EMOTIONAL MODULATION OF COGNITIVE SKILL LEARNING

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
Psychology and Neuroscience in the Graduate School
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ABSTRACT

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Abstract

In this set of studies the modulation of feedback-based cognitive skill learning was investigated by modulating a probabilistic classification learning (PCL) task to be either emotional or neutral. In the current task, based on the *weather prediction* task, cue cards were presented on the screen and subjects were asked to predict what they would come across while walking in the woods, in the emotional condition a snake/spider or in the neutral condition a flower/mushroom.

Chapter 1 is a review of the animal and human literature of multiple memory systems, amygdala modulation of multiple memory systems, and sleep-dependent procedural memory consolidation.

Chapter 2 examined how emotional arousal affected performance, strategy use, and sympathetic nervous system activation in our manipulated PCL task. Subjects highly fearful of the outcomes in the emotional condition showed overall greater skin conductance responses compared to the other groups, as well as retardation in initial cue-outcome acquisition. Individuals who were not fearful of the outcome stimuli used more complex (optimal) strategies after a 24-hr period of memory consolidation relative to the other groups, reflecting greater implicit knowledge of the probabilistic task structure.

The purpose of the experiment in Chapter 3 was to examine consolidation-based stabilization and enhancement in an emotional cognitive skill task. There was no effect of sleep on retention or savings on percent correct or strategy use in both the emotional and neutral PCL task. These results conform to recent evidence that probabilistic learning does *not* show sleep-dependent performance enhancements.

Chapter 4 investigated the neural correlates of emotional PCL with functional magnetic resonance imaging. There was greater amygdala and striatal activity in the emotional versus neutral group on Day 1. There was also increased activity in the striatum on Day 2, suggesting an early and lasting bias of emotion on procedural learning. Additionally, there were differences in neural recruitment by subjects using complex versus simple implicit strategies.

The findings from this series of experiments have implications for the assessment of psychopathologies that show dysfunction in affective and striatal areas, such as obsessive-compulsive disorder and Tourette's syndrome, and for the development, eventually, of optimal therapies.

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I would also like to thank Elizabeth Phelps, Ph.D., for whom I worked for two years at NYU after graduating from Vassar. Dr. Phelps ushered me into the world of cognitive neuroscience and I am grateful I had the opportunity to work with her.

Many people helped me with aspects of these experiments, from running subjects to analyzing data. The members of the "LaBaratory" have not just been my colleagues, there are my friends as well, and I am grateful to have had the opportunity to work with and have the support of this team of outstanding individuals.

At Duke I have also had the opportunity to pursue my passion for music and enjoyed several years of playing principal flute with the Duke Symphony, under Harry

Davidson, Ph.D. I am grateful for this experience which helped keep my own cognitive and affective sides in balance.

I would also like to acknowledge my parents. My parents are my rocks. Their unwavering love and support is truly an amazing gift. They have taught me not only to be a strong, caring, independent person, but have shown me by example that it is possible to lead a balanced life in academia, something that at times is easy to forget!

Lastly, I dedicate this work to my grandmother Mary Ellen Ready, who I called Meme. Meme was a truly amazing woman. She and my grandfather raised three daughters (two Ph.D's and one M.D.), and then went back to school herself and got her Ph.D. at age 61 and taught college courses until she was too ill to leave the house. Meme was a true renaissance woman; an intellectual, a musician, a poet. And she always found time to bring tomatoes from her garden to the homeless shelter. I wish I could have known Meme as an adult, because every day I am amazed by her. Thank you Meme for sharing yourself with me while you were here. I dedicate this work to you.

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1. Introduction

A substantial portion of memories of our pasts involve emotional situations, either positive (weddings, births, successes) or negative (break-ups, deaths, failures). The influence of emotion on the explicit recall of information has been widely studied in humans (see LaBar & Cabeza, 2006, for review). It is also known that emotion affects not only our conscious memories, but can influence future decisions and actions in ways in which we are unaware. An extreme example of nonconscious responses based on an emotionally arousing experience is in patients with Post Traumatic Stress Disorder (PTSD), who show a hypervigilance to external stimuli. Patients with PTSD may not even be aware of the environmental stimuli that trigger emotional reactions such as panic attacks and flashbacks. These types of extreme emotional responses are usually thought of as results of conditioning: a cue related to an original trauma triggers a reaction. In both animals and humans fear conditioning is dependent on the integrity of the amygdala, and takes place on a nondeclarative or implicit level (LeDoux, 1996). If amygdala-dependent emotion can influence other forms of nondeclarative learning, such as procedural habit learning, in humans is not yet known. Although interactions between emotion and declarative memory systems have been well-studied, the modulation of other memory systems remains relatively unexplored territory in humans.

To address whether emotion can modulate striatal-dependent procedural learning, this thesis combines information gleaned from three areas of research: 1) animal work demonstrating amygdalar modulation of multiple memory systems; 2) human neuroimaging work showing the involvement of the striatum in a procedural learning task; and 3) human and animal consolidation research showing the sleep-dependent nature of motor skill consolidation. I have incorporated these three somewhat disparate areas of research to investigate if emotional arousal can affect learning in a striatal-based cognitive skill learning task in humans. First, I will review literature demonstrating the existence of multiple memory systems. Second, I will review evidence of amygdalar modulation on multiple memory systems. In the third section I will review what is known about the influence of time and sleep on consolidation-based stabilization and enhancements in procedural learning and the possible modulation of memory consolidation by emotion.

1.1 Multiple Memory Systems

Research over the past several decades has supported the idea that different neural systems support different types of memory. The hippocampus has been shown to support spatial memory in both animals and humans, and in humans (and possibly other animals) serves the additional function of subserving consciously recollected experiences, also known as explicit or declarative memory. The striatum, part of the basal ganglia, supports the gradual learning of stimulus-response associations, and

comprises one form of implicit or nondeclarative memory. The fact that the hippocampus and striatum subserve different forms of memory has led to the theory that there are multiple memory systems in the brain (Cohen & Squire, 1980). While the hippocampal and striatal systems have been proposed to be primarily independent, recent research has suggested they interact and compete with one another, and that other structures, such as the amygdala, may modulate these different memory systems.

1.1.1 Differential role of hippocampus and striatum in memory

There is an abundance of evidence in both animals and humans that the hippocampal and striatal memory systems subserve different forms of memory, as reviewed below. A compelling evolutionary reason for this competition is the incompatible needs to learn invariant features of experiences as well as specific (variable) features of an event (Sherry & Schacter, 1987). The striatum is specialized to learn invariant, stimulus-response relationships and the development of "habits", whereas the hippocampus is designed to ignore common features and exaggerate variants in order to retrieve specific episodic instances.

Before reviewing the functional roles of the striatum and hippocampus, it is important to briefly consider their anatomy. The striatum is comprised of the caudate and putamen and is the main input structure of the basal ganglia. It receives projections from the cortex as well as dopamine projections from the Substantia nigra compacta (SNc), which contributes to modulating cortico-striatal plasticity. Output from the

striatum via the globus pallidus to the thalamus feeds back to many of its cortical inputs. The main role of the striatum is to integrate information from the cortex and the thalamus, guiding behavior by the learning of stimulus-response associations through fronto-striatal-thalamic loops (Alexander et al., 1986).

While the striatum was originally thought to be mainly involved in motor function, it has been shown to be important for cognitive skill learning as well (Shohamy et al., 2005; 2006). Different parts of the striatum have been implicated in different learning processes; the dorsal striatum is more involved in habit formation, like the gradual learning of stimulus-response associations, while the ventral striatum has been implicated in flexible place learning (Popescu, Saghyan, & Paré, 2007). The striatum receives input from other subcortical areas such as the amygdala. Projections from the basolateral amygdala (BLA) are densest in the ventral striatum, but there are substantial projections to the dorsal striatum as well (Ragsdale & Graybiel, 1988).

The hippocampus is part of the forebrain housed in the medial temporal lobe (MTL). It is comprised of the dentate gyrus, the *Cornu Ammonis* fields CA1-CA3, and the subiculum. The CA1-CA3 fields make up the hippocampus proper. Numerous cortical areas project to the hippocampus, such as the adjacent entorhinal, perirhinal and posterior parahippocampal cortices, which form an extended MTL memory system. The fornix is a major afferent and efferent transmission route for hippocampal pathways, particularly to subcortical regions. The hippocampus also receives input from a number

of subcortical areas such as the amygdala, thalamus, ventral tegmental area, raphe nuclei, and the locus coeruleus. In animals the hippocampus has been implicated primarily in spatial, contextual, and relational memory, and it has been suggested that the hippocampus might serve as a cognitive map of the environment, since neurons in the hippocampus have spatial firing fields (place cells) (see Best, White, & Minai, 2001). Place cells have recently been identified in humans as well, while navigating a virtual reality town (Peigneaux et al., 2003). In humans the hippocampus is not only involved in spatial memory but also for conscious recollection (declarative or explicit memory). Aspects of non-spatial forms of declarative memory have also been demonstrated in animal models, such as transitive inference tests that require inferences drawn about the relationship among objects that may form an evolutionary precursor to conscious recollection abilities in humans (Dusek & Eichenbaum, 1997). The integrity of the hippocampus is necessary for explicit recall of past events, as made evident by amnesics with selective MTL damage, and patients with neurodegenerative memory disorders such as Alzheimer's disease.

1.1.1.1 Double dissociation studies in animals

There is an abundance of evidence from animals that the hippocampus and striatum support different types of memory systems. Lesion studies have been especially useful in demonstrating these differences. Irreversible lesions of the striatum result in a

predominant tendency towards place learning (Thompson, Guilford, Hicks, 1980), while lesions of the fornix result in predominantly response learning (Descatro, 1974).

Several tasks have been developed that can be adapted to support either place (hippocampal) or response (striatal) –based learning. One of these tasks is the radial maze task. In this type of task animals obtain food pellets from multiple spatial locations (arms) in a maze, and accurate performance requires memory for previously visited arms. There are two versions of the radial maze task of interest: the "win-shift" paradigm required avoidance of previously baited arms, whereas in the "win-stay" version the same arm was consistently baited. When the fornix was lesioned spatial memory on the "win-shift" task was impaired, but cue-based memory on the "win-stay" version was facilitated. In contrast, lesions of the striatum had the opposite pattern of effects, with cue-based memory being impaired and spatial memory enhanced (Packard, Hirsh, & White, 1989). This double dissociation in lesion location and type of memory affected provided groundwork for the differentiation between hippocampal and striatal-based memory systems.

Similar results were obtained using a two-platform water maze task in which two rubber balls protruding from the water served as cues for escape (Packard & McGaugh, 1992). Rats strongly dislike being in water and will try to escape as quickly as possible. Thus one ball, the "correct" ball, was on a platform that could be mounted and escaped, while the other ball, the "incorrect" ball, was on a thin rod that provided no

escape to the rats. The balls differed visually, one having horizontal stripes and one having vertical stripes. As in the radial maze experiments there were two versions of the maze task that emphasized different strategies: in the spatial version of the task the correct platform was in the same location on every trial, but the visual appearance of the ball changed; in the cued version the correct platform was in different spatial locations but the visual pattern of the cue was consistent. Again fornix lesions impaired acquisition in the spatial version of the task, demonstrating the importance of the hippocampus to spatial memory, and caudate lesions impaired acquisition in the cued task, illustrating the caudate was more important in cue (or stimulus-response) based memory.

Cross maze tasks have been another hallmark method of dissociating between hippocampal spatial memory and striatal stimulus-response memory in rodents. In a cross maze, two T mazes are arranged so that the baited box can be approached from two start boxes. Rats were trained to obtain food from a consistently baited goal box starting from the same start point in the maze. Rats can either use the spatial location of the reinforced box to make their approach response (place learners), or can learn to approach the baited box by turning the body at a specific point in the maze (response learners). In a key experiment using a cross maze task and selective reversible lesions of the hippocampus or caudate, rats were trained on a cross maze for 6 trials a day for 7 days, starting from the same location on each trial (Packard & McGaugh, 1996). Rats

then received either intrahippocampal or intracaudate injections of either saline or lidocaine[1], and were subsequently placed in the maze from a novel position. When saline was injected into the hippocampus or caudate the rats exhibited place learning, approaching the same box that had been baited for the previous 7 days, suggesting the default for this type of task is place learning. When lidocaine was injected into the hippocampus this blocked the expression of place learning, which was not true when lidocaine was injected into the caudate. This study provided further evidence for the dissociable roles of hippocampal and striatal memory systems, with the functional integrity of the hippocampus, but not the caudate, being necessary for place learning in a cross maze task.

Interestingly, when rats were trained for 16 days on the cross maze task and then injected with saline the rats were predominantly response learners, suggesting that the default learning mode after extended training is response based. Intrahippocampal injections of lidocaine did not block the response learning, but rats that received intracaudate injections of lidocaine exhibited place learning, again supporting a dual systems theory of memory (Packard & McGaugh, 1996). However, this study additionally showed a switch from hippocampal to striatal-based memory systems over time. These results mirrored the earlier behavioral results of Restle (1957) that with

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[1] Lidocaine injections were used to selectively inactivate regions of the brain, but unlike lesions, the effects are reversible.

extended training in a cross maze rats switch from use of place learning to response learning. This switch from hippocampal to striatal-based memory makes sense because early in learning the hippocampus is needed for binding contextual information. The hippocampus also responds to novelty so when the task is new it will likely be active, whereas later in learning processing of contextual information is not as necessary as stimulus-response associations come to dominate behavior.

McDonald & White (1994) also demonstrated that both the hippocampal and striatal systems could provide an adequate learned solution in a maze learning task, but that early learning was hippocampally mediated, whereas extended training was striatally mediated, suggesting a shift from "declarative/spatial" to "habit/response" memory. Yet another plus-maze task with rats found that posttraining intrahippocampal infusions of the neurotransmitter glutamate following early trials preserved place learning, but blocked the switch to response learning usually seen after extended training (Packard, 1999). In contrast, posttraining intracaudate glutamate injections prevented the use of place learning and speeded the use of response learning. These studies provide evidence that hippocampal dependent place learning is acquired quicker than striatal-dependent response learning, but there is a shift in well-learned behavior from hippocampal to striatal-dependent processing.

Double dissociations in the type of memory subserved by the hippocampus and striatum are also observed after posttraining intracerebral drug injections (Packard &

Teather, 1997, 1998; Packard, Cahill, & McGaugh, 1994; Packard & White, 1991). Posttraining intrahippocampal injections of dopaminergic agonists enhanced spatial memory in a radial maze, while injections into the caudate enhanced cued memory (Packard & White, 1991). The glutamatergic NMDA receptor antagonist AP5 selectively impaired performance on the spatially-mediated hidden platform water maze task when injected into the hippocampus, but when injected into the striatum memory for the visual platform maze task was impaired (Packard & Teather, 1997). Important to note, the effects of posttraining injections on memory were time-dependent, with injections more than 2 hours after training having no effect on memory, implicating the hippocampus and striatum in the modulation of proximal memory consolidation (McGaugh, 1966).

The studies briefly reviewed above demonstrate that different types of learning and memory are dependent on the hippocampus and striatum, providing evidence for multiple memory systems in the brain with tasks that can support place or response learning.

1.1.1.2 Memory system interactions in humans

1.1.1.2.1 Double dissociation studies

In humans the dissociation between memory systems is not usually defined as "place" or "response" learning and memory, as in rats, but commonly is delineated as explicit (declarative) and procedural (habit) memory. People with amnesia and

neurodegenerative diseases that affect the MTL such as Alzheimer's disease have evidenced the necessity of an intact MTL for explicit memory. The integrity of the striatum has been demonstrated with research including patients who suffer damage to this area, such as Parkinson's and Huntington's disease patients. Patients with Parkinson's disease have a profound loss of dopamine containing neurons in the SNc, which leads to dopamine depletion in the basal ganglia. The loss of dopamine in these patients leads most prominently to a loss of motor control (not being able to initiate changes in movement, getting 'stuck'). Huntington's disease involves neuronal death in the striatum, also leading to the loss of motor control but is characterized by uncontrollable bursts of movement. While motor difficulties are hallmark symptoms of both Parkinson's and Huntington's disease, patients with these diseases also have cognitive deficits, especially in tasks that involve the incremental learning of cue-outcome associations via feedback. Thus two lines of tasks can be used to measure striatal-dependent learning in humans: motor skill learning and cognitive skill learning.

Motor sequence learning is a type of procedural learning that involves pressing a button or tracking a stylus corresponding to the location of a target on a screen or specialized apparatus. For serial reaction time (SRT) tasks, the targets follow a sequence in some blocks, while for other blocks they are randomly presented. Learning is measured as a decrease in RT to the targets in sequenced blocks. This type of motor skill has been important in dissociating the function of the MTL and striatum in humans.

Research with amnesic subjects has shown that they display normal motor skill learning, but are impaired at recognition memory (Tranel, Damasio, Damasio, & Brandt, 1994). In contrast, Parkinson's and Huntington's disease patients showed the opposite pattern, with impaired motor skill learning but normal levels of declarative memory recall (Heindel et al., 1989), demonstrating a double dissociation in function of the hippocampus and striatum in humans.

The most commonly used cognitive skill task to investigate the learning of cue-outcome associations in humans is a probabilistic classification learning (PCL) task known as the *weather prediction task* (Knowlton, Squire, & Gluck, 1994; Knowlton, Mangles, & Squire, 1996). In this task subjects are presented with a series of cards and are asked to predict the weather in a foreign city (rain or shine) based on the cards present on that trial. Following each trial the subject is given feedback as to if they predicted the weather correctly. The task is probabilistic such that the patterns of cards do not predict an outcome 100%, thus making it impossible for subjects to only use memorization strategies to correctly solve this task.

Parkinson's and Huntington's disease patients, who have selective striatal damage, performed worse than controls on the weather prediction task (Knowlton, Mangles, & Squire, 1996; Knowlton, Squire, & Gluck, 1994). In contrast, amnesics with damage to the medial temporal lobe performed as well as controls for the first 50 trials of the task, but were impaired as training progressed. A further dissociation between

explicit versus procedural memory was apparent on a posttraining declarative memory test in which Parkinson's disease subjects could recall specific details of the experiment, whereas amnesics could not. This double-dissociation between hippocampal and striatal-dependent memory mirrors work in animals and further illustrates that different brain areas contribute to different forms of memory, with the striatum being involved in stimulus-response learning as well as higher cognitive functions like categorization and the hippocampus in explicit recall.

Results from research with amnesics in PCL have been less straightforward than that with Parkinson's disease patients. As mentioned above, in an early study amnesics were impaired in later learning (after 50 trials) on the weather prediction task. (Knowlton, Squire, & Gluck, 1994). In a more recent study with hypoxic amnesics who had more localized hippocampal damage found that these patients were uniformly impaired on both early and late training of PCL tasks (Hopkins et al., 2004). Further, the learning rate of hypoxic amnesic patients on tasks that have a simpler probabilistic structure than the original weather prediction task is similar that of healthy controls (Shohamy et al., 2006), suggesting that task difficulty affects recruitment of the MTL. While the performance of amnesics on PCL tasks is not conclusive, the studies above suggest that the learning of category structures in a task such as the weather prediction task requires considerable hippocampal mediation.

Another recent study examined how patients with Parkinson's disease and amnestic mild cognitive impairment (aMCI), who have prominent MTL dysfunctions) performed on a sequential chaining task (Nagy et al., 2007). In this task each link of a chain was applied in a certain sequence. After each link was added subjects received feedback as to if it was the correct link or not. A post-learning probe trial tested subjects' declarative knowledge of the sequence. Parkinson's patients showed delayed learning of the chaining task, but their performance was spared on the declarative probe phase. In contrast, patients with aMCI showed intact learning during the training phase, but their performance was impaired on the probe phase. The results from this feedback-based cognitive skill task again illustrate the dissociable roles that the hippocampus and striatum play in memory.

As in animals, brain lesion studies in humans are exceedingly useful in differentiating the functions of focal areas of the brain. The human evidence with amnesics and Parkinson's and Huntington's disease patients shows dissociable roles of the hippocampus and striatum in memory, with the hippocampus mediating explicit recall and the striatum involved in the learning of stimulus-response/cue-outcome associations in both motor and cognitive skill-based tasks.

1.1.1.2.2 Neuroimaging of multiple memory systems

The technique of functional magnetic resonance imaging (fMRI) has added another layer of evidence to the multiple memory systems debate by showing blood flow and oxygenation changes in the brain as a correlate of neural activity.

Neuroimaging of both motor and cognitive tasks such as PCL have been instrumental in demonstrating the contributions of the striatum and hippocampus to different forms of memory.

Neuroimaging of motor skill SRT tasks has shown striatal activation with increased learning (e.g. Rauch et al., 1997), with performance correlating with striatal activation. Furthermore, the involvement of both the MTL and striatum has been demonstrated in motor skill tasks to function in an inverse manner, with the MTL being active early in learning and the striatum active in later learning (Jenkins et al., 1994), in support of the animal studies reviewed above. This negative relationship between the caudate and MTL has also been observed in other procedural learning tasks such as perceptual skill learning (Poldrack & Gabrieli, 2001), and cognitive planning tasks (Dagher, Owen, Boecker, & Brooks, 2001).

Imaging of the weather prediction task across several studies has shown consistent activation in the striatum (Poldrack et al., 1999, 2001; Aron et al., 2004; Moody et al., 2004), fitting with the view that the striatum is involved in cognitively-based habit learning. However, similar to studies with motor skill tasks, Poldrack and colleagues have shown that over the course of learning the weather prediction task, the striatum and MTL interact. In an important study it was found that there was negative signal change (deactivation) in the MTL compared to baseline trials that became more pronounced over the first 48 trials of learning and dissipated by the end of learning (96

trials) (Poldrack et al., 2001). In this study activity in the striatum was negatively correlated with activity in the MTL, and time-course analysis demonstrated that the striatum and MTL had a reciprocal relationship across trials, with the MTL being active and the striatum deactive early in learning, but as learning continued the MTL became deactivated and the striatum increasingly active. These results again fit with animal work that early in learning the hippocampus is important, and as learning of stimulus-response associations progresses learning becomes dependent on the striatum.

One recent study examined the effect of a dual tone-counting task on PCL performance and neural activations (Foerde, Knowlton, & Poldrack, 2006), and found that manipulating working memory load on the weather prediction task with a concurrent tone counting task affected the relation of activation between the hippocampus and striatum. The dual-task condition decreased explicit knowledge of the cue card predictiveness. Thus the dual-task condition involved more procedural learning than the single-task condition. On a post-learning probe trial, testing memory for cue-outcome associations, activation in the right hippocampus was correlated with performance in the single task condition, whereas activation in the putamen was correlated with performance in the dual task condition, further illustrating dissociations in the weather prediction task between declarative learning (single-task condition) and procedural learning (dual-task condition).

These studies reveal an interaction between the MTL and the striatum during cognitive skill learning. Interestingly, neuroimaging of Parkinson's disease patients while performing the weather prediction task revealed that they exhibit less activity in the striatum (specifically the caudate), than healthy controls, as well as greater activation in prefrontal and MTL regions (Moody, Bookheimer, Vanek, & Knowlton, 2004), suggesting that when the striatum is compromised, the explicit memory system may become active in situations in which it is normally inhibited (see Poldrack et al., 2001).

The aspect of classification learning for which the striatum is most important has been investigated by comparing feedback versus observational versions of the weather prediction task (Poldrack et al., 2001). In the feedback condition subjects viewed cue cards, made their outcome prediction, and received performance feedback on a trial-by-trial basis. In the observational condition, subjects viewed the correct outcome for each trial but did not make predictions or receive feedback. After passively viewing the trials and their outcomes, subjects in the observational condition were instructed to make predictions for specific cue cards to test their knowledge of the card patterns and outcomes. In the Poldrack et al. (2001) study of feedback versus observation learning in a PCL task, subjects in both conditions showed similar levels of accuracy. However, there was greater negative signal change in the MTL during the feedback vs. observational learning. Parkinson's disease patients also exhibit impairments on feedback-based weather prediction task, but they perform equivalently on the observational version,

providing further evidence for the role of the striatum specifically in feedback processing of classification tasks (Shohamy et al., 2004).

Humans also use differential hippocampal and caudate-based strategies when learning in a virtual radial maze (Iaria et al., 2003). Participants in this task were asked to retrieve objects from fixed locations in a virtual 8-arm radial maze for 3 trials and were then tested on a probe trial where the landmarks were no longer visible in the environment. The task could be performed using a spatial strategy (using landmarks) or a response strategy (using proprioceptive/egocentric information to make response), similar to rodent work (McDonald & White, 1994). Behavioral work with the virtual radial maze revealed that spatial learners performed poorly in the probe trial, since the visible landmark cues were not available (Iaria et al., 2003). With repeated training, however, half of participants shifted to a response strategy, demonstrating a switch from hippocampal-based to striatal-based learning, similar to what has been reported in rats (Packard & McGaugh, 1996). Functional neuroimaging of the virtual radial maze task revealed that participants who used spatial strategies had increased activity in the hippocampus, while participants who used response strategies had increased striatal activity. Additionally, patients with MTL damage who used a spatial strategy were significantly impaired compared to patients using response strategies. These findings mirror those in rodents and suggest a double dissociation in hippocampal/striatal memory function using a visuo-motor maze learning task in humans.

The data presented in this section demonstrate dissociable contributions of hippocampal and striatal memory systems in human patients with damage to the MTL (amnesics) and the striatum (Parkinson's and Huntington's disease). Functional neuroimaging has furthered our knowledge about the time-course and activity patterns of these areas while subjects perform skill and maze learning tasks, again implicating reciprocal influences of these structures that vary across individuals who learn using different strategies and that shift in time within subjects from the hippocampus to the striatum as a task is well-learned.

1.2 Amygdala modulation of multiple memory systems

The amygdala, a small almond shaped structure in the medial temporal lobe, has been implicated in the neurobiology of emotion. It has long been recognized that emotionally arousing events have a unique influence on memory, with some emotional events being enhanced, or, in some cases, impaired (James, 1890; Ekman & Davidson, 1994; Lane & Nadel, 2000). Two main theories predict differing roles of the amygdala in modulating memory - the *memory systems theory* and the *memory modulation hypothesis*. The *memory systems theory* proposes a selective role for the amygdala in processing emotional forms of classical conditioning but not other aspects of memory (Squire, Knowlton, & Musen, 1993). According to this theory, each type of nondeclarative memory is dependent on a specific set of brain regions: skills and habits are dependent on the striatum, priming is dependent on the neocortex, and nonassociative learning is

dependent on reflex pathways. However, there is no cross talk afforded between these regions, and the integrity of the amygdala is proposed to be *only* critical for emotional conditioning. In contrast, the *memory modulation hypothesis* posits that the amygdala interacts with other brain systems involved in memory processing regardless of the form of memory expressed (implicit or explicit) (Cahill & McGaugh, 1998).

1.2.1 Amygdala connectivity with hippocampus and striatum

There are an abundance of anatomical connections between the amygdala and both the hippocampus and striatum. Anatomical tracer studies have shown that the hippocampus and striatum receive efferent amygdala projections from the basolateral and lateral nuclei (see Alheid, de Olmos, & Beltramino, 1995 for review). The amygdala also has connections to the striatum in a ventral-to-dorsal gradient of fiber projections originating in the basolateral amygdala (BLA) (Pitkanen et al., 2000; Setlow, Roozendaal, & McGaugh, 2000). Additionally, the amygdala projects to several cortical regions that innervate both the hippocampus and striatum (such as the entorhinal cortex), and has projections to several subcortical regions (such as midbrain dopamine pathways) that can also influence hippocampal and striatal memory function (Packard & White, 1991). Furthermore, both the amygdala and striatum are part of the mesolimbic dopamine system (Packard & White, 1991). The nucleus accumbens in the ventral striatum has been termed the "limbic-motor interface" (Mogenson, 1984) because the rich BLA

projections to this area convey one mechanism by which emotional information influences behavioral output (Carlsen & Heinmer, 1986).

There are also direct glutamatergic projections from the amygdala to the hippocampus and striatum that provide a mechanism by which the amygdala could exert a modulatory influence on plasticity involved in declarative and procedural forms of learning and memory, respectively (Krettek & Price, 1978; Kita & Kitai, 1990; Pitkanen et al., 2000). In addition, the amygdala can affect gene transcription in the hippocampus and striatum, with injections of NMDA to the basolateral nucleus of the amygdala inducing *c-fos* expression in the dentate gyrus of the hippocampus and the striatum (Packard, Cahill, & McGaugh, 1994).

Given the abundance of evidence for the connections between the amygdala and striatum, the amygdala is in an anatomic position to exert emotional influences on striatal-based learning (Packard, Cahill, & McGaugh, 1994; Packard & Wingard, 2004), and indeed the amygdala has been shown to modulate procedural learning in navigational and motor tasks in rodents, as reviewed below. However, it remains unknown if the amygdala can modulate cognitive or motor-based skill learning in humans.

1.2.2 Amygdala modulation of multiple memory systems in animals

In a seminal study, McDonald & White (1993) showed that the hippocampus, striatum, and amygdala subserve different types of memory by creating three versions

of the radial arm maze task. In the win-shift version, each arm was baited and rats had to retrieve food from every arm, thus 'winning' food and 'shifting' to a new arm on the next trial. In the win-stay version, baited arms were cued by lights, and after the rat retrieved food from that arm it was rebaited, thus 'winning' food and 'staying' at that location. Finally, in a conditioned cue preference (CCP) version, only two arms in the maze were used, one lit and one dark, one baited and one not, and on a probe trial time spent in the previously baited arm was an index of preference for that arm. Hippocampal damage impaired acquisition on the win-shift and CCP versions, but not the win-stay version. Damage to the striatum impaired acquisition on the win-stay version, but not the CCP or win-shift version. Damage to the amygdala impaired acquisition of the CCP task but not the win-shift or win-stay tasks, demonstrating that the hippocampus, striatum, and amygdala can support different types of memory. However, just because these areas support specific types of memory does not rule out the possibility that activation of one area, such as the amygdala, can influence memory in the other areas.

To investigate whether the amygdala can modulate both hippocampal and striatal use of a maze task (that can be manipulated to emphasize either memory system), Packard and colleagues (1994) placed rats in either a hidden or visible platform water maze task. Rats were trained for several trials on one day, starting from different maze arms on each trial and were tested in a probe trial 24 hours later. In the hidden

platform version, the platform was submerged beneath the water in the same location on each trial, so animals could not use cues to find the platform. Instead, they relied on an internal spatial map of the maze, which in this situation is hippocampal dependent (Morris, Garrud, Rawlins, & O'Keefe, 1982). In contrast, when the platform was visible but moved to a different spatial location on each trial, learning was determined by striatal-dependent cue usage (Packard & McGaugh, 1992). Amphetamine, an indirect catecholamine agonist that locally increases neural activity, was injected into the hippocampus or striatum, as well as the BLA, posttraining on Day 1. Intrahippocampal plus BLA injections of amphetamine enhanced memory in the spatially dependent hidden platform maze task, but had no effect on the visible platform task. In contrast, intracaudate plus BLA injections had the opposite effect, enhancing memory on the visible platform maze task with no effect on performance on the hidden platform task (Packard, Cahill, & McGaugh, 1994). This important study demonstrated that amygdala activation selectively enhances memory in both hippocampal and striatal dependent learning tasks.

To test whether the amygdala was exerting its modulatory effects on hippocampal and striatal-based memory via a storage process within the amygdala or if the amygdala was modulating the storage of memory in other brain areas, posttraining amphetamine or saline was injected into the hippocampus, caudate, or amygdala, and before the retention test 24 hours later injections of lidocaine or saline were administered

into the same regions. Preretention intrahippocampal lidocaine injections blocked the expression of intrahippocampal amphetamine (administered posttraining) increases in the spatial hidden platform task, suggesting the hippocampus itself is a site of memory storage over this retention interval. Similar results were obtained with the caudate and the visible platform task. Posttraining intra-amygdala injections of amphetamine enhanced retention of both tasks. Preretention intra-amygdala lidocaine injections did not block these memory-enhancing effects of posttraining intra-amygdala amphetamine in either task, suggesting that the amygdala acts to enhance memory via a modulatory influence in other brain regions, and is not a locus of memory storage itself (Packard, Cahill, & McGaugh, 1994).

In another investigation examining the modulatory influence of the amygdala on hippocampal and striatal memory processes, the same hidden or visible platform water maze tasks were used (Packard & Teather, 1998). This set of experiments replicated the findings from Packard, Cahill, & McGaugh (1994), and further illustrated the modulatory role the amygdala can have on both hippocampal and striatal-based memory. Posttraining intra-amygdala administration of amphetamine again increased retention on both the hidden and visible platform maze tasks. On the hidden platform task, pre-retention injections of lidocaine into the hippocampus eliminated the beneficial effect of posttraining amygdala activation. Similarly, on the visible platform task, pre-retention injections of lidocaine into the caudate eliminated the posttraining

enhancements attributable to increased amygdala activity. The results from these studies demonstrate not only the functional dissociation between hippocampal and striatal-based memory, but the common amygdalar modulation of memory consolidation in both systems, depending on task demands.

The functional integrity of the amygdala is also necessary for the posttraining modulatory effects of drugs and hormones on memory in the hippocampus (Roozendaal, & McGaugh, 1997; Roozendaal, Nguyen, Power, & McGaugh, 1999; Packard & Chen, 1999) and striatum (Packard, Introini-Collison, & McGaugh, 1996) on other tasks that are selective for each of these memory systems. In sum, the experiments reviewed in this section suggest that efferent amygdala pathways are able to modulate memory in neural systems involving the hippocampus and striatum. It remains unknown if it is the direct projections to the striatum and hippocampus from the amygdala or the amygdala's projections to other cortical and subcortical regions that provide the main modulatory pathway for the amygdala to these brain areas. There is evidence for converging effects from both indirect and direct feedback pathways to affect processing in these structures (McGaugh, 2004).

1.2.3 Memory modulation by the amygdala in humans

In humans there is substantial evidence that the amygdala plays a key modulatory role in memory for emotional events (Cahill & McGaugh, 1998; LaBar & Cabeza, 2006), especially in facilitating long-term hippocampal-based explicit memory

(LaBar & Phelps, 1998; Dolcos, LaBar, & Cabeza, 2004; Cahill, 2000; Cahill & McGaugh, 1998). In one of the first studies to investigate how the amygdala influences explicit memory in humans, Cahill and colleagues (1996) had subjects watch highly negative and arousing videos while measuring glucose usage in the brain with positron emission tomography (PET), and they returned 3 weeks later for a memory test. Across subjects, long term memory was significantly correlated with the degree of amygdala activity while watching the videos for the first time. Another PET study investigated the effect of amygdala activity at encoding on 1-month delayed recall for pleasant and unpleasant pictures (Hamann et al., 1999). Across subjects, amygdala activity to either pleasant or unpleasant pictures was correlated with recall accuracy of the photos one month later. Such results provide evidence that amygdala activity at the time of encoding can enhance long-term recall of emotional material. These initial studies provide some support for the animal models but suffer from both spatial and temporal limitations of the PET technique.

Canli et al. (2000) used event-related fMRI to investigate the relationship between amygdala activity at encoding and the long-term retention of emotional stimuli. In this study subjects viewed photographs that ranged in emotional arousal and valence and memory was tested 3 weeks later. While again seeing a between-subjects correlation between amygdala activity during encoding and correct recall of photos, this technique was able to time-lock the activity to the onset of each picture. Furthermore, by

selectively averaging the data according to the participants' own arousal ratings, it was shown that amygdala activity was strongest for those items that were rated by each participant as the most emotionally intense. Another study that investigated neural activity with fMRI at encoding of emotional and neutral stimuli found that successful encoding activity in the amygdala and other MTL structures was greater and more highly correlated for emotional than neutral pictures (Dolcos, LaBar, & Cabeza, 2004).

Kensinger & Corkin (2004) showed amygdala-MTL interactions with event-related fMRI. In this study they found a link between amygdala activity, hippocampal activity, and subsequent memory. Activations in these regions were correlated with successful encoding of arousing, but not neutral words, suggesting that the amygdala is able to modulate the hippocampal memory system in humans. Another neuroimaging study of a verbal encoding task was performed in patients with hippocampal and amygdala damage (Richardson, Strange, & Dolan, 2004). Whereas hippocampal damage was associated with decreased recall for both neutral and emotional words, amygdala damage was only associated with performance on the emotional items. Interestingly, hippocampal activity during encoding for successfully remembered emotional items was correlated with degree of amygdala damage, while the severity of amygdala damage predicted reduced activity in the hippocampus for emotional versus neutral words, suggesting reciprocity in amygdala-hippocampal function in humans.

The studies just described all examined neural activity using PET or fMRI at the time of encoding. A more recent fMRI study examined amygdala and MTL activity during recall of emotional and neutral pictures 1 year post encoding (Dolcos, LaBar, & Cabeza, 2005). This study found that successful retrieval of emotional versus neutral pictures was accompanied by an increase in amygdala, entorhinal, and hippocampal activity. Moreover, the amygdala and hippocampal activity differentiated emotional memories recalled with a sense of recollection (with contextual details) from those recalled with a sense of familiarity (without contextual details). Another study examined neural activity during recall for "remember" versus "know" judgments for emotional and neutral photos and found that for neutral photos "remember" judgments were associated with increased activity in the parahippocampal cortex, where as "remember" judgments for emotional photos were correlated with increased activity in the amygdala (Sharot, Delgado, & Phelps, 2004). These studies illustrate that not only is the amygdala active during the encoding of emotional material, but during the recall of that information, and at both memory stages, it interacts with other MTL structures to enhance memory.

While there is substantial evidence for amygdala modulation of hippocampal-dependent memory in humans, to my knowledge there is no evidence that the amygdala can influence striatal-dependent procedural memory. Based on the abundance of rodent research demonstrating amygdalar modulation of the striatal habit memory system as

described in the previous section, and since direct projections connect the basolateral amygdala and the striatum, it is probable that the amygdala is able to modulate procedural memory in humans as well.

1.2.4 Stress affects modulation of multiple memory systems

Stress has been proposed to be a factor in modulating the usage of a hippocampal versus striatal memory system. Induction of a stressful state in rats, leading to activation of the amygdala, affects learning in the hidden or visible platform water maze task (Kim, Lee, Han, & Packard, 2001). Rats in this study were submitted to a pretraining stress regimen (footshock) and were subsequently trained to swim to a visibly cued escape platform in a fixed spatial location. On a probe trial 24 hours after training the visible platform was moved to a new location. Control rats that had not been stressed swam predominantly to the old platform location, indicating the usage of spatial memory. Rats that had been exposed to stress immediately prior to learning swam to the visible platform on the probe trial, demonstrating usage of a stimulus-response memory. An additional experiment in this study showed that lesions of the amygdala blocked stress-induced impairments on a hippocampal-dependent spatial memory task, demonstrating the importance of emotional state for the relative use of multiple memory systems in learned behavior.

Additional support for the emotional modulation of memory systems comes from a rodent study in which the amygdala was injected with anxiogenic drugs before

training on the water maze task (Packard & Wingard, 2004). Rats who received the pretraining amygdala injections demonstrated stimulus-response learning more than hippocampal-based spatial learning, which was not true in control rats. During acquisition of the task, latencies to find the platform was equal in both injected and control rats, but at the retention test 24 hours later the behavioral difference was detected, implicating the influence of the amygdala on the consolidation of striatal-dependent procedural learning.

Finally, a recent behavioral study investigated the effect of stress on biasing memory system usage in humans, and found that participants who were stressed before performing a task similar to the Morris water maze used a stimulus-response strategy significantly more often than controls (Schwabe et al., 2007). Similar to the rat studies, performance itself was not affected by stress, but strategy use was affected by stress. This is an important point that is not often considered in human studies. Most procedural learning tasks in humans use performance, whether it is reaction time or percent correct, as the main index of learning. The study by Schwabe and colleagues suggested that solely examining performance measures is shortsighted, and we could be missing out on important differences in *how* subjects are solving a task. Strategy measures have recently been developed for other procedural learning tasks, such as the weather prediction task (Meeter et al., 2006; Lagnado et al., 2006). Importantly, emotion may have effects on strategy use in the absence of accuracy measures.

In sum, stress-induced arousal activates the amygdala and biases the usage of strategies in animal learning tasks. Similar behavioral effects have been reported in humans, but the underlying neural correlates are unknown.

1.3 Memory Consolidation

As McGaugh (2002) has pointed out, lasting memories are not made instantly; they are created by the interaction of hormonal and brain systems that are activated by a given experience. Memory consolidation was originally defined as the conversion of a memory representation from a labile to more stable state. That definition has recently been expanded by Walker (2005) to state that consolidation not only involves the stabilization of memory, but that additional learning can occur without further practice. These two stages of consolidation -- stabilization and enhancement -- are thought to rely on different stages of the sleep/wake cycle, with stabilization of a memory taking place mainly during wake cycles, while memory enhancements rely mainly on sleep cycles.

Sleep has been shown to facilitate consolidation of both declarative and nondeclarative memories in humans (Marshall & Born, 2007). There are discrepancies in the evidence for the role of sleep in the consolidation of declarative memories, with some reports saying sleep enhances declarative memory (Drosopoulos, Schulza, Fischer, & Born, 2007), while others say this is not the case (Meienberg, 1977). Sleep is also important in the consolidation of relational memory (Ellenlogen et al., 2007). Much

research has demonstrated that sleep is especially important in the consolidation of procedural motor learning (Walker et al. 2002), as discussed in the next section.

1.3.1 Stabilization and enhancement of procedural learning

Consolidation-based stabilization can be effectively achieved during periods of wakefulness. Stickgold et al. (2000) demonstrated in a procedural visual task (identifying diagonal bars embedded against a background of horizontal bars) the mere passage of time stabilized the memory: there was no increased performance, but performance remained at the same level it was at the end of initial learning. With motor skill tasks, such as finger tapping sequence learning, memory was maintained over 3-12 hrs, but no improvements were found as measured by speed or accuracy (Walker et al. 2002, 2003).

In contrast, consolidation-based enhancement is putatively reliant on sleep. Motor tasks such as skilled reaching and the SRT task show increases in performance after a night's sleep (Karni et al., 1998). An important set of experiments using finger tapping sequences demonstrated that such enhancements are sleep, and not time, dependent (Walker et al., 2002, 2003). In these tasks implicit knowledge was tested after two blocks of sequence learning by interjecting random sequences. An increase in RT during the random blocks compared to the repeated blocks is taken as evidence that subjects learned the previously rehearsed sequence. Subjects were trained at either 10 am or 10 pm and were retested at various intervals across 24 hours. Subjects who

learned at 10 am and were tested at 10 pm following 12 hours of wake showed no performance improvements. However, after sleeping and being retested at 10 am there were dramatic improvements in speed and accuracy. Another group of subjects was trained at 10 pm and retested at 10 am following a night's sleep, and these subjects showed significant improvements. When retested again at 10 pm following 12 hours of wake, no further improvements were observed. This set of experiments was seminal in demonstrating that overnight improvements in procedural motor learning are sleep-dependent (but see Song et al., 2007 for recent lack of replication using a SRT task).

Daytime naps can also be beneficial. In a visual skill learning task, performance deteriorated with repeated practice during the day, but these decrements were ameliorated with short naps, and longer naps that included REM sleep led to performance increases (Mednick et al., 2002). In a SRT task subjects who had a 60-90 minute nap during the day showed significant improvements over awake subjects, although this was at the expense of subsequent overnight learning (Walker & Stickgold, 2005).

Recent evidence suggests that procedural and declarative memory may interact during sleep-dependent consolidation. One such study examined the consolidation of both implicit and explicit knowledge in a SRT task (Fischer, Drosopoulos, Tsen, & Born, 2006). Subjects learned a sequence and were tested for their implicit knowledge of the sequence though random blocks. Subjects' explicit memory of the sequence was assessed

by a generation task in which they had to predict the sequential target positions. Two groups learned the sequence in an initial session, half returning after 9 hours of sleep or wakefulness. At the end of the initial training session, the two groups had comparable implicit sequence knowledge, and neither group reported explicit memory of the sequence. However, after the 9-hour interval, subjects who had slept showed a gain in explicit knowledge compared to the group who had no sleep. Performance at retesting did not show any correlation in performance with explicit knowledge; both groups displayed equivalent overnight enhancements. This study is interesting because it suggests that multiple memory systems may not be completely independent, and there could be an interaction between implicit and explicit memory systems during sleep dependent off-line learning.

Another group of researchers has also investigated the interaction between implicit and explicit memory systems during consolidation (Brown & Robertson, 2007). In this experiment sleep-dependent consolidation of a procedural motor task (the SRT task) was disrupted by the declarative learning of word-pair associations, while procedural learning disrupted consolidation of declarative material. These interactions were only observed over a period of wakefulness, not over a night of sleep, suggesting that these procedural memories were still labile during the wakeful state. This experiment, along with the one by Fischer and colleagues, demonstrates that the

procedural and declarative memory systems may not be entirely independent, but rather may interact and influence each other off-line.

1.3.2 Sleep and brain plasticity

Sleep has been proposed to be a key component in consolidation-based memory enhancement, as reviewed above. Memory formation and consolidation are dependent on brain plasticity. If sleep is indeed a crucial mediator of memory consolidation, then sleep-dependent brain plasticity is necessary. In humans, functional neuroimaging has afforded researchers the opportunity to investigate if sleep does in fact change brain activity patterns both during sleep and during performance of the task itself before and after sleep.

Based on animal studies that have shown brain activity "replaying" a task that was learned during sleep (Datta, 2000), Maquet used functional neuroimaging to investigate brain activity during learning and during sleep postlearning (Maquet, 2000). These researchers found that patterns of brain activity expressed during daytime training of a SRT task reappeared during REM stages of sleep, whereas this was not true for subjects who did not receive daytime training of the task. A subsequent study showed that the amount of learning that occurred in the original daytime practice correlated positively with the amount of reactivation during REM sleep (Peigneux et al., 2003). These results demonstrate that it was not just experiencing the task that changes

brain activity during sleep, but the process of learning itself that influences sleep-related brain plasticity.

Similar findings have been reported with a hippocampal-based task involving route learning in a virtual town (Peigneux et al., 2004). In this task initial daytime acquisition activated the hippocampus, and during posttraining sleep there was a reemergence of hippocampal activation, specifically during slow wave sleep (SWS). The amount of hippocampal reactivation during SWS was proportional to the amount of improvement on the task the next day, suggesting that sleep-related brain plasticity led to off-line memory improvement.

One can also examine brain activity while performing a task before and after a night of sleep. This technique addresses if sleep in fact restructures the neural representation of a memory. Using a SRT task, which shows marked sleep-dependent learning enhancements, neuroimaging post-sleep revealed increased activation in motor control structures, suggesting the improved sequencing of motor movements (Walker et al., 2005)? The medial prefrontal cortex and hippocampus also increased in activity while performing the SRT after a night's sleep, and these areas have been identified as supporting improved sequencing of motor movements (Poldrack & Rodriguez, 2003). In addition to areas of increased activation after sleep, some regions had decreased activity post sleep, such as in the parietal cortices, perhaps reflecting the decreased need for

conscious spatial monitoring, and the limbic forebrain, suggesting decreased emotional task burden after sleep.

Another study examined brain activity while performing a sequential finger movement task initially as well as at retest the next day, with one group of subjects having a night's sleep before retesting, and one group being sleep-deprived (Fischer et al., 2005). As expected, the group who had sleep performed better at retesting than the sleep deprived group. This improvement was correlated with decreased activation in prefrontal, premotor, and primary motor cortical areas. These studies demonstrate that sleep-dependent motor learning reorganization of memory occurs in several brain regions so that when performed again it can be executed more quickly, accurately, and more automatically.

While most of these experiments used motor-based skill tasks, Walker and colleagues have also investigated the role of sleep in a non-motor procedural learning task -- visual texture discrimination (Walker et al., 2005). In this task, after sleep there was increased activation in primary visual cortex as well as increases in other visual processing stream components that promote an improvement in stimulus form and target location identification. There was also decreased activity in the right temporal pole, a region involved in emotional visual processing. Thus, sleep appears not only to reorganize the representation of a motor skill procedural learning task but also of a

visual skill one as well. If sleep can provide the same benefit to cognitive procedural skills like probabilistic classification learning is yet unknown.

1.3.3 Amygdala and hormone modulation of memory consolidation

There is ample evidence that hormone release in response to an emotionally arousing situation affects memory consolidation. Stress hormones such as epinephrine and cortisol are released from the adrenal medulla after an emotionally arousing experience. In rats, footshock significantly enhances norepinephrine (NE) release in the amygdala (Galvez, 1996), and drugs and hormones that enhance memory consolidation potentiate NE release in the amygdala (see McGaugh, 2002). Epinephrine modulates memory consolidation by activating ß-adrenergic receptors on the vagal afferents projecting to brainstem nuclei, which in turn sends noradrenergic projections to the amygdala. The activation of ß-adrenoceptors in the basolateral amygdala (BLA) is critical for the memory-modulatory effects of corticosterone and epinephrine.

The stria terminalis (ST) is an amygdala output pathway that projects to other brain regions and is critical for modulating the effects of the amygdala on other brain regions. There are direct projections from the amygdala to the caudate via the ST (Kita & Kitai, 1990), and projections from the BLA to the nucleus accumbens via the ST mediate glucocorticoid effects on memory consolidation (Setlow, Roozendaal, & McGaugh, 2000). Lesions of the ST block the memory modulating effects of treatments to the amygdala (Liang & McGaugh, 1983), like posttraining intra-amygdala infusions of NE

(Liang, McGaugh, & Yao, 1990). ST lesions also block the memory-enhancing effects induced by a cholinergic agonist in the caudate nucleus after avoidance training (Packard, 1999). Thus the ST plays an important role in modulating hormonal effects on memory consolidation in other brain regions such as the striatum.

In addition to the ST, the BLA is especially critical for the modulatory influences on consolidation. Posttraining infusions of noradrenergic agonists into the BLA enhances memory for several types of training, such as inhibitory avoidance and water maze spatial training (Ferry & McGaugh, 1999; Hatfield & McGaugh, 1999). Lesions of the BLA (Roozendaal & McGaugh, 1996) and infusions of ß-adrenoceptors antagonists into the BLA (Quirarte, Roozendaal, & McGaugh, 1997) block the memory-modulatory effects of glucocorticoids. Infusions of glucocorticoid agonists into the BLA actually enhance memory consolidation (Roozendaal & McGaugh, 1997). Both posttraining electrical stimulation of the BLA in rats (McGaugh & Gold, 1976) and posttraining intra-amygdala infusions of drugs that affect noradrenergic and opioid receptors enhanced memory consolidation on inhibitory avoidance tasks (Gallagher et al., 1981; Liang, Juler, & McGaugh, 1986). In addition, lesions to the BLA (Cahill & McGaugh, 1991) or infusions of ß-adrenoceptor antagonists into the BLA (Liang, Juler, & McGaugh, 1986) block the memory enhancing effects of posttraining intra-amygdala epinephrine injections. Thus, the evidence presented here highlights the importance of the amygdala

(the BLA and ST in particular) in memory consolidation of multiple memory systems via hormones which are released in response to emotionally arousing situations.

1.3.4 Effects of emotion and sleep on memory consolidation

How emotion affects sleep-dependent memory consolidation is an issue that has only recently begun to be examined. Previous studies examining the effect of emotion on memory have shown that insertion of a delay between encoding and retrieval testing increases emotional enhancements on memory (Kleinsmith & Kaplan, 1963; Sharot & Phelps, 2004). These results suggest that some emotional influences on memory are slow, taking hours to days for enhancements to appear. Animal work has also shown the time-dependent nature of the amygdala modulation of memory (Packard, Cahill, & McGaugh, 1994).

One recent study in humans has directly examined the role of sleep in the consolidation of emotional declarative memory (Hu, Stylos-Allen, & Walker, 2006). Subjects in this study viewed emotional and neutral photographs and either returned after 12 hours of sleep or wake and made remember/know judgments about the photos. Selective sleep effects were found for emotionally arousing photographs, with recognition accuracy improving significantly after a night's sleep.

As reviewed in section 1.1.3.2, there is substantial support in the animal literature for the modulation of striatal-based memory by the amygdala, and most of these effects are only seen after a delay, usually 24 hours or more (Packard, Cahill, & McGaugh,

1994). However, the effect of emotion and sleep on procedural learning in humans is a research area that has remained unexplored, thus motivating the current work.

1.4 Conclusion

Both animal and human studies have demonstrated the dissociation between hippocampal and striatal-based memory systems. Modulation of these multiple memory systems can occur by activation or inactivation of other neural structures, such as the amygdala. The amygdala is in a position to modulate hippocampal and striatal learning and memory since it has direct efferent projections to both the hippocampus and striatum. In non-human animals, the amygdala has been shown to modulate both hippocampal and striatal-based memory in a time-dependent manner. Moreover, stress can bias which memory system is used when a task permits the usage of multiple systems. Neuroimaging research in humans has furthered our understanding of the influence of the amygdala on hippocampal-based learning and memory, but it remains unknown if emotional arousal is able to modulate striatal-based learning in humans. Consolidation-based stabilization and enhancement of striatal-dependent learning and memory has primarily been explored using motor-skill tasks in humans, but whether similar enhancements are evidenced in other forms of procedural learning (like cognitive skill learning) has not been well-explored. Additionally, how emotion modulates the consolidation of procedural learning is another open area of investigation.

Thus the current set of experimental studies comprising this thesis addresses three main questions: 1) does emotional arousal on a striatal-dependent procedural learning task affect performance; 2) does sleep play a role in the consolidation-based enhancement of cognitive skill learning, and is this process affected by emotional arousal; and 3) does emotion lead to engagement of the amygdala during cognitive skill learning, and is this activity associated with a bias towards a particular learning strategy.

2. Fear-relevancy and probabilistic learning

2.1 Introduction

Learning from emotional experiences is an important survival skill across species. Environmental contingencies predicting negative or positive outcomes provide key information useful for assessing the motivational value of selected actions and to assist decision-making processes in guiding future behavior. One form of contingency learning involves the gradual acquisition of cue-outcome associations guided by feedback (*procedural* or *habit learning*; Mishkin, Malamut, & Bachevalier, 1984). While much research has examined the cognitive and neural mechanisms underlying this form of learning, the influence of emotion has not been systematically addressed, as it has for other domains of memory (LaBar & Cabeza, 2006). Here we examine how individual differences in fear-relevancy modulate behavioral performance and strategy use on a probabilistic classification learning (PCL) task that involves trial-and-error learning of associations between cues and outcomes that vary in emotional salience.

In the standard version of a PCL task (the '*weather prediction'* task) (Knowlton, Squire, & Gluck, 1994), participants predict the weather in a foreign city (rain or sunshine) based on the presence of 1-3 cards (out of 4). Across training participants learn to probability match the appearance of the cue cards by choosing the outcome with the

same probability that they are reinforced. Given that individuals tend to have little insight into their performance, there has been interest in characterizing the underlying response patterns, or strategies, used to solve the task. To accomplish this objective, each participant's data was mathematically modeled across trial blocks to determine the goodness-of-fit to an 'ideal' responder following particular response patterns. Least mean square estimates indicate that participants interchangeably use at least three classes of strategies varying in optimality: 1) *no identifiable* strategy; 2) *simple* strategies involving the use of one cue to make predictions; and 3) *complex* strategies involving the use of multiple cues and knowledge of the underlying probabilistic structure (Gluck et al., 2002; Meeter et al., 2006; Lagnado et al., 2006).

Probabilistic learning of this sort is likely to be important for assessing the motivational and emotional relevance of stimulus contingencies in real-life scenarios. However, it is not known how PCL performance or strategy use is impacted by varying the salience of the outcomes. Although the weather prediction task involves hypothetical outcomes with an inherent affective valence (rain/sunshine), neuroimaging studies suggest that the standard version of this task does activate emotional processing networks (e.g., Poldrack et al., 2001; Foerde et al., 2006). To provide an experimental model of probabilistic *emotional* contingency learning, we created two versions of a PCL task in which neutral cue cards predicted either fearful or neutral outcomes. Instead of

predicting weather, participants predicted what they would encounter while walking in the woods. The outcomes were pictures of biologically-prepared phobic stimuli (snakes/spiders) and environmental control stimuli (flowers/mushrooms) commonly employed in studies of fear conditioning (e.g., Öhman & Soares, 1994). Training was extended across two consecutive days to investigate learning both initially and after a 24-hr period of consolidation, since emotional effects on memory sometimes emerge following a delay (Kleinsmith & Kaplan, 1963; Sharot & Phelps, 2004). Participants were subdivided into 'fearful' and 'control' subgroups according to self-report inventories of snake and spider phobia to assess the contribution of individual differences in fear-relevancy to task performance.

We hypothesized that individual differences in fear-relevancy would impact learning in the following ways. First, fearful participants confronted with emotional outcomes should exhibit impairments, especially early in training, due to their inability to focus resources on learning the probabilistic associations. The behavior of these participants was predicted to resemble that of individuals who are emotionally distracted while learning the standard weather prediction task (Steidl, Mohi-uddin, & Anderson, 2006). In addition to slower learning rates, we further predicted that fearful participants in the emotional condition would exhibit: (1) impaired explicit knowledge of the task parameters, (2) greater use of suboptimal learning strategies, and (3) higher

skin conductance responses (SCRs), an index of sympathetic arousal, to the cue cards. In contrast, non-fearful participants run in the emotional condition should show benefits on learning rates and/or strategy use, particularly after a period of consolidation, as predicted by studies of emotional influences on procedural learning in non-human animals (Packard, Cahill, & McGaugh, 1994). If supported, these findings would be important in revealing how learning cue-outcome associations is modulated by personal salience, with potential implications for understanding the diverse effects of emotion on memory systems in affective health and disease.

2.2 Methods

2.2.1 Participants

Participants (N = 114) were Duke University students who either received course credit for participation or were recruited through posted advertisements and reimbursed at a rate of $10/hour. All participants were screened by a self-report questionnaire for history of neurologic and psychiatric illness, substance abuse, and current psychotropic medication use. Participants were screened for depression by the Beck Depression Inventory (BDI) (Beck et al., 1961). Although no participant reported a specific phobia of snakes or spiders, individuals who scored within 2 *SD*'s of the phobic norms on questionnaires assessing attitudes towards snakes and spiders were

categorized as 'fearful' for the purposes of this study (Klorman et al., 1974). Following Aron et al. (2004), individuals who did not score above chance after the first 50 trials were not included in the data analyses ('non-learners'). The final sample (N = 78) included 22 controls in the emotional condition (9 female, M_{age} = 21.4 yrs), 25 controls in the neutral condition (15 female, M_{age} = 21.3 yrs), 15 fearful participants in the emotional condition (13 female, M_{age} = 20.1 yrs), and 16 fearful participants in the neutral condition (13 females, M_{age} = 19.8 yrs). To ensure that the fearful and control groups did not differ on other emotional characteristics, questionnaires were administered assessing emotional experience (Positive and Negative Affect Schedule; Watson, Clark, & Tellegen, 1988), affect intensity (Affect Intensity Measure; Larsen, 1984), and current stress levels (Daily Stress Inventory; Brantley & Jones, 1993), which showed no differences between groups (all F's < 1.5). The groups also did not differ in the reported amount of sleep between the two training days. The Institutional Review Board at Duke University approved the experimental protocol and human subjects procedures.

2.2.2 Stimuli

The card cue stimuli used were similar to those used previous weather prediction experiments and were acquired from the Russ Poldrack lab at UCLA (Aron et al., 2004). The outcome stimuli were taken from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1997). Unlike in the original weather

prediction task, which only presents a single 'rain' and 'sunshine' exemplar, here six exemplars of each outcome type were presented in random order to minimize emotional habituation to the outcome photographs. According to the IAPS norms, the snake and spider pictures were rated lower in valence than the flower and mushroom pictures, *M* (*SD*): 3.7 (1.9) snakes, 3.8 (1.9) spiders, 6.8 (1.7) flowers, 5.3 (1.6) mushrooms. Snakes and spiders were also rated as more arousing than the flower and mushroom pictures: 6.4 (2) snakes, 5.5 (2.2) spiders, 3.0 (2.2) flowers, 3.0 (2.3) mushrooms. Low-level visual properties, including luminance, contrast, color content, and picture size were equated across the outcome exemplars.

2.2.3 Study Design

The task design was modeled after that used by Aron et al. (2004). Between one and three (out of four) cue cards appeared on the screen at a time, comprising 14 possible cue patterns. These patterns were associated with two outcomes in a probabilistic manner. For example, one pattern had cue cards 2, 3, and 4 present, and appeared 4 times (4% of the total trials). The probability that outcome A occurred with this pattern was 75%, while the probability that outcome B occurred was 25% (see Table 1). Since outcome A occurred over 50% of the time, this outcome was considered 'correct'. Participants were randomly assigned to receive either the emotional (snake/ spider) or neutral (flower/ mushroom) outcomes. Participants completed 100 trials on

the first day of training (two runs of 50 trials each), and another 100 trials the following day.

Table 1: Relation among cues and outcomes.

Pattern	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Cue 1	0	0	0	0	0	0	0	1	1	1	1	1	1	1
Cue 2	0	0	0	1	1	1	1	0	0	0	0	1	1	1
Cue 3	0	1	1	0	0	1	1	0	0	1	1	0	0	1
Cue 4	1	0	1	0	1	0	1	0	1	0	1	0	1	0
# Times Appear	14	8	9	8	6	6	4	14	6	6	3	9	3	4
P (outcome A)	0.9	0.6	0.9	0.4	0.8	0.5	0.8	0.1	0.5	0.2	0.7	0.1	0.3	0.3
P (outcome B)	0.1	0.3	0.1	0.6	0.2	0.5	0.3	0.9	0.5	0.8	0.3	0.9	0.7	0.8

On each trial, one of the 14 card patterns appeared and remained on the screen for 4 sec, at which time the subject was prompted to respond with a left button press for outcome A and a right button press for outcome B. Participants then heard a high-frequency feedback tone (duration = 500 msec) when they predicted the correct outcome and four 100 msec bursts of white noise at 80 db when they did not predict the correct outcome (Knowlton et al., 1996; Shohamy et al., 2004; Aron et al., 2004). Unlike previous versions of the weather prediction task, the correct outcome photo was displayed in a dynamic fashion, first appearing small in the center of the screen for 300 msec and then appearing at full screen for 700 msec to create a looming effect toward the viewer. There was a 4-7 sec fixation screen inter-trial interval (Figure 1). The first 25 trials on Day 1 were pseudo-randomized such that an equal number of patterns appeared that were

'easy' (highly predictive) or 'hard' (less predictive). This procedure was conducted to reduce the number of non-learners, as indicated by pilot testing. The following 75 trials on Day 1 and all 100 trials on Day 2 were fully randomized.

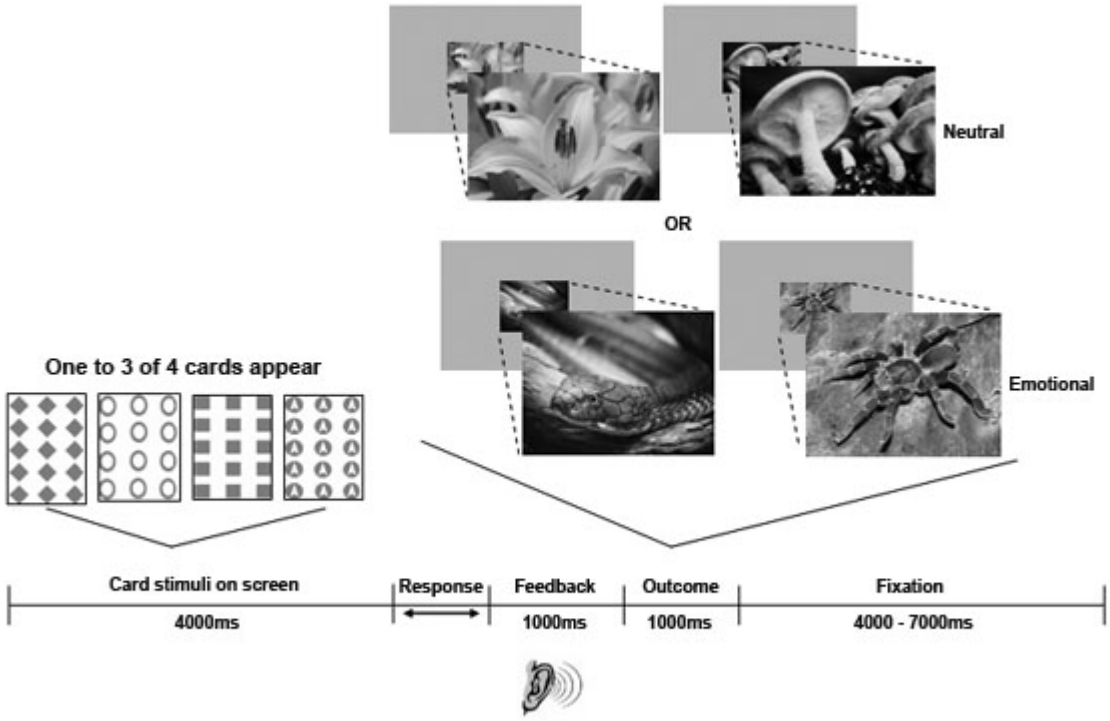

Figure 1: Trial structure of the modified weather prediction task. Participants were run either in the emotional version (snake/spider outcomes) or the neutral version (flower/mushroom outcomes). Outcomes were presented in a dynamic, looming manner.

2.2.4 Explicit Strategy Questionnaire

Explicit memory was assessed via a questionnaire concerning strategy use and cue-outcome probabilities after both Day 1 and Day 2, as in Gluck et al. (2002). The questions assessed how the participants thought they performed and what strategy they thought they were using. Participants also rated the percentage of time they thought each card predicted one of the two outcomes in the experiment.

2.2.5 Behavioral Analysis

Unless stated otherwise, behavioral and SCR data were analyzed by a mixed ANOVA and Bonferroni-corrected post-hoc tests, with Group as a between-subjects factor and Day and Run as within-subjects factors.

2.2.6 Implicit Learning Strategy Analysis

Implicit learning strategies were evaluated using mathematical models to fit each participant's data to the ideal data if a subject were reliably following a particular strategy using procedures detailed by Lagnado et al. (2006). Separate strategy analyses were conducted for each run in each group to assess changes in strategy use across the experiment. The performance of individual participants was compared to that of an ideal participant performing one of three different strategies: 1) "simple strategies" encompassing both singleton and one-cue strategies; 2) "complex strategies" including

both multi-match and multi-max strategies; or 3) "no identifiable strategy" (for details, see Lagnado et al., 2006). A maximum likelihood estimation score was computed to evaluate the likelihood that each participant's pattern of responses followed a certain strategy across consecutive 50-trial runs of the experiment. The number of subjects using each of the strategy types was subjected to a chi-square goodness of fit test to assess if the usage of the three strategies was equally distributed among participants in each group. To test if there were differences between groups in strategy usage within runs, chi-square tests for independence were calculated. Linear regression analyses were conducted to determine the relationship between strategy use and behavioral accuracy, and between strategy use and an aggregate score of snake and spider phobia.

2.2.7 Skin Conductance Responses (SCR)

SCR was recorded from the middle phalanges of the second and third digits of each participant's non-dominant hand (BIOPAC Systems, Goleta, CA). The responses were monitored at 250Hz and stored offline using AcqKnowledge Software for subsequent analysis (BIOPAC Systems, Goleta, CA). The physiologic data were time-locked to cue card onset, scored for the amplitude of the first interval response, and square-root transformed to attain normality according to conventional methods, as previously described (LaBar et al., 2004). Missing data occurred for 5 participants, and 12 participants were classified as 'nonresponders', meaning they did not show any

measurable SCRs and were thus removed from the analyses (LaBar et al., 2004). Thus, the SCR data were scored from the remaining 62 participants (16 controls in the emotional condition, 21 controls in the neutral condition, 14 fearful participants in the emotional condition, and 11 fearful participants in the neutral condition).

2.3 Results

2.3.1 Ratings

To validate the IAPS norms in our sample, all participants rated the 6 exemplars of each of the snake, spider, flower, and mushroom outcomes on 5-point valence and arousal manikin scales after completion of the study on Day 2 (1 = negative to 5 = positive; 1 = non arousing to 5 = most arousing). Overall, flowers and mushrooms were rated more positively than snakes and spiders, *M* (*SD*): 3.9 (0.5) flowers, 2.8 (0.4) mushrooms, 2.3 (0.7) snakes, 1.9 (0.8) spiders. Snakes and spiders were also rated more arousing than flowers and mushrooms: 3.1 (0.78) snakes, 3.2 (0.91) spiders, 2.3 (0.79) flowers, 1.8 (0.65) mushrooms. Correlations between the snake questionnaire scores and the snake photo ratings showed that the more fearful participants were of snakes, the higher were their arousal, $r(53) = 0.51$, $p < .0001$, and valence, $r(53) = 0.28$, $p < .04$, ratings of the snake photos. The same was true for the spider questionnaire scores and arousal $r(53) = 0.53$, $p < .0001$, and valence ratings $r(53) = 0.54$, $p < .0001$ for spider photos

2.3.2 Learning Rate

For percent optimal responses, there was a main effect of Day, $F(1, 74) = 65.82$, $p < .0001$, a main effect of Run, $F(1, 74) = 16.75$, $p < .0001$, and a Day x Run interaction $F(1, 74) = 5.72$, $p < .02$, indicating that participants showed increased learning across Days and Runs, especially on Day 1 (see Figure 2). Importantly, there was also a significant Day x Run x Group interaction $F(3, 74) = 3.1$, $p = .04$, and a trend for a main Group effect, $F(3, 74) = 2.15$, $p = .10$. Follow-up ANOVAs showed that the Day x Run interaction was only significant for the fearful subjects in the emotional condition $F(1, 14) = 9.54$, $p < .008$, who exhibited an initial deficit in learning accuracy relative to the other groups. This finding was confirmed by a correlational analysis computed between accuracy and an aggregate snake/spider phobia score, which were inversely correlated on the first run of Day 1, $r(53) = -.33$, $p < .05$. These results provide evidence that increased fearfulness towards snakes and spiders hindered the initial acquisition of card/outcome probabilities.

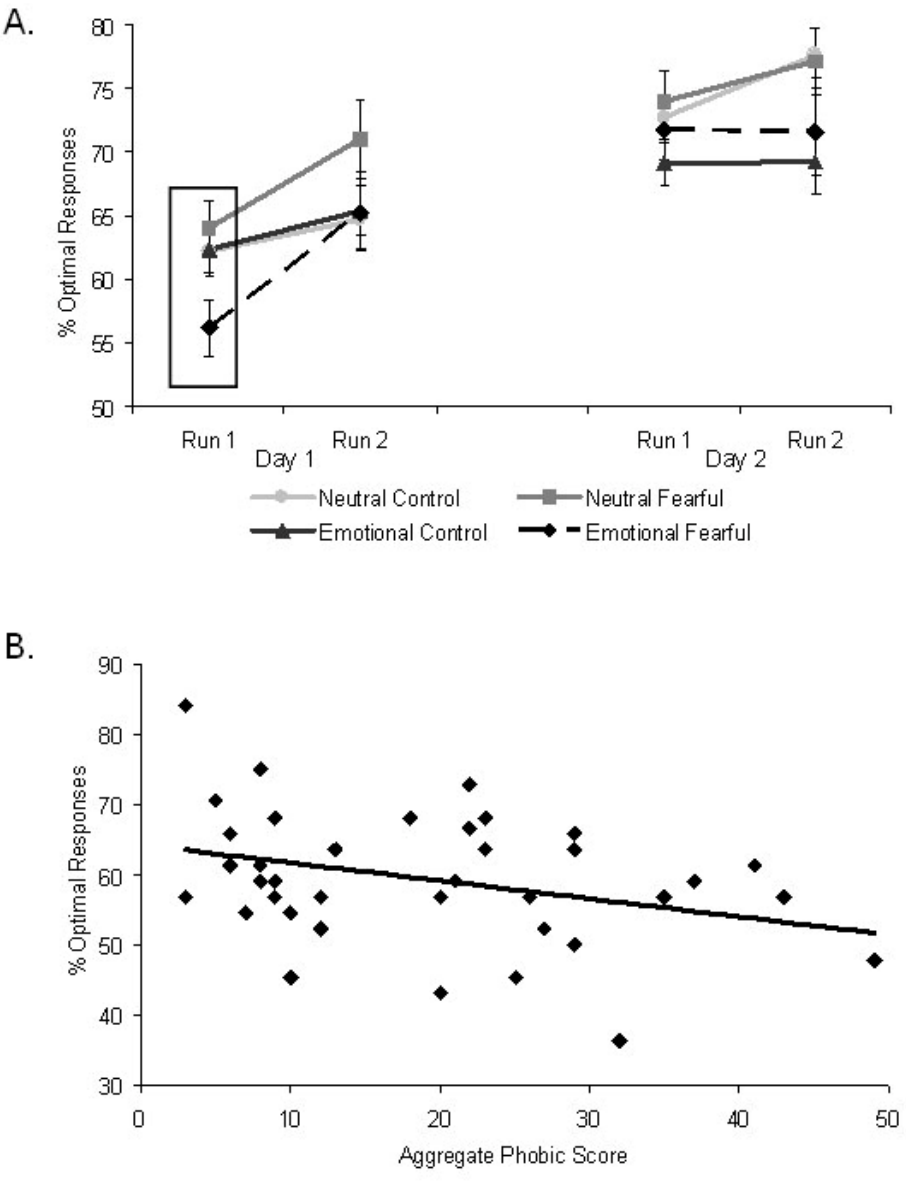

Figure 2: Learning rates over time as a function of experimental group. (A) Participants fearful of the snakes and spiders performed worse on the first run compared to the other groups. (B) Aggregate snake/spider phobia score correlates inversely with performance.

2.3.3 Implicit Learning Strategies

Although performance was equated across the groups by the end of training on Day 1, it is possible that other emotional differences emerge when task strategy is taken into consideration. Therefore, strategy use (simple, complex, nonidentifiable) was mathematically modeled, and the proportion of participants using each strategy was characterized for each group and run. Participants who were fearful of the emotional outcomes did not exhibit a strategy preference early in training (Day 1 Run 1: $\chi^2(2) = .4$, $p = .82$). Because strategy use optimality and performance accuracy were correlated overall during this initial training, $r\ (78) = .36$, $p < .001$, the increased usage of nonidentifiable strategies in these participants had adverse behavioral consequences. In contrast, all other groups used simple and complex strategies to a greater extent than nonidentifiable strategies throughout training (all $\chi^2(2) > 6$, p's $< .03$). A direct comparison of strategy use across groups revealed that control participants in the emotional condition were more likely to use complex strategies than the other groups by the end of training (Day 2, Run 2: $\chi^2(3) = 9.77$, $p < .02$). This relationship was confirmed by correlating strategy use and aggregate phobia scores for participants in the emotional condition, which showed an inverse relationship between optimal strategy use and phobia scores at the end of training, $r(78) = -.37$, $p < .03$. Thus, the presence of emotion in the outcomes had

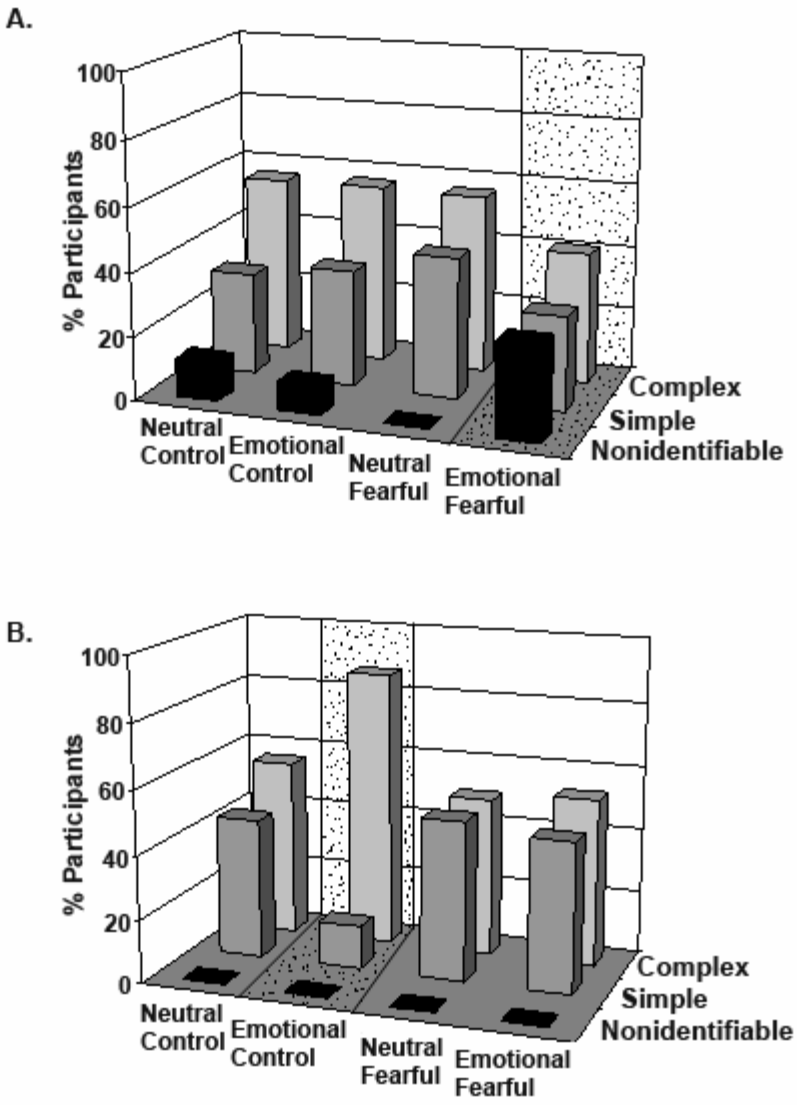

Figure 3: Implicit strategy use over time as a function of experimental group. (A) Fearful participants run on the emotional version of the task showed no strategy preference during initial training (Day 1 Run 1), whereas the other groups used simple and complex strategies than nonidentifiable ones. (B) At the end of training (Day 2 Run 2), more control participants run on the emotional version of the task used complex strategies than the other groups.

differential effects on strategy use over time as a function of individual differences in fear-relevancy (Figure 3).

2.3.4 Reaction Time (RT)

There was a main effect of Day, F (1, 74) = 35.00, $p < .0001$, a main effect of Run, F (1, 74) = 8.63, $p < .0004$, and a Day x Run interaction, F (1, 74) = 6.06, $p < .02$. Results demonstrate that as learning progressed participants responded more quickly, particularly on Day 1. There was no effect of experimental group on reaction time. It should be noted that participants were asked to withhold their response until a prompt appeared 4 sec after cue card onset, which likely minimized reaction time effects.

2.3.5 Explicit Strategy Questionnaire

Participants' free-response descriptions of how they made their predictions were coded as belonging to one or more of the following six strategies: 1) guessing; 2) using the suit of the cards; 3) using the number of cards in a series or combination of cards; 4) placement of cards on the screen; 5) matching the patterns/shapes/colors of cards with those associated with an outcome; or 6) gut/intuition. On Day 1, all groups used the suit of the cards to make their predictions more than the other strategies (all $\chi^2(5) > 20$, p's < .001), *except* the fearful subjects in the emotional condition, who had no strategy

preference. On Day 2, all groups showed an explicit preference towards using card suit over any other strategy (all $\chi^2(5) > 20$, p's $< .001$).

The four cue cards had different strengths of predicting the outcomes. Whereas some cards (diamond and arrow) were strong predictors, others (square and circle) were weak predictors. Participants' explicit estimates of card-outcome probabilities showed a main effect of card strength, F (1, 72) = 26.45, $p < .0001$, a main effect of Day, F (1, 72) = 3.47, $p = .07$, and an interaction between card strength and Day, F (1, 72) = 6.75, $p < .02$. Follow-up tests showed that strong cards were more likely to be rated as good predictors on Day 2 than Day 1, t (75) = 2.59, $p < .02$, with no difference in ratings for the weak cards. The presence of emotional outcomes did not modify awareness of card strength, demonstrating a dissociation between emotional effects on implicit versus explicit learning strategies.

2.3.6 Skin Conductance

A mixed ANOVA revealed main effects of Day, F (1, 58) = 4.92, $p < .03$, Run, F (1, 58) = 5.3, $p < .025$, Group, F (3, 58) = 3.36, $p < .025$, and a Day x Run interaction, F (1, 58) = 7.26, $p < .01$. As depicted in Figure 4, SCRs to the cue cards were lower on Day 2 relative to Day 1, reflecting a general habituation over testing sessions. However, the interaction with Run indicates a tendency for SCRs to increase over time on Day 2 relative to Day 1, perhaps due to increased insight (see above) or, alternatively, to emotions concerning

the anticipation of task termination. Bonferroni-corrected post-hoc tests showed that the Group difference was driven by enhanced SCRs for fearful participants in the emotional condition relative to both controls (p = .053) and fearful participants (p = .06) in the neutral condition. Nonfearful participants in the emotional condition exhibited an intermediate level of arousal.

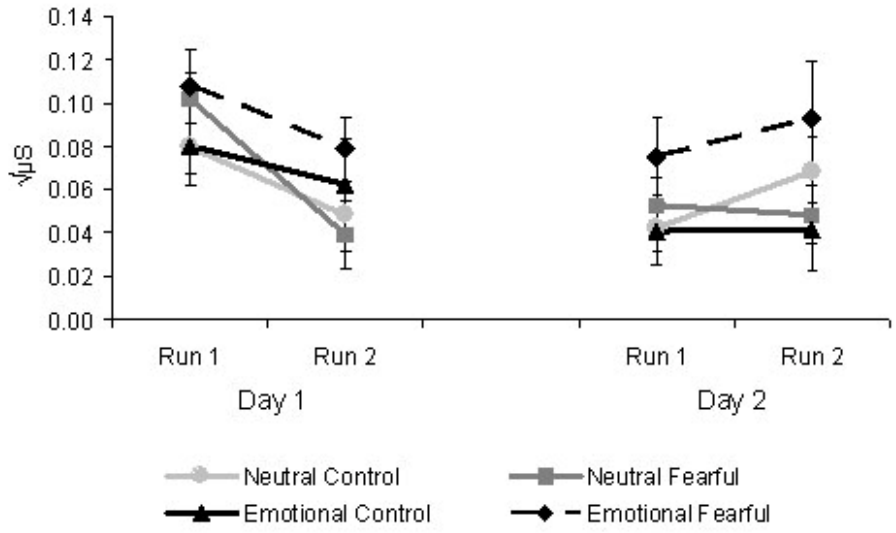

Figure 4: Skin conductance response (SCR) to cue card presentation over time as a function of experimental group. SCRs were higher overall for fearful participants run on the emotional version of the task compared to participants run on the neutral version of the task. μs = microsiemens.

2.4 Discussion

The present study revealed novel influences of emotion on feedback-based learning determined by the fear-relevancy of outcomes paired with predictive cues. Across two days of training, participants learned to associate cue cards with either emotional (snake/spider) or neutral (flower/mushroom) outcomes in a probabilistic manner. Interestingly, the same emotional manipulation yielded both impaired and enhanced learning, depending on individual differences in attitudes towards the outcome stimuli. Individuals fearful of the emotional outcomes had higher SCRs to the cue cards and exhibited reduced insight, suboptimal strategy use, and retardation in initial learning relative to the other groups. Individuals who were *not* fearful of the emotional outcomes used more complex (optimal) strategies after a 24-hr period of memory consolidation relative to the other groups, reflecting greater implicit knowledge of the task structure. These results show that (1) task-relevant emotional arousal has diverse effects on feedback-based learning across individuals, (2) strategy use is important to consider because emotional effects do not always impact indices of performance or explicit knowledge, and (3) emotional effects are time-variant, occurring either during initial training or following a period of memory consolidation. Altogether, these findings advance an understanding of how individual differences in emotion impact memory systems that govern the learning of probabilistic stimulus contingencies.

Because salient life events are rarely deterministic, the results from this PCL task are likely to generalize to real-world situations in which complex information about regularities in the environment is extracted to guide behavior.

Accumulating evidence from a variety of disciplines has supported the idea that emotional arousal has beneficial influences on explicit forms of learning and memory (McGaugh, 2004; LaBar & Cabeza, 2006). However, the findings in the present study implicate impairing effects of emotional arousal on probabilistic contingency learning, with self-reported level of fearfulness towards the emotional outcome categories negatively correlating with performance on the first 50 trials. Mathematical modeling revealed that fearful participants confronted by emotional outcomes were the only group who had no strategy preference early in training, being equally likely to use complex, simple, or nonidentifiable strategies. On Day 1, these individuals were also less likely than the other groups to attend to the suit of the cards explicitly, and had greater SCRs to the cue cards throughout training. Because these behavioral and psychophysiological patterns were specific to fearful participants run on the *emotional* version of the task, they are not indicative of trait differences in general learning abilities.

The initial learning impairment in fearful individuals could be due to a variety of converging factors. For instance, fearful individuals could be particularly susceptible to

the distracting influence of highly fear-relevant photographs that diverts processing resources away from the primary task, leading to cognitive overload (see Anderson, 2005). In support of this idea, Steidl and colleagues (Steidl et al., 2006) showed that task-irrelevant emotional distraction impaired initial learning on the standard weather prediction task. Emotional distraction is commonly reported on variety of attention-demanding paradigms (e.g., Dolcos & McCarthy, 2006; Wang et al., 2006) and may play an important role in PCL tasks. Alternatively, high emotional arousal may impair the binding of objects and their contexts in working memory (Mather, 2006), which would retard learning the probabilistic associations between cues and emotional outcomes. A failure of source binding would be more specific than that of general distraction, but performance would be affected similarly. Finally, studies of decision-making have suggested that under conditions of high arousal, people are often insensitive to probability estimates as the mere *possibility* of an emotional outcome is weighted more heavily (Rottenstreich & Hsee, 2001; Sunstein, 2003; Slovic & Peters, 2006). Thus, people may be more likely to use heuristics or to make inexact probability estimates when confronted with immediate fear-relevant outcomes. It is noteworthy that, unlike the other experimental groups, the fear-relevant group run in the emotional condition showed no bias towards using optimal strategies early in training. Future studies are

warranted to clarify whether these or other mechanisms underlie the observed learning impairments.

In contrast, nonfearful individuals run in the emotional condition showed greater proportional use of complex strategies relative to the other groups at the end of training on Day 2. For the purpose of the present study, complex strategy use was defined to include both *multi-match* strategies, in which participants distribute their predictions similarly to the learned probabilities, and *multi-max* strategies, in which participants choose the most probable outcome given the cue card pattern. The bias towards using more optimal strategies indicates greater implicit knowledge of the complex probability structure inherent to the task. Interestingly, this effect was dissociated from both performance measures and explicit knowledge of card predictability, which did not differ across groups by the end of training. A preliminary study (Thomas & LaBar, 2007) suggests that the emotional biasing of implicit strategy use does not occur for participants who receive 200 massed training trials (without an intervening 24-hr retention interval between testing sessions). Thus, a period of memory consolidation appears to be necessary to observe this emotional benefit, consistent with animal models of emotional influences on procedural learning (Packard, Cahill, & McGaugh, 1994). These results implicate a specific influence of emotion on implicit knowledge of probabilistic associations and highlight the importance of considering

strategy use when interpreting emotional effects on PCL tasks, since they are not always manifested in accuracy measures.

In sum, the present study demonstrates separable influences of emotion on feedback-based learning according to individual differences in fear-relevancy. Most experimental studies of emotional memory have emphasized the beneficial effects of emotion on encoding and consolidation processes. Here we report evidence for both implicit strategy benefits following extended training in nonfearful participants exposed to emotional outcomes, and impairments in learning rates, implicit strategy use and self-insight during initial training in fearful participants exposed to the same outcomes. These findings have implications for understanding how individual differences in emotional salience can lead to diverse and sometimes opposing effects on learning and memory systems. Future work can take advantage of the brain-behavioral correlations inherent in neuroimaging research to reveal the dynamics of interacting neural systems that mediate these effects and to characterize their dysregulation in anxiety disorders.

3. Consolidation of cognitive skill learning

3.1 Introduction

After an initial learning experience (acquisition), the representation of that experience in the brain undergoes a multi-stage process called *memory consolidation*. Memory consolidation transforms an experience from a labile short-term trace into a stable long-term trace (see Izquierdo & Medina, 1997; Izquierdo & McGaugh, 2000; Bliss & Collingridge, 1993). Initially, memory consolidation takes place at a local cellular level over a period of minutes to hours, with molecular changes underlying consolidation being required for only a short time (see Eichenbaum, 1996; Brown & Silva, 2004). A second time window then emerges during sleep, at which time memories are re-activated and re-consolidated in the relevant neural circuits that encoded the initial information (Pavlides & Winson, 1989; Wilson & McNaughton, 1994; Peigneux et al., 2004). Finally, over a period of months to years, systems-based consolidation is thought to take place in which representations of events are transferred to permanent storage sites in the cortex (Anagnostaras, Maren, & Fanselow, 1999). Graded retrograde amnesia in humans, defined as a greater memory deficit for information acquired recently versus remotely, can occur for events that happened years prior (Brown, 2002).

Memory consolidation was originally thought to solely involve the stabilization of a memory trace over time. More recently the definition of consolidation has been expanded to include the enhancement of performance in the absence of further practice. Based on studies of motor skill learning in humans, Walker and colleagues have argued that *stabilization* of a memory occurs over periods of several hours of wakefulness, whereas enhancement in performance is usually only seen after a period of sleep (Walker, 2005; Walker & Stickgold, 2006). Most of the research on performance effects of memory consolidation has involved motor-based procedural learning tasks such as the serial reaction time (SRT) task or motor sequence learning tasks that rely on processing taking place in frontostriatal circuits (Walker et al., 2005; Walker et al., 2002; Walker et al., 2003). For instance, several experiments by Walker and colleagues have demonstrated that improvements in performance without further practice in finger tapping tasks are dependent on sleep, and not the mere passage of time (Walker et al., 2002, 2003). In this finger tapping task, subjects pressed four keys on a keyboard repeating a five-element sequence shown as numbers on a computer screen. Subjects were trained either in the morning or evening and were retested 12 hours later. Subjects trained in the morning showed no performance increase after 12 hours of wakefulness, but did show a 20% improvement after a night's sleep. The group that was trained at night displayed dramatic improvements after a night's sleep, but had no additional

gains in performance after another 12 waking hours. Maintenance of performance levels in both speed and accuracy were observed following 3-12 waking hours, showing evidence for stabilization of memories but without the improvement in performance that followed a night's sleep. Such sleep-dependent improvements in performance are also observed in other motor procedural tasks such as the rotor pursuit task (Smith & MacNeill, 1994).

Recent research, however, has begun to challenge a clear-cut differentiation between wake-based stabilization and sleep-based enhancement of procedural learning. For instance, Robertson and colleagues (2004) found that declarative awareness influenced sleep- vs. time-dependent improvements in a SRT task. In this experiment, subjects were either explicitly informed about the presence of a repeating sequence or remained naïve to the presence of the sequence. In this task an asterisk appeared on the screen at particular locations and subjects had to press a key corresponding to the location. Increased RT during random compared to repeated sequenced blocks was taken as evidence of learning. Performance improvements in the explicitly informed group were *only* seen after sleep, but performance improvements in uninformed subjects were observed during both wake and sleep periods. This finding suggests that implicit learning about the sequence may benefit from the mere passage of time but explicit knowledge does not.

In another finger tapping experiment, improvements were found within the first day of training (training every 4 hours for 12 hours), although overnight improvements compared to the final performance from the first day were more dramatic (Walker et al., 2003). Although these authors downplayed the improvements on the first day, recent evidence has emerged to support within-day performance increases (Song et al., 2007a). In this study, a variant of the SRT task was created with *probabilistic* sequences to minimize the contributions of explicit knowledge to task performance (Robertson & Cohen, 2006; Song et al., 2007b). General skill versus sequence-specific learning was also dissociated, with sequence-specific learning defined as decreased RT and increased accuracy on sequenced triplets that occurred with high versus low frequency, and general skill being quantified by average RT and accuracy over all trials. Subjects in this study were either informed of the presence of a sequence (informed group) or remained naïve to existence of a sequence (incidental group). While awareness of the sequence affected RT during cued blocks, it did not affect a probe trial in which there was no cue to either group of the presence of a sequence. Daytime enhancements were observed for overall RT measures, but no sleep-dependent consolidation was apparent as measured by general skill or sequence-specific learning. Interestingly, enhancement in overall speed occurred only if the off-line period was during the day, and not with sleep. Song and colleagues argue that in finger-tapping tasks especially, and to a lesser extent in SRT

tasks, learning does not occur on a purely implicit level. Thus, there is an emerging literature that challenges whether procedural learning improvements are dependent on sleep when performance is not confounded by explicit knowledge.

The beneficial effects of emotion on learning and memory also tend to strengthen when a retention period intervenes between encoding and retrieval. The effect of emotion on explicit memory in particular has been extensively researched. An early seminal study showed that emotional benefits on explicit memory only occurred after the passage of time (Kleinsmith & Kaplan, 1963). In this experiment, high and low arousing words were paired with digits, and subjects were asked to recall these digits immediately or at several time points following encoding, ranging from minutes to days. Immediately after learning, subjects recalled more digits paired with low-arousing than high-arousing words. However, with retention intervals of 20 min to one week, there was an increase in the number of high-arousing paired associates remembered and a concomitant decrease in the number of neutral paired associates remembered. Other studies have replicated and extended these results to indicate a critical role of emotional arousal rather than valence (Baddeley, 1982; Levonian, 1966; Walker & Tarte, 1963; Sharot & Phelps, 2004; LaBar & Phelps, 1998), consistent with predictions based on animal models of emotional memory (McGaugh, 2004).

Sleep-specific emotional enhancements of declarative memory have been demonstrated in humans. One study examined memory for arousing and neutral pictures 12 hours after an initial exposure session, one group having sleep and one remaining awake (Hu, Stylos-Allan, & Walker, 2006). Recognition memory was assessed with a "remember," "know", or "new" task. Selective sleep enhancements were seen for recognition accuracy for "know" judgments of arousing pictures, and there was also an overnight increase in memory bias for "remember" judgments, with subjects being more conservative in their "remember" assertions after sleep. Another study examined recall of neutral and emotional texts after a night of sleep (Wager, Gais, & Born, 2001). In this experiment emotional memory enhancements were correlated with late-night REM sleep, suggesting the consolidation of emotional versus neutral material may depend on specific sleep stages.

The influence of emotion on consolidation of *procedural* learning has only recently been investigated. Steidl and colleagues (2006) presented subjects with either task-irrelevant emotional or neutral photographs during the weather prediction task. While emotional interference adversely affected learning initially, there was an additional long-term benefit on the consolidation of learning that emerged 2-3 months (but not one week) after training. In contrast, arousal did enhance recognition memory for the picture contexts in which the task was performed more immediately. This

dissociation implicates a longer-term effect of emotion on memory consolidation for procedural learning than that shown for declarative memory, perhaps reflecting systems-based consolidation. Emotional effects on within-day memory stabilization processes were not examined.

In Chapter 2, we found that nonfearful participants run on the emotional version of the modified weather prediction task used more complex task strategies with further training 24 hours after encoding. Although there were no performance differences between groups, one interpretation of this result is that these participants benefited from a night's sleep relative to other groups in consolidating their memories for the probabilistic task structure, which led to a greater incorporation of multiple card features when making responses on the task the following day. However, as recently reported by Song et al. (2007) and discussed above, it is not clear whether *probabilistic* skill learning tasks also undergo wakeful periods of memory stabilization and further performance enhancements during a night of sleep, especially when explicit knowledge is taken into consideration. Furthermore, the weather prediction task is less motor-based than other procedural learning tasks studied to date with regard to benefits following periods of wake- and sleep-dependent off-line memory consolidation.

Thus the motivation of the current experiment was two-fold: 1) to examine the influence of off-line time-dependent and sleep-dependent changes in performance of a

feedback-based cognitive skill learning task; and 2) to investigate the effects of negative emotion on these processes. The classic weather prediction paradigm (Knowlton et al., 1994) was modified as described in Chapter 2 to be either neutral or emotional by having the cue card patterns predict either fearful (snake/spider) or neutral (flower/mushroom) outcomes. To examine the time course of memory stabilization and consolidation (as defined by performance maintenance and enhancement, respectively), the retention interval was varied between successive testing sessions. For each emotional outcome condition, one group completed all 200 trials in one sitting (massed training); a second group completed 100 trials in the morning and 100 trials 6 hours later (spaced training, within-day); and a final group completed 100 trials on one day and another 100 trials 24 hours later (spaced training, sleep-dependent). This yielded a total of 6 experimental groups: 2 Outcome Emotions (fearful, neutral) X 3 Retention Intervals (0 hr, 6 hr, 24 hr).

Two dependent measures of consolidation were extracted from the data. First, a measure of *retention* was determined by comparing learning during the time periods flanking the retention interval (Session 2 Run 1 minus Session 1 Run 2). This measure is similar to that used by Song et al. (2007) and provides an assessment of the influence of retention interval on performance without much additional practice, as inherent in the expanded definition of consolidation provided earlier. Second, a measure of *savings (re-learning)* was extracted by comparing learning rates following the retention interval

across groups (Session 2 Run 2 minus Session 2 Run 1). This measure is relied upon by Walker and colleagues (2002, 2003) in their assessment of the influence of sleep and wakeful periods on motor-based procedural learning.

Since the present task is probabilistic in nature, it more closely resembles the probabilistic SRT task of Song et al. (2007a, b) than the motor-based button press tasks used by Walker and colleagues. Therefore we hypothesized that we would see stabilization in both the 6 hr and 24 hr groups, with no further increases in retention or savings with a night's sleep. Based on the animal work reviewed in Chapter 1, enhanced performance on procedural learning tasks with emotional arousal occurs after a 24-hour period including sleep (see McGaugh 2004 for review). However, as reported in Chapter 2, we saw no emotional benefits in performance indices after a 24-hr retention interval, although there were effects on implicit strategy use. Therefore we hypothesized that we would see an increase in retention and/or savings of complex strategy use in the emotional condition for subjects with the longest retention interval (including sleep) between training periods. Because explicit knowledge can influence consolidation of skill learning (Robertson et al., 2004), assessments of knowledge of the relevant feature dimensions and card predictability were also obtained as in Chapter 2. It was predicted that subjects would gain some explicit knowledge about the predictability of the cue cards, but that, as in Chapter 2, this would not differ between emotional groups. We

expected explicit knowledge of the cue-outcome probabilities to increase with learning and with longer retention intervals, since declarative knowledge has been shown to be consolidated over a night's sleep in humans, as discussed above.

Finally, we note that our main interest with respect to emotion was in understanding mechanisms underlying enhancements in learning in nonfearful participants rather than the initial decrements in performance in fearful participants described in Chapter 2. Therefore, individuals were selected for the present study that were not highly fearful of the emotional outcomes. Furthermore, because only the fearful participants in Chapter 2 exhibited higher skin conductance responses, this measure is not examined here.

3.2 Methods

3.2.1 Subjects

Participants (N = 170) were Duke University students who either received course credit or were recruited through posted advertisements and reimbursed at a rate of $10/hour. All participants were screened by a self-report questionnaire for history of neurologic and psychiatric illness, substance abuse, current psychotropic medication use, and for depression by the Beck Depression Inventory (Beck et al., 1961). Although no participant reported a specific phobia of snakes or spiders, individuals who scored

within 2 *SD*'s of the phobic norms on questionnaires assessing attitudes towards snakes and spiders were categorized as 'fearful' for the purposes of this study and were not included in our analysis (Klorman et al., 1974). Following Aron et al. (2004), individuals who did not score above chance after the first 50 trials were not included in the data analyses ('non-learners'). This left a total of 31 subjects in the 0 hr neutral group (M_{age} 22.35 years, 17 female), 26 subjects in the 6 hr neutral group (M_{age} 21.54 years, 15 female), 25 subjects in the 24 hr neutral group (M_{age} 21.32 years, 15 female), 22 subjects in the 0 hr emotional group (M_{age} 19.32 years, 14 female), 19 subjects in the 6 hr emotional group (M_{age} 19.94 years, 11 female), and 22 subjects in the 24 hr emotional group (M_{age} 21.36 years, 9 female). Participants in the 24 hr groups are the same as those reported in Chapter 2. To ensure that the groups did not differ on other emotional characteristics, questionnaires were administered assessing emotional experience (Positive and Negative Affect Schedule; Watson, Clark, & Tellegen, 1988), affect intensity (Affect Intensity Measure; Larsen, 1984), and current stress levels (Daily Stress Inventory; Brantley & Jones, 1993), which showed no differences between groups (all F's < 1.5). The Institutional Review Board at Duke University approved the experimental protocol and human subjects procedures.

3.2.1 Stimuli

The card cue and outcome stimuli are the same as described in Chapter 2.

3.2.2 Study Design

The task and trial designs were modeled after that used by Aron et al. (2004) and are the same as in Chapter 2. Participants were randomly assigned to either the emotional or the neutral group. These subjects were then randomly assigned to be in the 0 hr, 6 hr, or 24 hr retention interval condition. Subjects in the 0 hr condition had a 5-minute break between consecutive 100-trial training sessions.

3.2.3 Strategy Questionnaire

Explicit memory was assessed with a questionnaire concerning strategy use and cue card/probability associations, as in Gluck et al. (2002) at the end of Session 2 for subjects in the 0hr condition, and at the end of both Session 1 and Session 2 in the 6hr and 24hr condition. . The questions assessed what strategy they thought they were using and their ratings of how predictive each cue card was of the outcomes, as described in Chapter 2.

3.2.5 Implicit Learning Strategy Analysis

Implicit learning strategies were evaluated using mathematical models to fit each subject's data to the ideal data if a subject were reliably following a particular strategy using procedures detailed by Lagnado et al. (2006) and described in Chapter 2. In each of the six conditions the number of subjects using each of the strategy types ('simple',

'complex', 'nonidentifiable') was calculated based on goodness of fit models to an ideal responder following each strategy type across trial runs. Chi-square tests determined differences in proportional strategy use across groups as a function of the same *retention* and *savings* indices described in the Introduction.

3.3 Results

3.3.1 Ratings

All participants rated the 6 exemplars of snakes, spiders, flowers, and mushrooms on a 5-point manikin scale for valence and arousal after completion of the study (1 negative to 5 positive; 1 non arousing to 5 most arousing). Overall, flowers and mushrooms were rated more positively than snakes and spiders, t (140) = 17.13, p < .0001. Snakes and spiders were rated as more arousing than flowers and mushrooms, t (140) = 15.06, p < .0001, confirming the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1997) norms.

3.3.2 Reaction Time (RT)

First we sought to determine whether RT differed across groups during Session 1 (prior to the retention interval manipulation). An ANOVA with Run as the within-subjects factor and Retention Interval and Emotion as between-subjects factors revealed a main effect of Run, F (1, 139) = 19.03, p < .0001, indicating decreased RT on Run 2. Then,

to examine our consolidation indices, separate ANOVAs were conducted with Retention Interval and Emotion as between-subjects factors on our *savings* and *retention* scores. The *retention* measure revealed a main effect of Retention Interval, F (2, 139) = 3.21, $p < .05$. Bonferroni-corrected post-hoc tests indicated that the 0 hr subjects exhibited less of a decrease in RT from the end of Session 1 to the start of Session 2 than the 24 hr subjects, $p = .067$.

3.3.3 Learning Rate

During initial training (Session 1), an ANOVA with Run as the within-subjects factor and Retention Interval and Emotion as between-subjects factors revealed a main effect of Run, $F(1, 139) = 19.03$, $p < .0001$, with increased performance overall on Run 2. An ANOVA on *retention* scores found no effects of Retention Interval or Emotion, all $Fs < 1.1$. An ANOVA on *savings* scores also found no effects of Retention Interval or Emotion, all $Fs < 1$.

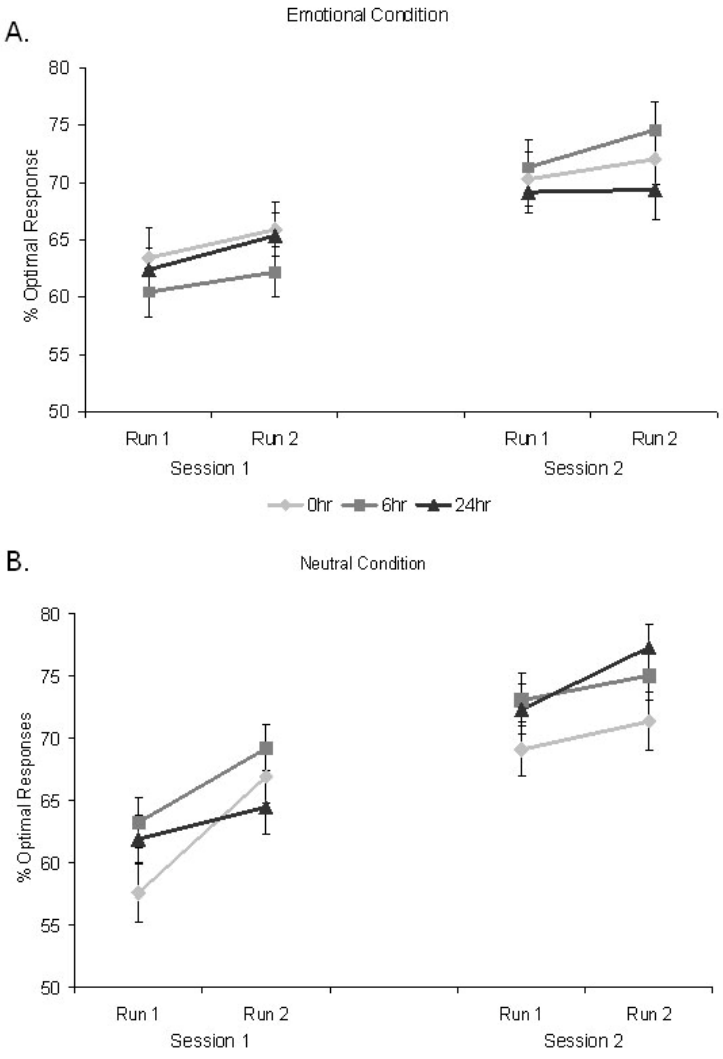

Figure 5: Performance by emotional and neutral groups at all retention intervals. There were no behavioral differences in learning.

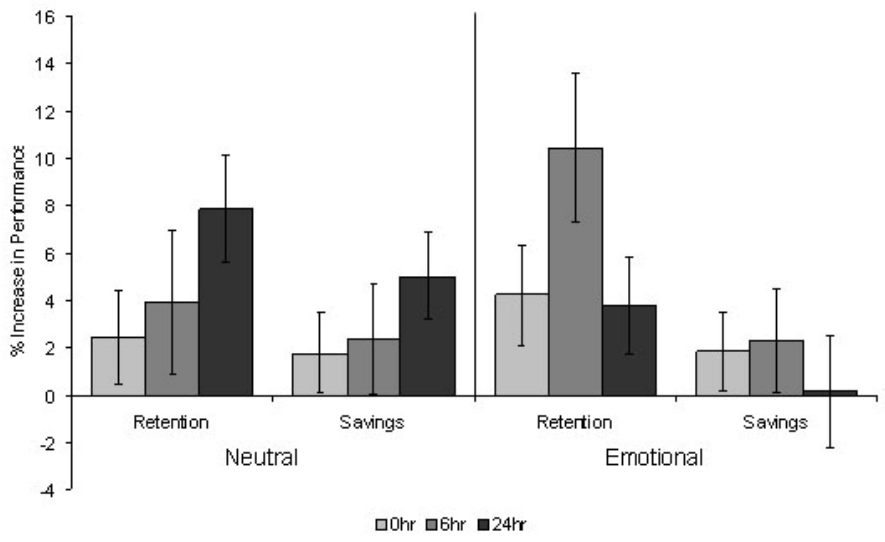

Figure 6: Retention and Savings for Neutral and Emotional conditions at all retention intervals. None of the differences were significant.

3.3.4 Implicit Learning Strategy

For each of the six subject groups, strategy use for each run was analyzed using chi-square goodness-of-fit tests to assess if the distribution of subjects using each of three strategy types was equal. All χ^2 values were significant in all runs in all groups (all $\chi^2(2) > 6.2$, p's $< .045$) except for subjects in Session 1 of the Neutral task version, where χ^2 values for the 0 hr and 6 hr groups trended towards significance, $\chi^2(2) < 6$, p's $< .08$. These results indicate that all participants generally used "simple" and "complex" strategies more than "nonidentifiable" ones.

To determine the impact of retention interval on consolidation of strategy use, we subjected the analyses to the same *retention* and *savings* difference scores. These analyses showed a significant *savings* in complex strategy use in the 24 hr Emotional group only, $\chi^2(2) = 7.93$, $p < .0005$. No other effects were significant, all other $\chi^2(2) < .7$, p's $> .4$.

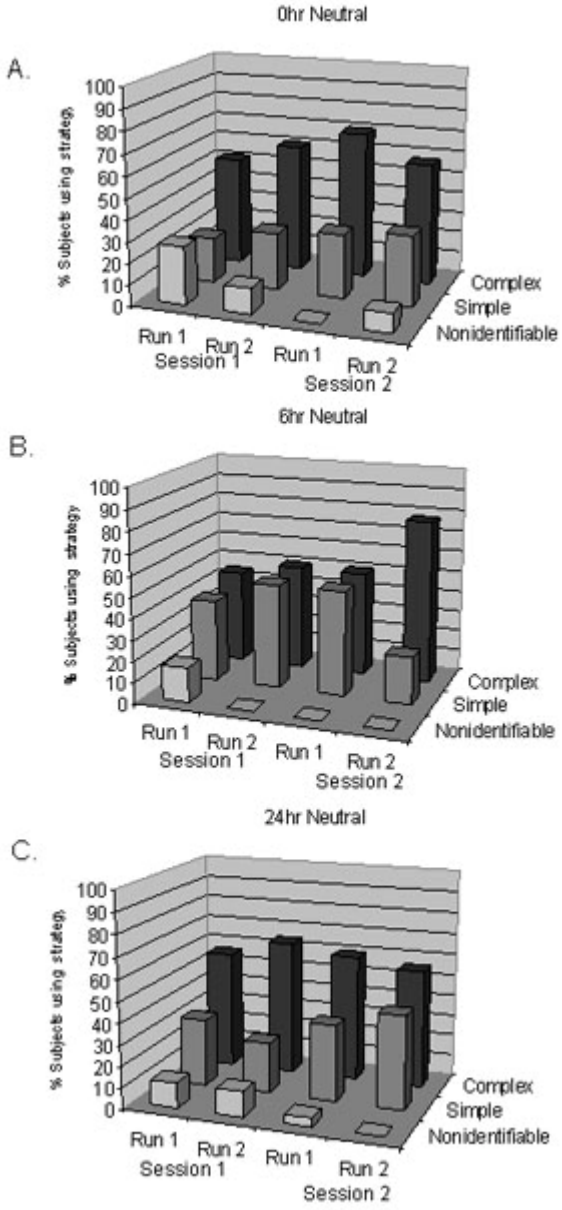

Figure 7: Implicit strategy use in the neutral condition: (A) 0hr (B) 6hr (C) 24hr

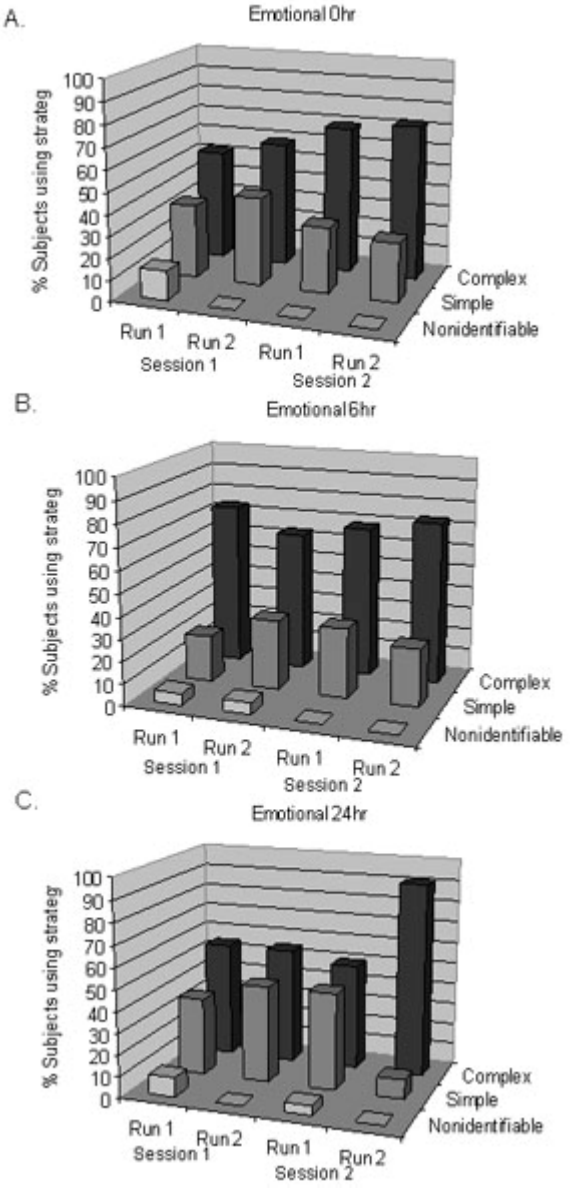

Figure 8: Implicit strategy use in the emotional condition: (A) 0hr (B) 6hr (C) 24hr

3.3.5 Correlation of Implicit Strategy Use with Performance

There was a significant correlation between strategy use and performance in all four runs, with higher performance being correlated with more complex strategy use: Run 1, r (145) = .5, $p < .0001$; Run 2, r (145) = .28, $p < .001$; Run 3, r (145) = .18, $p < .04$; Run 4, r (145) = .24, $p < .003$.

3.3.6 Explicit Strategy Questionnaire

As in Chapter 2, participants' free-response descriptions of which strategy they thought they used were coded as belonging to one or more of the following six strategies: 1) guessing; 2) using the suit; 3) the number of cards in a series or combination of cards; 4) placement of cards on the screen; 5) matching the patterns/shapes/colors of cards with those associated with a snake/spider/flower/mushroom; or 6) gut/intuition. Chi-square goodness of fit tests were run to assess if there was an equal distribution of people reporting using each type of strategy for all groups. Across all groups, χ^2 values were significant, $\chi^2(5) > 24$, p's < .0002, signifying an unequal distribution of reported strategy use. All groups used the suit of the cue cards to make their predictions more than any of the other 5 strategies.

The four cue cards had different strengths of predicting the outcomes. Strong cards (diamond and arrow) were strong predictors of the outcomes, whereas weak cards (square and circle) were weak predictors. At the end of learning, subjects rated the

strong cards as more predictive of the outcomes than weak cards, t (144) = 4.43, $p < .0001$, with no differences as a function of Retention Interval or Emotion, Fs (1, 88) < 1.5, p's > .3. There was no difference between subjects' ratings of cue card predictability from the end of Session 1 to the end of Session 2 for subjects in the 6 hr and 24 hr conditions (explicit knowledge was only tested once at the end of training for subjects in the 0 hr condition).

3.4 Discussion

The effect of retention interval and emotional outcomes on feedback-based cognitive skill learning was investigated using a modified PCL task. Indices of consolidation based on both *retention* of information over a delay period (without much additional practice) and *savings* of learning following a delay period were investigated using dependent variables of accuracy, reaction time, implicit strategy use, and explicit knowledge of card predictability. There were no significant effects of retention interval (0 hr, 6 hr, or 24 hr) on the retention or savings measures of learning, although subjects in the 24 hr conditions tended to show relatively faster RT following the delay.

The lack of increased performance in the 6 hr and 24 hr retention conditions indicates a stabilization of learning -- while performance was not significantly improved when returning after 6 or 24 hours, it remained at a similar level as it was at the end of learning in the first session, conforming to Walker's (2005) definition of memory

stabilization, and consistent with our experimental hypotheses. These results extend the recent findings of Song et al. (2007a, b) from the domain of probabilistic motor skill learning to the domain of probabilistic cognitive skill learning. Both of these studies stand in contrast to the Walker et al. (2002, 2003) data that employed deterministic motor sequence learning tasks. The probabilistic nature of the tasks reduces the potentially confounding influence of explicit knowledge to task performance. In the present study, subjects did display some explicit knowledge of the cues' predictive value; however, this explicit knowledge was not affected by the main variables of interest (emotion, retention interval). Thus, sleep-based performance enhancements in skill learning may reflect the consolidation of this explicit knowledge and its contribution to task performance.

The investigation of how emotion influences consolidation of cognitive skill learning was also investigated through an experimental manipulation of the task outcomes. For participants run in the emotional condition, results indicated a stabilization of learning at both 6 hours and 24 hours after initial training, but no further enhancements following a night of sleep. This finding was not due to ceiling effects after initial training, since all groups had similar accuracy levels prior to the retention interval manipulation.

However, there was evidence for a *savings* in complex strategy use that was selective for subjects run in the emotional condition with a 24 hr retention interval.

Furthermore, as reported in Chapter 2, the 24 hr emotion group used complex strategies to a greater extent than the 24 hr neutral group by the end of training. This combination of results suggests a greater reliance on striatal-based procedural memory usage during a PCL task for participants who experience emotional outcomes and a night of sleep. Therefore, while 24 hours may not be enough time to observe consolidation-based enhancements on emotional learning as measured by percent correct, it could be enough time to see consolidation-based enhancements on strategy use in emotional situations.

In this way, the present results go beyond those by Steidl and colleagues (2006) -- who reported no benefit of task-irrelevant arousal on PCL performance until a retention interval of 3 months -- by showing that strategy use is impacted over a shorter time scale. In the future it would be beneficial to have groups of subjects come back over the course of days to weeks to months to track the extended time course of strategy- vs. performance-based consolidation enhancements. Furthermore, functional neuroimaging studies should help elucidate whether emotion-induced changes in complex strategy use alters activity in striatal-based memory systems over extended training in a PCL task, a topic which is taken up in the following chapter.

4. Neuroimaging of emotional procedural learning.

4.1 Introduction

Because of its ubiquity and importance, dedicated neural systems have evolved to regulate interactions between emotional information processing and mechanisms of learning. In humans, emotional learning and memory can occur either at an implicit (nonconscious or nondeclarative) level or at an explicit (conscious or declarative) level. Much cognitive neuroscience research has elucidated emotional influences on explicit memory, focusing on the functional relationship between the amygdala and the medial temporal lobe memory system (Phelps, 2004; Dolcos et al., 2004; Greenberg et al., 2005). However, very little work has examined emotional influences on implicit memory (but see Thomas & LaBar, 2005). Implicit memory is mediated by multiple brain regions according to the type of memory process involved. For example, repetition priming is dependent on activity decrements in unimodal sensory regions of neocortex (Schacter & Buckner, 1998; but see Dobbins et al., 2004), whereas procedural (habit) learning is dependent on the striatum (Packard & Teather, 1998; Knowlton, Squire, & Gluck, 1994).

Procedural learning is one form of implicit memory that involves the learning of repeated stimulus-response associations. This type of learning can emphasize either

cognitive or motor skill learning. In procedural learning information is acquired gradually across many trials, a characteristic that has been identified across species (Mishkin et al., 1984). In rodents, basal ganglia damage impairs learning of stimulus-response associations (Packard, 1999) and the gradual learning of cue-outcome relations (Packard et al., 1989). In Parkinson's disease, degeneration of dopamine-containing neurons in the substantia nigra disrupts basal ganglia function (Robertson & Robertson, 1987). Parkinson's patients are impaired at feedback-based procedural learning tasks whereas amnesic patients are not, demonstrating dissociable roles of the hippocampus and striatum in memory (Knowlton, Mangles, & Squire, 1996; Shohamy et al., 2004; but see Hopkins et al., 2004).

Given that the amygdala has connections to the striatum via a gradient of ventral-to-dorsal fiber projections (Pitkanen et al., 2000), it is in an anatomically favorable position to exert emotional influences on the striatal memory system, and indeed the amygdala has been shown to modulate procedural learning in navigational and motor tasks in rodents (Packard et al., 1994; Packard & Teather, 1997). Despite the support for amygdalar modulation of striatal-based memory in animals, such a role for the amygdala has not been established in humans, thus motivating the current study.

A commonly used striatal-dependent habit-learning task in humans involves probabilistic classification learning (PCL). The cue-outcome associations in this task are

probabilistic; information from a single trial is not reliable and not as important as information accrued across many trials. The standard version of the weather prediction task has an implicit valence associated with the outcome (rain is typically negative whereas sunshine is positive). However, the amygdala is not activated in fMRI studies of this version of the task (e.g., Poldrack et al., 1999), and amnesic patients whose damage includes the amygdala perform equivalently to controls for the first 50 trials (Knowlton, Mangles, & Squire, 1996). Thus, the hypothetical valence value of the weather outcomes is insufficiently arousing to engage an amygdala-based learning system, similar to other studies of preference formation via social interaction (Tranel & Damasio, 1993) and mere exposure (Elliott & Dolan, 1999) tasks.

Imaging during the weather prediction task has revealed that the medial temporal lobe (MTL) is active very early during learning and gradually becomes deactivated, whereas striatal activity increases across learning (Poldrack et al., 1999; 2001). Such results suggest that the declarative hippocampal-based memory system is active early in learning as subjects are attempting to explicitly figure out the cue-outcome associations, and when those explicit strategies do not prove beneficial, they switch to a procedural skill learning strategy. Although these two studies used a blocked design, more recent studies using event-related fMRI showed that neural activity time-locked to the presentation of the cue card stimuli (versus a fixation cross) exhibits

similar effects, with additional feedback-related recruitment in midbrain regions (Aron et al., 2004, 2006).

One study examined the effect of a dual tone-counting task on PCL performance and neural activations (Foerde et al., 2006), and found that in the dual versus single-task condition there was greater dorsolateral prefrontal cortex activation, but that striatal activation did not differ between the two conditions. On a post-learning probe trial, activation in the right hippocampus was correlated with performance in the single task condition, whereas activation in the putamen was correlated with performance in the dual task condition. Interestingly, performance levels did not differ across the two conditions, suggesting that PCL learning can occur via different brain systems depending on task demands. The results from this study demonstrate that PCL learning can occur via distinct neural routes, even when performance remains equivalent between groups. Whether differences in activation patterns emerge as a function of implicit learning strategies (Lagnado et al., 2006) when performance is equated is unknown.

The present study focused on achieving three goals: (1) to replicate the findings of Poldrack and colleagues regarding time-variant trade-offs between MTL and striatal-dependent memory systems over the course of PCL training; (2) to determine how manipulations of fearfulness of the outcomes impacts brain activity in the amygdala and

PCL-learning pathways; and (3) to compare the neural correlates of simple vs. complex strategy use. As in Chapter 2, a between-groups design was employed in which participants either received emotional (snake/spider) outcomes or neutral (flower/mushroom) outcomes across two days of PCL training in an fMRI scanner. An event-related design was implemented, with analysis of the blood-oxygenation-level-dependent (BOLD) hemodynamic response modeled to cue-card onset.

The following predictions were made. First, based on the Poldrack findings, we hypothesized that MTL activity would be observed early on in learning, with concomitant deactivations in the striatum, whereas this relationship would reverse as learning progressed. Second, based on animal models of amygdala-striatal interactions during procedural learning tasks (Packard et al., 1994), we hypothesized that subjects in the emotional condition would show greater activation of the amygdala and associated frontolimbic regions relative to subjects receiving neutral outcomes. Because nonfearful participants in the emotional conditions of Chapters 2 and 3 showed no performance advantages but did exhibit greater use of complex strategies, we hypothesized the same behavioral effects here (fearful subjects were not scanned; see Methods). Finally, implicit strategy use was modeled using the same mathematical techniques as described in Chapter 2. It was predicted that complex strategy use would engage amygdalo-striatal systems to a greater extent than simple strategies, given that a greater proportion of

emotional participants were expected to show complex strategies and the use of these strategies reflects greater implicit knowledge and use of the probabilistic task structure.

4.2 Methods

4.2.1 Subjects

Participants were local residents and were recruited through the Brain Imaging and Analysis Center at Duke University Medical Center, and were reimbursed at the rate of $20/hr. The Institutional Review Board at Duke University approved the experimental protocol and human subjects procedures. A total of 34 subjects provided informed written consent to participate in this study. All participants were screened by a self-report questionnaire for history of neurologic and psychiatric illness, substance abuse, current psychotropic medication use, and for depression by the Beck Depression Inventory (Beck et al., 1961). No subject scored within 2 *SD*'s of the phobic norms on questionnaires assessing attitudes towards snakes and spiders (Klorman et al., 1974). Following Aron et al. (2004), individuals who did not score above chance after the first 50 trials were not included in the final analyses ('non-learners'). To ensure that the groups did not differ on other emotional characteristics, questionnaires were administered assessing emotional experience (Positive and Negative Affect Schedule; Watson, Clark, & Tellegen, 1988), affect intensity (Affect Intensity Measure; Larsen,

1984), and current stress levels (Daily Stress Inventory; Brantley & Jones, 1993), which showed no differences between groups (all F's < 2.0). The groups also did not differ in the reported amount of sleep between the two training days. One subject was discarded because of an incidental MRI finding. One subject's data was not included because he did not respond to over half of the trials in the first run, and 4 subjects were not included because they did not complete training on Day 2. This left a total of 11 subjects in the emotional condition (M_{age} = 23.2, 6 female) and 7 in the neutral condition (M_{age} = 23.1, 5 female).

4.2.2 Stimuli

The card cue and outcome stimuli are the same as described in Chapter 2.

4.2.3 Study Design

The task and trial designs were modeled after that used by Aron et al. (2004) and are the same as in Chapters 2 and 3. Participants were randomly assigned to either the emotional or the neutral group, and completed 100 trials of the task and returned 24 hours later for another 100 trials.

4.2.4 Strategy Questionnaire

Explicit memory was assessed at the end of the experiment with a questionnaire concerning strategy use and cue card/probability associations, as in Gluck et al. (2002).

The questions assessed what strategy they thought they were using and their ratings of how predictive each cue card was of the outcomes.

4.2.5 Procedure

Before scanning on Day 1, subjects briefly practiced 5 random PCL trials to familiarize them with task requirements. Instructions appeared on the screen prior to the practice trials that read: "In this experiment you will see between one and three cards appear on the upper portion of the screen. The cards will have geometric patterns in them. On each trial you will try to predict the correct outcome for that trial based on the cards on the screen. You are to pretend that you are walking in the woods, and based on the cards on the screen you predict whether you are going to come across a SNAKE (FLOWER) or SPIDER (MUSHROOM) in your path. If you think the cards predict that you come across a SNAKE (FLOWER) press the button with your index finger. If you think the cards predict you'll come across a SPIDER (MUSHROOM) press the button with your middle finger. The cards will be on the screen for a few seconds and then you will see a prompt to "Respond Now", at which point you will make your decision. You will hear feedback through the headphones -- a beep if you predict correctly, bursts of white noise if you predict incorrectly. You have 3 sec to make your prediction. At the beginning, you will be guessing as to the correct outcomes based on the cards on the

screen, but hopefully over time it will get easier to make your prediction as to whether the correct outcome is SNAKE (FLOWER) or SPIDER (MUSHROOM)."

After the instructions, structural MRI scans were obtained. Then the two functional scans were run (50 trials each, 10.5 min duration), with a short break between scans. Subjects used right index and middle fingers to press buttons on the MR-compatible button box.

4.2.6 MRI Acquisition

Scanning was performed on a General Electric 4T LX Nvi MRI scanner system equipped with 41 mT/m gradients (General Electric, Waukesha, Wisconsin, USA). A quadrature birdcage radio frequency (RF) head coil was used to transmit and receive. Sixty-eight high-resolution structural images were acquired using a 3D fast SPGR pulse sequence (TR = 500 ms; TE = 20 ms; FOV = 24 cm; image matrix = 256^2; voxel size = 1 mm x 1 mm x 1.9 mm) and used for coregistration with the functional data. These structural images were aligned in the near axial plane defined by the anterior and posterior commissures. Whole brain functional images were acquired using a gradient-recalled inward spiral pulse sequence (Glover & Law, 2001; Guo & Song, 2003) sensitive to blood oxygenation level dependent (BOLD) contrast (TR = 2000 ms; TE = 31 ms; FOV = 24 cm; image matrix = 64^2; $\alpha = 60°$; voxel size = 3.75 x 3.75 x 3.8 mm; 34 contiguous axial slices). This protocol is effective at reducing MRI-induced signal artifacts in frontolimbic

regions at high field strength (Wang et al., 2005). These functional images were similarly aligned as the structural images. A semi-automated high-order shimming program ensured global field homogeneity. Runs consisted of the acquisition of 310 brain volumes and began with 4 discarded RF excitations to allow for steady state equilibrium.

4.2.7 fMRI Data Analysis

Tools from the FMRIB software library (http://www.fmrib.ox.ac.uk/fsl) were used for initial analysis. The images were realigned and spatially smoothed using an 8-mm full-width half-maximum Gaussian kernel. Translational movement parameters never exceeded 0.5 of a voxel in any subject. A nonlinear high-pass filter with a 66-s cut-off was used to temporally filter the data. A four-step registration procedure was used where the skull was stripped using the Brain Extraction Tool (BET), functional images were registered to the matched-bandwidth high-resolution scan, then to the MP-RAGE structure image, and then to standard Montreal Neurologic Institute (MNI) space, using affine linear transformations (Jenkinson & Smith, 2001).

After preprocessing, statistical analyses were performed at the single-subject level by using the general linear model within FSL (FEAT, FMRI Expert Analysis Tool). Each cue card presentation was modeled as an impulse convolved with a canonical hemodynamic response function (HRF) along with its temporal derivative. Specific

comparisons of interest were tested by using linear contrasts. After analysis at the individual level, the results were spatially normalized to the MNI–152 template using FSL's FLIRT registration tool for group effect analyses. Mixed-effects group analyses were performed for each contrast by using FSL's FEAT tool, (FMRI Expert Analysis Tool). The contrasts reported here include: 1) overall activations and deactivations across runs on Day 1 to test MTL-striatal differences across training trials (replication of Poldrack et al., 2001); 2) differences between Emotional and Neutral group activations for each of the runs on Days 1 and 2; 3) overall activations for complex versus simple strategy use. Higher-level statistical maps were thresholded by using clusters determined by $t > 3.30$ and a cluster significance threshold of $p = .001$. For clusters in our *a priori* areas of interest (MTL, amygdala, striatum), we allowed $t > 1.96$ and a cluster significance threshold of $p = .05$. Only clusters of 20 or more voxels are reported.

4.3 Behavioral Results

4.3.1 Ratings

Participants rated the 6 exemplars of snakes, spiders, flowers, and mushrooms on 5-point manikin scales for valence and arousal after completion of the study (1 negative to 5 positive; 1 least arousing to 5 most arousing). Due to technical difficulties, 3 participants did not complete the photo ratings. Replicating results from Chapters 2 and

3, overall flowers and mushrooms were rated more positive than snakes and spiders in a paired t-test, t (24) = 4.38, $p < .0001$. Snakes and spiders were rated more arousing than flowers and mushrooms, t (24) = 4.96, $p < .0001$, verifying the emotional outcome manipulation.

4.3.2 Reaction Time (RT)

A mixed ANOVA was run on RT with Day (1 or 2) and Run (1 or 2) as within-subjects factors and Emotional Outcome (Emotional or Neutral) as a between-subjects factor. There were no significant effects. Unlike in the behavioral study in Chapter 2, subjects were not getting faster as the experiment progressed. This is most likely due to the small sample size.

4.3.3 Learning Rate

A mixed ANOVA with Day and Run as within-subjects factors and Emotion as the between-subjects factor revealed no significant effects.

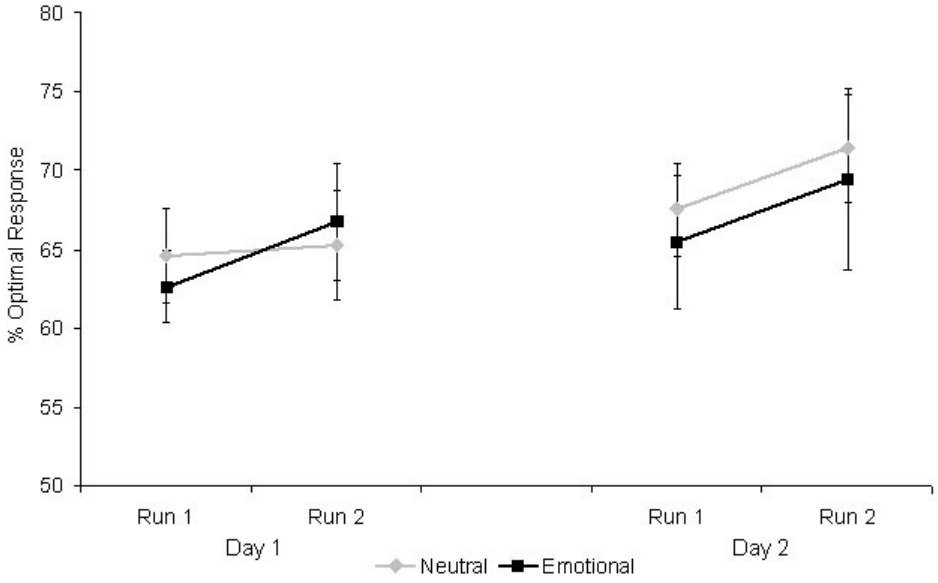

Figure 9: Performance by neutral and emotional subjects. No differences were significant between groups or across Days and Runs.

4.3.4 Implicit Learning Strategy

The number of subjects in each of the four experimental runs using each of three strategy types (non identifiable, simple, or complex) was calculated by the mathematical modeling least mean squares procedures described in Chapter 2. There was no subject that used a nonidentifiable strategy at any point during the study. Because of the small sample size, we were not able to compute chi-square tests on the runs and groups separately. We therefore created a composite index of the proportion of subjects in each condition using simple and complex strategies throughout training. Overall a higher proportion of subjects in the emotional condition used complex strategies versus the neutral condition (70.45% emotional, 57.14% neutral); however this difference was not

significant, $\chi^2(3) = 1.34$, $p = .25$. With a larger sample size, we expect to see an increase in complex strategy use in the emotional condition.

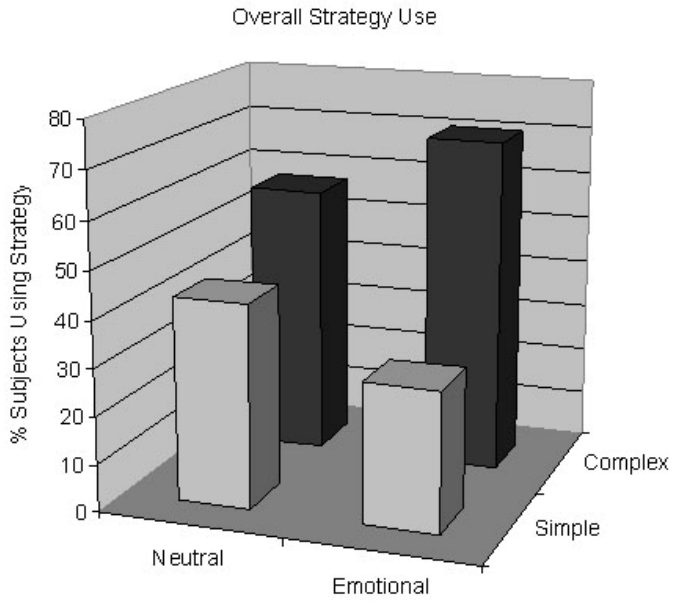

Figure 10: Overall implicit strategy use in emotional and neutral conditions. Differences in strategy use were not significant.

4.3.5 Explicit Strategy Questionnaire

As in Chapters 2 and 3, participants' free-response descriptions of which strategy they thought they used were coded as belonging to one or more of the following six strategies: 1) guessing; 2) using the suit; 3) the number of cards in a series or combination of cards; 4) placement of cards on the screen; 5) matching the patterns/shapes/colors of cards with those associated with a

snake/spider/flower/mushroom; or 6) gut/intuition. Chi-square goodness of fit tests were run subjects in each group to assess if there was an equal distribution of people reporting using each type of strategy. On both days, both groups used the suit of the cue cards to make their predictions more than any of the other 5 strategies (all $\chi^2(5) > 14$, p's $< .02$, except Day 2 Emotional group, $\chi^2(5) = 10.14$, $p = .07$). There were no group differences in explicit knowledge of strong and weak cue card ratings.

4.4 Neuroimaging Results

4.4.1 Activations and Deactivations on Day 1 and Day 2

Activations and deactivations in the entire brain and areas of interest were examined on all 100 trials on Day 1 and all 100 trials on Day 2. The left hippocampus was active on Day 1, while the left parahippocampus and left putamen were active on Day 2. Surprisingly, the left caudate showed relative *deactivation* on Day 2, suggesting dissociation in striatal use on Day 2.

Table 2: Activations and deactivations on Day 1 and Day 2 in the entire brain at $p < .001$ and areas of interest at lower thresholds of $p < .05$.

Day 1

	Whole brain						Regions of Interest					
		x	y	z	Mean *t*	Voxel ct		x	y	z	Mean *t*	Voxel ct
Activations	L Cuneus	-2	-92	22	3.34	15271	L Hippocampus	-34	-30	-6	2.26	30
Dectivations	R Supplementary Motor Area	2	2	50	3.49	38073						

Day 2

	Whole brain						Regions of Interest					
		x	y	z	Mean *t*	Voxel ct		x	y	z	Mean *t*	Voxel ct
Activations							L Parahippocampus	-16	-30	-14	2.07	26
							L Putamen	-28	-12	0	2.19	22
							L Putamen	-26	10	-4	2.20	23
							L Parahippocampus	-12	0	-24	2.60	705
Dectivations							L Caudate	-6	12	-2	2.15	29

4.4.2 Activations and Deactivations on Day 1 Run 1 and Day 1 Run 2

Following findings from Poldrack and colleagues (Poldrack et al., 1999, 2001), differences in activation and deactivation were analyzed across runs on Day 1 to examine tradeoffs in MTL-striatal activation patterns as a function of training extent. Data from all participants were combined for these analyses to assess the main effect of time (Run) on overall activation patterns. The Poldrack findings were only partially supported in our sample. The deactivation of the caudate in Run 1 but not Run 2 conforms to Poldrack's findings (see Figure 11). However, the MTL patterns differed from prior studies. The right parahippocampal gyrus was active throughout training on Day 1, and there was no evidence for time-delayed MTL deactivation. Interestingly, the left amygdala was more active overall during Run 1 than Run 2, although, as reported below, this effect was greater for subjects in the Emotional condition. Other regions in the frontal and occipito-temporal cortices showed time-dependent effects, as summarized in Table 3.

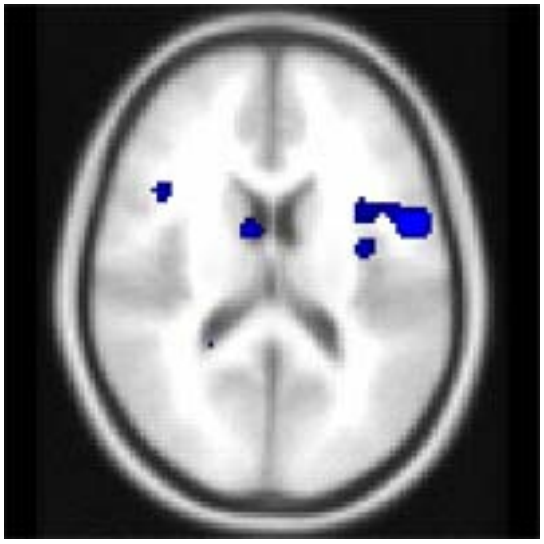

Figure 11: Decreased caudate activity in Day 1 Run 1.

Table 3: Areas active and deactive in Run 1 but not Run 2, and Run 2 but not Run 1. Activations and deactivations reported in the entire brain at $p < .001$ and areas of interest at lower thresholds of $p < .05$.

	Whole brain							Regions of Interest						
		Run sig. in	x	y	z	Mean *t*	Voxel ct		Run sig. in	x	y	z	Mean *t*	Voxel ct
Activations	L Medial Superior Frontal	Run 1	-2	62	10	3.41	54	L Amygdala	Run 1	-20	2	-20	2.91	338
	L Inferfior Frontal	Run 1	-52	42	2	3.45	21							
	L Calcarine	Run 1	2	-90	4	4.32	8876							
	R Middle Occipital	Run 2	50	-82	0	3.71	29							
	L Cuneus	Run 2	0	-90	24	3.69	191							
Deactivations	R Middle Frontal	Run 1	36	44	28	3.53	101	L Caudate	Run 1	-10	0	16	2.94	373
	R Insula	Run 1	34	-6	16	3.43	32							
	L Middle temporal	Run 2	-52	0	-18	3.39	28							
	R Lingual	Run 2	20	-98	-8	3.43	21							
	L Middle Occipital	Run 2	-26	-92	10	3.47	32							
	L Cuneus	Run 2	-18	-60	24	3.64	125							
	R Precuneus	Run 2	6	-66	40	3.21	29							

4.4.3 Emotional Modulation of PCL Training

As expected, early in training (Day 1 Run 1), limbic and paralimbic regions such as the amygdala, orbitofrontal cortex, temporal pole and parahippocampal gyrus were more active in the Emotional condition, as well as regions of superior frontal and visual

cortices (see Figure 12). Interestingly, although many regions showed habituation effects across runs within Days of training, the Emotional group recruited more activity in the caudate nucleus and other frontal and occipitotemporal regions at the end of training on Day 1. Many of these regions were also activated more for the Emotional group at the beginning of training on Day 2, with additional recruitment of the putamen and other occipitotemporal areas at this time. The Neutral group had few activations that were greater than in the Emotional group, although there were some localization differences within the frontal lobes, parahippocampal gyrus and cerebellum (see Table 4).

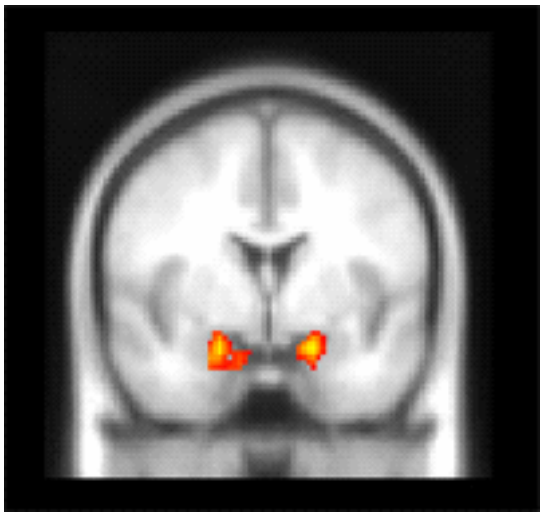

Figure 12: Greater amygdala activity in Day 1 Run 1 for Emotional > Neutral.

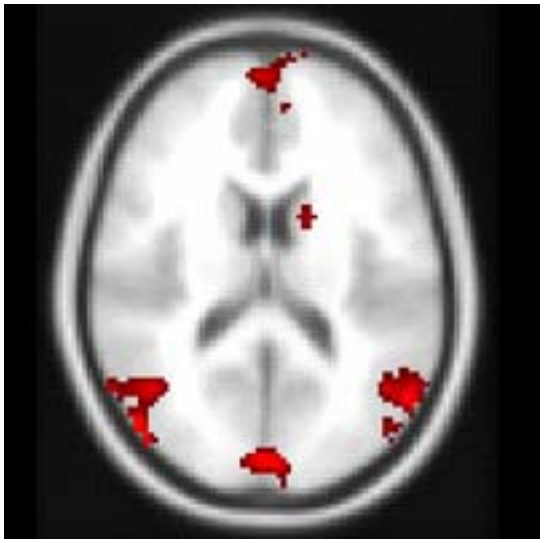

Figure 13: Greater caudate activity in Day 2 Run 1 for Emotional > Neutral.

Table 4: Areas of greater activity in Emotional vs. Neutral and Neutral vs. Emotional in the entire brain at $p < .001$ and areas of interest at lower thresholds of $p < .05$.

Emotional > Neutral

	Whole brain						Regions of interest					
		x	y	z	Mean *t*	Voxel ct		x	y	z	Mean *t*	Voxel ct
Run 1	R Inferior OFC	54	32	-4	3.36	32	R Parahippocampus	18	0	-20	2.35	1892
	R Temporal Pole	52	16	-16	3.41	31	L Amygdala	-20	2	-18	3.00	503
	R Superior Frontal	14	56	34	3.41	22						
	L Superior Medial Frontal	2	62	26	3.47	276						
	L Calcerine	0	-88	4	4.63	13862						
Run 2	R middle Temporal	50	-6	-26	3.33	31	L Caudate	-18	6	18	2.00	32
	L SupraMarginal	-64	-50	26	3.35	61	L Caudate	-18	24	6	2.10	67
	L Superior Occipital	-12	-90	30	3.36	20	L ParaHippocampus	-18	-22	-24	2.10	108
	L Superior Frontal	-22	62	22	3.39	20	R Parahippocampus	26	-38	-12	2.13	570
	L Middle Occipital	-52	-74	2	3.47	201						
	R Cuneus	6	-90	24	3.53	174						
	R Middle Occipital	48	-82	0	3.65	33						
Run 3	L Precentral	-30	-16	68	3.36	39	L Putamen	-28	-12	0	2.58	21
	L Superior Medial Frontal	0	56	4	3.39	20	R Parahippocampus	16	2	-20	2.88	197
	L Middle Frontal	-40	16	54	3.41	28	R Caudate	16	6	18	2.95	117
	L Piroform cortex	-20	6	-16	3.41	65						
	R Inferior OFC	46	26	-16	3.61	72						
	L Superior Frontal	-16	56	32	3.64	573						
	R Inferior Frontal	54	34	4	3.67	38						
	R Superior Frontal	16	28	48	3.68	533						
	R Inferior Occipital	36	-80	-16	3.70	23						
	L Lingual	-26	-50	-8	3.71	226						
	R Cerebellum	38	-56	-24	3.77	229						
	L Fusiform	-40	-52	-24	3.78	866						
	R Medial Occipital	46	-76	0	3.83	1385						
	L Medial Occipital	-52	-74	2	3.98	1547						
Run 4	L Cerebellum	-36	-76	-20	3.40	22	L Parahippocampus	-26	-12	-30	2.33	32
	R Middle Occipital	46	-78	14	3.45	50						
	L Inferior Temporal	-48	-46	-18	3.49	28						
	L Lingual	-20	-74	-12	3.79	145						

Neutral > Emotional

	Whole brain						Regions of interest					
		x	y	z	Mean *t*	Voxel ct		x	y	z	Mean *t*	Voxel ct
Run 1							L Parahippocampus	-26	-42	-10	1.99	182
Run 2												
Run 3	R Cerebellum	42	-62	-28	3.36	87	L Putamen	-20	2	10	1.98	49
	L Posterior Cingulum	0	-40	24	3.43	26	L Parahippocampus	-16	-2	-18	2.01	283
	R Superior Medial Frontal	10	58	34	3.49	40						
Run 4	R Cerebellum	34	-78	-24	3.54	220	L Parahippocampus	-14	0	-24	1.90	80
	L Cerebellum	-24	-88	-28	3.56	25						

4.4.4 Neural Regions Supporting Different Implicit Strategies

To assess whether implicit strategy use recruits distinct neural systems, each participant was classified as following "complex" or "simple" strategies for each run according to the mathematical modeling methods described above. Data were then pooled across experimental groups and runs as a function of strategy type. Complex strategy use was associated with greater activity in the putamen, parahippocampus and amygdala, along with other frontotemporal regions. Simple strategy use was associated with greater activity in the caudate and ventral occipitotemporal regions, as well as other localization differences within frontal cortex (see Table 5). These findings suggest that amygdala-dependent emotional processing was associated with greater complex strategy use, visual areas are recruited to a greater extent for simple strategies, and different subregions within the striatum are associated with different strategy types.

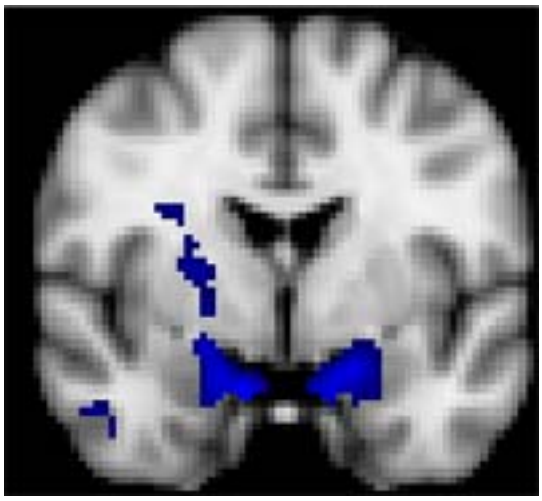

Figure 14: Greater amygdala activity in Complex vs. Simple implicit strategy use.

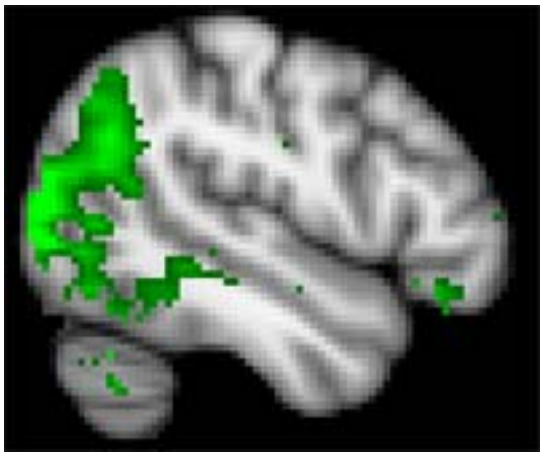

Figure 15: Greater occipital activation in Simple vs. Complex implicit strategy use.

Table 5: Areas of increased activity in Simple vs. Complex and Complex vs. Simple implicit strategy use in the entire brain at $p < .001$ and areas of interest at lower thresholds of $p < .05$.

	Whole brain						Regions of interest					
		x	y	z	Mean *t*	Voxel ct		x	y	z	Mean *t*	Voxel ct
Simple > Complex	L Medial Superior Frontal	-10	56	26	3.30	23	R Caudate	18	12	18	3.69	33
	L Inferior Frontal	-40	48	-12	3.40	28						
	R Calearine	24	-60	6	3.54	58						
	R Inferior Frontal	52	26	-10	3.56	22						
	R Fusiform	24	-36	-20	3.57	71						
	R Medial Superior Frontal	4	58	24	3.60	344						
	R Lingual	20	-66	-10	3.65	72						
	L Mid Occipital	-52	-76	2	3.79	319						
	L Lingual	-10	-40	-4	3.79	1349						
	R Inferior Occipital	40	-66	-12	3.89	1291						
	L Cuneus	-12	-94	26	3.99	825						
Complex > Simple	L Middle Temporal	-56	-32	-4	3.42	47	R Putamen	24	8	-10	3.58	25
	R Middle Frontal	32	20	48	3.43	313	L Parahippocampus	-12	0	-24	3.95	114
	R Middle Temporal	56	-32	-8	3.52	75	R Amygdala	28	4	-20	3.97	186
	R Medial Superior Frontal	0	62	16	3.78	633						
	L Inferior Frontal	-50	42	-2	3.79	75						
	R Cerebellum	-34	-66	-22	3.99	3938						
	L Cuneus	2	-92	20	4.68	1604						

4.5 Discussion

In this neuroimaging study of emotional PCL, there were three main findings. First, we partially replicated the findings of Poldrack and colleagues (Poldrack et al., 1999; 2001), showing greater deactivation of the caudate in the first 50 trials of learning with increased activation in the hippocampus on Day 1. Second, our emotional manipulation successfully activated the amygdala, and subjects in the emotional condition showed greater subsequent usage of striatal areas later in learning. Third, implicit strategy comparisons suggest reliance on different structures for usage of simple versus complex strategies, with the right caudate and visual regions being more active for simple strategies and limbic areas and the putamen more active for complex ones. These findings are suggestive of differences in neural recruitment between emotional and neutral forms of PCL and as a function of strategy use, which have been previously unexplored in the literature.

There were no behavioral differences in learning across runs or emotion conditions in this study. Although equivalent learning rates across emotion conditions were reported in Chapters 2 and 3, the lack of a training effect on learning rates is likely due to our small sample size. Previous weather prediction fMRI studies have used small sample sizes and (N = 8) subjects and report significant learning (Aron et al., 2004; Poldrack et al., 1999), but our task differs from the traditional weather prediction task in

that we have multiple exemplars of each outcome that most likely makes the cue–outcome association more difficult to acquire. Additionally, not all neuroimaging studies of PCL report behavior (i.e., Poldrack et al., 2001).

The studies by Poldrack et al. (1999, 2001) illustrated an inverse relationship between MTL and striatal activity during PCL learning. The present study confirmed that the caudate is relatively deactivated in the first 50 trials of learning, an effect that dissipated by the end of training on Day 1. This pattern supports the idea that procedural learning areas come on-line somewhat later in learning. There was also overall significant hippocampal activity on Day 1 but not Day 2, again supporting the Poldrack findings (1999; 2001). However, there was decreased activity in the R caudate averaged across all 100 trials on Day 2. This went against our hypothesis and could be due to the fact that more people were using complex strategies on Day 2, and in our analysis complex strategy use was associated with increased putamen activity while simple associated with caudate activity.

In the Poldrack et al. (2001) study, task demands were manipulated to emphasize either declarative or procedural learning. The declarative version of the weather prediction task involved paired-associate learning between the cue cards and outcomes, while the procedural version involved trial-by-trial feedback. MTL activity was greater in the declarative-based paired-associate task while the striatum was more active in the

feedback-based task, demonstrating that the engagement of these multiple memory systems can be modulated by task demands. However, importantly, this was a blocked-design study and the alternate task version was used as the baseline. Stark and Squire (2001) have shown that hippocampal deactivation is highly sensitive to the control condition being used as a comparator. Therefore the role of the hippocampus in PCL learning remains to be clarified.

Seger & Cincotta (2005) manipulated the weather prediction task to be either deterministic or probabilistic, therefore emphasizing different memory systems. Performance on the two tasks did not differ, but activations did, with the probabilistic task leading to greater activation of the caudate and extrastriate visual areas, and the deterministic task led to greater activity in the left superior frontal gyrus, suggesting that while performance may not differ with certain task demands, the neural mechanisms underlying learning may in fact be different depending on task manipulation.

In the current study the manipulation of task was by the outcome photographs as being either fearful or neutral in nature. Subjects exposed to snake/spider outcomes showed increased amygdala and orbitofrontal cortex activity early in learning, consistent with the emotional arousal manipulation. The amygdala activity habituated with further training, as reported in prior studies of conditioned learning (Buchel et al.,

1998; LaBar et al., 1998) and habituation of facial expressions (Breiter et al., 1996). Later in training, subjects in the Emotional condition recruited caudate and putamen regions to a greater extent than those in the Neutral condition, which may be indicative of a bias towards striatal-based learning with additional training. This pattern is consistent with our original hypothesis based on animal models of amygdala-striatal interactions during procedural learning task (see McGaugh, 2004; McGaugh, 2000). However, more conclusive evidence of these interactions requires functional connectivity modeling.

The behavioral results suggested that more subjects in the emotional condition used complex strategies, although this effect was not significant with the small sample size, and this strategy usage was more variable across runs than reported in Chapter 2. Therefore, for the purposes of fMRI analysis, differences in neural substrates corresponding to strategy use was assessed by pooling data across all subjects and runs as a function of strategy use type. Interestingly, complex strategy use was associated with greater amygdala and parahippocampal activity in a region located just medial to the amygdala (sometimes called periamygdaloid cortex). This result is suggestive of an association between emotional processing and complex strategy use. Second, different parts of the striatum were specialized for each strategy condition, with the caudate being more active for simple strategies, and the putamen for complex strategies. Finally, visual processing regions along ventral occipitotemporal gyri were more active for subjects

using simple strategies, perhaps due to a greater reliance on analysis of perceptual features of the cue cards for making their cue-outcome predictions.

Differing roles between the caudate and putamen in reward and feedback processing have been postulated, with the caudate being correlated with reward-prediction error and the putamen with stimulus-action-reward association (Haruno & Kawato, 2006). These authors propose that the caudate is mainly engaged in the learning process of comparing actual and predicted events (see also Davidson et al., 2004; O'Doherty et al., 2004; Delgado et al., 2005), and the putamen is involved in the more complex prediction of outcomes. Following this idea, the putamen could be more active in subjects using optimal strategies because they have developed a more complex representation of the cue-outcome probability structure.

In sum, there are three main results of this initial inquiry into the neural systems involved in cognitive skill learning: 1) Poldrack's findings of initial deactivation of the caudate is supported although the hippocampal effects were not; 2) amygdala activation is greater during PCL tasks involving fearful outcomes, which, if supported by functional connectivity analysis, may serve as a biasing signal to engage more complex strategy use that depends on procedural learning systems; 3) differing patterns of striatal activation emerge for subjects using complex and simple strategies, with those using simple strategies showing more caudate and visual activity and those using

complex strategies using more putamen and amygdaloid activity. This study thus lays the groundwork for a larger neuroimaging study of the neural underpinnings of the emotional modulation of procedural cognitive skill learning and strategy differences.

5 General Discussion

How emotion affects memory is an area of broad interest, from animal neurophysiology research to cognitive neuroscience and clinical psychopathology. Given that emotion is known to influence memory is dramatic ways, such as increased explicit recall for emotional information in humans (see LaBar & Cabeza, 2006), and enhanced learning in animals in both hippocampal and striatal learning tasks (Packard, Cahill, & McGaugh, 1994), it is somewhat surprising that the role of emotion in influencing procedural learning and memory in humans has not been well-examined. The goal of this work was to gain a greater understanding of how emotion can influence behavior, consolidation, and neural activity in a procedural cognitive skill task.

The task utilized was a probabilistic classification learning task manipulated to be either high or low in emotional arousal. The *weather prediction* task first proposed by Knowlton and colleagues (Knowlton, Squire, & Gluck, 1994) met the criteria of a task that is dependent (at least in part) on the striatum, with both neuroimaging (Poldrack et al., 1999; 2001; Aron et al., 2004; 2006; Foerde et al., 2006) and patient (Knowlton, Mangles, & Squire, 1996; Shohamy et al., 2004; 2006) studies substantiating the critical involvement of the striatum in this probabilistic classification learning (PCL) task. In the original weather prediction task cue cards are presented on the screen in certain

combinations and subjects are asked to make predictions about the weather in a foreign city. Feedback is given after each trial. For the purposes of examining the effect of task-relevant emotional arousal on PCL, we manipulated the outcomes to be either high in arousal/low in valence, or low in arousal/neutral in valence. Photographs of snakes and spiders were used in the emotional condition and photographs of flowers and mushrooms were used in the neutral condition (photos taken from the IAPS pictures set; Lang, Bradley, & Cuthbert, 1996). Subjects were asked to predict based on cue card combinations what they would come across while walking in the woods, in the emotional condition a snake/spider or in the neutral condition a flower/mushroom, in a between-groups design. The outcome stimuli were presented in a dramatic 'looming' fashion, starting small in the center of the screen and expanding to fill the entire screen, in order to increase the emotional impact of the emotional photographs. Six exemplars of each outcomes type were employed to reduce habituation to the photographs. All three experiments in this body of work employed the neutral and emotional PCL task as described above.

Chapter 2 examined how emotional arousal affected performance and sympathetic nervous system activation in our manipulated PCL task. Based on the mounting evidence that subjects use different implicit strategies (patterns of responding) to solve this task (Gluck et al., 2002; Meeter et al., 2006; Lagnado et al., 2006), we

evaluated implicit strategy use (following Lagnado et al., 2006) as well as traditional percent optimal responding. Skin conductance response (SCR) was collected and time-locked to the cue card onset following the techniques outlined in LaBar et al. (2004). Subjects performed 100 trials of the task and returned 24 hours later to complete another 100 trials in order to evaluate how emotion may impact the consolidation of PCL. A recent study that examined task-irrelevant emotional arousal on the weather prediction task found initial impairments in learning (Steidl et al., 2006). Therefore we hypothesized that our task-relevant manipulation would have negative effects on early learning. In this experiment we specifically included subjects highly fearful of the emotional outcome stimuli, with the prediction that these subjects would show interference effects on learning (performance and strategy use) in the emotional condition due most likely to the overwhelming nature of being confronted with looming images of what they are afraid of, as well as show overall greater SCR due to this arousal.

There were two main results from our study in Chapter 2, with the emotional manipulation yielding both impaired and enhanced learning, depending on the fear-relevancy of the outcome stimuli. First, subjects highly fearful of the outcomes in the emotional condition showed overall greater SCR compared to the other groups, as well as retardation in initial cue-outcome acquisition and no bias towards using any specific

strategy on either the implicit or explicit level early in learning. Second, individuals who were not fearful of the outcome stimuli used more complex (optimal) strategies after a 24-hr period of memory consolidation relative to the other groups, reflecting greater implicit knowledge of the probabilistic task structure. These results suggest the importance of examining *how* subjects are making their decisions in PCL. Emotional controls did not differ in their percent correct from subjects in the neutral condition; it was only when examining their pattern of responding that a difference in learning emerged.

The purpose of the experiment in Chapter 3 was twofold: 1) to examine consolidation-based stabilization and enhancement in a cognitive skill task; and 2) to investigate how emotion may modulate this consolidation. Based on motor-skill tasks in humans, there is a theory that stabilization of memory takes place over hours of wakefulness, while enhancement in performance is usually only seen after a period involving sleep (Walker et al., 2005; Walker & Stickgold, 2006). These motor-skill tasks, while engaging procedural learning systems (Walker et al., 2005), may not be as procedural as once thought, and thus the contribution of explicit hippocampal-based and procedural striatal-based memory processes in observed motor-skill sleep-dependent enhancements is impossible to disentangle (see Song et al., 2007a). Recent evidence suggests that sleep may not be important in probabilistic motor-skill learning

(Song et al., 2007a). Based on this study, which is closer in nature to the current study since it is probabilistic, we hypothesized that we would not see sleep-dependent enhancements in PCL.

To examine the time course of memory stabilization and consolidation the retention interval between 100 trial testing sessions was varied (0hr, 6hr, or 24hr), and participants were either in the emotional or neutral version of task. We used two dependent measures of consolidation: *retention* was calculated as the difference in learning between the two training sessions (Session 2 Run 1 minus Session 1 Run 2); and *savings* was assessed by comparing learning rates following the retention interval (Session 2 Run 2 minus Session 2 Run 1). As in Chapter 2, we examined both percent correct and implicit strategy use.

It has been demonstrated that sleep is important in the consolidation of declarative emotional memories (Hu, Stylos-Allan, & Walker, 2006; Wagner, Gais, & Born, 2001), but its influence on procedural learning in humans remains uncertain. Based on animal work, emotional arousal increases performance after a 24 hour period including sleep on procedural tasks (Packard, Cahill, & McGaugh, 2004). We therefore hypothesized that we would see an increase in retention and savings in the emotional condition for subjects in the 24hr condition.

Consistent with Song et al. (2007a), there was no effect of sleep on retention or savings on percent correct in both the emotional and neutral PCL task. There was also no effect of sleep on retention as on implicit strategy use. Savings measures showed a significant difference in distribution of implicit strategy use for the 24hr emotional group. However, when examining overall strategy use at the end of learning there was no difference in distribution between the retention intervals in the emotional condition, suggesting that sleep did not affect consolidation of emotional probabilistic associations. The lack of increased performance in the 6hr and 24hr retention condition indicates a stabilization of learning – while performance did not improve over time, it remained at a similar level as at the end of Session 1.

Chapter 4 addressed the issue of the neural correlates of emotional PCL. It was hypothesized based on neuroimaging studies that there would be an inverse relationship between the hippocampus and striatum (Poldrack et al., 1999; 2001). Our data partially confirm this finding, with relative deactivation of the caudate in Day 1 Run 1, and overall hippocampal activation on Day 1. Based on animal work demonstrating the beneficial effect of amygdala activity on striatal learning paradigms (see McGaugh, 2000) we hypothesized that we would see an increase in the procedural memory system in the emotional condition. We further postulated that this bias would be especially apparent on Day 2, since the increase in learning with amygdala activity in

animals takes place after a period of consolidation, usually 24 hours (Packard, Cahill, & McGaugh, 1994). There was greater activity in the putamen in Day 1 Run 1 in the emotional versus neutral condition, as well as increased activity in striatal areas on Day 2, suggesting an early and lasting bias of emotion on procedural learning areas. Additionally, we examined differences in neural recruitment by subjects using complex versus simple implicit strategies, and found that different strategy use recruited different areas of the striatum, with subjects using simple strategies showing greater caudate activity and subjects using complex strategies showing greater activation in the putamen. There is evidence that while the caudate is generally active in probabilistic learning situations, the putamen is involved in more complex learning of stimulus-outcome associations (Haruno & Kawato, 2006). The current findings are suggestive of differences in neural recruitment between emotional and neutral PCL and in subjects using simple and complex strategies.

5.1 Implicit and Explicit Knowledge in PCL

While PCL is thought to be mainly a procedural learning task reliant on the integrity of the striatum, subjects report more explicit knowledge of cue card predictiveness and self-insight into performance (Lagnado et al., 2006; Lagnado et al., 2007), than originally postulated (Gluck et al., 2002). In Chapter 2 individual fear-relevancy of the emotional outcomes influenced both implicit and explicit strategy use

early on in learning. High emotional arousal in fearful subjects impaired explicit self-insight into learning as well as acquisition of probabilistic knowledge as evidenced by percent correct and implicit strategy use. Subjects in all groups rated the cue cards highly predictive of the outcomes as more predictive than cue cards that weakly predicted the outcomes. Additionally, explicit knowledge of cue-card predictiveness increased from Day 1 to Day 2, consistent that explicit knowledge increases with practice in a PCL task (Lagnado et al., 2006). Emotion did not affect cue card strength predictiveness ratings. In Chapter 3 subjects again reported using suit to make their predictions. Subjects also rated strong cards as more predictive than weak cards. Explicit knowledge of the task was not manipulated by retention interval or emotion.

Our results contribute to the emerging literature that PCL, while implicated with striatal function in both neuroimaging and patient studies, does not only involve procedural learning. This makes it an ideal task to test the influence of the amygdala on multiple memory systems in humans. In animals activation of the amygdala can bias learning to depend on either hippocampal or striatal regions depending on task demands (Packard, Cahill, & McGaugh, 1994; Packard & Teather, 1998). Studies with increased working memory load during PCL (Foerde et al., 2006), paired-associate versus feedback-based learning (Poldrack et al., 2001), and probabilistic versus deterministic sequences (Seger & Cincotta, 2005), provide evidence that PCL can be

manipulated to emphasize different memory systems. It would be interesting in future work to investigate how the amygdala can influence both procedural and declarative memory in a PCL task. One could manipulate the task to be reliant on declarative memory with a deterministic sequence, and assess how emotion affects that versus a more procedural version of the task with a concurrent tone-counting task. This current PCL task is unique, because like the water and radial maze studies with rats, by using the same stimuli and exposure to emotional information learning systems can be selectively emphasized.

5.2 Implicit Strategy Use and Performance

It is important to note that optimal strategy use was not always correlated with better performance. In Chapter 2 strategy use and optimality and performance accuracy were correlated in Day 1 Run 1. In Chapter 3 there was a significant correlation between strategy use and performance in all four runs. Somewhat surprisingly, even though subjects in the emotional condition were using significantly more complex strategies at the end of learning on Day 2 than other groups, this did not translate to increased percent correct. There is therefore not a direct, consistent correlation between implicit strategy use and performance.

In the first exploration of implicit strategy use in the weather prediction task, Gluck and colleagues reported that at the end of learning performance was correlated

with strategy use, with subjects using multi-cue strategies performing better than subjects using strategies based on one cue (Gluck et al., 2002). However, the division of strategies in that experiment have since been expanded upon and the evidence has not been conclusive that increased strategy use *always* lead to better performance, and studies do not always even examine this correlation (Meeter et al., 2006; Lagnado et al., 2006). One reason why there was not increased performance with optimal strategies is that subjects can perform quite well using single-cue strategies. A subject who focuses on one highly predictive card can achieve 75% optimal responding, similar to the level of optimal responding usually obtained in PCL tasks (Gluck et al., 2002). There is therefore not a great need to use complex strategies since simple ones work most of the time. Even so, investigation of *how* people are solving PCL tasks has led to differences unidentifiable by solely examining percent correct.

For example, application of implicit strategy analyses to patient data showed that hypoxic patients who performed overall worse than controls on the weather prediction task did not use complex strategies as much as controls (Hopkins et al., 2004). Further analyses of these data indicated that controls and hypoxics used similar strategies early on in learning, but that control subjects switched to more complex strategies while hypoxics persisted in using simple or random strategies (Meeter et al., 2006). Therefore even though implicit strategy use may not correlate exactly with performance, it is still

an important learning measure to consider in PCL tasks, as evidenced in Chapter 2 by the increase in complex strategy use at the end of learning in the emotional versus neural group in Chapter 2. Neuroimaging data from Chapter 4 also suggests differential neural recruitment depending on optimality of strategy use. It would be beneficial to further investigate how people are making their decisions in PCL tasks, increasing the types of strategies used as well as gaining a greater understanding of the neural underpinnings of different implicit strategies and their correlation with performance.

5.3 Clinical Significance of Current Work

The current set of studies investigates the modulation of a striatal-based learning task by emotion. Alterations of striatal function have been implicated in several affective disorders such as obsessive-compulsive disorder (OCD; Remijnse et al., 2006, Robinson et al., 1995; Pujol et al., 2004), Tourette's syndrome (Bloch et al., 2005), and trichotillomania (see Chamberlain et al., 2007). A recent rodent study has mimicked OCD behaviors in mice lacking a gene only found in the striatum, with excessive grooming resulting in hair loss and skin injuries, as well as anxiety-like traits (Welch et al., 2007). Anxiety is also attributed to dysfunctions of the amygdala and hippocampus (see Bishop, 2007 for review), so a finer understanding of the interaction between the amygdala and striatum can help shed light on disorders that involve intrusive thoughts, repetitive behaviors, and anxiety such as OCD.

Many anxiety disorders, including phobias, panic disorder, and post-traumatic stress disorder, are characterized by automatic influences of emotion on attention and memory (MacLeod et al., 1986). The studies conducted here and future studies can advance knowledge about the relevant neural circuits through which emotion modifies the acquisition and consolidation of procedural learning, with implications for the assessment and treatment of implicit memory biases for emotional stimuli in neuropsychiatric populations.

There is an abundance of support for implicit, but not explicit, memory biases for threatening information in generalized anxiety disorder (Williams et al., 1988) and generalized social phobia (Amir et al., 2000). There is also evidence for implicit memory biases in PTSD (Amir et al., 1996), and these patients have exaggerated amygdala responses to reminders of traumatic events (Rauch et al., 1996) and during presentation of masked emotional facial expressions (Rauch et al., 2000). Furthermore, the amygdala and other regions of the mesolimbic dopamine (DA) pathway are implicated in drug addiction (Volkow et al., 2002), drug reward processing, and drug-related memories and conditioned responses (Koob & Bloom, 1988). Further exploration of the interaction of the amygdala with other brain regions involved in anxiety can be undertaken with the novel manipulation of the PCL task in these studies, leading to a greater understanding of how emotional outcomes are unconsciously linked to predictive cues and

consolidated over time, with implications for understanding the neurobiology of dysfunctional implicit emotional learning that accompanies anxiety disorders and drug addiction.

References

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience, 9*, 357-381.

Alheid, G. F., de Olmos, J. S., & Beltramino, C. A. (1995). *The Rat Nervous System*. San Diego: Academic Press.

Amir, N., McNally, R.J., Riemann, B.C., & Clements, C. (1996). Implicit memory bias for threat in panic disorder: Application of the white noise paradigm. *Behaviour Research & Therapy, 34*, 157-162.

Amir, N., Foa, E.B., & Coles, M.E. (2000). Implicit memory for threat-relevant information in generalized social phobia. *Journal of Abnormal Psychology, 109*, 713-720.

Anagnostaras, S. G., Maren, S., & Fanselow, M. S. (1999). Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: within-subjects examination. *Journal of Neuroscience, 19*(3), 1106-1114.

Anderson, A. K. (2005). Affective influences on the attentional dynamics supporting awareness. *Journal of Experimental Psychology: General, 134*(2), 258-281.

Aron, A. R., Shohamy, D., Clark, J., Myers, C., Gluck, M. A., & Poldrack, R. A. (2004). Human midbrain sensitivity to cognitive feedback and uncertainty during classification learning. *Journal of Neurophysiology, 92*(2), 1144-1152.

Baddeley, A. D. (1982). Implications of neuropsychological evidence for theories of normal memory. *Philosophical Transactions of the Royal Society of London B Biological Sciences, 298*(1089), 59-72.

Beck, A. T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561-571.

Best, P. J., White, A. M., & Minai, A. (2001). Spatial processing in the brain: the activity of hippocampal place cells. *Annual Review of Neuroscience, 24*, 459-486.

Bishop, S. J. (2007). Neurocognitive mechanisms of anxiety: an integrative account. *Trends in Cognitive Science, 11*(7), 307-316.

Bliss, T. V., & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature, 361*(6407), 31-39.

Brantley, P. J., & Jones, G. N. (1993). Daily stress and stress-related disorders. *Annals of Behavioral Medicine, 15*, 17-25.

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., et al. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron, 17*(5), 875-887.

Brown, A. S. (2002). Consolidation theory and retrograde amnesia in humans. *Psychonomical Bulletin & Review, 9*(3), 403-425.

Brown, R., & Silva, A. J. (2004). Molecular and cellular cognition; the unraveling of memory retrieval. *Cell, 117*(1), 3-4.

Brown, R. M., & Robertson, E. M. (2007). Inducing motor skill improvements with a declarative task. *Nature Neuroscience, 10*(2), 148-149.

Buchel, C., Morris, J., Dolan, R. J., & Friston, K. J. (1998). Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron, 20*(5), 947-957.

Cahill, L., & McGaugh, J.L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neuroscience, 21*, 523-543.

Cahill, L. (2000). Neurobiological mechanisms of emotionally influenced, long-term memory. *Progressive Brain Research, 126*, 29-37.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., et al. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceedings of the National Academy of Sciences USA, 93*(15), 8016-8021.

Cahill, L., & McGaugh, J. L. (1990). Amygdaloid complex lesions differentially affect

retention of tasks using appetitive and aversive reinforcement. *Behavioral Neuroscience, 104*(4), 532-543.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D., & Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *Journal of Neuroscience, 20*(19), RC99.

Carlsen, J., & Heimer, L. (1986). The projection from the parataenial thalamic nucleus, as demonstrated by the Phaseolus vulgaris-leucoagglutinin (PHA-L) method, identifies a subterritorial organization of the ventral striatum. *Brain Research, 374*(2), 375-379.

Chamberlain, S. R., Fineberg, N. A., Blackwell, A. D., Clark, L., Robbins, T. W., & Sahakian, B. J. (2007). A neuropsychological comparison of obsessive-compulsive disorder and trichotillomania. *Neuropsychologia, 45*(4), 654-662.

Cohen, N. a. S., L.R. (1980). Preserved learning and retention of pattern analyzing skill in amnesia: Dissociation of knowing how and knowing that. *Science, 210*, 207-210.

Dagher, A., Owen, A. M., Boecker, H., & Brooks, D. J. (2001). The role of the striatum and hippocampus in planning: a PET activation study in Parkinson's disease. *Brain, 124*(Pt 5), 1020-1032.

Datta, S. (2000). Avoidance task training potentiates phasic pontine-wave density in the rat: A mechanism for sleep-dependent plasticity. *Journal of Neuroscience, 20*(22), 8607-8613.

Davidson, M. C., Horvitz, J. C., Tottenham, N., Fossella, J. A., Watts, R., Ulug, A. M., et al. (2004). Differential cingulate and caudate activation following unexpected nonrewarding stimuli. *Neuroimage, 23*(3), 1039-1045.

DeCastro, J. M. (1974). A selective spatial discrimination deficit after fornicotomy in the rat. *Behavioral Biology, 12*, 373-382.

Delgado, M. R., Miller, M. M., Inati, S., & Phelps, E. A. (2005). An fMRI study of reward-related probability learning. *Neuroimage, 24*(3), 862-873.

Dobbins, I. G., Schnyer, D. M., Verfaellie, M., & Schacter, D. L. (2004). Cortical activity

reductions during repetition priming can result from rapid response learning. *Nature, 428*(6980), 316-319.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2004). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron, 42*(5), 855-863.

Dolcos, F., LaBar, K. S., & Cabeza, R. (2005). Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. *Proceedings of the National Academy of Sciences USA, 102*(7), 2626-2631.

Dolcos, F., & McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *Journal of Neuroscience, 26*(7), 2072-2079.

Drosopoulos, S., Schulze, C., Fischer, S., & Born, J. (2007). Sleep's function in the spontaneous recovery and consolidation of memories. *Journal of Experimental Psychology: General, 136*(2), 169-183.

Dusek, J. A., & Eichenbaum, H. (1997). The hippocampus and memory for orderly stimulus relations. *Proceedings of the National Academy of Sciences USA, 94*(13), 7109-7114.

Eichenbaum, H. (1996). Learning from LTP: a comment on recent attempts to identify cellular and molecular mechanisms of memory. *Learning & Memory, 3*(2-3), 61-73.

Ekman, P., & Davidson, R. J. (1994). *The Nature of Emotion: Fundamental Questions*. New York: Oxford University Press.

Ellenbogen, J. M., Hu, P. T., Payne, J. D., Titone, D., & Walker, M. P. (2007). Human relational memory requires time and sleep. *Proceedings of the National Academy of Sciences USA, 104*(18), 7723-7728.

Elliott, R., & Dolan, R. J. (1999). Differential neural responses during performance of matching and nonmatching to sample tasks at two delay intervals. *Journal of Neuroscience, 19*(12), 5066-5073.

Etchamendy, N., & Bohbot, V. D. (2007). Spontaneous navigational strategies and performance in the virtual town. *Hippocampus, 17*(8), 595-599.

Ferry, B., & McGaugh, J. L. (1999). Clenbuterol administration into the basolateral amygdala post-training enhances retention in an inhibitory avoidance task. *Neurobiology of Learning & Memory, 72*(1), 8-12.

Fischer, S., Drosopoulos, S., Tsen, J., & Born, J. (2006). Implicit learning -- explicit knowing: a role for sleep in memory system interaction. *Journal of Cognitive Neuroscience, 18*(3), 311-319.

Fischer, S., Nitschke, M. F., Melchert, U. H., Erdmann, C., & Born, J. (2005). Motor memory consolidation in sleep shapes more effective neuronal representations. *Journal of Neuroscience, 25*(49), 11248-11255.

Foerde, K., Knowlton, B. J., & Poldrack, R. A. (2006). Modulation of competing memory systems by distraction. *Proceedings of the National Academy of Sciences USA, 103*(31), 11778-11783.

Gallagher, M., Kapp, B. S., McNall, C. L., & Pascoe, J. P. (1981). Opiate effects in the amygdala central nucleus on heart rate conditioning in rabbits. *Pharmacology Biochemistry & Behavior, 14*(4), 497-505.

Galvez, R., Mesches, M. H., & McGaugh, J. L. (1996). Norepinephrine release in the amygdala in response to footshock stimulation. *Neurobiology of Learning & Memory, 66*(3), 253-257.

Glover, G. H., & Law, C. S. (2001). Spiral-in/out BOLD fMRI for increased SNR and reduced susceptibility artifacts. *Magnetic Resonance Medicine, 46*(3), 515-522.

Gluck, M. A., Shohamy, D., & Myers, C. (2002). How do people solve the "weather prediction" task?: individual variability in strategies for probabilistic category learning. *Learning & Memory, 9*(6), 408-418.

Greenberg, D. L., Rice, H. J., Cooper, J. J., Cabeza, R., Rubin, D. C., & LaBar, K. S. (2005). Co-activation of the amygdala, hippocampus and inferior frontal gyrus during autobiographical memory retrieval. *Neuropsychologia, 43*(5), 659-674.

Guo, H., & Song, A. W. (2003). Single-shot spiral image acquisition with embedded z-shimming for susceptibility signal recovery. *Journal of Magnetic Resonance*

Imaging, 18(3), 389-395.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nature Neuroscience, 2*(3), 289-293.

Haruno, M., & Kawato, M. (2006). Different neural correlates of reward expectation and reward expectation error in the putamen and caudate nucleus during stimulus-action-reward association learning. *Journal of Neurophysiology, 95*(2), 948-959.

Hatfield, T., & McGaugh, J. L. (1999). Norepinephrine infused into the basolateral amygdala posttraining enhances retention in a spatial water maze task. *Neurobiology of Learning & Memory, 71*(2), 232-239.

Heindel, W. C., Salmon, D. P., Shults, C. W., Walicke, P. A., & Butters, N. (1989). Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. *Journal of Neuroscience, 9*(2), 582-587.

Heuer, F., & Reisberg, D. (1990). Vivid memories of emotional events: the accuracy of remembered minutiae. *Memory & Cognition, 18*(5), 496-506.

Hopkins, R. O., Myers, C. E., Shohamy, D., Grossman, S., & Gluck, M. (2004). Impaired probabilistic category learning in hypoxic subjects with hippocampal damage. *Neuropsychologia, 42*(4), 524-535.

Hu, P., Stylos-Allan, M., & Walker, M. P. (2006). Sleep facilitates consolidation of emotional declarative memory. *Psychological Science, 17*(10), 891-898.

Iaria, G., Petrides, M., Dagher, A., Pike, B., & Bohbot, V. D. (2003). Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. *Journal of Neuroscience, 23*(13), 5945-5952.

Izquierdo, I., & McGaugh, J. L. (2000). Behavioural pharmacology and its contribution to the molecular basis of memory consolidation. *Behavioral Pharmacology, 11*(7-8), 517-534.

Izquierdo, I., & Medina, J. H. (1997). Memory formation: the sequence of biochemical

events in the hippocampus and its connection to activity in other brain structures. *Neurobiology of Learning & Memory, 68*(3), 285-316.

James, W. (1890). *The Principles of Psychology. Authorized edition.* New York: Dover Publications, Inc.

Jenkins, I. H., Brooks, D. J., Nixon, P. D., Frackowiak, R. S., & Passingham, R. E. (1994). Motor sequence learning: a study with positron emission tomography. *Journal of Neuroscience, 14*(6), 3775-3790.

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis, 5*(2), 143-156.

Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M. M., Turner, R., et al. (1998). The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences USA, 95*(3), 861-868.

Kensinger, E. A., & Corkin, S. (2004). Two routes to emotional memory: distinct neural processes for valence and arousal. *Proceedings of the National Academy of Sciences USA, 101*(9), 3310-3315.

Kim, J. J., Lee, H. J., Han, J. S., & Packard, M. G. (2001). Amygdala is critical for stress-induced modulation of hippocampal long-term potentiation and learning. *Journal of Neuroscience, 21*(14), 5222-5228.

Kita, H., & Kitai, S. T. (1990). Amygdaloid projections to the frontal cortex and the striatum in the rat. *Journal of Computational Neurology, 298*(1), 40-49.

Kleinsmith, L. J., & Kaplan, S. (1963). Paired associate learning as a function of arousal and interpolated interval. *Journal of Experimental Psychology, 65*, 190-193.

Klorman, R., Weerts, T. C., Hastings, J. E., Melamed, B. G., & Lang, P. J. (1974). Psychometric description of some specific fear questionnaires. *Behavior Therapy, 5*, 401-409.

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science, 273*(5280), 1399-1402.

Knowlton, B. J., Squire, L. R., & Gluck, M. A. (1994). Probabilistic classification learning in amnesia. *Learning & Memory, 1*(2), 106-120.

Koob, G. F., & Bloom, F. E. (1988). Cellular and molecular mechanisms of drug dependence. *Science, 242*(4879), 715-723.

Krettek, J. E., & Price, J. L. (1978). Amygdaloid projections to subcortical structures within the basal forebrain and brainstem in the rat and cat. *Journal of Computational Neurology, 178*(2), 225-254.

LaBar, K. S., & Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature Reviews Neuroscience, 7*(1), 54-64.

LaBar, K. S., Cook, C. A., Torpey, D. C., & Welsh-Bohmer, K. A. (2004). Impact of healthy aging on awareness and fear conditioning. *Behavioral Neuroscience, 118*(5), 905-915.

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., & Phelps, E. A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron, 20*(5), 937-945.

LaBar, K. S., & Phelps, E. A. (1998). Arousal-Mediated Memory Consolidation: Role of the Medial Temporal Lobe in Humans. *Psychological Science, 9*(6), 490-493.

Lagnado, D. A., Newell, B. R., Kahan, S., & Shanks, D. R. (2006). Insight and strategy in multiple-cue learning. *Journal of Experimental Psychology: General, 135*(2), 162-183.

Lane, R. D., & Nadel, L. (2000). *Cognitive Neuroscience of Emotion*. Oxford: Oxford University Press.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). International Affective Picture System (IAPS): Technical manual and affective ratings. NIMH Center for the Study of Emotion and Attention.

Larsen, R. J. (1984). Theory and measurement of affect intensity as an individual difference characteristic. *Dissertation Abstracts International, 45*, 07B.

LeDoux, J. E. (1996). *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*. New York: Simon & Schuster.

Levonian, E. (1966). Evoked potential in relation to subsequent alpha frequency. *Science, 152*(726), 1280-1282.

Liang, K. C., Juler, R. G., & McGaugh, J. L. (1986). Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. *Brain Research, 368*(1), 125-133.

Liang, K. C., & McGaugh, J. L. (1983). Lesions of the stria terminalis attenuate the enhancing effect of post-training epinephrine on retention of an inhibitory avoidance response. *Behavioral Brain Research, 9*(1), 49-58.

Liang, K. C., McGaugh, J. L., & Yao, H. Y. (1990). Involvement of amygdala pathways in the influence of post-training intra-amygdala norepinephrine and peripheral epinephrine on memory storage. *Brain Research, 508*(2), 225-233.

MacLeod, C., Mathews, A., & Tata, P. (1986). Attentional bias in emotional disorders. *Journal of Abnormal Psychology, 95*, 15-20.

Maquet, P. (2000). Functional neuroimaging of normal human sleep by positron emission tomography. *Journal of Sleep Research, 9*(3), 207-231.

Marshall, L., & Born, J. (2007). The contribution of sleep to hippocampus-dependent memory consolidation. *Trends in Cognitive Science, 11*(10), 442-450.

Mather, M., Mitchell, K. J., Raye, C. L., Novak, D. L., Greene, E. J., & Johnson, M. K. (2006). Emotional arousal can impair feature binding in working memory. *Journal of Cognitive Neuroscience, 18*(4), 614-625.

McDonald, R. J., & White, N. M. (1993). A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. *Behavioral Neuroscience, 107*(1), 3-22.

McDonald, R. J., & White, N. M. (1994). Parallel information processing in the water maze: evidence for independent memory systems involving dorsal striatum and hippocampus. *Behavioral and Neural Biology, 61*(3), 260-270.

McGaugh, J. L. (1966). Time-dependent processes in memory storage. *Science, 153*(742), 1351-1358.

McGaugh, J. L. (2002). Memory consolidation and the amygdala: a systems perspective. *Trends in Neuroscience, 25*(9), 456.

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual Review of Neuroscience, 27*, 1-28.

McGaugh, J. L., & Gold, P. E. (1976). Modulation of memory by electrical stimulation of the brain. In M. R. Rosenzweig & E. L. Bennett (Eds.), *Neutral Mechanisms of Learning and Memory* (pp. 549-560). Cambridge: MIT Press.

Mednick, S. C., Nakayama, K., Cantero, J. L., Atienza, M., Levin, A. A., Pathak, N., et al. (2002). The restorative effect of naps on perceptual deterioration. *Nature Neuroscience, 5*(7), 677-681.

Meeter, M., Myers, C. E., Shohamy, D., Hopkins, R. O., & Gluck, M. A. (2006). Strategies in probabilistic categorization: results from a new way of analyzing performance. *Learning & Memory, 13*(2), 230-239.

Meienberg, P. (1977). The tonic aspects of human REM sleep during long-term intensive verbal learning. *Physiological Psychology, 5*, 250-256.

Mishkin, M., Malamut, B., & Bachevalier, J. (1984). Memories and habits: two neural systems. In G. Lynch, J. L. McGaugh & N. W. Weinburger (Eds.), *Neurobiology of learning and memory* (pp. 65-77). New York: Guilford Press.

Mogenson, G. J. (1984). Limbic-motor integration. *Progressive Physiological Psychology, 12*, 117-170.

Moody, T. D., Bookheimer, S. Y., Vanek, Z., & Knowlton, B. J. (2004). An implicit learning task activates medial temporal lobe in patients with Parkinson's disease. *Behavioral Neuroscience, 118*(2), 438-442.

Morris, R. G., Garrud, P., Rawlins, J. N., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature, 297*(5868), 681-683.

Nagy, H., Keri, S., Myers, C. E., Benedek, G., Shohamy, D., & Gluck, M. A. (2007). Cognitive sequence learning in Parkinson's disease and amnestic mild cognitive impairment: Dissociation between sequential and non-sequential learning of associations. *Neuropsychologia, 45*(7), 1386-1392.

Newell, B. R., Lagnado, D. A., & Shanks, D. R. (2007). Challenging the role of implicit processes in probabilistic category learning. *Psychonomic Bulletin & Review, 14*(3), 505-511.

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K. J., & Dolan, R. J. (2001). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science, 304*, 452-454.

Öhman, A., & Soares, J. J. F. (1994). "Unconscious Anxiety": Phobic responses to masked stimuli. *Journal of Abnormal Psychology, 103*(2), 231-240.

Packard, M. G. (1999). Glutamate infused posttraining into the hippocampus or caudate-putamen differentially strengthens place and response learning. *Proceedings of the National Academy of Sciences USA, 96*(22), 12881-12886.

Packard, M. G., Cahill, L., & McGaugh, J. L. (1994). Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proceedings of the National Academy of Sciences USA, 91*, 8477-8481.

Packard, M. G., & Chen, S. A. (1999). The basolateral amygdala is a co-factor in memory enhancement produced by intrahippocampal glutamate injections. *Psychobiology, 27*, 377-385.

Packard, M. G., Hirsh, R., & White, N. M. (1989). Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. *Journal of Neuroscience, 9*(5), 1465-1472.

Packard, M. G., Introini-Collison, I., & McGaugh, J. L. (1996). Stria terminalis lesions attenuate memory enhancement produced by intracaudate nucleus injections of oxotremorine. *Neurobiology of Learning & Memory, 65*(3), 278-282.

Packard, M. G., & McGaugh, J. L. (1992). Double dissociation of fornix and caudate

nucleus lesions on acquisition of two water maze tasks: further evidence for multiple memory systems. *Behavioral Neuroscience, 106*(3), 439-446.

Packard, M. G., & McGaugh, J. L. (1996). Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiology of Learning & Memory, 65*(1), 65-72.

Packard, M. G., & Teather, L. A. (1997). Double dissociation of hippocampal and dorsal-striatal memory systems by posttraining intracerebral injections of 2-amino-5-phosphonopentanoic acid. *Behavioral Neuroscience, 111*(3), 543-551.

Packard, M. G., & Teather, L. A. (1998). Amygdala modulation of multiple memory systems: hippocampus and caudate-putamen. *Neurobiology of Learning & Memory, 69*(2), 163-203.

Packard, M. G., & White, N. M. (1991). Dissociation of hippocampus and caudate nucleus memory systems by posttraining intracerebral injection of dopamine agonists. *Behavioral Neuroscience, 105*(2), 295-306.

Packard, M. G., & Wingard, J. C. (2004). Amygdala and "emotional" modulation of the relative use of multiple memory systems. *Neurobiology of Learning & Memory, 82*(3), 243-252.

Pavlides, C., & Winson, J. (1989). Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *Journal of Neuroscience, 9*(8), 2907-2918.

Peigneux, P., Laureys, S., Fuchs, S., Collette, F., Perrin, F., Reggers, J., et al. (2004). Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron, 44*(3), 535-545.

Peigneux, P., Laureys, S., Fuchs, S., Destrebecqz, A., Collette, F., Delbeuck, X., et al. (2003). Learned material content and acquisition level modulate cerebral reactivation during posttraining rapid-eye-movements sleep. *Neuroimage, 20*(1), 125-134.

Phelps, E. A. (2004). Human emotion and memory: interactions of the amygdala and hippocampal complex. *Current Opinion in Neurobiology, 14*(2), 198-202.

Pitkanen, A., Pikkarainen, M., Nurminen, N., & Ylinen, A. (2000). Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat. A review. *Annals of the New York Academy of Sciences, 911*, 369-391.

Poldrack, R. A., Clark, J., Pare-Blagoev, E. J., Shohamy, D., Creso Moyano, J., Myers, C., et al. (2001). Interactive memory systems in the human brain. *Nature, 414*(6863), 546-550.

Poldrack, R. A., & Gabrieli, J. D. (2001). Characterizing the neural mechanisms of skill learning and repetition priming: evidence from mirror reading. *Brain, 124*(Pt 1), 67-82.

Poldrack, R. A., Prabhakaran, V., Seger, C. A., & Gabrieli, J. D. (1999). Striatal activation during acquisition of a cognitive skill. *Neuropsychology, 13*(4), 564-574.

Poldrack, R. A., & Rodriguez, P. (2003). Sequence learning: what's the hippocampus to do? *Neuron, 37*(6), 891-893.

Poldrack, R. A., Sabb, F. W., Foerde, K., Tom, S. M., Asarnow, R. F., Bookheimer, S. Y., et al. (2005). The neural correlates of motor skill automaticity. *Journal of Neuroscience, 25*(22), 5356-5364.

Popescu, A. T., Saghyan, A. A., & Pare, D. (2007). NMDA-dependent facilitation of corticostriatal plasticity by the amygdala. *Proceedings of the National Academy of Sciences USA, 104*(1), 341-346.

Pujol, J., Soriano-Mas, C., Alonso, P., Cardoner, N., Menchon, J. M., Deus, J., et al. (2004). Mapping structural brain alterations in obsessive-compulsive disorder. *Archives of General Psychiatry, 61*(7), 720-730.

Quirarte, G. L., Roozendaal, B., & McGaugh, J. L. (1997). Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. *Proceedings of the National Academy of Sciences USA, 94*(25), 14048-14053.

Ragsdale, C. W., Jr., & Graybiel, A. M. (1988). Fibers from the basolateral nucleus of the amygdala selectively innervate striosomes in the caudate nucleus of the cat.

Journal of Computational Neurology, 269(4), 506-522.

Rauch, S. L., van der Kolk, B.A., Fisler, R.E., Alpert, N.M., Orr, S.P., Savage, C.R., Rischman, A.J., Jenike, M.A., & Pitman, R.K. (1996). A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Archives of General Psychiatry, 53*, 380-387.

Rauch, S. L., Whalen, P. J., Savage, C. R., Curran, T., Kendrick, A., Brown, H. D., et al. (1997). Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Human Brain Mapping, 5*(2), 124-132.

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., et al. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biological Psychiatry, 47*(9), 769-776.

Remijnse, P. L., Nielen, M. M., van Balkom, A. J., Cath, D. C., van Oppen, P., Uylings, H. B., et al. (2006). Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder. *Archives of General Psychiatry, 63*(11), 1225-1236.

Restle, F. (1957). Discrimination of cues in mazes: a resolution of the place-vs.-response question. *Psychological Review, 64*(4), 217-228.

Richardson, M. P., Strange, B. A., & Dolan, R. J. (2004). Encoding of emotional memories depends on amygdala and hippocampus and their interactions. *Nature Neuroscience, 7*(3), 278-285.

Robertson, E. M., & Cohen, D. A. (2006). Understanding consolidation through the architecture of memories. *Neuroscientist, 12*(3), 261-271.

Robertson, E. M., Pascual-Leone, A., & Press, D. Z. (2004). Awareness modifies the skill-learning benefits of sleep. *Current Biology, 14*(3), 208-212.

Robinson, D., Wu, H., Munne, R. A., Ashtari, M., Alvir, J. M., Lerner, G., et al. (1995). Reduced caudate nucleus volume in obsessive-compulsive disorder. *Archives of General Psychiatry, 52*(5), 393-398.

Roozendaal, B., & McGaugh, J. L. (1996). Amygdaloid nuclei lesions differentially affect glucocorticoid-induced memory enhancement in an inhibitory avoidance task. *Neurobiology of Learning & Memory, 65*(1), 1-8.

Roozendaal, B., & McGaugh, J. L. (1997). Glucocorticoid receptor agonist and antagonist administration into the basolateral but not central amygdala modulates memory storage. *Neurobiology of Learning & Memory, 67*(2), 176-179.

Roozendaal, B., Nguyen, B. T., Power, A. E., & McGaugh, J. L. (1999). Basolateral amygdala noradrenergic influence enables enhancement of memory consolidation induced by hippocampal glucocorticoid receptor activation. *Proceedings of the National Academy of Sciences USA, 96*(20), 11642-11647.

Rottenstreich, Y., & Hsee, C. K. (2001). Money, kisses, and electric shocks: on the affective psychology of risk. *Psychological Science, 12*(3), 185-190.

Schacter, D. L., & Buckner, R. L. (1998). Priming and the brain. *Neuron, 20*, 185-195.

Schwabe, L., Oitzl, M. S., Philippsen, C., Richter, S., Bohringer, A., Wippich, W., et al. (2007). Stress modulates the use of spatial versus stimulus-response learning strategies in humans. *Learning & Memory, 14*, 109-116.

Seger, C. A., & Cincotta, C. M. (2005). The roles of the caudate nucleus in human classification learning. *Journal of Neuroscience, 25*(11), 2941-2951.

Setlow, B., Roozendaal, B., & McGaugh, J. L. (2000). Involvement of a basolateral amygdala complex-nucleus accumbens pathway in glucocorticoid-induced modulation of memory consolidation. *European Journal of Neuroscience, 12*(1), 367-375.

Sharot, T., Delgado, M. R., & Phelps, E. A. (2004). How emotion enhances the feeling of remembering. *Nature Neuroscience, 7*(12), 1376-1380.

Sharot, T., & Phelps, E. A. (2004). How arousal modulates memory: disentangling the effects of attention and retention. *Cognitive, Affective, & Behavioral Neuroscience, 4*(3), 294-306.

Sherry, D. F., & Schacter, D.L. (1987). The evolution of multiple memory systems. *Psychological Review, 94*(4), 439-454.

Shohamy, D., Myers, C. E., Geghman, K. D., Sage, J., & Gluck, M. A. (2006). L-dopa impairs learning, but spares generalization, in Parkinson's disease. *Neuropsychologia, 44*(5), 774-784.

Shohamy, D., Myers, C. E., Grossman, S., Sage, J., & Gluck, M. A. (2005). The role of dopamine in cognitive sequence learning: evidence from Parkinson's disease. *Behavioral Brain Research, 156*(2), 191-199.

Shohamy, D., Myers, C. E., Grossman, S., Sage, J., Gluck, M. A., & Poldrack, R. A. (2004). Cortico-striatal contributions to feedback-based learning: converging data from neuroimaging and neuropsychology. *Brain, 127*(Pt 4), 851-859.

Slovic, P., & Peters, E. (2006). Risk perception and affect. *Current Directions in Psychological Science, 15*, 322-325.

Smith, C., & MacNeill, C. (1994). Impaired motor memory for a pursuit rotor task following Stage 2 sleep loss in college students. *Journal of Sleep Research, 3*(4), 206-213.

Song, S., Howard, J. H., Jr., & Howard, D. V. (2007a). Sleep does not benefit probabilistic motor sequence learning. *Journal of Neuroscience, 27*(46), 12475-12483.

Song, S., Howard, J. H., Jr., & Howard, D. V. (2007b). Implicit probabilistic sequence learning is independent of explicit awareness. *Learning & Memory, 14*(3), 167-176.

Squire, L. R., Knowlton, B., & Musen, G. (1993). The Structure and Organization of Memory. *Annual Review of Psychology, 44*, 453-495.

Stark, C. E., & Squire, L. R. (2001). When zero is not zero: the problem of ambiguous baseline conditions in fMRI. *Proceedings of the National Academy of Sciences USA, 98*(22), 12760-12766.

Steidl, S., Mohi-uddin, S., & Anderson, A. K. (2006). Effects of emotional arousal on multiple memory systems: evidence from declarative and procedural learning. *Learning & Memory, 13*(5), 650-658.

Stickgold, R., Whidbee, D., Schirmer, B., Patel, V., & Hobson, J. A. (2000). Visual discrimination task improvement: A multi-step process occurring during sleep. *Journal of Cognitive Neuroscience, 12*(2), 246-254.

Sunstein, C. R. (2003). Terrorism and probability neglect. *The Journal of Risk and Uncertainty, 26*, 121-136.

Thomas, L.A., & LaBar, K.S. (2005). Emotional arousal enhances word repetition priming. *Cognition & Emotion, 19*(7), 1027-1047.

Thomas, L.A., & LaBar, K.S. (2006). Probabilistic classification learning is sleep-dependent and modulated by emotional outcomes. Program No. 164.8/Z30. 2006 Neuroscience Meeting Planner. Atlanta, GA: Society for Neuroscience.

Thompson, G. W., Guilford, M. O., & Hicks, L. H. (1980). Effects of caudate and cortical lesions on place and response learning in rats. *Physiological Psychology, 8*, 473-479.

Tranel, D., & Damasio, A. R. (1993). The covert learning of affective valence does not require structures in hippocampal system or amygdala. *Journal of Cognitive Neuroscience, 5*, 79-88.

Tranel, D., Damasio, A. R., Damasio, H., & Brandt, J. P. (1994). Sensorimotor skill learning in amnesia: additional evidence for the neural basis of nondeclarative memory. *Learning & Memory, 1*(3), 165-179.

Volkow, N. D., Fowler, J. S., Wang, G. J., & Goldstein, R. Z. (2002). Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. *Neurobiology of Learning & Memory, 78*(3), 610-624.

Wagner, U., Gais, S., & Born, J. (2001). Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learning & Memory, 8*(2), 112-119.

Walker, E. L., & Tarte, R. (1963). Memory storage as a function of arousal and time with homogeneous and heterogeneous lists. *Verbal Learning & Verbal Behavioral, 2*, 113-119.

Walker, M. P. (2005). A refined model of sleep and the time course of memory formation. *Behavioral Brain Science, 28*(1), 51-64.

Walker, M. P., Brakefield, T., Hobson, J. A., & Stickgold, R. (2003). Dissociable stages of human memory consolidation and reconsolidation. *Nature, 425*(6958), 616-620.

Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A., & Stickgold, R. (2002). Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron, 35*(1), 205-211.

Walker, M. P., Brakefield, T., Seidman, J., Morgan, A., Hobson, J. A., & Stickgold, R. (2003). Sleep and the time course of motor skill learning. *Learning & Memory, 10*(4), 275-284.

Walker, M. P., & Stickgold, R. (2005). It's practice, with sleep, that makes perfect: implications of sleep-dependent learning and plasticity for skill performance. *Clinical Sports Medicine, 24*(2), 301-317.

Walker, M. P., Stickgold, R., Jolesz, F. A., & Yoo, S. S. (2005b). The functional anatomy of sleep-dependent visual skill learning. *Cerebral Cortex, 15*(11), 1666-1675.

Wang, L., McCarthy, G., Song, A. W., & LaBar, K. S. (2005). Amygdala activation to sad pictures during high-field (4 tesla) functional magnetic resonance imaging. *Emotion, 5*(1), 12-22.

Watson, D., Clark, L.A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affects: the PANAS scales. *Journal of Personality & Social Psychology, 54*(6), 1063-1070.

Welch, J. M., Lu, J., Rodriguez, R. M., Trotta, N. C., Peca, J., Ding, J. D., et al. (2007). Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. *Nature, 448*(7156), 894-900.

Williams, J. M. G., Watts, F.N., MacLeod, C., & Mathews, A. (1988). *Cognitive psychology and emotional disorders*. New York: Wiley.

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science, 265*(5172), 676-679.

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Thomas, L.A., & LaBar, K.S. (2005). Emotional arousal enhances word repetition priming. *Cognition and Emotion*, *19*(7), 1027-1047.

Phelps, E.A., & Thomas, L.A. (2003). Race, behavior and the brain: The role of neuroimaging in understanding complex human behaviors. *Political Psychology*, *24*, 747-758.

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2005	Conference Travel Fellowship, Duke University
2004	Graduate Student Travel Award to Cognitive Neuroscience of Category Learning Workshop, NYC
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