Distinct Medial Temporal Lobe Network States as Neural Contexts for Motivated Memory Formation

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Abstract In this chapter we examine how motivation creates a neural context for learning by dynamically engaging medial temporal lobe (MTL) systems. We review findings demonstrating that distinct modulatory networks, centered on the ventral tegmental area (VTA) and amygdala, are coherently recruited during specific motivational states and shunt encoding to hippocampal versus cortical MTL systems during learning. We posit that these shifts in encoding substrate serve to tailor both the content and form of memory representations, and speculate that these different representations support current and future adaptive behavior.

Memories are not veridical, but rather selective representations of the environment. Understanding memory selectivity is a fundamental aim of memory research, and a rich literature accumulated over a century has documented properties of external events that are likely to change the brain to create lasting memories. Events that are distinctive, salient, or emotional, are better remembered. The intrinsic properties of events explain many features of memory selectivity, but the brain is a dynamic system. In order to understand how experience become memories, we must begin to characterize not only the properties of external events, but also the state of the brain during encoding.

Motivation as an Adaptive Neural Context for Encoding

One potentially powerful taxonomy of brain states defines them in relationship to motivated behaviors. Animals actively acquire information from the environment—both intentionally and incidentally—as they strive to achieve their goals.

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Neural systems underlying motivation translate goals into actions that in turn support adaptive behavior. A long history of learning theory has examined how motivation supports learning (Daw and Doya 2006; Wise 2004; Schultz 2016). This literature has mainly focused on simple Pavlovian (*stimulus-stimulus*) and instrumental (*stimulus-response-outcome*) learning. Although it has long been known that motivational states modulate neurophysiology throughout the brain, their influence on memory formation remained relatively unexamined for decades.

Emerging research has now demonstrated a critical role for motivation in guiding forms of memory that rely on engagement of the hippocampus and the surrounding medial temporal lobe (MTL) cortex. These studies have investigated how motivation, mostly in the reward domain, influences declarative memory, relational learning, and generalization (Shohamy and Adcock 2010; Miendlarzewska et al. 2016). This literature broadly suggests that systems underlying motivation interact with the MTL to support episodic memory, and generally enhance, episodic memory encoding. We propose that ultimately it is the state of an individual's neuromodulatory circuits in response to motivational incentives, and hence the MTL memory systems engaged during encoding, that precisely determine the content and form of memory.

Below we review the recent evidence indicating that motivation supports memory formation, and that distinct motivational states may correspond to distinct neural contexts for memory formation. We propose a model in which encoding during motivated behavior reflects the specific interactions of neuromodulatory and MTL memory systems engaged by motivational states, to create adaptive memory.

Motivational Goals Are Complex and Encompass Both Action and Learning

An important assumption of our proposed model is that motivation is not a unitary construct, but rather encompasses multiple dimensions. These dimensions include not only characteristics of actions, which include energization (*vigor*) and orientation (*approach, avoidance*), but also the incentives posed by accumulating evidence and by information itself. We refer to these latter information-based motivational states as *interrogative* and *imperative* motivational states. Within our framework, interrogative states reflect information processing that not only supports an individual's immediate goals but also supports resolving goal conflicts and future goal attainment. Imperative states reflect information processing that is predominantly focused on supporting an individual's immediate, unconflicted goals. As examples, when an individual encounters a threatening snake on a hike, she may have an imperative goal of avoiding the present, immediate threat. However, if a fellow hiker mentions the great view of the sunset from the trail, she may have an interrogative goal of learning all of the best locations to capture this view.

It has been extensively argued that objective descriptors of external incentives are insufficient characterizations of motivational states, in that many incentive structures may be framed as either approaching good or avoiding bad outcomes (Strauman and Wilson 2010; Higgins 1998). Assessing individuals' incentives for information processing may be similarly complex. A reward may be likely to evoke an interrogative state, but in the face of high stakes opportunities or social evaluation, the same reward incentive could evoke an imperative goal (Mobbs et al. 2009a; Yu 2015; Ariely et al. 2009). For example, if the hiker found out there was only five minutes before sunset, her information processing may reflect an imperative goal state. Similarly, prior knowledge that snakes could appear somewhere on a trail may evoke an interrogative goal state for avoiding threats. Despite these complexities, however, substantial evidence supports a predisposition for reward incentives to evoke interrogative goal states and punishment incentives to evoke imperative goal states, as we review below.

An Investigative Approach to Motivated Memory

Compared to motivation for action, operationalizing the outcomes of motivation to learn presents additional challenges. Motivation for action can be directly manipulated by the nature of the incentive (i.e., punishment versus reward) and assessed by measuring behavior (i.e., reaction time or number of button presses as measures of effort or vigor). Motivation for learning, in contrast, does not have an established behavioral signature. To address this challenge, our approach emphasizes the activation of discrete neuromodulatory brain systems as the most direct indicator of distinct motivational states for learning, with the form and content of memory serving as their behavioral read-out.

We focus our review and our recent experimental work on two discrete neuromodulatory systems, centered on the ventral tegmental area (VTA) and the amygdala. The VTA has been associated with relatively interrogative goal-oriented behaviors, such as exploration. The amygdala has been associated with relatively imperative goal-oriented behaviors, such as freezing. (See Fig. 1). Literature in the present review is organized, in part, based on the use of different incentive conditions, namely reward and punishment. These incentives have been shown to reliably, albeit not uniquely, engage distinct brain centers for motivation: the VTA and amygdala, respectively (described below). Thus, characterizing discrete influences of reward and punishment allows us to examine the neural architecture of encoding and the declarative memories formed as participants engage in similar encoding tasks while under varying modulatory influences that reflect interrogative and imperative goal states (See Fig. 4 for an example of our own approach.) Note that when the evidence is available, however, we focus on the neuromodulatory system that is engaged, rather than the valence of the incentive.

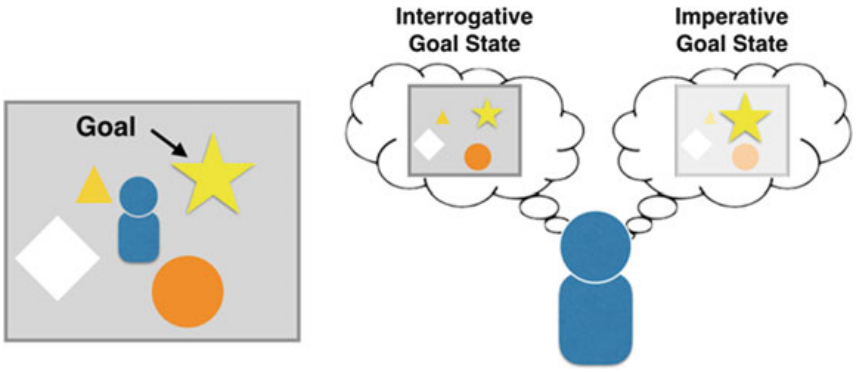

Fig. 1 Characterizing motivational states related to information-seeking. Here we elaborate on a conventional view of motivation as a valenced state of approach or avoidance. We posit an additional characterization of motivational states as they relate to information-seeking in a complex environment. We assume first that multiple goals compete and second that the strength of evidence for actions varies. *Interrogative goal states* emerge when actions to achieve goals are diffuse, conflicting, or under-determined, requiring resolution and active information seeking. *Imperative states* emerge when goals are salient, unconflicted, or urgent and additional information is of limited utility

Operationalizing Memory as an Outcome of Motivational State

To understand the memory outcomes of specific motivational states requires characterizing memory beyond binary construct of remembering versus forgetting to examine the form and content of memories. We predict that interrogative motivational states will support rich, relational memories that support later wayfinding (or disambiguation), whereas imperative motivational states will support sparse, feature-focused, item-based memories that support decisive action. While the entirety of the MTL is typically engaged during episodic memory encoding, a large body of research has shown that MTL subdivisions are specialized to support distinct forms of memory representations, with important distinctions between the MTL cortex and the hippocampus proper(Davachi 2006; Eichenbaum et al. 2007; Ranganath 2010; Eichenbaum et al. 1994). The behavioral patterns we describe are closely aligned with these MTL specializations and make clear anatomical predictions about motivated encoding, as follows.

The cortical MTL, including perirhinal and parahippocampal cortices, supports the encoding of unitized, isolated representations of items or contexts, respectively. This encoding supports familiarity-based memory judgments, item-specific details, and priming. Conversely, the hippocampus proper supports encoding of the relationships between unitized constructs. Encoding in the hippocampus supports more relational forms of memory, such as recollection-based memory judgments, memory for the relationships amongst items, and the binding of items in their broader contexts. For example, patients with non-specific MTL resections show deficits in memory for items and details about the context in which they were encoded,

whereas patients with specific hippocampal resections have intact memory for items but show deficits in identifying the broader contexts associated with individual items (Giovanello et al. 2003; Quamme et al. 2007; Hannula et al. 2015). This organizational schema allows us to test mechanistic hypotheses about the precise impact of motivation on memory by investigating how motivation influences encoding supported by the hippocampus versus MTL cortex.

Specifically, we predict that to the degree that interrogative motivational goals engage the hippocampus proper during encoding, memories will include detailed, relational representations of the environment. These representations will include items associated with reward incentives and features of the environment in which they were encountered. Conversely, we predict that to the degree that imperative motivational goals engage the cortical MTL during encoding, memories will include sparse feature-based memories associated with threats, absent the details of the surrounding environment. We further predict that the engagement of the hippocampus and cortical MTL during these motivational states will depend on engagement of discrete neuromodulatory systems. Specifically, we predict that VTA neuromodulation will facilitate hippocampal encoding during interrogative goal states and amygdala neuromodulation will facilitate cortical MTL encoding during imperative goal states. While there will be strong tendencies for reward and punishment incentives to elicit interrogative and imperative goal states, respectively, we predict that the final determinant of memory specialization will be the neuromodulatory systems engaged during encoding. For example, rewarding contexts that engage amygdala and cortical MTL would still result in feature-based mnemonic representations, while punishing contexts that engage VTA and hippocampus would still result in relational mnemonic representations.

Considerable empirical evidence from animal and human literatures supports these general predictions. First, we will review literatures demonstrating that VTA engagement, which is reliably associated with reward-based motivation, biases information processing toward hippocampal-dependent memory encoding. Next, we will review literature demonstrating that amygdala engagement, which is reliably associated with punishments, biases information processing toward cortical MTL-dependent encoding. Finally, we will then expand our arguments to discuss how large scale networks beyond the MTL, VTA, and amygdala, in conjunction with activation of neuromodulatory neurotransmitter systems, support motivated memory encoding.

The Role of the VTA in Motivated Behavior

This section reviews literatures implicating the role of the VTA in motivated behavior associated with interrogative goal states. In our model, interrogative goal states reflect when individuals' motivational drive is oriented not only towards obtaining an immediate goal but also gathering information about the environment to support future adaptive behavior. Thus, this state reflects a balance between

initiating motivated behaviors and an active state of environmental exploration. Given the extant literature, we focus this review on reward-motivated behaviors, as the majority of studies investigating the VTA have characterized this neuromodulatory system using reward incentives (i.e., food, drugs, monetary rewards). There are instances, however, when punishment incentives can engage the VTA and evoke interrogative goal states (Salamone 1994; Bromberg-Martin et al. 2010).

A long history of animal research has implicated the VTA (and other midbrain dopamine nuclei), in motivated behavior. Observations that animals will forgo ecologically important rewards, such as sex or food, to self-stimulate the VTA or its targets in the ventral striatum provided early evidence that the mesolimbic dopamine system is intimately involved with motivation (Olds and Milner 1954). Since these early observations, a large literature has associated VTA activity with the initiation and propagation of motivated behaviors. Dopamine release in the rodent ventral striatum, including dopamine release in response to optogenetic stimulation of the VTA, initiates a variety of motivated behaviors (Ikemoto and Panksepp 1999; Adamantidis et al. 2011; Fink and Smith 1980) consistent with interrogative goal states. Along with immediate goal pursuit, VTA activation or dopaminergic stimulation of efferent projection targets results in behavioral activation and a variety of exploratory behaviors, including orientation to novel stimuli and environments (Ikemoto and Panksepp 1999; Düzel et al. 2010; Kakade and Dayan 2002). Theoretical models have suggested that these exploratory behaviors emerge in motivationally-relevant environments in order to support future goal attainment (Kakade and Dayan 2002).

A large body of research has also characterized a role for the VTA in motivated learning, particularly associative learning. VTA firing tracks learning about associations between neutral cues and their rewarding outcomes in both Pavlovian conditioning (stimulus-outcome), and instrumental learning (stimulus-response-outcome; Schultz 2016). Specifically, VTA neurons increase their firing in response to cues that predict rewards and track prediction errors between anticipated rewards and actual reward outcomes. Activation of dopamine neurons in the VTA via optogenetic stimulation results in patterns of behavior similar to those evoked by VTA prediction errors (Steinberg et al. 2013; Adamantidis et al. 2011; Kim et al. 2012), implying that VTA activation is sufficient for motivated learning. These learning-related patterns are not specific to rewards, as VTA neurons have also been shown to respond to novel, salient, and punishing stimuli and to code for information that contributes to future goal attainment, including motivational value, environmental orientation, and increasing the precision of predictions (Bromberg-Martin et al. 2010). For example, VTA neurons have been shown to respond to cues indicating the nature of upcoming rewards (Bromberg-Martin and Hikosaka 2009). Together, these studies demonstrate that VTA neurons not only track the "value" of cues for reward outcomes, but also encode general properties of the environment that relate to obtaining future rewards.

In parallel with this animal literature, human neuroimaging has supported a role for the VTA in both motivated behaviors and motivated learning. Functional

magnetic resonance imaging (fMRI) and electrophysiological studies have reliably documented VTA activation during reward motivated behaviors (D'Ardenne et al. 2008; Murray et al. 2008; Zaghloul et al. 2009; Carter et al. 2009; Krebs et al. 2011). While the majority of these studies were performed in the domain of reward motivation, research has also shown VTA activation in humans in response to other salient events, such as novelty, surprise, and loss avoidance (Krebs et al. 2011; Krebs et al. 2009; Bunzeck and Düzel 2006; Boll et al. 2013; Carter et al. 2009). In addition to reward-motivated behaviors, both the VTA and its targets in the striatum have been associated with motivated learning in Pavlovian and instrumental conditioning paradigms (D'Ardenne et al. 2008; Murray et al. 2008; McClure et al. 2003; Pagnoni et al. 2002). Further, pharmacological challenges have shown that both behavioral and neural associative learning signals are amplified when participants are given dopamine agonists versus dopamine antagonists (Pessiglione et al. 2006).

Together, these findings show that the VTA not only supports the initiation of motivated behaviors, but also supports learning about salient features of the environment that predict rewards, or more generally, information relevant to future goal attainment. Further, these properties of the VTA seem to be homologous across rodents, non-human primates, and humans.

VTA Activation Facilitates Hippocampus-Dependent Encoding

We next review literatures implicating a role for the VTA in hippocampal-dependent motivated memory encoding. As detailed above, reward motivation has been shown to reliably engage the VTA. Thus in this section, we include studies that directly characterize VTA activation as it relates to memory encoding, as well as studies that characterize how reward motivation influences memory encoding. Together, the reviewed research demonstrates that VTA activity, which is reliably engaged during reward (or interrogative) motivation, facilitates hippocampus-dependent encoding and results in rich relational memories of motivationally-relevant environments. Notably, prior research has also demonstrated contexts in which reward incentives can actually engage more imperative goal states, (i.e., reward-induced anxiety, "choking"), which we detail in a subsequent section (see section "Dissecting the Relationship Between Valence and Incentivized Information Processing").

Structural connectivity between the VTA and hippocampus has been shown across species. Neuroanatomical studies in rodent and non-human primate have documented monosynaptic, afferent projections from dopamine neurons in the VTA to the hippocampus (Amaral and Cowan 1980; Samson et al. 1990). Dopamine receptors, predominantly D1/D5 like receptors, have been identified throughout the hippocampus in both rodents and non-human primates (Ciliax et al. 2000;

Khan et al. 2000; Bergson et al. 1995). More recently, human neuroimaging has characterized indirect markers of structural connectivity between the VTA and hippocampus. FMRI studies have documented significant connectivity between these regions at rest, which are thought to reflect the intrinsic connectivity of the human brain (Murty et al. 2014; Kahn and Shohamy 2013). Further, diffusion tensor imaging (DTI) studies have documented white matter tracts originating in the dopaminergic midbrain and terminating in the hippocampus (Kwon and Jang 2014). Finally, post-mortem studies and PET studies have provided evidence for expression of dopamine receptors in the human hippocampus (Mukherjee et al. 2002; Khan et al. 2000; Little et al. 1995; Camps et al. 1990). Together, these studies show that the neuroanatomical architecture of the brain supports structural connectivity between the VTA and hippocampus.

In addition to neuroanatomy, VTA projections to the hippocampus are known to dynamically modulate hippocampal neurophysiology in a manner which could facilitate memory encoding. Dopamine agonists that mimic VTA activation have been shown to lower hippocampal firing thresholds (Hammad and Wagner 2006). Further, dopamine has been shown to stabilize hippocampal place fields, ensembles of neurons that represent the environment (Tran et al. 2008; Martig and Mizumori 2011). Both of these neuromodulatory processes should directly influence the initial encoding of memory traces within the hippocampus.

Beyond modulating encoding, dopamine and VTA activation have each been shown to facilitate long-term plasticity in the hippocampus (Lisman et al. 2011; Wang and Morris 2010). For example, dopaminergic stimulation results in LTP-like enhancements in the firing of hippocampal neurons, and the blockade of dopamine receptors in the hippocampus abolishes the effect of standard LTP-induction procedures (Huang and Kandel 1995). More recent evidence suggests that the VTA could also support systems-level memory consolidation, a process by which memory representations are reactivated and stabilized throughout the brain after encoding. Specifically, rodent studies have shown a preferential 'replay' of rewarding events after encoding, such that the sequence of neurons firing in the VTA and hippocampus during motivated encoding is repeated offline (Valdes et al. 2011; Singer and Frank 2009; Gomperts et al. 2015). In conjunction with enhancing encoding, these plasticity-related processes could stabilize long-term representations of motivationally-relevant environments.

Finally, dopaminergic neuromodulation and VTA activation have been shown to directly affect hippocampal-dependent memories. Rodent studies have shown engagement of the mesolimbic dopamine system, including the VTA, during successful spatial memory encoding (DeCoteau et al. 2007; Martig et al. 2009; Khan et al. 2000; Rossato et al. 2009). Further, dopamine release prior to and during encoding strengthens hippocampus-dependent memory representations, and dopamine antagonism at the time of encoding can disrupt long-term memory (Wang and Morris 2010; Salvetti et al. 2014; O'Carroll et al. 2006). For example, exposure to novel environments, which is known to engage the VTA, enhances performance on a hippocampal-dependent spatial learning task; further, this effect is abolished by dopamine antagonists (Li et al. 2003). More recently, it has been shown that

optogenetic stimulation of VTA afferents to the hippocampus stabilized neural place fields and increased performance on a hippocampal-dependent spatial navigation task (McNamara et al. 2014). Thus, the rodent literature demonstrates that both VTA activation and dopaminergic neuromodulation support hippocampal-based memory encoding.

Similar to these animal studies, an emerging literature in humans has supported a role for VTA engagement in supporting hippocampal-dependent memories during motivated learning. We focus our review on neurobehavioral studies looking at the influence of reward motivation, a putative proxy for VTA engagement, on declarative memory encoding. Critically, these human studies have provided a more detailed characterization of how VTA activation and/or reward motivation influences the form and content of the memories. Initial studies investigating reward's influence on episodic memory tested memory for information that was explicitly incentivized. In an early study in this literature, participants were presented with either high ($5) or low ($0.10) reward cues, which indicated how much participants could earn if they could successfully remember target images that followed each cue (Adcock et al. 2006). At a 24-h memory test, participants had significantly better memory for items associated with high versus low rewards, demonstrating that reward motivation enhanced episodic memory. Interestingly, the benefits of reward motivation enhanced recollection-based memory judgments, which are thought to contain information about the item being tested and details of the broader encoding context. Similarly, studies have shown participants to have better memory for pictures that were predictive of high versus low rewards, and for the temporal context in which they were encoded (Wittmann et al. 2005). These initial studies suggest that reward motivation not only enhances memory for rewarding items, but also supports relational memory between items and their broader context.

Since these initial studies, research has provided additional evidence that reward motivation enhances relational memory. For example, a recent study demonstrated that incentivizing encoding of pairs of object images resulted in better memory for the relationship between those images (Wolosin et al. 2012). Specifically, participants were able to discriminate pairs of items that appeared together versus pairs of items that were rearranged (i.e., presented during encoding but not together). In our own work, we found that reward motivation improved memory for spatial locations and broader environmental contexts during a spatial navigation task (Murty et al. 2011). In this study, participants completed a virtual Morris Water Task, in which hidden platforms had to be identified by successfully encoding relationships between discrete environmental cues. Within this task, participants had better spatial navigation when incentivized with monetary rewards compared to a non-rewarded control condition (and compared to punishment incentives). Together these findings show that reward motivation facilitates relational memory for items that are explicitly rewarded as well as rewarded items within their broader spatial context.

Further work in human fMRI supports the assertion that reward motivation facilitates memory encoding via interactions between the VTA and hippocampus, via mechanisms which are convergent with the extant animal research. Specifically,

fMRI studies have demonstrated that activation of the VTA and hippocampus predict declarative memory both for trial-unique cues that predict reward (Bunzeck et al. 2012; Wittmann et al. 2005), as well as for information that is explicitly incentivized during encoding (Adcock et al. 2006; Cohen et al. 2014; Callan and Schweighofer 2008; Wolosin et al. 2012). In the reward-motivated memory encoding paradigm described above (Adcock et al. 2006), successful memory encoding (i.e. subsequently remembered versus subsequently forgotten items) in the high reward condition was associated with greater activation in VTA and hippocampus, as well as increased connectivity between these regions. In contrast, there was no increase in activation or connectivity between VTA and hippocampus in the low reward condition. Subsequent research has bolstered this conclusion that interactions between the VTA and hippocampus predict the successful encoding of information incentivized with monetary rewards (Adcock et al. 2006; Cohen et al. 2014; Callan and Schweighofer 2008; Wolosin et al. 2012). These studies suggest that reward-motivated enhancements in relational memory are supported by VTA neuromodulation over the hippocampus.

More recently, research has begun to characterize how rewarding contexts not only enhance memory for reward-associated items but also memory for neutral information presented in rewarding contexts, i.e. information that was not explicitly incentivized or predictive of upcoming rewards. For example, in a recent study we placed individuals in either high or low rewarding context, by having them anticipate making instrumental responses to earn either $2 (high reward) or $0.10 (low rewards; Murty and Adcock 2014). During these states of either high or low reward anticipation, participants were incidentally presented with novel, salient images. On a surprise memory test, we found that individuals had better memory for this neutral information when they were anticipating high versus low reward. Similarly, a recent study had participants incidentally encode neutral images, unrelated to reward outcomes, that were embedded in either high or low reward predicting scenes (Gruber et al. 2016). During a surprise memory test, participants had better memory for the neutral images embedded in the high versus low reward context. Together, these findings extend the domains in which reward motivation can support memory. Where prior studies demonstrated better relational memory for reward-related items, these studies show that reward can also enhance memory for neutral information embedded in rewarding contexts. This latter observation is consistent with the proposed role of reward motivation, and its putative activation of the VTA, in supporting interrogative goal pursuit. Neutral information that is embedded in motivationally-relevant contexts theoretically could act as reward-predicting cues or provide information of the acquisition of future goals (Fu and Anderson 2008).

Human neuroimaging studies have related enhancements in memory for neutral information presented in rewarding contexts to interactions between the VTA and hippocampus. In our work, we found that in rewarding contexts, VTA activity predicts subsequent increases in hippocampal sensitivity to surprising neutral information (Murty and Adcock 2014). Similarly, a recent study showed enhanced memory for neutral images embedded in reward-predicting contexts

(Loh et al. 2015). Authors found that these increases in hippocampal-dependent memory were only evident when the reward-predicting cues engaged the VTA; this suggests that VTA activation rather than intrinsic properties of the incentives determined enhanced memory formation. Together, these studies demonstrate that the same circuitry guiding reward-motivated memory enhancements also supports enhanced memory for neutral information embedded in rewarding contexts.

In sum, evidence across human, non-human primate, and rodent studies suggest that VTA activation, often elicited by reward, promotes relational memory via engagement of hippocampal-dependent encoding. Animal studies have shown that dopamine promotes better encoding in the hippocampus, and direct dopamine modulation enhances the stabilization of rewarding items in long-term memory. Human research has further demonstrated that reward motivation, as well as VTA-hippocampal interactions, specifically support rich mnemonic representations of motivationally-relevant environments, that include (1) reward-associated items, (2) relationships amongst items in rewarding environments, (3) relationships of rewarded items in their broader environmental context, and (4) neutral items encountered during reward pursuit.

The Role of the Amygdala in Motivated Behavior

This section reviews literatures implicating a role for the amygdala in motivated behavior associated with imperative goal states. Here, we operationalize imperative goal states as motivational drive oriented towards obtaining an immediate, compulsory goal, and not the surrounding motivationally-relevant environment. Given the extant literature, we focus this review on punishment-motivated and threat-related behaviors, which have been shown to both induce imperative goal states and engage the amygdala. We note that many of the behaviors described involve coordinated interactions between the VTA and amygdala (Salamone 1994). In this section, however, we focus on the amygdala, as its engagement is necessary and sufficient to engage a variety of behaviors associated with imperative goal states.

A long history of animal research has implicated the amygdala in behaviors associated with imperative goal states, starting with early observations that animals with amygdala lesions fail to exhibit stereotypical responses to imminent threats. Within rodent and non-human primate literatures, amygdala activity and its functional afferents have been implicated in the generation of freezing and startle behaviors (Blanchard and Blanchard 1969; Fendt 2001; Davis 1992), sympathetic arousal in response to threats and punishment (Korte 2001), and active avoidance (Reilly and Bornovalova 2005). Rodents with amygdala lesions fail to show typical avoidance of open fields and elevated arms of mazes (Davis 1992), environments where they may be more vulnerable to threat. Similarly, rodents will typically avoid spatial locations that were previously associated with punishment; however,

following amygdala lesions the animals re-approach these areas (Xue et al. 2012). Together, these findings suggest that the amygdala supports reflexive behaviors that contribute to the animal's immediate goal (in these studies, typically avoiding threats); this in turn reduces exploration of goal-relevant environments.

Interestingly, the role of the amygdala in punishment-motivated behavior may also depend on dopaminergic projections from the VTA. Dopamine depletion can disrupt and dopamine administration can facilitate a variety of punishment-motivated behaviors (Salamone 1994). Interestingly, when punishment avoidance and reward pursuit coincide, amygdala lesions can actually result in increased reward-motivated behaviors (Xue et al. 2012). Thus, the amygdala may play a role in determining the orientation of dopamine's role in motivation. These findings suggest that amygdala neuromodulation may asymmetrically promote the instantiation of punishment motivation at the expense of reward/approach-related behaviors; how this balance relates to interrogative versus imperative goal states remains to be investigated.

Like the VTA, the amygdala is also centrally implicated in motivated learning. Early rodent and non-human primate studies show that lesions to the amygdala result in deficits in fear conditioning (LeDoux 1992; LaBar and Cabeza 2006), the learned association of a reflexive response to intrinsically threatening stimuli with a neutral stimulus that predicts punishment (Choi et al. 2010; Holahan and White 2004; Rorick-Kehn and Steinmetz 2005). Animals with amygdala lesions fail to show the typical freezing or startle response elicited by such cues that predict threats (Blanchard and Blanchard 1969; Hitchcock and Davis 1986; Campeau and Davis 1995; Kim and Davis 1993; Phillips and LeDoux 1992; Kim et al. 1993).

Further analysis of amygdala subregions during fear conditioning demonstrate that the behaviors associated with imperative goal states may map most closely onto central regions of the amygdala, implicated in noradrenergic responses and arousal. Interestingly, these central regions promote freezing/behavioral inhibition and may actually inhibit active avoidance (Choi et al. 2010; Davis 1992). Active avoidance of threats may depend instead on basolateral portions of the amygdala. Thus, the basolateral portions of the amygdala, which have also been shown to track associations between neutral cues and reward (Murray 2007; Baxter and Murray 2002), may thus contribute to a subset of avoidance behaviors that are more interrogative in nature.

Research in humans has bolstered support for the role of the amygdala in imperative goal states. Patients with amygdala lesions have deficits in perceiving and reflexively responding to imminent environmental threats (Broks et al. 1998; Adolphs et al. 2005; Scott et al. 1997), such as eliciting startle responses to neutral cues predicting threat. Functional neuroimaging studies have further demonstrated amygdala activation with the anticipation (Hahn et al. 2010) and active avoidance of punishments (Mobbs et al. 2007, 2009b; Schlund and Cataldo 2010). Similarly, the human amygdala has been associated with punishment-motivated reinforcement learning, as both lesion and human neuroimaging studies have implicated the amygdala during Pavlovian fear conditioning and instrumental avoidance

(LaBar et al. 1995, 1998; Büchel et al. 1998; Prevost et al. 2011, 2012), particularly regions within the central amygdala. However, the spatial resolution of many of these lesion and neuroimaging studies have made it difficult to discern the contributions of central and basolateral portions of the amygdala.

Together, these findings show that the amygdala supports a variety of motivated behaviors associated with imperative goal states, mainly in the domain of threat and punishment avoidance. Fast stereotyped responses provide a means to fulfill an individual's immediate goals to avoid a threat at the expense of gaining information about the surrounding environment. Further, these properties of the amygdala appear to be homologous across rodents, non-human primates, and humans.

Amygdala Activation Facilitates Cortical-MTL Dependent Encoding

We next review literatures on the role of the amygdala in cortical MTL-dependent memory encoding. As detailed above, punishment motivation and threats have been shown to reliably engage the amygdala, thus we include studies that either modulate amygdala activation or investigate memory encoding in these contexts. The reviewed research demonstrates that amygdala activation, which is reliably engaged during threat processing and punishment motivation, facilitates cortical MTL-dependent encoding. Further, engagement of cortical MTL results in sparse, de-contextualized, item-based representations of potential threats. Notably, prior research has demonstrated contexts in which reward incentives can elicit imperative goal states, (i.e., reward-induced anxiety, "choking"), and result in cortical MTL-dependent encoding (reviewed in section "Dissecting the Relationship Between Valence and Incentivized Information Processing").

Structurally, the amygdala has direct efferent projections throughout both the hippocampus and surrounding cortical MTL (McGaugh 2004), and stimulation of the amygdala can increase long-term potentiation in both of these regions (Ikegaya et al. 1995; Akirav and Richter-Levin 1999; Frey et al. 2001). Further, rodent studies have demonstrated that stimulation of the amygdala during and after encoding can facilitate memory encoding across the MTL, including both cortical MTL and hippocampus (McGaugh 2004). For example, pharmacological activation of the amygdala enhanced memory for safety platforms in a MTL-dependent spatial navigation task (Roozendaal and McGaugh 1997; Roozendaal et al. 1999) and these enhancements in memory were blocked by amygdala lesions (Roozendaal et al. 1996; Roozendaal and McGaugh 1997). Similarly, amygdala modulation over the MTL, including both the hippocampus and cortical MTL, has been shown to support contextual conditioning, in which threatening stimuli become associated with the surrounding environment (Rudy 2009; Fanselow 2000). These early rodent studies detailing the functional and structural connectivity of the amygdala reveal

an organization that cannot discriminate between cortical MTL versus hippocampus encoding.

In spite of this evidence, there is accumulating evidence that amygdala neuromodulation may bias encoding towards cortical MTL structures. In rodents, activation of the amygdala results in increased coupling amongst cortical MTL regions, which was subsequently related to memory enhancements (Paz et al. 2006). Further, lesions to the rodent amygdala have been shown to selectively impair memory processes depending on cortical MTL-dependent encoding while sparing hippocampal-dependent encoding (Farovik et al. 2011). Through a series of behavioral modelling techniques, the authors demonstrated that amygdala lesions following encoding resulted in a failure to retrieve memories putatively stored in cortical MTL regions. Complementing these findings, research has demonstrated that amygdala engagement can interfere with the use of hippocampal-dependent memories during motivated behaviors. In these studies, rodents performed spatial navigation tasks that depended on using hippocampal-dependent memories. Critically, lesions of the amygdala increased the use of hippocampal-dependent memories during motivated behaviors. Conversely, stimulation of the amygdala decreased the use of hippocampal dependent memories.(Kim et al. 2001; McDonald and White 1993; Roozendaal et al. 2003). Together these studies suggest that amygdala activation promotes cortical MTL dependent encoding over hippocampal-dependent encoding.

Research from humans has similarly indicated that amygdala activation may shunt encoding towards cortical-MTL, resulting in item-based, sparse representations of the environment that are focused on the immediate goals of the individual. The majority of the human evidence for amygdala involvement in memory encoding emerges from studies testing memory for intrinsically aversive items such as trial-unique pictures of snakes and spiders (LaBar and Cabeza 2006). We first review these studies of memory for intrinsically threatening items, before reviewing the emerging literature explicitly investigating the influence of punishment motivation on encoding.

Human studies reliably show a memory advantage for intrinsically aversive memoranda or aversive environments compared to neutral memoranda (LaBar and Cabeza 2006; Bennion et al. 2013). However, these studies typically only probe item-based memory, which could be supported by either cortical MTL- or hippocampus-dependent encoding. A growing body of literature, however, has shown that threat-related stimuli actually disrupt relational memory processes when it is explicitly probed. For example, behavioral research has shown intrinsically threatening items result in worse source memory for encoding contexts (Dougal et al. 2007; Rimmele et al. 2011, 2012) and worse recognition memory for contexts presented simultaneous to threats (Steinmetz and Kensinger 2013; Kensinger et al. 2007a). Similarly, individuals are impaired at relational binding of threatening items with each other in memory (Onoda et al. 2009), as well as relational updating of memories that once contained a threatening item (Sakaki et al. 2014). Together, this research suggests that environmental threat, which is

strongly associated with amygdala activation, can support item-based memories but actually disrupts relational memory processes.

In parallel to these behavioral findings, neuroimaging research has begun to characterize MTL engagement during memory encoding for intrinsically threatening items. We recently conducted a meta-analysis of successful memory encoding for intrinsically threatening items. We found that successful memory for threatening versus neutral items was associated with amygdala, but not VTA, activation. Further, we also revealed reliable engagement of both the cortical MTL and hippocampus during emotional memory encoding (Murty et al. 2010). Thus, this meta-analysis suggested that the amygdala neuromodulation could support both cortical MTL and hippocampus activation during encoding. There are important caveats to consider when addressing the role of amygdala neuromodulation on MTL encoding from this meta-analysis. Firstly, the spatial resolution of a meta-analysis is somewhat poor, as spatial information becomes blurred by combining data across multiple studies (Nee et al. 2007). Thus it may be difficult to delineate hippocampal engagement from amygdala and cortical MTL given their spatial proximity. Further, the meta-analysis does not avail the opportunity to investigate dynamic relationships between the amygdala and MTL during encoding (i.e. amygdala neuromodulation of the MTL). Reliable activation of the amygdala, cortical MTL, and hippocampus during memory encoding could be evoked by different subsets of trials within the same study. Finally, this meta-analysis was not able to dissect how different memory tasks and/or arousal levels influenced engagement of different MTL regions. Thus, this early meta-analysis provides evidence for amygdala, cortical MTL, and hippocampal engagement during memory encoding, but cannot speak to the relationship amongst these regions.

When studies have directly examined the relationship amongst these structures in detail, they have found that amygdala engagement selectively increases cortical MTL-dependent encoding but not hippocampus-dependent encoding. Amygdala activation during encoding was found to predict memory for threatening items, a cortical MTL-dependent process; but did not predict relational memory for items and their surrounding contexts, a hippocampal-dependent measure (Dougal et al. 2007; Kensinger and Schacter 2006). Similarly, studies directly investigating interactions of the amygdala and MTL have demonstrated that successful encoding of emotional memories were associated with amygdala-cortical MTL functional interactions (Dolcos et al. 2004; Ritchey et al. 2008), but not amygdala-hippocampus interactions. These neuroimaging results are corroborated by the human lesion literature, which shows that patients with hippocampal lesions that spare amygdala and cortical MTL, still show a memory advantage for intrinsically threatening items (Hamann et al. 1997a, b). Together, these findings suggest that amygdala engagement facilitates cortical-MTL supported, item-based representations of the environment, devoid of relationships between items and their surrounding environment.

The studies reviewed above focus on memory for intrinsically emotional information. Recently, our laboratory and others have begun to investigate the specific role of punishment motivation on MTL-dependent memory encoding. Dovetailing

well with the emotional memory literature, we find that punishment motivation results in item-based representations of threatening stimuli devoid of information about the surrounding environment. In an early study, we directly compared the influence of reward and punishment motivation on allocentric spatial navigation during a virtual reality water task paradigm (Murty et al. 2011). In this study, we found that, compared to reward and neutral (no incentive) motivation, punishment motivation impaired encoding of the environment in which threatening items existed. However, this first study was purely behavioral and thus could not relate these behavioral patterns to amygdala-cortical MTL interactions.

To characterize the neural architecture underlying encoding, we next turned to a punishment-motivated encoding paradigm (Murty et al. 2012), by modifying the design of Adcock et al. (2006) described above. In this paradigm, before each item to be memorized, participants saw cues that indicated whether or not forgetting the image would be punished by a shock; thus, the shock could be avoided by successful encoding. We found that punishment motivation enhanced memory for items directly associated with threat. However, neuroimaging revealed circuitry distinct from those identified in reward-motivated memory encoding. Whereas reward motivation was associated with VTA-hippocampal interactions, we found that successful punishment-motivated memory was associated with amygdala-cortical MTL interactions. Although punishment motivation was still associated with enhanced recognition memory for motivationally relevant items, successful encoding was predicted by amygdala interactions with cortical MTL.

We observed a similar neuromodulation of cortical MTL in a study comparing incidental encoding in rewarding versus punishing contexts (Murty et al. 2016a). Specifically, we adapted the paradigm utilized by Murty and Adcock (2014), in which neutral surprising items were embedded in states of high or low reward motivation contexts, to test the impact of punishment incentives (See Fig. 2). Using a configural memory task that specifically indexed hippocampal representations, we saw that while reward incentives enhanced memory for neutral items relative to no rewards, we found no motivation benefit on memory when participants were avoiding punishments. Directly comparing the encoding-related fMRI activations under the two incentive conditions revealed discrete states of encoding under reward versus punishment motivation: a double dissociation of MTL-dependent encoding, such that reward facilitated hippocampus activation without any modulation of cortical MTL, and punishment motivation facilitated cortical MTL activation without any modulation of the hippocampus. Thus, across multiple studies, we have found that punishment motivation facilitates learning via mechanisms distinct from reward motivation, enhancing memory for items and not the surrounding contextual details.

Similar behavioral and neural profiles have also been demonstrated in studies investigating punishment's influence on memory. In line with our own findings, emerging research shows that memory encoding of neutral items associated with threat engages both the amygdala and cortical MTL-dependent encoding, and in some contexts actually impairs hippocampal-dependent encoding (Schwarze et al. 2012; Qin et al. 2012). For example, a recent study had participants encode neutral

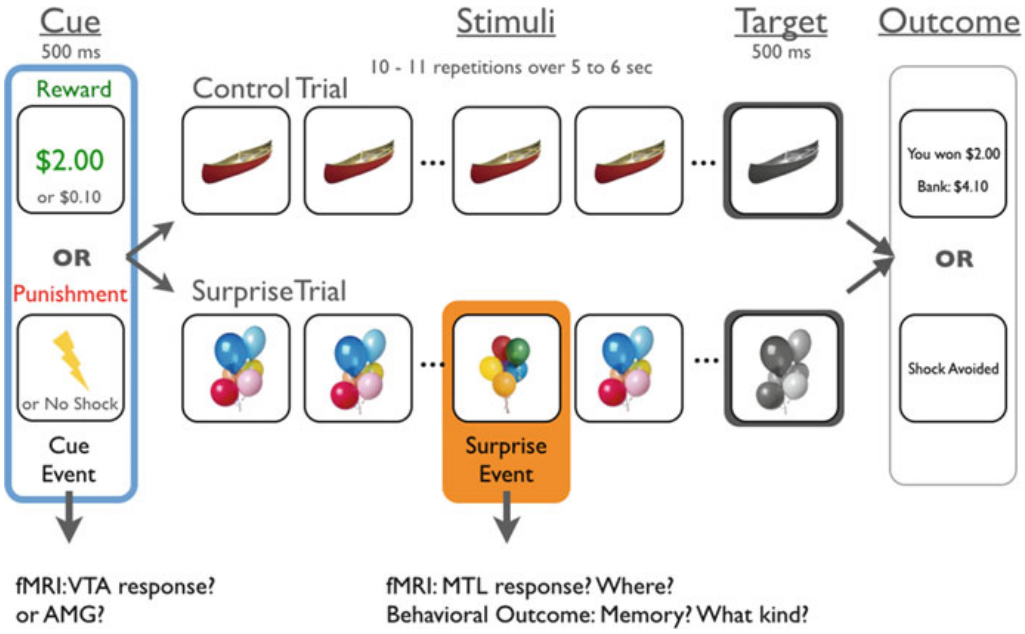

Fig. 2 Example investigative approach to motivated memory. Memory formation for neutral stimuli is examined in the same behavioral task under contrasting incentive structures. In the illustrated paradigm, incidental encoding of unexpected events is examined during a reaction time task incentivized in two different motivational contexts: reward incentives or punishment incentives (Each context includes a low-motivation control condition). Both groups are working to press a button when the repeating stimulus turns to a grayscale image. On some trials a surprise occurs, irrelevant to performance. In these contrasting motivational contexts, we examine anticipatory engagement of brain networks implicated in motivation (indexed by fMRI activation in the VTA or amygdala (AMG above). We then relate the state of these modulatory networks to MTL responses elicited by surprising events and to memory outcomes in each context

information that was associated with varying levels of threat of unavoidable shock (Bauch et al. 2014). The authors found that increasing threat of shock enhanced item-based memory responses and associated encoding-related activity in cortical MTL. Further, the authors found that increased threat of shock impaired associative-based memory (i.e., relational memories) and was associated with decreased encoding-related activity in the hippocampus.

In sum, evidence across human, primate, and rodent studies suggests that motivational contexts that engage the amygdala result in item-based memory encoding via neuromoduation of cortical MTL-dependent encoding. The amygdala has strong projections to cortical MTL, and, has been shown to facilitate encoding by cortical MTL. These lines of research suggest that punishment motivation, as well as amygdala cortical-MTL interactions, specifically supports representations in line with imperative goal orientations. Specifically, memory is enhanced for the targets of goal orientation (i.e., threatening items or items directly associated with punishments), but impaired memory for contextual information and other aspects of relational memory. Thus, the literature offers mounting evidence that, in general,

amygdala activation results in a state of learning distinct from that resulting from VTA activation.

Dissecting the Relationship Between Valence and Incentivized Information Processing

Thus far, we have reviewed literatures characterizing how the VTA and amygdala, respectively, support memory encoding. Most studies have characterized VTA engagement using reward incentives and amygdala engagement using punishment incentives and/or threat. Notable exceptions exist in the literature, however, in which reward incentives can engage the amygdala and punishment incentives can engage the VTA. Within our theoretical perspective, it is not the valence of the incentive which dictates targets in the MTL during encoding; rather it is the neuromodulatory system which is engaged by the goal state of the motivational context. Below, we provide examples of reward eliciting amygdala engagement/imperative goal states and punishment eliciting VTA engagement/interrogative goal states. Further, where available, we discuss the downstream consequences on memory encoding within these contexts.

While reward incentives may generally foster interrogative goal states, high reward salience may elicit an imperative goal states. One domain in which this has been well studied is addiction. Specifically, while VTA reward systems (and BL amygdala) are implicated in initiation of drug use, in addicted individuals, well-learned drug cues result in central amygdala activation. These highly salient drug cues, which elicit amygdala activation, result in devaluation of other motivationally-relevant goals to solely orient animals towards the drug reward (Lesscher and Vanderschuren 2012). Similarly, exogenous stimulation of the amygdala during reward conditioning results in compulsive, reflexive reward seeking (Robinson et al. 2014). Critically, contexts and neurobehavioral states (Wingard and Packard 2008; Packard 2009) associated with highly salient drugs of abuse putatively impair hippocampal-dependent encoding in favor of striatal learning. Motivated learning in these contexts has been shown to result in rigid representations between drug cues and actions to obtain them, which are insensitive to information about the surrounding contextual environment (i.e., habits) (Yin and Knowlton 2006). Thus, in the context of addiction, a reward incentive can actually engage an imperative goal state and disrupt hippocampus-dependent encoding.

Similarly, research has shown that increasing the salience of incentives during reward-motivated behavior can actually induce states of perceived threat, that is, "choking" (Mobbs et al. 2009a; Yu 2015; Ariely et al. 2009)—implying imperative goals. For example, one study demonstrated that offering people rewards in a high-stakes situation resulted in greater errors on a variety of both motor and cognitive tasks (Ariely et al. 2009). These deficits were interpreted to result from individuals perceiving rewards as stressful, yielding states of high physiological arousal; this

threat-like state may be associated with engagement of the amygdala, particularly the central amygdala (as reviewed above).

This concept of "choking" has also been demonstrated in the domain of reward-motivated memory encoding. For example, research has shown that incentives to encode information for monetary rewards can induce anxiety in some participants (Callan and Schweighofer 2008). Critically, participants that reported greater states of anxiety showed reduced engagement of the VTA and hippocampus, and had worse memory performance. Similarly, when we used a complementary approach to investigate this phenomenon by measuring individuals' physiological arousal during our motivated spatial navigation paradigm (Murty et al. 2011), we found that hippocampal-dependent memory encoding was worse when individuals had high arousal responses. This pattern held both within and across participants, and even in a reward context: The sub-group of participants who reliably showed hippocampal-memory deficits in reward contexts showed physiological responses indistinguishable from the group of participants who performed learning in a punishment context. Together, these findings show that when reward incentives induce states of anxiety or high physiological arousal (which are both associated with amygdala activation), their memory profiles resemble those associated with imperative goal states.

While punishment incentives reliably engage the amygdala and imperative goal states, there are also contexts in which punishments can evoke interrogative goal states. One context in which this emerges is when individuals have warning about a distal punishment, and do not have any imminent potentials of harm (Mobbs et al. 2015). In this context, the punishment incentive may be less salient, and thus individuals' goal orientation can be divided both between the threat and other features of the environment, i.e. an interrogative goal state. In line with this interpretation, human neuroimaging has demonstrated that when a threat is distal and avoidable, and individuals are not susceptible to immediate harm, there is robust engagement of the hippocampus; but, as the threat approaches hippocampal engagement diminishes (Mobbs et al. 2009b).

This prior study suggests that when punishment incentives do not induce a state of immediate threat in an individual, they may engage interrogative goal states. In line with this interpretation, research using less salient punishment incentives, such as monetary loss, have shown engagement of VTA instead of amygdala neuromodulation (Carter et al. 2009; Delgado et al. 2011). For example, amygdala activation has been shown to track the avoidance of electrical shock punishments which may be more salient and elicit imperative goal states, but not monetary loss punishments which are less salient and may elicit interrogative goals despite being negatively valenced incentives (Delgado et al. 2011). Interestingly, a recent study investigating the influence of punishment motivation on memory encoding, showed that the threat of monetary losses facilitated VTA and hippocampal engagement and further resulted in better relational memory. Thus, even a punishment incentive can result in better relational memory if it engages the VTA and hippocampus.

These findings highlight that the relationship between an incentive's valence and downstream neuromodulatory engagement is not direct. Reward incentives can

reliably elicit interrogative goal states and engage the VTA. However, in contexts when a reward incentive becomes highly salient or is interpreted as threatening, the incentive can elicit an imperative goal state and facilitate amygdala neuromodulation. Similarly, punishment incentives reliably elicit imperative goal states and engage the amygdala. However, in contexts when a punishment incentive is less salient and may not directly threaten an individual, the incentive can elicit an interrogative goal state and facilitate VTA neuromodulation. These findings support a key facet of our model: the form and content of memory will be determined by the neuromodulatory systems engaged during encoding rather than the valence of the incentive states.

Proposed Model: Current Motivation Organizes MTL Networks to Shape the Content and Form of Memory

Together the reviewed findings support a nuanced model of motivated memory in which the motivational state of an individual during encoding shapes the neural substrates supporting memory (Fig. 3). This, in turn leads to qualitatively different mnemonic representations of the environment. Specifically, this model proposes that memory encoding under interrogative motivation is supported by VTA and dopaminergic neuromodulation, and is more common under reward incentives. In contrast, memory encoding under imperative motivation is supported by amygdala neuromodulation, and is more common under punishment incentives.

Engagement of these distinct neuromodulatory systems shunts memory processing towards different MTL encoding substrates. Interrogative motivation facilitates hippocampal-dependent encoding processes whereas imperative motivation facilitates cortical MTL-encoding processes. Finally, the model predicts that differential engagement of these MTL substrates results in the storage of quantitatively and qualitatively different representations of the environment in long-term memory. Specifically, under interrogative motivation, environmental representations are relational, such that relationships between individual items and their surrounding contexts are maintained. Conversely, under imperative motivation, environmental representations are reduced, such that features directly associated with goals are extracted and stored without relational context.

The majority of research supporting this model comes from studies investigating reward incentives that engage states of interrogative motivation, and punishment incentives that engage states of imperative motivation. However, high salience rewards and low salience punishments may engage imperative and interrogative goal states, respectively. One open question is under what conditions VTA and amygdala-based networks might both be engaged during encoding. Active avoidance is one candidate context: during active avoidance of a discretely localized threat, both interrogative (way-finding) and imperative (flight) motives and behaviors are appropriate with co-activation of VTA and amygdala. We propose that final

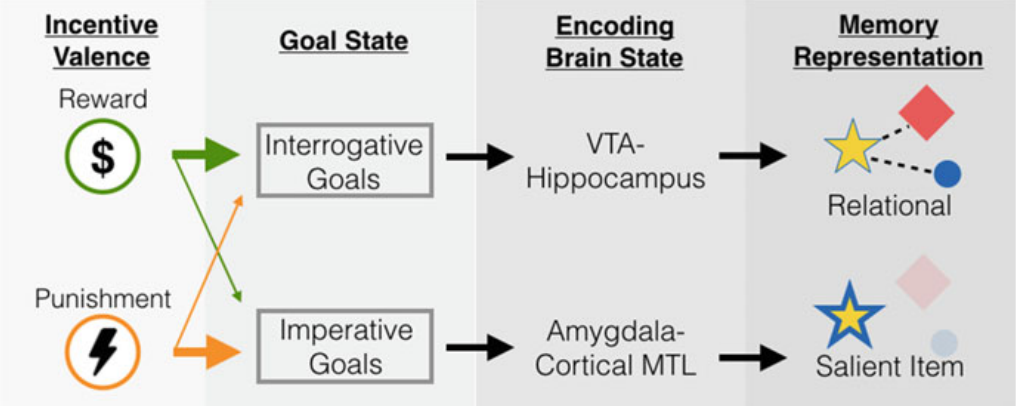

Fig. 3 A neurobehavioral model of motivation's influence on MTL-dependent memory. In the current model, we propose that the valence of motivational incentives (Incentive Valence above) can drive discrete states of MTL-dependent memory encoding. We delineate motivational states (Goal States) that are centered on 'interrogative' goals, which are associated with exploratory behaviors that support disambiguation of goal conflict and future goal attainment, versus 'imperative' states in which resources are captured by a highly salient and proximal immediate goal. We propose that interrogative and imperative goals are strongly, but not exclusively, associated with states of reward and punishment motivation, respectively. Critically, we believe that these motivational states result in neuromodulation over discrete MTL targets (Encoding Brain State). Namely, interrogative goals facilitate VTA-hippocampal interactions, whereas imperative goals facilitate 'amygdala cortical-MTL' interactions. In turn, engagement of these learning systems result in distinct representations of the environment: with hippocampal engagement supporting relational representations of multiple aspects of the environment, but cortical MTL engagement supporting unitized extraction of salient features directly relevant to an individual's goals (Memory Representations)

determinant of memory encoding will be the neuromodulatory systems engaged; thus, an important open question is how such joint activation would influence memory.

Mechanisms of Motivated Memory Specialization

The research reviewed above provides evidence that incentive contexts engage distinct coherent network states, including distinct regions in the MTL, during encoding. However, these prior studies do not offer a mechanistic account of how or why VTA versus amygdala activation would bias the MTL toward hippocampal versus cortical encoding, respectively. Accumulating evidence from psychology and neuroscience literatures provides several potential mechanisms for this functional organization. Below, we detail three possibilities. They are not mutually exclusive and are potentially synergistic. These mechanisms are as follows: intrinsic organization of functional neuroanatomy, differences in neurochemical engagement, and activation of distinct behaviors.

Intrinsic Network Connectivity Biases Information Flow

Intrinsic connectivity between discrete brain regions has been proposed to be a significant determinant of how neural networks are organized to guide cognition (Van Dijk et al. 2010). Intrinsic connectivity of the amygdala and VTA with cortical MTL and hippocampus is probably insufficient to explain the functional organization described in this model. Anatomically, the VTA innervates, though not uniformly, the entire MTL (Swanson 1982; Gasbarri et al. 1994). The amygdala, on the other hand, has stronger direct projections to MTL cortex, but also projects to the hippocampus proper (Packard and Wingard 2004).

Despite this, there are marked differences, however, in the relative connectivity of VTA and amygdala with broader cortical regions. These cortical regions may act as intermediaries in evoking preferential engagement of hippocampus or cortical MTL (Fig. 4). For example, activation of lateral prefrontal cortex (PFC) has been implicated in hippocampal-dependent encoding and relational memory (Blumenfeld and Ranganath 2007), whereas item-related memory can occur in its absence (Blumenfeld et al. 2011). Dopaminergic inputs from the VTA are thought to modulate PFC activity as it relates to a variety of executive functions (Bergson et al. 1995; Williams and Goldman-Rakic 1995; Sawaguchi and Goldman-Rakic 1991; Durstewitz et al. 2000). On the contrary, amygdala activation has been demonstrated to impede PFC activation during working and episodic memory (Dolcos and McCarthy 2006) and patients with amygdala lesions show enhanced PFC-dependent working memory performance (Morgan et al. 2012), suggesting that amygdala engagement during encoding could inhibit PFC function.

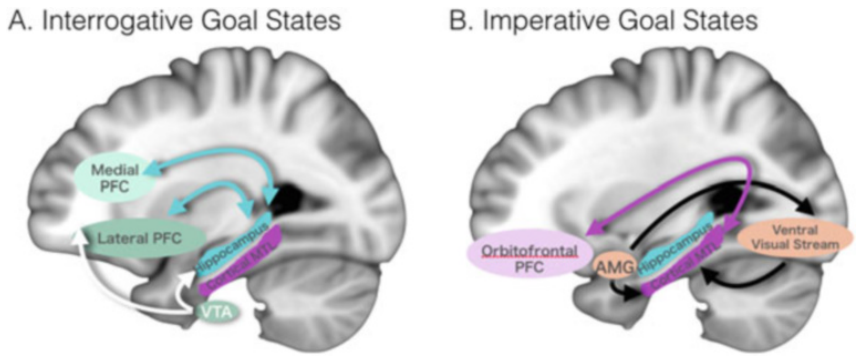

Fig. 4 Intrinsic network connectivity may delineate medial temporal lobe targets during motivated learning. Beyond direct modulation of the MTL, the amygdala and VTA could support differential MTL-dependent encoding by modulating discrete cortical targets. Here, we propose that the VTA may indirectly support hippocampal-dependent encoding by supporting working memory functions in the dorsomedial, dorsolateral and ventrolateral prefrontal cortex (white), which have been shown to support relational memory processes. We further propose that the amygdala supports cortical MTL dependent encoding by facilitating perceptual processing throughout the ventral visual stream, which has strong connectivity with the cortical MTL. Note that the arrows in this schematic are intended to indicate functional relationships shaped via neuromodulation, not monosynaptic projections; see text for details

The VTA has rich anatomical connectivity with dorsal and ventrolateral prefrontal cortex (Durstewitz et al. 2000; Bergson et al. 1995; Williams and Goldman-Rakic 1993, 1998), whereas the amygdala has only sparse anatomical connectivity with these regions (Amaral and Price 1984). This anatomical bias suggests that facilitation of these prefrontal regions by the VTA, versus the sparse projections from the amygdala, could specifically support relational memory encoding in the hippocampus.

Conversely, the amygdala has significant connectivity with the ventral visual stream (Amaral and Cowan 1980; Amaral and Price 1984), but VTA projections to these regions are sparse (Swanson 1982). Amygdala projections to targets in the ventral visual stream have been implicated in supporting enhanced detection and perception of environmental threats (Pessoa and Adolphs 2010). Anatomically, the cortical MTL is thought to be the most anterior portion of the ventral visual stream and has rich connectivity (Suzuki and Amaral 1994), while the hippocampus does not receive any direct inputs from posterior regions of the ventral visual stream. Selective enhancement of ventral visual-stream processing via amygdala connectivity could facilitate cortical MTL-dependent encoding over hippocampal-dependent encoding.

These differential connectivity patterns of the VTA and amygdala with PFC and ventral visual stream are well-positioned to shunt encoding activity toward specific MTL subdivisions during motivated encoding. In our own study of MTL network responses to surprising events under reward versus punishment incentives, we observed these predicted dissociations in prefrontal and visual ventral stream connectivity (Murty et al. 2016a). Specifically, under reward incentives, we observed hippocampal responses to surprising events and functional connectivity between hippocampus and dorsomedial PFC; whereas under punishment incentives, we observed parahippocampal cortex responses to surprises and connectivity with orbitofrontal cortex. Similarly, research has shown simultaneous engagement of the VTA and lateral PFC during reward-motivated encoding (Cohen et al. 2014, 2016), as well as co-engagement of the amygdala and ventral visual stream during the encoding of intrinsically threatening items (Kensinger et al. 2007b; Mickley Steinmetz et al. 2010). Together, these findings provide preliminary evidence of regions outside of the VTA, amygdala, and MTL supporting motivated memory encoding, but future research needs to detail their exact role.

Broadcast Actions of Neuromodulatory Transmitters Reconfigure Networks

In the imaging data discussed above, we have used fMRI activation of VTA and amygdala as indices of neuromodulation during motivational states; these robust fMRI signals can be related to both interrogative and imperative motivational states and to memory outcomes. Excitation of these nuclei is closely associated with release of dopamine and norepinephrine, although via different mechanisms. VTA

activation may indirectly reflect dopamine release from VTA terminals: it has been shown to correlate with displacement (presumably by endogenous dopamine) of radioligand from dopamine receptors in striatum (Schott et al. 2008), but activity in non-dopaminergic neurons within VTA would also contribute to this signal. Amygdala activation as detected by conventional fMRI is likely to reflect the larger central nucleus, which is closely associated with arousal and increased noradrenergic activity. Both dopamine and norepinephrine act as global neuromodulators capable of rapidly reconfiguring neural networks.

Direct evidence of these network effects of neuromodulators has come primarily from invertebrate models (see Marder 2012 for review), but a few studies in humans have used analyses that characterize topology within and between brain networks to quantitate configural shifts associated with changes in motivational context (Kinnison et al. 2012) and used pharmacological challenges in fMRI to demonstrate their neurochemical origins. For example, dopaminergic enhancement and antagonism have opposing effects on resting state networks centered on the midbrain (Cole et al. 2013a, b). One compelling pharmacological fMRI study has demonstrated rapid reconfiguration of network connectivity in response to acute stressors; these increases were diminished by beta-adrenergic blockade (Hermans et al. 2011).

It should be noted that neuromodulatory transmitters alter brain function at multiple levels of functioning. Dopamine, for example, impacts cellular-level physiology, modulating synaptic learning signals (Calabresi et al. 2007; Lisman et al., 2011; Reynolds and Wickens 2002), altering neuronal excitability (Henze et al. 2000; Nicola et al. 2000), enhancing the signal-to-noise ratio (Durstewitz and Seamans 2008; Thurley et al. 2008), impacting the temporal patterning of neural activity (Walters et al. 2000), and sharpening cortical tuning (Hains and Arnsten 2008). These cellular changes necessarily translate to changes at the circuit and network levels and may be synergistic.

In summary, because neuromodulators such as dopamine and norepinephrine can rapidly reconfigure brain networks in response to the organism's current environment, they are well suited to establishing large-scale dynamic neural contexts during interrogative and imperative states. These neuromodulators act at multiple levels, an important open question is disentangling the actions of anatomical nuclei detectable with fMRI (or specific subdivisions of these like the central nucleus) from the broadcast actions of neuromodulators they are associated with. One early effort on this front (de Voogd et al. 2016) suggests that for memory formation, it is not arousal or noradrenergic tone, but amygdala activation *per se,* that is key.

Distinct Behavioral Responses to Incentives Could Separately Influence Memory

Early evidence from behavioral neuroscience has shown that motivational contexts change how organisms interact with their environments. Specifically, reward motivation has been associated with increased exploratory and novelty-seeking behaviors (Ikemoto and Panksepp 1999), whereas punishment motivation has been associated with increased freezing and escape behaviors (Davis 1992). Similarly, social and cognitive psychology literatures have demonstrated that individuals change their orientation and interactions with the environment under states of approaching rewards and avoiding punishments. Validated models have shown that positive affect and reward motivation promote exploration and active engagement with the environment, whereas negative affect and punishment motivation draw a response specifically to environmental threats (Elliot 2008; Elliot and Thrash 2002). Changing individuals' interactions with their environment changes the information available for encoding into long-term memory, and could, as a result, modulate the locus of MTL-dependent encoding. Changes in how individuals interact with their environment could thus potentially guide the organization of memory systems.

In line with these models, behavioral studies in humans have demonstrated attentional broadening during reward-focused states versus attentional narrowing during punishment-focused states (Fredrickson 2004). Specifically, during states of broadened attention and exploration elicited by reward motivation, individuals have increased capacity to attend to multiple features of the environment. This type of attentional state to multiple features provides the opportunity for the hippocampus to construct a more elaborated, integrative representation of the environment. This proposal suggests that manipulations that taxed attentional systems would in turn result in deficits in reward-motivated memory enhancements. Conversely, during avoidance of punishment motivation, individuals may narrowly attend to environmental threats or avenues for escape. Given narrow attention, only itemized constructs are available to encode into long-term memory, a process specialized in the cortical MTL. This interpretation converges with literatures showing a prioritization of attention towards threatening stimuli (Pessoa et al. 2010). This proposal suggests that manipulations that tax attentional systems may not affect punishment-motivated memory enhancements, as potentially threatening stimuli would remain prioritized (Dolcos et al. 2011).

A framework that considers information-seeking, for example interrogative and imperative motivational states, allows for more complex predictions about relationships between incentive valence, attention, and behavior. As noted above, in addiction or other compulsive (imperative) reward-seeking, we would expect amygdala activation and thus narrowed attention. On the other hand, during active avoidance of a discretely localized threat, both interrogative (way-finding) and imperative (flight) motives and behaviors are appropriate.

Open Questions and Future Directions

The model presented here offers first, a theoretical framework for understanding motivation to learn as it relates to complex incentives; and second, a systems-level characterization of motivational states as specific neural contexts for memory formation. We describe the impact of distinct motivational states on medial temporal lobe function, and we further propose that the specifics of the neural contexts will serve to encode memories structured to support similar future behavior. Our model implies differential behavioral impacts for memories formed under interrogative versus imperative goal orientation incentives, based on broad correlations between incentive structures and these states, but holds that the neural responses to incentives are the ultimate determinants of memory modulation.

Extensions of the work into more ecologically valid domains may help isolate the environmental determinants of these states, but a key constraint on these efforts is the lability and state-dependence of motivation itself. Advances in methods for decoding motivational states from the brain are needed both to better predict responses to extrinsic motivators, including money and primary rewards, and to understand intrinsic motivational drives, like curiosity.

Our proposed model implies distinct effects of motivational context at memory encoding on future behavior. Extant research has focused on how motivation influences memory, and here we specify how different motivational states influence its content and form. Emerging research has begun to investigate how memories encoded in motivationally-relevant contexts support adaptive behavior and decision-making (Murty et al. 2016b; Wimmer and Shohamy 2012; Gluth et al. 2015). In line with our model predictions, emerging research shows that reward-motivated, hippocampal-dependent (versus cortical MTL-dependent) memories preferentially support adaptive decision-making to obtain rewards (Murty et al. 2016b; Wimmer and Shohamy 2012; Gluth et al. 2015). Future research will need to test the converse: whether cortical MTL-dependent (versus hippocampally-encoded) memories preferentially support future behaviors specifically consistent with imperative motivation.

This evolving picture of how motivational states impact the medial temporal lobe system complements the long-established body of research on the role of motivation in associative and skill learning. With a precise and nuanced understanding of the antecedents, neural mechanisms and behavioral impact of motivation on memory formation, researchers are positioned to help develop tools to optimize learning for a wide range of contexts, from education to learning-based psychotherapies for mental disorders.

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