

Dissociable Influence of Reward and Punishment Motivation on Declarative Memory

Encoding and its Underlying Neurophysiology

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor of Philosophy in the Department of
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ABSTRACT

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Abstract

Memories are not veridical representations of the environment. Rather, an individual's goals can influence how the surrounding environment is represented in long-term memory. The present dissertation aims to delineate the influence of reward and punishment motivation on human declarative memory encoding and its underlying neural circuitry. Chapter 1 provides a theoretical framework for investigating the influence of motivation on declarative memory. This chapter will review the animal and human literatures on declarative memory encoding, reward and punishment motivation, and the influence of motivation on learning and memory. Chapter 2 presents a study examining the behavioral effects of reward and punishment motivation on declarative memory encoding. Chapter 3 presents a study examining the neural circuitry underlying punishment-motivated declarative encoding using functional magnetic resonance imaging (fMRI), and compares these findings to previous studies of reward-motivated declarative encoding. Chapter 4 presents a study examining the influence of reward and punishment motivation on neural sensitivity to and declarative memory for unexpected events using fMRI. Finally, Chapter 5 synthesizes these results and proposes a model of how and why motivational valence has distinct influences on declarative memory encoding. Results indicated that behaviorally, reward motivation resulted in more enriched representations of the environment compared to punishment motivation. Neurally, these motivational states engaged distinct neuromodulatory

systems and medial temporal lobe (MTL) targets during encoding. Specifically, results indicated that reward motivation supports interactions between the ventral tegmental area and the hippocampus, whereas punishment motivation supports interactions between the amygdala and parahippocampal cortex. Together, these findings suggest that reward and punishment engage distinct systems of encoding and result in the storage of qualitatively different representations of the environment into long-term memory.

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1. Introduction

Memories are not veridical representations of the environment. Rather, an individual's goals can influence how his or her environment is represented in long-term memory. For example, an individual may memorize the location of a soon-to-be opened restaurant when she is hungry, however, she may not remember this location if she encountered the restaurant after a big meal. Within this theoretical framework, the motivational state of an organism can influence how and what it encodes. Although an extensive literature from behaviorist and learning theorists has studied how reinforcement and feedback affect memory (Rescorla and Wagner, 1972; Pearce and Bouton, 2001; Pavlov and Anrep, 2003), relatively little research has focused on how motivational drive affects memory.

Previous research has demonstrated that motivation can influence declarative memory, such that incentivizing the successful encoding of information with rewards can enhance long-term memory. This influence of motivation on memory has been demonstrated for a variety of memoranda including scenes (Adcock et al., 2006), trivia information (Murayama and Kuhbandner, 2011), words (Callan and Schweighofer, 2008), and object pairs (Wolosin et al., 2012). Although these data contribute to the characterization of the influence of motivation on declarative memory encoding, these studies have focused almost exclusively on reward motivation. However, motivation is

not a unitary construct, and there are distinct ways of motivating behavior. Research suggests that reward and punishment motivation influence behavior via distinct neuromodulatory systems (Berridge and Robinson, 1998; Davis and Whalen, 2001; Wise, 2004; Lang and Bradley, 2009), and influential models of motivation have described different behavioral effects when individuals are motivated to earn rewards versus avoid punishments (Elliot, 2008; Lang and Bradley, 2009). These differences in neural engagement and expressed behavior suggest that these motivational states should differentially influence declarative memory encoding. Thus, the neural systems engaged during reward and punishment motivation may result in different modulatory influences on declarative memory neurophysiology and behavior. The present dissertation aims to delineate these differences.

The remainder of this chapter will review the animal and human literatures detailing the psychological and neural underpinnings of declarative memory and motivation. First, the literature on the neural systems underlying declarative memory encoding will be reviewed. This section will emphasize how memory-encoding processes are organized across the medial temporal lobe (MTL), as differential engagement of this region can lead to different representations of the environment. Second, the literature on the neural systems underlying reward motivation and their influence on learning and memory will be reviewed. Third, the literature on the neural

systems underlying punishment motivation and their influence on learning and memory will be reviewed. Understanding how these motivational systems influence memory encoding in other domains may provide insight into how they might influence human declarative memory. Fourth, the literature on how these two neuromodulatory systems can interact in certain behavioral contexts will be reviewed. Finally, these literatures will be synthesized to propose a model of how motivational valence may have distinct influences on declarative memory encoding. This proposed model will be tested in the later chapters of this dissertation.

1.1 Neural Systems Guiding Declarative Memory Encoding

1.1.1 Declarative Memory Encoding in the Medial Temporal Lobe

Declarative memory is a type of memory that refers to information that can be consciously recalled such as facts and knowledge (Cohen and Squire, 1980; Gabrieli, 1998). Declarative memory has classically been organized into three phases: encoding, consolidation, and retrieval. Encoding refers to the processes by which information in the environment is initially transformed into a neural memory trace. As mentioned above, not all information from the environment is encoded into this initial neural trace. Consolidation refers to post-encoding processes in which an initial memory trace is stabilized into a more durable neural representation. Retrieval refers to the reactivation of a previously stored memory representation. As this dissertation aims to characterize

how motivation influences the initial storage of information from the environment into long-term memory representations, this section will focus on declarative memory encoding.

The MTL, including the hippocampus and the surrounding perirhinal and parahippocampal cortices, have been implicated as critical mediators of declarative memory encoding (Eichenbaum, 2004; Nadel and Hardt, 2011). Early lesion studies in humans demonstrated that damage to the medial temporal lobes, either by temporal lobectomy or hypoxic injuries, resulted in a specific deficit in the encoding of new declarative memories (Scoville and Milner, 1957; Cohen and Squire, 1980). Interestingly, these patients' memory was spared in other domains such as procedural memory and associative conditioning (Scoville and Milner, 1957; Cohen and Squire, 1980). These findings indicate that the MTL has a specific role in declarative memory processes. More recently, the study of declarative memory encoding in humans has relied on the neuroimaging of subsequent memory paradigms. In these paradigms, participants are presented with lists of information during an encoding session while fMRI data is collected. Then, data from this encoding session is contrasted between subsequently remembered versus forgotten memoranda. Experiments utilizing this design have reliably demonstrated increased MTL activations for the successful encoding of declarative memories (Spaniol et al., 2009; Kim, 2011). These hemodynamic findings,

which are indirect measures of neural activity, have been confirmed with direct recordings from human MTL neurons. In epilepsy patients, hippocampal firing rates are greater during the encoding of memoranda that are subsequently remembered versus forgotten (Cameron et al., 2001; Axmacher et al., 2006; Rutishauser et al., 2010). Thus, across a variety of domains, including lesion, functional neuroimaging, and electrophysiological studies, the human literature has supported that the medial temporal lobes are critical for declarative memory encoding.

Non-human animal studies, specifically in rodents and non-human primates, have provided evidence confirming the MTL's role in declarative memory encoding (Aggleton and Pearce, 2001). In rodents, a widely used declarative memory paradigm has been the Morris water task (Morris et al., 1982). During this task, rodents are placed in a pool where they must generate spatial maps using cues from the surrounding environment in order to find escape platforms. Critically, during this task, rodents with lesions to the hippocampus show severe impairments in finding escape platform locations (Morris et al., 1982; Sutherland et al., 1982). Similar memory deficits have been demonstrated in rodents using other spatial memory and object recognition paradigms (Aggleton and Pearce, 2001; Winters et al., 2008). In non-human primates, lesions to the MTL result in deficits for declarative memory encoding in a variety of domains, including memory for objects, scenes, and spatial layouts (Aggleton and Pearce, 2001;

Winters et al., 2008). Thus, animal studies have reconfirmed the MTL's role in declarative memory encoding. Recent studies have translated these rodent and non-human primate paradigms for study in humans and have demonstrated similar findings (Astur et al., 1998; Olsen et al., 2009; Doeller et al., 2010; Sutherland, 2010). For example, in a virtual reality version of the Morris water task, patients with MTL resections had severe impairments in accurate spatial navigation (Astur et al., 2002). Critically, this homology of functional neuroanatomy indicates that animal studies can help inform human declarative memory processes.

1.1.2 Organization of the Medial Temporal Lobe in Declarative Memory

While the entirety of the MTL is typically engaged during declarative memory encoding, important distinctions have been made regarding the specific functions of the hippocampus proper and the surrounding MTL cortex (Davachi, 2006; Ranganath, 2010). Cortical MTL, including perirhinal and parahippocampal cortices, supports the encoding of unitized, isolated representations of items and contexts, respectively. The hippocampus proper supports the encoding of integrative relationships between these unitized constructs and binds them into flexible, mnemonic representations. For example, memory for a specific book cover or a library you once visited could be supported by cortical MTL regions, however, remembering you first saw that book cover in a specific library would be supported by the hippocampus. In humans, various

researchers have used fMRI to demonstrate this relationship between unitized and flexible encoding by the cortical MTL and hippocampus, respectively (Davachi et al., 2003; Ranganath et al., 2004; Kensinger and Schacter, 2006; Staresina and Davachi, 2008; Qin et al., 2009; Staresina and Davachi, 2009; Diana et al., 2010; Staresina and Davachi, 2010). This is exemplified in a recent study (Staresina and Davachi, 2008), in which Staresina and colleagues demonstrated that successful memory for items and their associated encoding context was predicted by hippocampal encoding activations, whereas memory for items in the absence of their context was predicted by encoding-related activations in the cortical MTL. Human lesion studies have reconfirmed this organization within the MTL. Specifically, patients with hippocampus lesions are able to encode items and contexts in isolation, but they have prominent deficits of memory for items and the contexts in which they were presented (Ranganath, 2010).

Similar dissociations between the hippocampus and cortical MTL have been demonstrated in the rodent and non-human primate literatures (Brown et al., 2010). For example, damage to the rodent cortical MTL results in deficits in item-based conditioning (Bucci et al., 2002) as well as in discrimination between reinforced and non-reinforced contexts (Burwell et al., 2004). However, damage to the hippocampus proper does not disrupt these processes (Bucci et al., 2002; Burwell et al., 2004), though it does disrupt conditioning procedures in which reinforcement is dependent on items being

presented within specific spatial contexts (Ito et al., 2006). This evidence supports the idea that the cortical MTL and hippocampus differentially represent the environment during memory encoding.

These animal and human findings suggest that the pattern of MTL regions engaged during encoding can determine how an individual forms mnemonic representations of their environment. Given this, neuromodulatory systems that preferentially engage specific regions of the MTL during encoding should significantly influence this process. The facilitation of the cortical MTL during encoding would support rigid, unified representations of items and contexts, while the facilitation of the hippocampus during encoding would support bound, flexible representations of items within the context they were encountered. Thus, one mechanism by which an individual's motivational state may systematically influence declarative memory is via engagement of specific sub regions of the MTL during encoding.

1.2 Reward Motivation

1.2.1 Ventral Tegmental Area and Reward Motivation

Observations that animals will forgo obtaining ecologically valid rewards, such as sex or food, to self stimulate the ventral tegmental area (VTA) or its targets in the ventral striatum provided initial evidence that the mesolimbic dopamine system is intimately involved in reward motivation (Olds and Milner, 1954). In this context,

reward motivation refers to behavioral and neural responses that facilitate current and future receipt of rewards. Rodent models of reward motivation have shown that stimulated dopamine release in the nucleus accumbens, a region in the ventral striatum, increases the pursuit of rewards and exploratory behaviors (Ikemoto and Panksepp, 1999). Additionally, a recent study demonstrated that optogenetic activation of dopamine neurons in the VTA increases reward-motivated behaviors (Adamantidis et al., 2011). Studies of dopamine depletion and VTA inactivation in rodents have shown that the absence of dopaminergic activation impaired rodents pursuit of rewards, but did not affect the consumption of rewards or the associated hedonic responses (Bakshi and Kelley, 1991b, a; Agmo et al., 1995; Ikemoto and Panksepp, 1996). Thus this system seems to have a specified role in motivation-related processes as opposed to hedonic- or consumption-related processes. In these studies, the absence of dopaminergic activation specifically impaired rodent's motivational drive to pursue rewards. These rodent findings suggest that the VTA guides reward-motivated behaviors via dopaminergic neuromodulation.

In humans, increases in dopaminergic tone have been associated with increases in a variety of reward-motivated behaviors such as novelty-seeking personalities (Munafò et al., 2008), pathological gambling (Dagher and Robbins, 2009), and other addictive tendencies (Dayan, 2009). Further, neuroimaging studies have demonstrated

activations in the VTA as well as its mesolimbic and mesocortical targets during the anticipation of appetitive reinforcers, a neural signature thought to reflect reward motivation (Knutson et al., 2001; Adcock et al., 2006; D'Ardenne et al., 2008; Duzel et al., 2009). In one such paradigm, the monetary incentive delay (MID) task, participants are shown reward cues that indicate how much money they can earn for a speeded-button press to a target image (Knutson et al., 2000; Knutson et al., 2001; Knutson et al., 2003; Carter et al., 2009; Balodis et al., 2012). A meta-analysis of fMRI studies using this paradigm demonstrated greater activation of the mesolimbic and mesocortical dopamine system during reward motivation versus reward outcomes (Knutson and Greer, 2008), further elucidating the role of the system in motivation-related rather than consumption- or hedonic-related processes. Further, a recent study revealed that VTA fMRI activation during an MID task predicted dopamine release in the striatum, measured by positron emission tomography (PET) measures of raclopride displacement (Schott et al., 2008). Together these findings provide evidence for the role of the dopaminergic neuromodulatory system, centered on the VTA, during reward motivation.

1.2.2 Reward Motivation in Learning and Memory

Previous research has demonstrated that the same mesolimbic and mesocortical systems engaged during reward motivation, including the VTA, are also engaged

during reward-motivated learning. Single-unit recording studies in primates have demonstrated that neurons in the dopaminergic midbrain gradually acquire reward prediction error signals during both Pavlovian and instrumental appetitive learning (Schultz and Romo, 1990; Schultz et al., 1997; Fiorillo et al., 2003). Drug and lesion studies in rodents and primates have reconfirmed the critical role for the VTA's modulatory signal during these reinforcement-learning processes (Parkinson et al., 2002; Faure et al., 2005). Furthermore, activation of dopamine neurons in the VTA can influence or mimic reward-motivated reinforcement learning (Tsai et al., 2009; Adamantidis et al., 2011; Kim et al., 2012).

Human studies have also provided evidence associating the VTA with reward-motivated reinforcement learning. Functional neuroimaging and electrophysiological studies in human have documented an association between hemodynamic signals in the dopaminergic midbrain, including the VTA, and its targets in the striatum during reward-prediction and positive reinforcement learning (D'Ardenne et al., 2008; Murray et al., 2008; Zaghoul et al., 2009). These relationships have been demonstrated for both primary reinforcers, such as juice, and secondary reinforcers, such as monetary rewards, suggesting that the human brain encodes these relationships similarly (Valentin and O'Doherty, 2009; Kim et al., 2011a). Critically, these VTA activations are sensitive to pharmacological manipulations of dopamine (Pessiglione et al., 2008) and a recent case

study demonstrated directly that dopamine release in the human striatum predicted behavior during a rewarded reinforcement-learning task (Kishida et al., 2011). Together these studies support that the VTA mediates reward-motivated reinforcement learning in humans as well as rodents and non-human primates.

Importantly, VTA activation and the mesolimbic dopamine system also play a critical role in reward-motivated declarative memory. Dopamine neurons in the VTA directly project to the hippocampus (Amaral and Cowan, 1980; Samson et al., 1990; Lewis et al., 2001). Further, dopamine is critical for the facilitation of long-term potentiation, a molecular mechanism that putatively guides the encoding of long-term memory (Huang and Kandel, 1995; Li et al., 2003). Specifically, dopaminergic stimulation can result 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). Functionally, rodent studies have implicated the mesolimbic dopamine system, including the VTA, and the MTL during MTL-dependent declarative and working memory paradigms (DeCoteau et al., 2007; Martig et al., 2009; Rossato et al., 2009; Martig and Mizumori, 2011). Critically, these effects may be specific to dopamine release during or prior to encoding rather than post-encoding or during retrieval (Bethus et al., 2010; Wang and Morris, 2010). Long-term memory can be blocked by giving rodents D1/D5 receptor antagonists at the time

of, but not after, encoding (O'Carroll et al., 2006; Wang et al., 2010). Additionally, the retrieval of hippocampus dependent memories does not require dopaminergic neuromodulation (O'Carroll et al., 2006). This rodent literature demonstrates that VTA activation and dopaminergic neuromodulation over the MTL supports reward-motivated declarative memory specifically during encoding.

As mentioned earlier, previous research has demonstrated that reward-motivation can also influence declarative memory encoding in humans. Convergent with these rodent studies, human fMRI studies have demonstrated engagement of the VTA and MTL during reward-motivated declarative memory encoding. Specifically, fMRI studies have demonstrated that activation of the VTA and the hippocampus predict declarative memory both for cues that predict reward (Wittmann et al., 2005; Bunzeck et al., 2012) and for information that is explicitly incentivized with monetary rewards (Adcock et al., 2006; Callan and Schweighofer, 2008; Wolosin et al., 2012). Further, interactions between the VTA and hippocampus predict both the successful encoding of information incentivized with monetary rewards (Adcock et al., 2006) and the extent of these memory enhancements across participants (Wolosin et al., 2012).

Beyond engagement of the VTA, these human neuroimaging studies also suggest that reward-motivated memory encoding may preferentially facilitate encoding processes in the hippocampus proper. In nearly all the studies of reward-motivated

declarative memory, successful encoding of rewarded memoranda within the MTL was associated with hippocampus activation alone (Wittmann et al., 2005; Adcock et al., 2006; Callan and Schweighofer, 2008) or simultaneous activation of hippocampus and cortical MTL (Bunzeck et al., 2012; Wolosin et al., 2012). Additionally, many of these studies demonstrated that reward motivation resulted in more detailed and flexible mnemonic representations of the environment, as demonstrated by enhanced source memory (Wittmann et al., 2005), subjective memory ratings consistent with recollection (Adcock et al., 2006), and enhanced binding of discrete objects (Wolosin et al., 2012). VTA co-activation with the hippocampus has also been demonstrated during non-motivated declarative memory encoding and has been associated with flexible (Shohamy and Adcock, 2010) and enriched representations (Wittmann et al., 2007) of memoranda. Thus, these findings suggest that reward motivation may specifically target the hippocampus during memory encoding, and engagement of this system results in the generation of flexible, detailed, and integrative representations of the environment.

1.3 Punishment Motivation

1.3.1 Amygdala and Punishment Motivation

The observation that animals with amygdala lesions fail to exhibit stereotypical avoidance responses to aversive stimuli led to early investigations of this structure's role in threat perception and motivation to avoid punishments (LeDoux, 1998). In this

context, punishment motivation refers to behavioral responses that facilitate current and future avoidance of aversive events. Within the rodent and non-human primate literature, amygdala activity and its functional projections have been implicated in the generation of freezing and startle behavior (Blanchard and Blanchard, 1969; Davis, 1992b; Davis, 1992a; Fendt, 2001), sympathetic arousal in response to threatening stimuli (Korte, 2001), and the avoidance of punishments and threats (Reilly and Bornovalova, 2005; Lang and Bradley, 2009). Rodents with amygdala lesions fail to show the typical avoidance profile of healthy rodents in open fields and elevated arms of mazes (Davis, 1992a), a behavioral assay of avoidance and punishment motivation. Further, inactivation of the amygdala results in an anti-punishment effect such that punishing stimuli have a diminished influence on rodent behavior (Margules, 1968; Shibata, 1982; Xue et al., 2012). Interestingly, if punishment coincides with the pursuit of rewards in these paradigms, amygdala lesions can actually result in increased reward-motivated behaviors. These rodent findings provide evidence that the amygdala organizes punishment-motivated behaviors.

Studies in humans have also shown a critical role for the amygdala in both the perception of threats and punishment motivation. Patients with amygdala lesions have deficits in perceiving environmental threats (Davis, 1992a; Adolphs et al., 2005b), avoiding unpleasant items (Bamford et al., 2009), factoring loss aversion into decision-

making (De Martino et al., 2010), and administering punishments during social decision-making games (Scheele et al., 2012). In humans, amygdala activations have been correlated with modulations of sympathetic arousal (LaBar et al., 1995) and cortisol release (Lanteaume et al., 2007; Root et al., 2009), physiological measures that are both associated with punishment-motivated behaviors (Lang and Bradley, 2009). Amygdala activations have also been demonstrated to account for a variety of personality traits that reflect enhanced motivation to avoid threats, such as harm avoidance (Hariri et al., 2005; Pezawas et al., 2005), social phobia (Mathew and Ho, 2006), and specific phobia (Rauch et al., 1995). Further, fMRI studies have demonstrated that amygdala activation is associated with the anticipation of punishments (Hahn et al., 2010) and the active avoidance of punishments (Mobbs et al., 2007; Mobbs et al., 2009b; Schlund and Cataldo, 2010). Together these findings provide evidence for the role of the amygdala neuromodulatory system during punishment motivation.

The engagement of the amygdala during punishment-motivated behaviors, however, may be sensitive to the nature of the punishing stimulus. A recent study demonstrated that the amygdala was engaged during the avoidance of electrical shock punishments but not monetary loss punishments (Delgado et al., 2011). Thus, the threat-value and efficacy of a punisher may dictate whether the amygdala will be engaged during behavior.

1.3.2 Punishment Motivation in Learning and Memory

The same amygdala neuromodulatory system engaged during punishment motivation is also engaged during punishment-motivated learning. Rodents and non-human primates with lesions to the amygdala show deficits in fear conditioning (LeDoux, 1998), the associative learning between neutral stimuli and intrinsically threatening stimuli. The amygdala has also been implicated in avoidance learning in a variety of paradigms (Choi et al., 2010; Holahan et al., 2004 ; Rorick-Kehn and Steinmetz, 2005). In the two-way signaled active avoidance paradigm, animals learn to avoid certain parts of their environment during the presentation of a neutral cue to avoid the receipt of a punishment stimulus (Cain and LeDoux, 2007; Choi et al., 2010). Analysis of the functional properties of amygdalar sub regions have demonstrated that the active avoidance of threats during this paradigm is dependent on the function of the basolateral portions of the amygdala, whereas the central amygdala may actually inhibit these behavioral processes (Choi et al., 2010). Similarly, studies in non-human primates have also demonstrated that punishment-motivated learning is associated with basolateral portions of the amygdala (Davis, 1992a). These animal studies provide substantial evidence that the amygdala plays a critical role in punishment-motivated reinforcement learning, and suggest that it may play a role in punishment-motivated declarative memory.

Human studies have also provided evidence associating the amygdala with punishment-motivated reinforcement learning. Both lesion and human neuroimaging studies have implicated the amygdala during fear conditioning (LaBar et al., 1995; Buchel et al., 1998; LaBar et al., 1998; Dunsmoor et al., 2011b). Further, fMRI studies have shown amygdala activation when individuals learn stimulus-response relationships in order to avoid punishments. A high-resolution fMRI study isolated these punishment-motivated reinforcement-learning activations to the central, but not basolateral, amygdala (Prevost et al., 2011). This high-resolution fMRI finding contradicts the rodent literature reviewed above, suggesting that the functional organization of the amygdala during avoidance motivated learning may differ substantially between rodents and humans. Despite these differences, human studies still support that the amygdala is generally associated with punishment-motivated reinforcement learning.

Importantly, amygdala neuromodulation also plays a critical role in punishment-motivated declarative memory. Structurally, the amygdala has efferent projections throughout the hippocampus and the surrounding cortical MTL (McGaugh, 2004). Stimulation of the amygdala results in increased long-term potentiation in the MTL (Ikegaya et al., 1995; Akirav and Richter-Levin, 1999; Frey et al., 2001). Functionally, rodent studies have demonstrated that stimulation of the amygdala post-encoding can influence threat-related and punishment-motivated MTL-dependent memory

(McGaugh, 2002; McGaugh, 2004). Further, pharmacological studies demonstrated that these neuromodulatory effects of the amygdala on the MTL are mediated by the release of adrenergic and steroid hormones (McGaugh and Roozendaal, 2002; Roozendaal et al., 2003; Roozendaal et al., 2008). For example, intra-amygdala injections of glucocorticoid agonists results in increased memory for contexts in which threats were encountered, and lesions to the amygdala disrupt these enhancements (Roozendaal and McGaugh, 1997b). More relevant to punishment-motivation, pharmacological activation of the amygdala enhanced memory for safety platforms during a hippocampus-dependent spatial navigation task (Roozendaal and McGaugh, 1997b; Roozendaal et al., 1999) and these enhancements in memory could be blocked by amygdala lesions (Roozendaal et al., 1996; Roozendaal and McGaugh, 1997a). Thus, the rodent literature demonstrates that amygdala activation and neuromodulation over the MTL supports threat-related and punishment-motivated declarative memory.

The human literature has yet to investigate the influence of punishment-motivation on declarative memory encoding and its underlying neural circuitry. However, a wealth of research has investigated the amygdala's role in influencing declarative memory encoding, emphasizing its role in enhancing memory for emotional memoranda (LaBar and Cabeza, 2006; Dolcos et al., 2011). Human patients with amygdala damage show a deficit in arousal mediated memory enhancements and a

selective deficit in recall of the emotional gist of information (Adolphs et al., 2000; Adolphs et al., 2005a). FMRI studies have demonstrated that the amygdala and MTL are associated with the encoding of emotional information. A recent meta-analysis demonstrated that there were reliable enhancements in subsequent memory-related activations in bilateral amygdala and MTL for emotional compared to neutral information (Murty et al., 2010). Further, fMRI studies have demonstrated greater functional coupling between the amygdala and MTL during the encoding of emotional compared to neutral information (Dolcos et al., 2004; Mackiewicz et al., 2006; Ritchey et al., 2008; Murty et al., 2009). This human lesion and neuroimaging evidence suggests that amygdala interactions with the MTL guide threat-related memory enhancements, and could potentially guide punishment-motivated memory enhancements.

Amygdala neuromodulation of the MTL may preferentially facilitate cortical MTL encoding processes relative to hippocampal encoding processes. In rodents, activation of the amygdala facilitates increased coupling amongst cortical MTL regions during emotional enhancements of memory (Paz et al., 2006). Additionally, lesions to the rodent amygdala results in a deficit in cortical-MTL encoding related memories, while sparing hippocampus encoding-related memories (Farovik et al., 2011). Human neuroimaging has also shown engagement of cortical MTL and amygdala-cortical MTL coupling during the encoding of emotional memories (Dolcos et al., 2004; Ritchey et al.,

2008). Furthermore, neuroimaging studies have demonstrated that amygdala activation during encoding predicts memory for items, a cortical MTL encoding process, but not the binding of items in the context in which they were presented (Kensinger and Schacter, 2006; Dougal et al., 2007), a hippocampus dependent encoding process. In line with these neuroimaging findings, behavioral studies have demonstrated that emotion and/or arousal results in a deficit in binding items in contexts (Rimmele et al., 2011; Rimmele et al., 2012) and binding amongst items (Onoda et al., 2009) and promotes gist-based declarative memory retrieval (Qin et al., 2012). These findings suggest that the amygdala, which is engaged during punishment motivation, may preferentially target the cortical MTL during memory encoding. Further, engagement of this system may result in the generation of item-based, unitized representations of the environment.

1.4 VTA and Amygdala Interactions during Motivated Behavior

In addition to the distinct effects demonstrated across reward and punishment motivation, significant overlap and interactions exist between the amygdala and VTA learning systems. Anatomical and neurophysiological studies have demonstrated connectivity both from the VTA to the amygdala and from the amygdala to the VTA (Beckstead et al., 1979; Oades and Halliday, 1987; Geisler and Zahm, 2005; Geisler et al., 2007). Further, the amygdala has been shown to project to the striatum (Gray, 1999), a region critical for VTA-mediated reward-related learning. In certain learning contexts,

both during reward- and punishment-motivated behaviors, these two systems have been demonstrated to interact to facilitate learning. However, the question of how and when these systems interact is still an active area of research. The next sections will review these literatures.

1.4.1 VTA Involvement in Punishment-Motivated Behavior

While a wealth of literature has demonstrated a significant role for the VTA in reward-motivated behavior, animal studies have demonstrated that the VTA is implicated in a variety of punishment-motivated behaviors. The dopaminergic midbrain has been demonstrated to respond to aversive stimuli. The response profiles of the midbrain to these stimuli are varied, such that some neurons show increased firing while others show decreased firing (Bromberg-Martin et al., 2010). Interestingly, there is co-localization of neurons with different response profiles throughout the dopaminergic midbrain, such that neurons in the substantia nigra show increased firing and neurons in the VTA show reduced firing in response to threatening stimuli. In line with these findings, a recent study of fear-conditioning has demonstrated reduced firing rates of VTA neurons in response to cues that predict punishments, and that the degree of this inhibition predicts conditioned response to punishment stimuli (Mileykovskiy and Morales, 2011). Further, disruption of phasic signaling from the VTA has been shown to impair fear-conditioning processes, such that fear-responses lose their specificity and

generalize to neutral environments (i.e. environments in which animals never received punishment) (Zweifel et al., 2011). Regarding active avoidance learning, rodent studies have demonstrated that disruption of the mesolimbic dopamine system impairs punishment-motivated, stimulus-response learning and MTL-dependent memory encoding (Salamone et al., 2005). For example, in a two-way signaled active-avoidance paradigm, rodents with a genetic knock-out of dopamine signaling showed diminished performance, a deficit that could not be accounted for by differences in general locomotion (Darvas et al., 2011). Interestingly, active avoidance behaviors could be restored by simultaneously restoring dopamine in the amygdala and striatum, but not either in isolation. These rodent studies demonstrate that the VTA has a definitive role in punishment-motivated behaviors, and indicate that its role may be specific to facilitating interactions between the amygdala and striatum. However, the exact behavioral factors contributing to the engagement of the mesolimbic dopamine system during punishment-motivated encoding remain unknown.

In humans the mesolimbic dopamine system, including the VTA, is also associated with punishment-motivated behaviors. Neuroimaging studies have shown VTA and ventral striatum activations during the anticipation and active avoidance of punishments (Carter et al., 2009; Delgado et al., 2011). Further, activation of the mesolimbic dopamine system has also been demonstrated to predict punishment-

motivated reinforcement learning (Delgado et al., 2008). Interestingly, in these neuroimaging studies, there is often co-activation of the ventral striatum and amygdala, suggesting an interactive role for these regions during punishment-motivated behaviors. In fact, a neuroimaging study demonstrated enhanced functional coupling between the amygdala and ventral striatum during the onset of salient aversive, but not appetitive, stimuli (Levita et al., 2009). Further, dopamine agonism and antagonism has been demonstrated to modulate amygdala-VTA connectivity during fear conditioning (Diaconescu et al., 2010). Similar to the rodent literature, the human literature suggests that the VTA and its mesolimbic targets are important for punishment-motivated behaviors, and specifically play a role in coordinating activity between the amygdala and striatum during these behavioral processes.

1.4.2 Amygdala Involvement in Reward-Motivated Behavior

The amygdala may also be important for reward motivation. Rodent and primate neurophysiology studies have demonstrated that neurons throughout the amygdala are sensitive to both rewarding and punishing reinforcers and cues that predict aversive or appetitive outcomes (Paton et al., 2006; Belova et al., 2007; Salzman et al., 2007; Belova et al., 2008), suggesting that the amygdala may be responsible for associative learning in a valence independent manner. However, lesion studies suggest a more complex relationship between amygdala function and reward-motivated behaviors. Amygdala

lesions often have no effect on the acquisition of simple-reward motivated behaviors, such as conditioned approach and rewarded reinforcement learning (Murray, 2007), but cause detriments in more complicated behaviors such as reward devaluation (Machado and Bachevalier, 2007; Murray and Izquierdo, 2007; Ostlund and Balleine, 2008; Johnson et al., 2009), stimulus inflation (Wassum et al., 2009), and delay discounting (Floresco and Ghods-Sharifi, 2007; Ghods-Sharifi et al., 2009). This pattern of behavioral deficits suggests that the amygdala's role in reward-motivated behavior is to represent or direct attention to the value of reinforcers and to associate those values with conditioned stimuli (Murray, 2007; Morrison and Salzman, 2010). This theory suggests that the amygdala contributes to reward-motivated learning only when the value of a given reinforcer is dynamic and needs updating, but may have a broader role in punishment-motivated learning.

Human studies have associated amygdala engagement with reward-related behaviors; however, the evidence is not as consistent as those in the rodent and non-human primate literatures. Human neuroimaging has shown amygdala responses during both the perception and successful encoding of intrinsically rewarding stimuli (Hamann and Mao, 2002; Hamann et al., 2002). Although amygdala activation has been demonstrated during reward-motivated behavior (Ernst et al., 2005), a meta-analysis of reward-motivated instrumental behavior did not show reliable activation of the

amygdala during either the anticipation or outcome of rewards (Knutson and Greer, 2008). Regarding learning, a few studies have shown engagement of the amygdala during reward-motivated reinforcement learning (Metereau and Dreher, 2012; Prevost et al., 2011) and reward-motivated declarative memory (Callan and Schweighofer, 2008), however, most studies do not find this association. In line with these neuroimaging findings, patients with amygdala lesions are insensitive to punishments but not rewards (De Martino et al., 2010). There have yet to be lesion studies using paradigms that involve the dynamic updating of stimulus values, such as reward devaluation and inflation.

An alternative role the amygdala may have in reward-motivated behaviors is in mediating physiological arousal. As detailed above, previous studies have shown that the amygdala is critical for mediating arousal responses in rodents, non-human primates, and humans. Additionally, reward-motivated behaviors are often associated with increased arousal (Low et al., 2008; Ariely et al., 2009; Mobbs et al., 2009a), measured by means of skin conductance and self-report. However, it is important to note that arousal during reward-motivated behavior may actually be detrimental to performance (Ariely et al., 2009; Mobbs et al., 2009a).

Together, these findings suggest that the amygdala plays a role in human reward-motivated behaviors; however, evidence for amygdala involvement in simple reward-

motivated behaviors is relatively weak. This suggests that the relationship between the amygdala and reward processes is more complex, and may reflect factors indirectly related to reward-motivated learning, such as arousal or dynamic changes in stimulus value.

1.5 A Theoretical Model of the Influence of Reward and Punishment Motivation on Declarative Memory

While there is relatively little evidence on the question of how reward and punishment motivation differentially influence declarative memory, findings from other literatures speak to how these motivational states may interact with memory encoding processes. A substantial body of evidence suggests that distinct systems guide reward and punishment motivation. Specifically, research suggests that reward and punishment motivation are supported by VTA and amygdala neuromodulation, respectively, although they overlap during certain learning contexts. In this context, neuromodulation refers to the regions that have regulatory control over the activation of their targets, and does not specifically necessitate control via neurochemical/neurotransmitter release. Additionally, evidence from declarative and emotional memory studies across animals and humans suggest that engagement of the VTA and amygdala have distinct effects on declarative memory encoding processes. Given these literatures, I propose that engagement of the VTA biases encoding processes towards the hippocampus, whereas engagement of the amygdala biases encoding processes towards the cortical MTL,

including the perirhinal and parahippocampal cortex. Critically, differential engagement of the hippocampus and cortical MTL during encoding results in the storage of different representations of the environment into long-term memory.

Given these findings, I propose the following model of how reward and punishment motivation may differentially influence declarative memory encoding. First, the model posits that an individual's current motivational state will influence how they encode their environment. Secondly, the model posits that reward and punishment motivation elicit unique motivational states in an individual, and thus have distinct consequences on memory encoding. Specifically, reward motivation preferentially engages VTA neuromodulation, which in turn biases individuals to encode flexible, relational representations of their environment via increased reliance on the hippocampus. In contrast, the proposed model suggests that punishment motivation preferentially engages amygdala neuromodulation, which in turn biases individuals to encode inflexible, unitary representations of objects and contexts in the environment via increased reliance on cortical MTL regions. Critically, this model proposes that the motivational state of an organism will facilitate different MTL regions independent of whether memory encoding is instrumental or incidental. For example, motivation would similarly affect memory both when individuals are explicitly trying to learn about

incentivized information and when individuals unintentionally learn about their environment during the pursuit of goals.

Although evidence from prior literatures support this model, studies have yet to directly test the predictions of the model. Specifically, open questions remain regarding (1) whether reward and punishment motivation have distinct influences on declarative memory, (2) whether punishment- and reward-motivated declarative memory encoding are subserved by similar or distinct neural systems, and (3) whether motivation results in similar MTL-dependent encoding processes during incidental and intentional encoding. The following chapters of this dissertation present studies testing the predictions of this model and evaluating the model's validity. Chapter 2 presents a study examining the behavioral effects of reward and punishment motivation on declarative memory. This study tests memory for flexible, integrative representations of environments, which the model predicts will be facilitated by reward but not punishment motivation. Chapter 3 presents a study examining the neural circuitry underlying punishment-motivated declarative encoding using fMRI. Critically, this study adapted a paradigm previously used to study reward-motivated encoding (Adcock et al., 2006), and thus allows for the comparison of this study's findings with the previous literature. Chapter 4 presents a study examining the influence of reward and punishment motivation on neural sensitivity to and memory for unexpected events.

In this study, declarative memory encoding was not explicitly incentivized, and thus this study tests whether the motivational state of an organism can change the incidental encoding of the environment. Finally, Chapter 5 will evaluate the findings from Chapters 2-4 in the context of the literature reviewed in Chapter 1 to test the proposed theoretical model of the influence of motivation on declarative memory encoding.

2. The Influence of Reward and Punishment Motivation on Spatial Declarative Memory

2.1 Introduction

Memories are not direct reflections of the environment, but are instead selective. How does this selectivity arise? Prior research suggests that motivation enhances learning and memory for behaviorally relevant information (Shohamy and Adcock, 2010), but there are qualitatively different ways of motivating an individual to learn. For example, a student could equally be motivated to perform well on a test either to earn a good grade or to avoid failing a course. Previous research has demonstrated varied effects on cognition and behavior by motivation to earn rewards versus motivation to avoid punishments (Elliot, 2008; Lang and Bradley, 2009), suggesting that these states would also produce different effects on declarative learning. The goal of this study was to characterize the shared and specific effects of reward versus punishment motivation on the encoding and use of declarative information, specifically information about spatial environments.

Previous research has demonstrated that motivation to learn enhances declarative memory. Specifically, reward incentives for successful encoding have been demonstrated to improve later memory retrieval (Adcock et al., 2006; Callan and Schweighofer, 2008; Murayama and Kuhbandner, 2011; Wolosin et al., 2012). However, extant human studies have only investigated reward motivation; to date no parallel

study has investigated the influence of punishment motivation – the opportunity to avoid punishments – on declarative learning. Reward and punishment motivation have been associated with distinct behaviors and neurophysiological states (Elliot, 2008; Lang and Bradley, 2009). Reward motivation is associated with behavioral activation, exploration, and positive affect (Ikemoto and Panksepp, 1999), whereas punishment motivation is associated with behavioral inhibition, stress, and anxiety (Davis and Whalen, 2001; Lang and Bradley, 2009). Given that these states differentially affect how individuals experience and interact with their environments, these states should also differentially influence how individuals learn about their environments.

The Morris water task is a paradigm widely used to investigate the encoding and subsequent retrieval of features of an environment and also offers important advantages for human study. In this spatial learning paradigm, rodents are placed in a pool and must use stored representations of the environment to navigate to a hidden platform. Rodent studies have demonstrated that performance on this task is sensitive to lesions of the hippocampus (Morris et al., 1982; Sutherland et al., 1982), a brain region known to support spatial and declarative learning (Eichenbaum, 2004; Nadel and Hardt, 2011). Like rodents, patients with hippocampal lesions or deficits show severe performance deficits on virtual reality versions of the task (Astur et al., 2002; Brandt et al., 2005). Thus, the virtual reality water task paradigm offers a valuable tool for connecting the

human and rodent memory literatures (Hamilton et al., 2009), albeit with some debate regarding functional equivalence due to differences in stress elicited across species (de Quervain et al., 1998). Furthermore, because the experimental design of the water task integrates immediate goal pursuit (e.g., finding platforms) with declarative memory, it is well suited for manipulating reinforcement and goal-orientation without significantly modifying memoranda or experimental design. Together, these features make the human water task a useful tool for investigating the influence of reward and punishment motivation on declarative learning.

In order to directly contrast effects of motivation by reward and punishment on declarative learning, the current study modified the Morris water task to include two platforms, one good and one bad, for each incentive condition (Figure 1). For the reward condition, reaching the good platform earned a reward, and touching the bad platform ended the trial. For the punishment condition, contacts with the bad platform resulted in mild shock and reaching the good platform ended the trial. Given the spatial nature of the task I was then able to assess the influence of motivation on learning and memory across multiple measures, including accuracy, learning rates, and precision.

Additionally, I recorded participants' skin conductance levels (SCLs) during navigation in order to explicitly investigate the relationships between arousal and motivated learning. Previous research has associated physiological arousal both with motivation

(Low et al., 2008) and learning (Roosendaal et al., 2008). However, the relationship amongst arousal, motivational orientation, and declarative memory has not been explicated. By investigating the influence of both rewards and punishments on water task performances as well as concurrent SCLs, the present study tested the hypothesis that reward and punishment motivation have differential influences on declarative memory, and that physiological arousal is an important determinant of how reinforcement effects motivated learning.

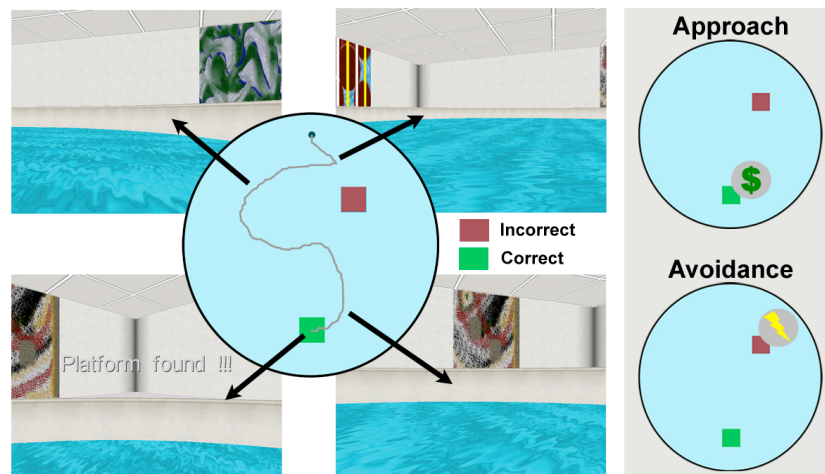


Figure 1: Virtual Reality Morris Water Task. A schematic of the modified virtual reality Morris water task to investigate the influence of reward and punishment motivation on spatial learning.

2.2 Methods

2.2.1 Participants

Forty-two healthy, right-handed participants received \$10/hour plus any monetary bonuses for study participation. Participants were randomly assigned to either

reward or punishment motivation groups. Data from three participants were excluded for computer malfunctions or poor baseline performance (less than or equal to chance), resulting in 39 participants (median age = 22, age range = 19-28), 19 participants in the reward group (seven female) and 20 participants in the punishment group (10 female).

2.2.2 Water Task Virtual Environment

The experimental task used a 3-dimensional virtual environment displayed on a 2-dimensional computer monitor. The environment consisted of a circular pool, 3.2 arbitrary units (a.u.) in diameter with a perimeter wall that extended 0.66 a.u. above the surface of the pool, centered in a square room, 16 a.u. in width and length and 3 a.u. in height. Depending on trial type, the pool contained two hidden platforms (correct and incorrect platforms), 0.66 a.u. in width and length, or no platforms at all (for probe trials). Using a keyboard, participants navigated through this environment from a first-person perspective. Four distal, easily distinguishable visual cues (abstract paintings, 3.a.u * 3.a.u) of equal size were located on each of the identical walls and were the only environmental features that could disambiguate locations. By changing the platform locations and visual cues, 8 unique environments were constructed. Environments were counterbalanced across conditions.

2.2.3 Procedure

Participants performed a spatial-memory task in both motivated and non-motivated conditions, with motivational reinforcement (i.e. reward or punishment) as a between-subjects factor. Participants navigated the environment using a first-person perspective to learn the platform locations, in order to reach correct platforms while avoiding the incorrect platform. Standard trials ended when the participants reached either the correct or incorrect platform or 60 seconds passed, at which point the correct platform became visible and the trial was considered incorrect. At the end of each trial, participants viewed visual feedback regarding their trial performance: text reading “correct,” “incorrect,” or “correct platform visible.” During probe trials, participants navigated for 60 seconds in an environment that did not contain any platforms, to allow for the measurement of spatial navigation performance over a fixed period of time. In motivated conditions, reward participants were given \$5 monetary bonuses for correct performance and punishment participants were given electrical shocks for incorrect performance. Electrical shocks, as opposed to monetary losses, were used because previous research has demonstrated that reward motivation networks are similarly engaged when individuals prepare to gain monetary rewards and avoid monetary losses (Carter et al., 2009). Additionally, electrical shocks more reliably elicit activation in punishment motivation neural circuitry (Delgado et al., 2008; Delgado et al., 2011). In

non-motivated conditions and motivated probe trials participants did not receive any reinforcement. Each participant received five trials in four unique environments (four standard trials and one probe trial, 10 second interstimulus intervals) for a motivated and a non-motivated condition, resulting in 20 trials per condition. During each trial of the navigation task, participants were placed in a new start location in a virtual environment containing a pool with two hidden platforms: one correct and one incorrect. Platform locations stayed constant in a given environment.

For the punishment motivation group, an MP-150 BIOPAC system (BIOPAC Systems, Goleta, CA) was used for the administration of shocks (for details see Dunsmoor et al., 2009). Shocks were calibrated to a level that was “highly irritating but not painful” using an ascending staircase procedure. For both groups, an MP-100 BIOPAC system (BIOPAC Systems, Goleta, CA) was used for collection of SCLs. SCLs were sampled and recorded at 200 Hz from the second and third digits of the left hand from trial onset to platform discovery, excluding time epochs containing reinforcement. SCLs were normalized by log-transformation. Three participants’ SCL data were not collected due to technical issues.

Following completion of the behavioral paradigm, participants completed a study-specific, self-report questionnaire to quantify individuals’ motivation to perform during the incentivized condition. Specifically, participants were asked “Were you more

motivated to perform during the shocked/reward session?" and indicated their responses on a five-point scale ranging from "not at all" to "yes."

2.2.4 Statistical Analysis

Statistical significance for spatial memory performance and SCLs was tested using general linear models with condition (motivated, non-motivated) as a within-subjects factor and group (reward, punishment) as a between-subjects factor. Accuracy and precision data from the first trial were excluded from statistical analysis because performance was at chance. Probe trials were analyzed by calculating the relative time participants spent in the quadrant of correct platforms compared to incorrect platforms. Relationships between arousal, motivation, and behavioral performance were analyzed using three different techniques. First, SCL measures were entered into a general linear model with trial performance (correct or incorrect) as a within-subjects factor and group (reward or punishment) as a between-subjects factor. Second, differences in SCL measures across condition (motivation - non-motivated SCL) were regressed against motivated-memory performance for reward and punishment groups, separately. Finally, differences in SCL measures across conditions (motivated - non-motivated SCL) were compared across low-performing and high-performing groups using two-sample t-tests for reward and punishment groups, separately. Results from all statistical analyses were considered significant at a level of $p < 0.05$.

2.3 Results

Results demonstrated that both monetary bonuses for correct performance ($t(19) = 22.342, p < 0.001$) and electrical shocks for incorrect performance ($t(18) = 23.369, p < 0.001$) increased self reports of motivation to perform, without any significant differences between groups ($t(37) = 1.211, p = 0.23$). Behavioral performance was then compared between motivated and non-motivated conditions across reward and punishment motivation groups. No effects of participant gender on spatial memory, motivation, or their interactions ($p > 0.15$) were evident; however, sample sizes were relatively small to detect interactions between sex, motivation, and memory. Despite equivalent motivation, rewards promoted better spatial learning and memory than punishments. Specifically, participants found more correct platform locations under reward compared to punishment motivation (group \times condition interaction: $F(1,37) = 5.37, p = 0.02$) (Figure 2A). Participants also showed a trend toward faster learning rates under reward compared to punishment motivation, such that linear decreases in trial latencies were steeper during the pursuit of rewards (group \times condition interaction: $F(1,37) = 2.37, p = 0.06$).

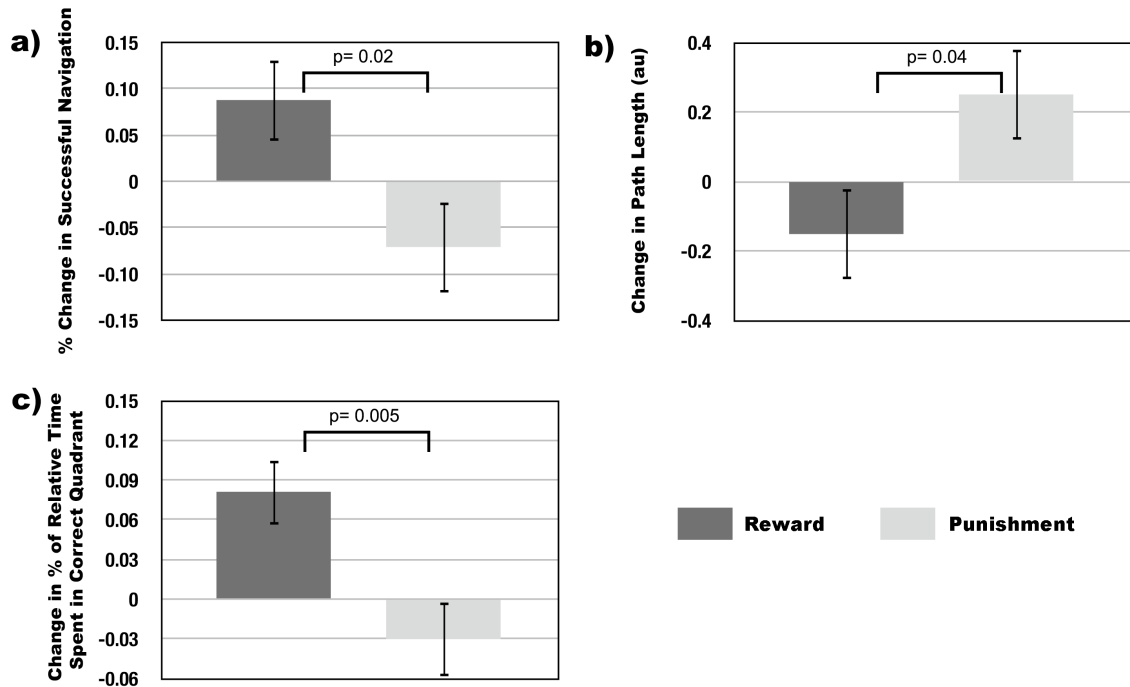


Figure 2: Spatial navigation performance across reward and punishment groups. Mean differences scores are shown between motivated and non-motivated conditions (error bars represent \pm SEM) in (A) the mean percentage of trials resulting in navigation to correct platform locations, (B) the mean path lengths (in arbitrary units) during navigation to correct platforms, and (C) the percentage of time spent in the quadrant containing the correct platform, relative to the total time in quadrants containing the correct and incorrect platforms, during probe trials when no platforms were present in the environment. P-values reflect group by condition interactions. Note for panels A and B, data from the first trial were not included, as participants did not have the opportunity to learn.

Further, participants demonstrated greater spatial precision in memory under reward compared to punishment motivation. On correct trials, path lengths were shorter

under reward compared to punishment motivation (group x condition interaction: $F(1,37) = 4.64, p = 0.04$) (Figure 2B). Additionally, during probe trials, in which participants were navigating in environments that did not contain any platforms navigation in the proximity of correct and incorrect platforms was compared across groups. For this analysis, proximity was defined as the percentage of time spent navigating in the quadrant of the virtual environment containing each platform. This analysis revealed that reward-motivated participants spent relatively more time in the proximity of correct platform locations ($[\text{correct platform}]/[\text{correct} + \text{incorrect platform}]$) than punishment-motivated participants (group x condition interaction: $F(1,37) = 8.81, p = 0.005$) (Figure 2C). Critically, this relative difference across groups was driven by the punishment group spending more time in the proximity of incorrect platform locations compared to the reward group ($F(1,37) = 5.58, p = 0.02$); there were no significant differences in time spent in the proximity of correct platform locations ($F(1,37) = 2.597, p = 0.12$). The probe trial data argue against the explanation that punishment-motivated participants might have neglected the correct platform locations due to a reinforcement bias toward avoiding the incorrect platform, and suggest instead that punishment resulted in a general deficit in learning.

Analysis of physiological data revealed that SCLs were higher in both motivated conditions compared to control conditions (main effect of condition: $F(1,34) = 11.1, p =$

0.002) with no difference between groups (group x condition interaction: $F(1,34) = 0.28$, $p = 0.60$) (Figure 4A, below). However, both within and across subjects, relationships between SCLs and memory were selective. For these analyses, memory was quantified as successful navigation to correct platform locations. Within subjects, SCLs were greater on incorrect than correct trials under reward but not punishment motivation (group x condition interaction: $F(2,30) = 5.712$, $t(30) = 2039$, $p = 0.02$) (Figure 3A). Across subjects, motivated SCL changes (motivated SCL – non-motivated SCL) were inversely correlated with performance under reward ($r(16) = -0.55$, $p = 0.02$) but not punishment motivation ($r(16) = 0.04$, $p = 0.86$) (Figure 3B), meaning that motivated-SCL response were a better predictor of performance for reward-motivated compared to punishment-motivated participants. Thus I demonstrated that low physiological arousal predicted memory success, but only under reward motivation.

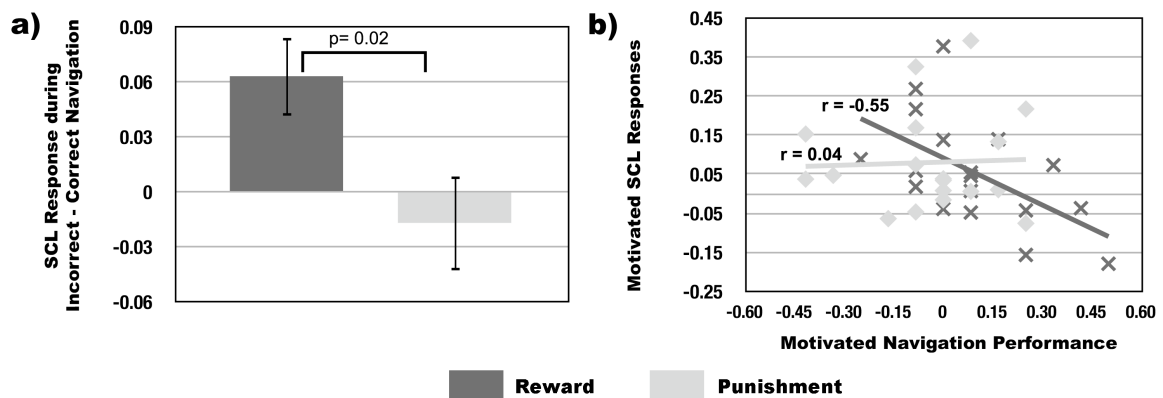


Figure 3: Relationships between spatial navigation performance and arousal across reward and punishment motivation groups. (A) Mean difference scores (error bars represent \pm SEM) for SCL responses during incorrect - correct platform locations were greater under reward compared to punishment motivation (reward [incorrect SCL – correct SCL] > punishment [incorrect SCL – correct SCL]). (B) Significant negative correlations were present between motivated SCL changes and spatial navigation performance under reward, but not punishment, motivation.

To confirm these findings, I compared motivated SCL changes between reward participants who showed reward-motivated performance benefits (REW+) and those who did not (REW-). REW+ participants were defined as individuals who found more correct platform locations in the reward-motivated condition compared to the non-motivated condition, where REW- participants were defined as individuals who had any deficit, or no change, in the reward-motivated condition. This analysis revealed that REW+ participants had significantly lower motivated SCL changes than REW- participants ($t(16) = -2.761$, $p = 0.014$) (Figure 4B). A similar performance split in punishment-motivated participants did not reveal any significant differences ($t(16) =$

0.770, $p = 0.452$)(Figure 4B). There was also no difference in motivated SCL changes between REW- and punishment-motivated participants ($t(24) = 1.082$, $p = 0.29$), suggesting that these two groups had similar arousal profiles during learning.

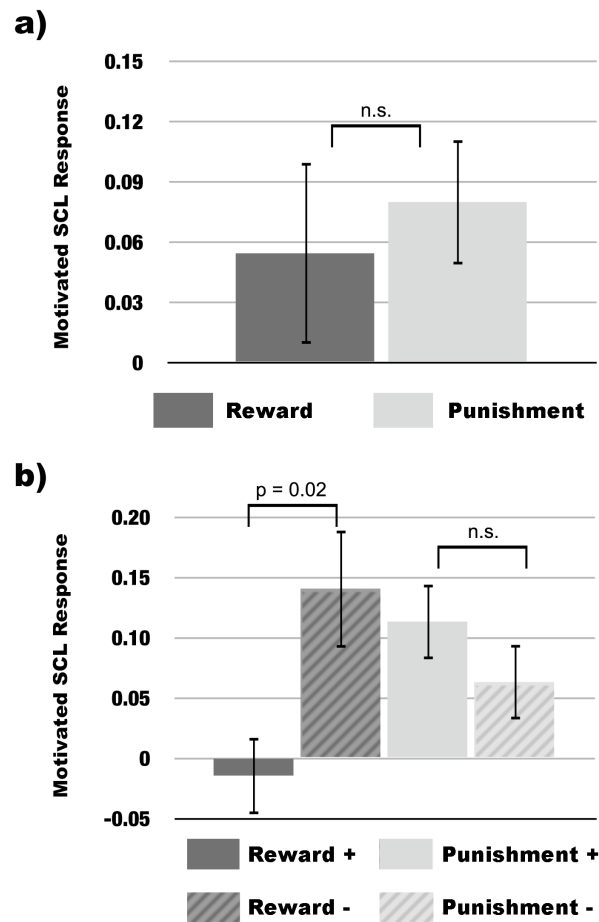


Figure 4: Motivated arousal responses across reward and punishment groups. (A) Mean differences (error bars represent \pm SEM) in motivated arousal changes (SCL motivated trials – SCL non-motivated trials) across participants in the reward and punishment groups. (B) Mean differences (error bars represent \pm SEM) of participants in the reward and punishment groups who showed performance benefits (Reward +, $n = 10$; Punishment +, $n = 6$) as well as those who showed either performance deficits or no difference (Reward -, $n = 8$; Punishment -, $n = 12$).

2.4 Discussion

The present study provides a novel characterization of how motivation to avoid punishments influences declarative learning in humans, and further provides evidence for differential effects of reward and punishment motivation on spatial learning.

Overall, the pursuit of monetary rewards resulted in better memory than the avoidance of electrical punishments. Further, the current study demonstrated a critical detrimental role for physiological arousal in motivated learning. Specifically, high arousal was associated with poor performance under reward motivation. This relationship was not evident for punishment-motivated participants, who as a group, showed worse performance. Finally, the study demonstrated that low-performing reward-motivated participants had arousal profiles similar to punishment-motivated participants.

This pattern of facilitation by reward motivation and impairment by punishment motivation differs from investigations of motivated learning in other domains. For simple associative responses such as stimulus-response learning (Delgado et al., 2008; Robinson et al., 2010; Prevost et al., 2011) and Pavlovian conditioning (Gottfried et al., 2002; Seymour et al., 2007; Pessiglione et al., 2008), earning rewards and avoiding punishments can both facilitate learning. However, Pavlovian and stimulus-response learning fundamentally differ from declarative memory, which necessitates that environmental features are encoded into long-term mnemonic representations. Further,

these separable kinds of learning are mediated by parallel neural systems (Iaria et al., 2003; Poldrack and Packard, 2003). Specifically, declarative learning is supported by the medial temporal lobes, including the hippocampus (Eichenbaum, 2004), as both humans and rodents with hippocampus lesions show severe deficits in declarative memory tasks, including spatial learning (Morris et al., 1982; Sutherland et al., 1982; Astur et al., 2002). Conversely, patients with hippocampal lesions do not show significant deficits in stimulus-response learning or simple Pavlovian learning (Squire, 1992). Together these findings suggest that the influence of reward and punishment motivation may be mediated by the specific neural substrate mediating learning, such that positive and negative reinforcements have divergent influences on hippocampus-dependent, declarative memory. However, future studies will need to directly compare positive and negative reinforcement on other forms of declarative memory, such as item memory or paired-associate learning.

The current study also identified a unique role for physiological arousal in mediating motivated learning. Separate lines of research have previously highlighted the role of arousal in learning and memory, and in motivated behavior. Regarding spatial memory, rodent studies have demonstrated that increases in physiological arousal, induced by either physiological or psycho-social stress, disrupt hippocampus-dependent declarative memory and promote stimulus-response learning in water maze

paradigms (Kim et al., 2001; Roozendaal et al., 2003; Kim et al., 2005). Both reward and punishment motivations have been associated with increases in physiological arousal (Low et al., 2008; Mobbs et al., 2009b); however, these studies did not investigate how changes in arousal related to goal-direct learning. Consistent with these prior findings, here both shocks and reward elicited equivalent SCLs; differences across motivation conditions only emerged when relating SCL to motivated memory performance. The current study demonstrates a novel aspect of reward motivation: If an individual responds to an incentive with high arousal, as typifies punishment motivation, performance will not benefit and may in fact suffer. These findings suggest that the subgroup of reward-motivated individuals who showed performance deficits may also be in a state typically elicited by punishment motivation. Outside of the domain of learning, reward motivation has been shown to elicit performance deficits in some individuals. Previous investigators have related this behavior to “choking under pressure, “ in which performance drops when reward incentives evoke stress responses and anxiety (Ariely et al., 2009; Mobbs et al., 2009a). One memory study has demonstrated anxiety-induced performance deficits in some subjects during reward-motivated declarative memory (Callan and Schweighofer, 2008); however, that study relied on self-report of anxiety given after the experimental task. The current study’s findings advance the literature by directly relating dynamic shifts in SCLs to memory

performance during reward-motivated learning both across and within subjects. The results point to physiological arousal as a potentially important inhibitor of motivated learning, with similar learning deficits in highly aroused reward states and in punishment.

The relationship between physiological arousal and motivated memory was specific to reward motivation. Despite equivalent overall arousal in the two groups, neither within- nor across-subject analysis revealed any significant relationships between spatial navigation accuracy and physiological arousal under punishment motivation. This pattern of findings may reflect greater heterogeneity in the motivated learning states evoked by reward incentives compared to punishment incentives. That is, punishment incentives may consistently evoke a state associated with physiological arousal, anxiety, and impaired learning, such that variability in these markers during motivation is not predictive of learning. Conversely, anxiety may only be evoked by reward incentives in a limited set of behavioral contexts. Given this variability, arousal would only be a valid index of variation in reward-, but not punishment-, induced stress and thus also reliably index variation in reward-induced learning impairments. Thus, in line with the stress and spatial navigation literature, I propose a model of motivated learning in which arousal dictates the efficacy of hippocampus-dependent spatial learning. However, our findings suggest that whereas punishment motivation reliably

evokes states of stress, reward motivation only evokes these states in a subgroup of participants. Future studies will need to investigate the relationship between positive and negative incentives, self-reported anxiety, and physiological marker such as SCL.

Although our study provided novel evidence regarding the influence of reward and punishment motivation on declarative memory, one aspect of our current experimental design limits the interpretation of our findings. This current study used electrical shocks instead of monetary losses to induce punishment motivation, as the threat of shock more reliably activates circuitry implicated in punishment motivation (Delgado et al., 2008; Delgado et al., 2011); however, this resulted in qualitatively different reinforcers, namely, electrical stimulation versus monetary bonuses. Although these reinforcers induced similar self-reports of motivation and SCLs, they fundamentally differ in that electrical stimulations are primary reinforcers whereas monetary rewards are secondary reinforcers. Although some studies have provided evidence that primary and secondary reinforcers are processed very similarly in the brain (Valentin and O'Doherty, 2009; Kim et al., 2011a), other studies have noted significant differences (Beck et al., 2010). Future studies using reinforcers within a similar qualitative domain, such as rewarding and punishing odors or juices, should test the prediction that, irrespective of valence, if a motivational state is accompanied by high arousal, hippocampal learning will be impaired, not enhanced.

In conclusion, I provide a novel characterization of how avoiding punishments influence declarative learning and demonstrate that reward and punishment motivations have differential influences on declarative learning and memory. Further, I demonstrated that individual interpretation of incentives is an important mediator of this effect. In general, reward motivation enhanced but punishment motivation interfered with the successful encoding and use of representations of the environment. The benefits of reward motivation were not seen in those individuals who became physiologically aroused during the pursuit of rewards. Together these findings support a model in which how one interprets and responds to an incentive, rather than its objective value, is what dictates the efficacy of learning. Future studies investigating the psychological and neural factors that determine the efficacy of learning incentives will contribute to a better understanding of how to motivate successful declarative learning for a given individual. However, individual differences notwithstanding, these data suggest that for declarative learning, specifically hippocampus-dependent spatial learning, reward is a better incentive than punishment.

3. The Neural Circuitry Underlying Punishment-Motivated Declarative Memory Encoding

3.1 Introduction

When faced with a threat, individuals are motivated to seek out and encode information to help avoid it. Candidate neural circuitry for the influence of motivation on declarative memory has been described under conditions of reward, but potential mechanisms under conditions of punishment remain open. In particular, punishment-motivated memory encoding could rely on systems specialized to process environmental threat. The current study characterized neural mechanisms of motivated declarative encoding when individuals expected that forgetting would be punished by mild electrical shocks.

Motivated behaviors, including declarative learning and memory (Shohamy and Adcock, 2010), have been demonstrated to be dependent on mesolimbic dopamine systems, especially the ventral tegmental area (VTA) (Berridge and Robinson, 1998; Wise, 2004). During reward-motivated declarative encoding, interactions between the VTA and hippocampus predict successful memorization of incentivized information (Adcock et al., 2006). In humans, reward- and punishment-motivation have both been associated with activation throughout the mesolimbic dopamine system, including the VTA (Carter et al., 2009; Delgado et al., 2011). Because punishment motivation, like reward motivation, can engage the VTA it is possible that punishment-motivated

encoding could also engage the VTA. Alternatively, punishment-motivated encoding may depend on amygdala neuromodulation. The amygdala and its interactions with the MTL have been critically implicated in enhancing memory for intrinsically threatening stimuli (LaBar and Cabeza, 2006), while, in humans, the VTA is not reliably activated during this type of emotional memory encoding (Murty et al., 2010).

The separate literatures on motivation and threat processing thus make distinct predictions about the neural systems supporting punishment-motivated declarative encoding. If punishment incentives evoke equivalent motivational states to reward incentives, the VTA should modulate declarative encoding. However, if punishment incentives lead individuals to perceive motivational cues or memoranda as environmental threats, the amygdala should modulate encoding. Additionally, the amygdala and VTA could facilitate learning jointly (Lalumiere et al., 2004; Darvas et al., 2011).

The goal of this study was to provide evidence to adjudicate these theoretical perspectives regarding the neural circuitry underlying punishment-motivated declarative encoding. During fMRI, motivational cues instructed participants whether forgetting memoranda (target scenes) would or would not be punished with a mild electrical shock (Figure 5). Twenty-four hours after encoding, participants were tested for scene recognition, but were not in fact punished, to isolate the effects of punishment

motivation during encoding. Analyses investigated how the threat of shock influenced recognition memory, encoding success activations (ESA, activations that are stronger for subsequently remembered versus forgotten memoranda), and functional connectivity. Critically, fMRI activations and functional connectivity were analyzed both prior to and during target scene encoding. Analyses aimed to delineate relative contributions of the VTA and amygdala and their interactions with the medial temporal lobe (MTL) during punishment-motivated encoding, thus informing models both of active avoidance and motivated memory.



Figure 5: Shock incentivized encoding task. Shock threat trials are depicted. During this task, participants were instructed that they could avoid getting shocks at a ~ 24 hour retrieval test by successfully remembering scenes following shock cues, and that there was no threat of shocks associated with scenes following no-shock cues. Importantly, no shocks were administered during the task or the retrieval session.

3.2 Methods

3.2.1 Participants

Twenty-five healthy, right-handed volunteers participated in this study. All participants gave written informed consent for a protocol approved by the Duke University Institutional Review Board. I excluded 7 participants because of excessive head motion (> 1.5 mm, 2 participants), insufficient trial types in conditions of interest (4 participants), or software malfunction during scanning (1 participant), which resulted in 18 participants (8 female, age range: 18-37; median age = 24) for the final analysis.

2.2.2 Task

FMRI was performed during a shock incentivized encoding task. During this task, participants studied scene images to avoid punishment, in the form of electrical simulations, for memory failures at a 24-hour retrieval test. On each trial, participants first viewed a motivational cue indicating the value of encoding an upcoming target scene. Participants either viewed a shock cue (a lightening bolt), which indicated that participants could avoid receiving an electrical shock at a 24-hour recognition test by successfully encoding the upcoming scene, or a no-shock cue (a lightening bolt with an overlaid cancel sign), which indicated that there was no threat of shock associated with memory for the upcoming scenes (see Fig.1). Regardless of the cue, I instructed participants to try to encode all stimuli. Following the cue (1 second), participants

viewed a fixation cross (2.5 – 6.5 seconds), followed by the target scene to be encoded (2 seconds). Target scenes were color photographs of indoor and outdoor scenes, each of which was novel. Pictures were pseudo-randomly divided into four sets of 60 that contained equal proportions of indoor and outdoor scenes. Assignment to study stimuli or recognition test foils were counterbalanced across participants. Following each target scene, participants performed a visual-motor distractor task to prevent further elaboration of the target and to allow for an active baseline for neuroimaging analyses (Stark and Squire, 2001). This distractor task required participants to indicate the direction of an arrowhead (left or right; three trials totaling 2.5 seconds, arrow duration 667 milliseconds, 250 millisecond interstimulus intervals) with a rapid congruent button press. Following the distractor task, participants viewed a screen with no fixation cross (4.5-18.5 seconds) and were instructed to remain alert for the next cue. Participants received 60 shock and 60 no-shock trials pseudo-randomized over 4 runs, each lasting 8 minutes and 34 seconds. Trial onsets, cue-scene intervals and trial order were optimized using Opt-seq software (<http://surfer.nmr.mgh.harvard.edu/optseq>).

2.2.3 Procedure

Prior to scanning, participants calibrated electrical shocks to a level that was “highly irritating but not painful” using an ascending staircase procedure with 5 mv increments (Dunsmoor et al., 2011b). Shocks were administered using the MP-150

BIOPAC system (BIOPAC systems, Goleta, CA). Following shock calibration, participants were given instructions for the task. Participants were told they would see a series of scene images preceded by motivational cues, and that memory for scenes would be tested at a 24-hour delay memory test. Participants were informed that each trial began with one of two cues, a shock or a no-shock cue. Critically participants were instructed that they would not receive any shocks during any runs of the task. Participants were instructed that they could avoid receiving shocks at the 24-hour retrieval session by successfully remembering scene images following shock cues, and that there was no threat of shock associated with scenes following no-shock cues.

Inside the scanner, participants performed four runs of the task. Prior to each run of the task, participants were given a single demonstration of the shock to increase the efficacy of the motivational cues. Following the task, participants performed one run of the localizer task (described below). Upon leaving the scanner, participants completed a post-scanning questionnaire in which they were asked to report how motivating they found the shock incentives on a scale of 1 (not motivating) to 5 (extremely motivating). Participants were then informed that the threat of shock was an instructional manipulation only, and no shocks would be given during the 24-hour retrieval session; however, their memory would still be tested.

The following day (22-26 hours after the encoding session), participants performed a recognition memory task for the target scenes. During this test, participants saw 120 studied scenes (60 shock, 60 no-shock) and 120 novel foil scenes in a randomized order. For each scene image, I asked participants to decide if each picture was “OLD” or “NEW” by pressing the “8” and “9” buttons, respectively, on a keyboard. Following each memory decision, participants had to indicate their confidence in their response (i.e., 1 = very sure, 2 = pretty sure, 3 = just guessing).

3.2.4 MRI Data Acquisition and Preprocessing

FMRI data was acquired on a 3.0T GE Signa MRI scanner using a standard echo-planar sequence (TE= 27 ms, flip = 77 degrees, TR = 1 second, 17 contiguous slices, size = 3.75 mm * 3.75 mm * 3.80 mm). Partial brain acquisition with a short TR was utilized to maximize the sampling rate in regions of interest. Brain images were acquired in an orientation that maximized coverage of the MTL, striatum, and medial prefrontal cortex, and thus excluded motor cortex, parietal cortex, and parts of the dorsal visual stream. Task data was acquired in four runs with 514 volumes each (8 minutes and 34 seconds). The first 12 volumes of each functional run was removed to allow for magnetic stabilization. Prior to the functional runs, a whole-brain inversion recovery spoiled gradient recalled (IR-SPGR) high-resolution anatomical image (voxel size = 1 mm, isotropic) was collected for spatial normalization. Prior to each run, a whole brain echo-

planar image (EPI, 34 contiguous slices) was collected with the same voxel size and orientation as partial EPI brain images to assist with normalization.

FMRI preprocessing was performed using SPM8 (www.fil.ion.ucl.ac.uk/spm) software to first realign images across runs and then smooth the data using an isotropic 4 mm³ full-width half-maximum kernel. Data was visually inspected on custom software to review for head motion and artifacts. Data was analyzed only if they exhibited less than 1.5 mm motion (absolute maximum). Images with transient noise artifacts (greater than 2.5 SD from mean) were replaced with interpolated data from neighboring time points (artifacts occurred in less than 1.5% of the data). Preprocessed functional images (partial brain EPI) were first registered to whole-brain EPI images. Then whole-brain EPI images were normalized to the MNI template using a 5th Degree B-spline interpolation. The normalization matrix was applied to their realigned functional images.

3.2.5 Behavioral Analysis

Self-reports of motivation to learn were submitted to a one-sample t-test. To measure differences in memory across conditions, corrected-recognition scores (Hits – False Alarms) were calculated separately for scenes following shock cues and no-shock cues, excluding guesses. Corrected-recognition scores were calculated separately for all responses and responses endorsed with confidence (“pretty sure” and “very sure”

responses). Corrected-recognition scores were then compared across shock and no-shock conditions using a paired t-test. Statistical thresholds were set at $p < 0.05$.

3.2.6 FMRI Analysis

3.2.6.1 General Linear Model

FMRI data analysis was performed using SPM8. I modeled individual-subject fMRI data using a General Linear Model (GLM). Separate regressors were created modeling the cue and target scene onsets, with even durations specified as 0.5 seconds and 1 second, respectively. In both cases, task regressors were convolved with a canonical hemodynamic response function (HRF) prior to analysis. Imaging data was normalized to the mean global signal across the functional volumes across the entire session, and high-pass filtered (less than 124 seconds).

A parametric design was utilized to investigate the effects of motivation condition and encoding success. Condition regressors weighted all trials equally for each of the (cue/target) X (shock/no-shock) event types. To investigate parametric modulation of brain activity by encoding success, additional regressors were constructed for each subject for each event type, weighted according to the subject's memory strength at retrieval for the scene presented on that trial (parametric ESA). Thus, trial weights for these regressors were greatest when scenes were most strongly remembered, intermediate when they were weakly remembered, and lowest when they were

forgotten. Specifically, for each participant I calculated the corrected-recognition scores (hits-false alarms) for stimuli endorsed as old with each confidence rating (“very sure”, “pretty sure”, and “just guessing”) at retrieval, with a value of zero assigned to trials in which scenes were subsequently forgotten. Thus, for each individual participant the values for the shock parametric ESA would be calculated as follows: $\text{ShockHit}_{(\text{VerySure})} - \text{FalseAlarm}_{(\text{VerySure})}$, $\text{ShockHit}_{(\text{PrettySure})} - \text{FalseAlarm}_{(\text{PrettySure})}$, $\text{ShockHit}_{(\text{JustGuessing})} - \text{FalseAlarm}_{(\text{JustGuessing})}$, $\text{Miss} = 0$. For example, for a single individual these parameters might be: Very Sure (0.45-0.10 = 0.35), Pretty Sure (0.35 – 0.20 = 0.15), Just Guessing (0.02-0.01 = 0.01); Forgotten (0). Individualized corrected-recognition scores for each confidence rating were then assigned to all the trials that elicited that confidence rating. Similar parametric analyses have previously been used to investigate encoding success activations in fMRI data (Kensinger et al., 2011; Ritchey et al., 2011). Using the GLM, individual maps of parameter estimates were generated for contrasts of interest: shock cue > no-shock cue, shock target scene > no-shock target scenes, parametric ESA shock cue > no-shock cue, and parametric ESA shock target scene > no-shock target scene. Group-level random-effects analyses were performed using one-sample t-tests.

3.2.6.2 Region of Interest Analyses

Region of interest (ROI) analyses were performed to confirm and visualize findings from the whole-volume GLM, directly compare the contributions of VTA and

amygdala, and to independently investigate brain-behavior relationships across individuals. ROIs were defined as follows: Mean beta-parameters were extracted from contrasts of interest from 8-mm spheres centered around peak coordinates derived from the amygdala localizer task and 8-mm spheres around peak coordinates in the VTA derived from a prior study investigated reward-motivated declarative memory encoding (Adcock et al., 2006). Amygdala ROIs were defined separately for each participant by intersecting peak activations from a contrast of fearful > control blocks in the independent localizer task (as determined by t-statistic) with left and right amygdala anatomical ROIs defined using the WFU PICKATLAS (<http://www.fmri.wfubmc.edu/cms/software>).

To confirm whole-volume GLM analyses in the VTA and amygdala, I submitted extracted beta-parameters to one-sample t-tests. To directly compare the contributions of VTA and amygdala, I submitted beta-parameters extracted from the left and right VTA and amygdala, respectively, to a two-factor, within-subject GLM. To investigate brain-behavior relationships across individuals, I regressed individual extracted beta-parameters against corrected recognition scores for scenes following shock versus no-shock cues, with guessed responses omitted.

3.2.6.3 Within-subject Amygdala Connectivity/Interactions

To assess functional interactions between the right amygdala and other neural regions, within-subjects regression analyses were performed using single-trial/beta-series analyses, (for a similar approach see Rissman et al., 2004; Ritchey et al., 2008). Connectivity analyses were limited to the right amygdala because GLM analyses were only significant on the right. A GLM was constructed for each participant that separately modeled cue and scene-target activations for each individual trial. Then, cue-related beta-values were extracted for each trial from the right amygdala ROI independently defined by the functional localizer. Next, for each participant, a GLM/multiple regression of single-trial data was constructed to identify neural regions that were correlated with the amygdala beta-series as a function of motivational cue (shock > no shock) or as a function of motivational cue and parametric encoding success interactions. Finally, separate GLMs were constructed to investigate how amygdala cue-related activations interacted with target-scene related activations across all other voxels. The former analysis identified regions that were functionally connected with the amygdala during motivational cue-presentations on a trial-by-trial basis, while the latter analysis identified regions where preparatory activations in the amygdala predicted responses to subsequent target-scene images on a trial-by-trial basis. Then, I generated

individual maps of parameter estimates reflecting amygdala interactions for contrasts of interest, and entered these into group-level, random-effects one-sample t-tests.

3.2.6.4 Statistical Thresholds

Statistical tests for whole-volume neuroimaging analyses were thresholded at a significance of $p < 0.001$ and a spatial extent for multiple comparisons yielding a cluster extent minimum of 14 voxels. This procedure corresponds to an overall alpha = 0.05 FWE rate, as calculated within AlphaSim (<http://afni.nimh.nih.gov/afni/doc/manual>), with 1000 Monte Carlo simulations.

3.3 Results

3.3.1 Behavioral Results

Analysis of self-reports revealed that the threat incentive significantly increased participants' motivation to perform on shock trials [$t(17) = 18.327, p < 0.001$]. Twenty-four hour delayed memory recognition for target scenes that followed shock cues [$t(17) = 9.821, p < 0.001$] and no-shock cues [$t(17) = 7.189, p < 0.001$] were both significantly greater than false alarms to new scenes (mean \pm SEM: shock = 53.7% \pm 2.2%, no shock = 47.7% \pm 3.0%, false alarm = 27.4% \pm 2.6%). The threat of shock enhanced scene encoding, such that corrected recognition rate (hits – false alarms, excluding guessing responses) were greater for target scenes following shock cues compared to no-shock cues [$t(17) =$

4.281, $p = 0.001$, Figure 6]. This comparison remained significant when all responses were included [$t(17) = 2.957$, $p = 0.009$].

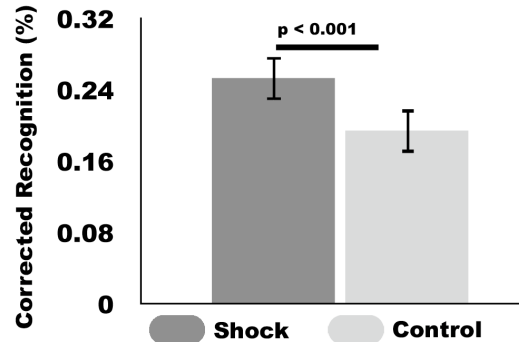


Figure 6: Punishment motivation influences scene encoding. Mean corrected recognition scores (hits – false alarms) for scenes following shock and no-shock cues (errors bars represent SEM). Depicted results exclude trials in which memory recognition was endorsed with “Just Guessing” confidence responses.

3.3.2 FMRI Results

3.3.2.1 Main Effect of Shock

To identify brain regions that were modulated by the threat of shock independent of memory, I compared activations across shock and no-shock trials. During the presentation of motivational cues, the contrast of shock cues compared to no-shock cues revealed greater activation in the right anterior cingulate cortex and less activation bilaterally in the fusiform gyrus (Table 1). During the presentation of target scenes, the threat of shock resulted in greater activation compared to no shock in the

right caudate/ventral striatum, left putamen, and bilateral fusiform gyrus, and less activation in the right superior frontal gyrus (Table 1).

3.3.2.2 Main Effect of Encoding Success

To identify which brain regions were more activated during successful than unsuccessful encoding, e.g. ESA, I used regressors parametrically related to memory strength at later recognition, irrespective of trial type. There were no ESAs during the presentation of cues. However, during the presentation of target scenes, posterior parahippocampal cortex showed a significant ESA, indicating that activation in this region increased with memory encoding strength (Table 1).

Table 1: Significant activations from threat of shock manipulation

Region	x	y	z	Z	k
Cue: shock > no-shock					
Anterior cingulate	18	32	12	3.6	64
Cue: no shock > shock					
Fusiform gyrus	-28	-56	-12	3.98	114
	32	-60	-14	3.45	28
Target scene: shock > no-shock					
Caudate/ventral striatum	-6	6	2	4.38	83
Fusiform gyrus	-48	-42	-20	3.65	44
	-46	-58	-14	3.59	20
Putamen	18	12	-4	3.34	24
Target scene: no-shock > shock					
Superior frontal gyrus	-26	58	20	3.73	18
Cue: encoding success activations					
No significant activations					
Target: encoding success activations					
Parahippocampal cortex	32	-48	-16	4.12	108

x, y, z = MNI coordinates; Z = z-score; k = cluster size

3.3.2.3 Threat of Shock and Encoding Success Interactions

To isolate regions implicated in memory encoding selectively during motivation to avoid punishments, I compared ESA parameter estimates in shock versus no-shock trials. I hereafter refer to these contrasts as shock-motivated ESAs. During the presentation of cues, shock-motivated ESAs were seen only in the right amygdala (Figure 7A). No significant interactions were seen in the reverse contrast. During the presentation of target scenes, neither shock-motivated ESAs nor the reverse contrast was significant.

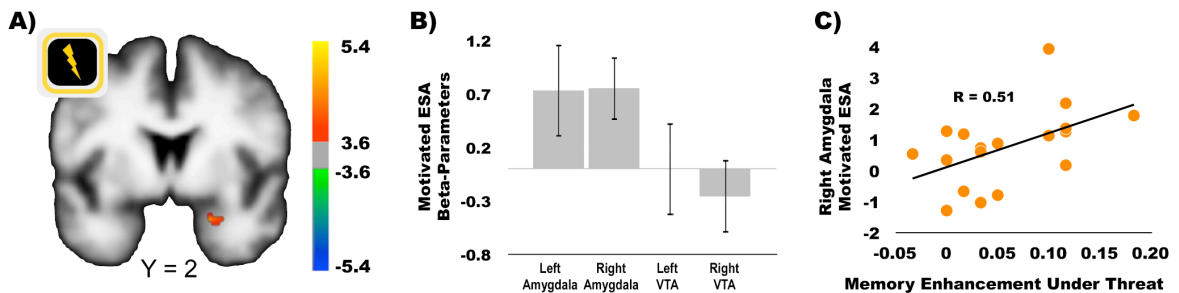


Figure 7: Punishment motivation increases preparatory encoding success activations in the amygdala. A) The right amygdala showed greater encoding success activations in response to shock cues compared to no-shock cues. B) Beta-parameters extracted from a-priori ROIs confirmed significant shock-motivated ESA (shock cue ESA > no-shock cue ESA) in the right amygdala, but not the left amygdala or bilaterally in the VTA. C) Across participants, shock-motivated ESAs during cue presentations were positively correlated with the extent to which memory was enhanced under threat of shock.

The complimentary ROI analyses also demonstrated shock-motivated ESAs in the right, but not left, amygdala [left: $t(17) = 1.705$, $p = 0.11$, right: $t(17) = 2.553$, $p = 0.02$, Figure 7B]. Interestingly, individual differences analysis revealed that amygdala activation during the presentation of cues predicted learning under threat: across subjects, shock-motivated ESAs from the right amygdala were positively correlated with shock-motivated recognition memory advantages [$F(17) = 6.858$, $p = 0.03$, $R = 0.51$, Figure 7C]. During the presentation of target scenes, there were no shock-motivated ESAs in the amygdala ROIs [left: $t(17) = 0.38$, $p = 0.71$, right: $t(17) = 0.72$, $p = 0.48$].

Regarding the dopaminergic midbrain, whole-volume analysis did not reveal any significant activations in the VTA or substantia nigra, even at a lenient threshold of $p < 0.05$, uncorrected. Further, ROI analyses of the VTA did not reveal any shock-motivated ESAs during the presentation of cues [left: $t(17) = -0.004$, $p = 0.997$, right: $t(17) = -0.75$, $p = 0.464$, Figure 7B] or target scenes [left: $t(17) = 1.14$, $p = 0.27$, right: $t(17) = 1.59$, $p = 0.13$].

To explicitly test whether punishment-motivated encoding was more associated with the amygdala compared to VTA, beta-parameters from shock-motivated ESAs at the presentation of cue were submitted to a two-factor (laterality and region), within-subject GLM. This analysis revealed a main effect of region [$F(17) = 8.446$, $p = 0.01$], such

that shock-motivated ESAs were greater in the amygdala compared to the VTA. Neither the laterality nor interaction term was statistically significant ($F > 1$).

3.3.2.4 Amygdala Functional Connectivity

To investigate how functional connectivity between the amygdala and other regions contributed to learning under threat, I ran a within-subjects, single-trial analysis on cue-related activations with the right amygdala functional ROI as the seed. During the presentation of cues, I found a significant interaction between condition (shock > no-shock) and encoding success connectivity, such that amygdala connectivity with the right parahippocampal cortex [$x, y, z = 34, -44, -6$; cluster extent = 23; $Z = 3.54$] and the right orbitofrontal cortex [$x, y, z = 40, 40, -10$; cluster extent = 15, $Z = 3.78$] predicting encoding success to a greater extent following shock than no-shock cues (Figure 8).

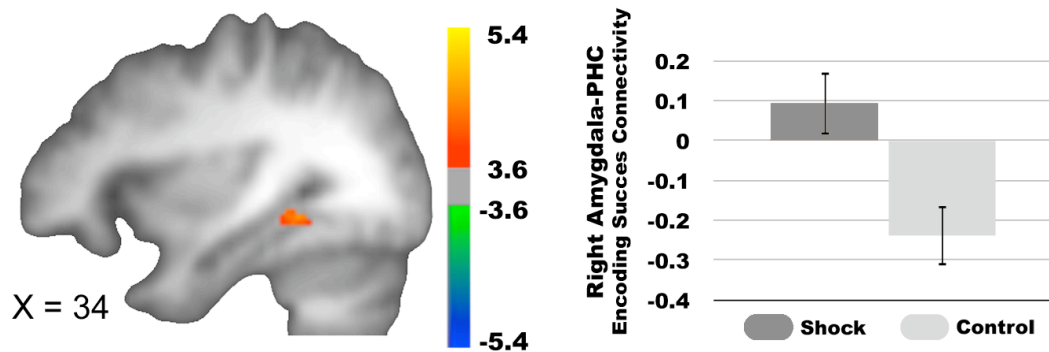


Figure 8: Amygdala-parahippocampal cortex connectivity and encoding success. The right amygdala and parahippocampal cortex showed significantly greater encoding success-related functional connectivity on a trial-by-trial basis, which is greater for strongly remembered > forgotten stimuli, following shock cues compared to no-shock cues.

3.3.2.5 Amygdala Cue and Target-Scene Interactions

To investigate whether motivational cue-evoked activity in the amygdala modulated processing of the upcoming target scene, I ran a single-trial analysis between cue-evoked activations in the amygdala and target scene-evoked activations on the same trial relative to no shock. The threat of shock increased trial-by-trial co-variation between cue-evoked activations in the right amygdala and scene-evoked activations bilaterally in the hippocampus (Figure 9A) as well as in the bilateral cerebellum, right middle temporal gyrus, and left insula (Table 2). Across participants, right amygdala – right hippocampus co-variation predicted shock-motivated recognition memory advantages [$F(17) = 4.449$, $p = 0.051$, $R=0.47$, Figure 9B).

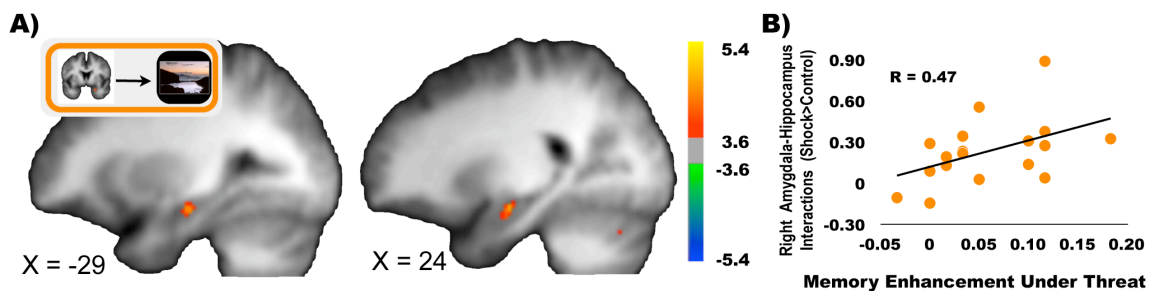


Figure 9: Preparatory amygdala activation predicts hippocampal scene encoding. A) Cue-related activation in the right amygdala showed greater co-variation with hippocampal scene encoding bilaterally during shock trials compared to no-shock trials. B) The extent of this co-variation in the right hippocampus was positively correlated with the extent to which an individual's memory was enhanced under the threat of shock.

Table 2: Significant interactions between the cue-related activations in the right amygdala and scene encoding activations

Amygdala interactions with target processing	x	y	z	Z	k
Shock > no-shock region					
Cerebellum	44	-58	-40	3.74	38
	4	-38	-12	3.68	103
	10	-44	-44	3.60	93
	10	52	-16	3.27	17
	-8	-54	-12	3.42	21
Hippocampus	26	-12	-16	3.66	37
	-26	-20	-14	3.47	24
Middle temporal gyrus	48	-14	-12	3.63	23
Insula	-32	22	-6	3.36	14
No-shock > shock					
No significant interactions					

x, y, z = MNI coordinates; Z = z-score; k = cluster size

3.4 Discussion

Although previous research has examined the effects of motivation on declarative memory encoding, this literature is limited and has focused on motivation to gain rewards. Here, I examined how an alternative motivator, the threat of punishment, influenced declarative memory encoding. I found that motivating individuals to memorize images with the threat of mild electrical shocks for forgetting resulted in better memory for those images. Successful declarative encoding under the threat of shock was associated with amygdala but not VTA engagement. Specifically, threat-related encoding was associated with right amygdala activation and functional connectivity of right amygdala with parahippocampal and orbitofrontal cortex.

Interestingly, engagement of these functional networks predicted successful encoding, suggesting a preparatory role for amygdala neuromodulation. Finally, I found that preparatory activations in the right amygdala predicted scene-evoked activations in the hippocampus, and further predicted punishment-motivated encoding performance across participants. Together, our findings demonstrate that the threat of shock engages amygdala rather than dopaminergic midbrain during encoding. Furthermore, they suggest that neuromodulatory signals from the amygdala influence different regions first during a threat cue and then during encoding of the memorandum to support punishment-motivated memory.

The current findings demonstrate that punishment motivation enhances intentional encoding, such that individuals better recognized scenes under the threat of punishment. Although previous studies have described better declarative memory for intrinsically threatening stimuli (Hamann, 2001; LaBar and Cabeza, 2006; Davis et al., 2011) and neutral stimuli paired with threats (Dunsmoor et al., 2011a; Schwarze et al., 2012), the efficacy of punishment motivation on neutral stimuli has not been investigated. Our findings show that avoidance motivation, like other forms of motivation (Callan and Schweighofer, 2008; Kang et al., 2009; Murayama and Kuhbandner, 2011), can enhance declarative memory. However, declarative memory facilitation by punishment motivation observed in the current study may be limited to

certain types of learning such as itemized learning. As Chapter 2 demonstrates, during spatial navigation punishment motivation has been shown to result in memory deficits. Thus, learning under threat may enhance some, but not all, forms of declarative memory.

I also demonstrated that threat of shock, even in the absence of actual punishment, enhances declarative learning. Here, motivation was induced purely by experimenter instruction, as shocks were never administered. Although previous animal studies have investigated the role of negative reinforcement on memory encoding (McGaugh, 2004), these studies were not able to dissociate motivation from the actual receipt of aversive stimuli. Thus, I have provided a novel characterization of how avoidance motivation influences declarative memory, even in the absence of punishment delivery.

Our fMRI analyses revealed that, under the threat of shock, right amygdala activation following shock compared to no-shock cues predicted punishment-motivated encoding, both during whole-volume and ROI analyses. Individual differences analyses revealed that these preparatory activations in the amygdala predicted punishment-motivated memory enhancements across participant. These findings suggest that neuromodulatory signals from the amygdala prepare individuals to encode information to avoid future punishments.

Previous research has implicated the amygdala in human avoidance behavior (Lang and Bradley, 2009), which I here extend to include intentional declarative learning. Neuroimaging studies have revealed amygdala activation when individuals prepare motor response to avoid penalties and punishments (Mobbs et al., 2007; Mobbs et al., 2009b; Schlund and Cataldo, 2010; Delgado et al., 2011) and learn simple stimulus-response contingencies to avoid penalties (Prevost et al., 2011). Thus, like most rodent studies, human active avoidance procedures typically investigated the implementation of simple motor behaviors to avoid punishment. Our study extends the human active avoidance literature by demonstrating that the amygdala's role in avoidance behavior can also encompass more cognitive processes, such as instrumental declarative memory encoding.

Our findings also expand the amygdala's role in declarative memory to include motivational effects on neutral material. A recent meta-analysis identified the right amygdala as the most consistently activated region during the successful encoding of intrinsically emotional stimuli (Murty et al., 2010). Further, during the anticipation of aversive events, preparatory signals from the amygdala contribute to emotional memory encoding (Mackiewicz et al., 2006). The current study shows that the amygdala's involvement in declarative memory is not limited to intrinsically threatening stimuli, but also includes neutral stimuli associated with potential future punishment.

Results also revealed that functional connectivity of the right amygdala with the parahippocampal and orbitofrontal cortices predicted punishment-motivated scene encoding. Specifically, under threat of shock, positive coupling of the right amygdala with the right parahippocampal and orbitofrontal cortices prior to scene encoding predicted encoding success. The amygdala and orbitofrontal cortex are strongly interconnected in non-human primates (Porrino et al., 1981; Amaral and Price, 1984; Ghashghaei and Barbas, 2002), and interactions between these regions have been demonstrated to support the valuation of aversive events in rodents (Schoenbaum et al., 2007) and non-human primates (Salzman et al., 2007). The current study only found significant differences in orbitofrontal cortex connectivity and did not reveal significant differences in orbitofrontal activations. This pattern suggests that the role of the orbitofrontal cortex in punishment-motivated encoding may only emerge via neuromodulatory interactions with the amygdala. The amygdala is also strongly interconnected with parahippocampal cortex in non-human primates (Suzuki and Amaral, 1994), and models of declarative memory have identified the parahippocampal cortex to be critical for transferring contextual information to the hippocampus (Davachi, 2006; Ranganath, 2010). Further, amygdala-parahippocampal interactions have previously been associated with declarative memory encoding for emotionally arousing stimuli and contexts (Dolcos et al., 2004; Alvarez et al., 2008; Ritchey et al.,

2008; Rudy, 2009). Thus, previous research provides the anatomical and functional foundation whereby amygdala interactions with the orbitofrontal and parahippocampal cortices could support punishment-motivated scene encoding.

The current results also revealed significant functional interactions between the amygdala and hippocampus during punishment-motivated encoding. However, the temporal dynamics of these interactions differed from amygdala interactions with parahippocampal and orbitofrontal cortices. Specifically, under threat of shock, preparatory, cue-evoked amygdala activations predicted subsequent scene-evoked hippocampus activations. This pattern of relationships suggests that motivational signals arising from the amygdala first modulate parahippocampal cortex prior to encoding and then subsequently modulate hippocampus during encoding.

Beyond temporal dynamics, the relationships with performance were different for amygdala connectivity with hippocampus versus parahippocampal cortex. Whereas amygdala interactions with parahippocampal cortex predicted punishment-motivated memory enhancements on a trial-by-trial basis, interactions with the hippocampus predicted enhancements only across participants. This difference in temporal dynamics and brain-behavior relationships suggests that the hippocampus and parahippocampal cortex have different mechanisms for facilitating punishment-motivated encoding. Modulation of parahippocampal cortex could reflect enhancements of perceptual

processing of scenes, giving its positions in the ventral visual stream, and could thus account for trial-by-trial variations in memory encoding strength. However, the relationship between punishment-motivated encoding and amygdala-hippocampus interactions was across subjects. This relationship suggests that mechanisms acting on a slower time scale were facilitating memory encoding by the hippocampus. One potential mechanism could be the triggering of noradrenaline- and glucocorticoid-mediated memory consolidation, which has been associated with phasic activation of limbic circuitry but a delayed memory enhancements which may not initiate until 20-minutes post encoding (Joels et al., 2011).

In light of our findings, I propose a model of punishment-motivated declarative learning in which the amygdala transfers valuation signals from the orbitofrontal cortex to prepare both the parahippocampal cortex and hippocampus for future encoding. Consistent with this interpretation, a recent neuroimaging study showed that the amygdala mediates the relationships between orbitofrontal cortex and MTL when individuals update aversive memories (Sakaki et al., 2011). I suggest that the orbitofrontal cortex-amygdala interaction observed in the current study facilitates two distinct mechanisms in the medial temporal lobes to promote declarative learning: a more perceptually driven facilitation of parahippocampal cortex that precedes learning

perhaps as a priming mechanism and a state-dependent facilitation of hippocampus that may reflect consolidation mechanism.

Our findings provide a novel characterization of the neural mechanisms mediating punishment-motivated declarative encoding and have important implications for models of motivated memory. Critically, our results demonstrate that punishment-motivated encoding is associated with amygdala neuromodulation rather than the dopaminergic midbrain. Analyses did not reveal any role for the VTA during punishment-motivated encoding, even at liberal thresholds. Using a similar design, previous research has found that reward cues engage preparatory activations in and coupling between the VTA and hippocampus to facilitate reward-motivated memory encoding (Adcock et al., 2006). Together, these findings demonstrate that reward and punishment motivation can engage unique neuromodulatory systems to support MTL-dependent encoding. When these systems are selectively engaged, reward and punishment may differentially influence memory representations. In line with this interpretation, reward and punishment motivation can have opposing effects during spatial learning in a modified virtual Morris water task, as discussed in Chapter 2. Future studies are warranted to determine the relative effectiveness of these motivators across a variety of learning experiences, including those in educational contexts.

The current study provides initial evidence for distinct systems guiding punishment- compared to reward-motivated encoding. Here, the signal averaging requirements and overall session length needed to conduct subsequent memory analyses precluded incorporating a reward motivation manipulation into the single session; thus, future studies will be needed to directly compare activations across these two motivational states. However, these future studies would need to address context effects of the incentives on each other, as well as on overall encoding. The shock cues used here may have evoked context-dependent modulations in encoding, as has been demonstrated during the encoding of intrinsically emotional stimuli (Anderson et al., 2006; Henckens et al., 2009; Knight and Mather, 2009); indeed, overall memory performance was lower for both conditions than in our prior report using a reward-motivation manipulation (Adcock et al., 2006). Future studies will be needed to investigate whether punishment motivation results in a general modulation of memory for all scenes. If so, these studies will need to characterize the neural mechanisms of such context-dependent modulation.

The present study investigated neural systems underlying declarative memory encoding when individuals were threatened with punishment for forgetting. Successful encoding under threat was associated with activation of the amygdala, not the VTA, supporting valence-specific models of motivation to learn. Amygdala activation was

evoked by mere threat and predicted memory advantages even in the absence of punishment, implying that threat expectations themselves can shape the contents of memory. I found that memory was enhanced when the amygdala interacted with the parahippocampal and orbitofrontal cortices before and with the hippocampus during experiences that were later remembered. The disparate time courses of cortical and hippocampal interactions with the amygdala suggests a synergistic mechanisms to enhance memory in service of avoiding future punishments.

4. Neural Circuitry Underlying the Influence of Reward and Punishment Motivation on Incidental Encoding of Expectancy Violations

4.1 Introduction

Unexpected events are better remembered than expected events and preferentially engage the medial temporal lobes (Rescorla and Wagner, 1972; Ranganath and Rainer, 2003; Kishiyama et al., 2004; Axmacher et al., 2010). It is adaptive for individuals to learn about unexpected events they encounter during goal pursuit. Expectancy violations signal environmental volatility and can act as a cue for individuals to update their representations of the environment for future behavior. However, not all unexpected events are encoded into individuals' long-term memory. The factors mediating the selectivity of memory for some surprising events, but not others, are still an active area of research. Because unexpected events may bear on future goal achievement, surprises encountered during the pursuit of a goal (i.e. during states of motivation) should be more salient than those encountered when no goal is active. Additionally, motivation has been demonstrated to modulate medial temporal lobe (MTL) neurophysiology and to be a critical determinant of long-term memory in other domains (see Chapter 1-3). Thus, activation of motivational states may help determine which expectancy violation events are subsequently remembered and forgotten. The valence of a goal state (i.e. whether individuals are pursuing a reward or avoiding a

punishment) may differentially influence the processing of expectancy violations. The current study investigated how reward and punishment motivation influence neural sensitivity to expectancy violations and declarative memory for these events. Critically, these expectancy violations were not incentivized, and thus this study also investigated how motivation influences the incidental encoding of surprising events.

Motivation has a broad influence on behavior and cognition (Elliot, 2008; Lang and Bradley, 2009), and therefore is a likely candidate for shaping individuals' memory for expectancy violations. However, the valence of a goal state (i.e. whether individuals are pursuing a reward or avoiding a punishment) may differentially influence the processing of expectancy violations. Reward and punishment motivation are associated with distinct neuromodulatory systems and behavioral states (see Chapter 1). Reward motivation is dependent on activation of the ventral tegmental area (VTA), and is associated with increases in exploratory and novelty-seeking behaviors (Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999). This motivational state has also been associated with a broadening of attention and executive function (Fredrickson, 2004). Conversely, punishment motivation is dependent on activation of the amygdala, and results in increased freezing, startle responses, and escape behaviors (Davis, 1992a). Additionally, this motivational state has been associated with a narrowing of attention towards the object of goal pursuit (Fredrickson, 2004; Elliot, 2008). These differences

suggest that the valence of a motivational state changes how individuals interact with the environment. Specifically, motivational valence could change how individuals process salient events encountered in the environment, even if those events are irrelevant to an individual's goals; such that, reward motivation will enhance and punishment motivation will impede the resources dedicated to processing salient, yet goal-irrelevant, stimuli.

The motivated memory literature further supports the idea that reward and punishment motivation may differentially influence the incidental encoding of expectancy violations. These motivational states have been demonstrated to engage distinct learning states and neural systems during declarative memory encoding. Reward motivation enhances and punishment motivation impedes hippocampus-dependent memory for spatial environments (see Chapter 2). Further, reward motivation results in the enhancement of encoding-related activations in the VTA and hippocampus (Adcock et al., 2006; Wolosin et al., 2012), whereas punishment motivation results in the enhancement of encoding-related activations in the amygdala and parahippocampal cortex (see Chapter 3). Together these findings suggest that motivational valence can effect how the MTL-declarative memory system represents the environment. However, the extant literature has only studied the influence of motivation on intentional encoding. Specifically, in these studies, research participants

have been explicitly incentivized to encode memoranda. Thus, engagement of the above neuromodulatory systems and MTL substrates may be limited to experiences when learning is explicitly rewarded or punished. Alternatively, activation of these neuromodulatory systems by motivation may automatically prime MTL substructures, i.e. hippocampus versus cortex, irrespective of whether learning is intentional or incidental. Thus, the encoding of memoranda would be similar when an individual's goal is to encode an object, and when an individual encounters an object during motivation to pursue other goals. However, to date, no study has investigated the behavioral or neural influences of motivation when an individual's goal is not explicitly learning, thus it remains unknown whether general increases in motivational drive will facilitate learning.

The current study investigated how reward versus punishment motivation influenced neural sensitivity to, and declarative memory for, expectancy violations. To investigate these processes, during the collection of fMRI data participants performed a motivated speeded-reaction time task that included expectancy violations amongst repeated object stimuli (Figure 10). Critically, the current design allowed for the independent measurements of activations in response to motivational cues and expectancy violations. Analyses aimed to identify distinct and common networks during reward and punishment motivation, and to characterize how engagement of these

systems influences expectancy violation processing in the MTL and incidental declarative memory.

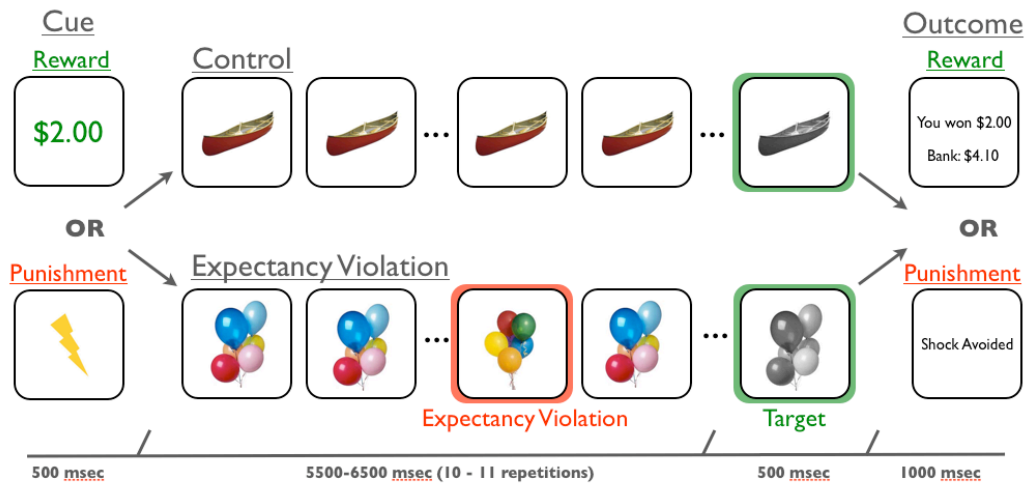


Figure 10: Motivated expectancy violation task. In each trial, participants first viewed either a high or low motivational cue that indicated the opportunity to earn a monetary bonus (reward group) or avoid an electrical stimulation (punishment group). In control trials, the cue was followed by serial repetitions of a trial-unique, color object image. After 10-11 repetitions that image turned gray-scale, to which participants were to make a speeded-button press. In expectancy violation trials, serial representations of the trial-unique color object image was interrupted by a novel, yet highly similar, object image at a temporally unpredictable time. Following the button press to the target, participants were presented an outcome screen that indicated their performance (i.e. whether they earned a monetary bonus or avoided a shock).

4.2 Methods

4.2.1 Participants

53 healthy, right-handed volunteers participated in this study. All participants gave written informed consent for a protocol approved by the Duke University Institutional Review Board (Durham, NC). Participants were randomly assigned to either reward or punishment motivation groups. Participants received \$20/hour plus any monetary bonuses for study participation. Data from four participants were excluded because of excessive head motion (> 1.5 mm, 1 participant), software malfunction during scanning (1 participant), and poor task comprehension (2 participants), resulting in 49 participants (median age = 25, age range = 18-36): 26 participants in the reward group (18 female) and 23 participants in the avoidance group (10 female). There were no significant differences in age ($t(47) = 0.19$, $p = 0.85$) or gender ($U = 376$, $p = 0.13$) across reward and punishment groups.

4.2.2 Task

To test for the effects of reward and punishment motivation on expectancy violation processing, participants performed a speeded-reaction time task to either earn monetary bonuses (reward group) or avoid electrical punishments (punishment group, Figure 10). This task was designed to manipulate two factors: participants' motivational state and the presence of expectancy violations. To manipulate motivational state, every

trial of the task began with a 500-ms cue that indicated whether a speeded-button press to a target image had a high or low incentive. In the reward group, a high incentive was a \$2.50 monetary bonus for a fast button press, and a low incentive was a \$0.10 monetary bonus for a fast button press. In the punishment group, a high incentive was avoiding an electrical stimulation for a fast button press, and the low incentive was only experimenter instruction. Thus, this condition could be considered a no-motivation condition in the shock group. Following a variable delay (between 5.5 and 6.5 seconds), the target appeared on the screen. Targets were trial-unique, gray-scale object images. If participants were sufficiently fast at responding to targets, participants received the outcomes indicated by the cues. The target reaction time for receiving a successful outcome was determined by an adaptive algorithm, which estimated the response time threshold at which the subject would be successful on ~65% of trials. Thresholds were calculated independently for each condition to ensure that reinforcement rates would be equated across all four conditions. Following the presentation of the target image, participants viewed an outcome screen that indicated their success on the current trial. In the reward group, to avoid the working memory demand of calculating total earnings, this screen also indicated participants' accumulated monetary earnings.

To manipulate expectancy violation, following the cue but prior to the target presentation, participants viewed 10-11 serial presentations of color object images for

409 ms with an inter-stimulus interval of 136 msec. During control trials (CO), participants viewed repeated presentations of a color version of the upcoming target stimulus. During expectancy violation trials (EV), participants viewed repeated presentations of a color version of the upcoming target stimulus interrupted by a highly similar, but novel image, this expectancy violation stimulus always appeared randomly between the fourth and eight object presentations.

4.2.3 Procedure

Prior to scanning, participants in the punishment group calibrated electrical shocks to a level that was “highly irritating but not painful” using an ascending staircase procedure with 5 mv increments (Dunsmoor et al., 2009). Shocks were administered using the MP-150 BIOPAC system (BIOPAC systems). Immediately prior to scanning, participants were shown a visual schematic of the task and given verbal instructions. Further, they were instructed that on some trials a different object would interrupt the stream of objects, however, that these interruptions were irrelevant to achieving their goal of earning money or avoiding shocks.

After entering the scanner, participants performed a non-incentivized, practice version of the task that consisted of 10 control trials (i.e. trials without any expectancy violations) under states of high motivation (High Incentive-CO) and low motivation (10 Low Incentive-CO) to familiarize them with this a paradigm and calibrate reaction time

thresholding. Two runs of the incentivized version of the task followed this practice session. During each run of the task, participants completed 10 High Incentive-CO, 10 Low-Incentive-CO, 10 High Incentive-EV, and 10 Low Incentive-EV trials. Trial order was pseudo-randomized across each run, with each run lasting 7 minutes and 56 seconds. Trial onsets, cue-scene intervals and trial order were optimized using Opt-seq software (<http://surfer.nmr.mgh.harvard.edu/optseq>).

Following scanning (approximately 30 minutes after the encoding session), participants performed a two-alternative forced-choice recognition memory task for objects that constituted expectancy violations. During this test, participants saw pairs of object images, one of which was an object that constituted an expectancy violation and the other a similar, yet novel, object. For each object pair, participants had to identify which object they saw during the encoding session by pressing either the “1” or “2” button to indicate the object on the left or right, respectively. Following each memory decision, participants had to indicate their confidence in their response (i.e. 1 = Very Sure, 2 = Pretty Sure, 3 = Just Guessing). Participants received 40 recognition memory trials (20 high incentive and 20 low incentive).

4.2.4 MRI Data Acquisition and Preprocessing

FMRI data was acquired on a 3.0T GE Signa MRI scanner using a standard echo-planar sequence (TE= 27 ms, flip = 77 degrees, TR = 2 seconds, 34 contiguous slices, size =

3.75 mm * 3.75 mm * 3.80 mm). Each of the two functional runs consisted of 238 volumes. Prior to the functional runs, I collected a whole-brain, inversion recovery, spoiled gradient (IR-SPGR) high resolution anatomical image (voxel size = 1 mm, isotropic) for use in spatial normalization.

fMRI preprocessing was performed using fMRI Expert Analysis Tool (FEAT) Version 5.92 as implemented in FSL 4.1.5.9 (www.fmrib.ox.ac.uk/fsl). The first six scans were discarded to allow for signal saturation. Bold images were then skull stripped using the Brain Extraction Tool (BET). Images were then realigned with run, intensity normalized by a single multiplicative factor, spatially smoothed with a 4.0 mm FWHM kernel, and subjected to a high-pass filter (100s). Spatial normalization was performed using a two-step procedure on fMRIB Linear Registration Tool (FLIRT). First, mean EPIs from each run were co-registered to the high-resolution anatomical image. Then, the high-resolution anatomical images was normalized to the high-resolution standard space image in MNI space using a non-linear transformation with a 10 mm warp resolution, as implemented by fMRI Non-Linear Registration Tool (FNIRT). All coordinates are reported in MNI space.

4.2.5 Behavioral Analysis

Reaction times and hit rates to target images were submitted to separate general linear models (GLMs) with motivation (high vs low trials) and expectancy violations

(EV vs CO) as within-subjects factors and group (reward vs punishment) as a between-subjects factor. Of note, the adaptive nature of our reaction time algorithm was explicitly programmed to keep reinforcement rates equivalent across conditions. For both of these GLMs, I tested for main effects of group, motivation, and expectancy violation and all interactions at a significance level of $p < 0.05$. Recognition memory for objects that constituted expectancy violations was tested by submitting the number of hits to a GLM with motivation as a within-subjects factor and group as a between-subjects factor.

4.2.6 FMRI Data Analysis

FMRI data was analyzed using FEAT version 5.92 as implemented in FSL 4.1.6. Time-series statistical analyses used FILM with local autocorrelation correction.

4.2.6.1 General Linear Model

To investigate task-related activations, first level (i.e. within-run) general linear models (GLMs) were constructed that included 8 regressors that modeled high incentive cues, low incentive cues, high incentive target images, low incentive target images, high-incentive-EV events, high incentive-CO events, low incentive-EV events, low incentive-CO events. The latency of CO events was determined by randomly sampling from the latency of EV events without replacement. All trial events were modeled with an event duration of zero seconds and a standard amplitude of one. These events were then convolved with a double-gamma hemodynamic response function. EV and CO events

were orthogonalized with respect to cue and target events. Using this GLM individual maps of parameter estimates were generated for four contrasts of interest: high incentive cue > low incentive cue, [high incentive EV + low incentive EV] > [high incentive CO + low incentive CO], high incentive EV > high incentive CO, and low incentive EV > low incentive CO. Critically, identical GLMs were constructed for participants in the reward and punishment groups allowing for comparison across groups.

4.2.6.2 Group Level Analysis: Whole Volume Analysis

Second-level analyses (i.e. across runs, but within-subject) were modeled using a fixed-effects analysis. Group-level analyses were modeled using mixed-effects analyses (FLAME 1) on the parameter estimates for contrasts of interest derived from the second level analysis. Contrasts of interest were first run within the rewarded and punishment groups using a one-sample or paired t-test, and then across groups using a two-sample t-test. Statistical tests for these fMRI analyses were set to an overall $p = 0.05$ FWE rate, as calculated within AlphaSim tool in AFNI with 1000 Monte Carlo simulations. This procedure corresponds to a voxel-wise significance of $p < 0.001$ and a cluster extent minimum of 33 voxels for the whole-brain and 15 voxels for the MTL region of interest (ROI) analyses, which included bilateral hippocampus and parahippocampal cortex as defined by WFU PICKATLAS.

4.2.6.3 Group Level Analysis: Region of Interest Analysis

ROI analyses were performed by extracting the weighted mean of contrasts of interest from probabilistic maps of neural regions selected a-priori. Regions of interest included the bilateral amygdala, bilateral nucleus accumbens, and bilateral VTA. The amygdala and nucleus accumbens ROIs were obtained from the Harvard Oxford Subcortical Probabilistic Atlas and the VTA ROIs were generated in-house. The probabilistic VTA ROI was constructed by averaging hand-drawn VTA ROIs from an independent sample of 50 participants (Shermohammed et al., 2012). These extracted values were analyzed with two-sample t-tests and simple regressions using SPSS 19 for Macintosh (www.spss.com). Additional ROI analyses were performed comparing MTL clusters showing significant motivation * expectancy violation interactions within the reward and punishment groups, respectively. For these analyses, mean beta-parameters were extracted from clusters within the MTL that showed corrected significance within each group. These extracted values were analyzed using a general linear model with region as a within-subjects factor and group (reward, punishment) as a between-subjects factor.

4.3 Results

4.3.1 Behavior: Speeded Reaction Time Task

To manipulate participant's motivational states, participants viewed cues that indicated whether a speeded-button press to a target image would result in a high or low incentive, earning a monetary bonus in the reward group or avoiding an electrical stimulation in the punishment group. Analysis of target reaction times (Table 5) revealed that both motivation [high versus low incentive: $F(47) = 21.02, p < 0.001$] and condition [EV versus CO: $F(47) = 15.46, p < 0.001$] decreased participants' reaction times to target images, without any significant interaction across these factors [condition*group: $F(47) = 0.14, p = 0.71$]. These findings suggest that incentive cues were successful in manipulating participants' motivational state, and expectancy violations were sufficiently salient to influence later behavior. Critically, there was no interaction of motivation or condition with group, suggesting that the motivational salience of incentives across reward and punishment groups was equivalent [motivation * group: $F(47) = 1.72, p = 0.20$, condition * group: $F(47) = 0.62, p = 0.44$, motivation * group * condition: $F(47) = 1.04, p = 0.31$].

Table 3: Behavioral performance on the speeded-reaction time task

Group	Condition	Reaction Time	Accuracy
Reward	High Incentive		
	EV	205.01 ± 4.63	73.3 ± 1.4
	Control	219.00 ± 5.41	71.7 ± 1.5

	Low Incentive		
	EV	214.62 ± 4.68	70.2 ± 1.8
	Control	223.78 ± 3.79	70.2 ± 1.6
Punishment	High Incentive		
	EV	205.2 ± 4.8	68.0 ± 3.1
	Control	211.8 ± 4.0	66.0 ± 3.3
	Low Incentive		
	EV	217.0 ± 4.0	66.6 ± 2.8
	Control	225.8 ± 6.1	65.8 ± 3.0

EV = expectancy violation; values = mean ± SEM

Despite significant differences in reaction times, our task was designed with an adaptive algorithm to equate target hit rate/positive feedback across conditions (Table 5), and thus there were no significant main effects or interactions in target success [$p > 0.15$].

4.3.2 FMRI: Main Effect of Motivation

To identify brain regions modulated by motivation, independent of expectancy violations, activations in response to high versus low incentive cues were compared. Motivation to earn monetary rewards (high vs low reward cues) and motivation to avoid punishments (shock vs no shock cues) resulted in similar engagement of a network of regions including key regions in the mesolimbic and mesocortical dopamine

systems (Figure 11A): Significant activations were observed in bilateral dorsolateral prefrontal cortex (PFC), ventrolateral PFC, premotor cortex, motor cortex, medial frontal cortex, dorsal anterior cingulate cortex, superior parietal cortex, inferior parietal cortex, ventral visual stream, hippocampus, parahippocampal cortex, amygdala, thalamus, dorsal striatum, ventral striatum, cerebellum, and the midbrain (encompassing the VTA). The direct contrast of high versus low incentive cues did not yield any significant activation differences across reward and punishment groups.

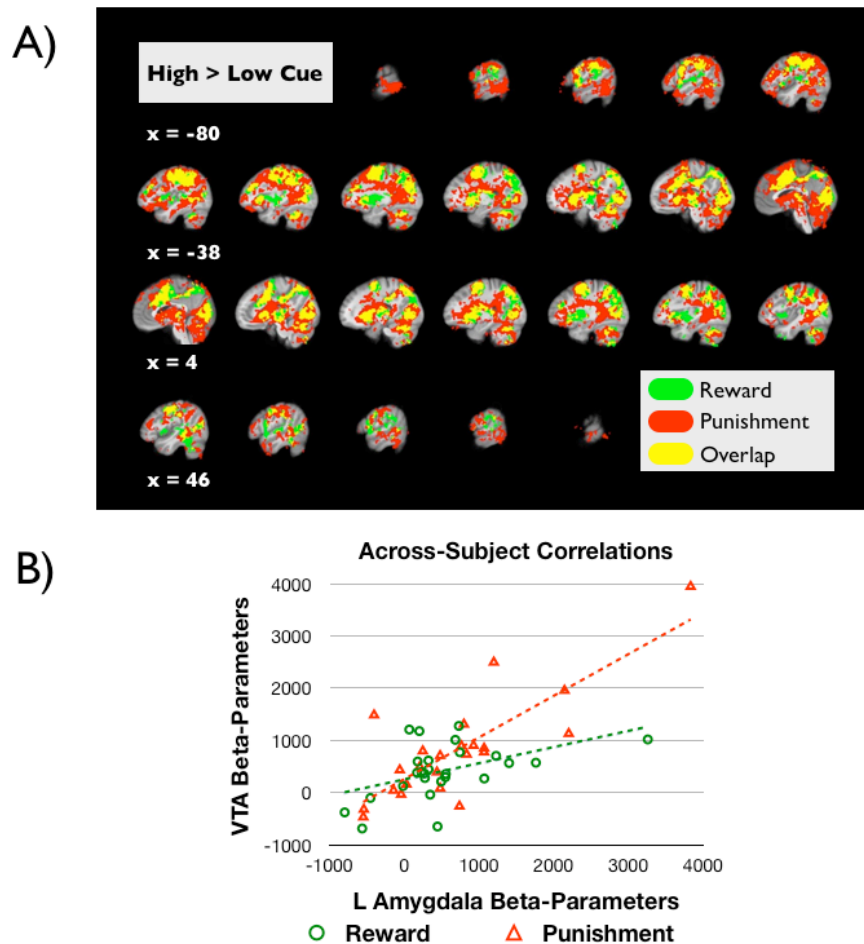


Figure 11: Main effect of reward and punishment motivation. A) Reward and punishment motivation resulted in greater activation throughout the mesolimbic and mesocortical dopamine network [reward = green, punishment = red, overlap = yellow]. B) There were greater interactions between the VTA and left amygdala under states of punishment motivation compared to reward motivation.

Analysis of extracted beta-parameters of ROIs yielded convergent findings to the whole-brain findings. Bilateral nucleus accumbens, VTA, and amygdala showed greater activations to high versus low incentive cues [left amygdala: $t(47) = 4.62$, $p < 0.001$; right

amygdala: $t(47) = 3.50$, $p < 0.001$; left nucleus accumbens: $t(47) = 5.37$, $p < 0.001$; right nucleus accumbens: $t(47) = 6.54$, $p < 0.001$; VTA: $t(47) = 5.297$, $p < 0.001$], without any significant differences across groups in the amygdala [left amygdala: $t(47) = -0.643$, $p = 0.52$; right amygdala: $t(47) = -1.26$,] and trends towards greater activations in the punishment group in the nucleus accumbens and VTA [$p = 0.22$; left nucleus accumbens: $t(47) = -1.74$, $p = 0.09$; right nucleus accumbens: $t(47) = -1.89$, $p = 0.07$; VTA: $t(47) = -1.69$, $p = 0.09$]. Interestingly, across-subject regression analysis revealed that there was greater correlated network activity between the VTA and left amygdala under punishment compared to reward motivation (punishment: $r(23) = 0.81$, reward: $r(26) = 0.48$, $p = 0.047$, Figure 11B), and a qualitatively similar relationship between the VTA and the right amygdala (punishment: $r(23) = 0.68$, reward: $r(26) = 0.43$, $p = 0.22$).

4.3.3 fMRI: Main Effect of Expectancy Violation

To identify brain regions modulated by the presence of expectancy violations independent of motivation, I compared brain activations in response to expectancy violation (EV) versus control (CO) events. In both groups, the presence of expectancy violations resulted in greater activations throughout a fronto-parietal network as well as regions in the MTL. Specifically, significant activations were seen in dorsolateral prefrontal cortex, pre-motor cortex, superior parietal cortex, inferior parietal cortex, ventral visual stream, cerebellum, as well as the right hippocampus (Table 4), however,

activation in the ventral striatum to expectancy violations was only seen in the reward motivation group. A direct comparison of expectancy violation processing across groups, revealed that, compared to the punishment group, the reward group showed greater sensitivity to expectancy violation events in the middle occipital gyrus, middle temporal gyrus, parahippocampal gyrus, inferior frontal gyrus, inferior parietal cortex, superior parietal cortex, superior temporal cortex, and inferior occipital gyrus. (Table 4). The reverse contrast (punishment group > reward group) did not yield any significant activation.

Table 4: Significant differences in expectancy violation activations across groups.

Region	x	y	z	Z	k
Reward > Punishment: EV > CO					
Middle Occipital Gyrus	46	-52	-10	4.55	363
	36	-84	-2	3.27	47
Middle Temporal Gyrus	56	-56	0	3.99	53
	-44	-64	2	3.69	54
	44	-64	18	3.49	54
Parahippocampal Gyrus	-38	-46	-16	3.85	194
Inferior Frontal Gyrus	34	6	16	3.58	53
Inferior/Superior Parietal Cortex	58	-54	30	3.57	379
	30	-48	50	3.02	36
	46	-48	46	3.39	171
Superior Temporal Gyrus	48	-38	4	3.30	96
Inferior Occipital Gyrus	-16	-92	-14	3.27	44
Punishment > Reward: EV > CO					
No significant activations					

x, y, z = MNI coordinates; Z = z-score; k = cluster size

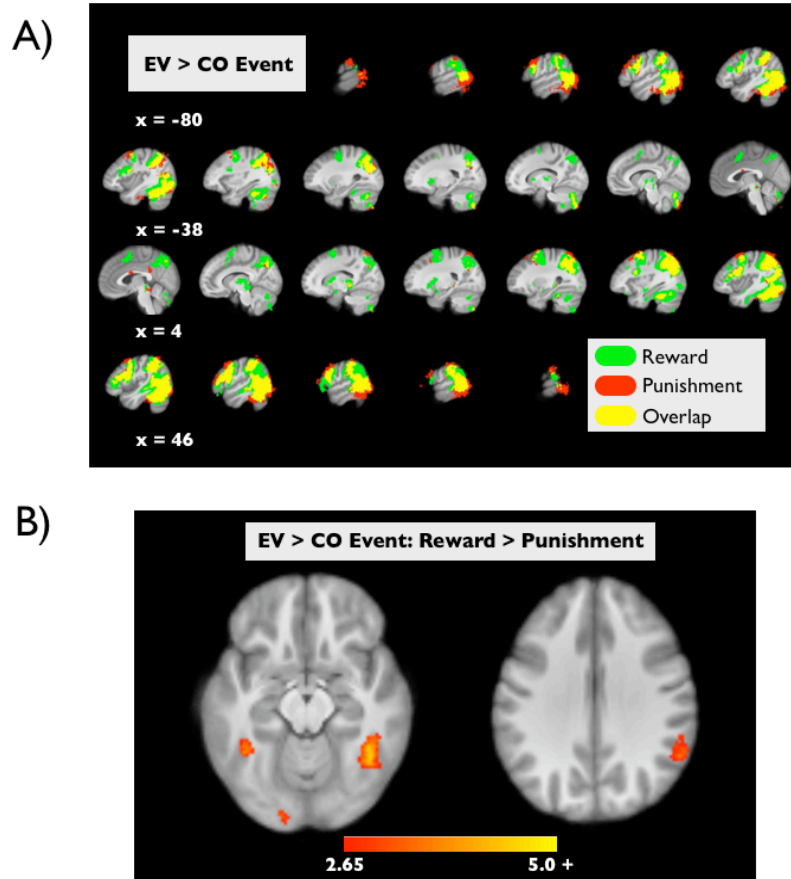


Figure 12: Expectancy violation processing in the reward and punishment group. A) Expectancy violation events resulted in greater activation throughout the fronto-parietal network as well as the MTL [reward = green, punishment = red, overlap = yellow]. B) There were significantly greater activations in the ventral visual stream and the parietal cortex in the reward compared to punishment group (see also Table 4).

4.3.4 FMRI: Influence of Motivation on Expectancy Violations

To characterize the influence of motivation on expectancy violation processing, I compared the processing of expectancy violations (EV > CO) in the context of high versus low motivation for each group separately. In the reward group, this analysis yielded only one significant cluster: the left hippocampus was more sensitive to expectancy violations in the context of high compared to low reward motivation [Table 5; Figure 12A]. In the punishment group, several clusters including the parahippocampal cortex, cingulate cortex, and globus pallidus showed more sensitivity to expectancy violations in the context of high compared to low punishment motivation [Table 5; Figure 12A]. Interestingly, an analysis of the MTL clusters, revealed a significant interaction of motivated expectancy violation processing in the PHC and hippocampus and group [$F(47) = 11.894$, $p = 0.001$, Figure 12B], such that motivated enhancements in expectancy violation processing in the hippocampus was present in the reward [$t(25) = 3.95$, $p = 0.001$] but not punishment group [$t(22) = 0.96$, $p = 0.35$], whereas in the PHC it was present in the punishment [$t(22) = 4.49$, $p < 0.001$] but not reward group [$t(25) = 0.76$, $p = 0.46$].

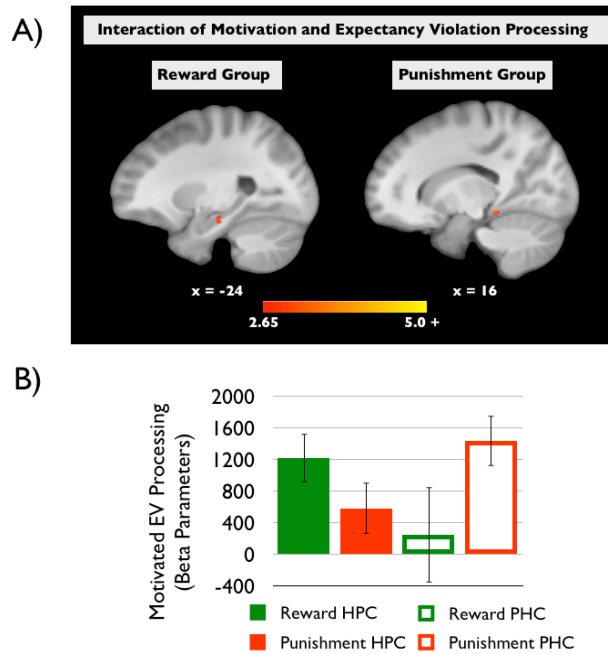


Figure 13: Motivation's Influence of motivation on expectancy violation processing in the MTL. A) Reward motivation enhanced hippocampal sensitivity to expectancy violations (left) and punishment motivation enhanced parahippocampal cortex sensitivity to expectancy violations (right). B) Extracted beta-parameters from the MTL clusters reveal a double dissociation between motivated expectancy violation processing in the MTL across reward and punishment groups.

Table 5: Interactions of motivation and expectancy violations by group.

Region	x	y	z	Z	k
Reward Group					
Hippocampus	-22	22	-6	3.14	16
Punishment Group					
Inferior Temporal Gyrus	-48	-4	-46	4.26	96
Pre-central Gyrus	-32	-18	48	4.12	61
Cerebellum	-40	-42	-32	4.05	335
	34	-64	-60	3.65	55
	-4	-56	-64	3.47	78
	22	-54	-64	3.26	41
	101				

	44	-64	-34	3.77	386
Middle Temporal Gyrus	56	-80	28	3.98	71
	-58	-72	28	3.55	106
	54	-58	10	3.5	45
Fusiform Gyrus	44	0	-30	3.86	87
Middle Occipital Gyrus	60	-74	-14	3.68	100
Parahippocampal Cortex	14	-36	-12	3.58	45
Medial Frontal Gyrus	-8	-22	62	3.56	150
Brainstem	-4	-36	-48	3.18	61
Globus Pallidus	-10	2	-2	3.18	33

x, y, z = MNI coordinates; Z = z-score; k = cluster size

4.3.5 Behavior: Memory for Expectancy Violations

Following scanning, participants performed a recognition memory task for objects that constituted expectancy violations (Figure 14). T-tests revealed that recognition memory for expectancy violation objects was greater than chance in the reward group on high motivation trials [high: $t(25) = 6.97$, $p < 0.001$; low: $t(25) = 0.50$, $p = 0.62$] and in the punishment group in both in the high and low motivation trials [high: $t(21) = 4.00$, $p = 0.001$; low: $t(21) = 2.00$, $p = 0.06$]. Further, I found a main effect of condition, such that motivation increased memory for expectancy violations [$F(46) = 10.63$, $p = 0.002$]. Further, I found a condition*group interaction [$F(46) = 4.29$, $p = 0.04$]. Specifically, results indicated that reward motivation increased recognition memory for expectancy violation objects [$t(25) = 4.89$, $p < 0.001$], but punishment motivation did not affect recognition memory [$t(21) = 0.68$, $p = 0.51$].

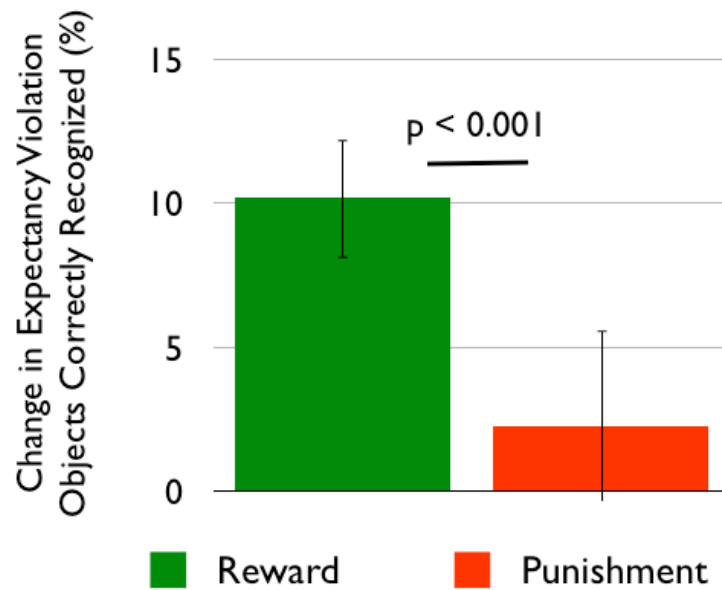


Figure 14: Influence of motivation on declarative memory for expectancy violations. Reward, but not punishment, motivation enhanced memory for objects that constituted expectancy violations.

4.4 Discussion

The current study investigated how reward and punishment motivation influenced neural sensitivity to and episodic memory for expectancy violations. Behaviorally, reward motivation increased declarative memory for expectancy violation events, whereas punishment motivation did not affect declarative memory. Neurally, reward and punishment motivation elicited greater preparatory activations in a similar network of regions, which were consistent with the mesolimbic and mesocortical dopamine system. However, punishment motivation resulted in greater functional

interactions between the amygdala and VTA. Regarding expectancy violation processing, compared to the punishment group, the reward group showed greater sensitivity to expectancy violations in visual processing and parietal regions, and a selective enhancement in hippocampal sensitivity in states of high motivation. Conversely, compared to the reward group, the punishment group showed greater sensitivity to expectancy violations in the parahippocampal cortex, medial PFC, and globus pallidus among other regions in states of high motivation. Together these findings suggest that reward and punishment motivation have distinct influences on how individuals encode salient information in the environment, even when learning is incidental.

Previous research has demonstrated that expectancy violations are better remembered than expected events (Ranganath et al., 2004). However, not all surprising events are stored in long-term memory. Given previous evidence that motivation can influence declarative memory encoding processes, the current study tested whether motivation may also guide the selectivity of which expectancy violation events are subsequently remembered. Although punishment motivation did not affect these processes, reward motivation enhanced declarative memory for expectancy violations. This finding provides novel evidence that motivation is a contributing factor in determining the selectivity of incidental memory encoding, specifically for salient

environmental information. The selectivity of these memory enhancements to states of reward, but not punishment, are consistent with the emotional and motivated memory literatures. As demonstrated in Chapter 2, reward motivation has been demonstrated to enhance memory for spatial environments during a Morris water task, a behavior that requires the encoding of global features of the entire environment not just the escape platform. Additionally, reward motivation has been demonstrated to enhance source memory, such that individuals have enhanced memory not only for incentivized information but also the context in which it was encoded (Wittmann et al., 2005). Thus, reward motivation has been demonstrated to increase memory for broad features of an environment, suggesting it may increase broad encoding of environmental contexts in which rewards are being pursued. Additionally, emotional memory studies have demonstrated that fear-driven memory enhancements are often limited to target memoranda, and often have no effect or a detrimental effect on encoding surrounding, fear-irrelevant information (Mather et al., 2009; Rimmele et al., 2011; Rimmele et al., 2012). These findings suggest a parallelism between punishment-motivated and fear-driven memory enhancements. This parallelism is unsurprising as punishment-motivated memory engages similar neural circuitry as emotional memory encoding, as demonstrated in Chapter 3.

fMRI analyses revealed that reward and punishment motivation both showed engagement of the mesolimbic and mesocortical dopamine system. Specifically, high motivation in both contexts was associated with increased activation in the VTA, dorsal striatum, ventral striatum/nucleus accumbens, MTL, and medial PFC. Additionally, both regions showed significant activations in the amygdala. Direct comparisons across the groups revealed that these regions were engaged to an equivalent extent across reward and punishment motivation. Although some studies have demonstrated engagement of separable networks across these two motivational states, previous research has also shown overlapping activations in many of these regions. Research has demonstrated activations of the ventral striatum during reward (Knutson et al., 2000; Knutson et al., 2001; Knutson et al., 2003; Knutson and Greer, 2008) and punishment motivation (Jensen et al., 2003; Delgado et al., 2008; Schlund and Cataldo, 2010; Delgado et al., 2011). Further, non-human primate physiology has characterized neurons in the VTA and nucleus accumbens that respond both to rewarding and punishing stimuli, and cues that predict either class of stimuli (Bromberg-Martin et al., 2010). Importantly, these studies have shown a spatial clustering of these neurons that are sensitive to each reinforcer class, however, the spatial organization is too small to detect with the current spatial resolution of our fMRI protocols. These findings are in line with models of motivated behavior that suggest that the dopaminergic neuromodulatory system is engaged for

any behaviors that require effort or behavioral activation (Salamone et al., 2005), regardless of valence. A more surprising result was that both groups showed significant amygdala activation. FMRI studies have reliably demonstrated amygdala activation during punishment motivation tasks (Delgado et al., 2008; Schlund and Cataldo, 2010; Delgado et al., 2011; but see Jensen et al., 2003), however, most studies do not demonstrate amygdala activation during reward motivation tasks (Knutson and Greer, 2008). Further, patients with amygdala lesions show impairments in punishment-related, but not reward-related, valuation processes (De Martino et al., 2010). Given these literatures, the amygdala activation seen during this study, especially in the reward group, may reflect physiological or cognitive processes that co-occur with reward motivation, but are mechanistically distinct. Previous research has demonstrated that the amygdala mediates physiological arousal responses (LaBar et al., 1995), and some studies, but not all, have demonstrated increased arousal during reward-motivated processes (see Chapter 2) (Low et al., 2008; Mobbs et al., 2009a). Thus, amygdala activation during this task may be tracking individuals' arousal states. Alternatively, the amygdala has been proposed to monitor vigilance and environmental ambiguity (Davis and Whalen, 2001). Unlike previous reward motivation tasks, during our task there was an added level of ambiguity. Participants did not know on which trials expectancy violations would occur. Potentially, under states of high reward

motivation vigilance to environmental ambiguity was enhanced. Future studies, explicitly monitoring physiological arousal and manipulating environmental ambiguity, will need to investigate the mechanistic role of the amygdala during reward motivated processes.

Although similar pattern of activations were seen across states of motivation elicited by reward and punishment, interactions between these regions differed across groups. Across subjects there were greater correlated patterns of activation between the VTA and the amygdala under punishment compared to reward motivation. These findings suggest that the amygdala and VTA may be more functionally interrelated under states of punishment motivation. Previous rodent studies have suggested that interactions between these two regions are critical in supporting punishment-related behaviors. Specifically, disruption of dopaminergic neuromodulation of the amygdala disrupts both fear-conditioning (Zweifel et al., 2011) and active avoidance learning (Darvas et al., 2011). Further, human neuroimaging has demonstrated greater coupling of the amygdala with the mesolimbic dopamine system, specifically the ventral striatum, during exposure to aversive versus appetitive tones (Levita et al., 2009). These findings suggest that punishment motivation is dependent on functional interactions between the VTA and the amygdala. Although in our study the amygdala was activated across both

motivational states, it played a more integrated role with motivational systems under punishment.

The current fMRI analyses also revealed that reward and punishment motivation resulted in significant differences in how unexpected, salient stimuli were processed. Within the medial temporal lobes, there was a double dissociation between expectancy violation processing and motivational valence. Specifically, under states of reward, but not punishment, there was increased sensitivity to expectancy violations in the hippocampus. Conversely, under states of punishment, but not reward, motivation there was increased sensitivity to expectancy violations in the parahippocampal cortex. Thus, motivational state influenced the targets of MTL encoding processes. Interestingly, this pattern of MTL engagement has also been demonstrated in neuroimaging studies of intentional motivated declarative memory encoding. Reward-motivated declarative encoding has been shown to engage the hippocampus (Adcock et al., 2006; Callan and Schweighofer, 2008; Wolosin et al., 2012), whereas punishment-motivated declarative encoding has been shown to engage the parahippocampal cortex (see Chapter 3). The parallels between the current study and these previous studies suggest that motivational states engage similar MTL-targets during encoding independent of whether encoding is instructed or incidental. In other words, motivation may prime how the MTL intrinsically encodes how the environment is represented in long-term memory.

However, it is important to note, that the current study did not have enough power to determine if the enhanced sensitivity in the MTL during expectancy violation processing reflected successful memory encoding. Future studies utilizing a similar design with more trials will need to specifically address this question.

There were also significant differences in expectancy violation processing outside of the MTL across motivational groups. Firstly, compared to the punishment group, the reward group showed greater sensitivity to expectancy violations throughout the ventral visual stream and parietal cortices. These brain regions are associated with guiding attentional processing of visual environments (Corbetta and Shulman, 2002). These findings are, thus, inline with the literature suggesting that reward motivation increases environmental exploration (Ikemoto and Panksepp, 1999). These enhancements in neural sensitivity were not modulated by high and low motivational cues, suggesting that this increased sensitivity in visual and parietal regions were a global response to the context of reward. Secondly, punishment, but not reward, motivation was associated with greater expectancy violation processing in a variety of regions, most notably in the medial prefrontal cortex. Unlike the findings in the ventral visual stream and parietal cortex detailed above, these findings were specific to states of high versus low punishment motivation. The medial PFC has been associated with monitoring environmental threat and evaluating the value of punishments (Mobbs et al.,

2010; Kim et al., 2011b; Schoenbaum et al., 2011). Given these findings, enhanced mPFC engagement in the current design may reflect enhanced processing of the threat relevance of the expectancy violations encountered during motivation. Alternatively, the mPFC has been demonstrated to mediate fear-extinction and emotional regulation processes (Schiller and Delgado, 2010; Kim et al., 2011b). These findings would suggest that in our task the mPFC is actively suppressing affective responses to expectancy violation events. The active down regulation of processing expectancy violations is inline with previous literatures detailing how punishment motivation narrows attentional resources towards goal-relevant objects (Fredrickson, 2004; Elliot, 2008). However, future studies need to further detail the role of the mPFC during expectancy violation processing under punishment motivation, and determine its consequence on expressed behaviors.

In summary, our findings characterize divergent influences of reward and punishment motivation on episodic memory for salient features of the environment. These findings show that these motivational states change how expectancy violation events are encoded in the medial temporal lobes and subsequently remembered. Interesting, both the behavioral and neural data parallel findings from studies investigating the influence of motivation on declarative memory for explicitly incentivized information. This parallelism supports a model of motivated memory in

which the mechanisms guiding the influence of motivation on memory are similar regardless of the learning goals of the individual. However, future studies will need to directly compare the influence of motivation on incidental and intentional encoding processes.

5. Discussion

Motivation has been demonstrated to influence the medial-temporal lobe circuitry underlying declarative memory. The extant literature detailing these processes has been limited to only studying the influence of reward-motivation. However, the rodent, non-human primate, and human motivation literatures have suggested that reward and punishment motivation engage distinct neuromodulatory systems and behavioral states (see Chapter 1), suggesting that activation of these motivational systems may have distinct influences on declarative memory encoding. The studies described in this dissertation demonstrate separable influences of reward and punishment motivation on declarative memory encoding and its underlying neural circuitry. The first study investigated the influence of these two motivational states on hippocampal-dependent spatial memory, and demonstrates an enhancement of memory under states of reward compared to punishment motivation. The second study investigated the neural circuitry underlying punishment-motivated memory encoding, and reveals that this motivational state engages neural circuitry distinct from those identified in previous studies of reward-motivated memory encoding. Critically, differences were found both in terms of which neuromodulatory systems and MTL-encoding substrates were engaged. The third study directly compared the influence of reward and punishment motivation on the incidental encoding of salient environmental

information. This study demonstrates that reward and punishment motivation distinctly influence MTL-sensitivity to expectancy violations and incidental memory for this information. Together these studies provide converging evidence that reward and punishment motivation facilitate encoding processes in different substrates of the MTL, which leads individuals to store different representations of their environment in long-term memory. In the rest of this chapter, I will briefly summarize each of these studies. Then, I will discuss some methodological issues pertaining to these studies. Finally, I will discuss how the studies presented in this dissertation support the model of motivated declarative memory encoding presented in Chapter 1 and propose several accounts of why this organization may occur.

5.1 Summary of Studies

Previous research has yet to compare how reward and punishment motivation influence declarative memory encoding. The study described in Chapter 2 compared how these two motivational states influenced declarative memory for spatial environments in a modified version of the Morris water task (Morris et al., 1982). Specifically, in this study, participants were incentivized to navigate to correct platforms while avoiding incorrect platforms by either earning rewards for successful navigation or receiving punishments for unsuccessful navigation. During this task, platform locations were hidden, thus, navigational performance relied on individuals' stored representations of the environment. Results demonstrated that reward motivation enhanced and punishment motivation disrupted memory for incentivized

environments. This pattern of behavior was demonstrated using multiple behavioral measures of memory performance including accuracy, precision, and learning rate. Performance during this task is thought to be dependent on hippocampus-mediated representations of the environment (Morris et al., 1982), suggesting that reward but not punishment motivation enhances hippocampus-dependent encoding processes. Thus, the findings further support that reward motivation facilitates the hippocampus during encoding, and provides novel evidence that punishment motivation engages different learning states than reward motivation. However, this first study was purely a behavioral study, and thus was not able to explicitly identify the neural circuitry engaged during the task.

Previous studies have characterized the neural circuitry underlying reward-motivated declarative encoding (Adcock et al., 2006; Callan and Schweighofer, 2008; Wolosin et al., 2012), but have not investigated punishment-motivated declarative encoding. The study described in Chapter 3 modified a design previously used to investigate reward-motivated declarative encoding (Adcock et al., 2006) to investigate the neural circuitry underlying punishment-motivated declarative encoding. This study demonstrated that under the threat of punishment, memory for incentivized information was enhanced. These punishment-motivated memory enhancements were associated with amygdala neuromodulation and enhancements in cortical MTL encoding processes. These findings diverge from findings in the reward-motivation literature, which showed that memory enhancements were associated with ventral tegmental area (VTA) neuromodulation and enhancements in hippocampal encoding processes.

The behavioral findings from Chapter 3's study may seem contradictory to the findings presented in Chapter 2, which showed that punishment motivation disrupted

spatial learning. However, item-based learning can be supported by cortical MTL processing in the absence of the hippocampus, whereas integrative spatial learning cannot (Astur et al., 2002; Davachi, 2006; Diana et al., 2010; Ranganath, 2010). In the paradigm used in Chapter 3, participants had to memorize scene images in isolation, which is an item-based form of learning. Thus, amygdala enhancements of cortical MTL processes could facilitate the unitized encoding of scene images, but not integrative representations of spatial environments from the water task.

The findings from Chapters 2 and 3 demonstrate that reward and punishment motivation have distinct influences both on the neural circuitry guiding memory encoding and long-term memory. However, these two studies focused on behavioral contexts of incentivized learning, such that participants were explicitly motivated to encode information into long-term memory. The study presented in Chapter 4 focused on understanding the influence of reward and punishment motivation on incidental memory encoding, i.e. how the environment is represented in memory when individuals are not explicitly trying to learn. This study investigated the encoding of salient, non-incentivized features of the environment while individuals were in states of either reward or punishment motivation. This study demonstrated that both motivational states evoked similar patterns of activation throughout the brain including the amygdala and VTA. However, punishment motivation resulted in greater functional interactions between the amygdala and VTA. This study also demonstrated that reward and punishment motivation facilitated neural sensitivity in unique MTL targets. Specifically, reward motivation enhanced hippocampus-dependent processing, whereas punishment motivation enhanced cortical MTL-dependent processing. In addition to these neural differences, the study demonstrated that motivational valence differentially

influenced incidental memory for salient features of the environment. Specifically, reward motivation enhanced memory, whereas punishment motivation did not have any effect on memory. These findings from Chapter 4 demonstrate that reward and punishment motivation differentially facilitate MTL sensitivity to the environment and change how this environmental information is stored in long-term memory.

5.2 Methodological Considerations

The studies described above provide converging evidence that separable systems guide the influence of reward and punishment motivation on declarative memory encoding. However, there are several methodological considerations, which limit the interpretation of the findings. Below, I describe these methodological issues, and suggest future studies to address these concerns.

5.2.1 Choice of Reinforcers

In the studies detailed in this dissertation, reward and punishment motivation were elicited by qualitatively different reinforcers. Monetary bonuses were used to incentivize participants in reward conditions, and electrical stimulations were used to incentivize participants in punishment conditions. The decision to use these qualitatively different reinforcers was made for two critical reasons. Firstly, previous functional magnetic resonance imaging (fMRI) research in humans has demonstrated that these reinforcers reliably engage the canonical reward and punishment motivation systems described in Chapter 1. Monetary bonuses have been demonstrated to engage neural circuitry throughout the mesolimbic and mesocortical dopamine system (Knutson and Greer, 2008), notably in the VTA, and electrical stimulations have been demonstrated to reliably elicit activations in the amygdala (Mobbs et al., 2009a; Mobbs et

al., 2009b; Delgado et al., 2011; Schwarze et al., 2012). Secondly, behavioral piloting as well as measures collected from the studies presented in Chapters 2 and 4 revealed that these two different classes of reinforcers were able to motivate participants to an equivalent degree. Participants in the reward and punishment groups reported equivalent motivation to perform when incentivized in the study described in Chapter 2. Additionally, in the study described in Chapter 4, participants in the reward and punishment group demonstrated equivalent enhancements in motivated behavior in high motivation conditions. Although the reinforcers were qualitatively different, they were able to elicit equivalent states of motivational activation.

Although the choice of these reinforcers was beneficial to the current aims of this dissertation, there were some limitations in their use. Mainly, the reinforcers did not only differ in their motivational valence but also differed in their qualia. Electrical stimulations are primary reinforcers. However, monetary bonuses are secondary reinforcers, which necessitate a level of abstraction to determine their motivational value. Previous neuroimaging research has demonstrated that primary and secondary reinforcers similarly modulate learning, both neurally and behaviorally (Valentin and O'Doherty, 2009; Kim, 2011). However, there have been some studies documenting that primary reinforcers engage different neural systems during learning than secondary reinforcers, both in the domain of reward learning and fear learning (Beck et al., 2010; Delgado et al., 2011; Metereau and Dreher, 2012). Given these differences, it will be critical for future studies to replicate the findings in this dissertation using reinforcers that are more equally matched. For example, studies could attempt to replicate the findings from chapters 2 and 4 using pleasant and unpleasant taste or odor stimuli as reinforcers, as opposed to monetary rewards and electrical stimulations. It is important

to note, however, that future studies using monetary losses as punishers should be interpreted with caution, as these stimuli do not reliably elicit activation in regions typically associated with punishment motivation (Carter et al., 2009; Delgado et al., 2011).

5.2.2 Choice of fMRI to Characterize Neural Activations

The studies described in Chapters 2 and 3 used fMRI to investigate the neural circuitry underlying the influence of motivation on memory encoding. There were many benefits to using fMRI for these specific investigations, as opposed to other assays of human neurophysiology. FMRI allows for in-vivo recordings from multiple brain regions in humans during awake behavior in real-time. Further, fMRI offers a relatively good temporal resolution while still allowing for the characterization of activation of subcortical structures, which was critical for the questions under investigation in this dissertation.

Although this method has many strengths there are some key limitations associated with its use. Firstly, fMRI is a correlative measure of human brain activation. FMRI measures changes in regional blood oxygenation in response to metabolic demands associated with neuronal activation, as opposed to direct electrophysiology. Although this measure is indirect, studies have demonstrated that there is a tight coupling between neuronal activity and changes in blood-oxygenation, thus making this measure a valid proxy of neuronal activity (Logothetis, 2008). However, future studies should corroborate the above findings using more direct measures of neural activity, such as intracranial recordings in the key areas of interest, mainly the amygdala, VTA, and MTL. While this convergent evidence would greatly strengthen the arguments of

this dissertation, it is important to note that access to intracranial recordings is limited to patient populations, such as epilepsy or Parkinson's disease patients, which introduces an additional confound.

Secondly, fMRI only looks at the neural correlates of activation under different behavioral contexts, and correlation does not necessitate causation. Thus, the regions and networks identified in the current studies can only be considered candidate regions guiding motivated memory processes, as the dependence of their function to behavior cannot be assessed with fMRI. Further, the causal influences of one region over another cannot be determined using this correlational method. Hence, fMRI allowed us to infer relationships between neuromodulatory regions and their targets, such as the amygdala and VTA modulating MTL neurophysiology, but the directionality and causality of these interactions could not be assayed. Future studies of patients with brain lesions will be needed to corroborate the role of the regions identified in this dissertation during motivated memory behaviors.

Finally, the spatial resolution of fMRI is course compared to the fine-grained neuroanatomy of many of the regions of interest, such as the VTA, amygdala, hippocampus, and cortical MTL. Importantly, the behavior of all of the above regions has been characterized using fMRI protocols with a spatial resolution similar to the studies described in this dissertation. fMRI scans with similar spatial protocols have been able to isolate the functional behavior of the VTA amongst other midbrain nuclei (Shermohammed et al., 2012), to distinguish between the functions of the cortical MTL versus the hippocampus during item and source memory processing (Davachi, 2006;

Ranganath, 2010), and to characterize the role of the amygdala during multiple punishment-motivated behaviors (Mobbs et al., 2007; Delgado et al., 2008; Mobbs et al., 2009b; Mobbs et al., 2010; Schlund and Cataldo, 2010; Delgado et al., 2011). However, the current spatial resolution was not fine enough to disassociate sub-regions of the amygdala, such as the basolateral and central amygdala. Critically, these regions have been demonstrated to be anatomically and functionally distinct (see Chapter 1), and they differentially contribute to reward- and punishment-motivated learning (Prevost et al., 2011). Within this dissertation, the amygdala was associated with punishment-motivated declarative memory encoding (see Chapter 3), as well as general states of reward and punishment motivation (see Chapter 4). However, it is unclear whether the clusters identified in these studies reflected basolateral or central amygdala activations, making their functional role in behavior difficult to interpret. Recent advancements in fMRI analysis allows for the characterization of small regions of interest in the brain at spatial resolutions fine enough to detail these sub-structures. It will be critical to detail the differential contributions of these sub-regions during behavior to fully characterize the amygdala's role in motivated memory encoding.

5.3 Model of Motivated Declarative Memory Encoding

The findings presented in this dissertation support and extend the model of motivated behaviors presented in Chapter 1. This updated model, depicted in Figure 15, suggests that reward and punishment motivation have distinct influences on declarative

memory encoding via engagement of distinct neural systems. Specifically, this model proposes that memory encoding under reward motivation is supported via VTA neuromodulation, whereas memory encoding under punishment motivation is supported by amygdala neuromodulation. Further, the model proposes that engagement of these distinct neuromodulatory systems results in differential engagement of MTL encoding substrates, such that reward motivation facilitates hippocampal-encoding processes and punishment motivation facilitates cortical MTL-encoding processes. This model further proposes that engagement of these different MTL substrates results in the storage of distinct representations of the environment in long-term memory.

Specifically, under reward motivation, environmental representations are enriched and flexible, such that relationships between individual items and their surrounding contexts are maintained. Conversely, under punishment motivation, environmental representations are specific and inflexible, such that information directly associated with punishments are stored in isolation, independent of the context in which they were encountered. Finally, this model proposes that motivation similarly influences declarative memory encoding regardless if an individual's goal is to learn or an individual is learning during the pursuit of other goals. Below, I will discuss how findings presented in this dissertation support the different components of this proposed model and how they fit into the larger literature.

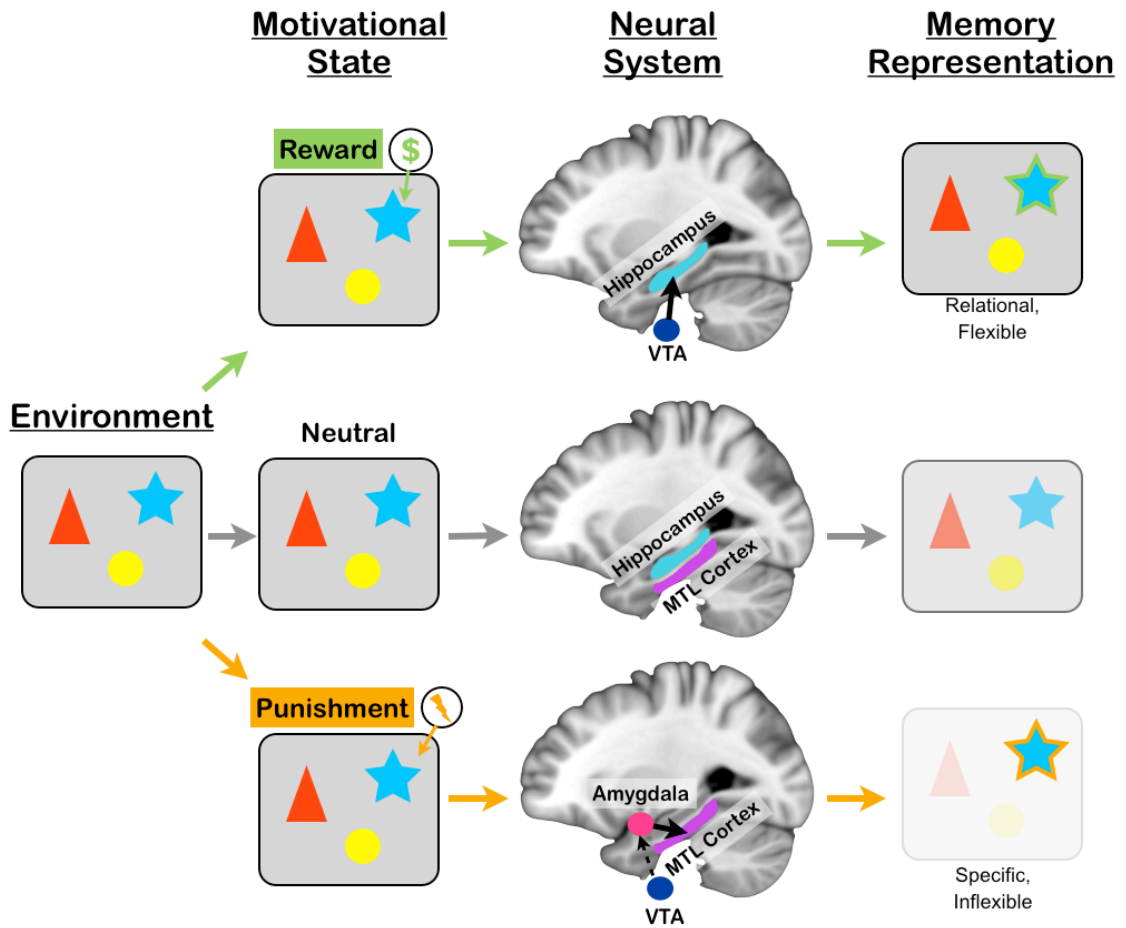


Figure 15: A model of the influence of reward and punishment motivation on declarative memory encoding.

5.3.1 Neuromodulatory Engagement

A key component of the proposed model is that reward and punishment motivation rely on distinct neuromodulatory systems during declarative memory encoding. Previous research has demonstrated that VTA activation is associated with the influence of reward motivation on declarative memory. In a reward-motivated memory

encoding task, VTA activation was not only predictive of successful memory encoding when information was incentivized with monetary bonuses (Adcock et al., 2006), but also individual differences in reward-motivated memory enhancements (Wolosin et al., 2012). The results from Chapter 3 demonstrate that amygdala activation is associated with the influence of punishment motivation on memory encoding. Specifically, during a punishment-motivated memory encoding task amygdala activation was predictive of both successful memory encoding of information incentivized by the threat of shock and individual differences in punishment-motivated memory enhancements. Further, in this study there was no evidence of VTA engagement during these processes, even at low statistical thresholds. These findings strongly suggest that reward and punishment motivation influence memory encoding distinctly via VTA and amygdala neuromodulation, respectively. Previous literatures, described in Chapter 1, suggest a separable role for the VTA and amygdala during other types of motivated-learning. The findings from this dissertation suggest that this dissociation extends to motivated declarative memory encoding.

The findings that the VTA and amygdala were co-activated during reward and punishment motivation, detailed in Chapter 4, superficially seem to contradict the proposed model. However, there are differences in the experimental paradigm and structure of the analysis in this study that may explain these discrepancies. In previous studies describing motivated-memory encoding, including the study described in Chapter 3, engagement of the VTA and amygdala were characterized by interactions between motivation and successful memory encoding. Hence, these studies specifically identified neuromodulatory systems that guided successful memory encoding under motivation, rather than motivation in isolation. However, given the constraints of the

experimental paradigm (see 4.4), the study presented in Chapter 4 only investigated the main effect of motivational cues independent of encoding success. Thus, the simultaneous engagement of the VTA and amygdala may be associated with states of both reward and punishment motivation, however, each system may separately contribute to encoding success. Specifically, the VTA may directly facilitate hippocampus-dependent encoding processes during reward motivation, but may only modulate amygdala reactivity during punishment motivation without having any effect on MTL-dependent encoding. In fact, the study presented in Chapter 4 also demonstrated greater functional interactions between the amygdala and VTA under punishment motivation.

5.3.2 Medial Temporal Lobe Engagement

The proposed model suggests that distinct neuromodulation via the VTA and amygdala under reward and punishment motivation results in differential engagement of MTL encoding substrates. Specifically, the model proposes that the VTA selectively enhances hippocampus-dependent encoding processes under reward motivation and that the amygdala selectively enhances cortical MTL-dependent encoding processes under punishment motivation. All three of the studies presented in this dissertation support this component of the model.

The study presented in Chapter 2 demonstrated that reward, but not punishment, motivation enhanced spatial memory during the Morris water task. Critically, successful performance on variants of this task have been demonstrated to be dependent on the hippocampus, such that participants that have lesions limited to the hippocampus have severe deficits during spatial navigation (Astur et al., 2002). Given these findings, this

study provides evidence that reward motivation promotes hippocampus-dependent encoding processes, whereas punishment motivation impairs these processes. However, it is important to note, that these are indirect measures of hippocampus-dependent encoding, as the neural circuitry underlying these behaviors was not assayed.

The study presented in Chapter 3 provided more direct support for engagement of the cortical MTL during punishment-motivated behaviors. This study demonstrated that correlated activations of the amygdala with the parahippocampal cortex, a region in the cortical MTL, predicted successful encoding under punishment motivation.

Interestingly, correlated activations of the VTA with the hippocampus have been demonstrated to predict successful reward-motivated encoding (Adcock et al., 2006). As predicted by the model, these studies demonstrate a double dissociation between reward and punishment motivation and encoding-related processes in the hippocampus and cortical MTL. Outside of the domain of motivated-memory, previous declarative memory encoding research has demonstrated correlated engagement of the amygdala with the parahippocampal cortex (Dolcos et al., 2004; Ritchey et al., 2008) as well as the VTA with the hippocampus (Shohamy and Wagner, 2008; Wittmann et al., 2007). These findings suggest that, independent of the behavioral context, engagement of the VTA and the amygdala may facilitate encoding processes in the cortical MTL versus hippocampus, respectively.

The study presented in Chapter 4 provides further evidence for enhanced neural sensitivity in different MTL regions during reward and punishment motivation. Results revealed that when participants were motivated to obtain rewards there was enhanced sensitivity in the hippocampus to expectancy violation events, whereas when

participants were motivated to avoid punishments there was enhanced sensitivity in the cortical MTL to expectancy violation events. Critically, neural sensitivity to these events reflected incidental encoding processes, as participants were not explicitly trying to learn about their surrounding environment. Thus, in light of the previous findings, reward and punishment motivation enhances MTL dependent encoding in the hippocampus and cortical MTL, respectively, independent of whether encoding is incidental or intentional. However, it is important to note that the increased sensitivity to expectancy violations characterized in the study presented in Chapter 4 did not explicitly reflect successful encoding processes. Similar studies, utilizing a design with sufficient power, will need to determine if these signals reflect encoding success on a trial-by-trial basis.

5.3.3 Long-Term Memory Representations

The proposed model suggests that engagement of distinct neuromodulatory systems and MTL targets during encoding results in individuals storing different representations of the environment in long-term memory. Specifically, the model proposes that reward motivation enhances memory for incentivized information as well as its relationship to the surrounding environment. Conversely, the model proposes that punishment motivation enhances memory only for incentivized information, and either has no effect or disrupts memory for the environment. Findings from the studies presented in this dissertation strongly support this component of the model

Behavioral findings support that reward motivation results in the storage of more

enriched, flexible representations of the environment in long-term memory. The study presented in Chapter 2 demonstrated that reward motivation enhanced spatial navigation performance in the Morris water task. Successful performance on this task requires that individuals represent an integrative map of platform locations in relation to the surrounding environment. Further, the study presented in Chapter 4 demonstrated that participants had better long-term memory for expectancy violation events, even though that information was not relevant to reinforcement. Together, these findings provide evidence that reward motivation results in enriched, flexible representations of the environment. Interestingly, behavioral contexts that engage the VTA and hippocampus during memory encoding also support enriched, flexible representations of the environment. Individuals that show greater activation of the VTA and hippocampus during encoding show more flexible representations of object pairs during an integrative encoding task (Shohamy and Wagner, 2008) and show better accuracy for recognizing the context in which scenes were presented during a source memory task (Wittmann et al., 2007). Further, behavioral studies have demonstrated a broadening of the focus of memory for intrinsically rewarding and positive memoranda such that peripheral information is enriched (Talarico et al., 2009; Yeghiyan and Yonelinas, 2011).

The behavioral findings from this dissertation also support that punishment motivation results in the storage of more overly specific, inflexible representations of the environment in long-term memory. Punishment motivation was demonstrated to enhance the encoding of information that was explicitly incentivized compared to non-incentivized information (see Chapter 3). However, punishment motivation also interfered with the integrative encoding of spatial environments (see Chapter 2), and

had no influence on the incidental encoding of environments (see Chapter 4). Together, these behavioral findings demonstrate that punishment motivation only enhances representations of incentivized information in the environment, and actually interferes with flexible binding of negatively reinforced information with other features of the environment. Interestingly, behavioral contexts that engage the amygdala impede relational memory (Onoda et al., 2009) and source memory processes (Kensinger and Schacter, 2006; Dougal et al., 2007). Further, threat-relevant information has been demonstrated to capture attention, resulting in memory deficits for the environment surrounding threatening items (Waring et al., 2010; Dolcos et al., 2011; Mather and Sutherland, 2011). Thus, any behavioral states that engage states similar to punishment motivation may result in the storage of specific, inflexible representations of the environment.

5.3.4 Rationale

The above sections describe how motivation engages neuromodulatory systems that preferentially target distinct regions in the MTL during encoding, but it does not speak to why this organization emerges. Accumulating evidence across the psychology and neuroscience literatures provide potential rationales for this functional organization. Below, I will detail two proposed, but not mutually exclusive, rationales for this functional organization: the activation of distinct behavioral states and the intrinsic organization of functional neuroanatomy.

5.3.4.1 Activation of Distinct Behavioral States

Early evidence from behavioral neuroscience demonstrated that reward and punishment motivation change how organisms interact with their environments.

Specifically, reward motivation results in increased exploratory and novelty-seeking behaviors (Ikemoto and Panksepp, 1999), whereas punishment motivation results in increased freezing and escape behaviors (Davis, 1992a). Similarly, social and cognitive psychology literatures have demonstrated that individuals change their orientation and interactions with the environment under states of approach and avoidance motivation, which parallel reward and punishment motivation (Elliot, 2008). Well accepted models have proposed that positive affect and approach motivation promote individuals to explore and actively engage with their environments, whereas negative affect and avoidance motivation draws individuals to only respond to environmental threats (Cacioppo et al., 1999; Fredrickson, 2004, Elliot, 2008). In line with these models, studies have demonstrated an attentional broadening during states of approach motivation and an attentional narrowing during states of avoidance motivation (Fredrickson, 2004).

This modulation of how individuals interact with their environment could potentially guide the organization of declarative memory systems. Mainly, during states of broadened attention and exploration elicited by reward motivation, individuals have the capacity to attend to multiple features the environment. This type of attention to multiple features of the environment provides the opportunity for the hippocampus to construct a more elaborated, integrative representation of the environment. Conversely, during punishment-motivated behaviors, individuals may only attend to environmental threats and escape routes. Given this focused attention, only itemized constructs are available to encode into long-term memory, a process mediated by the cortical-MTL. Thus, changing individuals' interactions with the environment changes the informational content available for individuals to encode into long-term memory, and thus could modulate the locus of MTL-encoding activity.

5.3.4.2 Intrinsic Organization of Functional Neuroanatomy

The intrinsic connectivity between discrete brain regions have been proposed to be a significant determinant of how neural networks are organized to guide cognition. Given this notion, the selective engagement of the hippocampus during reward motivation could be driven by the VTA's intrinsic connectivity, whereas the selective engagement of the cortical MTL during punishment motivation could be driven by the amygdala's intrinsic connectivity. Although both anatomical and functional connectivity between the VTA and hippocampus as well as between the AMG and cortical MTL have been documented (see Chapter 1.2.2, Chapter 1.3.2), the VTA is known to also project to the cortical MTL (Swanson, 1982; Gasbarri et al., 1994) and the AMG is known to also project to the hippocampus (Packard and Wingard, 2004). Thus, the intrinsic connectivity between these neuromodulatory systems and regions within the MTL is not sufficient to explain the functional organization proposed in this model.

The VTA and amygdala do, however, show differences in connectivity with cortical intermediaries that may preferentially engage the hippocampus and cortical MTL. The VTA has been demonstrated to have rich anatomical connectivity with the dorsolateral prefrontal cortex (dlPFC) (Williams and Goldman-Rakic, 1998), whereas the amygdala only has sparse anatomical connectivity with this region (Amaral and Price, 1984; Ghashghaei and Barbas, 2002). It has been proposed that dopaminergic signals arising from the VTA mediate dlPFC activity to modulate a variety of working memory processes (Durstewitz et al., 2000; Seamans and Yang, 2004; Hazy et al., 2006). Thus, VTA engagement during memory encoding would facilitate dlPFC function. Conversely, amygdala activation has been demonstrated to impede dlPFC activations during working memory (Dolcos et al., 2011) and patients with amygdala lesions have

been demonstrated to have enhancements in working memory (Morgan et al., 2012). Thus, amygdala engagement during memory encoding may impair dlPFC function. Critically, both dlPFC activation and working memory processing have been demonstrated to support hippocampus-dependent memory encoding (Blumenfeld and Ranganath, 2007; Gazzaley and Nobre, 2012). For example, a recent neuroimaging study demonstrated that activation of the dlPFC during working memory maintenance is predictive of successful relational binding in the hippocampus and long-term memory for these bound representations, whereas item-related encoding could occur in the absence of dlPFC activation (Blumenfeld et al., 2011). Given these findings, preferential facilitation of the dlPFC by the VTA, and not the amygdala, may specifically support memory encoding in the hippocampus.

The amygdala has been demonstrated to have significant connectivity with the ventral visual stream (Amaral and Cowan, 1980; Amaral and Price, 1984; Suzuki and Amaral, 1994), whereas the projections of the VTA to these regions are relatively sparse (Swanson, 1982). Anatomically, the cortical MTL is thought to be the most anterior portion of the ventral visual stream, and thus receives the majority of its efferent projections from more anterior portions of the ventral visual stream (Suzuki and Amaral, 1994). Conversely, the hippocampus does not receive any direct inputs from posterior regions of the ventral visual stream (van Strien et al., 2009). Thus, the selective enhancement of ventral visual-stream processing via amygdala connectivity could selectively facilitate cortical MTL encoding processes over hippocampal processes.

Thus differential connectivity patterns of the VTA and the amygdala with the dlPFC and ventral visual stream, respectively, could drive the specificity of MTL subregions engaged during reward and punishment motivation. However, future

studies, utilizing methods to assess intrinsic connectivity, such as DTI and resting-state connectivity, will need to address how VTA and amygdala connectivity with these cortical intermediaries mediate the relationship between motivation and MTL-dependent encoding.

5.4 Conclusions and Future Avenues of Research

In conclusion, reward and punishment motivation have distinct influences on declarative memory encoding. These differences emerge via engagement of distinct neuromodulatory systems, which in turn changes the locus of memory encoding processes within the MTL. Specifically, reward motivation engages VTA neuromodulation that facilitates hippocampus-dependent encoding processes, whereas punishment motivation engages amygdala neuromodulation that facilitates cortical MTL-dependent encoding processes. These changes in MTL engagement, in turn, change individuals' representations of the environment such that the representations are adaptive for future behavior. Rewarding events are stored in relationship to the features of the environment in which they were encountered such that these representations could facilitate exploration for additional rewards. Punishing events are stored in isolation of other environmental features such that these representations can facilitate the detection of imminent threats as well as immediate escape.

The studies reported in this dissertation provide evidence for the model of motivated declarative motivated encoding detailed above (Figure 15). In the first study, I showed that reward and punishment motivation change how individuals stored representations of spatial environments in long-term memory. However, this study only investigated declarative memory behaviorally, and was not able to characterize the

underlying neural circuitry. To address differences in neural circuitry, in the second study, I used fMRI to characterize the neural circuitry underlying punishment-motivated encoding and compared findings with previous studies of reward-motivated encoding. I demonstrated that similar to reward-motivated encoding, punishment-motivated encoding enhanced memory for incentivized information. However, punishment-motivated memory encoding was associated with a distinct neuromodulatory system and MTL-encoding substrate. Finally, in the third study, I used fMRI and behavioral measures to investigate the influence of reward and punishment motivation on incidental memory encoding, as opposed to the instrumental encoding paradigms used in the first two studies. This last study demonstrated that the incidental encoding of salient information encountered in rewarding and punishing contexts engaged similar MTL encoding substrates as contexts in which encoding is explicitly incentivized, and that memory for rewarding contexts are more enriched than punishing contexts.

Although the studies presented in this dissertation provide strong support for the model of motivated memory encoding presented in Figure 15, open questions still remain regarding the proposed model. The studies presented in this dissertation identify core differences in how the environment is stored in long-term memory under reward and punishment motivation; however, many of the details of how these representations differ remain untested. Future studies will need to further characterize how these motivational states influence the specificity, stability, and flexibility of declarative memories, as well as the accessibility of these memories to guide future adaptive

behaviors. Second, the studies described in this dissertation mainly focused on the engagement of neuromodulatory and MTL systems during encoding. However, many cognitive processes, which are mediated by regions outside of the MTL, are modulated by motivation and also contribute to declarative memory encoding. Future studies will need to address how these cognitive processes, such as working-memory, attention, and executive function, mediate the relationship between motivational drive and MTL-dependent encoding. Finally, the studies described in this dissertation emphasized the identification of regions and interactions between regions that contributed to motivated memory encoding, yet activity of a given region is not the only contributing factor to neural function. Neurochemistry can modulate both the responsivity of neural regions and how their activations contribute to later behavior. To fully understand the neural mechanisms guiding motivated-memory encoding, future studies will need to characterize the contribution of the different neurotransmitter systems implicated in these processes. Mainly, these studies will need to assay how variation in dopaminergic, noradrenergic, and corticosteroid tone modulate neural responses to incentive cues and encoding in the MTL. Together, these future avenues of research will provide a more comprehensive understanding of how motivation influences declarative memory encoding.

Although previous research has characterized how motivation influences declarative memory, this dissertation highlights a critical role for motivational valence in mediating this behavior. These findings have significant implications not only for neuroscience theory but also for real-world interventions. The behavioral findings supplement and extend the literatures characterizing the influence of affect and motivation on cognition, specifically during learning and memory. Additionally, these findings contribute to a better understanding of one of the oldest questions in declarative memory research, what factors determine which experiences gain access into long-term memory. Neurally, these findings further the literatures characterizing the influence of motivation on learning-related neurophysiology and characterizing how neuromodulatory regions can alter MTL neurophysiology during encoding. Outside of the domain of neuroscience, these findings have implications for the fields of education and psychiatry. For example, understanding how motivation can facilitate or impair specific types of learning can facilitate learning for students in educational settings and individuals with declarative memory deficits, such as older adults and psychiatric populations. Finally, understanding interactions between motivation and declarative memory circuitries could help provide a better understanding of diseases that may be caused by distortions in motivated learning, such as drug addiction, schizophrenia, and depression.

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Biography

Vishnu P. Murty was born on August 3, 1983 in Steubenville Ohio. He graduated from Brown University in May of 2005 with a Bachelor of Science in Neuroscience with honors. He then completed to a two-year post-baccalaureate fellowship at the National Institutes of Mental Health in the Clinical Brain Disorders Branch. He matriculated at Duke in 2007 in the Interdisciplinary Program in Cognitive Neuroscience and joined the Department of Neurobiology and the laboratories of Drs. R. Alison Adcock and Kevin S. LaBar in 2008. He is author to numerous scientific publications investigating the neural basis of the influence of emotion and motivation on declarative memory encoding, in journals such as *Journal of Neuroscience*, *Journal of Cognitive Neuroscience*, *Neuroimage*, and *Learning & Memory*.