cues and fixation break events followed a Poisson-like distribution of
703 median 845ms for NA session and 713ms for DA sessions (statistically different, t-test
704 on the mean of the log-transformed distributions: $p < 0.001$). To ensure that the activity
705 at the fixation break was not contaminated by the cue response, we also looked only
706 at fixation break events that occurred at least 500ms after the cue onset (83 % of NA
707 sessions and 75 % of DA sessions). However, all main results were similar both with
708 and without exclusion of the early fixation break events. To assess whether neurons
709 were activated at the fixation break, we compared the difference in firing rate before
710 and after the fixation break and the % of change in firing rate (by dividing by the firing
711 rate before the fixation break). We ran a similar analysis to assess whether neurons
712 were activated before the fixation break. When looking at the modulation of the evoked
713 activity a fixation break, we used the same methodological approach as for the analysis
714 of activity at cue onset. When looking at the effect of engagement in the next trial at
715 fixation break cue, we tested the following experimental factors: engagement in the
716 next trial. We then added to the regression the following confounds: task state change
717 (in the current trial), trial number, interaction between the effect of engagement in the
718 next trial and task state change and interaction between the effect of engagement in
719 the next trial and trial number. All results hold when adding the confounds. To assess
720 the size of the effect of engagement in the next trial, we ran the linear regression of
721 the effect of engaging in the next trial while taking into account the task condition on
722 the non-z-scored firing rate of neurons at fixation break and divided the regression
723 coefficient (difference between engage and non-engage conditions) by the fixed

724 intercept (mean firing rate across both conditions).

725 Second-level analyses were performed by comparing the distributions of regression
726 coefficients against zero or other distributions (paired t-test and unpaired t-test
727 respectively or ANOVA). Statistical reports include means of the distribution \pm standard
728 deviation to the mean, t-values or F-values and p-values.

729 **Conflict of interest**

730 The authors declare no competing financial interest.

731

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733

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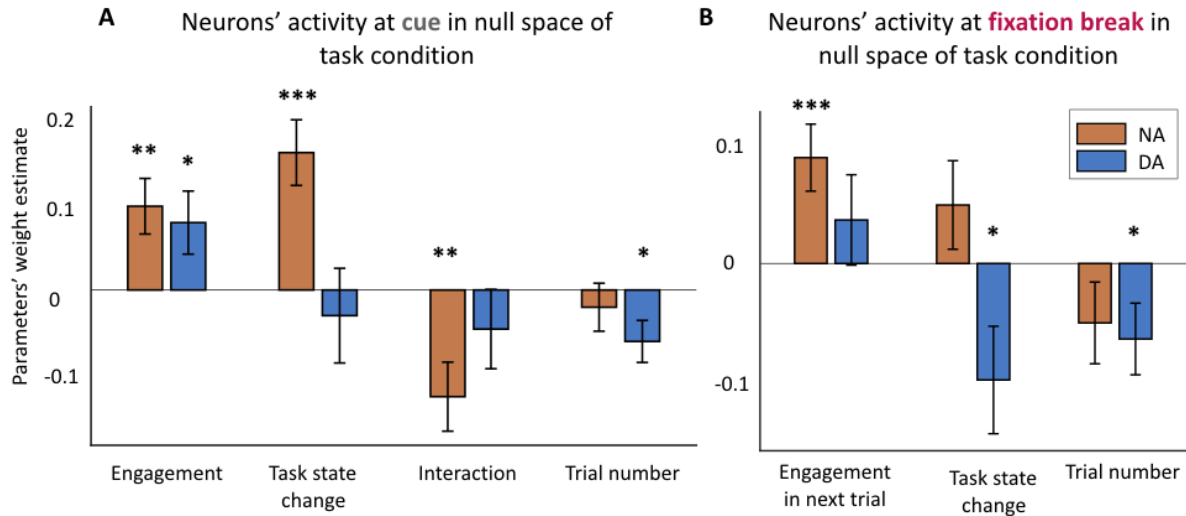
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962

963 **Supplemental figure**



964

965 *Supplemental figure 1: Confounds do not affect the effects described at cue and fixation break*

966 *A) Encoding of engagement, task state change and trial number in null space of task condition at cue*
967 *(0-500ms from cue onset). Noradrenergic neurons encoded significantly the task state change, the*
968 *engagement and the interaction (all $p < 0.01$). Dopaminergic neurons encoded only significantly the*
969 *engagement ($p < 0.05$) and the trial number ($p < 0.05$). Interactions between trial number and engagement*
970 *and trial number and task state change were non-significant for both populations (all $p > 0.19$). * $p < 0.05$;*
971 *** $p \leq 0.01$; *** $p \leq 0.001$*

972 *B) Encoding of engagement in the next trial in null space of task condition at fixation break (0-300ms*
973 *from fixation break). Noradrenergic neurons encoded significantly the engagement in the next trial*
974 *($p < 0.001$) even when we added the confounds: task state change and trial number (both $p < 0.15$).*
975 *Dopaminergic neurons were not significantly activated at the fixation break. However, their activity was*
976 *negatively modulated by the task state change ($p = 0.04$) and the trial number ($p = 0.04$). Interactions*
977 *between trial number and engagement in next trial and task state change and engagement in next trial*
978 *were non-significant for both populations (all $p > 0.23$). * $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$*