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1 **PERSPECTIVE**

2 **Dopamine and noradrenaline modulation of goal-directed behaviour in prefrontal**  
3 **areas: Toward a division of labour?**

4 Juan-Carlos Cerpa<sup>1,2\*</sup>, Etienne Coutureau<sup>1,2</sup>, Shauna L. Parkes<sup>1,2\*</sup>

5 <sup>1</sup>CNRS, Institut de Neurosciences Cognitives et Intégratives d'Aquitaine, UMR 5287, 33076  
6 Bordeaux, France.

7 <sup>2</sup>Université de Bordeaux, 33076 Bordeaux, France.

8

9 \*Corresponding authors: [juancarlos.cerpa@psy.ox.ac.uk](mailto:juancarlos.cerpa@psy.ox.ac.uk); [shauna.parkes@u-bordeaux.fr](mailto:shauna.parkes@u-bordeaux.fr)

10

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16

17 **ABSTRACT**

18 The prefrontal cortex is considered to be at the core of goal-directed behaviours. Notably, the  
19 medial prefrontal cortex (mPFC) is known to play an important role in learning action-  
20 outcome associations, as well as in detecting changes in this contingency. Previous studies  
21 have also highlighted a specific engagement of the dopaminergic pathway innervating the  
22 mPFC in adapting to changes in action causality. While previous research on goal-directed  
23 actions has primarily focused on the mPFC region, recent findings have revealed a distinct  
24 and specific role of the ventral and lateral orbitofrontal cortex (vIOFC). Indeed, vIOFC is not  
25 necessary to learn about action-outcome associations but appears specifically involved when  
26 outcome identity is unexpectedly changed. Unlike the mPFC, the vIOFC does not receive a  
27 strong dopaminergic innervation. However, it receives a dense noradrenergic innervation  
28 which might indicate a crucial role for this neuromodulator. In addition, several lines of  
29 evidence highlight a role for noradrenaline in adapting to changes in the environment. We  
30 therefore propose that the vIOFC's function in action control might be under the strong  
31 influence of the noradrenergic system. In the present paper, we review anatomical and  
32 functional evidence consistent with this proposal and suggest a direction for future studies  
33 that aims to shed light on the orbitofrontal mechanisms for flexible action control. Specifically,  
34 we suggest that dopaminergic modulation in the mPFC and noradrenergic modulation in the  
35 vIOFC may underlie distinct processes related to updating one's actions.

36

37 **I. Introduction**

38 Adaptive decision-making relies on an ability to assign specific consequences to  
39 distinct actions and to select actions that fulfil internal goals. The ability to behave in this  
40 goal-directed manner has been extensively studied using instrumental tasks in both humans  
41 and animals. In these tasks, the subject is asked to perform an action (e.g., press on a lever  
42 or keyboard) to obtain an outcome (e.g., food or monetary reward). Decades of studies in  
43 experimental psychology have demonstrated that this press can be mediated by a detailed  
44 representation of the association, or contingency, between the action and its specific  
45 outcome (Balleine & Dickinson 1998, de Wit & Dickinson 2009, Dickinson 1994).

46 However, in a changing environment, contingencies are not always stable. Indeed,  
47 the causal relationship between an action and its outcome can change such that this action  
48 is no longer necessary. Alternatively, the outcome associated with a given action might  
49 change. In both cases, the learner must be able to update their representation in order to  
50 adapt their behaviour. Interestingly, rodent studies have linked the former to the dorsomedial  
51 prefrontal cortex (dmPFC; area 32 or prelimbic cortex), and the latter to ventral and lateral  
52 regions of orbitofrontal cortex (vOFC). Therefore, it appears that distinct subareas of the  
53 prefrontal cortex (PFC) are at the core of these updating processes. Crucially, the PFC is  
54 strongly innervated by neuromodulatory systems, such as the noradrenergic and  
55 dopaminergic systems, which have a strong influence on its functions (Dalley et al 2004,  
56 Likhtik & Johansen 2019, Puig et al 2014, Robbins & Arnsten 2009). While the noradrenergic  
57 innervation is quantitatively homogeneous across the vOFC and the medial wall of the PFC,  
58 the dopaminergic innervation is much stronger in the medial wall compared to the vOFC  
59 (Descarries et al 1987, Murphy & Deutch 2018, Naneix et al 2012, Van Eden et al 1987).  
60 This might suggest differential contribution of neuromodulatory systems in the PFC.

61 Previous studies have demonstrated a role for dopaminergic neuromodulation in the  
62 dmPFC for goal-directed learning (Naneix et al 2009, Naneix et al 2012, Naneix et al 2013)  
63 however, we believe that a broader picture integrating neuromodulation of the PFC in goal-

64 directed behaviour is lacking. Here, we review anatomical evidence describing the  
65 neuromodulatory systems in the rodent PFC, with a specific focus on noradrenergic and  
66 dopaminergic innervation of the dmPFC and vOFC. We propose that dopaminergic and  
67 noradrenergic modulation of these two prefrontal regions is essential to the successful  
68 updating of action-outcome (A-O) associations, with a clear division of labour emerging at the  
69 level of both region and neuromodulatory system. Specifically, while dopaminergic  
70 modulation of dmPFC is necessary to update changes in causality (Naneix et al 2009,  
71 Naneix et al 2012, Naneix et al 2013), changes to the A-O that relate to outcome identity may  
72 require noradrenergic modulation of vOFC.

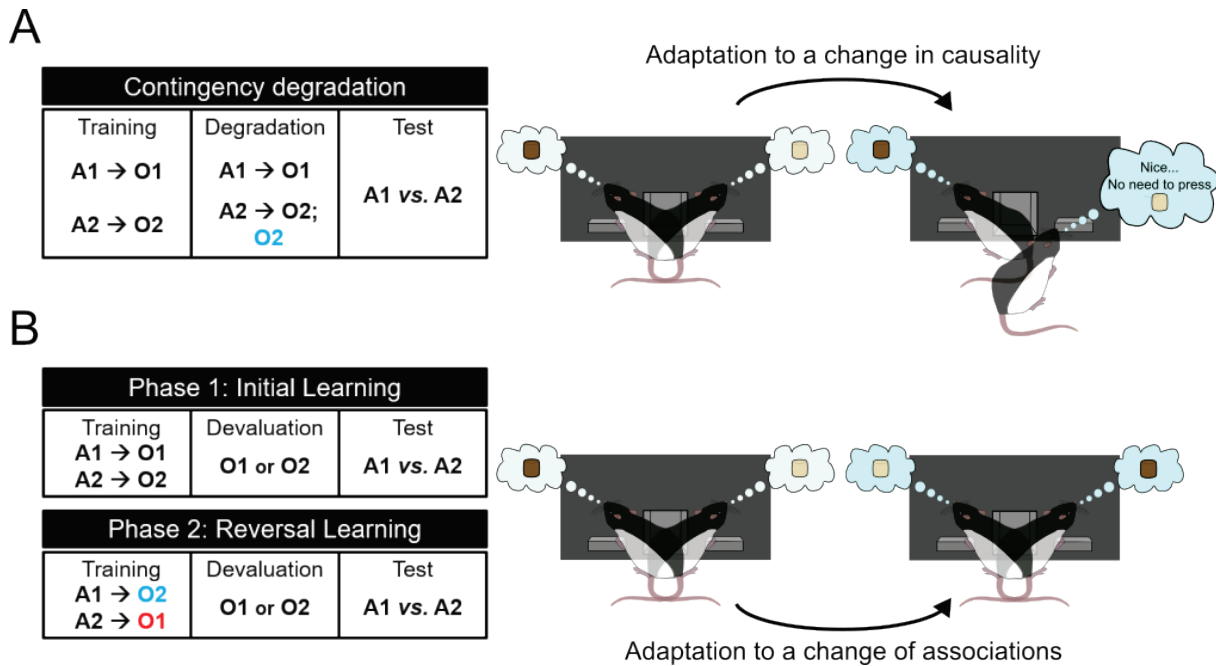
## 73 **II. Adapting to changes in action-outcome associations**

74 When a subject performs an action to obtain an outcome, it may do so because a  
75 reinforcing relationship has formed between antecedent stimuli and the response itself  
76 (habitual behaviour) or because the subject has knowledge of a causal relationship between  
77 the response and the outcome, and the desire to obtain that outcome (goal-directed  
78 behaviour) (Balleine & Dickinson 1998, Dickinson 1994; Dickinson 1985). One method to  
79 determine if behaviour is under habitual or goal-directed control is to assess the subject's  
80 knowledge of the causal relationship (or contingency) between the action and the outcome. A  
81 response under goal-directed control is sensitive to changes in this relationship whereas a  
82 response under habitual control is not (Balleine & Dickinson, 1998). Knowledge of the current  
83 action-outcome contingency integrates that the probability of obtaining an outcome by  
84 performing a given action ( $P_{o/a}$ ) is superior to the probability of obtaining an outcome without  
85 performing this action ( $P_{o/\emptyset}$ ). Hammond (1980) first demonstrated that actions can be  
86 sensitive to changes in this causal relationship. In this study, rats were trained to press a  
87 lever to earn a food outcome with a certain probability  $P_{o/a}$ . Once acquired, the contingency  
88 between lever pressing and food delivery was degraded. Specifically, while  $P_{o/a}$  remained  
89 unchanged,  $P_{o/\emptyset}$  was increased, by delivering free non-contingent food outcomes, to a value  
90 equal to  $P_{o/a}$ . Thus, it was no longer necessary to perform the action to obtain the reward and

91 rats progressively decreased responding on the lever when contingency degradation had  
92 occurred. Similar results have been obtained in experiments including two levers associated  
93 with two different food outcomes (see Figure 1A). Indeed, Colwill and Rescorla (1986), as  
94 well as Dickinson and Mulatero (1989), demonstrated that rats specifically decrease their  
95 responding on a degraded lever without changing their responding on a non-degraded lever.  
96 In addition, this response adjustment is subsequently found in a test conducted under  
97 extinction during which responses are only based on the mental representation of  
98 contingencies.

99         Other studies have shown that updating A-O associations is not limited to changes in  
100 causality. Animals can also update their knowledge of the A-O association when the outcome  
101 itself unexpectedly changes (for an example see Figure 1B). Interestingly, this adaptation  
102 appears to depend on an efficient coexistence of initial and new learning. For instance, in  
103 one of his many experiments, Rescorla (1996) trained rats with two actions, each associated  
104 with one food outcome (grain pellet or sucrose solution). Then, animals were trained with the  
105 reversed associations. To assess which associations were driving the behaviour, one of the  
106 food outcomes was devalued. Results of the test following this devaluation indicated that the  
107 treatment had a similar impact on the performance of both actions. These actions had been  
108 successively associated with the same outcome, therefore, it is likely that this behavioural  
109 pattern was due to an interference between both associations. A recent study has been  
110 critical to extending our understanding of this phenomenon (Bradfield & Balleine 2017).  
111 Using a similar protocol to the one of Rescorla, these authors showed that, during the test,  
112 rats based their responses on the reversed associations only after extended training under  
113 these associations. Furthermore, initial associations could be retrieved during the test if the  
114 reversed associations had been previously extinguished. Such interference can also be  
115 induced following shifts in the physical (Trask & Bouton, 2014) or temporal context (Goarin et  
116 al., 2018). Overall, these results suggest that action control after outcome identity reversal  
117 does not depend on erasure of initial learning. Rather, it appears that adaptation to

118 contingency changes requires, at least initially, interference mitigation between learning  
 119 episodes.



120

121 **Figure 1. A. Contingency degradation.** In a typical procedure, subjects are trained to  
 122 associate two actions (e.g., A1 and A2) with two different food outcomes (O1 and O2). Then,  
 123 one of these contingencies (A2→O2) is degraded by delivering one food outcome freely  
 124 (O2). This procedure leads to a specific reduction in responding on the lever associated with  
 125 this food outcome (A2) but leaves intact responding on the other lever (A1). This reduction is  
 126 also observed during an extinction test during which no food is delivered. Detection of a  
 127 change in causality is primordial for the animal to adapt to this change. Note that free  
 128 delivery of a third outcome is also often delivered during presentation of the non-degraded  
 129 lever (A1→O1) to control for increases in food port entries. **B. Outcome identity reversal.**  
 130 During an initial phase, animals are trained to associate two levers with two food outcomes  
 131 (e.g., A1→O1 and A2→O2). Then, during a reversal phase, the outcome associated with  
 132 each response is switched (i.e., A1→O2 and A2→O1). At each phase, animals are given an  
 133 outcome devaluation procedure and an extinction test to assess their learning of the  
 134 response-outcome contingencies.

135

136 How these learned associations can coexist is an intriguing question. Based on the  
 137 reinforcement-learning framework, it has been proposed that the animal acquires a mental  
 138 representation of the task, which conveys information about distinct task states and the  
 139 transition between these states (Behrens et al 2018, Bradfield & Hart 2020, Langdon et al  
 140 2019, Wilson et al 2014). Bradfield et al (2013) propose that the learning taking place during  
 141 outcome identity reversal comes from an expectation error regarding the transition from an

142 action (state 1) to a certain food outcome (state 2). Once encountered, this new configuration  
143 enters a new 'state representation'. Therefore, original and modified contingencies might be  
144 split into different internal representations allowing the animal to integrate both learning  
145 episodes and select the appropriate contingencies depending on its current beliefs.

146 In rodents, acquiring A-O associations and tracking these associations in a changing  
147 environment relies on the prefrontal cortex (PFC). Rather than working as a homogeneous  
148 unit, it appears that different prefrontal regions support distinct aspects of goal-directed  
149 learning. For a detailed review of the PFC functional contribution, we refer readers to recent  
150 reviews (Bradfield & Hart, 2020; Balleine 2019, Coutureau & Parkes 2018, Woon et al 2020).  
151 The acquisition of goal-directed responses requires the dorsomedial prefrontal cortex  
152 (dmPFC; or prelimbic cortex). Instrumental training rapidly induces synaptic plasticity within  
153 the dmPFC (Hart & Balleine 2016) and pre-training, but not post-training, excitotoxic lesions  
154 render the response insensitive to outcome devaluation (Balleine & Dickinson 1998, Corbit &  
155 Balleine, 2003; Killcross & Coutureau 2003, Ostlund & Balleine 2005). This specific role in  
156 the acquisition, but not performance, of goal-directed behaviour has been confirmed using  
157 pharmacological and chemogenetic inactivation, which have also revealed its functional  
158 interaction with thalamic and striatal structures (Alcaraz et al 2018, Hart et al 2018, Tran-Tu-  
159 Yen et al 2009). In addition to acquiring the A-O association, dmPFC is also necessary for  
160 detecting changes in the causal relationship between an action and its associated outcome.  
161 Disruption of this structure results in an inability for the animal to adjust its response when  
162 contingencies are degraded; that is, instrumental contingency degradation is impaired (Corbit  
163 & Balleine 2003, Coutureau et al 2012, Swanson et al 2017).

164 In contrast to dmPFC, several studies using the instrumental outcome devaluation  
165 task have shown that the orbitofrontal cortex (OFC) is not required for the acquisition of goal-  
166 directed actions (Gourley et al 2013, Ostlund & Balleine 2007, Panayi & Killcross 2018,  
167 Parkes et al 2018; Bradfield et al., 2015). Contingency degradation is also unimpaired in rats  
168 with lesions of the medial OFC, although the involvement of the vOFC in degradation  
169 remains unclear. Indeed, while some reports suggest that vOFC may be required to adapt to



170 changes in causal contingencies using a nose-poke response task (Zimmerman et al., 2017;  
171 Whyte et al., 2019), others indicate that vOFC is not required (Zimmerman et al., 2018).  
172 Moreover, the involvement of vOFC in the instrumental contingency degradation paradigms  
173 described in section II has not yet been assessed.

174         However, it appears that vOFC *is* required for goal-directed behaviour when  
175 competing A-O associations exist (e.g., Gremel & Costa, 2013; Gremel et al., 2016; Parkes  
176 et al 2018; Fresno et al., 2019). For example, we chemogenetically inhibited the vOFC while  
177 rats underwent an outcome identity reversal procedure or a procedure in which new  
178 outcomes were associated with familiar actions. We found that vOFC inhibition only impaired  
179 instrumental outcome devaluation if the A-O associations had been unexpectedly modified  
180 (Parkes et al., 2018). Similarly, vOFC inhibition impairs outcome devaluation in mice trained  
181 with two distinct schedules of reinforcement for a single action (Gremel & Costa, 2013;  
182 Gremel et al., 2016). Such training might lead to two different A-O associations for a single  
183 action, which could explain the involvement of vOFC in this version of the outcome  
184 devaluation task. These findings are consistent with current models that propose the OFC  
185 integrates a multitude of information to help disambiguate perceptually similar task state  
186 representations (Bradfield & Hart 2020, Wilson et al 2014). That is, the rodent vOFC might  
187 be crucial for the necessary partition of distinct A-O associations, thus facilitating behavioural  
188 adaptation in changing environments.

189         Nevertheless, it should be noted that, given the demonstrated role of vOFC in  
190 stimulus-guided behaviours (e.g., Gallagher et al. 1999; Pickens et al. 2003, 2005; Ostlund  
191 and Balleine 2007), it remains possible that deficits in goal-directed behaviours following  
192 vOFC inhibition might be attributed to the involvement of stimulus-outcome (S-O)  
193 associations. For instance, while the outcome-identity reversal task used in Parkes et al  
194 (2018) is typically considered action-guided (rather than stimulus-guided), it is possible that  
195 changes in action-outcome identity might require rats to learn about a shift in context or  
196 require S-O systems that are not normally dominant during initial acquisition (West et al.,

197 2013). Additional studies will be required to test whether or not the involvement of vOFC in  
198 goal-directed behaviour can be fully explained by potential S-O associations.

199         To our knowledge, the role of dmPFC in an instrumental outcome-identity reversal  
200 task has not been assessed. Nevertheless, unlike lateral OFC, lesion or inactivation of  
201 dmPFC does not impair performance in a value-based reversal task (Gourley et al 2010;  
202 Dalton et al 2016; Verharen et al 2020). However, interestingly, while Verharen et al (2020)  
203 found no performance impairment, a modelling analysis indicated that inactivation of dmPFC  
204 did alter integration of past positive and negative outcomes. Manning et al (2018) also  
205 observed that impairments in value-based reversal found in a mouse model of compulsive  
206 behavior are correlated to aberrant hyperactivity in the dmPFC. Therefore, under certain  
207 circumstances, dmPFC might be required for adapting to reversal manipulations. Specifically,  
208 the dmPFC might be crucial when attentional load or complexity is increased (Izquierdo et al  
209 2017, Bussey et al 1997). Lesions of dmPFC do impair performance in a three-lever reversal  
210 task (Kosaki & Watanabe, 2012) and damage to the dmPFC also alters performance when  
211 visuospatial cues must be used to guide behaviour (Sharpe & Killcross, 2018, Mukherjee &  
212 Caroni, 2019, Cordova et al 2014, Floresco et al 2008, Young & Shapiro 2009, Shaw et al  
213 2013, Ragozzino et al 1999). Sharpe et al (2019) have therefore proposed that,  
214 complementary to the OFC, the dmPFC might integrate higher-order information to guide  
215 behaviour. While present evidence suggests a similar complementary involvement of these  
216 two regions in our framework, more studies will be necessary to fully uncover the role of  
217 dmPFC in adapting to changes in instrumental outcome identity.

218         Overall, the available evidence indicates that the acquisition of initial A-O  
219 contingencies and adapting to changes in the causal A-O relationship requires the dmPFC  
220 but not the OFC (including both medial OFC and vOFC), although the involvement of vOFC  
221 in instrumental contingency degradation remains unclear. By contrast, adapting to changes  
222 in the A-O that relate to outcome identity may preferentially involve the vOFC rather than the  
223 dmPFC.

224

### 225 **III. Noradrenaline and dopamine differentially innervate the prefrontal cortex**

226 The main source of noradrenaline (NA) in the cortex is the locus coeruleus (LC,  
227 Nieuwenhuys 1985, Ungerstedt 1971; but see Robertson et al., 2013). While these inputs  
228 largely cover all cortical areas, evidence suggests that this innervation is slightly more  
229 significant in the PFC (Chandler et al 2014, Kobayashi et al 1974, Levitt & Moore 1978,  
230 Lindvall et al 1978, but see Morrison et al 1978). Interestingly, cortical innervation appears to  
231 follow two different routes, both originating in the LC (Morrison et al 1979, Morrison et al  
232 1981). Despite these different input trajectories, noradrenergic innervation is uniformly  
233 organised throughout the cortical mantle. Indeed, noradrenergic afferents are observed in all  
234 cortical layers but are denser in the superficial layer I than in deeper layers (Agster et al  
235 2013, Audet et al 1988, Descarries et al 1977, Levitt & Moore 1978). Both superficial and  
236 deep layers are innervated by the same noradrenergic fibres. These fibres pass through  
237 layer VI and, once their target is reached, they progress perpendicularly across the layers.  
238 Finally, the fibres arrive at the more superficial layer I where they are organised along the  
239 medio-lateral plane (Morrison et al 1981, Papadopoulos & Parnavelas 1991). These fibers  
240 contain a high density of varicosities (Agster et al 2013, Cerpa et al 2019) from which NA is  
241 released via synaptic and non-synaptic sites (Beaudet & Descarries 1978, Papadopoulos &  
242 Parnavelas 1991, Seguela et al 1990). Interestingly, varicosity density is significantly higher  
243 in the PFC compared to motor- and sensory-related cortical areas suggesting a greater NA  
244 release in the PFC (Agster et al 2013). Within the PFC, the density of NA fibers appears  
245 lower in the prelimbic cortex (or dmPFC) compared to the lateral OFC, although this  
246 observation was not statistically evaluated (Agster et al 2013).

247 In addition, we have recently studied the rostro-caudal organization of the  
248 noradrenergic innervation within different medial and orbital prefrontal subregions (Cerpa et  
249 al 2019). Our results indicate a particular rostro-caudal organization in the ventral OFC,  
250 which might be the principal entry point of NA afferents within the PFC. Without omitting the  
251 described role of NA in the dmPFC, these findings suggest that the vlOFC might represent  
252 an important target of the noradrenergic system. We also found a higher percentage of

253 varicosities in the anterior lateral OFC (versus the posterior region), which could suggest  
254 higher NA release. This is of particular interest given that functional heterogeneity (Panayi &  
255 Killcross 2018) and differences in connectivity (Barreiros et al 2020) have been reported for  
256 distinct rostro-caudal levels of the lateral OFC. A greater density of varicosities was also  
257 observed in the anterior portion of ventral OFC compared to its posterior region, whereas the  
258 reverse pattern was seen for fibres of passage (Cerpa et al., 2019), suggesting that  
259 functional specificities may also exist along the rostro-caudal axis of ventral OFC.

260         However, it appears that the clearest dissociation could be drawn between medial  
261 OFC and lateral OFC (Lopatina et al 2017; Bradfield & Hart 2020; Izquierdo 2017). The  
262 ventral OFC seems to share functional similarities with both (Izquierdo 2017), although this  
263 might be due to difficulties in selectively targeting the ventral OFC without affecting the  
264 adjacent medial or lateral regions. It should also be noted that anatomical studies have either  
265 grouped ventral OFC with medial OFC, thus dissociating the lateral OFC (Hoover & Vertes  
266 2007, 2011), or grouped the ventral and lateral regions of OFC, thus dissociating the medial  
267 OFC (Heilbronner et al 2016). Ventral OFC may therefore function as a “link” between medial  
268 and lateral parts of the OFC (Izquierdo 2017). In any case, it is very likely that lateral and  
269 ventral OFC, regardless of their (specific) roles might function in a complementary and  
270 coordinated manner. Given that ventral OFC and lateral OFC are not densely interconnected  
271 (Hoover & Vertes, 2011; Murphy & Deutch 2018), neuromodulators, such as noradrenaline,  
272 might support this coordination. An analysis of the influence of NA on neuronal ensembles in  
273 different OFC subregions may be an interesting avenue for future research.

274         LC neurons projecting to different targets are spatially segregated (Waterhouse et al  
275 1983; Schwarz et al 2015) and might differ morphologically (Loughlin et al 1986) and in their  
276 neuropeptidergic content (Simpson et al 1999). While divergent LC neurons exist, their  
277 number appears to be limited and a substantial proportion of LC neurons are biased toward a  
278 single target (Kebschull et al 2016; Plummer et al 2020). Interestingly, neurons projecting to  
279 a single target seem to form a coherent firing ensemble (Totah et al 2018) and some patterns  
280 of input/output relationships are observed in the LC (Schwarz et al 2015, Del Cid-Pellitero &

281 Garzon, 2011). Such specificity seems particularly important in the PFC. Indeed, neurons  
282 projecting to different prefrontal areas are spatially segregated (Chandler et al 2013;  
283 Uematsu et al 2015) and exhibit distinct functional, electrophysiological and molecular  
284 features compared to neurons projecting to other non-cortical areas (Chandler et al 2014;  
285 Uematsu et al 2017; Hirschberg et al 2017). Therefore, modern views have conferred to the  
286 LC a role in targeted and specific modulation (Chandler et al 2019; Likhtek & Johansen,  
287 2019).

288         Several elements differentiate the pattern of noradrenergic versus dopaminergic  
289 innervation of the PFC. First, while noradrenergic fibers are densest in superficial layers,  
290 dopaminergic fibers are more concentrated in deep layers of prefrontal areas anterior to the  
291 genu of corpus callosum (Fallon & Loughlin 1987). Interestingly, it appears that dopaminergic  
292 fibers in superficial and deeper layers have different origins (Berger et al 1991, Descarries et  
293 al 1987). Second, and in rodents only, dopaminergic innervation does not uniformly reach the  
294 entire cortical mantle. Some cortical areas, such as prefrontal areas, exhibit a high density of  
295 dopaminergic fibers, others, such as motor cortices, are mostly devoid of these afferents  
296 (Bentivoglio & Morelli 2005, Berger et al 1991). Of note, dopaminergic innervation in  
297 prefrontal areas, such as the medial PFC (Naneix et al 2012) and the OFC (Hoops et al  
298 2017), increases during adolescence. Moreover, within the PFC, dopaminergic innervation is  
299 not equivalently distributed between areas. Indeed, while the medial PFC receives strong  
300 dopaminergic innervation, the vOFC is much less innervated (Descarries et al 1987, Murphy  
301 & Deutch 2018, Naneix et al 2012, Van Eden et al 1987).

302         Nevertheless, like the LC-NA system, the dopaminergic system organization is well  
303 suited to provide discrete dopaminergic signals to its different targets. Evidence indicates  
304 that different projecting-neurons are topographically organized within the ventral tegmental  
305 area (VTA) and substantia nigra pars compacta (SNc). Thus, the majority of neurons  
306 projecting to a certain PFC area do not collateralize to other subcortical areas (Deniau et al  
307 1980; Fallon 1981; Albanese & Minciacchi, 1983; Beier et al 2015) or to another prefrontal

308 area (Beckstead 1976; Fallon & Moore, 1978; Swanson 1982; Loughlin & Fallon 1984; Sobel  
309 & Corbett, 1984; Lammel et al 2008; Chandler et al 2013).

310 Overall, it appears that OFC contains the most quantitatively unbalanced  
311 catecholaminergic innervation. While noradrenergic fibres are densely present in all  
312 subregions of the OFC, notably in superficial layers, only scarce dopaminergic innervation is  
313 observed. In addition, the density of dopaminergic varicosities is also smaller (Hoops et al  
314 2017) compared to noradrenergic varicosities (Agster et al 2013). This pattern might suggest  
315 a preponderant role for NA in the OFC. By contrast, dopaminergic and noradrenergic  
316 innervation are balanced within the dmPFC, and are most dense in the deep and superficial  
317 layers, respectively. Such patterns might indicate an important interplay between these  
318 neuromodulators within the dmPFC.

#### 319 **IV. DA-mPFC system for adapting to changes in causality**

320 The role of dopamine (DA) in goal-directed actions has been explored in a series of  
321 papers from Naneix and colleagues (Naneix et al 2009, Naneix et al 2012, Naneix et al  
322 2013). Depletion of dopaminergic afferents in the dmPFC using 6-OHDA neurotoxin did not  
323 impede acquisition of instrumental associations or outcome devaluation but contingency  
324 degradation was impaired such that rats failed to decrease responding on the degraded lever  
325 (Naneix et al 2009 but see Lex & Hauber 2010). In addition, infusion of D1/D2 receptors  
326 antagonist, flupenthixol, in the dmPFC during degradation replicated this deficit (Naneix et al  
327 2009). Interestingly, adolescent animals are also unable to show contingency degradation  
328 (Naneix et al 2012). Analysis of the prefrontal dopaminergic innervation maturation indicates  
329 lower dopaminergic fibers density and low DA levels in the dmPFC of adolescent rats.  
330 Moreover, perturbation of normal dopaminergic maturation within the dmPFC during  
331 adolescence renders rats insensitive to contingency degradation at adulthood (Naneix et al  
332 2013). Together, these results indicate that dopaminergic activity in dmPFC is not required  
333 for the initial acquisition of goal-directed actions or outcome-value based choice, but is  
334 essential for adapting to changes in the causal relationship between actions and outcomes.

335 While the role of dopaminergic signalling has been and is still strongly debated, a  
336 classical observation is that DA neurons respond phasically to unexpected reward and  
337 omission (Howe & Dombeck 2016, Saunders et al 2018, Schultz et al 1997, Schultz &  
338 Dickinson 2000). Using fiber photometry on dopaminergic fibers in the dmPFC, Ellwood et al  
339 (2017) found a signal corresponding to a positive, but not negative, reward prediction error.  
340 Unfortunately, similar recordings during an instrumental contingency degradation are lacking,  
341 nevertheless, this procedure is well suited to elicit such signals in the dmPFC when the  
342 animal receives a non-contingent food outcome. Moreover, while global stimulation of VTA  
343 neurons appears to have reinforcing properties (Adamantidis et al 2011, Saunders et al  
344 2018, Steinberg et al 2013), recent findings have suggested that specific dopaminergic VTA-  
345 dmPFC stimulation does not (Ellwood et al 2017, Popescu et al 2016). It has been proposed  
346 that dopaminergic signalling in the dmPFC could facilitate abandoning an outdated strategy  
347 for a new one. In line with this, earlier studies have indicated an important role for dmPFC  
348 DA in switching behavioural strategies (Floresco 2013, Floresco et al 2006, Stefani &  
349 Moghaddam 2006, Winter et al 2009). The dual-state theory of PFC DA function suggests  
350 that DA action on D1 or D2 receptors results in distinct effects on prefrontal networks and,  
351 thus, has distinct functional implications. A D1-state is thought to stabilize PFC networks by  
352 limiting the effect of distracting inputs and promoting persistent activity within a particular  
353 network. Therefore, under this state, PFC representations appear rigid and this might permit  
354 the use of a particular strategy. Whereas under a D2-state, inhibitory influences on PFC  
355 networks are alleviated, which renders representations more labile, and this could allow  
356 disengagement and development of new behavioural strategies (Durstewitz & Seamans  
357 2008, Seamans & Yang 2004).

358 According to this theory, a D2-state might be elicited by a rise of DA, which activates  
359 high-affinity D2 receptors at synaptic clefts, whereas smaller concentrations of DA are  
360 sufficient to maintain a D1-state. These distinct patterns of activation may result in different  
361 behavioural outputs. It is therefore possible that the rise of DA due to an unexpected  
362 outcome during contingency degradation allows a reorganization of the action-outcome

363 representation in the dmPFC and, hence, behavioural adaptation. Specific targeting of D1 or  
364 D2 receptors during contingency degradation would confirm this possibility. Consistent with  
365 this suggestion, the balance of D1 and D2 receptors is disturbed during adolescence, which  
366 might impede adaptations to contingency degradation at this stage of development (Naneix  
367 et al 2012).

368         Moreover, while both receptors can be found on the same neuron, a proportion of  
369 neurons express only one receptor (Gaspar et al 1995, Santana et al 2009, Gee et al 2012).  
370 Functional studies have also demonstrated that dopamine modulation through D1 and D2  
371 receptors might have distinct effects on prefrontal downstream outputs, including the  
372 basolateral amygdala or ventral striatum (Jenni et al., 2017; Vander Weele et al., 2018).  
373 These studies provide evidence for specific DA modulation of PFC efferent pathways,  
374 notably through D1 and D2 receptors, which may lead to distinct behavioural strategies  
375 (Weele et al 2019). It is interesting to note that a high proportion of dorsal striatum-projecting  
376 neurons in the dmPFC contain only D2 receptors (Gaspar et al 1995, Wang & Pickel 2002).  
377 Therefore, DA might have a strong effect on the interaction between dmPFC and pDMS,  
378 specifically during the detection of changes in instrumental contingencies (Yin et al 2005,  
379 Naneix et al 2009, Naneix et al 2013). More specific targeting is necessary to uncover the  
380 exact role of DA in A-O learning and updating.

381         Consistent with the dorso-ventral gradient of dopaminergic innervation observed in  
382 the medial PFC (Naneix et al 2009), its influence is not restricted to the dmPFC. Indeed, DA  
383 plays a role in the vmPFC (infralimbic cortex, area 25) in conditions where behaviour is  
384 habitual, *i.e.* responses are not guided by the representation of the outcome but are stimulus-  
385 triggered. DA infusion in the vmPFC during an outcome devaluation test restores goal-  
386 directed control (Hitchcott et al 2007) and DA appears to act via D2 receptors as D2 agonism  
387 restores sensitivity to contingency degradation (Barker et al 2013), which demonstrates the  
388 importance of the medial PFC as a crucial DA target for action control.

389         Compared to the medial PFC, dopaminergic innervation of the vOFC is scarce.  
390 Nevertheless, abnormal DA levels alter neuronal firing within the OFC (Nimitvilai et al 2017;



391 Homayoun & Moghaddam, 2008). An increase in DOPAC (one DA metabolite) levels in the  
392 OFC is also observed with increasing delays during a delay-discounting task (Winstanley et  
393 al 2006) and DA antagonists injected in OFC decrease impulsive behaviour in ‘high-  
394 impulsive’ individuals (Winstanley et al 2010). OFC D2 receptor antagonism also increases  
395 impulsive choice (Pardey et al 2013). It is possible that DA in OFC acts on reward-delay  
396 evaluation and, therefore, on impulsive behaviour. Consistent with this suggestion, OFC DA  
397 lesions modified rats’ tolerance of delays (Kheramin et al 2004) and DA antagonists in the  
398 OFC reduced animals’ willingness to work in a progressive-ratio task (Cetin et al 2004).  
399 Moreover, Winter et al (2009) used a task in which animals must choose between an  
400 “efficient” lever (*i.e.* requiring few presses to obtain one reward) and a “less-efficient” lever  
401 (*i.e.* requiring many presses for the same reward). After reaching a success criterion, these  
402 assignments were reversed. Successful adaptation to this change was impaired by D1  
403 receptor antagonism in OFC.

404         Therefore, despite its scarce dopaminergic innervation, we cannot rule out an  
405 involvement of DA signalling in the vOFC for action control. Interestingly, human studies  
406 have suggested that activity in midbrain dopamine neurons might influence expectancy  
407 representations in the OFC (Howard & Kahnt 2018), as well as its functional connectivity  
408 (Kahnt & Tobler 2017). Nevertheless, the density of DA innervation in rodent vOFC is lower  
409 and, therefore, we must be cautious with any strict comparison. Of note, our unpublished  
410 observations suggest that, in rodent OFC, the medial subregion might represent the principal  
411 DA recipient. Further studies are required to clarify the involvement of DA in the OFC in  
412 action-outcome learning and updating, however based on the available evidence it appears  
413 that, in rodents, DA plays a more prominent role in the dmPFC. It should also be noted that  
414 lateral OFC is essential for normal error signalling in VTA DA neurons (Takahashi et al 2011,  
415 Takahashi et al 2017). Therefore, it is possible that the crucial flow of information for  
416 updating processes might be from the OFC to the VTA rather than the reverse.

417

418

## 419 **V. NA-OFC system for adapting to changes related to outcome identity**

420 Unlike the dopaminergic system, very little is known about the role of the  
421 noradrenergic system in goal-directed behaviour. However, this system has been widely  
422 implicated in behavioural flexibility and adaptation to changing environments. A number of  
423 studies have used set-shifting tasks assessing aspects of behavioural flexibility in rodents  
424 (Birrell & Brown 2000) and, interestingly, a functional dissociation between dmPFC and OFC  
425 has been established. While the OFC is critical to cope with intradimensional shifts and  
426 reversals, the dmPFC is crucial for extradimensional shifts (Birrell & Brown 2000, Chase et al  
427 2012), and both require noradrenergic signalling. In the dmPFC, depletion (McGaughy et al  
428 2008, Newman et al 2008) and chemogenetic inactivation of LC inputs (Cope et al 2019)  
429 replicate lesion impairments, whereas pharmacological treatments increasing NA levels  
430 counteract such deleterious effects (Newman et al 2008), perhaps via alpha1 receptors in the  
431 dmPFC (Lapiz & Morilak 2006). Depletion of noradrenergic afferents in the OFC also leads to  
432 deficits akin to those induced by lesions (Mokler et al 2017). Interestingly, young rats  
433 exhibited similar deficits to those found in adult rats with OFC and dmPFC lesions (Mokler et  
434 al 2017). An analysis of the NA innervation ontogenesis has revealed that noradrenergic fiber  
435 density does not change during development. However, in young rats, high levels of the  
436 noradrenergic-transporter (NET) are found in OFC and dmPFC and these NET levels  
437 decrease until adulthood (Bradshaw et al 2016). A high density of NET during adolescence  
438 might indicate a low level of available NA in these areas and, thus, explain the observed  
439 deficits.

440 The role of noradrenergic signalling in behavioural flexibility has also been elaborated  
441 based on the properties of LC responses. Indeed, LC neurons respond phasically to an  
442 expected food delivery but rapidly shift their response to a stimulus predicting this food  
443 outcome (Aston-Jones et al 1994). Similar findings have been found in rodents such that,  
444 early in training, LC neurons respond heavily to a food-predictive stimulus (CS+) while they  
445 do not respond to a non-predictive stimulus (Bouret & Sara 2004, Sara & Segal 1991).  
446 Detailed analysis of these responses showed that they are tightly related to the correct

447 behavioural response following the CS+ (e.g., 'go' response) and are absent after an  
448 erroneous behavioural response following a non-predictive stimulus (Bouret & Sara 2004).  
449 Furthermore, if these stimuli-outcome associations are reversed, LC neurons stop  
450 responding after the previous predictive stimulus and start responding after the new one  
451 (Aston-Jones et al 1997, Sara & Segal 1991). Strikingly, this neuronal adaptation always  
452 precedes similar adaptations in LC forebrain targets. LC adapted responses also appear  
453 before changes at the behavioural level indicating that noradrenergic activity plays a  
454 prominent role in the behavioural adaptation to changes in the environment (Bouret & Sara  
455 2004).

456 In an influential proposal, Bouret and Sara (2005) hypothesized that these  
457 behavioural adaptations could be the result of neural network modulation by NA.  
458 Noradrenergic signals might act in prefrontal targets by signalling a meaningful stimulus, and  
459 thus provoking a network reorganization that accounts for behavioural changes (Sara &  
460 Bouret 2012). This noradrenergic signalling seems to be strongly influenced by  
461 environmental uncertainty. For instance, the more rarely the CS+ is presented, the stronger  
462 the LC response to that CS (Aston-Jones et al 1994). LC phasic responses can also be  
463 observed after illumination of a light signalling trial start and may elicit an orienting response  
464 from the animal (Bouret & Sara 2004). Moreover, while LC responses after reward delivery  
465 rapidly switch to the stimulus period, LC responses can reappear, transiently, at reward  
466 delivery in some circumstances. Indeed, the LC responds to reward when new CSs are  
467 introduced, when a reversal occurs, or when reward is reintroduced after previous extinction  
468 (Bouret & Sara 2004). Therefore, NA signalling appears to be triggered by unpredicted but  
469 relevant stimuli and, by this means, could influence behaviour.

470 Such a role for NA has been described by Yu and Dayan who proposed that NA  
471 signals uncertainty as a result of unexpected events in a task (Dayan & Yu 2006, Yu &  
472 Dayan 2005). Giving an interpretation very close to the network-reset signal, the authors  
473 proposed that this NA signal interrupts ongoing cognitive processes to integrate new  
474 unexpected observations from a changing environment. Studies in humans have used pupil

475 size changes as an indirect, although not specific, measure of LC activity (de Gee et al 2017,  
476 Joshi et al 2016). An increase in pupil diameter has been shown to reflect surprise or  
477 unexpected uncertainty in predictive-inference tasks, which is crucial for belief updating  
478 (Nassar et al 2012, Preuschoff et al 2011). In addition, this process has been causally linked  
479 to noradrenergic activity using systemic injection of an adrenergic receptor antagonist  
480 (Jepma et al 2018). Whether an interrupting signal or a resetting signal, both views confer  
481 the NA with the ability to reconfigure brain activity. In humans, an example of such  
482 reconfiguration might occur in a frontoparietal network, including the ventral PFC, which  
483 could be crucial to redirect attention to a salient and unexpected stimulus (Corbetta et al  
484 2008, Corbetta & Shulman 2002).

485         While these previous studies have focused on the involvement of NA signalling in  
486 stimulus-guided behaviours, we propose that LC-derived NA signalling may be tied not only  
487 to stimulus-outcome (Pavlovian) behaviours but also to action-outcome (goal-directed)  
488 behaviours. That is, we hypothesise that NA signalling in the OFC is required for learning  
489 about new outcomes *per se*, regardless of whether those outcomes are predicted by  
490 Pavlovian stimuli or earned via instrumental responding. It has already been proposed that  
491 noradrenergic signalling in the lateral OFC might allow flexible integration of changes in the  
492 environment during stimulus-guided behaviour (Sadacca et al 2016) and, while the role of  
493 noradrenergic signalling in instrumental behaviours has received little attention, our recent  
494 findings do introduce unexpected events as a key element for the OFC's involvement in goal-  
495 directed behaviour (Parkes et al 2018) and, critically, we also recently obtained preliminary  
496 data that NA depletion in vOFC, but not dmPFC, impairs performance on an instrumental  
497 outcome identity reversal task (Cerpa et al 2018). A recent study has also suggested that  
498 noradrenergic signalling arising from an unexpected outcome might modify inferred choice  
499 representation decoded in the human OFC (Muller et al 2019).

500         Therefore, we believe that noradrenergic signalling might be a crucial component for  
501 action-guided learning. As such, we argue that noradrenergic signalling permits behavioural  
502 adaptation in response to value-based *and* identity-based modifications. Specifically, we

503 propose that noradrenergic signalling in the vOFC may be required to associate new  
504 outcomes to already acquired actions. We can imagine that (initially) during outcome identity  
505 reversal, the animal's expectation is mismatched to the actual received outcome. If this is the  
506 case, one would predict an increase in LC responses and NA release in the OFC. This  
507 prediction could be tested using the recently developed fluorescent NA biosensor (Feng et al  
508 2019), which has been successfully used to detect NA release in the medial PFC (Kjaerby et  
509 al 2020). Selective neurotoxins (McGaughy et al 2008, Milstein et al 2007) as well as  
510 development of viral-based targeting of noradrenergic pathways (Cerpa et al 2020, Hayat et  
511 al 2020, Hirschberg et al 2017, Uematsu et al 2017) will also allow causal assessment of the  
512 NA signalling in the vOFC in updating action-outcome associations.

513         While the OFC constitutes an ideal noradrenergic target for adaptation to a change in  
514 action-outcome associations, previous findings have also claimed that NA in the dmPFC  
515 plays a crucial role in mnemonic processes (Robbins & Arnsten 2009). Indeed, pharmacological  
516 manipulations have implicated noradrenergic receptors in the mPFC (and primate  
517 dorsolateral PFC) in working memory (Arnsten 2000; Ramos et al 2005, 2006; Wang et al  
518 2007). Other processes, such as consolidation, recall, (Tronel et al 2004, Eschenko et al  
519 2012) and strategy adaptation (Tervo et al 2014), notably in a set-shifting task (McGaughy et  
520 al 2008, Newman et al 2008; Cope et al 2019), also appear to depend on NA in the dmPFC.  
521 In addition, LC projections to the vmPFC are involved in the acquisition and recall of fear  
522 extinction (Mueller et al 2008; Uematsu et al 2017). Consistent with a role in behavioural  
523 flexibility, LC neurons respond when a reward is unexpected and this influences activity in  
524 dmPFC neurons (Bouret & Sara 2004). Interestingly, another aspect of the dmPFC role in  
525 action control is to shape behaviour based on contextual cues available in the environment  
526 (Moorman & Aston-Jones 2015, Sharpe & Killcross 2014, Sharpe et al 2019). In the late 70s,  
527 Mason and Iversen (1978) demonstrated an impaired ability to use contextual cues to build  
528 behaviour following lesion of the noradrenergic dorsal bundle in rats. Critically, this  
529 manipulation had a larger impact on NA levels in the 'cortex'. While it is not possible to infer a

530 role specific to the dmPFC based on these results, further studies might shed new light on  
531 the noradrenergic modulation in the dmPFC for this function.

532 Overall, while we propose that NA signalling in vOFC is required for adapting to  
533 changes in outcome identity, at this stage, we cannot fully exclude a role for NA in dmPFC-  
534 dependent adaptation to changes in instrumental contingencies. However, van der Meulen et  
535 al (2007) were unable to detect any change in NA levels in the medial wall of the PFC after  
536 instrumental contingency modification, but a rise in DA levels was observed. Also, as  
537 previously mentioned, our preliminary results suggest that NA signalling in dmPFC is not  
538 required for A-O updating in an instrumental outcome identity reversal task (Cerpa et al.,  
539 2018). Nevertheless, understanding the conditions under which NA or DA (or both) intervene  
540 in the dmPFC is an important avenue for future studies.

#### 541 **VI. Other neuromodulatory systems**

542 In the previous sections, we have focused on the dopaminergic and noradrenergic  
543 modulation of PFC. However, other neuromodulators, including serotonin and acetylcholine,  
544 also exert strong effects on PFC. Serotonergic neurons in the PFC mainly originate from  
545 dorsal raphe (DR) nucleus (Hoover & Vertes 2007, Murphy & Deutch 2018) and strongly  
546 innervate superficial and deep layers in the PFC (Linley et al 2013). Similarly to NA and DA,  
547 serotonin neurons preferentially terminate in one prefrontal area and very few neurons  
548 collateralize between medial PFC and OFC, suggesting again a possible specific modulation  
549 of their functions (Chandler et al 2013). Serotonin has been previously proposed as an  
550 important neuromodulator in the OFC (Roberts 2011) and disruption of serotonergic activity  
551 and availability, mainly in the OFC, disrupts performance in reversal paradigms in rodents  
552 (Lapiz-Bluhm et al 2009, Masaki et al 2006) and primates (Clarke et al 2007). Fibre  
553 photometry on OFC-projecting DR neurons also revealed an activation of these neurons  
554 before a lever press and at reward consumption (Ren et al 2018). Moreover, it was shown  
555 that systemic administration of a serotonin 1B agonist impairs performance in an  
556 instrumental outcome devaluation task without disrupting the acquisition of the instrumental  
557 response (Corbit et al 2019), suggesting a role for these receptors in encoding the specific

558 features of reward (Corbit et al 2019). It has not yet been assessed if serotonin agonism also  
559 disrupts instrumental contingency degradation or outcome identity reversal. Moreover,  
560 whether or not the observed impairment in outcome devaluation is due to serotonergic  
561 modulation of PFC remains to be determined.

562 In contrast to serotonergic neurons, cholinergic neurons are less compacted and are  
563 found in nuclei distributed along the basal forebrain. Neurons from these different nuclei  
564 innervate the PFC, and other cortical areas, via separated routes (Bloem et al 2014).  
565 Interestingly, neurons from one of these nuclei, nucleus basalis, mainly collateralize to  
566 innervate the different prefrontal areas (Chandler et al 2013). Therefore, it is possible that  
567 cholinergic activity might have a global influence in the PFC. Cholinergic interneurons  
568 (ChAT+) regulating excitation of other interneurons and pyramidal neurons are also found in  
569 the mPFC of rodents (Granger et al 2020, Obermayer et al 2019) and might provide a finer  
570 cholinergic modulation within the PFC. Outside of the PFC, ChAT+ neurons in the posterior  
571 dorsomedial striatum (pDMS) have been implicated in goal-directed behaviour but only after  
572 changes in the action-outcome contingency (Bradfield et al., 2013; Matamales et al., 2016).  
573 Specifically, removing the excitatory input from the parafascicular thalamus to ChAT+  
574 neurons in pDMS has no effect on initial goal-directed learning but does impair contingency  
575 degradation and outcome identity reversal (Bradfield et al., 2013).

576 Overall, in addition to DA and NA, there is clear evidence that both the serotonergic and  
577 cholinergic systems also play a role in goal-directed behaviours. Nevertheless, additional  
578 work is required to understand their contribution to this behaviour, particularly at the level of  
579 PFC subregions. We hope that future studies will elucidate the respective role of these  
580 different neuromodulators in action control.

## 581 **VII. Concluding remarks**

582 Adaptation to environmental changes is the core of goal-directed behaviour. To cope  
583 with these changes, current evidence highlights the importance of distinct PFC areas, such  
584 as the dmPFC and the OFC. Here, we have argued that dopaminergic modulation in the  
585 dmPFC and noradrenergic modulation in the vOFC may underlie distinct processes related

586 to updating one's actions. Specifically, we propose that while dopaminergic activity within the  
587 mPFC is required for encoding changes in action causality, adapting to changes in outcome  
588 identity requires noradrenergic modulation of the lateral OFC (see Figure 2). Several lines of  
589 evidence support this hypothesis. First, it is well established that the dmPFC is required  
590 during initial acquisition of A-O associations and to detect a degradation of this association.  
591 By contrast, the medial and ventrolateral regions of OFC do not appear to be required for  
592 either of these learning processes. Although, it should be noted that studies assessing the  
593 effect of vOFC inhibition on instrumental contingency degradation are lacking and those that  
594 do exist have produced mixed results. Nevertheless, we and others have recently shown that  
595 the OFC *is* required for other associative processes underlying goal-directed behaviour. The  
596 medial OFC is necessary to retrieve a representation of the instrumental outcome, whereas  
597 ventral and lateral regions of OFC appear to track changes in A-O associations that relate to  
598 outcome identity. Specifically, rats with vOFC inhibition appear unable to segregate multiple  
599 A-O associations, which might result from a weaker representation of outcome features that  
600 render rats unable to form (or distinguish between) distinct learning experiences (Wilson et  
601 al., 2014).

602         Second, both dmPFC and OFC areas are under the strong influence of  
603 neuromodulatory systems, including dopamine and noradrenaline. Importantly, while NA  
604 innervation across the medial PFC and orbitofrontal cortex is relatively uniform, DA  
605 innervation is greater in dmPFC than vOFC. Consistent with the prominent dopaminergic  
606 innervation of the medial wall of the PFC, DA in the dmPFC is crucial for goal-directed  
607 behaviour. Specifically, depletion of DA in mPFC impairs instrumental contingency  
608 degradation but leaves outcome devaluation intact (Naneix et al., 2009). By contrast, at  
609 present, very little is known about the role of NA in action control. Nevertheless, the vOFC  
610 appears to be a particularly important NA target and we argue that NA signalling in vOFC,  
611 but not dmPFC, plays a specific role in adapting to changes in outcome identity (Cerpa et al.,  
612 2018). Noradrenergic signalling in the vOFC has already been proposed as a mechanism to  
613 allow flexible integration of changes in the environment related to stimulus-guided behaviours



614 (Sadacca et al 2016). Here, we propose a similar mechanism underlying outcome-related  
615 changes in action-guided behaviour. That is, noradrenergic signalling supports behavioural  
616 adaptation in response to value-based *and* identity-based modifications.

617         While the investigation of noradrenergic modulation in the vIOFC is an exciting goal  
618 for future studies, we do not exclude a role for NA in the dmPFC in goal-directed behaviour.  
619 Rather, we believe that systematic, well-controlled studies are necessary to reveal the  
620 potential role of NA, as well as DA, in these different prefrontal subareas. Moreover, while  
621 NA modulation appears to be region-specific, reports indicate that the LC-NA system could  
622 act on broad, yet functionally pertinent, brain networks in rodents (Barsegyan et al 2019,  
623 Plummer et al 2020, Zerbi et al 2019) and humans (Hermans et al 2011). It is therefore  
624 possible that NA does not act exclusively on the OFC (or the dmPFC) and future studies  
625 would need to identify broader circuits (including striatal and thalamic structures) on which  
626 NA could act simultaneously. Indeed, we believe that direct comparisons at the level of  
627 structure and neuromodulatory systems are required to better understand how the  
628 neuromodulation of distinct prefrontal areas contributes to the various learning processes  
629 underlying goal-directed behaviour.

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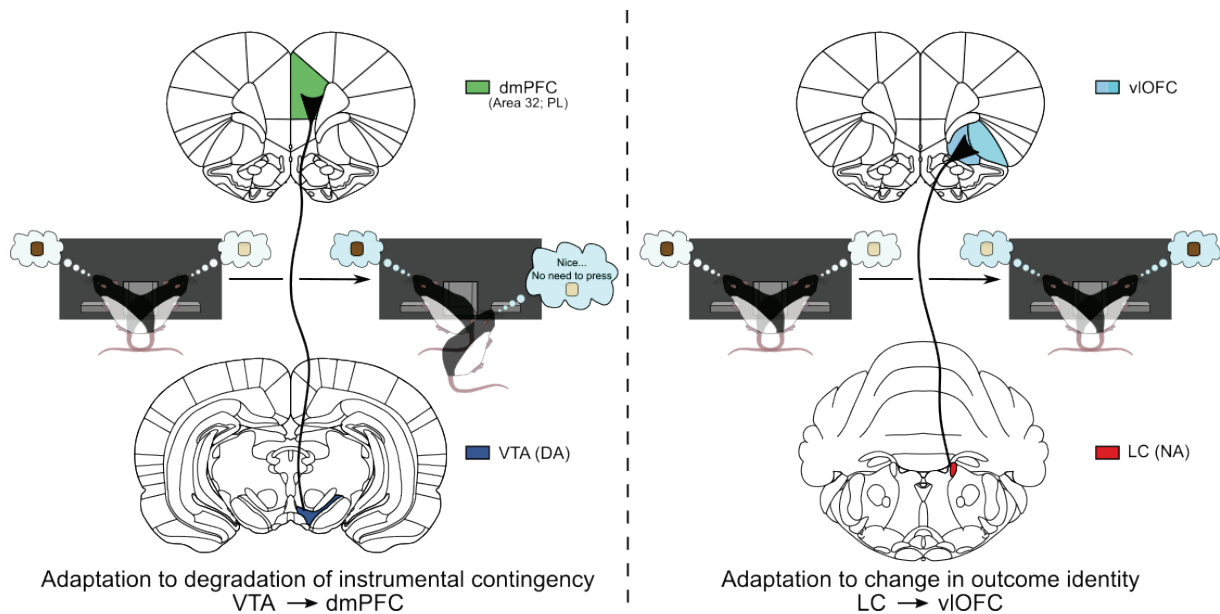
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645 **Figure 2.** We propose a complementary involvement of the medial and orbitofrontal cortices  
 646 in adapting to changes in action-outcome associations. Specific neuromodulatory pathways  
 647 are well positioned to modulate the activity and functions of these cortical areas. The  
 648 available evidence suggests that dopaminergic activity within the dmPFC is required for  
 649 encoding causality-related changes in the action-outcome relationship (left panel) whereas  
 650 adapting to changes in outcome identity may require noradrenergic modulation of the vOFC  
 651 (right panel). dmPFC: dorsomedial prefrontal cortex; PL: prelimbic cortex; VTA: ventral  
 652 tegmental area; DA: dopamine; LC: locus coeruleus; NA: noradrenaline; vOFC: ventral and  
 653 lateral regions of OFC.

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## 655 References

- 656 Adamantidis, A. R., Tsai, H. C., Boutrel, B., Zhang, F., Stuber, G. D., Budygin, E. A., . . . de  
 657 Lecea, L. (2011). Optogenetic interrogation of dopaminergic modulation of the  
 658 multiple phases of reward-seeking behavior. *J Neurosci*, *31*(30), 10829-10835.  
 659 doi:10.1523/JNEUROSCI.2246-11.2011
- 660 Agster, K. L., Mejias-Aponte, C. A., Clark, B. D., & Waterhouse, B. D. (2013). Evidence for a  
 661 regional specificity in the density and distribution of noradrenergic varicosities in rat  
 662 cortex. *J Comp Neurol*, *521*(10), 2195-2207. doi:10.1002/cne.23270
- 663 Albanese, A., & Minciacchi, D. (1983). Organization of the ascending projections from the  
 664 ventral tegmental area: a multiple fluorescent retrograde tracer study in the rat. *J  
 665 Comp Neurol*, *216*(4), 406-420. doi:10.1002/cne.902160406
- 666 Alcaraz, F., Fresno, V., Marchand, A. R., Kremer, E. J., Coutureau, E., & Wolff, M. (2018).  
 667 Thalamocortical and corticothalamic pathways differentially contribute to goal-directed  
 668 behaviors in the rat. *Elife*, *7*. doi:10.7554/eLife.32517
- 669 Arnsten, A. F. (2000). Through the looking glass: differential noradrenergic modulation of  
 670 prefrontal cortical function. *Neural Plast*, *7*(1-2), 133-146. doi:10.1155/NP.2000.133
- 671 Aston-Jones, G., Rajkowski, J., & Kubiak, P. (1997). Conditioned responses of monkey locus  
 672 coeruleus neurons anticipate acquisition of discriminative behavior in a vigilance task.  
 673 *Neuroscience*, *80*(3), 697-715. doi:10.1016/s0306-4522(97)00060-2
- 674 Aston-Jones, G., Rajkowski, J., Kubiak, P., & Alexinsky, T. (1994). Locus coeruleus neurons  
 675 in monkey are selectively activated by attended cues in a vigilance task. *J Neurosci*,  
 676 *14*(7), 4467-4480. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/8027789>

677 Audet, M. A., Doucet, G., Oleskevich, S., & Descarries, L. (1988). Quantified regional and  
678 laminar distribution of the noradrenaline innervation in the anterior half of the adult rat  
679 cerebral cortex. *J Comp Neurol*, 274(3), 307-318. doi:10.1002/cne.902740302

680 Balleine, B. W. (2019). The Meaning of Behavior: Discriminating Reflex and Volition in the  
681 Brain. *Neuron*, 104(1), 47-62. doi:10.1016/j.neuron.2019.09.024

682 Balleine, B. W., & Dickinson, A. (1998). Goal-directed instrumental action: contingency and  
683 incentive learning and their cortical substrates. *Neuropharmacology*, 37(4-5), 407-  
684 419. doi:10.1016/s0028-3908(98)00033-1

685 Barker, J. M., Torregrossa, M. M., & Taylor, J. R. (2013). Bidirectional modulation of  
686 infralimbic dopamine D1 and D2 receptor activity regulates flexible reward seeking.  
687 *Front Neurosci*, 7, 126. doi:10.3389/fnins.2013.00126

688 Barreiros, I. V., Panayi, M. C., & Walton, M. E. (2020). Organisation of afferents along the  
689 anterior-posterior and medial-lateral axes of the rat OFC. *BioRxiv*.  
690 doi:https://doi.org/10.1101/2020.08.28.272591

691 Barsegyan, A., Mirone, G., Ronzoni, G., Guo, C., Song, Q., van Kuppeveld, D., . . .  
692 Roozendaal, B. (2019). Glucocorticoid enhancement of recognition memory via  
693 basolateral amygdala-driven facilitation of prelimbic cortex interactions. *Proc Natl  
694 Acad Sci U S A*, 116(14), 7077-7082. doi:10.1073/pnas.1901513116

695 Beaudet, A., & Descarries, L. (1978). The monoamine innervation of rat cerebral cortex:  
696 synaptic and nonsynaptic axon terminals. *Neuroscience*, 3(10), 851-860.  
697 doi:10.1016/0306-4522(78)90115-x

698 Beckstead, R. M. (1976). Convergent thalamic and mesencephalic projections to the anterior  
699 medial cortex in the rat. *J Comp Neurol*, 166(4), 403-416.  
700 doi:10.1002/cne.901660403

701 Behrens, T. E. J., Muller, T. H., Whittington, J. C. R., Mark, S., Baram, A. B., Stachenfeld, K.  
702 L., & Kurth-Nelson, Z. (2018). What Is a Cognitive Map? Organizing Knowledge for  
703 Flexible Behavior. *Neuron*, 100(2), 490-509. doi:10.1016/j.neuron.2018.10.002

704 Beier, K. T., Steinberg, E. E., DeLoach, K. E., Xie, S., Miyamichi, K., Schwarz, L., . . . Luo, L.  
705 (2015). Circuit Architecture of VTA Dopamine Neurons Revealed by Systematic  
706 Input-Output Mapping. *Cell*, 162(3), 622-634. doi:10.1016/j.cell.2015.07.015

707 Bentivoglio, M., & Morelli, M. (2005). The organization and circuits of mesencephalic  
708 dopaminergic neurons and the distribution of dopamine receptors in the brain. In S. B.  
709 Dunnett, M. Bentivoglio, A. Bjorklund, & T. Hokfelt (Eds.), *Handbook of Chemical  
710 Neuroanatomy* (Vol. 21, pp. 1-107): Elsevier.

711 Berger, B., Gaspar, P., & Verney, C. (1991). Dopaminergic innervation of the cerebral cortex:  
712 unexpected differences between rodents and primates. *Trends Neurosci*, 14(1), 21-  
713 27. doi:10.1016/0166-2236(91)90179-x

714 Birrell, J. M., & Brown, V. J. (2000). Medial frontal cortex mediates perceptual attentional set  
715 shifting in the rat. *J Neurosci*, 20(11), 4320-4324. Retrieved from  
716 https://www.ncbi.nlm.nih.gov/pubmed/10818167

717 Bloem, B., Schoppink, L., Rotaru, D. C., Faiz, A., Hendriks, P., Mansvelder, H. D., . . .  
718 Wouterlood, F. G. (2014). Topographic mapping between basal forebrain cholinergic  
719 neurons and the medial prefrontal cortex in mice. *J Neurosci*, 34(49), 16234-16246.  
720 doi:10.1523/JNEUROSCI.3011-14.2014

721 Bouret, S., & Sara, S. J. (2004). Reward expectation, orientation of attention and locus  
722 coeruleus-medial frontal cortex interplay during learning. 20(3), 791-802. Retrieved  
723 from Sara, SJ: sjsara@ccr.jussieu.fr

724 Bouret, S., & Sara, S. J. (2005). Network reset: a simplified overarching theory of locus  
725 coeruleus noradrenaline function. *Trends Neurosci*, 28(11), 574-582.  
726 doi:10.1016/j.tins.2005.09.002

727 Bradfield, L. A., & Balleine, B. W. (2017). Thalamic Control of Dorsomedial Striatum  
728 Regulates Internal State to Guide Goal-Directed Action Selection. *J Neurosci*, 37(13),  
729 3721-3733. doi:10.1523/JNEUROSCI.3860-16.2017

730 Bradfield, L. A., Bertran-Gonzalez, J., Chieng, B., & Balleine, B. W. (2013). The  
731 thalamostriatal pathway and cholinergic control of goal-directed action: interlacing

732 new with existing learning in the striatum. *Neuron*, 79(1), 153-166.  
733 doi:10.1016/j.neuron.2013.04.039

734 Bradfield, L. A., Dezfouli, A., van Holstein, M., Chieng, B., & Balleine, B. W. (2015). Medial  
735 Orbitofrontal Cortex Mediates Outcome Retrieval in Partially Observable Task  
736 Situations. *Neuron*, 88(6), 1268-1280. doi:10.1016/j.neuron.2015.10.044

737 Bradfield, L. A., & Hart, G. (2020). Rodent medial and lateral orbitofrontal cortices represent  
738 unique components of cognitive maps of task space. *Neurosci Biobehav Rev*, 108,  
739 287-294. doi:10.1016/j.neubiorev.2019.11.009

740 Bradfield, L. A., Hart, G., & Balleine, B. W. (2018). Inferring action-dependent outcome  
741 representations depends on anterior but not posterior medial orbitofrontal cortex.  
742 *Neurobiol Learn Mem*. doi:10.1016/j.nlm.2018.09.008

743 Bradshaw, S. E., Agster, K. L., Waterhouse, B. D., & McGaughy, J. A. (2016). Age-related  
744 changes in prefrontal norepinephrine transporter density: The basis for improved  
745 cognitive flexibility after low doses of atomoxetine in adolescent rats. *Brain Res*,  
746 1641(Pt B), 245-257. doi:10.1016/j.brainres.2016.01.001

747 Bussey, T. J., Muir, J. L., Everitt, B. J., & Robbins, T. W. (1997). Triple dissociation of  
748 anterior cingulate, posterior cingulate, and medial frontal cortices on visual  
749 discrimination tasks using a touchscreen testing procedure for the rat. *Behav*  
750 *Neurosci*, 111(5), 920-936. doi:10.1037//0735-7044.111.5.920

751 Cerpa, J. C., Marchand, A. R., & Coutureau, E. (2019). Distinct regional patterns in  
752 noradrenergic innervation of the rat prefrontal cortex. *J Chem Neuroanat*, 96, 102-  
753 109. doi:10.1016/j.jchemneu.2019.01.002

754 Cerpa, J. C., Marchand, A. R., Salafranke, Y., Pape, J. R., Kremer, E. J., & Coutureau, E.  
755 (2020). Targeting Catecholaminergic Systems in Transgenic Rats With a CAV-2  
756 Vector Harboring a Cre-Dependent DREADD Cassette. *Front Mol Neurosci*, 13, 121.  
757 doi:10.3389/fnmol.2020.00121

758 Cerpa, J. C., Marchand, A. R., Wolff, M., Parkes, S. L., & Coutureau, E. (2018).  
759 *Noradrenergic modulation of the orbitofrontal cortex mediates flexibility of goal-*  
760 *directed behavior*. Program No. 325.09. 2018 Neuroscience Meeting Planner. San  
761 Diego, CA: Society for Neuroscience, 2018. Online.

762 Cetin, T., Freudenberg, F., Fuchtemeier, M., & Koch, M. (2004). Dopamine in the  
763 orbitofrontal cortex regulates operant responding under a progressive ratio of  
764 reinforcement in rats. *Neurosci Lett*, 370(2-3), 114-117.  
765 doi:10.1016/j.neulet.2004.08.002

766 Chandler, D. J., Gao, W. J., & Waterhouse, B. D. (2014). Heterogeneous organization of the  
767 locus coeruleus projections to prefrontal and motor cortices. *Proc Natl Acad Sci U S*  
768 *A*, 111(18), 6816-6821. doi:10.1073/pnas.1320827111

769 Chandler, D. J., Jensen, P., McCall, J. G., Pickering, A. E., Schwarz, L. A., & Totah, N. K.  
770 (2019). Redefining Noradrenergic Neuromodulation of Behavior: Impacts of a  
771 Modular Locus Coeruleus Architecture. *J Neurosci*, 39(42), 8239-8249.  
772 doi:10.1523/JNEUROSCI.1164-19.2019

773 Chandler, D. J., Lamperski, C. S., & Waterhouse, B. D. (2013). Identification and distribution  
774 of projections from monoaminergic and cholinergic nuclei to functionally differentiated  
775 subregions of prefrontal cortex. *Brain Res*, 1522, 38-58.  
776 doi:10.1016/j.brainres.2013.04.057

777 Chase, E. A., Tait, D. S., & Brown, V. J. (2012). Lesions of the orbital prefrontal cortex impair  
778 the formation of attentional set in rats. *Eur J Neurosci*, 36(3), 2368-2375.  
779 doi:10.1111/j.1460-9568.2012.08141.x

780 Clarke, H. F., Walker, S. C., Dalley, J. W., Robbins, T. W., & Roberts, A. C. (2007). Cognitive  
781 inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically  
782 specific. *Cereb Cortex*, 17(1), 18-27. doi:10.1093/cercor/bhj120

783 Colwill, R. M., & Rescorla, R. A. (1986). Associative structures in instrumental learning. In  
784 (Vol. 20, pp. 55-104). New York: Academic Press.

785 Cope, Z. A., Vazey, E. M., Floresco, S. B., & Aston Jones, G. S. (2019). DREADD-mediated  
786 modulation of locus coeruleus inputs to mPFC improves strategy set-shifting.  
787 *Neurobiol Learn Mem*, *161*, 1-11. doi:10.1016/j.nlm.2019.02.009

788 Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain:  
789 from environment to theory of mind. *Neuron*, *58*(3), 306-324.  
790 doi:10.1016/j.neuron.2008.04.017

791 Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention  
792 in the brain. *Nat Rev Neurosci*, *3*(3), 201-215. doi:10.1038/nrn755

793 Corbit, L., Kendig, M., & Moul, C. (2019). The role of serotonin 1B in the representation of  
794 outcomes. *Sci Rep*, *9*(1), 2497. doi:10.1038/s41598-019-38938-4

795 Corbit, L. H., & Balleine, B. W. (2003). The role of prelimbic cortex in instrumental  
796 conditioning. *Behav Brain Res*, *146*(1-2), 145-157. Retrieved from  
797 <https://www.ncbi.nlm.nih.gov/pubmed/14643467>

798 Cordova, C. A., Jackson, D., Langdon, K. D., Hewlett, K. A., & Corbett, D. (2014). Impaired  
799 executive function following ischemic stroke in the rat medial prefrontal cortex. *Behav*  
800 *Brain Res*, *258*, 106-111. doi:10.1016/j.bbr.2013.10.022

801 Coutureau, E., Esclassan, F., Di Scala, G., & Marchand, A. R. (2012). The role of the rat  
802 medial prefrontal cortex in adapting to changes in instrumental contingency. *PLoS*  
803 *One*, *7*(4), e33302. doi:10.1371/journal.pone.0033302

804 Coutureau, E., & Parkes, S. L. (2018). Cortical Determinants of Goal-Directed Behavior. In R.  
805 Morris, A. Bornstein, & A. Shenhav (Eds.), *Goal-Directed Decision Making* (pp. 179-  
806 197): Academic Press.

807 Dalley, J. W., Cardinal, R. N., & Robbins, T. W. (2004). Prefrontal executive and cognitive  
808 functions in rodents: neural and neurochemical substrates. *Neurosci Biobehav Rev*,  
809 *28*(7), 771-784. Retrieved from D:\W3\Articles  
810 téléchargés\PDF\ D\Dalley\_NBBR\_2004\_PfcRatReview.pdf  
811 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15555683)  
812 [\\_uids=15555683](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15555683)

813 Dalton, G. L., Wang, N. Y., Phillips, A. G., & Floresco, S. B. (2016). Multifaceted  
814 Contributions by Different Regions of the Orbitofrontal and Medial Prefrontal Cortex to  
815 Probabilistic Reversal Learning. *J Neurosci*, *36*(6), 1996-2006.  
816 doi:10.1523/JNEUROSCI.3366-15.2016

817 Dayan, P., & Yu, A. J. (2006). Phasic norepinephrine: a neural interrupt signal for  
818 unexpected events. *Network*, *17*(4), 335-350. doi:10.1080/09548980601004024

819 de Gee, J. W., Colizoli, O., Kloosterman, N. A., Knapen, T., Nieuwenhuis, S., & Donner, T. H.  
820 (2017). Dynamic modulation of decision biases by brainstem arousal systems. *Elife*,  
821 *6*. doi:10.7554/eLife.23232

822 de Wit, S., & Dickinson, A. (2009). Associative theories of goal-directed behaviour: a case for  
823 animal-human translational models. *Psychol Res*, *73*(4), 463-476.  
824 doi:10.1007/s00426-009-0230-6

825 Del Cid-Pellitero, E., & Garzon, M. (2011). Hypocretin1/OrexinA-containing axons innervate  
826 locus coeruleus neurons that project to the Rat medial prefrontal cortex. Implication in  
827 the sleep-wakefulness cycle and cortical activation. *Synapse*, *65*(9), 843-857.  
828 doi:10.1002/syn.20912

829 Deniau, J. M., Thierry, A. M., & Feger, J. (1980). Electrophysiological identification of  
830 mesencephalic ventromedial tegmental (VMT) neurons projecting to the frontal  
831 cortex, septum and nucleus accumbens. *Brain Res*, *189*(2), 315-326.  
832 doi:10.1016/0006-8993(80)90093-1

833 Descarries, L., Lemay, B., Doucet, G., & Berger, B. (1987). Regional and laminar density of  
834 the dopamine innervation in adult rat cerebral cortex. *Neuroscience*, *21*(3), 807-824.  
835 Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/3627435>

836 Descarries, L., Watkins, K. C., & Lapierre, Y. (1977). Noradrenergic axon terminals in the  
837 cerebral cortex of rat. III. Topometric ultrastructural analysis. *Brain Res*, *133*(2), 197-  
838 222. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/902092>

- 839 Dickinson, A. (1985). Actions and habits: the development of behavioural anatomy.  
840 *Philosophical Transactions of The Royal Society B*, 308(1135), 67-78.  
841 doi:<https://doi.org/10.1098/rstb.1985.0010>
- 842 Dickinson, A. (1994). Instrumental Conditioning. In N. J. Mackintosh (Ed.), *Animal Learning*  
843 *and Cognition* (pp. 45-79): Academic Press.
- 844 Dickinson, A., & Mulatero, C. W. (1989). Reinforcer specificity of the suppression of  
845 instrumental performance on a non-contingent schedule. *Behav Processes*, 19(1-3),  
846 167-180. doi:10.1016/0376-6357(89)90039-9
- 847 Durstewitz, D., & Seamans, J. K. (2008). The dual-state theory of prefrontal cortex dopamine  
848 function with relevance to catechol-o-methyltransferase genotypes and  
849 schizophrenia. *Biol Psychiatry*, 64(9), 739-749. doi:10.1016/j.biopsych.2008.05.015
- 850 Ellwood, I. T., Patel, T., Wadia, V., Lee, A. T., Liptak, A. T., Bender, K. J., & Sohal, V. S.  
851 (2017). Tonic or Phasic Stimulation of Dopaminergic Projections to Prefrontal Cortex  
852 Causes Mice to Maintain or Deviate from Previously Learned Behavioral Strategies. *J*  
853 *Neurosci*, 37(35), 8315-8329. doi:10.1523/JNEUROSCI.1221-17.2017
- 854 Eschenko, O., Magri, C., Panzeri, S., & Sara, S. J. (2012). Noradrenergic neurons of the  
855 locus coeruleus are phase locked to cortical up-down states during sleep. *Cereb*  
856 *Cortex*, 22(2), 426-435. doi:10.1093/cercor/bhr121
- 857 Fallon, J. H. (1981). Collateralization of monoamine neurons: mesotelencephalic dopamine  
858 projections to caudate, septum, and frontal cortex. *J Neurosci*, 1(12), 1361-1368.  
859 Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/6172572>
- 860 Fallon, J. H., & Loughlin, A. (1987). Monoamine Innervation of Cerebral Cortex and a Theory  
861 of the Role of Monoamines in Cerebral Cortex and Basal Ganglia. In E. G. Jones & A.  
862 Peters (Eds.), *Cerebral Cortex* (Vol. 6): Springer, Boston, MA.
- 863 Fallon, J. H., & Moore, R. Y. (1978). Catecholamine innervation of the basal forebrain. IV.  
864 Topography of the dopamine projection to the basal forebrain and neostriatum. *J*  
865 *Comp Neurol*, 180(3), 545-580. doi:10.1002/cne.901800310
- 866 Feng, J., Zhang, C., Lischinsky, J. E., Jing, M., Zhou, J., Wang, H., . . . Li, Y. (2019). A  
867 Genetically Encoded Fluorescent Sensor for Rapid and Specific In Vivo Detection of  
868 Norepinephrine. *Neuron*, 102(4), 745-761 e748. doi:10.1016/j.neuron.2019.02.037
- 869 Floresco, S. B. (2013). Prefrontal dopamine and behavioral flexibility: shifting from an  
870 "inverted-U" toward a family of functions. *Front Neurosci*, 7, 62.  
871 doi:10.3389/fnins.2013.00062
- 872 Floresco, S. B., Block, A. E., & Tse, M. T. (2008). Inactivation of the medial prefrontal cortex  
873 of the rat impairs strategy set-shifting, but not reversal learning, using a novel,  
874 automated procedure. *Behav Brain Res*, 190(1), 85-96.  
875 doi:10.1016/j.bbr.2008.02.008
- 876 Floresco, S. B., Magyar, O., Ghods-Sharifi, S., Vexelman, C., & Tse, M. T. (2006). Multiple  
877 dopamine receptor subtypes in the medial prefrontal cortex of the rat regulate set-  
878 shifting. *Neuropsychopharmacology*, 31(2), 297-309. doi:10.1038/sj.npp.1300825
- 879 Fresno, V., Parkes, S. L., Faugere, A., Coutureau, E., & Wolff, M. (2019). A thalamocortical  
880 circuit for updating action-outcome associations. *Elife*, 8. doi:10.7554/eLife.46187
- 881 Gallagher, M., McMahan, R. W., & Schoenbaum, G. (1999). Orbitofrontal cortex and  
882 representation of incentive value in associative learning. *J Neurosci*, 19(15), 6610-  
883 6614. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/10414988>
- 884 Gaspar, P., Bloch, B., & Le Moine, C. (1995). D1 and D2 receptor gene expression in the rat  
885 frontal cortex: cellular localization in different classes of efferent neurons. *Eur J*  
886 *Neurosci*, 7(5), 1050-1063. doi:10.1111/j.1460-9568.1995.tb01092.x
- 887 Gee, S., Ellwood, I., Patel, T., Luongo, F., Deisseroth, K., & Sohal, V. S. (2012). Synaptic  
888 activity unmask dopamine D2 receptor modulation of a specific class of layer V  
889 pyramidal neurons in prefrontal cortex. *J Neurosci*, 32(14), 4959-4971.  
890 doi:10.1523/JNEUROSCI.5835-11.2012
- 891 Goarin, E. H. F., Lingawi, N. W., & Laurent, V. (2018). Role Played by the Passage of Time  
892 in Reversal Learning. *Front Behav Neurosci*, 12, 75. doi:10.3389/fnbeh.2018.00075

893 Gourley, S. L., Lee, A. S., Howell, J. L., Pittenger, C., & Taylor, J. R. (2010). Dissociable  
894 regulation of instrumental action within mouse prefrontal cortex. *Eur J Neurosci*,  
895 32(10), 1726-1734. doi:10.1111/j.1460-9568.2010.07438.x

896 Gourley, S. L., Olevska, A., Zimmermann, K. S., Ressler, K. J., Dileone, R. J., & Taylor, J. R.  
897 (2013). The orbitofrontal cortex regulates outcome-based decision-making via the  
898 lateral striatum. *Eur J Neurosci*, 38(3), 2382-2388. doi:10.1111/ejn.12239

899 Granger, A. J., Wang, W., Robertson, K., El-Rifai, M., Zanello, A. F., Bistrong, K., . . .  
900 Sabatini, B. L. (2020). Cortical ChAT(+) neurons co-transmit acetylcholine and GABA  
901 in a target- and brain-region-specific manner. *Elife*, 9. doi:10.7554/eLife.57749

902 Gremel, C. M., Chancey, J. H., Atwood, B. K., Luo, G., Neve, R., Ramakrishnan, C., . . .  
903 Costa, R. M. (2016). Endocannabinoid Modulation of Orbitostriatal Circuits Gates  
904 Habit Formation. *Neuron*, 90(6), 1312-1324. doi:10.1016/j.neuron.2016.04.043

905 Gremel, C. M., & Costa, R. M. (2013). Orbitofrontal and striatal circuits dynamically encode  
906 the shift between goal-directed and habitual actions. *Nat Commun*, 4, 2264.  
907 doi:10.1038/ncomms3264

908 Hammond, L. J. (1980). The effect of contingency upon the appetitive conditioning of free-  
909 operant behavior. *J Exp Anal Behav*, 34(3), 297-304. doi:10.1901/jeab.1980.34-297

910 Hart, G., & Balleine, B. W. (2016). Consolidation of Goal-Directed Action Depends on  
911 MAPK/ERK Signaling in Rodent Prelimbic Cortex. *J Neurosci*, 36(47), 11974-11986.  
912 doi:10.1523/JNEUROSCI.1772-16.2016

913 Hart, G., Bradfield, L. A., Fok, S. Y., Chieng, B., & Balleine, B. W. (2018). The Bilateral  
914 Prefronto-striatal Pathway Is Necessary for Learning New Goal-Directed Actions.  
915 *Curr Biol*, 28(14), 2218-2229 e2217. doi:10.1016/j.cub.2018.05.028

916 Hayat, H., Regev, N., Matosevich, N., Sales, A., Paredes-Rodriguez, E., Krom, A. J., . . . Nir,  
917 Y. (2020). Locus coeruleus norepinephrine activity mediates sensory-evoked  
918 awakenings from sleep. *Sci Adv*, 6(15), eaaz4232. doi:10.1126/sciadv.aaz4232

919 Heilbronner, S. R., Rodriguez-Romaguera, J., Quirk, G. J., Groenewegen, H. J., & Haber, S.  
920 N. (2016). Circuit-Based Corticostriatal Homologies Between Rat and Primate. *Biol*  
921 *Psychiatry*, 80(7), 509-521. doi:10.1016/j.biopsych.2016.05.012

922 Hermans, E. J., van Marle, H. J., Ossewaarde, L., Henckens, M. J., Qin, S., van Kesteren, M.  
923 T., . . . Fernandez, G. (2011). Stress-related noradrenergic activity prompts large-  
924 scale neural network reconfiguration. *Science*, 334(6059), 1151-1153.  
925 doi:10.1126/science.1209603

926 Hirschberg, S., Li, Y., Randall, A., Kremer, E. J., & Pickering, A. E. (2017). Functional  
927 dichotomy in spinal- vs prefrontal-projecting locus coeruleus modules splits  
928 descending noradrenergic analgesia from ascending aversion and anxiety in rats.  
929 *Elife*, 6. doi:10.7554/eLife.29808

930 Hitchcott, P. K., Quinn, J. J., & Taylor, J. R. (2007). Bidirectional modulation of goal-directed  
931 actions by prefrontal cortical dopamine. *Cereb Cortex*, 17(12), 2820-2827.  
932 doi:10.1093/cercor/bhm010

933 Homayoun, H., & Moghaddam, B. (2008). Orbitofrontal cortex neurons as a common target  
934 for classic and glutamatergic antipsychotic drugs. *Proc Natl Acad Sci U S A*, 105(46),  
935 18041-18046. doi:10.1073/pnas.0806669105

936 Hoops, D., Reynolds, L. M., Restrepo-Lozano, J. M., & Flores, C. (2018). Dopamine  
937 Development in the Mouse Orbital Prefrontal Cortex Is Protracted and Sensitive to  
938 Amphetamine in Adolescence. *eNeuro*, 5(1). doi:10.1523/ENEURO.0372-17.2017

939 Hoover, W. B., & Vertes, R. P. (2007). Anatomical analysis of afferent projections to the  
940 medial prefrontal cortex in the rat. *Brain Struct Funct*, 212(2), 149-179.  
941 doi:10.1007/s00429-007-0150-4

942 Hoover, W. B., & Vertes, R. P. (2011). Projections of the medial orbital and ventral orbital  
943 cortex in the rat. *J Comp Neurol*, 519(18), 3766-3801. doi:10.1002/cne.22733

944 Howard, J. D., & Kahnt, T. (2018). Identity prediction errors in the human midbrain update  
945 reward-identity expectations in the orbitofrontal cortex. *Nat Commun*, 9(1), 1611.  
946 doi:10.1038/s41467-018-04055-5

947 Howe, M. W., & Dombeck, D. A. (2016). Rapid signalling in distinct dopaminergic axons  
948 during locomotion and reward. *Nature*, 535(7613), 505-510. doi:10.1038/nature18942

949 Izquierdo, A. (2017). Functional Heterogeneity within Rat Orbitofrontal Cortex in Reward  
950 Learning and Decision Making. *J Neurosci*, 37(44), 10529-10540.  
951 doi:10.1523/JNEUROSCI.1678-17.2017

952 Izquierdo, A., Brigman, J. L., Radke, A. K., Rudebeck, P. H., & Holmes, A. (2017). The  
953 neural basis of reversal learning: An updated perspective. *Neuroscience*, 345, 12-26.  
954 doi:10.1016/j.neuroscience.2016.03.021

955 Jenni, N. L., Larkin, J. D., & Floresco, S. B. (2017). Prefrontal Dopamine D1 and D2  
956 Receptors Regulate Dissociable Aspects of Decision Making via Distinct Ventral  
957 Striatal and Amygdalar Circuits. *J Neurosci*, 37(26), 6200-6213.  
958 doi:10.1523/JNEUROSCI.0030-17.2017

959 Jepma, M., Brown, S., Murphy, P. R., Koelewijn, S. C., de Vries, B., van den Maagdenberg,  
960 A. M., & Nieuwenhuis, S. (2018). Noradrenergic and Cholinergic Modulation of Belief  
961 Updating. *J Cogn Neurosci*, 1-18. doi:10.1162/jocn\_a\_01317

962 Joshi, S., Li, Y., Kalwani, R. M., & Gold, J. I. (2016). Relationships between Pupil Diameter  
963 and Neuronal Activity in the Locus Coeruleus, Colliculi, and Cingulate Cortex.  
964 *Neuron*, 89(1), 221-234. doi:10.1016/j.neuron.2015.11.028

965 Kahnt, T., & Tobler, P. N. (2017). Dopamine Modulates the Functional Organization of the  
966 Orbitofrontal Cortex. *J Neurosci*, 37(6), 1493-1504. doi:10.1523/JNEUROSCI.2827-  
967 16.2016

968 Keeschull, J. M., Garcia da Silva, P., Reid, A. P., Peikon, I. D., Albeanu, D. F., & Zador, A. M.  
969 (2016). High-Throughput Mapping of Single-Neuron Projections by Sequencing of  
970 Barcoded RNA. *Neuron*, 91(5), 975-987. doi:10.1016/j.neuron.2016.07.036

971 Kheramin, S., Body, S., Ho, M. Y., Velazquez-Martinez, D. N., Bradshaw, C. M., Szabadi, E.,  
972 . . . Anderson, I. M. (2004). Effects of orbital prefrontal cortex dopamine depletion on  
973 inter-temporal choice: a quantitative analysis. *Psychopharmacology (Berl)*, 175(2),  
974 206-214. doi:10.1007/s00213-004-1813-y

975 Killcross, S., & Coutureau, E. (2003). Coordination of actions and habits in the medial  
976 prefrontal cortex of rats. *Cereb Cortex*, 13(4), 400-408. doi:10.1093/cercor/13.4.400

977 Kjaerby, C., Andersen, M., Hauglund, N., Ding, F., Wang, W., Xu, Q., . . . Nedergaard, M.  
978 (2020). Dynamic fluctuations of the locus coeruleus-norepinephrine system underlie  
979 sleep state transitions. *BioRxiv*. doi:https://doi.org/10.1101/2020.09.01.274977

980 Kobayashi, R. M., Palkovits, M., Kopin, I. J., & Jacobowitz, D. M. (1974). Biochemical  
981 mapping of noradrenergic nerves arising from the rat locus coeruleus. *Brain Res*,  
982 77(2), 269-279. doi:10.1016/0006-8993(74)90790-2

983 Kosaki, Y., & Watanabe, S. (2012). Dissociable roles of the medial prefrontal cortex, the  
984 anterior cingulate cortex, and the hippocampus in behavioural flexibility revealed by  
985 serial reversal of three-choice discrimination in rats. *Behav Brain Res*, 227(1), 81-90.  
986 doi:10.1016/j.bbr.2011.10.039

987 Lammel, S., Hetzel, A., Hackel, O., Jones, I., Liss, B., & Roeper, J. (2008). Unique properties  
988 of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system.  
989 *Neuron*, 57(5), 760-773. doi:10.1016/j.neuron.2008.01.022

990 Langdon, A. J., Song, M., & Niv, Y. (2019). Uncovering the 'state': tracing the hidden state  
991 representations that structure learning and decision-making. *Behav Processes*,  
992 103891. doi:10.1016/j.beproc.2019.103891

993 Lapid, M. D., & Morilak, D. A. (2006). Noradrenergic modulation of cognitive function in rat  
994 medial prefrontal cortex as measured by attentional set shifting capability.  
995 *Neuroscience*, 137(3), 1039-1049. doi:10.1016/j.neuroscience.2005.09.031

996 Lapid-Bluhm, M. D., Soto-Pina, A. E., Hensler, J. G., & Morilak, D. A. (2009). Chronic  
997 intermittent cold stress and serotonin depletion induce deficits of reversal learning in  
998 an attentional set-shifting test in rats. *Psychopharmacology (Berl)*, 202(1-3), 329-341.  
999 doi:10.1007/s00213-008-1224-6



- 1000 Levitt, P., & Moore, R. Y. (1978). Noradrenaline neuron innervation of the neocortex in the  
1001 rat. *Brain Res*, 139(2), 219-231. Retrieved from  
1002 <https://www.ncbi.nlm.nih.gov/pubmed/624057>
- 1003 Lex, B., & Hauber, W. (2010). The role of dopamine in the prelimbic cortex and the  
1004 dorsomedial striatum in instrumental conditioning. *Cereb Cortex*, 20(4), 873-883.  
1005 doi:10.1093/cercor/bhp151
- 1006 Likhtik, E., & Johansen, J. P. (2019). Neuromodulation in circuits of aversive emotional  
1007 learning. *Nat Neurosci*, 22(10), 1586-1597. doi:10.1038/s41593-019-0503-3
- 1008 Lindvall, O., Bjorklund, A., & Divac, I. (1978). Organization of catecholamine neurons  
1009 projecting to the frontal cortex in the rat. *Brain Res*, 142(1), 1-24. Retrieved from  
1010 <https://www.ncbi.nlm.nih.gov/pubmed/626911>
- 1011 Linley, S. B., Hoover, W. B., & Vertes, R. P. (2013). Pattern of distribution of serotonergic  
1012 fibers to the orbitomedial and insular cortex in the rat. *J Chem Neuroanat*, 48-49, 29-  
1013 45. doi:10.1016/j.jchemneu.2012.12.006
- 1014 Lopatina, N., Sadacca, B. F., McDannald, M. A., Styer, C. V., Peterson, J. F., Cheer, J. F., &  
1015 Schoenbaum, G. (2017). Ensembles in medial and lateral orbitofrontal cortex  
1016 construct cognitive maps emphasizing different features of the behavioral landscape.  
1017 *Behav Neurosci*, 131(3), 201-212. doi:10.1037/bne0000195
- 1018 Loughlin, S. E., & Fallon, J. H. (1984). Substantia nigra and ventral tegmental area  
1019 projections to cortex: topography and collateralization. *Neuroscience*, 11(2), 425-435.  
1020 doi:10.1016/0306-4522(84)90034-4
- 1021 Loughlin, S. E., Foote, S. L., & Grzanna, R. (1986). Efferent projections of nucleus locus  
1022 coeruleus: morphologic subpopulations have different efferent targets. *Neuroscience*,  
1023 18(2), 307-319. doi:10.1016/0306-4522(86)90156-9
- 1024 Manning, E. E., Dombrowski, A. Y., Torregrossa, M. M., & Ahmari, S. E. (2019). Impaired  
1025 instrumental reversal learning is associated with increased medial prefrontal cortex  
1026 activity in Sapap3 knockout mouse model of compulsive behavior.  
1027 *Neuropsychopharmacology*, 44(8), 1494-1504. doi:10.1038/s41386-018-0307-2
- 1028 Masaki, D., Yokoyama, C., Kinoshita, S., Tsuchida, H., Nakatomi, Y., Yoshimoto, K., & Fukui,  
1029 K. (2006). Relationship between limbic and cortical 5-HT neurotransmission and  
1030 acquisition and reversal learning in a go/no-go task in rats. *Psychopharmacology*  
1031 (*Berl*), 189(2), 249-258. doi:10.1007/s00213-006-0559-0
- 1032 Mason, S. T., & Iversen, S. D. (1978). Reward, attention and the dorsal noradrenergic  
1033 bundle. *Brain Res*, 150(1), 135-148. doi:10.1016/0006-8993(78)90658-3
- 1034 Matamales, M., Skrbis, Z., Hatch, R. J., Balleine, B. W., Gotz, J., & Bertran-Gonzalez, J.  
1035 (2016). Aging-Related Dysfunction of Striatal Cholinergic Interneurons Produces  
1036 Conflict in Action Selection. *Neuron*, 90(2), 362-373.  
1037 doi:10.1016/j.neuron.2016.03.006
- 1038 McGaughy, J., Ross, R. S., & Eichenbaum, H. (2008). Noradrenergic, but not cholinergic,  
1039 deafferentation of prefrontal cortex impairs attentional set-shifting. *Neuroscience*,  
1040 153(1), 63-71. doi:10.1016/j.neuroscience.2008.01.064
- 1041 Milstein, J. A., Lehmann, O., Theobald, D. E., Dalley, J. W., & Robbins, T. W. (2007).  
1042 Selective depletion of cortical noradrenaline by anti-dopamine beta-hydroxylase-  
1043 saporin impairs attentional function and enhances the effects of guanfacine in the rat.  
1044 *Psychopharmacology (Berl)*, 190(1), 51-63. doi:10.1007/s00213-006-0594-x
- 1045 Mokler, D. J., Miller, C. E., & McGaughy, J. A. (2017). Evidence for a role of corticopetal,  
1046 noradrenergic systems in the development of executive function. *Neurobiol Learn*  
1047 *Mem*, 143, 94-100. doi:10.1016/j.nlm.2017.02.011
- 1048 Moorman, D. E., & Aston-Jones, G. (2015). Prefrontal neurons encode context-based  
1049 response execution and inhibition in reward seeking and extinction. *Proc Natl Acad*  
1050 *Sci U S A*, 112(30), 9472-9477. doi:10.1073/pnas.1507611112
- 1051 Morrison, J. H., Grzanna, R., Molliver, M. E., & Coyle, J. T. (1978). The distribution and  
1052 orientation of noradrenergic fibers in neocortex of the rat: an immunofluorescence  
1053 study. *J Comp Neurol*, 181(1), 17-39. doi:10.1002/cne.901810103

- 1054 Morrison, J. H., Molliver, M. E., & Grzanna, R. (1979). Noradrenergic innervation of cerebral  
1055 cortex: widespread effects of local cortical lesions. *Science*, 205(4403), 313-316.  
1056 Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/451605>
- 1057 Morrison, J. H., Molliver, M. E., Grzanna, R., & Coyle, J. T. (1981). The intra-cortical  
1058 trajectory of the coeruleo-cortical projection in the rat: a tangentially organized cortical  
1059 afferent. *Neuroscience*, 6(2), 139-158. Retrieved from  
1060 <https://www.ncbi.nlm.nih.gov/pubmed/7012664>
- 1061 Mueller, D., Porter, J. T., & Quirk, G. J. (2008). Noradrenergic signaling in infralimbic cortex  
1062 increases cell excitability and strengthens memory for fear extinction. *J Neurosci*,  
1063 28(2), 369-375. doi:10.1523/JNEUROSCI.3248-07.2008
- 1064 Mukherjee, A., & Caroni, P. (2018). Infralimbic cortex is required for learning alternatives to  
1065 prelimbic promoted associations through reciprocal connectivity. *Nat Commun*, 9(1),  
1066 2727. doi:10.1038/s41467-018-05318-x
- 1067 Muller, T. H., Mars, R. B., Behrens, T. E., & O'Reilly, J. X. (2019). Control of entropy in neural  
1068 models of environmental state. *Elife*, 8. doi:10.7554/eLife.39404
- 1069 Murphy, M. J. M., & Deutch, A. Y. (2018). Organization of afferents to the orbitofrontal cortex  
1070 in the rat. *J Comp Neurol*, 526(9), 1498-1526. doi:10.1002/cne.24424
- 1071 Naneix, F., Marchand, A. R., Di Scala, G., Pape, J. R., & Coutureau, E. (2009). A role for  
1072 medial prefrontal dopaminergic innervation in instrumental conditioning. *J Neurosci*,  
1073 29(20), 6599-6606. doi:10.1523/JNEUROSCI.1234-09.2009
- 1074 Naneix, F., Marchand, A. R., Di Scala, G., Pape, J. R., & Coutureau, E. (2012). Parallel  
1075 maturation of goal-directed behavior and dopaminergic systems during adolescence.  
1076 *J Neurosci*, 32(46), 16223-16232. doi:10.1523/JNEUROSCI.3080-12.2012
- 1077 Naneix, F., Marchand, A. R., Pichon, A., Pape, J. R., & Coutureau, E. (2013). Adolescent  
1078 stimulation of D2 receptors alters the maturation of dopamine-dependent goal-  
1079 directed behavior. *Neuropsychopharmacology*, 38(8), 1566-1574.  
1080 doi:10.1038/npp.2013.55
- 1081 Nassar, M. R., Rumsey, K. M., Wilson, R. C., Parikh, K., Heasley, B., & Gold, J. I. (2012).  
1082 Rational regulation of learning dynamics by pupil-linked arousal systems. *Nat*  
1083 *Neurosci*, 15(7), 1040-1046. doi:10.1038/nn.3130
- 1084 Newman, L. A., Darling, J., & McGaughy, J. (2008). Atomoxetine reverses attentional deficits  
1085 produced by noradrenergic deafferentation of medial prefrontal cortex.  
1086 *Psychopharmacology (Berl)*, 200(1), 39-50. doi:10.1007/s00213-008-1097-8
- 1087 Nieuwenhuys, R. (1985). *Chemoarchitecture of the Brain*: Springer-Verlag Berlin Heidelberg.
- 1088 Nimitvilai, S., Lopez, M. F., Mulholland, P. J., & Woodward, J. J. (2017). Ethanol  
1089 Dependence Abolishes Monoamine and GIRK (Kir3) Channel Inhibition of  
1090 Orbitofrontal Cortex Excitability. *Neuropsychopharmacology*, 42(9), 1800-1812.  
1091 doi:10.1038/npp.2017.22
- 1092 Obermayer, J., Luchicchi, A., Heistek, T. S., de Kloet, S. F., Terra, H., Bruinsma, B., . . .  
1093 Mansvelder, H. D. (2019). Prefrontal cortical ChAT-VIP interneurons provide local  
1094 excitation by cholinergic synaptic transmission and control attention. *Nat Commun*,  
1095 10(1), 5280. doi:10.1038/s41467-019-13244-9
- 1096 Ostlund, S. B., & Balleine, B. W. (2005). Lesions of medial prefrontal cortex disrupt the  
1097 acquisition but not the expression of goal-directed learning. *J Neurosci*, 25(34), 7763-  
1098 7770. doi:10.1523/JNEUROSCI.1921-05.2005
- 1099 Ostlund, S. B., & Balleine, B. W. (2007). Orbitofrontal cortex mediates outcome encoding in  
1100 Pavlovian but not instrumental conditioning. *J Neurosci*, 27(18), 4819-4825.  
1101 doi:10.1523/JNEUROSCI.5443-06.2007
- 1102 Panayi, M. C., & Killcross, S. (2018). Functional heterogeneity within the rodent lateral  
1103 orbitofrontal cortex dissociates outcome devaluation and reversal learning deficits.  
1104 *Elife*, 7. doi:10.7554/eLife.37357
- 1105 Papadopoulos, G. C., & Parnavelas, J. G. (1991). Monoamine systems in the cerebral  
1106 cortex: evidence for anatomical specificity. *Prog Neurobiol*, 36(3), 195-200. Retrieved  
1107 from <https://www.ncbi.nlm.nih.gov/pubmed/2017550>

1108 Pardey, M. C., Kumar, N. N., Goodchild, A. K., & Cornish, J. L. (2013). Catecholamine  
1109 receptors differentially mediate impulsive choice in the medial prefrontal and  
1110 orbitofrontal cortex. *J Psychopharmacol*, *27*(2), 203-212.  
1111 doi:10.1177/0269881112465497

1112 Parkes, S. L., Ravassard, P. M., Cerpa, J. C., Wolff, M., Ferreira, G., & Coutureau, E. (2018).  
1113 Insular and Ventrolateral Orbitofrontal Cortices Differentially Contribute to Goal-  
1114 Directed Behavior in Rodents. *Cereb Cortex*, *28*(7), 2313-2325.  
1115 doi:10.1093/cercor/bhx132

1116 Pickens, C. L., Saddoris, M. P., Gallagher, M., & Holland, P. C. (2005). Orbitofrontal lesions  
1117 impair use of cue-outcome associations in a devaluation task. *Behav Neurosci*,  
1118 *119*(1), 317-322. doi:10.1037/0735-7044.119.1.317

1119 Pickens, C. L., Saddoris, M. P., Setlow, B., Gallagher, M., Holland, P. C., & Schoenbaum, G.  
1120 (2003). Different roles for orbitofrontal cortex and basolateral amygdala in a reinforcer  
1121 devaluation task. *J Neurosci*, *23*(35), 11078-11084. Retrieved from  
1122 <https://www.ncbi.nlm.nih.gov/pubmed/14657165>

1123 Plummer, N. W., Chandler, D. J., Powell, J. M., Scappini, E. L., Waterhouse, B. D., &  
1124 Jensen, P. (2020). An Intersectional Viral-Genetic Method for Fluorescent Tracing of  
1125 Axon Collaterals Reveals Details of Noradrenergic Locus Coeruleus Structure.  
1126 *eNeuro*, *7*(3). doi:10.1523/ENEURO.0010-20.2020

1127 Poe, G. R., Foote, S., Eschenko, O., Johansen, J. P., Bouret, S., Aston-Jones, G., . . . Sara,  
1128 S. J. (2020). Locus coeruleus: a new look at the blue spot. *Nat Rev Neurosci*.  
1129 doi:10.1038/s41583-020-0360-9

1130 Popescu, A. T., Zhou, M. R., & Poo, M. M. (2016). Phasic dopamine release in the medial  
1131 prefrontal cortex enhances stimulus discrimination. *Proc Natl Acad Sci U S A*,  
1132 *113*(22), E3169-3176. doi:10.1073/pnas.1606098113

1133 Preuschoff, K., Hart, B. M., & Einhauser, W. (2011). Pupil Dilation Signals Surprise:  
1134 Evidence for Noradrenaline's Role in Decision Making. *Front Neurosci*, *5*, 115.  
1135 doi:10.3389/fnins.2011.00115

1136 Puig, M. V., Rose, J., Schmidt, R., & Freund, N. (2014). Dopamine modulation of learning  
1137 and memory in the prefrontal cortex: insights from studies in primates, rodents, and  
1138 birds. *Front Neural Circuits*, *8*, 93. doi:10.3389/fncir.2014.00093

1139 Ragozzino, M. E., Detrick, S., & Kesner, R. P. (1999). Involvement of the prelimbic-  
1140 infralimbic areas of the rodent prefrontal cortex in behavioral flexibility for place and  
1141 response learning. *J Neurosci*, *19*(11), 4585-4594. Retrieved from  
1142 <https://www.ncbi.nlm.nih.gov/pubmed/10341256>

1143 Ramos, B. P., Colgan, L., Nou, E., Ovadia, S., Wilson, S. R., & Arnsten, A. F. (2005). The  
1144 beta-1 adrenergic antagonist, betaxolol, improves working memory performance in  
1145 rats and monkeys. *Biol Psychiatry*, *58*(11), 894-900.  
1146 doi:10.1016/j.biopsych.2005.05.022

1147 Ramos, B. P., Stark, D., Verduzco, L., van Dyck, C. H., & Arnsten, A. F. (2006). Alpha2A-  
1148 adrenoceptor stimulation improves prefrontal cortical regulation of behavior through  
1149 inhibition of cAMP signaling in aging animals. *Learn Mem*, *13*(6), 770-776.  
1150 doi:10.1101/lm.298006

1151 Ren, J., Friedmann, D., Xiong, J., Liu, C. D., Ferguson, B. R., Weerakkody, T., . . . Luo, L.  
1152 (2018). Anatomically Defined and Functionally Distinct Dorsal Raphe Serotonin Sub-  
1153 systems. *Cell*, *175*(2), 472-487 e420. doi:10.1016/j.cell.2018.07.043

1154 Rescorla, R. A. (1996). Response-outcome associations remain functional through  
1155 interference treatments. *Learning & Behavior*, *24*(4), 450-458.  
1156 doi:10.3758/BF03199016

1157 Robbins, T. W., & Arnsten, A. F. (2009). The neuropsychopharmacology of fronto-executive  
1158 function: monoaminergic modulation. *Annu Rev Neurosci*, *32*, 267-287.  
1159 doi:10.1146/annurev.neuro.051508.135535

1160 Roberts, A. C. (2011). The importance of serotonin for orbitofrontal function. *Biol Psychiatry*,  
1161 *69*(12), 1185-1191. doi:10.1016/j.biopsych.2010.12.037

- 1162 Robertson, S. D., Plummer, N. W., de Marchena, J., & Jensen, P. (2013). Developmental  
1163 origins of central norepinephrine neuron diversity. *Nat Neurosci*, *16*(8), 1016-1023.  
1164 doi:10.1038/nn.3458
- 1165 Rudebeck, P. H., & Murray, E. A. (2011). Dissociable effects of subtotal lesions within the  
1166 macaque orbital prefrontal cortex on reward-guided behavior. *J Neurosci*, *31*(29),  
1167 10569-10578. doi:10.1523/JNEUROSCI.0091-11.2011
- 1168 Sadacca, B. F., Wikenheiser, A. M., & Schoenbaum, G. (2016). Toward a theoretical role for  
1169 tonic norepinephrine in the orbitofrontal cortex in facilitating flexible learning.  
1170 *Neuroscience*. doi:10.1016/j.neuroscience.2016.04.017
- 1171 Santana, N., Mengod, G., & Artigas, F. (2009). Quantitative analysis of the expression of  
1172 dopamine D1 and D2 receptors in pyramidal and GABAergic neurons of the rat  
1173 prefrontal cortex. *Cereb Cortex*, *19*(4), 849-860. doi:10.1093/cercor/bhn134
- 1174 Sara, S. J., & Bouret, S. (2012). Orienting and reorienting: the locus coeruleus mediates  
1175 cognition through arousal. *Neuron*, *76*(1), 130-141. doi:10.1016/j.neuron.2012.09.011
- 1176 Sara, S. J., & Segal, M. (1991). Plasticity of sensory responses of locus coeruleus neurons in  
1177 the behaving rat: implications for cognition. *Prog Brain Res*, *88*, 571-585.  
1178 doi:10.1016/s0079-6123(08)63835-2
- 1179 Saunders, B. T., Richard, J. M., Margolis, E. B., & Janak, P. H. (2018). Dopamine neurons  
1180 create Pavlovian conditioned stimuli with circuit-defined motivational properties. *Nat*  
1181 *Neurosci*, *21*(8), 1072-1083. doi:10.1038/s41593-018-0191-4
- 1182 Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and  
1183 reward. *Science*, *275*(5306), 1593-1599. doi:10.1126/science.275.5306.1593
- 1184 Schultz, W., & Dickinson, A. (2000). Neuronal coding of prediction errors. *Annu Rev*  
1185 *Neurosci*, *23*, 473-500. doi:10.1146/annurev.neuro.23.1.473
- 1186 Schwarz, L. A., Miyamichi, K., Gao, X. J., Beier, K. T., Weissbourd, B., DeLoach, K. E., . . .  
1187 Luo, L. (2015). Viral-genetic tracing of the input-output organization of a central  
1188 noradrenaline circuit. *Nature*, *524*(7563), 88-92. doi:10.1038/nature14600
- 1189 Seamans, J. K., & Yang, C. R. (2004). The principal features and mechanisms of dopamine  
1190 modulation in the prefrontal cortex. *Prog Neurobiol*, *74*(1), 1-58.  
1191 doi:10.1016/j.pneurobio.2004.05.006
- 1192 Seguela, P., Watkins, K. C., Geffard, M., & Descarries, L. (1990). Noradrenaline axon  
1193 terminals in adult rat neocortex: an immunocytochemical analysis in serial thin  
1194 sections. *Neuroscience*, *35*(2), 249-264. Retrieved from  
1195 <https://www.ncbi.nlm.nih.gov/pubmed/2116602>
- 1196 Sharpe, M. J., & Killcross, S. (2014). The prelimbic cortex uses higher-order cues to  
1197 modulate both the acquisition and expression of conditioned fear. *Front Syst*  
1198 *Neurosci*, *8*, 235. doi:10.3389/fnsys.2014.00235
- 1199 Sharpe, M. J., & Killcross, S. (2018). Modulation of attention and action in the medial  
1200 prefrontal cortex of rats. *Psychol Rev*, *125*(5), 822-843. doi:10.1037/rev0000118
- 1201 Sharpe, M. J., Stalnaker, T., Schuck, N. W., Killcross, S., Schoenbaum, G., & Niv, Y. (2019).  
1202 An Integrated Model of Action Selection: Distinct Modes of Cortical Control of Striatal  
1203 Decision Making. *Annu Rev Psychol*, *70*, 53-76. doi:10.1146/annurev-psych-010418-  
1204 102824
- 1205 Shaw, C. L., Watson, G. D. R., Hallock, H. L., Cline, K. M., & Griffin, A. L. (2013). The role of  
1206 the medial prefrontal cortex in the acquisition, retention, and reversal of a tactile  
1207 visuospatial conditional discrimination task. *Behav Brain Res*, *236*(1), 94-101.  
1208 doi:10.1016/j.bbr.2012.08.024
- 1209 Simpson, K. L., Waterhouse, B. D., & Lin, R. C. (1999). Origin, distribution, and morphology  
1210 of galaninergic fibers in the rodent trigeminal system. *J Comp Neurol*, *411*(3), 524-  
1211 534. doi:10.1002/(sici)1096-9861(19990830)411:3<524::aid-cne13>3.0.co;2-x
- 1212 Sobel, E., & Corbett, D. (1984). Axonal branching of ventral tegmental and raphe projections  
1213 to the frontal cortex in the rat. *Neurosci Lett*, *48*(2), 121-125. doi:10.1016/0304-  
1214 3940(84)90006-5
- 1215 Stefani, M. R., & Moghaddam, B. (2006). Rule learning and reward contingency are  
1216 associated with dissociable patterns of dopamine activation in the rat prefrontal

1217 cortex, nucleus accumbens, and dorsal striatum. *J Neurosci*, 26(34), 8810-8818.  
1218 doi:10.1523/JNEUROSCI.1656-06.2006

1219 Steinberg, E. E., Keiflin, R., Boivin, J. R., Witten, I. B., Deisseroth, K., & Janak, P. H. (2013).  
1220 A causal link between prediction errors, dopamine neurons and learning. *Nat*  
1221 *Neurosci*, 16(7), 966-973. doi:10.1038/nn.3413

1222 Swanson, A. M., DePoy, L. M., & Gourley, S. L. (2017). Inhibiting Rho kinase promotes goal-  
1223 directed decision making and blocks habitual responding for cocaine. *Nat Commun*,  
1224 8(1), 1861. doi:10.1038/s41467-017-01915-4

1225 Swanson, L. W. (1982). The projections of the ventral tegmental area and adjacent regions:  
1226 a combined fluorescent retrograde tracer and immunofluorescence study in the rat.  
1227 *Brain Res Bull*, 9(1-6), 321-353. doi:10.1016/0361-9230(82)90145-9

1228 Takahashi, Y. K., Roesch, M. R., Wilson, R. C., Toreson, K., O'Donnell, P., Niv, Y., &  
1229 Schoenbaum, G. (2011). Expectancy-related changes in firing of dopamine neurons  
1230 depend on orbitofrontal cortex. *Nat Neurosci*, 14(12), 1590-1597.  
1231 doi:10.1038/nn.2957

1232 Takahashi, Y. K., Stalnaker, T. A., Roesch, M. R., & Schoenbaum, G. (2017). Effects of  
1233 inference on dopaminergic prediction errors depend on orbitofrontal processing.  
1234 *Behav Neurosci*, 131(2), 127-134. doi:10.1037/bne0000192

1235 Tervo, D. G. R., Proskurin, M., Manakov, M., Kabra, M., Vollmer, A., Branson, K., & Karpova,  
1236 A. Y. (2014). Behavioral variability through stochastic choice and its gating by anterior  
1237 cingulate cortex. *Cell*, 159(1), 21-32. doi:10.1016/j.cell.2014.08.037

1238 Totah, N. K. B., Logothetis, N. K., & Eschenko, O. (2019). Noradrenergic ensemble-based  
1239 modulation of cognition over multiple timescales. *Brain Res*, 1709, 50-66.  
1240 doi:10.1016/j.brainres.2018.12.031

1241 Tran-Tu-Yen, D. A., Marchand, A. R., Pape, J. R., Di Scala, G., & Coutureau, E. (2009).  
1242 Transient role of the rat prelimbic cortex in goal-directed behaviour. *Eur J Neurosci*,  
1243 30(3), 464-471. doi:10.1111/j.1460-9568.2009.06834.x

1244 Trask, S., & Bouton, M. E. (2014). Contextual control of operant behavior: evidence for  
1245 hierarchical associations in instrumental learning. *Learn Behav*, 42(3), 281-288.  
1246 doi:10.3758/s13420-014-0145-y

1247 Tronel, S., Feenstra, M. G., & Sara, S. J. (2004). Noradrenergic action in prefrontal cortex in  
1248 the late stage of memory consolidation. *Learn Mem*, 11(4), 453-458.  
1249 doi:10.1101/lm.74504

1250 Uematsu, A., Tan, B. Z., & Johansen, J. P. (2015). Projection specificity in heterogeneous  
1251 locus coeruleus cell populations: implications for learning and memory. *Learn Mem*,  
1252 22(9), 444-451. doi:10.1101/lm.037283.114

1253 Uematsu, A., Tan, B. Z., Ycu, E. A., Cuevas, J. S., Koivumaa, J., Junyent, F., . . . Johansen,  
1254 J. P. (2017). Modular organization of the brainstem noradrenaline system coordinates  
1255 opposing learning states. *Nat Neurosci*, 20(11), 1602-1611. doi:10.1038/nn.4642

1256 Ungerstedt, U. (1971). Stereotaxic mapping of the monoamine pathways in the rat brain.  
1257 *Acta Physiol Scand Suppl*, 367, 1-48. Retrieved from  
1258 <https://www.ncbi.nlm.nih.gov/pubmed/4109331>

1259 van der Meulen, J. A., Joosten, R. N., de Bruin, J. P., & Feenstra, M. G. (2007). Dopamine  
1260 and noradrenaline efflux in the medial prefrontal cortex during serial reversals and  
1261 extinction of instrumental goal-directed behavior. *Cereb Cortex*, 17(6), 1444-1453.  
1262 doi:10.1093/cercor/bhl057

1263 Van Eden, C. G., Hoorneman, E. M., Buijs, R. M., Matthijssen, M. A., Geffard, M., & Uylings,  
1264 H. B. (1987). Immunocytochemical localization of dopamine in the prefrontal cortex of  
1265 the rat at the light and electron microscopical level. *Neuroscience*, 22(3), 849-862.  
1266 doi:10.1016/0306-4522(87)92964-2

1267 Vander Weele, C. M., Siciliano, C. A., Matthews, G. A., Namburi, P., Izadmehr, E. M.,  
1268 Espinel, I. C., . . . Tye, K. M. (2018). Dopamine enhances signal-to-noise ratio in  
1269 cortical-brainstem encoding of aversive stimuli. *Nature*, 563(7731), 397-401.  
1270 doi:10.1038/s41586-018-0682-1

1271 Verharen, J. P. H., den Ouden, H. E. M., Adan, R. A. H., & Vanderschuren, L. (2020).  
1272 Modulation of value-based decision making behavior by subregions of the rat  
1273 prefrontal cortex. *Psychopharmacology (Berl)*, 237(5), 1267-1280.  
1274 doi:10.1007/s00213-020-05454-7

1275 Walton, M. E., Behrens, T. E., Buckley, M. J., Rudebeck, P. H., & Rushworth, M. F. (2010).  
1276 Separable learning systems in the macaque brain and the role of orbitofrontal cortex  
1277 in contingent learning. *Neuron*, 65(6), 927-939. doi:10.1016/j.neuron.2010.02.027

1278 Wang, H., & Pickel, V. M. (2002). Dopamine D2 receptors are present in prefrontal cortical  
1279 afferents and their targets in patches of the rat caudate-putamen nucleus. *J Comp  
1280 Neurol*, 442(4), 392-404. doi:10.1002/cne.10086

1281 Wang, M., Ramos, B. P., Paspalas, C. D., Shu, Y., Simen, A., Duque, A., . . . Arnsten, A. F.  
1282 (2007). Alpha2A-adrenoceptors strengthen working memory networks by inhibiting  
1283 cAMP-HCN channel signaling in prefrontal cortex. *Cell*, 129(2), 397-410.  
1284 doi:10.1016/j.cell.2007.03.015

1285 Waterhouse, B. D., Lin, C. S., Burne, R. A., & Woodward, D. J. (1983). The distribution of  
1286 neocortical projection neurons in the locus coeruleus. *J Comp Neurol*, 217(4), 418-  
1287 431. doi:10.1002/cne.902170406

1288 Weele, C. M. V., Siciliano, C. A., & Tye, K. M. (2019). Dopamine tunes prefrontal outputs to  
1289 orchestrate aversive processing. *Brain Res*, 1713, 16-31.  
1290 doi:10.1016/j.brainres.2018.11.044

1291 West, E. A., Forcelli, P. A., McCue, D. L., & Malkova, L. (2013). Differential effects of  
1292 serotonin-specific and excitotoxic lesions of OFC on conditioned reinforcer  
1293 devaluation and extinction in rats. *Behav Brain Res*, 246, 10-14.  
1294 doi:10.1016/j.bbr.2013.02.027

1295 Whyte, A. J., Kietzman, H. W., Swanson, A. M., Butkovich, L. M., Barbee, B. R., Bassell, G.  
1296 J., . . . Gourley, S. L. (2019). Reward-Related Expectations Trigger Dendritic Spine  
1297 Plasticity in the Mouse Ventrolateral Orbitofrontal Cortex. *J Neurosci*, 39(23), 4595-  
1298 4605. doi:10.1523/JNEUROSCI.2031-18.2019

1299 Wilson, R. C., Takahashi, Y. K., Schoenbaum, G., & Niv, Y. (2014). Orbitofrontal cortex as a  
1300 cognitive map of task space. *Neuron*, 81(2), 267-279.  
1301 doi:10.1016/j.neuron.2013.11.005

1302 Winstanley, C. A., Theobald, D. E., Dalley, J. W., Cardinal, R. N., & Robbins, T. W. (2006).  
1303 Double dissociation between serotonergic and dopaminergic modulation of medial  
1304 prefrontal and orbitofrontal cortex during a test of impulsive choice. *Cereb Cortex*,  
1305 16(1), 106-114. doi:10.1093/cercor/bhi088

1306 Winstanley, C. A., Zeeb, F. D., Bedard, A., Fu, K., Lai, B., Steele, C., & Wong, A. C. (2010).  
1307 Dopaminergic modulation of the orbitofrontal cortex affects attention, motivation and  
1308 impulsive responding in rats performing the five-choice serial reaction time task.  
1309 *Behav Brain Res*, 210(2), 263-272. doi:10.1016/j.bbr.2010.02.044

1310 Winter, S., Dieckmann, M., & Schwabe, K. (2009). Dopamine in the prefrontal cortex  
1311 regulates rats behavioral flexibility to changing reward value. *Behav Brain Res*,  
1312 198(1), 206-213. doi:10.1016/j.bbr.2008.10.040

1313 Woon, E. P., Sequeira, M. K., Barbee, B. R., & Gourley, S. L. (2020). Involvement of the  
1314 rodent prelimbic and medial orbitofrontal cortices in goal-directed action: A brief  
1315 review. *J Neurosci Res*, 98(6), 1020-1030. doi:10.1002/jnr.24567

1316 Yin, H. H., Knowlton, B. J., & Balleine, B. W. (2005). Blockade of NMDA receptors in the  
1317 dorsomedial striatum prevents action-outcome learning in instrumental conditioning.  
1318 *Eur J Neurosci*, 22(2), 505-512. doi:10.1111/j.1460-9568.2005.04219.x

1319 Young, J. J., & Shapiro, M. L. (2009). Double dissociation and hierarchical organization of  
1320 strategy switches and reversals in the rat PFC. *Behav Neurosci*, 123(5), 1028-1035.  
1321 doi:10.1037/a0016822

1322 Yu, A. J., & Dayan, P. (2005). Uncertainty, neuromodulation, and attention. *Neuron*, 46(4),  
1323 681-692. Retrieved from Yu, AJ: feraina@gatsby.ucl.ac.uk

1324 Zerbi, V., Floriou-Servou, A., Markicevic, M., Vermeiren, Y., Sturman, O., Privitera, M., . . .  
1325 Bohacek, J. (2019). Rapid Reconfiguration of the Functional Connectome after

1326 Chemogenetic Locus Coeruleus Activation. *Neuron*, 103(4), 702-718 e705.  
1327 doi:10.1016/j.neuron.2019.05.034  
1328 Zimmermann, K. S., Li, C. C., Rainnie, D. G., Ressler, K. J., & Gourley, S. L. (2018). Memory  
1329 Retention Involves the Ventrolateral Orbitofrontal Cortex: Comparison with the  
1330 Basolateral Amygdala. *Neuropsychopharmacology*, 43(3), 674.  
1331 doi:10.1038/npp.2017.219  
1332 Zimmermann, K. S., Yamin, J. A., Rainnie, D. G., Ressler, K. J., & Gourley, S. L. (2017).  
1333 Connections of the Mouse Orbitofrontal Cortex and Regulation of Goal-Directed  
1334 Action Selection by Brain-Derived Neurotrophic Factor. *Biol Psychiatry*, 81(4), 366-  
1335 377. doi:10.1016/j.biopsych.2015.10.026