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**PERSPECTIVE**

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

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## 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 (vIOFC). Indeed, vIOFC is not necessary to learn about action-outcome associations but appears specifically involved when outcome identity is unexpectedly changed. Unlike the mPFC, the vIOFC 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 vIOFC'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 vIOFC 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 (vOFC). 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 vOFC and the medial wall of the PFC, the dopaminergic innervation is much stronger in the medial wall compared to the vOFC (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 vOFC. 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 vOFC.

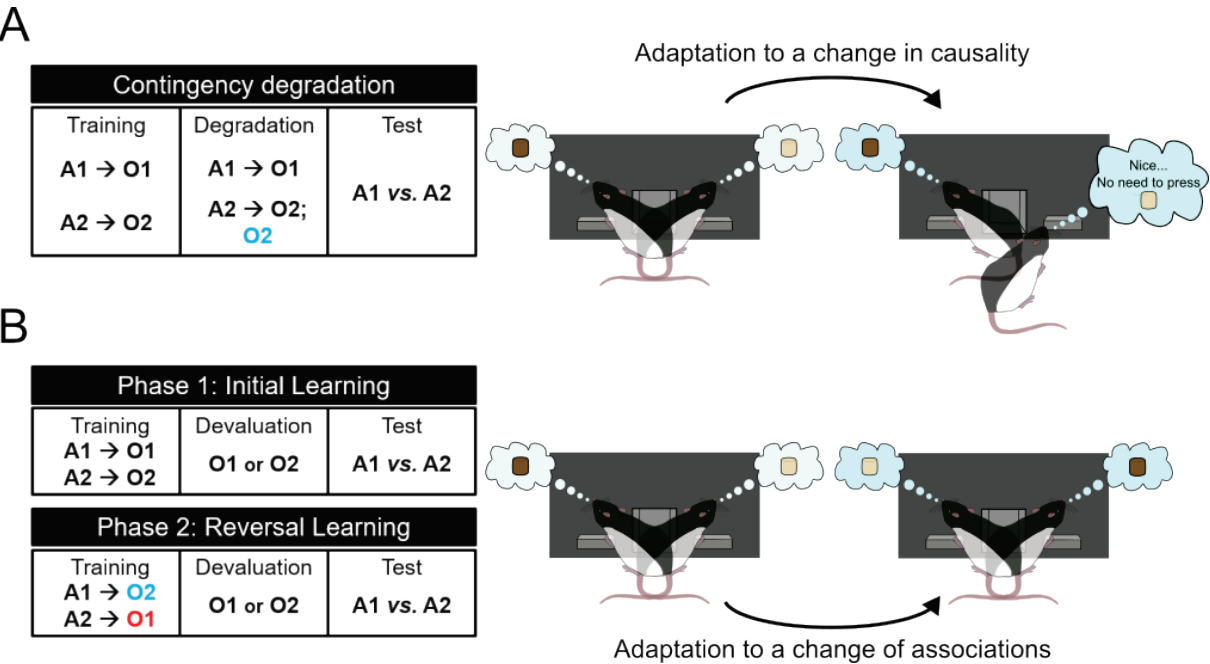
## **II. Adapting to changes in action-outcome associations**

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 ( $P_{o/\emptyset}$ ). 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,  $P_{o/\emptyset}$  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 ( $A2 \rightarrow O2$ ) 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 ( $A1 \rightarrow O1$ ) 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.,  $A1 \rightarrow O1$  and  $A2 \rightarrow O2$ ). Then, during a reversal phase, the outcome associated with each response is switched (i.e.,  $A1 \rightarrow O2$  and  $A2 \rightarrow O1$ ). 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

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

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

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

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

However, it appears that vOFC *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 vOFC while rats underwent an outcome identity reversal procedure or a procedure in which new outcomes were associated with familiar actions. We found that vOFC inhibition only impaired instrumental outcome devaluation if the A-O associations had been unexpectedly modified (Parkes et al., 2018). Similarly, vOFC 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 vOFC 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 vOFC 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 vOFC 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 vOFC 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 vOFC 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 vOFC), although the involvement of vOFC in instrumental contingency degradation remains unclear. By contrast, adapting to changes in the A-O that relate to outcome identity may preferentially involve the vOFC 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 vOFC 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 &

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

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

Nevertheless, like the LC-NA system, the dopaminergic system organization is well suited to provide discrete dopaminergic signals to its different targets. Evidence indicates that different projecting-neurons are topographically organized within the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc). Thus, the majority of neurons projecting to a certain PFC area do not collateralize to other subcortical areas (Deniau et al 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 vOFC 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 vOFC 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 vOFC 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 vOFC, 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 vOFC 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 vOFC 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 mnemonic 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 vOFC 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. Serotonergic 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 serotonergic 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

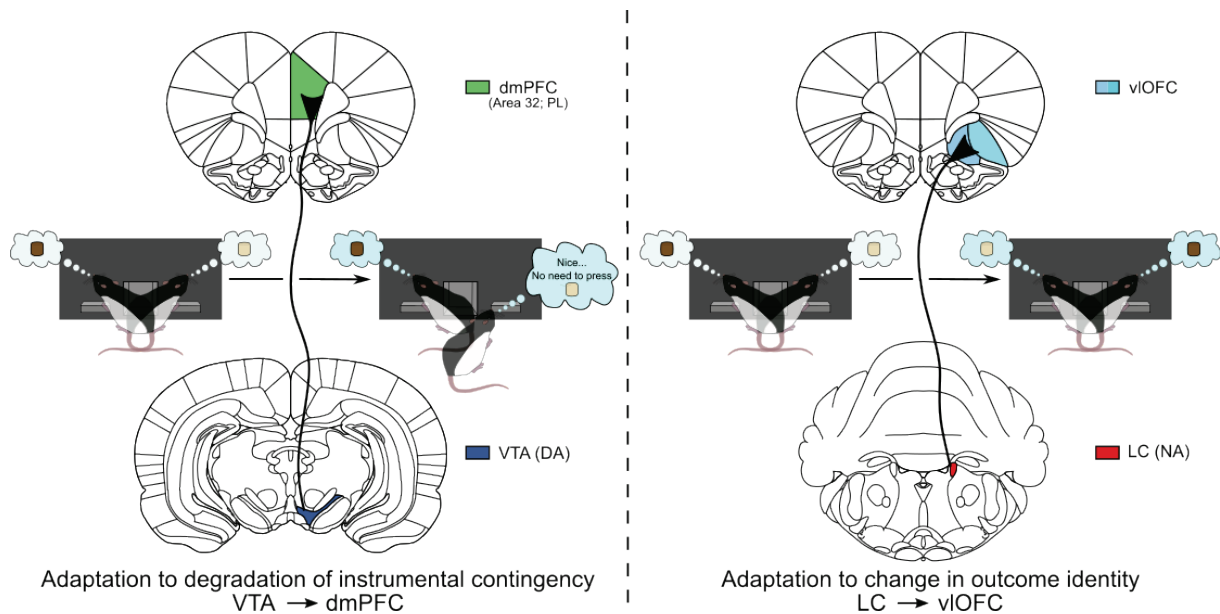
Adaptation to environmental changes is the core of goal-directed behaviour. To cope with these changes, current evidence highlights the importance of distinct PFC areas, such as the dmPFC and the OFC. Here, we have argued that dopaminergic modulation in the dmPFC and noradrenergic modulation in the vOFC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

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

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



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

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