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REVIEW

TOWARD A THEORETICAL ROLE FOR TONIC NOREPINEPHRINE IN THE ORBITOFRONTAL CORTEX IN FACILITATING FLEXIBLE LEARNING

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Abstract—To adaptively respond in a complex, changing world, animals need to flexibly update their understanding of the world when their expectations are violated. Though several brain regions in rodents and primates have been implicated in aspects of this updating, current models of orbitofrontal cortex (OFC) and norepinephrine neurons of the locus coeruleus (LC-NE) suggest that each plays a role in responding to environmental change, where the OFC allows updating of prior learning to occur without overwriting or unlearning one's previous understanding of the world that changed, while elevated tonic NE allows for increased flexibility in behavior that tracks an animal's uncertainty. In light of recent studies highlighting a specific LC-NE projection to the OFC, in this review we discuss current models of OFC and NE function, and their potential synergy in the updating of associations following environmental change.

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Key words: orbitofrontal cortex, norepinephrine, reinforcement learning, ensemble states, flexible learning.

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INTRODUCTION

We, like all animals, live in a constantly changing world. When there's a change in something familiar (e.g. usually delicious and safe oysters just made me sick), we're confronted with a difficult problem: which beliefs do we update based on this new knowledge? Do we assign this new knowledge to the familiar thing (oysters from this restaurant must be less safe than I thought they were, and I shouldn't eat them) or do we blame something new (today was very different: it was really hot outside and there was a new chef; oysters at this restaurant are otherwise just fine to eat)? Choices like these have been the focus of formal models of learning, where they are termed a 'credit assignment' problem (Sutton, 1984; Dayan and Balleine, 2002). While most models focus on assigning credit or blame to specific behaviors, other models instead update beliefs about the world. In such models, each configuration of features to which learning can be assigned is termed a 'state': the dilemma is then between assigning learning to an existing state, or creating a new state to index the unexpected experience (Redish et al., 2007; Wilson et al., 2014). These formal models require two features: a way to represent the existing states to which learning can be assigned, and a mechanism by which new states can be created if necessary.

While it is clear that the brain has a framework for implementing the state-representing and creating functions captured by these models, the exact mechanisms and circuits involved are still debated. Identifying the precise mechanism of state creation would be useful, as some psychiatric disorders (e.g. traumatic stress disorders, drug abuse, problem gambling) have been proposed to arise from difficulty in updating previous learning with new knowledge as, for example, when sounds that were formerly predictors of threats are now non-threatening, or when the use of a formerly pleasurable drug no longer evokes the same pleasure or now leads to adverse outcomes (Hyman, 2005; Redish et al., 2007; Gershman et al., 2013; Vanes et al., 2014). While there are several neural circuits implicated in 'state representation', or signaling features

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Abbreviations: LC, locus coeruleus; LC-NE, norepinephrine neurons of the locus coeruleus; mPFC, medial prefrontal; NE, noradrenergic; OFC, orbitofrontal cortex.

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of which state an animal is in (specifically: OFC, hippocampus, dorsal striatum, and cholinergic interneurons of the striatum), there are limited data concerning what pushes new states to be created. As NE rises with increasing mismatches between familiar things and their expected outcomes, or more specifically, when there are mismatches of expected task contingencies (either between an animal's choice and the outcome of that choice, or between salient outcomes and their predictors in the environment), computational theories of tonic NE function note that this uncertainty signal may play a role in driving behavioral change to cope with a changing environment (Yu and Dayan, 2005; Cohen et al., 2007; Doya, 2008). These models of NE function (along with recent experimental work; Tervo et al., 2014) focus on the role of rising NE in controlling the variability and flexibility of ongoing behavior or attention (as has been attributed to tonic NE release in the cingulate [ACC] and medial prefrontal [mPFC] cortices), both essential features in overall cognitive flexibility. However, if this uncertainty signal were additionally available to state-representing circuits, it would be ideal for driving state updating for the assignment of new learning (Courville et al., 2006), and indeed the OFC receives robust input from norepinephrine neurons of the locus coeruleus (LC-NE; Agster et al., 2013). Thus, based on these data, we posit that rising tonic levels of NE in OFC could serve as a state creation signal, allowing the creation of new associations in a novel state rather than modifying previously learnt associations in an existing state. This proposal adds an additional complementary role for tonic NE in driving cognitive flexibility. Indeed, recent reports on the anatomical specificity of NE projections in the forebrain (Chandler et al., 2013, 2014b) show that a unique subset of neurons project to each of these frontal targets (OFC, ACC, mPFC), leading to the tantalizing possibility that subsets of locus coeruleus (LC) neurons selectively modulate each of these aspects of flexible behavior including our hypothesized role for NE in OFC, independently. In what follows, we outline the literature describing the parallel roles of OFC and NE neurons and our hypothesis that NE in the OFC is a critical signal driving the assignment of learning to a new or old associative state.

The orbitofrontal cortex (OFC) as a database of associations

As mentioned, one prominent 'state-representing' circuit is the OFC. The impairment in flexible learning caused by OFC lesions (Teitelbaum, 1964; Schoenbaum et al., 2002; Stalnaker et al., 2007; Rudebeck and Murray, 2008) and inactivation (Ghods-Sharifi et al., 2008; Burke et al., 2009) is described by recent modeling (Wilson et al., 2014) as an inability to create a new state to which learning can be assigned following a change in reward contingencies (e.g. a cue that predicted reward no longer does). This proposal holds that, with an intact OFC, learning following a change in reward contingences allows the old associations to be preserved, tagged by the old OFC state. This process has the dual benefit of allowing the new associations to be acquired more rapidly while preserving the old associations, so they can be rapidly re-expressed by reactivating the OFC ensemble encoding the old state if it is encountered. This model predicts that the failure to signal a new state (caused by inactivation of the OFC, or damage from psychostimulant use for example Schoenbaum et al., 2004; Lucantonio et al., 2015) will cause old task contingencies be overwritten, resulting in both slower acquisition of the new task contingencies and slower recovery or reinstatement of the old associations. Notably, this model also describes OFC's role in a range of other tasks (Stalnaker et al., 2015)

Damage to the OFC causes deficits consistent with a loss of state information, and the activity of OFC neurons themselves is well described by models of learning state representations. For example, while there are many potential correlates that might constitute a state representation, one prominent example is in representing psychological or neural states through the relative firing rates of ensembles of neurons (Abeles et al., 1995). Such 'firing rate-state' models have been successful in modeling both choice-related hidden variables and the dynamics of perceptual processes (Seidemann et al., 1996; Jones et al., 2007; Kemere et al., 2008; Bollimunta et al., 2012; Deco et al., 2013; Moran and Katz, 2014). In order to be considered a state in the context of reinforcement learning, certain features for these ensemble states are essential: (1) differentiable representations of each relevant feature of a state to which credit could be assigned and (2) the stability of representations in the absence of learning and changes in state representation with learning.

The activity of OFC neurons seems to meet the above criteria, as (1) OFC neurons fire to all relevant cues and events in both Pavlovian and instrumental tasks, including exhibiting differential activity to different task phases (i.e. are therefore able to represent all relevant features of task space/outcome prediction space) and change their sensitivity to specific task parameters on the basis of their relevance, (e.g. compare Schoenbaum and Eichenbaum, 1995; Ramus and Eichenbaum, 2000) or (Lara et al., 2009), and (2) OFC neurons remap (in seemingly random fashion) following reversal, as compared to other areas that track value more clearly (Stalnaker et al., 2009). Interestingly, remapping in OFC seems to *lag* the remapping of neurons in other regions (like the amygdala), and behavior (Schoenbaum et al., 1999), further suggesting that the activity of OFC neurons is correlated not with changes in behavior following errors in prediction, but instead is correlated with the assignment of new learning once a new constellation of cues is selected for credit assignment. Taken together, OFC seems a likely candidate to represent states akin to reinforcement learning state-space models, as lesions of OFC impair behavior as an inability to use reinforcement learning states might, and the activity of OFC neurons seems to meet criteria for encoding task states. So, if the OFC is responsible for representing states, what tells the OFC when to map out a new state?

A role for tonic norepinephrine in state creation

Tonic activity in noradrenergic (NE) neurons of the LC could be responsible for driving a remapping process in

the OFC in response to changes in state. This need arises when task contingencies change dramatically and outcomes fail to match expectations, and one sees a rise in tonic NE in precisely these circumstances (Aston-Jones et al., 1997). This rise in tonic NE has been described as generally facilitating behavioral exploration (Aston-Jones et al., 1999; Shea-Brown et al., 2008; Jepma and Nieuwenhuis, 2011), with decreases in tonic NE described as facilitating the exploitation of particular task contingencies. These theories seem quite reasonable, as NE tone seems inextricably linked to behavior precisely when task contingencies are changing and the production of exploratory behavior would be advantageous: changes in LC activity are correlated with environmental uncertainty (Payzan-LeNestour et al., 2013), are correlated with changes in learning rate (Nassar et al., 2012), and precede changes in behavior (Bouret and Sara, 2004). Further, NE seems to have causal role in changing behavior and associative representations, as increases in global NE tone facilitate reversal (Seu et al., 2009) and extinction learning (Merlo and Izquierdo, 1967; Janak and Corbit, 2011), while decreases in NE tone in the cortex impair extinction (Mason and Fibiger, 1979; McCormick and Thompson, 1982), a topic recently reviewed in detail (Mueller and Cahill, 2010). Recently, modulation of NE release specifically in the ACC has been shown to have direct control of LC-NE over the stochastic versus strategic choice behavior (Tervo et al., 2014).

Though it has a direct role in guiding behavior, attention, and learning under changing contingencies, what are the potential circuit mechanisms of this action? One hypothesis is that NE acts as a 'network reset' switch for remapping cortical representations (Bouret and Sara, 2005). This seems particularly plausible, as tonic NE has been specifically implicated in functional connectivity changes that might lead to remapping-like effects by changing the relative strength of afferent vs. local, intrinsic input to a region (Hasselmo et al., 1997). Indeed, increases in NE tone can induce sudden changes in both local (Wallace et al., 2014) and global (Hermans et al., 2011) network connectivity and directly facilitate sensory cortical remapping (Greuel et al., 1988).

The anatomical and theoretical relationship between OFC and norepinephrine

Given the complementary roles of the OFC and LC-NE neurons, one might suspect that LC norepinephrine ought to have an influence over OFC, and indeed a recent quantification of NE input to the cortex has shown NE projections to both medial and lateral OFC are equivalent to other frontal cortical areas (Agster et al., 2013). Additional fresh evidence for LC-NE to OFC connectivity comes from several recent studies using transgenic rodents, which have highlighted subtle details of LC input to OFC. One study explored the relationship of inputs to LC neurons on the subsequent projections of those neurons (Schwarz et al., 2015). This study demonstrated that LC neurons projecting to the OFC receive inputs from an array of structures, including the central amygdala, auditory cortex, hippocampus, and the olfactory bulb, highlighting the breadth of information integrated in OFC projecting LC neurons. A second set of studies recently demonstrated a surprising specificity in LC-NE projections to frontal cortices, such that there is limited overlap between the LC's NE projections to OFC, PL and ACC (Chandler and Waterhouse, 2012; Chandler et al., 2013). Further work by this group has demonstrated unique physiological markers for neurons participating in the LC's array of projections (Chandler et al., 2014a). Taken together, these results raise the possibility of independent NE regulation of different frontal cortical regions, suggesting that NE's theorized roles in behavioral, attentional and associative flexibility are perhaps dissociable.

With the OFC's role in processing state information, NE's theorized role in driving an updating of cortical representations, and a specific connection from LC to OFC, we predict NE could exercise a direct control over the stability of OFC state representations and, thereby, affect the flexibility of learning and behavior. Our speculations on exactly how this might proceed in a standard contingency-reversal task are outlined in the schematic of Fig. 1. Under normal circumstances (Fig. 1A), a detection of the change in contingencies leads to a rise in tonic NE, which leads to a setting-aside of old cue-response behaviors and old cue-outcome associations: behavior approaches chance, and OFC activity is less correlated with the initial ensemble state (state 1). Acquisition of the reversal leads to a subsequent drop in NE (as confidence in task contingencies rises), which allows stabilization of a new set of cue-response behaviors and a new OFC state (state 2). With NE held artificially low via pharmacology or optogenetics (Fig. 1B), we predict OFC representations will become quite stable, sticking in an initial state following a change of task contingencies. A reversal of behavior may well proceed more slowly, as old contingencies are more difficult to disregard and the animal has difficulty in developing a model of the task. Conversely, with NE held artificially high (Fig. 1C), we predict OFC representations will become reliably unstable, cycling through a sequence of potential states trial-after-trial. Predicting how this would influence the resultant behavior are difficult as reversals might proceed quickly initially, since prior contingencies are disregarded, but more slowly thereafter, if unstable OFC state representations force acquisition to proceed through othercircuits.

However, does all current evidence point to a role of NE in OFC in state creation? Within this model of OFC, a rise in NE tone might enable creation of a new state in which to assign new associations (with old associations preserved). In contrast, associations might also be disregarded because they are erased and re-written, and, in fact, large increases in systemic NE do seem to facilitate old task contingencies being overwritten, as measured by a loss of renewal after extinction (Janak and Corbit, 2011); this loss of renewal is contrary to the predictions of new state creation with increases in NE. However, the interpretation of these data

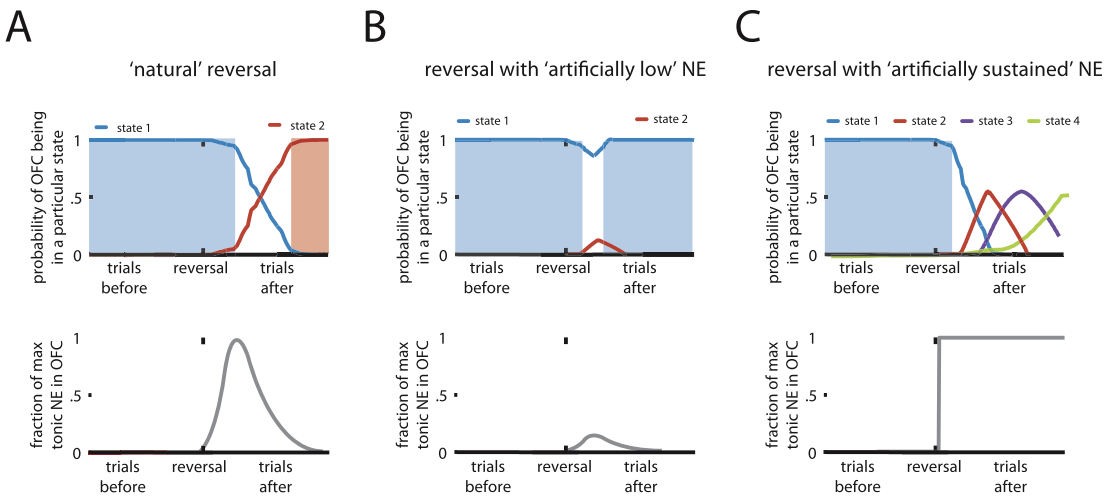

Fig. 1. Schematic for the hypothesized dynamics of OFC and tonic NE under normal reversals and manipulation of tonic NE levels (A) in a standard contingency reversal task, a detection of change leads to a rise of tonic NE, which we propose leads to a discarding of old cue-outcome associations, exemplified by OFC activity being less correlated with the initial ensemble state (state 1). As animals acquire the reversal, levels of NE drop, which allows stabilization of a new OFC state (state 2). (B) If, during the same task, NE was to be held artificially low, we would predict OFC representations should be stable in spite of the contingency change, remaining in an initial state. With OFC stuck reflecting pre-reversal associations, the reversal of behavior should proceed more slowly. (C) Conversely, if NE were to be held artificially high, this proposal would predict that OFC representations would likely become unstable, cycling through a sequence of potential states trial-after-trial. While reversal might proceed quickly initially (with pre-reversal OFC associations disregarded), the difficulty in developing a stable OFC state with NE high forces would acquisition to proceed through other (model-free) circuits, and overall the behavioral reversal might proceed at the same overall rate or slightly more quickly than under 'natural' circumstances.

is complicated. Firstly, a sustained elevated level of NE tone might engage cortical areas differently than the rise and fall of NE following an environmental change; sustained elevation of NE in the ACC leads to a prolonged period of behavioral variability (Tervo et al., 2014), and similarly elevated levels of NE in the OFC may prevent stable state creation. Secondly, NE, like other monoamines, seems to impart its influence with an 'inverted U-shaped' function, such that intermediate increases in tonic NE may have fundamentally different effects than maximal increases (Berridge and Waterhouse, 2003). In addition, as noted NE neurons show exquisite specificity in their terminal fields, such that projections including those to OFC, mPFC, and ACC, are made by separate subpopulations of NE neurons (Chandler et al., 2013). The functional importance of this anatomical insight is supported by site-specific manipulations, as ablation of NE inputs to mPFC disrupts mPFC-dependent set-shifting behavior, but has no impact on OFC-dependent reversal learning (McGaughy et al., 2008), a sign that there may be fundamental differences between local and global manipulation of NE in a range of learning tasks.

While we propose a specific role for norepinephrine in OFC, we hasten to note that OFC receives a full complement of monoaminergic inputs, all of which have a role in promoting OFC-dependent cognitive flexibility. For example, dopamine and serotonin in the OFC have been shown to competing roles in reversal learning as low levels of serotonin lead to impaired reversal learning in primates (Clarke et al., 2004; Evers et al., 2005) and rats (Nomura, 1992; Bari et al., 2010; Furr et al., 2012), though this might be receptor dependent (see Boulougouris et al., 2008), and low levels of dopamine can speed reversal learning (Crofts et al., 2001), while high levels can lead to perseverative responding (Ridley et al., 1981; Cools et al., 2001). While NE and serotonin have also been described as having competing roles in promoting flexible behavior (Boureau and Dayan, 2011), for our purposes the relevant comparison is between NE and dopamine. The hippocampus has been proposed to play a role in representing associative states similar to the role we describe for OFC here, and Redish and colleagues have a prominent model (Redish et al., 2007), extended by others (Gershman et al., 2010), suggesting low levels of dopamine in the hippocampus might produce the state-creating effects we attribute to rising tonic NE in the OFC. Here NE and dopamine might be complimentary, such that both the rise of NE and fall in DA might be necessary for new state creation, or each alone may be sufficient. Indeed, there well may be multiple ways these monoamines can interact and give rise to a balance of stable and flexible behavior, as their balance in the frontal cortex seems essential for local circuit function thought to underlie aspects of working memory and cognitive control (Arnsten et al., 2012), and the study of their interaction in OFC in the cognitive flexibility described here may be particularly fruitful.

In summary, OFC lesions and inactivation cause impairment in flexible learning and behavior, which have been described by recent modeling work as an inability to create a new state to which learning can be assigned, following a change in reward contingencies. Tonic activity in NE neurons of the LC rises when task contingencies change and outcomes fail to match expectations, systemic increases in NE tone facilitate reversal and extinction learning, site specific manipulations of NE have unique effects in each of the LC's frontal terminal fields, and changes in LC activity

precede changes in behavior. These effects of NE might occur if NE were acting within the OFC to enable creation of a new state to assign new associations (with old associations preserved), with a rise in tonic NE serving as a potential signal for animals to disregard old cue-outcome associations by remapping cortical representations. This process, though complementary, could be distinct from the proposed role of NE in other frontal circuits in controlling behavioral or attentional flexibility. While this hypothesis is speculative, it is consistent with the clear complementary roles of OFC and LC-NE in current modeling work and recent results describing new anatomical details of a LC-OFC relationship. And, importantly this hypothesis is testable. Experiments combining single unit recording with optogenetic approaches to selectively manipulate LC-NE projections to the OFC can be done to test the necessity and sufficiency of NE in updating OFC representations.

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