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

Juan-Carlos Cerpa, Etienne Coutureau, Shauna L. Parkes, Shauna Parkes

▶ **To cite this version:**

Juan-Carlos Cerpa, Etienne Coutureau, Shauna L. Parkes, Shauna Parkes. Dopamine and noradrenaline modulation of goal-directed behaviour in prefrontal areas: Toward a division of labour?. 2020. hal-02993215

HAL Id: hal-02993215
https://hal.science/hal-02993215

Preprint submitted on 6 Nov 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

PERSPECTIVE

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

Juan-Carlos Cerpa[1,2*], Etienne Coutureau[1,2], Shauna L. Parkes[1,2*]

[1]CNRS, Institut de Neurosciences Cognitives et Intégratives d'Aquitaine, UMR 5287, 33076 Bordeaux, France.

[2]Université de Bordeaux, 33076 Bordeaux, France.

*Corresponding authors: juancarlos.cerpa@psy.ox.ac.uk; shauna.parkes@u-bordeaux.fr

Acknowledgements

This work was supported by research grants from the National Alliance for Research on Schizophrenia and Depression (27402 awarded to SP) and the French National Agency for Scientific Research (ANR-19-CE37-0004-07 CoCoChoice awarded to SP and ANR-19-CE37-0008 NORAD to EC).

ABSTRACT

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

I. Introduction

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

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

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

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

II. Adapting to changes in action-outcome associations

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

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

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

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

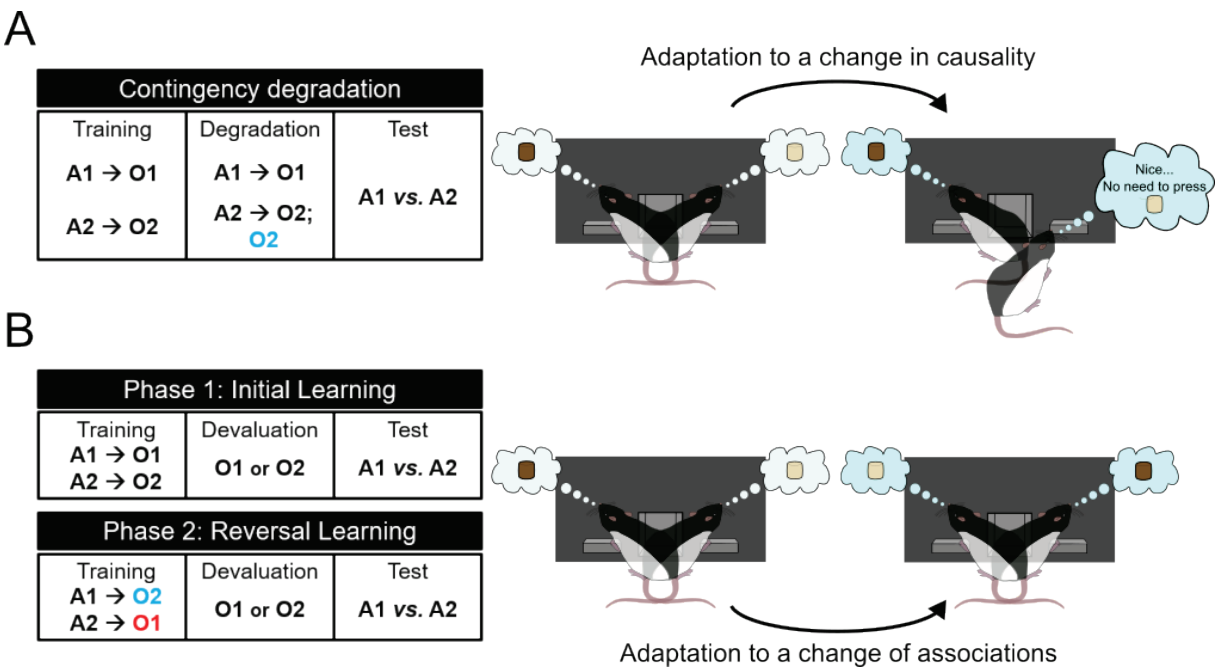


Figure 1. **A. Contingency degradation.** In a typical procedure, subjects are trained to associate two actions (e.g., A1 and A2) with two different food outcomes (O1 and O2). Then, one of these contingencies (A2→O2) is degraded by delivering one food outcome freely (O2). This procedure leads to a specific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

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

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

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

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

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

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

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

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

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

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

III. Noradrenaline and dopamine differentially innervate the prefrontal cortex

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

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

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

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

LC neurons projecting to different targets are spatially segregated (Waterhouse et al 1983; Schwarz et al 2015) and might differ morphologically (Loughlin et al 1986) and in their neuropeptidergic content (Simpson et al 1999). While divergent LC neurons exist, their number appears to be limited and a substantial proportion of LC neurons are biased toward a single target (Kebschull et al 2016; Plummer et al 2020). Interestingly, neurons projecting to a single target seem to form a coherent firing ensemble (Totah et al 2018) and some patterns 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 vlOFC 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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

VI. Other neuromodulatory systems

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

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

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

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

VII. Concluding remarks

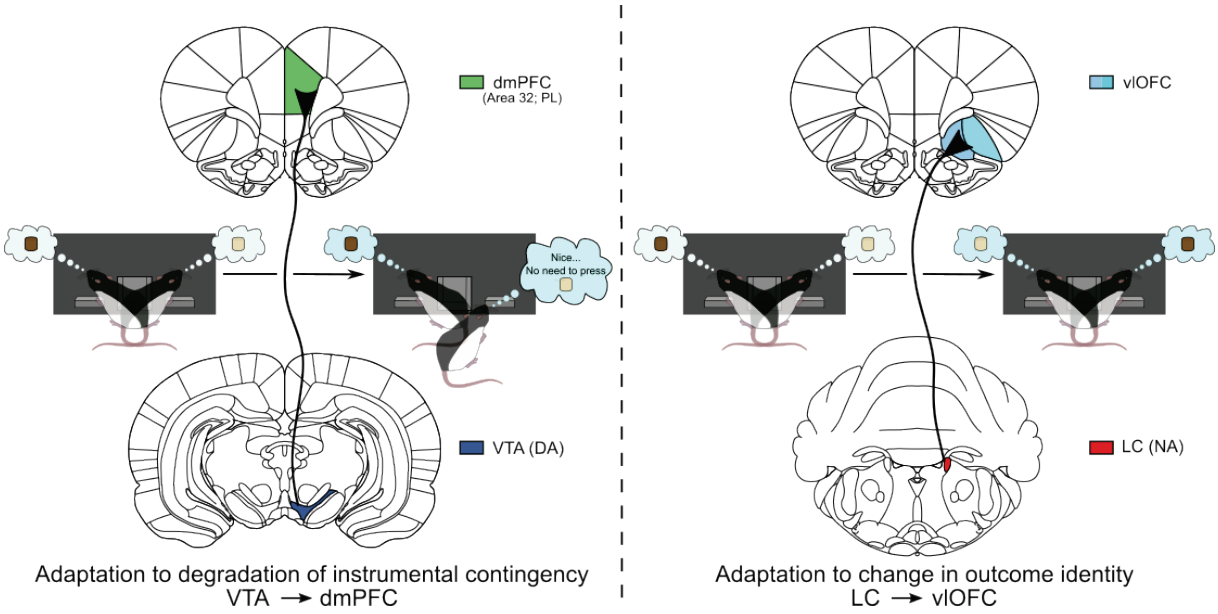
Adaptation to environmental changes is the core of goal-directed behaviour. To cope with these changes, current evidence highlights the importance of distinct PFC areas, such as the dmPFC and the OFC. Here, we have argued that dopaminergic modulation in the dmPFC and noradrenergic modulation in the vlOFC 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 vlOFC 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 vlOFC 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 vlOFC. 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 vlOFC
610 appears to be a particularly important NA target and we argue that NA signalling in vlOFC,
611 but not dmPFC, plays a specific role in adapting to changes in outcome identity (Cerpa et al.,
612 2018). Noradrenergic signalling in the vlOFC has already been proposed as a mechanism to
613 allow flexible integration of changes in the environment related to stimulus-guided behaviours

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

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



644

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 vlOFC
651 (right panel). dmPFC: dorsomedial prefrontal cortex; PL: prelimbic cortex; VTA: ventral
652 tegmental area; DA: dopamine; LC: locus coeruleus; NA: noradrenaline; vlOFC: ventral and
653 lateral regions of OFC.

654

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 noradenergic 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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Dalley, J. W., Cardinal, R. N., & Robbins, T. W. (2004). Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. *Neurosci Biobehav Rev, 28*(7), 771-784. Retrieved from D:\W3\Articles téléchargés\PDF_D\Dalley_NBBR_2004_PfcRatReview.pdf
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15555683

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

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

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

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

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

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

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

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

Dickinson, A. (1985). Actions and habits: the development of behavioural anatomy. *Philosophical Transactions of The Royal Society B, 308*(1135), 67-78. doi:https://doi.org/10.1098/rstb.1985.0010

Dickinson, A. (1994). Instrumental Conditioning. In N. J. Mackintosh (Ed.), *Animal Learning and Cognition* (pp. 45-79): Academic Press.

Dickinson, A., & Mulatero, C. W. (1989). Reinforcer specificity of the suppression of instrumental performance on a non-contingent schedule. *Behav Processes, 19*(1-3), 167-180. doi:10.1016/0376-6357(89)90039-9

Durstewitz, D., & Seamans, J. K. (2008). The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyltransferase genotypes and schizophrenia. *Biol Psychiatry, 64*(9), 739-749. doi:10.1016/j.biopsych.2008.05.015

Ellwood, I. T., Patel, T., Wadia, V., Lee, A. T., Liptak, A. T., Bender, K. J., & Sohal, V. S. (2017). Tonic or Phasic Stimulation of Dopaminergic Projections to Prefrontal Cortex Causes Mice to Maintain or Deviate from Previously Learned Behavioral Strategies. *J Neurosci, 37*(35), 8315-8329. doi:10.1523/JNEUROSCI.1221-17.2017

Eschenko, O., Magri, C., Panzeri, S., & Sara, S. J. (2012). Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. *Cereb Cortex, 22*(2), 426-435. doi:10.1093/cercor/bhr121

Fallon, J. H. (1981). Collateralization of monoamine neurons: mesotelencephalic dopamine projections to caudate, septum, and frontal cortex. *J Neurosci, 1*(12), 1361-1368. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/6172572

Fallon, J. H., & Loughlin, A. (1987). Monoamine Innervation of Cerebral Cortex and a Theory of the Role of Monoamines in Cerebral Cortex and Basal Ganglia. In E. G. Jones & A. Peters (Eds.), *Cerebral Cortex* (Vol. 6): Springer, Boston, MA.

Fallon, J. H., & Moore, R. Y. (1978). Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. *J Comp Neurol, 180*(3), 545-580. doi:10.1002/cne.901800310

Feng, J., Zhang, C., Lischinsky, J. E., Jing, M., Zhou, J., Wang, H., . . . Li, Y. (2019). A Genetically Encoded Fluorescent Sensor for Rapid and Specific In Vivo Detection of Norepinephrine. *Neuron, 102*(4), 745-761 e748. doi:10.1016/j.neuron.2019.02.037

Floresco, S. B. (2013). Prefrontal dopamine and behavioral flexibility: shifting from an "inverted-U" toward a family of functions. *Front Neurosci, 7*, 62. doi:10.3389/fnins.2013.00062

Floresco, S. B., Block, A. E., & Tse, M. T. (2008). Inactivation of the medial prefrontal cortex of the rat impairs strategy set-shifting, but not reversal learning, using a novel, automated procedure. *Behav Brain Res, 190*(1), 85-96. doi:10.1016/j.bbr.2008.02.008

Floresco, S. B., Magyar, O., Ghods-Sharifi, S., Vexelman, C., & Tse, M. T. (2006). Multiple dopamine receptor subtypes in the medial prefrontal cortex of the rat regulate set-shifting. *Neuropsychopharmacology, 31*(2), 297-309. doi:10.1038/sj.npp.1300825

Fresno, V., Parkes, S. L., Faugere, A., Coutureau, E., & Wolff, M. (2019). A thalamocortical circuit for updating action-outcome associations. *Elife, 8*. doi:10.7554/eLife.46187

Gallagher, M., McMahan, R. W., & Schoenbaum, G. (1999). Orbitofrontal cortex and representation of incentive value in associative learning. *J Neurosci, 19*(15), 6610-6614. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10414988

Gaspar, P., Bloch, B., & Le Moine, C. (1995). D1 and D2 receptor gene expression in the rat frontal cortex: cellular localization in different classes of efferent neurons. *Eur J Neurosci, 7*(5), 1050-1063. doi:10.1111/j.1460-9568.1995.tb01092.x

Gee, S., Ellwood, I., Patel, T., Luongo, F., Deisseroth, K., & Sohal, V. S. (2012). Synaptic activity unmasks dopamine D2 receptor modulation of a specific class of layer V pyramidal neurons in prefrontal cortex. *J Neurosci, 32*(14), 4959-4971. doi:10.1523/JNEUROSCI.5835-11.2012

Goarin, E. H. F., Lingawi, N. W., & Laurent, V. (2018). Role Played by the Passage of Time in Reversal Learning. *Front Behav Neurosci, 12*, 75. doi:10.3389/fnbeh.2018.00075

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Jepma, M., Brown, S., Murphy, P. R., Koelewijn, S. C., de Vries, B., van den Maagdenberg, A. M., & Nieuwenhuis, S. (2018). Noradrenergic and Cholinergic Modulation of Belief Updating. *J Cogn Neurosci*, 1-18. doi:10.1162/jocn_a_01317

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

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

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

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

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

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

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

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

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

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

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

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

Levitt, P., & Moore, R. Y. (1978). Noradrenaline neuron innervation of the neocortex in the rat. *Brain Res, 139*(2), 219-231. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/624057

Lex, B., & Hauber, W. (2010). The role of dopamine in the prelimbic cortex and the dorsomedial striatum in instrumental conditioning. *Cereb Cortex, 20*(4), 873-883. doi:10.1093/cercor/bhp151

Likhtik, E., & Johansen, J. P. (2019). Neuromodulation in circuits of aversive emotional learning. *Nat Neurosci, 22*(10), 1586-1597. doi:10.1038/s41593-019-0503-3

Lindvall, O., Bjorklund, A., & Divac, I. (1978). Organization of catecholamine neurons projecting to the frontal cortex in the rat. *Brain Res, 142*(1), 1-24. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/626911

Linley, S. B., Hoover, W. B., & Vertes, R. P. (2013). Pattern of distribution of serotonergic fibers to the orbitomedial and insular cortex in the rat. *J Chem Neuroanat, 48-49*, 29-45. doi:10.1016/j.jchemneu.2012.12.006

Lopatina, N., Sadacca, B. F., McDannald, M. A., Styer, C. V., Peterson, J. F., Cheer, J. F., & Schoenbaum, G. (2017). Ensembles in medial and lateral orbitofrontal cortex construct cognitive maps emphasizing different features of the behavioral landscape. *Behav Neurosci, 131*(3), 201-212. doi:10.1037/bne0000195

Loughlin, S. E., & Fallon, J. H. (1984). Substantia nigra and ventral tegmental area projections to cortex: topography and collateralization. *Neuroscience, 11*(2), 425-435. doi:10.1016/0306-4522(84)90034-4

Loughlin, S. E., Foote, S. L., & Grzanna, R. (1986). Efferent projections of nucleus locus coeruleus: morphologic subpopulations have different efferent targets. *Neuroscience, 18*(2), 307-319. doi:10.1016/0306-4522(86)90156-9

Manning, E. E., Dombrovski, A. Y., Torregrossa, M. M., & Ahmari, S. E. (2019). Impaired instrumental reversal learning is associated with increased medial prefrontal cortex activity in Sapap3 knockout mouse model of compulsive behavior. *Neuropsychopharmacology, 44*(8), 1494-1504. doi:10.1038/s41386-018-0307-2

Masaki, D., Yokoyama, C., Kinoshita, S., Tsuchida, H., Nakatomi, Y., Yoshimoto, K., & Fukui, K. (2006). Relationship between limbic and cortical 5-HT neurotransmission and acquisition and reversal learning in a go/no-go task in rats. *Psychopharmacology (Berl), 189*(2), 249-258. doi:10.1007/s00213-006-0559-0

Mason, S. T., & Iversen, S. D. (1978). Reward, attention and the dorsal noradrenergic bundle. *Brain Res, 150*(1), 135-148. doi:10.1016/0006-8993(78)90658-3

Matamales, M., Skrbis, Z., Hatch, R. J., Balleine, B. W., Gotz, J., & Bertran-Gonzalez, J. (2016). Aging-Related Dysfunction of Striatal Cholinergic Interneurons Produces Conflict in Action Selection. *Neuron, 90*(2), 362-373. doi:10.1016/j.neuron.2016.03.006

McGaughy, J., Ross, R. S., & Eichenbaum, H. (2008). Noradrenergic, but not cholinergic, deafferentation of prefrontal cortex impairs attentional set-shifting. *Neuroscience, 153*(1), 63-71. doi:10.1016/j.neuroscience.2008.01.064

Milstein, J. A., Lehmann, O., Theobald, D. E., Dalley, J. W., & Robbins, T. W. (2007). Selective depletion of cortical noradrenaline by anti-dopamine beta-hydroxylase-saporin impairs attentional function and enhances the effects of guanfacine in the rat. *Psychopharmacology (Berl), 190*(1), 51-63. doi:10.1007/s00213-006-0594-x

Mokler, D. J., Miller, C. E., & McGaughy, J. A. (2017). Evidence for a role of corticopetal, noradrenergic systems in the development of executive function. *Neurobiol Learn Mem, 143*, 94-100. doi:10.1016/j.nlm.2017.02.011

Moorman, D. E., & Aston-Jones, G. (2015). Prefrontal neurons encode context-based response execution and inhibition in reward seeking and extinction. *Proc Natl Acad Sci U S A, 112*(30), 9472-9477. doi:10.1073/pnas.1507611112

Morrison, J. H., Grzanna, R., Molliver, M. E., & Coyle, J. T. (1978). The distribution and orientation of noradrenergic fibers in neocortex of the rat: an immunofluorescence study. *J Comp Neurol, 181*(1), 17-39. doi:10.1002/cne.901810103

Morrison, J. H., Molliver, M. E., & Grzanna, R. (1979). Noradrenergic innervation of cerebral cortex: widespread effects of local cortical lesions. *Science, 205*(4403), 313-316. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/451605

Morrison, J. H., Molliver, M. E., Grzanna, R., & Coyle, J. T. (1981). The intra-cortical trajectory of the coeruleo-cortical projection in the rat: a tangentially organized cortical afferent. *Neuroscience, 6*(2), 139-158. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7012664

Mueller, D., Porter, J. T., & Quirk, G. J. (2008). Noradrenergic signaling in infralimbic cortex increases cell excitability and strengthens memory for fear extinction. *J Neurosci, 28*(2), 369-375. doi:10.1523/JNEUROSCI.3248-07.2008

Mukherjee, A., & Caroni, P. (2018). Infralimbic cortex is required for learning alternatives to prelimbic promoted associations through reciprocal connectivity. *Nat Commun, 9*(1), 2727. doi:10.1038/s41467-018-05318-x

Muller, T. H., Mars, R. B., Behrens, T. E., & O'Reilly, J. X. (2019). Control of entropy in neural models of environmental state. *Elife, 8*. doi:10.7554/eLife.39404

Murphy, M. J. M., & Deutch, A. Y. (2018). Organization of afferents to the orbitofrontal cortex in the rat. *J Comp Neurol, 526*(9), 1498-1526. doi:10.1002/cne.24424

Naneix, F., Marchand, A. R., Di Scala, G., Pape, J. R., & Coutureau, E. (2009). A role for medial prefrontal dopaminergic innervation in instrumental conditioning. *J Neurosci, 29*(20), 6599-6606. doi:10.1523/JNEUROSCI.1234-09.2009

Naneix, F., Marchand, A. R., Di Scala, G., Pape, J. R., & Coutureau, E. (2012). Parallel maturation of goal-directed behavior and dopaminergic systems during adolescence. *J Neurosci, 32*(46), 16223-16232. doi:10.1523/JNEUROSCI.3080-12.2012

Naneix, F., Marchand, A. R., Pichon, A., Pape, J. R., & Coutureau, E. (2013). Adolescent stimulation of D2 receptors alters the maturation of dopamine-dependent goal-directed behavior. *Neuropsychopharmacology, 38*(8), 1566-1574. doi:10.1038/npp.2013.55

Nassar, M. R., Rumsey, K. M., Wilson, R. C., Parikh, K., Heasly, B., & Gold, J. I. (2012). Rational regulation of learning dynamics by pupil-linked arousal systems. *Nat Neurosci, 15*(7), 1040-1046. doi:10.1038/nn.3130

Newman, L. A., Darling, J., & McGaughy, J. (2008). Atomoxetine reverses attentional deficits produced by noradrenergic deafferentation of medial prefrontal cortex. *Psychopharmacology (Berl), 200*(1), 39-50. doi:10.1007/s00213-008-1097-8

Nieuwenhuys, R. (1985). *Chemoarchitecture of the Brain*: Springer-Verlag Berlin Heidelberg.

Nimitvilai, S., Lopez, M. F., Mulholland, P. J., & Woodward, J. J. (2017). Ethanol Dependence Abolishes Monoamine and GIRK (Kir3) Channel Inhibition of Orbitofrontal Cortex Excitability. *Neuropsychopharmacology, 42*(9), 1800-1812. doi:10.1038/npp.2017.22

Obermayer, J., Luchicchi, A., Heistek, T. S., de Kloet, S. F., Terra, H., Bruinsma, B., . . . Mansvelder, H. D. (2019). Prefrontal cortical ChAT-VIP interneurons provide local excitation by cholinergic synaptic transmission and control attention. *Nat Commun, 10*(1), 5280. doi:10.1038/s41467-019-13244-9

Ostlund, S. B., & Balleine, B. W. (2005). Lesions of medial prefrontal cortex disrupt the acquisition but not the expression of goal-directed learning. *J Neurosci, 25*(34), 7763-7770. doi:10.1523/JNEUROSCI.1921-05.2005

Ostlund, S. B., & Balleine, B. W. (2007). Orbitofrontal cortex mediates outcome encoding in Pavlovian but not instrumental conditioning. *J Neurosci, 27*(18), 4819-4825. doi:10.1523/JNEUROSCI.5443-06.2007

Panayi, M. C., & Killcross, S. (2018). Functional heterogeneity within the rodent lateral orbitofrontal cortex dissociates outcome devaluation and reversal learning deficits. *Elife, 7*. doi:10.7554/eLife.37357

Papadopoulos, G. C., & Parnavelas, J. G. (1991). Monoamine systems in the cerebral cortex: evidence for anatomical specificity. *Prog Neurobiol, 36*(3), 195-200. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/2017550

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

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

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

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

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

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

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

Preuschoff, K., t Hart, B. M., & Einhauser, W. (2011). Pupil Dilation Signals Surprise: Evidence for Noradrenaline's Role in Decision Making. *Front Neurosci, 5*, 115. doi:10.3389/fnins.2011.00115

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

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

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

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

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

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

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

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

Robertson, S. D., Plummer, N. W., de Marchena, J., & Jensen, P. (2013). Developmental origins of central norepinephrine neuron diversity. *Nat Neurosci, 16*(8), 1016-1023. doi:10.1038/nn.3458

Rudebeck, P. H., & Murray, E. A. (2011). Dissociable effects of subtotal lesions within the macaque orbital prefrontal cortex on reward-guided behavior. *J Neurosci, 31*(29), 10569-10578. doi:10.1523/JNEUROSCI.0091-11.2011

Sadacca, B. F., Wikenheiser, A. M., & Schoenbaum, G. (2016). Toward a theoretical role for tonic norepinephrine in the orbitofrontal cortex in facilitating flexible learning. *Neuroscience*. doi:10.1016/j.neuroscience.2016.04.017

Santana, N., Mengod, G., & Artigas, F. (2009). Quantitative analysis of the expression of dopamine D1 and D2 receptors in pyramidal and GABAergic neurons of the rat prefrontal cortex. *Cereb Cortex, 19*(4), 849-860. doi:10.1093/cercor/bhn134

Sara, S. J., & Bouret, S. (2012). Orienting and reorienting: the locus coeruleus mediates cognition through arousal. *Neuron, 76*(1), 130-141. doi:10.1016/j.neuron.2012.09.011

Sara, S. J., & Segal, M. (1991). Plasticity of sensory responses of locus coeruleus neurons in the behaving rat: implications for cognition. *Prog Brain Res, 88*, 571-585. doi:10.1016/s0079-6123(08)63835-2

Saunders, B. T., Richard, J. M., Margolis, E. B., & Janak, P. H. (2018). Dopamine neurons create Pavlovian conditioned stimuli with circuit-defined motivational properties. *Nat Neurosci, 21*(8), 1072-1083. doi:10.1038/s41593-018-0191-4

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science, 275*(5306), 1593-1599. doi:10.1126/science.275.5306.1593

Schultz, W., & Dickinson, A. (2000). Neuronal coding of prediction errors. *Annu Rev Neurosci, 23*, 473-500. doi:10.1146/annurev.neuro.23.1.473

Schwarz, L. A., Miyamichi, K., Gao, X. J., Beier, K. T., Weissbourd, B., DeLoach, K. E., . . . Luo, L. (2015). Viral-genetic tracing of the input-output organization of a central noradrenaline circuit. *Nature, 524*(7563), 88-92. doi:10.1038/nature14600

Seamans, J. K., & Yang, C. R. (2004). The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog Neurobiol, 74*(1), 1-58. doi:10.1016/j.pneurobio.2004.05.006

Seguela, P., Watkins, K. C., Geffard, M., & Descarries, L. (1990). Noradrenaline axon terminals in adult rat neocortex: an immunocytochemical analysis in serial thin sections. *Neuroscience, 35*(2), 249-264. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/2116602

Sharpe, M. J., & Killcross, S. (2014). The prelimbic cortex uses higher-order cues to modulate both the acquisition and expression of conditioned fear. *Front Syst Neurosci, 8*, 235. doi:10.3389/fnsys.2014.00235

Sharpe, M. J., & Killcross, S. (2018). Modulation of attention and action in the medial prefrontal cortex of rats. *Psychol Rev, 125*(5), 822-843. doi:10.1037/rev0000118

Sharpe, M. J., Stalnaker, T., Schuck, N. W., Killcross, S., Schoenbaum, G., & Niv, Y. (2019). An Integrated Model of Action Selection: Distinct Modes of Cortical Control of Striatal Decision Making. *Annu Rev Psychol, 70*, 53-76. doi:10.1146/annurev-psych-010418-102824

Shaw, C. L., Watson, G. D. R., Hallock, H. L., Cline, K. M., & Griffin, A. L. (2013). The role of the medial prefrontal cortex in the acquisition, retention, and reversal of a tactile visuospatial conditional discrimination task. *Behav Brain Res, 236*(1), 94-101. doi:10.1016/j.bbr.2012.08.024

Simpson, K. L., Waterhouse, B. D., & Lin, R. C. (1999). Origin, distribution, and morphology of galaninergic fibers in the rodent trigeminal system. *J Comp Neurol, 411*(3), 524-534. doi:10.1002/(sici)1096-9861(19990830)411:3<524::aid-cne13>3.0.co;2-x

Sobel, E., & Corbett, D. (1984). Axonal branching of ventral tegmental and raphe projections to the frontal cortex in the rat. *Neurosci Lett, 48*(2), 121-125. doi:10.1016/0304-3940(84)90006-5

Stefani, M. R., & Moghaddam, B. (2006). Rule learning and reward contingency are associated with dissociable patterns of dopamine activation in the rat prefrontal

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Chemogenetic Locus Coeruleus Activation. *Neuron, 103*(4), 702-718 e705. doi:10.1016/j.neuron.2019.05.034

Zimmermann, K. S., Li, C. C., Rainnie, D. G., Ressler, K. J., & Gourley, S. L. (2018). Memory Retention Involves the Ventrolateral Orbitofrontal Cortex: Comparison with the Basolateral Amygdala. *Neuropsychopharmacology, 43*(3), 674. doi:10.1038/npp.2017.219

Zimmermann, K. S., Yamin, J. A., Rainnie, D. G., Ressler, K. J., & Gourley, S. L. (2017). Connections of the Mouse Orbitofrontal Cortex and Regulation of Goal-Directed Action Selection by Brain-Derived Neurotrophic Factor. *Biol Psychiatry, 81*(4), 366-377. doi:10.1016/j.biopsych.2015.10.026