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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.

Contents

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