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Complementary influences of noradrenaline and dopamine in orchestrating a motivated social behavior

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Noradrenaline (NA) and dopamine (DA) modulate motivated behavior, yet their contributions to social interactions are difficult to disentangle due to overlapping responses and the unstructured nature of free behavior. We address this challenge by using a natural and spontaneous maternal behavior called 'pup retrieval'. Here, we synthesize recent work demonstrating that NA and DA play complementary but temporally dissociable roles during pup retrieval. The NA released from the locus coeruleus (LC) invigorates ongoing retrieval behavior, mobilizing downstream circuits to drive goal-directed action in response to pup distress. In contrast, dopamine released from the ventral tegmental area (VTA) improves future retrieval behavior by reducing latency across trials. These findings suggest a model in which NA governs the execution of the current caregiving episode, while DA updates motivational value to optimize future maternal responses. This framework may generalize to other forms of social and affiliative behavior requiring coordination between imminent action and long-term learning.

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The monoamine neurotransmitters noradrenaline (NA) and dopamine (DA) are fundamental to motivated behavior. The NA and DA have very similar molecular structures, their receptors exhibit crosstalk [e.g., Refs. [1–3]], they are sometimes released from the same synaptic terminals [4], and they exhibit similar response properties with respect to arousal state and salient stimuli [5]. Consequently, it can be difficult to distinguish their respective contributions to behavior. Moreover, quantifying the precision of the relationship between NA and DA and social interactions is complicated by the unstructured nature of free behavior. Here, I present recent data from my group on the contribution of NA release from the locus coeruleus (LC) and DA release from the ventral tegmental area (VTA) to the performance of an easily quantified, but richly controlled maternal behavior. These data argue that both the LC NA and VTA DA systems are essential for the behavior, but each exerts a distinct influence on motivation and reinforcement during retrieval. Synthesizing these findings with data gathered during structured but artificial tasks, we conclude that activity in those paradigms is broadly concordant with the influence of these two systems on maternal care and potentially other social behaviors. The NA released from LC neurons acutely invigorates ongoing retrieval behavior, mobilizing downstream circuits such as anterior cingulate cortex (ACC) to drive goal-directed action in response to pup distress. In contrast, DA released from the VTA neurons acts through a reinforcement learning mechanism to shape future behavioral performance, reducing latency, and increasing efficiency across trials. Together, these findings support a model in which NA invigorates the current behavioral trial, while DA prospectively updates motivational value to improve future behavioral trials.

Pup retrieval as a natural behavior model for social motivation

One of the most important aspects of maternal care in mice is keeping the pups warm and comfortable in the nest. Lacking hearing, vision, and thermoregulation, when pups get separated from the nest (either naturally or by an experimenter) they become cold and distressed; they alert the mother by emitting repetitive ultrasonic (50–80 kHz) vocalizations (USVs) [6,7]. The proper response to these cries is for the mother to locate the pup and retrieve it to the nest (pup retrieval). Typically, neither primiparous (first-time) mothers nor nulliparous (virgin) females spontaneously respond to USVs or pup distress with retrieval. Rather, over time the female begins to connect signs of a pup in distress with the need to retrieve it [6,7,8*]. Experience with pups, either through sharing a home cage with them or

through brief periods of daily exposure, reliably elicits maternal behavior in virgin females, a process known as 'priming' [9-15,16**,17]. Under certain conditions, sires will also retrieve pups, but they do so much less efficiently and reliably [8*]. Therefore, here we focus exclusively on evidence from females (dams and virgins). Pup retrieval presents several advantages as a model for studying social motivation. First, it is overt and easy to observe. Second, while the behavior appears simple, it is associated with complex neurochemical events. Third, it is dynamic, as the female improves over time. Finally, and critically, each retrieval inherently constitutes a discrete trial, enabling precise temporal alignment of neural signals across repeated events (e.g., search, contact with the pup, lifting the pup, and returning the pup, etc.) These features make pup retrieval an ideal system for probing how neuromodulators regulate both immediate action and longer-term motivational change in a social context.

Noradrenaline and dopamine and motivational salience and reward

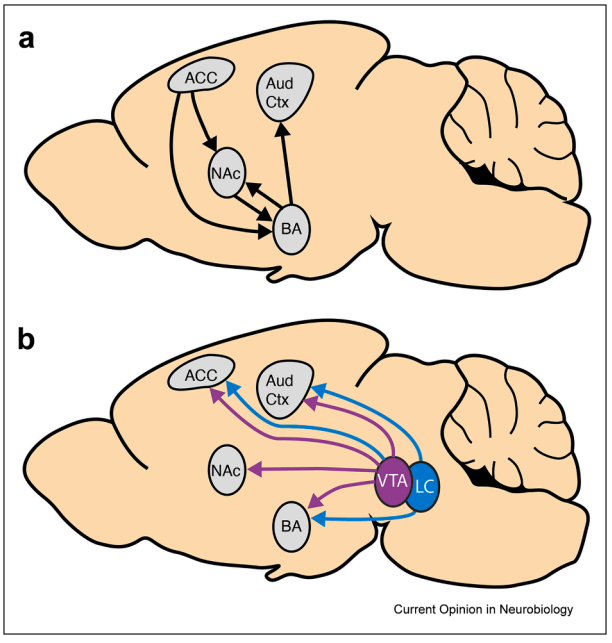
All motivated behavior requires associating cues with outcomes. Motivational salience and reward value are related concepts that are each reflected in neural activity across many brain regions and pathways [18,19]. Both quantities signal the detection of behaviorally significant stimuli or events, but reward signals respond specifically to positive or appetitive cues. On the other hand, salience signals denote that something important just happened, regardless of whether the outcome was desirable or aversive. Importantly, either type of cue can have immediate consequences for ongoing behavior or predictive value regarding future outcomes. Activation of either the NA or DA system contributes to an elevated arousal state [5]. The LC NA neurons exhibit higher firing rates during stress and are activated by both unexpected aversive events and novel or reward-predicting stimuli [20]. Firing in LC neurons signals the importance of a stimulus, irrespective of its valence, thus encoding salience.

On the other hand, these properties can be somewhat blurred between the NA and DA systems owing to functional heterogeneity and diversity within each nucleus. In contrast with the traditional view that the LC broadcasts a single coherent state variable to the entire brain, recently there has been significant interest in the possibility of functional diversity among LC neurons according to their projection targets [21–23]. Nevertheless, heterogeneous firing patterns among LC neurons are not evident under all conditions [24**,25**]. Likewise, there is a diversity of properties among VTA DA neurons [26]. Classically, VTA DA neurons respond only to reward and thus signal positive valence; however, recent data show that DA release measured in the striatum is sensitive to aversive events (e.g., tail pinch or air puff) [27–29]. DA is also required for some forms of avoidance learning [30]. These findings could reflect the contribution of salience neurons in the lateral portion of the VTA [31].

Locus coeruleus noradrenaline and ventral tegmental area dopamine neurons target brain regions that are important for maternal behavior

To understand how NA and DA coordinate maternal retrieval, our recent work has focused on several critical targets of VTA DA neurons and/or LC NA neurons: the ACC, the basal amygdala (BA), and the nucleus accumbens (NAc) (Figure 1a). In addition to the interconnectivity of these retrieval-related regions, they are all bound together by overlapping input from LC and VTA (Figure 1b). We found that ACC is important for maternal retrieval behavior [8*], confirming a finding made more than 50 years ago by Slotnick [32]. Our work shows that ACC is under the influence of NA from LC, and that there is also a projection to ACC from VTA DA neurons. Both VTA DA and LC NA neurons send input to the BA. The BA is activated during maternal behavior and in response to multi-modal pup stimuli [33]. It has been suggested that BA influences appetitive maternal behaviors (e.g., retrieval) through its projections to the nucleus accumbens and the ventral pallidum [34,35]. We recently reported that there are BA neurons that project to the auditory cortex, respond to pup odor, and

Figure 1



Noradrenergic and dopaminergic circuitry for pup retrieval. (**a**) A simplified schematic of the connections among a few key nuclei of interest with regard to pup retrieval. (**b**) A simplified schematic of the regions in (**a**), showing their inputs from LC and VTA. LC, locus coeruleus; VTA, ventral tegmental area.

are active during the search for pups [17]. Finally, DA release in NAc is consistently associated with maternal behavior or stimuli [36–41]. There is NA release in parts of the NAc shell, but most of it comes from other noradrenergic cell groups including the nucleus of the solitary tract [42]. The LC also targets the VTA and may thereby indirectly modulate DA release in the NAc [43,44].

Locus coeruleus noradrenaline neurons fire in phasic bursts that are locked to subsequent behavior

In one recent study, we made chronic single-neuron recordings with electrophysiology and optical recordings of population activity with fiber photometry in awake, freely behaving mice while they actively retrieved pups [24**]. The LC activity consists of slowly changing 'tonic' firing patterns and more rapid burst firing patterns (phasic); therefore we considered whether LC activity would more closely reflect gradually evolving social conditions or would be sensitive to finer temporal structure on the timescale of contact with another mouse. We clearly showed that in maternally experienced mice, LC neurons rapidly respond to pup contact with a reliable phasic burst, evident at the single-unit or population level, suggesting that LC may play an important and specific role in motivating pup retrieval. We made several unexpected findings. First, the magnitude of the LC response to pup contact was very stable over the duration of our experiments (days to weeks). Second, these responses appeared abruptly and at full amplitude on the very first retrieval; thus, there was no evidence that the strength of LC responses was related to increasing motivational salience of pups. Third, mere contact did not drive phasic responses, because they were absent in trials where contact was made but the pup was abandoned and not retrieved. Finally, we observed that LC population activity was highly correlated with and temporally led the instantaneous velocity of the mouse as it returns to the nest with the pup (Figure 2a); outside of these events, LC activity was not correlated with velocity. Based on these observations, we conclude that NA from LC acutely mobilizes widespread downstream targets to perform this goal-directed behavior [24**].

Anterior cingulate cortex is a target of locus coeruleus noradrenaline neurons that mediates sensitivity to distress in others

Based on our observation that LC NA was more closely correlated with goal-directed action than with sensory events, in a second study, we focused on downstream targets of LC that more directly facilitate retrieval [8*]. Through a whole-brain activity screen, we unexpectedly found that ACC was one of the most differentially activated brain regions when comparing retrieving mice to non-retrieving mice. It was also one of the most differentially active regions when comparing dams to sires [8*]. Interestingly, ACC has been repeatedly implicated in sensitivity to the distress of other individuals [45,46*,47,48]. This region also receives input from LC NA neurons, making it a potential point of noradrenergic regulation of maternal care. When we recorded from either excitatory or inhibitory neurons, we observed sex-differential activation surrounding each retrieval event. Chemogenetic inactivation of the excitatory population in ACC led to decreased expedience and reliability of retrieval and increased parental neglect. In fact, specific chemogenetic inactivation of only LC neurons that project to ACC produced similar results [8*]. Another critical target that receives salience signals from LC is the BA, but the role of that connection in maternal behavior awaits further exploration. We find that these observations are consistent with LC spurring immediate action regarding pup retrieval.

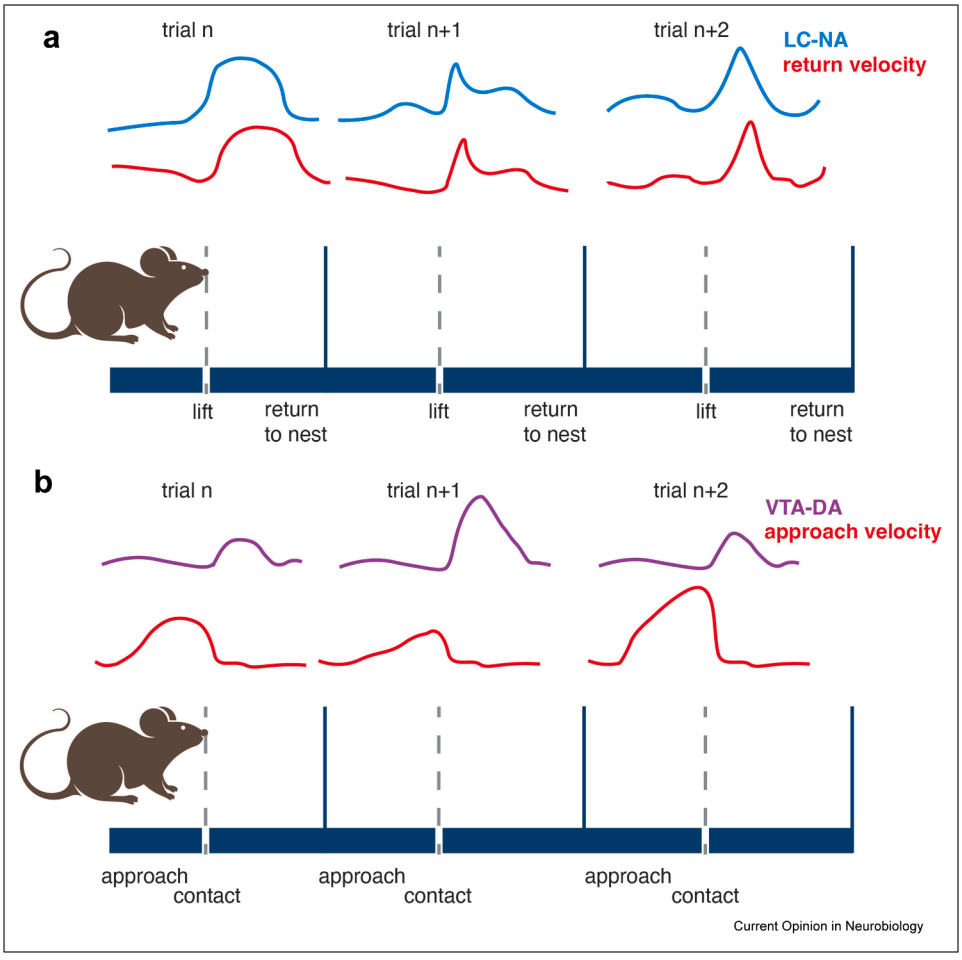
Dopamine is essential for long term learning but not acute performance

In light of our finding that the magnitude of LC activity does not correlate with retrieval performance or the salience of pups, in a third recently published study, we examined the mesolimbic DA system for retrieval-related activity [16**]. We monitored the trial-by-trial performance of the mouse as a function of the outcomes and DA signals on previous trials. We found that the difference in approach velocity of the mouse towards the pup (a measure of change in motivation) between two trials was positively correlated with the magnitude of the DA signal on the first trial [16] (Figure 2b). In other words, the update in the value of pup interaction for each trial was proportional to the reinforcement received on the prior trial. To more rigorously test this hypothesis, we adopted a closed-loop design in which inhibition of the midbrain VTA DA neurons was triggered by proximity to the pup's starting location. The DA activity was otherwise unaffected. We also inactivated DA neurons only on alternating trials to observe both the long-term and acute consequences of DA inactivation. We found that mice in which DA signaling suppressed were much slower to learn and perform retrieval [16**]. Strikingly, there was no difference in performance between trials with and without inactivation, arguing that the effect is not acute, but reflects learning [16**]. Based on these observations, we conclude that DA does not participate in ongoing behavior but rather updates the motivational value of retrieval for future trials.

Comparison of noradrenaline and dopamine activity during maternal care with activity in other contexts

The pattern of results we observed in LC and DA activity—'do it now' versus 'do it better next time'—is

Figure 2



Temporally-dissociable effects of NA and DA on pup retrieval. (**a**) LC NA activity (cyan) is tightly correlated with and temporally leads return velocity (red) during the current trial's nest return phase. (**b**) VTA DA activity (purple) on a given trial predicts approach velocity (red) on subsequent trials. Note that low DA on trial n (small purple peak) is followed by slow approach on trial n+1 (small red peak), while larger DA on trial n+1 is followed by faster approach on trial n+2 (large red peak). This demonstrates that NA invigorates the current behavioral episode while DA shapes future performance through reinforcement learning. DA, dopamine; LC, locus coeruleus; NA, noradrenaline; VTA, ventral tegmental area.

broadly consistent with current thinking about activity during artificial tasks. For example, while early investigations of LC NA neurons focused on cue responses, a newer model argues that these neurons are more closely associated with motivating behavior [49]. The LC activity is more tightly time-locked to subsequent behavior than to preceding cues [50–54]. Therefore the model predicts that phasic LC bursts link sensory cues to specific goal-directed behaviors. In early trials, when the female contacts a pup, there is no response in LC. Subsequently, responses to pup contact appear only when the female follows through with retrieval of the pup. The activity is aligned to the initiation of the return to the nest, but at no other time is LC activity correlated with the mouse's velocity [24**] (Figure 2a). Such correlations were also observed between phasic LC activity and approach velocity to a learned reward location [55,56]. This temporal offset could facilitate learning of other types of sequential behavior including by pacing and sequencing constituent behaviors exhibited in aggressive or mating encounters. The asynchronous actions of NA and DA may be a more general property of these two systems, rather than just a feature of social learning. The balance between these two systems may enable greater stability of learning where there are short-term and more distant goals to be learned. Imagine, for example, a complex maze in which an individual's local moves eventually allow the animal to achieve longer-term goals. I would predict that NA is more associated with individual steps, whereas DA activity would be more reinforcing for the ultimate rewarded target.

The LC activity during pup retrieval appears to be coordinated and highly synchronized among neurons. Robust retrieval-aligned bursts were evident in all single neurons we recorded and were large and well above background in optical recordings. Indeed, in most cases, they were the largest events we observed in our experiments. This strongly suggests that these events are pervasive and involve most or all neurons in LC. This contrasts with recent studies arguing that LC activity is highly target-specific. Recent findings have spurred many to rethink the classical view of neuromodulatory systems, particularly LC, as disseminating a monolithic signal to the entire brain [21–23]. This evidence includes neuroanatomical structures in LC that could support local release from a small number of neurons, independent of the activity of other neurons [57]. Widefield and multi-field 2-photon imaging of release of NA or Ca^{2+} activity in LC synaptic terminals shows modest differences between cortical areas [21,22]. Pup retrieval offers a behaviorally relevant context in which to test the idea of heterogeneity among LC and VTA neurons and a network of downstream targets in which to compare signals.

The VTA DA neurons use a reinforcement-learning mechanism in which pup contact is the primary reward. This conclusion is consistent with several observations. First, the magnitude of the DA signal on a given trial is inversely correlated with performance on that trial. Second, the magnitude of the DA signal on a given trial is positively correlated with performance on subsequent trials. Finally, optogenetic inactivation of VTA DA neurons does not affect the current trial, but decreases the motivation to perform future retrieval. These observations are most consistent with a leading [58] hypothesis that VTA DA neurons encode a quantity called reward prediction error (RPE). This hypothesis is somewhat controversial, with other groups proposing more elaborate and nuanced models [e.g., Ref. [59]] or models more closely linked to motor action [e.g., Refs. [60,61]]. Our data do not exclude such models under other conditions, but in our experiments they are best explained by RPE.

Some of our hypotheses are based on correlational data, for example the correlational patterns depicted in Figure 2. Nevertheless they are supported by some perturbation or lesion effects of various levels of precision. Chemogenetic experiments that selectively inactivated LC neurons that project to the ACC revealed that mothers became more neglectful of their pups including extending retrieval latencies [8*]. This result is broadly concordant with the findings of Thomas and Palmiter, who showed that knockout of the noradrenergic system by deleting DA beta hydroxylase (DBH) impairs retrieval behavior, and that restoration of DBH just before birth [62] re-enables retrieval. Our own closed-loop optogenetic experiments demonstrate the necessity of contact-driven DA responses for improvement in retrieval behavior over time [16**]. This finding meshes well with classic experiments by Numan linking the same pathway to the appetitive drive for pups [34,63].

Future directions

Of course, there are several important areas for future study. First, the most advanced line of research into the biochemical underpinnings of retrieval behavior and its genesis centers around the involvement of oxytocin. This small peptide acts in the auditory cortex to prepare for acoustically-guided retrieval [64] and also helps suppress infant-directed aggression [65*]. Moreover, there is strong evidence that it is released in the brains of mice that merely observe pup retrieval [9]. Therefore, this may be a mechanism for observational learning, but the interactions between oxytocin and the LC NA and VTA DA systems need clarification. Oxytocin is known to directly boost VTA activity, potentially enhancing social reward [66]. Similar mechanisms could suppress NA in targets of LC including the ACC and the amygdala, potentially serving an anxiolytic function. Second, it remains unclear how prefrontal and frontal brain areas interact with the subcortical circuits for retrieval described here. For example, Tasaka et al. [67**] identify a circuit from the orbitofrontal cortex that modulates DA release and performance during retrieval tasks. Finally, the time scales we look at here are at the order of individual and adjacent or subsequent trials. Slow acting hormones, such as estradiol or prolactin, can regulate maternal motivation at even longer time scales. For example, surges in these chemicals can help consolidate the dopaminergic changes in maternal motivation we see here through synaptic remodeling in specific cell types in the medial preoptic area (MPOA) [for review see [68**]].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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