

1 **Periaqueductal gray passes over disappointment and signals continuity of remaining**
2 **reward expectancy**

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14 **Keywords**

15 Lateral habenula, Periaqueductal gray, Reward expectation, Disappointment, Resilience,

16 Social bonding

17 **Abstract**

18 Disappointment is a vital factor in the learning and adjustment of strategies in reward-seeking
19 behaviors. It helps them conserve energy in environments where rewards are scarce, while
20 also increasing their chances of maximizing rewards by prompting them to escape to
21 environments where richer rewards are anticipated (e.g., migration). However, another key
22 factor in obtaining the reward is the ability to monitor the remaining possibilities of obtaining
23 the outcome and to tolerate the disappointment in order to continue with subsequent actions.
24 The periaqueductal gray (PAG) has been reported as one of the key brain regions in regulating
25 negative emotions and escape behaviors in animals. The present study suggests that the PAG
26 could also play a critical role in inhibiting escape behaviors and facilitating ongoing motivated
27 behaviors to overcome disappointing events. We found that PAG activity is tonically
28 suppressed by reward expectancy as animals engage in a task to acquire a reward outcome.
29 This tonic suppression of PAG activity was sustained during a series of sequential task
30 procedures as long as the expectancy of reward outcomes persisted. Notably, the tonic
31 suppression of PAG activity showed a significant correlation with the persistence of animals'
32 reward-seeking behavior while overcoming intermittent disappointing events. This finding
33 highlights that the balance between distinct tonic signaling in the PAG, which signals
34 remaining reward expectancy, and phasic signaling in the LHb, which signals disappointment,
35 could play a crucial role in determining whether animals continue or discontinue reward-
36 seeking behaviors when they encounter an unexpected negative event. This mechanism
37 would be essential for animals to efficiently navigate complex environments with various
38 reward volatilities and ultimately contributes to maximizing their reward acquisition.

39 Introduction

40 During reward-seeking behaviors, humans and animals occasionally encounter
41 disappointing events that diminish their engagement and even prompt them to leave the
42 environment. Disappointment could be a crucial factor, for example, in environments where
43 resources become scarce, helping animals adjust their behavioral patterns to minimize
44 unnecessary energy expenditure (e.g., by hibernating) or migrate to environments with richer
45 resources.¹⁻⁶ However, in real life, we often need to pass through a series of unexpected
46 events, some of which may be disappointing or irrelevant to immediate gratification, to
47 achieve our desired outcomes ultimately.⁷ Thus, we hypothesized that there would be
48 another important neuronal mechanism that signals the remaining reward expectancy,
49 helping us overcome disappointing events and continue motivated behaviors until we reach
50 our desired goals.⁸⁻¹⁰ Then, how does the animal brain signal disappointment and the
51 remaining reward expectancy when encountering a disappointing event?

52 To solve this question, we examined the lateral habenula (LHb) and periaqueductal
53 gray (PAG), key brain regions involved in the regulation of negative mood in animals.¹¹⁻¹³ The
54 LHb is a well-known primary input to dopamine neurons, especially signaling
55 disappointment¹⁴ and aversiveness¹⁵ from stimuli. Thus, dysfunction of the LHb has been
56 extensively studied as a promising therapeutic target for treating major depressive
57 disorder.¹⁶⁻¹⁹ In the present study, we raised a question regarding a feature of the LHb
58 response, which primarily involves phasic firing lasting 100-500 ms.²⁰ This rapid signaling is
59 crucial for animals to quickly learn and identify significant objects in a complex environment,
60 where various valued objects are presented sequentially, and to promptly guide their actions
61 step-by-step accordingly.²¹⁻²⁴ However, if an animal's reward-seeking behavior, which
62 involves a series of sequential actions, is solely regulated by the phasic signaling of the LHb,
63 the animal would easily abandon or leave the ongoing motivated behavior every time it
64 encounters a disappointing event.

65 Therefore, we investigated another key brain region involved in the regulation of
66 negative moods, the PAG.²⁵⁻²⁷ Notably, PAG activity has primarily been reported to play a
67 pivotal role in controlling coping strategies in response to aversive stimuli, such as defensive
68 and escape behaviors.²⁸ As a result, the PAG has been suggested to be a critical brain area
69 that can provide therapeutic interventions not only for mental disorders²⁹⁻³¹ but also for
70 movement disorders related to the control of involuntary behaviors.³²⁻³⁷ This has been further
71 supported by previous studies showing that PAG manipulation affects pain, analgesia,³⁸
72 uncontrollable freezing behaviors,³⁹ and involuntary vocalizations.⁴⁰ Moreover, the PAG has
73 crucial efferents that project to the motor control system, such as the raphe interpositus,
74 which regulates gaze fixation in primates.⁴¹ Hence, we could expect that the PAG would not
75 only trigger escape behaviors but also play a critical role in controlling escape and sustaining
76 reward-seeking behaviors when an animal encounters a disappointing event.

77 In summary, we investigated how the LHb and PAG neurons signal disappointment
78 and the remaining reward expectancy to understand how an animal decides whether to
79 overcome or leave a disappointing event. As a result, we found a significant correlation
80 between PAG activity and the continuity of reward-seeking behavior in animals, which could
81 help them overcome disappointing events and ultimately obtain their desired rewards.

82 **Results**

83 To record the neuronal and behavioral responses of rhesus macaque monkeys while passing
84 through a series of disappointing events before ultimately obtaining a reward outcome, we
85 devised a scene-based foraging/Pavlovian task. In this task, two different foraging and
86 Pavlovian tasks were conducted on a shared background scene image (Fig. 1A). As a result,
87 the monkeys were able to predict different reward outcomes for each group of scene images
88 based on the average reward outcomes experienced in the foraging and Pavlovian tasks.
89 Therefore, the monkeys experienced multiple changes in reward predictions throughout the
90 task, depending on the appearance of each group of scene images and tasks.

91 **Reward expectation facilitates visual attention to contexts**

92 We firstly found that reward experiences facilitate the visual attention of primates.
93 Each trial of the task started with the appearance of a scene image (Fig. 1A, scene onset),
94 which allowed the monkey's free-viewing for 1 s and then remained as a background scene
95 until the end of the trial, during which either the Pavlovian or foraging task was performed.
96 The monkeys experienced large amount of juice rewards in both foraging and Pavlovian tasks
97 in the high-valued scenes (Fig. 2A and C), while they received small amount of juice rewards
98 in the foraging task and airpuff punishments in the Pavlovian task in the low-valued scenes
99 (Fig. 2B and D). As a result, at the start of a trial, monkeys could predict greater reward
100 outcomes from the appearance of the high-valued scenes compared to low-valued scenes
101 (Fig. 1B).

102 As the monkeys experienced larger rewards, their free viewing became more focused
103 on high-valued scenes (Fig. 1F, outside). For the background scene images, we used face and
104 landscape images, as they are representative examples of social and spatial contexts that
105 animals encounter during reward-seeking behaviors in real life.⁴² When we used face images
106 as the background scene images, they showed more pronounced gazes toward the eye
107 regions in the high-valued face scene images than in the low-valued scene images,
108 accompanied by stronger scene viewing of the high-valued face images (Fig. 1E and F, inside).

109 Through an additional experiment where the influence of reward and punishment on
110 scene gaze was examined respectively, we confirmed that the effect of value on monkeys'
111 gaze for scene images was particularly regulated by the predicted values of reward rather
112 than airpuff punishment in this task design (Supplementary Fig. S1). The monkeys' gaze
113 toward the scene images was more focused on those with expected high-value rewards, even
114 if they included an airpuff punishment, and it decreased for images with expected low-value
115 rewards, even if there was no airpuff punishment.

116

117 **Continuity of reward expectancy facilitates subsequent actions even after disappointment**

118 We then found that the reward expectancy from the scene images continuously
119 facilitated subsequent actions of animals in the next step. As described above, each trial
120 began with the appearance of a scene image and the monkeys' free viewing for 1 s (Fig. 1A).
121 In the meantime, although the monkeys' gaze was more focused on the high-valued scenes
122 than on the low-valued scenes, we found that their gaze toward the scene images commonly
123 increased during the 50-150 ms period for both scenes, reaching over 90% and being

124 sustained until the next stimuli appeared (Fig. 1F, outside). At the onset of the low-valued
125 scenes, the monkeys sometimes closed their eyes or shifted their gaze away from the scene
126 image during the free viewing period. However, they soon returned their gaze to the scene
127 and prepared to perform the subsequent task. This indicates that the monkeys had a strong
128 motivational engagement for the subsequent task procedures in both scene groups. Notably,
129 these highly motivated states in both scenes consistently facilitated subsequent behaviors.

130 After a free-viewing of the scene for 1 s, a fixation point (FP) appeared at the center
131 of the screen, and either the foraging task or the Pavlovian task was initiated (Fig. 2). The
132 foraging task and Pavlovian task were distinguished by different shapes of the FP (Fig. 2A-B,
133 foraging task, square; Fig. 2C-D, Pavlovian task, circle). Once the FP appeared at the center of
134 the scenes, the monkeys quickly fixated their gaze on the FP within 20 ms, whether it
135 indicated the foraging task or the Pavlovian task (Fig. 3D and H). In both foraging and
136 Pavlovian tasks, the start time at which monkeys' gaze reached the FP was significantly
137 quicker in high-valued scenes than in low-valued scenes. In addition to the speed of the
138 fixation start time, the monkeys exhibited higher fixation rates in high-valued scenes
139 compared to low-valued scenes (Fig. 3C and G). However, even in low-valued scenes,
140 monkeys initiated fixation on the FP within 20 ms (Fig. 3D and H, blue), and the fixation rates
141 were over 95% (Fig. 3C and G, blue). This implies that the monkeys were in a strong
142 motivational state in both high-valued and low-valued scenes. Indeed, even before the FP
143 onset, about 90% of the monkeys' gaze had already stayed on the location where the FP
144 would appear (Fig. 3 A-B and E-F).

145 This result implies that as long as reward expectancy is sustained, animals can
146 maintain a strong motivational state even after disappointment. How, then, do the neural
147 mechanisms in the brain operate to sustain such a strong motivational state in animals, even
148 after the disappointment?

149

150 **PAG neurons signal reward expectancy using tonic activity**

151 We found that the neuronal activity of the PAG was tonically modulated by the
152 expectancy of reward outcomes. Along with the monkeys' gaze behaviors, we recorded
153 neuronal activities in the LHb and PAG (Fig. 2). When a scene image appeared at the beginning
154 of a task trial, neuronal activity in both brain regions was inhibited by high-valued scenes and
155 excited by low-valued scenes (Fig. 1C and D). However, their responses exhibited distinct
156 characteristics, with the PAG primarily showing tonic firing, while the LHb responded with
157 phasic firing. We notably found that the reward expectancy induced by the scene onset had
158 a significant and continuous effect not only on the continuity of the monkeys' subsequent
159 scene-viewing behaviors (Fig. 1F, outside) but also on the tonic activity of PAG neurons, which
160 persisted from scene onset to FP onset (Fig. 1D).

161 The phasic LHb response was advantageous for rapidly encoding value information
162 from the scene images, with a short latency of around 150 ms (Fig. 1C). The neuronal activity
163 of LHb was suppressed by high-valued scenes and excited by low-valued scenes. The
164 difference between these two scenes persisted for about 450 ms, after which their firing rates
165 quickly recovered to baseline levels of neuronal activity, similar to those before the onset of
166 the scene. This enabled the LHb to cease its response to the scene images before the next

167 stimuli appeared and to prepare for subsequent responses in the following steps (Fig. 4J and
168 5J, before 0 ms).

169 In contrast, the tonic activities of PAG slowly encoded the value information provided
170 by the scene onset, starting around 300 ms (Fig. 1D). The neuronal activity of the PAG was
171 also inhibited in response to high-valued scenes and slightly excited in response to low-valued
172 scenes. However, after the value responses, the PAG activity did not quickly recover to
173 baseline levels as the LHb responses did. Meanwhile, the PAG responses exhibited a more
174 pronounced tendency to steadily sustain the tonic suppression in both high- and low-valued
175 scenes until the next visual information was presented (Fig. 4N and 5N, before 0 ms). This
176 result implies that PAG activity could tonically regulate the persistence of the task-engaged
177 state in animals from a reward-informative stimulus to a subsequent reward-informative
178 stimulus.

179

180 **Tonic PAG activity passes over disappointment and signals the continuity of reward** 181 **expectancy until the goal is ultimately obtained**

182 We found that the PAG response is specifically tuned to signal the continuity of reward
183 expectancy, even when disappointment occurs during the sequential procedures of reward-
184 seeking behaviors. As described above, the PAG neurons exhibited tonic suppression despite
185 the disappointment induced by the low-valued scene (Fig. 1D). Especially through the foraging
186 task, we observed additional evidence showing that PAG activity was able to maintain tonic
187 suppression despite further disappointments occurring, until the reward was ultimately
188 obtained (Fig. 2A-B; Fig. 4M-P).

189 The foraging task was designed to observe behavioral and neural responses when
190 temporary disappointment occurs during sequential task procedures, but the possibility of
191 obtaining a reward outcome is 100% guaranteed. The foraging task began with the
192 appearance of the square-shaped FP on the scene images. Once the monkeys completed gaze
193 fixation on the FP, the FP disappeared, and good or bad objects appeared randomly on the
194 left or right side (Fig. 2A-B, Object onset). The appearance of the good object allowed the
195 monkeys to receive a reward immediately upon completing gaze fixation on it
196 (Supplementary Movie S1). In contrast, the bad object required avoiding gaze toward it
197 (Supplementary Movie S2). The monkeys could avoid the bad object by either not making a
198 saccade toward it for 1 s or making a saccade but breaking the fixation within 500 ms. After
199 the monkeys successfully avoided gazing at the bad object, the FP reappeared. Subsequently,
200 the monkeys were finally able to find the good object and received a reward by fixating on it.
201 The monkeys performed these instrumental behaviors with a success rate of over 95%. Even
202 if they failed, the same trial was repeated until they succeeded, ultimately receiving a reward
203 outcome with a 100% probability.

204 On the one hand, we found that the phasic response of the LHb was proficient in
205 encoding the value difference between good and bad objects (Fig. 4K-L). The appearance of
206 the bad object was another disappointing event for the monkeys, as it incurred additional
207 temporal and effort costs compared to the good object. As a result, LHb activity was inhibited
208 by the presence of good objects and excited by the presence of bad objects.

209 On the other hand, we found that the tonic activity of the PAG maintained its tonic
210 suppression state throughout the sequential procedures of the foraging task, even when good
211 or bad objects appeared, ultimately leading to a 100% probability of obtaining a reward
212 outcome (Fig. 4O-P). We observed that the tonic suppression of the PAG, which began with
213 the initial scene onset (Fig. 4M), was sustained until the FP onset (Fig. 4N) and continued even
214 after either the good or bad objects appeared (Fig. 4O-P). Although PAG activities were
215 slightly excited by the appearance of either good or bad objects, their activities quickly
216 declined and returned to a level lower than baseline (Fig. 4O-P, before 0 ms). As a result, the
217 firing rates of the PAG neurons remained lower than baseline levels when FP reappeared
218 following the avoidance of the bad object.

219

220 **Distinct Lhb and PAG responses signal disappointment and continuity of remaining reward** 221 **expectancy**

222 On the contrary, we also confirmed that PAG activity becomes tonically excited when
223 the reward expectancy is completely extinguished during an ongoing motivated behavior, and
224 remains in a tonically excited state until the end of the trial. This was evident in the Pavlovian
225 task, which dramatically altered the remaining reward expectancy, sustaining it in high-valued
226 scenes and completely extinguishing it in low-valued scenes.

227 In the high-valued scenes, the Pavlovian task resulted in different probabilities of
228 obtaining rewards (100%, 50%, 0%) depending on the object presented (Fig. 2C;
229 Supplementary Movie 3). Ultimately, the appearance of the FP-indicating the Pavlovian task
230 in the high-valued scenes resulted in an average probability of obtaining rewards of 50% (the
231 average of 100%, 50%, and 0%). This implies that it caused disappointment compared to the
232 100% probability of obtaining rewards in the foraging task (Fig. 2A), but there is still a
233 possibility of obtaining rewards.

234 On the other hand, in the low-valued scene, when the Pavlovian task began with the
235 appearance of the FP, the probability of obtaining rewards was completely extinguished to
236 0%, leaving only the prediction of punishment (Fig. 2D; Supplementary Movie 4). This not only
237 caused disappointment compared to the 100% probability of obtaining rewards in the
238 foraging task, but also implies that the possibility of obtaining rewards within the trial was
239 completely extinguished (Fig. 2B and D).

240 As a result of the common disappointment in both high- and low-valued scenes, Lhb
241 activities were excited by the FP-indicating the Pavlovian task (Fig. 5J). However, PAG
242 exhibited different patterns of excitation and inhibition in response to the FP, depending on
243 whether the Pavlovian task was initiated in high-valued or low-valued scenes (Fig. 5N).

244 In the low-valued scenes, the PAG became excited when the expectancy of reward
245 outcomes was completely extinguished by the appearance of the FP-indicating the Pavlovian
246 task (Fig. 5N). Then, this tonically excited state of PAG activity was sustained until the end of
247 the trial, remaining slightly above baseline levels when an object appeared after the FP (Fig.
248 5P, before 0 ms). The PAG activity was not responsive to variations in punishment probability
249 (100%, 50%, or 0% airpuff), differentiated by the appearance of objects (Fig. 5P), but had no
250 significant impact on the previously extinguished remaining reward expectancy.

251 In contrast, in the high-valued scenes, the Pavlovian task induced disappointment but
252 still allowed the monkeys to maintain the expectancy of obtaining rewards, even though the
253 probability was reduced. As a result, when the FP-indicating the Pavlovian task appeared in
254 the high-valued scenes, the PAG remained in a suppressed state until an object appeared (Fig.
255 5O, before 0 ms). Subsequently, the neuronal activities of the PAG were significantly
256 differentiated by the 100%, 50%, and 0% reward objects. When the objects associated with
257 100% or 50% reward probabilities appeared, the PAG activity remained in a tonically
258 suppressed state, but it became excited in response to the 0% reward object, which also
259 signifies the complete extinction of reward expectancy within that trial (Fig. 5O).

260 Consequently, we suggest that the distinct phasic LHb and tonic PAG responses could
261 play separate roles in signaling disappointment and remaining reward expectancy. How, then,
262 do changes in the tonic activity of the PAG contribute to behavioral responses when animals
263 encounter an event that switches the remaining reward expectancy on or off?

264

265 **Tonic PAG activity facilitates subsequent actions based on inhibitory motor control**

266 Finally, we propose that the tonic activity of PAG neurons could signal the continuity
267 of remaining reward expectancy and facilitate subsequent actions based on inhibitory motor
268 control. Our findings have so far revealed that PAG neurons exhibited tonic inhibition during
269 the foraging task, which guaranteed a 100% probability of obtaining a reward (Fig. 4M-P). This
270 tonic inhibition of the PAG corresponded to the continuity of reward expectancy, facilitating
271 monkeys' persistent visual attention throughout the task trials (Fig. 4A-D). Additionally,
272 during this period, we observed that their overall eye movements were suppressed (Fig. 4E-
273 H) while the PAG exhibited tonic inhibition. This inhibitory control of eye movements could
274 reflect an increase in gaze fixation on the scene images, indicating the persistence of visual
275 attention. Along with this, our further evidence suggests that the inhibitory control of eye
276 movements could play additional crucial roles in facilitating the execution of subsequent
277 actions.

278 This was evident in the Pavlovian task, which did not require any instrumental actions
279 and allowed us to observe the natural behaviors of the monkeys. When the FP-indicating
280 Pavlovian task appeared in low-valued scenes, the monkeys' remaining reward expectancy
281 was completely extinguished. As a result, PAG activity was tonically excited (Fig. 5N and P),
282 and the monkeys exhibited an increase in eye movements (Fig. 5F and H), which in turn
283 resulted in a decrease in scene gaze compared to high-valued scenes (Fig. 5B and D).
284 Consequently, PAG activity (Fig. 5O-P, before 0 ms) and eye movements (Fig. 5G-H, before 0
285 ms) at the time of object onset were greater in low-valued scenes than in high-valued scenes
286 (Fig. 6A). Ultimately, we found that PAG activity observed at the time of object onset was
287 significantly correlated with the distance of the monkeys' eye movements before the object
288 onset (Fig. 6B).

289 Even after the object appeared, the differences in eye movements between the high-
290 valued and low-valued scenes persisted and were sustained until the end of the trial (Fig. 6C).
291 Thus, when the object subsequently appeared in the Pavlovian task, the monkeys in the low-
292 valued scenes experienced slowness in locating their gaze on the object (Fig. 6D), and even

293 after making a saccade, their gaze did not remain fixated as long as it did in the high-valued
294 scenes (Fig. 6E).

295 Discussion

296 Tonic PAG activity and remaining reward expectancy in overcoming disappointment

297 This study proposes that when animals encounter disappointing events, they could
298 overcome disappointment and continue reward-seeking behaviors through a balance
299 between distinct phasic and tonic signals from the LHb and PAG.

300 The LHb is well-known as one of the primary inputs to the substantia nigra pars
301 compacta (SNc) and ventral tegmental area (VTA) dopamine neurons for signaling
302 disappointment.^{14,43-46} This neuronal pathway is essential for adaptability, flexibility, and
303 learning of animal behaviors as it can modulate neuronal plasticity in the basal ganglia via
304 dopamine transmission.⁴⁷⁻⁵⁰ The LHb responds to disappointing events with phasic firings
305 based on the concept of reward prediction error, which calculates the discrepancy between
306 actual outcomes and predicted values.^{21,51-53} Consequently, when an animal obtains a reward
307 larger than expected, it suppresses LHb activity, enhances dopamine release to the striatum,
308 and activates the direct pathway within the basal ganglia system. This pathway projects to
309 the superior colliculus (SC), thalamus, and pedunculopontine nucleus (PPN), thereby
310 facilitating the associated actions via the substantia nigra pars reticulata (SNr) and the internal
311 segment of the globus pallidus (GPi).⁵⁴⁻⁵⁶ Conversely, when the reward is smaller than
312 expected, LHb activity is stimulated, leading to reduced dopamine release and activation of
313 the indirect pathway, which includes the external segment of the globus pallidus (GPe) and
314 the subthalamic nucleus (STN), thereby suppressing the associated actions.⁵⁷⁻⁶¹

315 However, to optimize reward acquisition, animals often need to overcome
316 disappointment and sustain reward-seeking behaviors by considering additional factors (e.g.,
317 good or bad) beyond these prediction errors (i.g., better or worse). For instance, during
318 reward-seeking behaviors, animals may encounter a disappointing event that is relatively
319 worse than expected but could still hold an absolute value worth pursuing.⁶² Our findings
320 revealed distinct phasic and tonic neuronal responses in the LHb and PAG, representing
321 disappointment and remaining reward expectancy, respectively. Notably, the PAG activity
322 was proficient at signaling reward expectancy throughout task trials, persisting until the
323 desired reward was achieved (Fig. 4M-P and 5M-P). Meanwhile, despite occasional
324 disappointments, the monkeys consistently engaged in a series of task procedures with
325 heightened visual attention (Fig. 4A-D and 5A-D).

326 On the one hand, the PAG has reciprocal connections with the LHb, which should not
327 be overlooked as a potential node for exchanging tonic signaling between them and guiding
328 animals to overcome disappointing events.⁶³⁻⁶⁷ On the other hand, the PAG also establishes
329 neuronal networks with other critical brain regions in the reward system, such as the ventral
330 pallidum^{68,69} and amygdala (AMY).⁷⁰⁻⁷³ In previous studies, we particularly reported similar
331 tonic activity patterns in amygdala neurons, which facilitated extraordinary goal-directed eye
332 movements within the range of express saccades.^{74,75} Therefore, we suggest that this tonic
333 signaling from the amygdala could be a strong candidate for modulating dopamine activity
334 via the amygdalo-nigral pathway,^{76,77} and dopamine neurons could, in turn, integrate tonic
335 signals from the PAG and phasic signals from the LHb (Fig. 7). Finally, further studies on the
336 reciprocal connections of the PAG with the LHb and amygdala could deepen our
337 understanding of how animals overcome disappointment and sustain reward-seeking

338 behaviors, ultimately achieving desired outcomes. Indeed, the PAG has recently been
339 highlighted as a potential therapeutic target for major depressive disorder,⁷⁸⁻⁸⁰ which could
340 expand treatment approaches and complement LHb studies aimed at improving sustained
341 antidepressant effects.⁸¹⁻⁸³

342

343 **Tonic suppression of PAG activity in bridging sequential reward-seeking behaviors**

344 Next, our findings suggest that the tonic activity of the PAG could play a crucial role in
345 bridging sequential motor actions involved in reinforcement learning. This is evident in the
346 correlation between the tonic signaling of the PAG and the anticipatory gaze of monkeys,
347 which consistently maintained their gaze on the background scene images where their tasks
348 took place (Fig. 1E-F). Thereby, the anticipatory gaze enabled monkeys to prepare for
349 subsequent actions (Fig. 3D-E and H-I), allowing them to detect the FP with greater speed and
350 gaze rates (Fig. 3).

351 This is an essential component in the motor skill behaviors of animals, as it allows a
352 sequence of actions to be interconnected and executed as cohesive behavioral units (i.g.,
353 motor chunk).⁸⁴⁻⁸⁶ As a result, animals could improve the speed and accuracy of a series of
354 sequential procedures in reward-seeking behaviors.^{87,88} This is exemplified by our previous
355 study, which examined motor skill acquisition in monkeys using a 2x5 task.⁸⁹ The 2x5 task
356 involved training the monkeys to learn and remember the sequence of pressing five pairs of
357 buttons, which illuminated from a total of 16 buttons, in a predetermined order. Following a
358 series of training sessions, the monkeys exhibited skilled behavior in which, upon pressing
359 one button, they were able to locate their gaze on the next button they would press before
360 it illuminated. As a result, they could perform subsequent actions with exceptional speed and
361 accuracy, leading to faster reward acquisition.

362 Furthermore, this reinforcement between behavioral units could also play a pivotal
363 role in gating subsequent behaviors sequentially. For example, monkeys initiate eye contact
364 before engaging in social behaviors like lip-smacking.⁹⁰ Sequentially, lip-smacking induces
365 synchronization of the animal's behavior, facilitating emotional exchange and cooperative
366 actions, which, in turn, promotes a series of various subsequent behaviors.⁹¹⁻⁹³ Thus, the tonic
367 signaling of the PAG, which supported the monkeys' anticipatory gaze toward face scene
368 images (Fig. 1), could play a crucial role in enhancing the likelihood of animals engaging in
369 subsequent social behaviors. These motor skills, including social behaviors, are important
370 sources of natural rewards and pleasure in the lives of humans and animals.⁹⁴⁻⁹⁶ In this way,
371 social interactions between animals have been shown to improve stress coping,⁹⁷⁻⁹⁹ mitigate
372 aversive responses to unpleasant stimuli, and enhance the persistence of ongoing motivated
373 behaviors.¹⁰⁰⁻¹⁰⁴ Therefore, from the perspective of reinforcement learning, we suggest that
374 the tonic activity of the PAG can provide additional reward resources for overcoming
375 disappointing events and continuing ongoing motivated behaviors by facilitating the
376 connection between sequential motor actions.

377

378 **Tonic PAG activity in inhibitory control of unnecessary movements**

379 Lastly, we suggest that tonic PAG activity can contribute to the inhibitory control of
380 unnecessary movements, which could potentially implicate its significant role in movement
381 disorders. In the present study, we observed that monkeys exhibited strong inhibition of

382 unnecessary eye movements during highly motivated anticipatory scene viewing (Fig. 4E-H
383 and 5E-G). The inhibitory motor control can play a crucial role in regulating impulsivity,
384 guiding action selection, and prioritizing the sequence of actions in human and animal
385 behavior.¹⁰⁵⁻¹⁰⁷ Thereby, this process ultimately improves the speed and accuracy of desired
386 behaviors and smooths out the motion of humans and animals in response to the
387 overwhelming influence of information processed through various sensory inputs that flow
388 into the brain.¹⁰⁸⁻¹¹¹

389 These findings could further provide valuable insights into the implications of PAG
390 activity in movement disorders, such as Parkinson's disease. Parkinson's disease is
391 characterized by abnormalities in the initiation and speed of actions (e.g., akinesia and
392 bradykinesia).⁴⁸ On the other hand, another significant symptom observed in this disease is
393 the impairment in suppressing unnecessary movements, such as tremors and dyskinesia.
394 These symptoms manifest abnormalities not only in limb movements but also in eye
395 movements.¹¹²⁻¹¹⁴ For example, a Parkinson's disease patient in a previous study exhibited
396 frequent abnormal repetitive saccades and fixation patterns during word reading, leading to
397 more frequent unnecessary eye movements compared to a healthy individual.¹¹⁵ As a result,
398 this impaired overall reading speed and comprehension.

399 A key characteristic of Parkinson's disease is the degeneration of dopaminergic
400 neurons in the SNc. Additionally, the PAG, along with surrounding brainstem regions, has also
401 been reported as an area showing significant changes in patients and animal models with
402 Parkinsonian symptoms.^{32,37,116-120} However, there is still a lack of research on the role of the
403 PAG in Parkinsonian symptoms. The dopamine deficits in Parkinson's patients have primarily
404 been reported in the caudal dorsal lateral part of the SNc, which projects to the tail of the
405 striatum (i.e., the caudal part of the striatum).¹²¹⁻¹²⁴ This neuronal pathway from the caudal
406 dorsal lateral part of SNc to the tail of the striatum plays a crucial role in regulating automatic
407 movements.¹²⁵⁻¹²⁹ Consequently, neurodegeneration in this pathway can impair the function
408 of the indirect pathway, which is responsible for the inhibitory control of unnecessary
409 automatic movements,¹³⁰⁻¹³² and the decrease in PAG activity may affect its interaction with
410 these basal ganglia circuits.

411 Importantly, the PAG is also recognized as a critical integrator of emotional responses
412 and outputs in the emotional motor system, projecting to the spinal cord, forebrain,
413 cerebellum, and other brainstem regions to control movement (Fig. 7).¹³³⁻¹³⁶ For instance,
414 dysfunction of the PAG might impair eye movement control in Parkinsonism through its
415 connections, distinct from basal ganglia output, to the brainstem areas associated with the
416 oculomotor system.¹³⁷⁻¹³⁹ Future studies investigating the specific mechanisms of PAG activity
417 and its interplay with basal ganglia circuits could significantly enhance our understanding of
418 the pathophysiology of movement disorders and identify new therapeutic targets.

419

420 **Materials and Methods**

421 **General Procedures**

422 Two male *Macaca mulatta* monkeys were used for this study. (CH, 10-year-old, 15 kg and KI,
423 10-year-old, 9.5 kg). All animal care and experimental procedures were approved by the
424 Animal Care and Use Committee of the National Eye Institute and complied with the Public
425 Health Service Policy on the Humane Care and Use of Laboratory Animals. Apple juice (high-
426 value, 600 μ l; low-value, 200 μ l) and airpuff (10-20 psi, 100 ms) were used as reward and
427 punishment outcomes in the task. Partial data from the LHb and behavioral recordings were
428 used in related publications that tested the same task protocol.^{21,92} The monkeys' eye
429 positions ($n = 72$) were recorded using an EyeLink 1000 Plus eye tracker (SR Research) and
430 were simultaneously recorded with neuronal signals via Blip software
431 (www.robilis.com/blip/).

432

433 **Scene-based foraging/Pavlovian task**

434 A trial of the scene-based foraging/Pavlovian task began with the appearance of a scene
435 image (size: 40°; (2 faces + 2 landscapes) \times 4 scene groups = 16 scene images per block), which
436 was maintained as the background scene throughout the trial (Fig. 1B). After 1 s of free
437 viewing, a FP indicating either the foraging or Pavlovian task appeared at the center of the
438 scene, and the respective task began. Each block of the task consisted of 384 trials, with tasks
439 presented in a pseudo-random order (foraging task, 192 trials; Pavlovian task, 192 trials).
440 Additionally, 32 non-cued free outcomes (8 high-value rewards, 8 low-value rewards, 16
441 punishments) were randomly delivered between task trials without any visual stimuli.

442

443 **Background scene images**

444 We created four groups of background scene images, each contextually associated with
445 different reward and punishment outcome experiences (Supplementary Fig. S1): high-value
446 reward without punishment (Rwd++ Pun-), high-value reward with punishment (Rwd++ Pun+),
447 low-value reward without punishment (Rwd+ Pun-), and low-value reward with punishment
448 (Rwd+ Pun+). This study focused on data from high-valued scenes (Rwd++ Pun-) and low-
449 valued scenes (Rwd+ Pun+) to address the primary research question (Supplementary Fig. S1).
450 As a result, monkeys received a large amount of juice reward for completing foraging tasks in
451 the high-valued scenes and a small amount of juice reward in the low-valued scenes (Fig. 1A).
452 During Pavlovian tasks, in the high-valued scenes, monkeys received rewards of the same size
453 as those in the foraging tasks. In contrast, in the low-valued scenes, monkeys received airpuff
454 punishment outcomes instead of juice rewards. The background scene images were collected
455 from Google Earth (<https://www.google.com/earth/>), OpenAerialMap
456 (<https://openaerialmap.org>), and Face Database (<https://fei.edu.br/~cet/facedatabase.html>).

457

458 **Foraging task**

459 The foraging task began with the appearance of a square-shaped FP (size, 2°), requiring the
460 monkeys to fixate on it for more than 700 ms within 1 s (Fig. 4). After the fixation, one of the
461 good or bad objects (size, 10°) appeared on either the left or right side (15°) of the background
462 scene image. Monkeys were then required to fixate on the good object (500 ms) within 1 s to
463 receive a reward. If the bad object appeared after fixation, monkeys had to avoid it by either
464 not making a saccade to the object for 1 s or by fixating on the bad object for no more than
465 500 ms. If the monkey successfully avoided the bad object, it disappeared from the scene,
466 and the FP reappeared at the center of the scene. The monkey was then required to fixate on

467 the FP again. Afterward, the good object was presented again on either side of the scene, and
468 the trial could be completed by fixating on the good object to acquire the reward. If the
469 monkey failed to avoid the bad object or failed to fixate on the FP or the good object, the
470 visual stimuli disappeared, accompanied by a beep sound. The trial was then repeated from
471 the scene onset until the monkey correctly completed the task and acquired the reward.
472 Therefore, monkeys could earn fixed amounts of reward outcomes for each scene image in
473 the block. The good object appeared first in 1/3 of the trials and after the bad object in 2/3 of
474 the trials. Each scene image had different fractal images¹²⁹ for the respective good and bad
475 objects.

476

477 **Pavlovian task**

478 The Pavlovian task began with the appearance of a circular FP, which required no action from
479 the monkeys for 1 s (Fig. 5). After 1 s, one of three objects (100%, 50%, or 0% probability)
480 appeared on the left or right side of the background scene image for 1.5 s. Monkeys then
481 received a reward or punishment outcome based on the probabilities associated with each
482 object. One second after the outcome delivery began, the background scene disappeared,
483 and the next trial started after approximately 7 s. Each scene image had different fractal
484 objects representing the respective objects.

485

486 **Electrophysiology**

487 We recorded 34 neurons from the LHb and 44 neurons from the PAG in two monkeys: CH
488 (LHb, 15; PAG, 30) and KI (LHb, 19; PAG, 14). Single-unit neuronal activity was recorded using
489 glass-coated electrodes (diameter 0.38 mm, 1 M Ω , Alpha-Omega) connected to a
490 microelectrode AC amplifier (model 1800; A-M Systems; gain, 10k; filters, 0.1 to 10 kHz) and
491 a band-pass filter (model 3384; Krohn-Hite). The electrode was advanced using an oil-driven
492 micro-manipulator (MO-97A, Narishige) through a guide tube and an 8° tilted posterior
493 chamber. Recording sites were confirmed via vertical MRI scanning (4.7 T, Bruker) with a
494 gadolinium-filled grid (1 mm-spacing) and Elgjoy deposits marking the PAG.¹⁴⁰ Neuronal firing
495 was monitored in real-time and isolated using custom voltage- and time-based windows in
496 Blip software.

497

498 **Statistical Analysis**

499 We presented data as mean \pm standard error of the mean. The statistical significances were
500 analyzed using the Wilcoxon matched-pairs signed rank test, one-way repeated measures
501 analysis of variance (ANOVA) with Bonferroni post hoc test, and Pearson correlation analysis
502 using Prism9 (GraphPad Software). The average firing rates of neurons and gaze probabilities
503 were smoothed by Gaussian kernel ($\sigma = 10$ ms) using MATLAB (MathWorks).

504

505

506 **AUTHOR CONTRIBUTIONS**

507 Conceptualization, H.L. and O.H.; Methodology, H.L. and O.H.; Software, H.L. and O.H.; Formal
508 Analysis, H.L. and O.H.; Investigation, H.L. and O.H.; Writing –Original Draft, H.L.; Writing –
509 Review & Editing, H.L. and O.H.; Visualization, H.L. and O.H.; Supervision, O.H.; Project
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520

521 **DECLARATION OF INTERESTS**

522 The authors declare no competing interests.

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901

902

903 **Figure 1 Neuronal responses and anticipatory gazes in scene viewing**

904 (A) In the scene-based foraging/Pavlovian task, each trial began with the free viewing of a
905 scene image. Each group of scene images provided respective reward outcomes from the
906 foraging and Pavlovian tasks. Consequently, the monkeys freely viewed each group of scene
907 images based on the average rewards they had experienced during both tasks.

908 (B) Midlines indicate the average amount of juice reward and airpuff punishment provided to
909 each group of scenes from the foraging and Pavlovian tasks. Bars indicate the maximum and
910 minimum amounts of the outcomes.

911 (C, D) Left, recording sites are marked with orange dotted lines, indicating the locations of the
912 LHb and PAG. Right, the average firing rates of LHb and PAG in response to scene onset. The
913 purple shaded areas represent the differences in neuronal responses between high-valued
914 and low-valued scenes.

915 (E) An example heatmap illustrating monkeys' gaze on face scene images.

916 (F) Outside, the probabilities of gaze on face scene images during the free-viewing period
917 (Scene zone, $40^\circ \times 40^\circ$). Inside, the probabilities of gaze on the eye regions of face scene
918 images during the free-viewing period (Eye zone, $4^\circ \times 3^\circ$). Please see Supplementary Fig. 1 for
919 additional information and *P* values.

920

921 **Figure 2 Neuronal and behavioral responses in foraging and Pavlovian tasks**

922 (A) The histograms (10 ms bins) showing neuronal activity in the LHb (top) and PAG (bottom)
923 during the foraging task with high-valued scenes. The histograms are aligned to the onset of
924 each stimulus during the task procedures (scene onset, FP onset, and object onset). The green
925 dotted line indicates baseline neuronal activity measured for 200 ms before scene onset. The
926 green shaded areas represent changes in neuronal activity compared to baseline levels during
927 the task procedures.

928 (B) The histograms show the same data as in A, but for low-valued scenes.

929 (C-D) The histograms show the same data as in A and B, respectively, for the Pavlovian task.

930

931 **Figure 3 Reward expectancy facilitates subsequent actions**

932 (A) The probabilities of anticipatory gaze before the FP onset, where the gaze was located at
933 the position where the FP would appear (FP zone, $10^\circ \times 10^\circ$). The purple shaded areas
934 represent differences in responses between high-valued and low-valued scenes or between
935 good objects and bad objects. The green shaded areas indicate the monkeys' gaze on the
936 location where the FP appeared, starting from scene onset and maintained throughout the
937 subsequent task procedures. The purple shaded areas highlight the differences in gaze
938 responses between high-valued and low-valued scenes.

939 (B) The probabilities of gaze on the FP after its appearance.

940 (C) The fixation start time, representing the gaze-reaching time for monkeys to initiate
941 fixation on the FP (Wilcoxon matched-pairs signed rank test; $**P < 0.01$, $n = 72$).

942 (D) The fixation rate, indicating the percentage of time monkeys maintained their gaze on the
943 FP to engage in the next task procedure (Wilcoxon matched-pairs signed rank test; $****P <$
944 0.0001 , $n = 72$).

945 (E-F) Same as A-B, respectively, for the Pavlovian task.

946 (G-H) Same as C-D, respectively, for the Pavlovian task.

947

948 **Figure 4 Tonic inhibition of PAG signals continuity of reward expectancy in foraging task**

949 (A-D) The probabilities of gaze fixation on scene images during the foraging task. The purple
950 shaded areas represent differences in responses between high-valued and low-valued scenes,
951 or between 100% objects and 0% objects. The green dotted line indicates baseline levels
952 measured for 200 ms before scene onset, while the green shaded areas represent changes in
953 gaze responses relative to baseline during the task procedures.

954 (E-H) Same as A-D, but for the velocity of eye movement.

955 (I-L) The Lhb activity shown in figures 2A-B aligned with the gaze response presented in A-H.

956 (M-P) The PAG activity corresponds to the data presented in I-L.

957

958 **Figure 5 Tonic excitation of PAG signals complete extinction of reward expectancy in**
959 **Pavlovian task**

960 (A-D) The probabilities of gaze fixation on scene images during the Pavlovian task. The purple
961 shaded areas represent differences in gaze responses between high-valued and low-valued
962 scenes. The green dotted line indicates baseline levels measured for 200 ms before scene
963 onset, while the green shaded areas represent changes in gaze responses relative to baseline
964 during the task procedures.

965 (E-H) Same as A-D, but for the velocity of eye movement.

966 (I-L) The Lhb activity shown in figures 2C-D aligned with the gaze response presented in A-H.

967 (M-P) The PAG activity corresponds to the data presented in I-L.

968

969 **Figure 6 Implications of tonic PAG activity on subsequent behaviors through the inhibitory**
970 **control of eye movements**

971 (A) Left, the average firing rates of PAG neurons before object onset during the Pavlovian task.
972 The firing rates were quantified for PAG neurons, as shown in figures 5O-P, during the - 200–
973 0 ms period preceding object onset. Right, the average eye movement distance before object
974 onset in the Pavlovian task. The distances were quantified during the - 200–0 ms period
975 preceding object onset (Wilcoxon matched-pairs signed rank test; $***P < 0.001$, $****P <$
976 0.0001 , $n = 44$).

977 (B) The correlation between the average firing rates of PAG neurons (from A, left) and the
978 average eye movement distances (from B, right) (Pearson correlation analysis; $r < 0.05$, $*P <$
979 0.05 , $n = 44$).

980 (C) The average eye movement distance after object onset in the Pavlovian task. The distances
981 were quantified for 1 s after object onset, as shown in figures A-D.

982 (D) The time to initiate gaze on the object after object onset in the Pavlovian task. The start
983 time for the monkeys' gaze reaching the object was analyzed.

984 (E) The duration of gaze fixation on the objects after object onset in the Pavlovian task. The
985 gaze-holding duration was measured for 1.5 s.

986

987 **Figure 7 Hypothetical neuronal mechanisms underlying inhibitory control of movements**

988 The interconnection between the PAG and AMY could play a key role in the inhibitory control
989 of movements via dopamine neurons in the SNc and VTA. This pathway could enable
990 dopamine neurons to integrate tonic signals from the PAG with phasic signals from the Lhb.

991 Furthermore, the PAG could be essential for integrating emotional information from the AMY
992 and LHb, thereby orchestrating movement control through additional interactions with brain
993 regions such as the forebrain, cerebellum, and other brainstem areas.

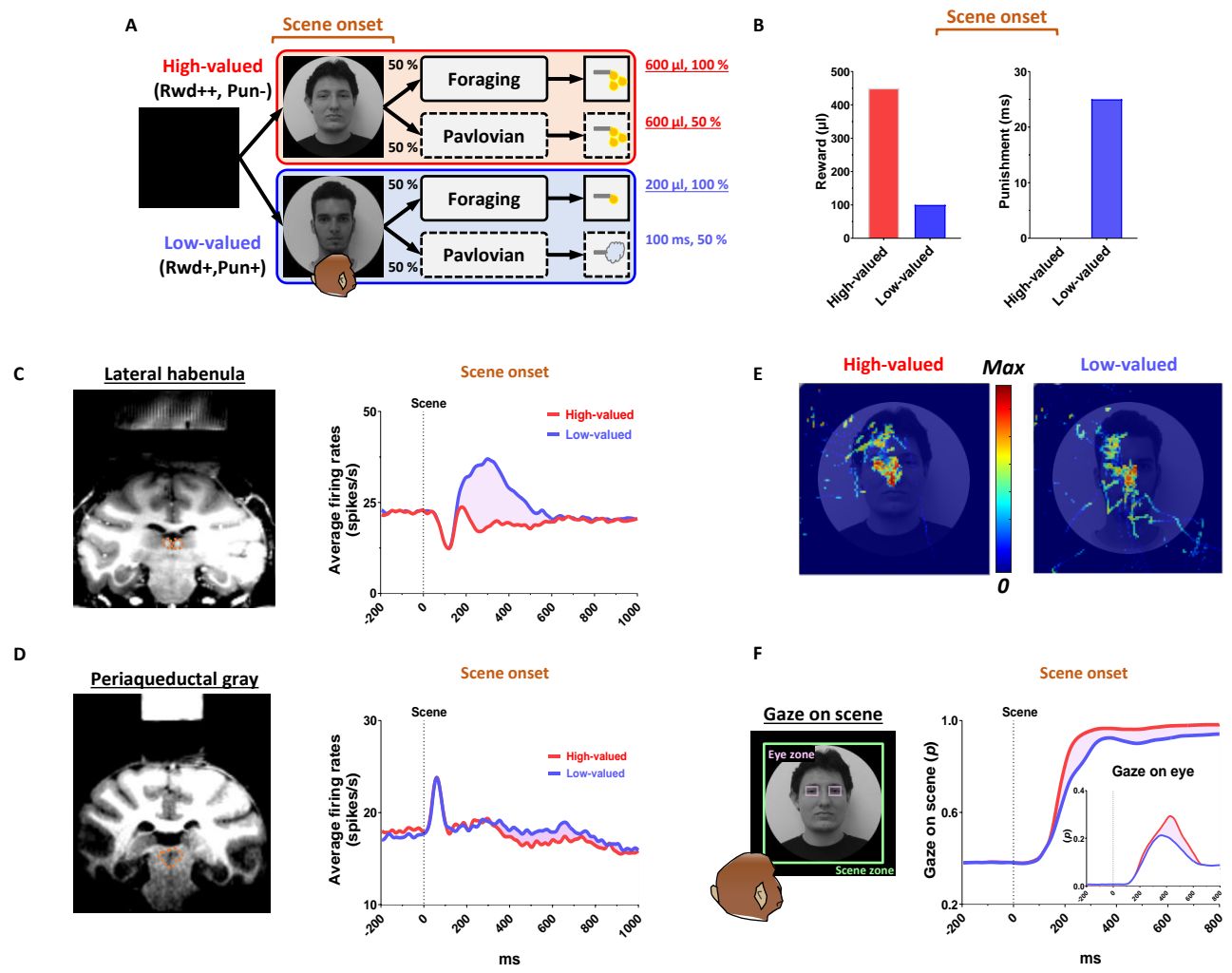
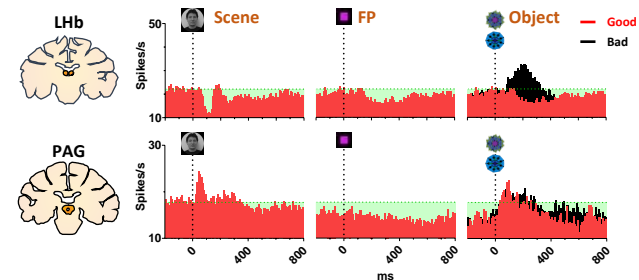
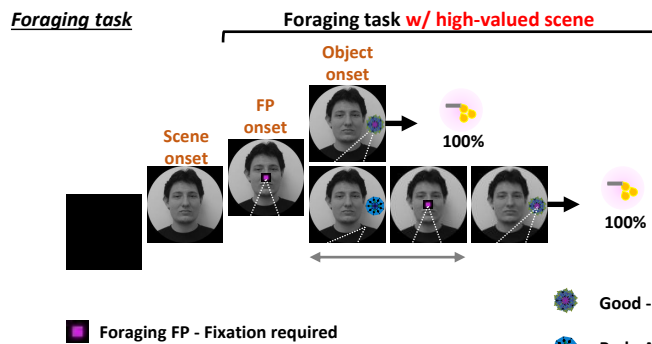


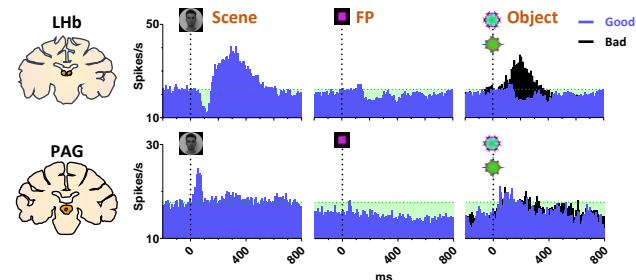
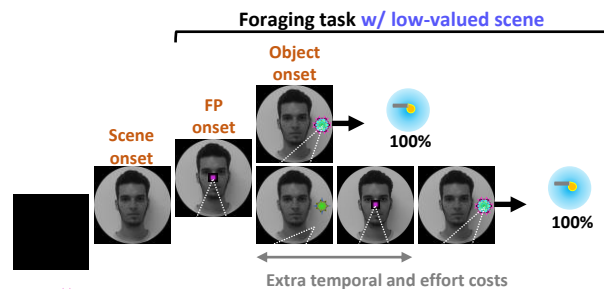
Fig1

A

Foraging task

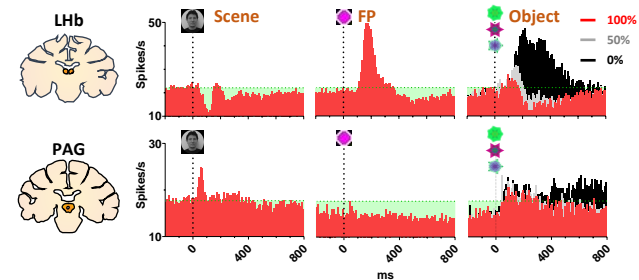
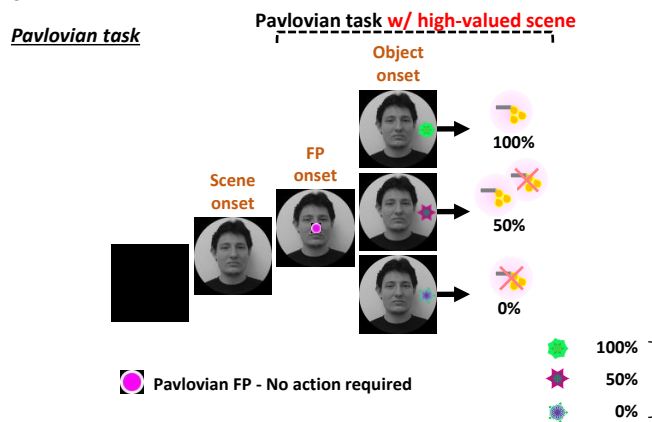


B

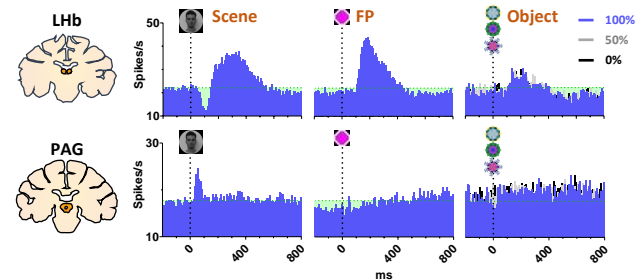
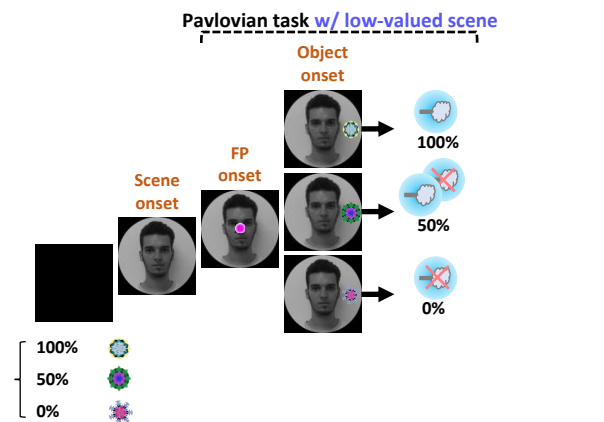


C

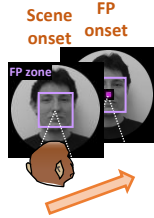
Pavlovian task



D



Foraging task



Pavlovian task

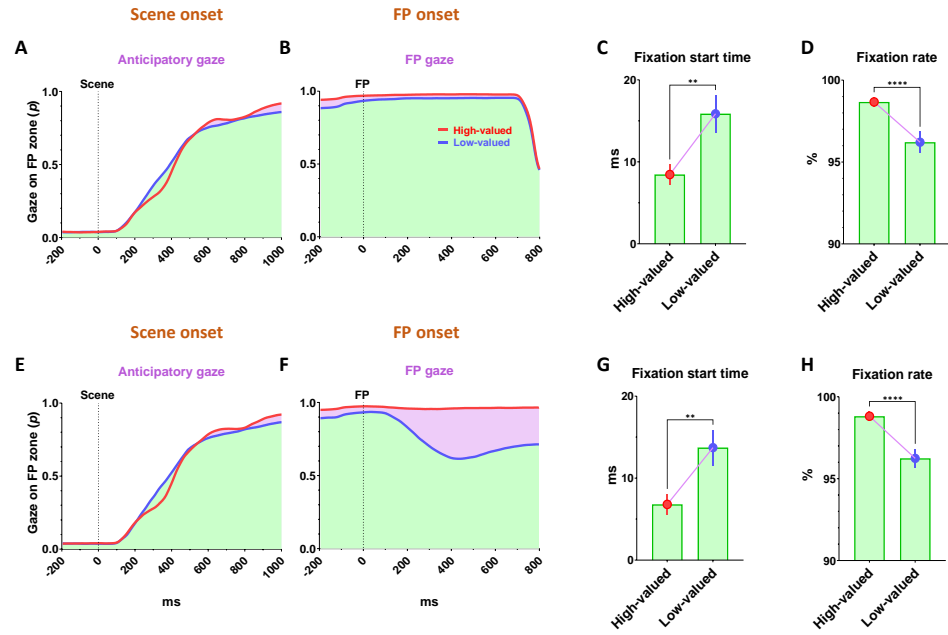
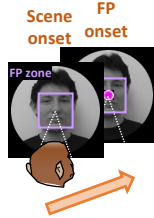


Fig3

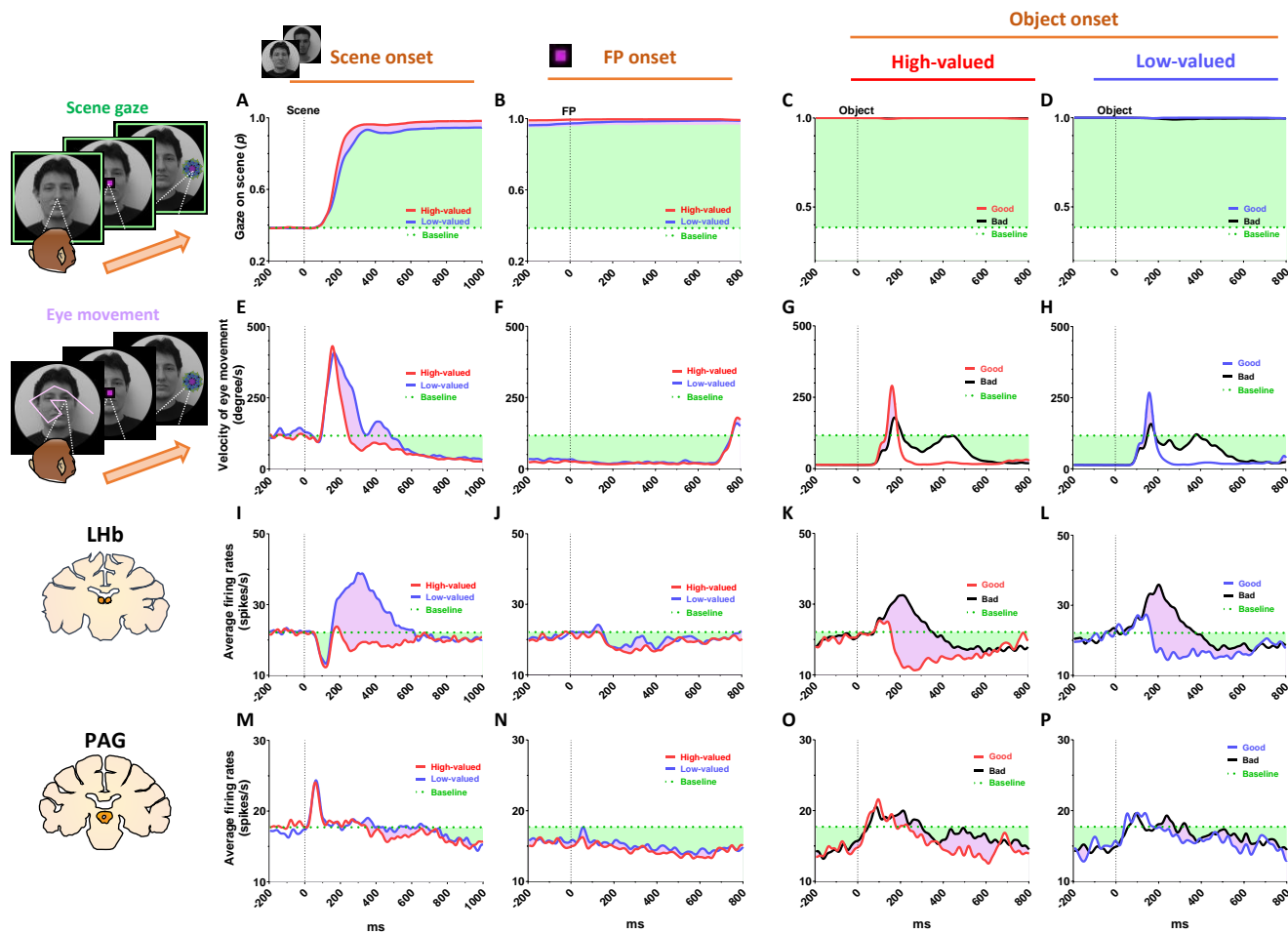
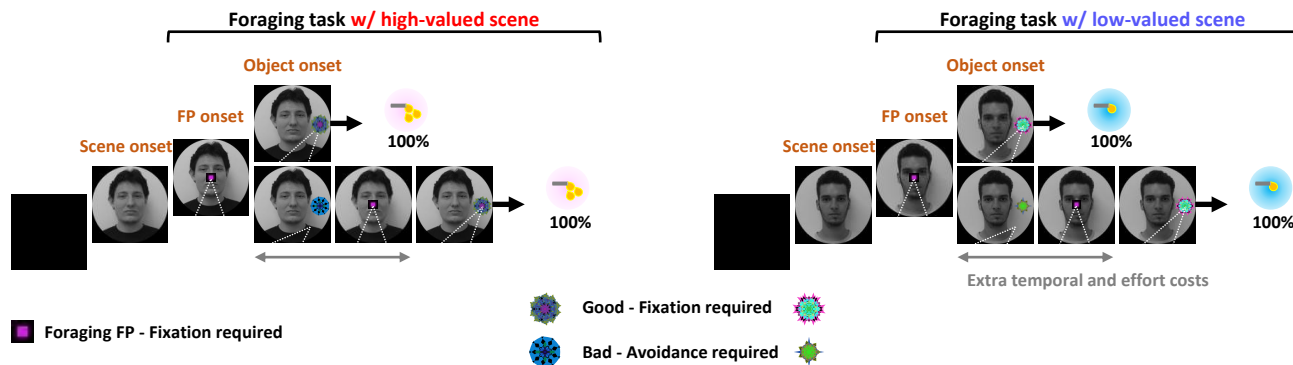


Fig4

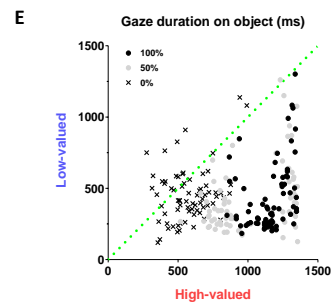
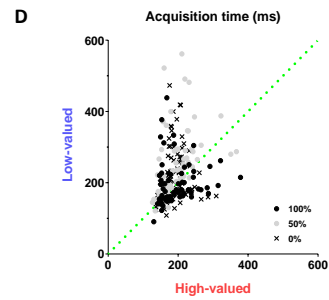
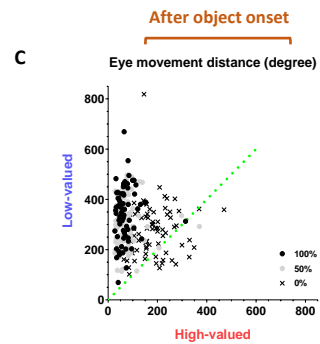
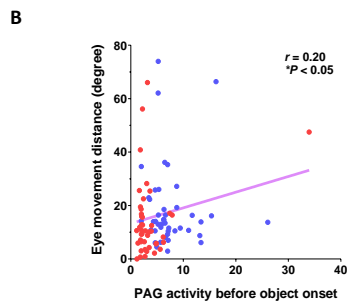
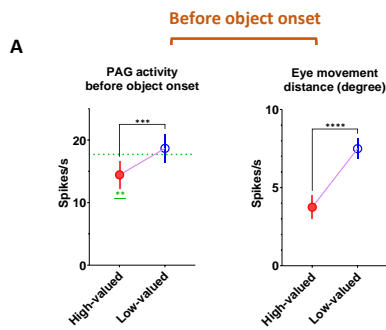
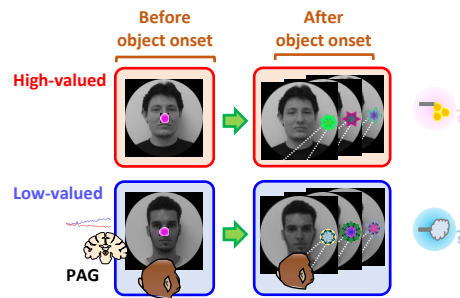


Fig6

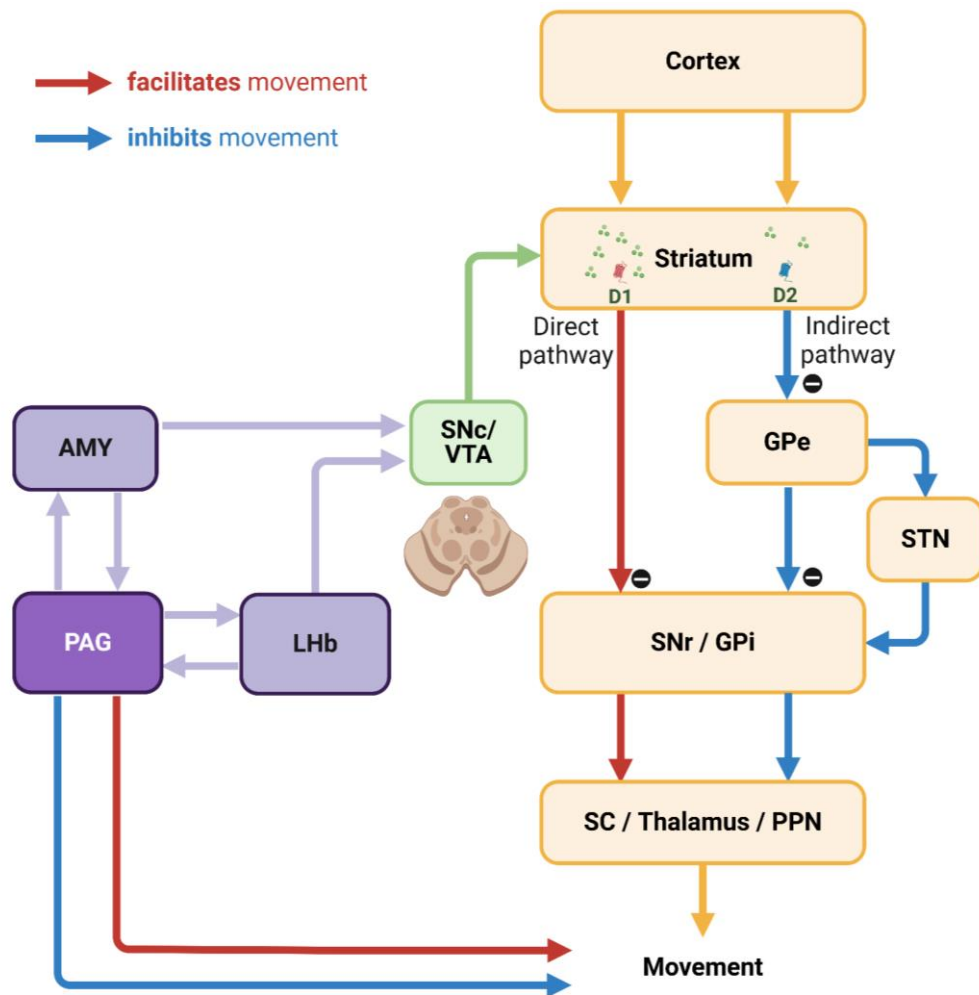


Fig7