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EXAMINING MEMORY CONSOLIDATION AND RECONSOLIDATION IN AN APPETITIVE PAVLOVIAN TASK

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THESIS

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
College of Liberal Arts and Sciences
at the University of Kentucky

By

Jonathan Jenn-Sheng Chow

Lexington, Kentucky

Directors: Dr. Michael T. Bardo, Professor of Psychology

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ABSTRACT OF THESIS

EXAMINING MEMORY CONSOLIDATION AND RECONSOLIDATION IN AN APPETITIVE PAVLOVIAN TASK

Memory plays an important role in defining how one behaves. The neurobiological mechanisms of memory have been studied extensively in animal models and the NMDA glutamate receptor has been identified to play an important role in the consolidation and reconsolidation of appetitive memories. Certain memories, depending on what was learned, can function differently and can be more difficult to disrupt based on a number of factors. Currently, no study has examined whether or not a reward-predictive stimulus attributed with incentive value is more difficult to disrupt than a stimulus that functions as a general reward-predictor. To determine the role of the NMDA receptor on memory consolidation with different functioning reward-predictive stimuli rats underwent a Pavlovian conditioned approach, where a post-session NMDA receptor antagonist was administered daily. Furthermore, to determine the role of the NMDA receptor on memory reconsolidation, another set of rats were trained on a Pavlovian conditioned approach task, after training was complete rats were presented with a reward-predictive stimuli followed by an administration of a NMDA receptor antagonist and then re-tested.

KEYWORDS: Memory, Consolidation, Reconsolidation, Incentive Salience, Pavlovian Conditioning

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January 5, 2015

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TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER 1: Introduction

Background

Every day people experience different events, whether it is meeting someone new, going to a familiar coffee shop, or just sitting at home watching a rerun on television. Some of these experiences are more easily remembered than others. For example, accidentally bumping into a random stranger and getting pushed over is most likely more memorable than accidentally bumping into a random stranger and just saying "sorry". These experiences all form a person's memory, and memories shape an individual's character and personality. With memory playing such a large role in defining how one behaves and acts, it is not surprising that it is a heavily studied topic in many fields such as psychology, biology, and neuroscience.

Memory Formation

In psychology, memory has been studied for decades and many different aspects of it have been revealed. How someone forgets overtime (Ebbinghaus, 1913), the amount of information that can be stored in the short term (Miller, 1956), and how information learned in one setting can be more easily recalled in the same setting (Godden & Baddeley, 1975) are just a few of the aspects of memory that have been uncovered. Through these experiments, theories of how memories are formed and used have been described as well. These models for memory formation and use can differ from one another. For example, one model by Atkinson and Shiffrin (1968) suggests that information is taken into short-term storage and through rehearsal it ends up in a long-term storage, while another model by Baddeley and Hitch (1974) suggests that memory is

constantly active, receiving inputs from the senses, and can be manipulated when active. While the specifics in how memory is formed and maintained are still being debated, the general theory is that memories are encoded, stored, and once stored become retrievable.

Interestingly, around the same time that psychological models for memory started developing, the biological mechanisms that drive memory formation were also being studied. One of the biological mechanisms that was discovered, and is still heavily studied today is long-term potentiation (LTP). LTP is derived from Hebbian theory, which is the idea that connections between neurons are strengthened upon repeated and persistent communication (Hebb, 1949). While LTP essentially emphasizes the same concepts as Hebbian theory, it goes on to further hypothesize that new connections, including more dendritic growth, can drive neural plasticity that could underlie learning and memory (Lynch, 2004). Furthermore, it has been shown that glutamate, the major excitatory neurotransmitter in the central nervous system, plays a large role in LTP, especially α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptor signaling. Briefly, NMDA receptor activation allows for Ca^{2+} to enter the neuron where it then activates calmodulin-dependent protein kinase II (CaMKII). Following activation of CaMKII, various signaling cascades (e.g. CREB and Zif268 (Abel & Lattal, 2001; Tronson & Taylor, 2007)) promote an increase in the number of AMPA receptors expressed on the cell membrane, thus allowing more Na^{+} to enter the neuron which then allows for further membrane depolarization and subsequent action potential (Malenka & Nicoll, 1999). This process is believed to be the underlying mechanism that drives synaptic plasticity and the consolidation of a memory. It has been shown that NMDA antagonism results in the blockade of learning and

memory in a variety of behavioral tasks, including fear conditioning, spatial learning, working memory, and instrumental learning (Riedel et al. 2003; Kelley, 2004). There is also evidence that NMDA signaling mediates basic Pavlovian conditioning. In a study by Di Ciano and colleagues (2001), it was demonstrated that pre-session microinfusions of the NMDA antagonist AP-5 into the nucleus accumbens core disrupted the acquisition of Pavlovian conditioning. However, microinfusions of AP-5 into the nucleus accumbens core did not affect any of the previously learned Pavlovian associations, indicating that once memory is consolidated, it is believed to be stable (McGaugh, 2000).

Once a memory becomes stable, this does not mean that it cannot be modified. After a memory is consolidated and stable, through rehearsal or repetition it can be strengthened or even updated to include new information (Bandura et al., 1974; Morris & Jones, 1990). This process of strengthening or updating memory with use is called reconsolidation. During memory reconsolidation, it is theorized that memories are destabilized at retrieval and require restabilization in order to be stored again, thus suggesting that memories become active and labile during retrieval (Lewis, 1979; Nader, 2003). During memory reactivation, induction of memory retrieval where the memory becomes destabilized for use, it has been hypothesized that memory can be disrupted and can lead to an alteration in the memory itself, leaving open the possibility that memory for something as simple as light predicting food, a shock, or drug can be changed or even erased. The clinical implications for memory reconsolidation have drawn a large amount of attention within the past decade, with studies examining both aversive and appetitive memories believed to play a role in various psychopathologies, like anxiety, post-traumatic stress, and substance abuse disorders.

Neurobiological Mechanisms of Memory Reconsolidation

Currently, studies examining memory reconsolidation follow the basic paradigm of reactivating a memory, by presenting some cue associated with the memory, and causing some disruption, usually with a protein synthesis inhibitor or a receptor antagonist, immediately after retrieval and then re-testing the memory at a later date. For example, in a study by Schafe & LeDoux (2000) rats were conditioned to a tone that predicted shock, leading to a freezing response at the sound of the tone. Rats were then exposed briefly to the tone under extinction, thus reactivating the memory. Immediately following the memory reactivation rats were treated with saline or the protein synthesis inhibitor anisomycin. The following test, under extinction, demonstrated that rats treated with anisomycin showed less freezing than saline treated animals toward the tone, suggesting an alteration in the tone memory. However, protein synthesis occurs as a result of various intracellular cascades and could be elicited by a number of other different events, making it difficult to determine the specific pathways that are involved with memory reconsolidation. Determining the neurotransmitter receptor systems related to the reconsolidation process can result in understanding more specific signaling pathways involved. Interestingly, the molecular targets used in memory reconsolidation most commonly involve the NMDA receptor and the β-adrenergic receptor (Debiec & LeDoux, 2004; Lee & Everitt, 2008). Using the β-adrenergic receptor antagonist propranolol, instead of a protein synthesis inhibitor Debiec & LeDoux (2004) obtained similar results to Schafe & LeDoux (2000), namely propranolol treatment immediately after memory reactivation prevented reconsolidation of a stimulus predictive of shock

and reduced freezing during tests. Another study by Flint and colleagues (2013) examined the role of the NMDA receptor by using a passive avoidance paradigm. Rats started on one side of a two-chamber compartment, where a door opened allowing access into a different compartment. If rats crossed over to the other compartment, the door would close and the rats were shocked. Rats quickly developed an aversion to the shock compartment and refused to cross over when the door was open. Following this, animals were briefly placed into the side paired with shock and administered MK-801, a NMDA receptor antagonist, immediately afterwards. On the following day, animals underwent the passive avoidance task and it was found that rats treated with MK-801 after the reactivation task explored the compartment that had previously been paired with shock, thus demonstrating a disruption in the memory.

While the studies above examined aversive memories in rodent models, human studies have also examined how memory reconsolidation can be used to treat aversive memories. A study by van Stegeren and colleagues (1998) found that negative and upsetting emotional memories could be disrupted by administrating propranolol after reactivation. Another study by Saladin and colleagues (2013) used a similar method to examine the role of the β-adrenergic receptor on both negative and positive emotional memories. In that study, individuals with post-traumatic stress disorder (PTSD) went through an emotional recall task where stressful memories and alcohol-related memories were reactivated. Afterwards, patients were given a treatment of propranolol. Interestingly, it was found that the aversive stressful memories were disrupted, whereas appetitive alcohol-related memories were not altered.

Divergence between the role of β-adrenergic receptor and glutamatergic receptor signaling in aversive and appetitive memory reconsolidation has been found in the rodent literature as well. β-adrenergic receptor signaling is more specific to aversive memories, while glutamatergic signaling seems to be involved in both aversive and appetitive memories. For example, Milton and colleagues (2012) trained rats in a Pavlovian conditioning paradigm for an ethanol reward and then tested them for Pavlovian instrumental transfer, where the presence of the previously conditioned stimulus for ethanol modulates some ongoing operant responding. Animals that had memories reactivated and then disrupted with MK-801 for the conditioned stimulus associated with ethanol showed decreased rates of alcohol-related responding during the Pavlovian instrumental transfer, while animals treated with propranolol did not. Collectively, these results suggest that both glutamatergic and β-adrenergic receptor blockade can affect emotional memory reconsolidation, specifically with conditioned fear memories (Debiec & LeDoux, 2004), however appetitive memories seem to be affected more specifically by NMDA receptor antagonism (Lee & Everitt, 2008; Milton & Everitt, 2010).

Drug Memories and Memory Reconsolidation

One type of appetitive memory that has recently been a target for memory reconsolidation is drug-related memory. Most drug-related memories are elicited by stimuli that are consistently and contiguously paired with the direct effects of drugs of abuse (e.g. drug paraphernalia). These stimuli can come to influence and impel abuse-related behavior through associative processes (Hogarth et al. 2010). Furthermore, stimulus control over abuse-related behavior is long lasting where months and years after long periods of abstinence relapse can occur (Ciccocioppo et al. 2001; Grimm et al.,

2011). In a series of studies by Lee and colleagues (2006), abuse-related behavior such as cocaine seeking and cue-induced cocaine seeking were examined. Animals were trained to press a lever that produced a light paired with a cocaine infusion. Following cocaine self-administration, animals were presented with the reward-predictive light and underwent a disruption in memory reconsolidation with Zif268 antisense oligodeoxynucleotides that knocked down the immediate-early gene transcript Zif268, thus preventing protein synthesis. Further testing demonstrated that animals that had their memory disrupted showed subsequent decreases in cue-maintained cocaine seeking. While this study used a protein knock down procedure, another study by von der Goltz and colleagues (2009) demonstrated similar results showing memory disruption for cue-induced alcohol-seeking using MK-801. Additionally, using MK-801 to disrupt memory reconsolidation to a cocaine cue also reduces cocaine-related responding in Pavlovian instrumental transfer (Lee & Everitt, 2008). With a growing body of evidence beginning to reveal a large overlap between basic learning and memory processes and substance-abuse disorders, including a relationship between stimulus-reward learning and abuse-related behavior, using memory reconsolidation to disrupt the reward-predictive association of stimuli could be one method for treating abuse-like behavior (Torregrossa & Taylor, 2011; Everitt & Robbins, 2005).

Reward-Predictive Stimuli and Memory

Stimulus-reward learning occurs when an otherwise neutral stimulus is paired with a reward. The cue, a conditioned stimulus (CS), becomes a predictor of the reward, an unconditioned stimulus (US). Through repeated pairings of the CS and US, stimuli that have been paired with reward can influence a number of behavior. For example,

reward-predictive stimuli can act as conditioned reinforcers, facilitating novel operant responses to earn access to the stimuli alone (Mackintosh, 1974; Williams, 1994; Shahan, 2010). Reward predictive stimuli have also been shown to elicit different conditioned responses, like compelling an individual to approach and interact with the stimulus (sign-tracking; Brown & Jenkins, 1968; Hearst & Jenkins, 1974) or compelling an individual to approach the location of forthcoming reinforcement delivery (goal-tracking; Boakes, 1977). Currently, an increasing number of studies have used a Pavlovian conditioned approach (PCA) task, where a single lever located next to a food receptacle reliably predicts a non-contingent food reward to elicit sign-tracking or goal-tracking responses from an animal. Animals that sign-track are theorized to have attributed "incentive salience" or value to the lever that is above and beyond the predictive nature of the CS (Saunders & Robinson, 2010). This is reflected by the gnawing, chewing, and grabbing responses to the lever, where these conditioned responses seem to reflect the unconditioned responses that the food US elicits (Brown & Jenkins, 1968; Boakes, 1977). Furthermore, this attribution of "incentive salience" has been supported by the fact that the lever CS serves as a more robust conditioned reinforcer in animals that sign-track versus those that goal track to a lever CS (Robinson et al., 2009). Contrary to sign-trackers, goal-trackers are theorized to *not* have attributed incentive value to the lever stimulus, instead directing responding to the food receptacle. Furthermore, both sign-tracking and goal-tracking responses are learned, as non-paired presentation of the lever and food results in the lack of both sign-tracking and goal-tracking responses (Chang et al., 2012). Collectively, the evidence above suggests that something different is learned about reward-associated stimuli that elicit a sign-tracking response versus those that elicit

a goal-tracking response. Thus, individual differences in the propensity to sign-tracking may be reflective of differential learning about reward-associated stimuli and may underlie differential vulnerability to the reinforcing effects of drugs of abuse and their associated cues (Clark et al., 2012).

The differences in conditioned approach behavior towards a CS have recently gained increasing interest in the field of reward and motivation related to abuse-like behavior. Differential abuse-like behavior are seen in animals that have a propensity to sign-track during PCA training. Animals that sign-track have been shown to be more sensitive to cocaine and alcohol reinforcement (Beckmann et al. 2011; Saunders & Robinson 2011; Anderson et al. 2011) and have enhanced reinstatement of cocaine-seeking behavior by priming injections of cocaine or cocaine-associated cues (Saunders & Robinson 2010). Additionally, sign tracking during PCA also is relate to other risk factors known to predict vulnerability to abuse-related behavior, like novelty seeking (Beckmann et al. 2011) and impulsivity (Tomie et al. 1998; Flagel et al. 2010).

It has been hypothesized that different neurobehavioral valuation systems, or the associate processes that are involved in learning about the function of a Pavlovian conditioned stimulus (Toates, 1997; Boakes, 1977), may underlie the different conditioned response topographies exhibited by sign- and goal-tracking behavior, and the propensity for these different valuation systems to govern stimulus-reward learning may play a role in individual differences of substance abuse vulnerability (Clark et al., 2012). However, little is known about the proposed different neurobehavioral valuation systems and how one valuation system may come to govern a stimulus-reward relationship over a different valuation system. Furthermore, it is not known whether or not these two

different stimulus-reward learning processes reflected in sign- and goal-tracking behavior are mediated by different memory profiles.

Sign-tracking vs. Goal-tracking – Memory Function

As outlined previously, through a PCA procedure, animals can be either identified as sign- or goal-trackers. In a study by Blaiss and Janak (2007), a light and tone CS+ was predictive of a sucrose solution reward and entries into the port of reward delivery was measured (goal-tracking). In that study, both consolidation and reconsolidation were examined, where one group of animals were treated every post-session during acquisition and another group of animals underwent a disruption of memory reconsolidation post-session using amphetamine or anisomycin. The results of this experiment demonstrated that animals treated with amphetamine or anisomycin during acquisition, post-session, showed either enhanced or impaired learning of the PCA task, respectively. In contrast, animals treated with amphetamine or anisomycin during memory reconsolidation showed no effect on goal-tracking. While these results suggest that there is a difference in consolidation and reconsolidation of a Pavlovian memory, the experiment only examined goal-tracking. In most PCA tasks, only a single response type, sign- or goal-tracking can be obtained within an animal, thus making it difficult to examine the possible different valuation systems.

A novel method to examine possible differences in valuation systems and memory profiles underlying stimulus-reward learning was developed by Beckmann and Chow (2014). This procedure, a 2-conditioned stimulus Pavlovian conditioned approach (2-CS PCA) task, uses two different and independent stimuli to elicit exclusive sign-

tracking or goal-tracking responses within an animal. By using a lever or tone that predicts a non-contingent sucrose pellet reward, exclusive sign-tracking or goal-tracking is obtained to the lever CS and tone CS, respectively. While animals can exhibit both sign- and goal-tracking to the lever CS (Flagel et al., 2009), animals under the 2-CS PCA procedure tend to exhibit sign-tracking behavior. On the contrary, tones tend to elicit exclusive goal-tracking behavior, unless food is made contingent upon a sign-tracking response (Cleland & Davey, 1983; Holland, 1977; Harrison, 1979). Further examination using reversal learning, omission contingencies, extinction, conditioned reinforcement, and choice following training on the 2-CS PCA, has indicated that sign-tracking responses to a lever stimulus are more persistent than goal-tracking responses to a tone, and that the lever CS has more value relative to the tone CS. Thus, the results from this procedure suggest that the lever stimulus gains incentive value above and beyond the normal reward-predictive value, while the tone stimulus does not. Furthermore, it is believed that the neurobehavioral systems governing the differences in learning about a lever and tone CS might reflect different memory profiles, where memories of the lever CS are more resistant to disruption due to the value associated with it. This suggests that the strength of the lever stimulus memory could be different than that of the tone. Similarly, drug memories are strong and long lasting, and can be triggered by a number of environmental stimuli after long periods of abstinence (Volkow et al., 2008; Grimm & Shaham, 2002). Collectively, the results above suggest that similar memory processes may mediate the relationship between sign-tracking and abuse-related behavior.

Statement of Hypothesis

The goal of the following experiments was to use the 2-CS PCA task in order to examine i) the role of NMDA receptors on the consolidation of reward-predictive stimuli, and ii) the differential reconsolidation of a reward-predictive stimulus that has gained incentive value (lever) relative to one that has not (tone). It was hypothesized that through the blockade of NMDA receptors during acquisition of each relationship learning would be impaired to the lever CS, a stimulus attributed with incentive value, and the tone CS. It was also hypothesized that, relative to a tone CS, a lever CS that has been attributed with incentive value would require greater reconsolidation inhibition to alter the existing memory.

CHAPTER 2: Main Experiments

Through associative learning reward-predictive stimuli can influence behavior, however the way that a reward-predictive stimuli is learned and functions for an individual can differ (Toates, 1997; Boakes, 1977). Studies using a PCA task have shown that individuals that have a propensity to sign-track are prone to abuse-like behaviors (Tomie et al. 1998; Flagel et al. 2010; Beckmann et al. 2011). Furthermore, stimuli that elicit sign-tracking behavior have also been shown to serve as more robust conditioned reinforcers, take longer to extinguish, and can bias choice in probabilistic discounting (Beckmann & Chow, 2014). Additionally, these differences in conditioned responses to stimuli are hypothesized to be governed by different neurobehavioral valuation systems (Clark et al., 2012) which in turn could be driven by different memory processes as well. In order to study these differences in memory reflected in sign- and goal-tracking responses the 2-CS PCA task was utilized to investigate these valuation systems. The goal of the following experiments was to use the 2-CS PCA task in order to examine the role of NMDA receptors on the consolidation of reward-predictive stimuli, and the differential reconsolidation of a reward-predictive stimulus.

Experiment 1: Consolidation

Methods

Subjects

Twelve male Sprague-Dawley rats (Harlan Inc.; Indianapolis, IN, USA), weighing approximately 250-275 g at the beginning of experimentation, were used. Rats were individually housed in a temperature-controlled environment with a 12:12 hr

light:dark cycle, with lights on at 0600 h. The rats were first acclimated to the colony environment and handled daily for one week prior to experimentation. All experimentation was conducted during the light phase. All rats had *ad libitum* access to food and water in their home cage. All experimental protocols were conducted according to the 2010 *NIH Guide for the Care and Use of Laboratory Animals* (8^{th} edition) and were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

Apparatus

Experiments were conducted in operant conditioning chambers (ENV-008, MED Associates, St. Albans, VT) that were enclosed within sound-attenuating compartments (ENV-018M, MED Associates). Each chamber was connected to a personal computer interface (SG-502, MED Associates), and all chambers were operated using MED-PC. Within each operant chamber, a 5.1 x 5.1 cm recessed food receptacle (ENV-200R2MA) outfitted with a head-entry detector (ENV-254-CB) was located on the front response panel of the chamber, two retractable response levers were mounted on either side of the food receptacle (ENV-122CM; 6 cm above metal rod floor), two white cue lights (ENV-221M) were mounted at 4.1 cm and 8.2 cm above each response lever, and a tone generator (ENV-223 HAM) was located above the top left cue light. The back response panel was outfitted with a single retractable response lever (ENV-122CM; directly opposite of the food receptacle); two nosepoke response lights (ENV-114BM; 6 cm above metal rod floor and directly opposite to front response levers) were mounted on either side of the retractable response lever, and a house-light (ENV-227M) was located

12 cm above the response lever. Food pellets (45-mg Noyes Precision Pellets; Research Diets, Inc., New Brunswick, NJ) were delivered via a dispenser (ENV-203M-45).

Drug

(+)-MK-801 hydrogen maleate was purchased from Sigma-Aldrich (St. Louis, MO, USA) and mixed in sterile saline (0.9% NaCl). MK-801 is a NMDA receptor antagonist and was selected due to its effects on learning and memory (Riedel et al., 2003; Wegener et al., 2011). Furthermore, the dose of MK-801 (0.1 mg/kg) used in this experiment was selected due to its pharmacokinetic effects in relation to behavior and the formation of memory as seen in previous research (Wozniak et al., 1990; Wegener et al., 2011; Lee & Everitt, 2008; Milton et al., 2012). While MK-801 is specific to the NMDA glutamate receptor, there has been some evidence that MK-801 can bind non-specifically to nicotinic acetylcholine receptors and inhibit monoamine transporters, however the studies examining MK-801 on these other systems were done *in vitro* (Ramoa et al., 1990; Iravani et al., 1999; Gainetdinov et al., 2001). Both nicotinic acetylcholine receptors and monoamines, such as serotonin and dopamine, have been reported to have some effect on memory formation (Felix & Levin, 1997; Aleisa et al., 2006; Gonzalez-Burgos & Feria-Velasco, 2008; Buhot et al., 2000; Sherry et al., 2005; Tronson & Taylor 2007), thus making it a possibility that MK-801 may have an effect on some other system. In addition, AP-5, a more selective NMDA receptor antagonist could be used, however due to its inability to pass the blood brain barrier (Morris, 1989) a specific brain region would be required. Some areas of specific interest that could be telling about incentive valuation of reward-predictive stimuli may include the nucleus accumbens core

or nucleus accumbens shell (Saunders & Robinson, 2012; Chang et al., 2012), however these studies examined the role of dopamine and not glutamate.

Procedure

Magazine Shaping

During the last two days of acclimation to the colony, immediately after animals were handled, 10 to 15 food pellets (45-mg Noyes Precision Pellets; Research Diets, Inc., New Brunswick, NJ, USA) were dropped into their home cages. Following the week of habituation, animals were trained to retrieve food pellets from the food receptacle for two consecutive days. Animals were placed in the operant chambers and given 40 minutes to retrieve and consume 16 food pellets, delivered on a 60s fixed time schedule.

2-CS PCA Task

Following magazine shaping, 2-CS PCA training commenced. During each training session, a single response lever adjacent to the food receptacle (counterbalanced for side) was inserted into the chamber or a 40 KHz tone was presented for 8s. Immediately after lever retraction or tone cessation, a food pellet was non-contingently delivered into the receptacle. Stimulus presentations were separated by a 90s variable time inter-trial-interval (ITI), ranging from 12s to 286s (Fleshler & Hoffman, 1962) that began immediately after pellet delivery. Each session consisted of 32 total trials, comprised of 16 lever insertions and 16 tone presentations in a pseudorandom order, where no more than four presentations of the same stimulus occurred consecutively. Sign-tracking (ST) responses were recorded as lever presses, while goal-tracking (GT) responses were recorded as breaks of a photo beam within the food receptacle during

stimulus presentation. Head entries into the food receptacle during the ITI period were recorded as GT-ITI. Additionally, head entries into the food receptacle during the 8s period before each trial (8s pre-CS) were recorded.

Memory Consolidation

During the 14 days of 2-CS PCA training, animals (n=12) were given a post-session treatment MK-801 (0.1 mg/kg i.p.; Lee & Everitt, 2008; Flint et al., 2013) or saline immediately following completion of the last trial.

Analysis

Linear mixed effects modeling, with sessions (continuous) and stimulus (nominal: tone vs. lever) as within-subject factors and treatment (nominal: saline vs. MK-801) as a between-subject factor, was used to analyze rates of responding (sign-tracking, goal-tracking, and 8s pre-CS) and the probability difference score (the probability of making a sign-tracking response minus the probability of making a goal-tracking response) during the acquisition of the 2-CS PCA task with post-session treatments. In addition, another linear mixed effects modeling with sessions (continuous), and response type (nominal: sign-tracking vs. goal-tracking) as within-subject factors, was used to analyze rates of sign-tracking to the lever and goal-tracking to the tone.

Results

Figure 1 illustrates the post-session treatments on response rates for sign-tracking (1A), goal-tracking (1B), and the 8s pre-CS period (1C) to the two stimuli, as well as the probability difference score (1D). Linear mixed effects modeling indicated a significant

main effect of session on sign-tracking [$F(1,10) = 6.88$, $p < 0.05$] and goal-tracking [$F(1,10) = 16.68$, $p < 0.05$] rates, indicating an increase in rates over session. A main effect of stimulus on sign-tracking [$F(1,10) = 27.52$, $p < 0.05$] and goal-tracking [$F(1,10) = 8.25$, $p < 0.05$] rates were also obtained, indicating differences in response types across the two stimuli, where a lever CS produced sign-tracking and a tone CS produced goal-tracking. A significant main effect of stimulus on the probability difference score [$F(1,10) = 38.58$, $p < 0.05$] revealed that the likelihood of obtaining a sign- or goal-tracking response depended on the stimulus presented, again indicating that the lever produced sign-tracking and the tone produced goal-tracking. A significant main effect of post-session treatment on sign-tracking rates [$F(1,10) = 16.91$, $p < 0.05$], indicated animals treated with saline sign-tracked and those treated with MK-801 did not.

Furthermore, linear mixed effects modeling revealed a significant session x treatment interaction on sign-tracking rates [$F(1,10) = 7.05$, $p < 0.05$], indicating that post-session treatments of MK-801 prevented sign-tracking through the training period while post-session saline did not. A significant interaction of session x stimulus was revealed for sign-tracking [$F(1,10) = 6.88$, $p < 0.05$] and goal-tracking [$F(1,10) = 14.30$, $p < 0.05$], revealing that the sign-tracking rates were lever specific and goal-tracking rates were tone specific. Additionally, a significant interaction of session x stimulus for the probability difference score [$F(1,10) = 17.77$, $p < 0.05$] also indicated the specificity of sign- and goal-tracking to the lever CS and tone CS, respectively. Linear mixed effects modeling revealed significant interactions of treatment x stimulus for sign-tracking [$F(1,10) = 16.91$, $p < 0.05$] and goal-tracking [$F(1,10) = 6.32$, $p < 0.05$] rates, demonstrating that the saline treatments elicited sign-tracking to the lever CS and goal-

tracking to the tone CS, while post-session MK-801 treatments impeded both sign- and goal-tracking rates. Furthermore, a significant interaction of treatment x stimulus on the probability difference score [$F(1,10) = 21.96$, $p < 0.05$] indicated that the likelihood of getting a sign- or goal-tracking response to the two stimuli depended on the post-session treatment.

Finally, linear mixed effects modeling revealed a significant interaction of session x stimulus x treatment on sign-tracking [$F(1,10) = 7.05$, $p < 0.05$] and goal-tracking [$F(1,10) = 9.71$, $p < 0.05$] rates. Thus, post-session treatments of saline resulted in exclusive sign-tracking to the lever CS and exclusive goal-tracking to the tone CS over the training period, while post-session MK-801 treatments produced almost no sign-tracking to the lever CS and minimal goal-tracking to the lever CS and tone CS over the training sessions. In an addition, there was a significant interaction of session x stimulus x treatment on the difference in response probability score [$F(1,10) = 18.00$, $p < 0.05$], suggesting that animals treated with saline were more likely to sign-track to the lever and goal-track to the tone over sessions, while animals that received MK-801 post-session treatments were less likely to sign- or goal-track to either stimulus. Finally, linear mixed effects revealed no significant effects or interactions for the 8s pre-CS rates [$p > 0.05$] indicating no differences in responding during this period.

Additionally, there were no significant differences between sign-tracking and goal-tracking response rates to the lever and tone, respectively [$F(1,5) = 1.19$, $p > 0.05$].

Experiment 2: Memory Reconsolidation

Methods

Subjects

Twenty-four male Sprague-Dawley rats (Harlan Inc.; Indianapolis, IN, USA), weighing approximately 250-275 g at the beginning of experimentation, were used. Rats were individually housed in a temperature-controlled environment with a 12:12 hr light:dark cycle, with lights on at 0600 h. The rats were first acclimated to the colony environment and handled daily for one week prior to experimentation. All experimentation was conducted during the light phase. All rats had *ad libitum* access to food and water in their home cage. All experimental protocols were conducted according to the 2010 *NIH Guide for the Care and Use of Laboratory Animals* (8^{th} edition) and were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

Apparatus

Experiments were conducted in operant conditioning chambers (ENV-008, MED Associates, St. Albans, VT) that were enclosed within sound-attenuating compartments (ENV-018M, MED Associates). Each chamber was connected to a personal computer interface (SG-502, MED Associates), and all chambers were operated using MED-PC. Within each operant chamber, a 5.1 x 5.1 cm recessed food receptacle (ENV-200R2MA) outfitted with a head-entry detector (ENV-254-CB) was located on the front response panel of the chamber, two retractable response levers were mounted on either side of the food receptacle (ENV-122CM; 6 cm above metal rod floor), two white cue lights (ENV-

221M) were mounted at 4.1 cm and 8.2 cm above each response lever, and a tone generator (ENV-223 HAM) was located above the top left cue light. The back response panel was outfitted with a single retractable response lever (ENV-122CM; directly opposite of the food receptacle); two nosepoke response lights (ENV-114BM; 6 cm above metal rod floor and directly opposite to front response levers) were mounted on either side of the retractable response lever, and a house-light (ENV-227M) was located 12 cm above the response lever. Food pellets (45-mg Noyes Precision Pellets; Research Diets, Inc., New Brunswick, NJ) were delivered via a dispenser (ENV-203M-45).

Drug

(+)-MK-801 hydrogen maleate was purchased from Sigma-Aldrich (St. Louis, MO, USA) and mixed in sterile saline (0.9% NaCl).

Procedure

Magazine Shaping

During the last two days of acclimation to the colony, immediately after animals were handled, 10 to 15 food pellets (45-mg Noyes Precision Pellets; Research Diets, Inc., New Brunswick, NJ, USA) were dropped into their home cages. Following the week of habituation, animals were trained to retrieve food pellets from the food receptacle for two consecutive days. Animals were placed in the operant chambers and given 40 minutes to retrieve and consume 16 food pellets, delivered on a 60s fixed time schedule.

2-CS PCA Task

Following magazine shaping, 2-CS PCA training commenced. During each training session, a single response lever adjacent to the food receptacle (counterbalanced for side) was inserted into the chamber or a 40 KHz tone was presented for 8s. Immediately after lever retraction or tone cessation, a food pellet was non-contingently delivered into the receptacle. Stimulus presentations were separated by a 90s variable time inter-trial-interval (ITI), ranging from 12s to 286s (Fleshler & Hoffman, 1962) that began immediately after pellet delivery. Each session consisted of 32 total trials, comprised of 16 lever insertions and 16 tone presentations in a pseudorandom order, where no more than four presentations of the same stimulus occurred consecutively. Sign-tracking (ST) responses were recorded as lever presses, while goal-tracking (GT) responses were recorded as breaks of a photo beam within the food receptacle during stimulus presentation. Head entries into the food receptacle during the ITI period were recorded as GT-ITI. Additionally, head entries into the food receptacle during the 8s period before each trial (8s pre-CS) were recorded.

Memory Reconsolidation

Following 14 days of 2-CS PCA training animals (n=24) were matched for performance, based on sign- and goal-tracking rates, and divided into four groups (n = 6/group; lever+saline, tone+saline, lever+MK-801, and tone+MK-801). All animals were placed into the operant chambers and given a single presentation of either the previously conditioned lever CS or tone CS after a 90s fixed time (FT) – ITI. Following the presentation of the single stimulus animals were taken out and immediately given either an injection of saline or MK-801 (0.1 mg/kg i.p.) and returned to the colony. On the following day animals were tested on the 2-CS PCA task under extinction.

Analysis

Linear mixed effects modeling, with sessions (continuous) and stimulus (nominal: tone vs. lever) as within-subject factors and treatment (nominal: saline vs. MK-801) and CS presented (nominal: tone vs. lever) as between-subject factors, were used to determine if there were any differences in sign-tracking and goal-tracking rates of the matched groups. In addition, another linear mixed effects modeling with sessions (continuous), and response type (nominal: sign-tracking vs. goal-tracking) as within-subject factors was used to analyze rates of sign-tracking to the lever and goal-tracking to the tone.

Finally a linear mixed effects model, with block (continuous: 4 trials per block of each stimulus type) and stimulus (nominal: tone vs. lever) as within-subject factors and treatment (nominal: saline vs. MK-801) and CS presented (nominal: tone vs. lever) as between-subject factors, was used to examine the effects of the reconsolidation treatment on sign-tracking and goal-tracking response rates and sign-tracking and goal-tracking probability. Furthermore, another linear mixed effects modeling with block (continuous) and response type (nominal: sign-tracking vs. goal-tracking) as within-subject factors and treatment (nominal: saline vs. MK-801) and CS presented (nominal: tone vs lever) as a between-subject factors, was used to analyze response rates and response probability for sign-tracking to the lever and goal-tracking to the tone.

Results

Figure 2 illustrates the sign-tracking (2A) and goal-tracking (2B) rates of the matched groups. Linear mixed effects modeling revealed a significant main effect of session on sign-tracking [$F(1,20) = 7.82$, $p < 0.05$] and goal-tracking [$F(1,20) = 38.39$, $p < 0.05$], with rates indicating that both sign- and goal-tracking rates increased over the training period. Linear mixed effects modeling revealed there was a significant main effect of stimulus on sign-tracking [$F(1,20) = 143.52$, $p < 0.05$] and goal-tracking [$F(1,20) = 69.40$, $p < 0.05$] rates, where the lever CS elicited sign-tracking and the tone CS elicited goal-tracking. Additionally there was a significant between stimulus x session interaction on sign-tracking [$F(1,20) = 7.82$, $p < 0.05$] and goal-tracking [$F(1,20) = 53.29$, $p < 0.05$] rates, suggesting that sign-tracking and goal-tracking responses to the lever CS and tone CS, respectively, increased over session. Furthermore, there was no significant interaction of treatment x CS presented x stimulus x session on sign-tracking [$F(1,20) = 0.00$, $p > 0.05$] or goal-tracking [$F(1,20) = 0.04$, $p > 0.05$] rates. Collectively, these results indicate no differences in the matched groups and that animals were exclusively sign-tracking to the lever CS and exclusively goal-tracking to the tone CS. Additionally, there were no differences in sign-tracking rates to the lever CS and goal-tracking rates to the tone CS [$F(1,23) = 3.01$, $p > 0.05$].

Figure 3 shows sign-tracking (3A) and goal-tracking (3B) rates, as well as sign-tracking (3C) and goal-tracking (3D) probabilities across the four blocks of trials during the test. Linear mixed effects modeling revealed a significant main effect of block on sign-tracking rates [$F(1,20) = 34.00$, $p < 0.05$] and probability [$F(1,20) = 22.62$, $p < 0.05$], as well as goal-tracking rates [$F(1,20) = 36.50$, $p < 0.05$] and probability [$F(1,20)$

= 83.50, $p < 0.05$], indicating that both sign- and goal-tracking response rates and probabilities decreased over the four trial blocks. Linear mixed effects modeling also revealed a significant main effect of stimulus on sign-tracking rates [$F(1,20) = 111.43$, $p < 0.05$] and probability [$F(1,20) = 305.32$, $p < 0.05$], as well as goal-tracking rates [$F(1,20) = 49.74$, $p < 0.05$] and probability [$F(1,20) = 70.31$, $p < 0.05$]. These results indicate that the sign-tracking responses were made to the lever CS and goal-tracking responses were made to the tone CS. Furthermore, linear mixed effects modeling revealed a significant interaction of block x stimulus on sign-tracking rates [$F(1,20) = 34.00$, $p < 0.05$] and probability [$F(1,20) = 22.62$, $p < 0.05$], as well as goal-tracking rates [$F(1,20) = 32.01$, $p < 0.05$] and probability [$F(1,20) = 46.91$, $p < 0.05$], indicating that that sign-tracking and goal-tracking response rates decreased over the four trial blocks.

However, linear mixed effects modeling revealed no significant interaction of treatment x CS presented x stimulus x block on sign-tracking [$F(1,20) = 0.89$, $p > 0.05$] or goal-tracking [$F(1,20) = 0.08$, $p > 0.05$] rates or sign-tracking [$F(1,20) = 0.97$, $p > 0.05$] or goal-tracking [$F(1,20) = 0.00$, $p > 0.05$] probabilities, suggesting that the reconsolidation treatment on the lever CS and tone CS had no effect. However, there was a main effect of response type in the sign-tracking and goal-tracking rates [$F(1,20) = 26.52$, $p < 0.05$] and probability [$F(1,20) = 69.78$, $p < 0.05$] thus indicating that goal-tracking extinguishes faster than sign-tracking.

Discussion: Experiment 1 and 2

The results using a 2-CS PCA procedure demonstrated that there was a disruption in learning of the reward-predictive stimuli of animals treated with MK-801 post-session.

Animals that were treated with MK-801 post-session showed no sign-tracking or goal-tracking responding to the lever CS. On the contrary, saline treated animals showed learning and elicited exclusive sign-tracking and goal-tracking responding to the lever CS and tone CS, respectively. Collectively, these results indicate that the NMDA receptor plays a role in the consolidation of learning as seen in other experiments (Alaghband & Marshall, 2012; McLamb et al., 1990; de Lima et al., 2005).

Results from the second experiment again indicated that animals showed explicit sign-tracking and goal-tracking to the lever CS and tone CS, respectively. However, there was no effect of the reconsolidation manipulation on the lever stimulus in both conditions. However, across blocks there was a decrease in the rate of responding to tone overall in both conditions. Relative to sign-tracking to the lever, extinction rates for goal-tracking to the tone were higher for both saline and MK-801 treated animals, suggesting a difference in the persistence of the two different stimulus memories, with the lever CS memory being stronger than the tone CS.

The strength of a memory plays a large role in the effects of altering a memory during reconsolidation (Lee et al., 2006). From the results collected in the preliminary experiment, alternative methods may be required to further examine these differences in memory strength. Some of these methods may include increasing the length or the number of the reactivation trials, since memory reactivation might require some "warm-up" (Tronson & Taylor, 2007). For example, a study by Alaghband and Marshall (2013) used cocaine conditioned place preference (CPP) and multiple reactivation sessions during the reconsolidation phase to understand how the strength of some memories requires more disruption. In the CPP experiment, rats were conditioned with cocaine in

one context and then tested for their preference. Following preference conditioning, animals were treated with MK-801 after a reactivation test, where they were placed in the cocaine context briefly. It was found that the initial test did not have an effect on preference scores. However, reactivating and retreating with MK-801 seemed to have an effect in reducing cocaine CPP. The results of this experiment suggest that something like cocaine CPP might create a strong memory between cocaine and the CPP context and that repeated memory disruption is required to abolish the drug memory.

CHAPTER 3: Revisiting Reconsolidation

Results from Experiment 2: Memory Reconsolidation indicated that the single stimulus presentation followed by a treatment of MK-801 (0.1 mg/kg) or saline did not differ on subsequent responding thus suggesting the manipulation used did not have an effect. In order to further investigate this idea of reconsolidation and memories associated with a conditioned stimuli more presentations to elicit a stronger reactivation was used in attempts to examine memory strength in a reconsolidation paradigm. It was hypothesized that presenting animals with more than one presentation of the lever CS or tone CS should allow for reactivation and a disruption in the reconsolidation of the stimulus memory, where animals presented with the lever CS and treated with MK-801 should show less responding during the test day than animals presented with the tone CS or treated with saline. Similar effects were expected with animals presented with the tone CS and treated with MK-801 as well, where the responding to the tone CS should be lower than animals presented with the lever CS or treated with saline. Furthermore, it was also hypothesized that, relative to a tone CS, a lever CS that has been attributed with incentive value should be harder to disrupt.

Experiment 3: Reconsolidation – Multiple Stimulus Presentations

Methods

Subjects

Twenty-four male Sprague-Dawley rats (Harlan Inc.; Indianapolis, IN, USA), weighing approximately 250-275 g at the beginning of experimentation, were used. Rats were individually housed in a temperature-controlled environment with a 12:12 hr

light:dark cycle, with lights on at 0600 h. The rats were first acclimated to the colony environment and handled daily for one week prior to experimentation. All experimentation was conducted during the light phase. All rats had *ad libitum* access to food and water in their home cage. All experimental protocols were conducted according to the 2010 *NIH Guide for the Care and Use of Laboratory Animals* (8^{th} edition) and were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

Apparatus

Experiments were conducted in operant conditioning chambers (ENV-008, MED Associates, St. Albans, VT) that were enclosed within sound-attenuating compartments (ENV-018M, MED Associates). Each chamber was connected to a personal computer interface (SG-502, MED Associates), and all chambers were operated using MED-PC. Within each operant chamber, a 5.1 x 5.1 cm recessed food receptacle (ENV-200R2MA) outfitted with a head-entry detector (ENV-254-CB) was located on the front response panel of the chamber, two retractable response levers were mounted on either side of the food receptacle (ENV-122CM; 6 cm above metal rod floor), two white cue lights (ENV-221M) were mounted at 4.1 cm and 8.2 cm above each response lever, and a tone generator (ENV-223 HAM) was located above the top left cue light. The back response panel was outfitted with a single retractable response lever (ENV-122CM; directly opposite of the food receptacle); two nosepoke response lights (ENV-114BM; 6 cm above metal rod floor and directly opposite to front response levers) were mounted on either side of the retractable response lever, and a house-light (ENV-227M) was located

12 cm above the response lever. Food pellets (45-mg Noyes Precision Pellets; Research Diets, Inc., New Brunswick, NJ) were delivered via a dispenser (ENV-203M-45).

Drug

(+)-MK-801 hydrogen maleate was purchased from Sigma-Aldrich (St. Louis, MO, USA) and mixed in sterile saline (0.9% NaCl).

Procedure

Magazine Shaping

During the last two days of acclimation to the colony, immediately after animals were handled, 10 to 15 food pellets (45-mg Noyes Precision Pellets; Research Diets, Inc., New Brunswick, NJ, USA) were dropped into their home cages. Following the week of habituation, animals were trained to retrieve food pellets from the food receptacle for two consecutive days. Animals were placed in the operant chambers and given 40 minutes to retrieve and consume 16 food pellets, delivered on a 60s fixed time schedule.

2-CS PCA Task

Following magazine shaping, 2-CS PCA training commenced. During each training session, a single response lever adjacent to the food receptacle (counterbalanced for side) was inserted into the chamber or a 40 KHz tone was presented for 8s. Immediately after lever retraction or tone cessation, a food pellet was non-contingently delivered into the receptacle. Stimulus presentations were separated by a 90s variable time inter-trial-interval (ITI), ranging from 12s to 286s (Fleshler & Hoffman, 1962) that began immediately after pellet delivery. Each session consisted of 32 total trials,

comprised of 16 lever insertions and 16 tone presentations in a pseudorandom order, where no more than four presentations of the same stimulus occurred consecutively. Sign-tracking (ST) responses were recorded as lever presses, while goal-tracking (GT) responses were recorded as breaks of a photo beam within the food receptacle during stimulus presentation. Head entries into the food receptacle during the ITI period were recorded as GT-ITI. Additionally, head entries into the food receptacle during the 8s period before each trial (8s pre-CS) were recorded.

Memory Reconsolidation – Multiple Presentations

Following 14 days of 2-CS PCA training animals (n=24) were matched for performance, based on sign- and goal-tracking rates, and divided into four groups (n = 6/group; lever+saline, tone+saline, lever+MK-801, and tone+MK-801). All animals were placed into the operant chambers and given four presentations of either the previously conditioned lever CS or tone CS with a 90s FT-ITI. Following the presentations of the stimulus animals were taken out and immediately given either an injection of saline or MK-801 (0.1 mg/kg i.p.) and returned to the colony. On the following day animals were tested on the 2-CS PCA task under extinction.

Analysis

Linear mixed effects modeling, with sessions (continuous) and stimulus (nominal: tone vs. lever) as within-subject factors and treatment (nominal: saline vs. MK-801) and CS presented (nominal: tone vs. lever) as between-subject factors, were used to determine if there were any differences in sign-tracking and goal-tracking rates of the matched groups. In addition, another linear mixed effects modeling with sessions (continuous),

and response type (nominal: sign-tracking vs. goal-tracking) as within-subject factors was used to analyze rates of sign-tracking to the lever and goal-tracking to the tone.

Finally a linear mixed effects model, with block (continuous: 4 trials per block of each stimulus type) and stimulus (nominal: tone vs. lever) as within-subject factors and treatment (nominal: saline vs. MK-801) and CS presented (nominal: tone vs. lever) as between-subject factors, was used to examine the effects of the reconsolidation treatment on sign-tracking and goal-tracking response rates and sign-tracking and goal-tracking probability. Furthermore, another linear mixed effects modeling with block (continuous), stimulus (nominal: tone vs. lever), response type (nominal: sign-tracking vs. goal-tracking) as within-subject factors and treatment (nominal: saline vs. MK-801) and CS presented (nominal: tone vs lever) as a between-subject factors, was used to analyze response rates and response probability for sign-tracking to the lever and goal-tracking to the tone.

Results

Figure 4 illustrates the sign-tracking (4A) and goal-tracking (4B) rates of the matched groups. Linear mixed effects modeling revealed a significant main effect of session on sign-tracking [$F(1,20) = 35.52$, $p < 0.05$] and goal-tracking [$F(1,20) = 12.44$, $p < 0.05$], with rates indicating that both sign- and goal-tracking rates increased over the training period. Linear mixed effects modeling revealed there was a significant main effect of stimulus on sign-tracking [$F(1,20) = 50.58$, $p < 0.05$] and goal-tracking [$F(1,20) = 20.37$, $p < 0.05$] rates, where the lever CS elicited sign-tracking and the tone CS elicited goal-tracking. Additionally there was a significant between stimulus x session

interaction on sign-tracking [$F(1,20) = 35.52$, $p < 0.05$] and goal-tracking [$F(1,20) = 28.27$, $p < 0.05$] rates, suggesting that sign-tracking and goal-tracking responses to the lever CS and tone CS, respectively, increased over session. Furthermore, there was no significant interaction of treatment x CS presented x stimulus x session on sign-tracking [$F(1,20) = 0.21$, $p > 0.05$] or goal-tracking [$F(1,20) = 0.00$, $p > 0.05$] rates. Collectively, these results indicate no differences in the matched groups and that animals were exclusively sign-tracking to the lever CS and exclusively goal-tracking to the tone CS. Additionally, there were differences in sign-tracking rates to the lever CS and goal-tracking rates to the tone CS [$F(1,23) = 5.03$, $p < 0.05$].

Figure 5 shows sign-tracking (5A) and goal-tracking (5B) rates, as well as sign-tracking (5C) and goal-tracking (5D) probabilities across the four blocks of trials during the test. Linear mixed effects modeling revealed a significant main effect of block on sign-tracking rates [$F(1,20) = 33.08$, $p < 0.05$] and probability [$F(1,20) = 11.85$, $p < 0.05$], as well as goal-tracking rates [$F(1,20) = 19.35$, $p < 0.05$] and probability [$F(1,20) = 50.20$, $p < 0.05$], indicating that both sign- and goal-tracking response rates and probabilities decreased over the four trial blocks. Linear mixed effects modeling also revealed a significant main effect of stimulus on sign-tracking rates [$F(1,20) = 52.87$, $p < 0.05$] and probability [$F(1,20) = 129.15$, $p < 0.05$], as well as goal-tracking rates [$F(1,20) = 25.38$, $p < 0.05$] and probability [$F(1,20) = 49.02$, $p < 0.05$]. These results indicate that the sign-tracking responses were made to the lever CS and goal-tracking responses were made to the tone CS. Furthermore, linear mixed effects modeling revealed a significant interaction of block x stimulus on sign-tracking rates [$F(1,20) = 33.08$, $p < 0.05$] and probability [$F(1,20) = 11.85$, $p < 0.05$], as well as goal-tracking rates [$F(1,20) = 12.55$, p

< 0.05] and probability [$F(1,20) = 15.42$, $p < 0.05$], indicating that that sign-tracking and goal-tracking response rates decreased over the four trial blocks.

However, linear mixed effects modeling revealed no significant interaction of treatment x CS presented x stimulus x block on sign-tracking [$F(1,20) = 0.35$, $p > 0.05$] or goal-tracking [$F(1,20) = 0.05$, $p > 0.05$] rates or sign-tracking [$F(1,20) = 0.02$, $p > 0.05$] or goal-tracking [$F(1,20) = 0.01$, $p > 0.05$] probabilities, suggesting that the reconsolidation treatment on the lever CS and tone CS had no effect.

The results from the third experiment again indicated that animals showed explicit sign-tracking and goal-tracking to the lever CS and tone CS, respectively. However, there was no effect of the reconsolidation manipulation on the lever stimulus in both conditions despite the multiple presentations of the lever CS or tone CS. Furthermore, there were no differences in the response type on sign-tracking and goal-tracking rates, but a main effect of response type on probability [$F(1,20) = 8.99$, $p > 0.05$] suggesting that the likelihood of a obtaining a goal-tracking response decreased quicker than sign-tracking.

Discussion

The results reported in these three experiments reveal a number of interesting aspects regarding memory consolidation and memory reconsolidation on a PCA task. In the first experiment it was found that NMDA receptor blockade can prevent the consolidation of a lever CS and tone CS memory. Results from the second experiment demonstrated that the administration of MK-801 post reactivation of a single presentation of the previously conditioned stimuli did not have any effect on subsequent tests, suggesting that memory reconsolidation of these conditioned stimuli was not disrupted.

To follow up on the lack of an effect, experiment 3 examined the idea of a needing greater a greater number of presentations to reactivate a PCA memory. The results of experiment 3, where four presentations of the previously conditioned were presented and then MK-801 was administered, again demonstrated no disruption following the memory reconsolidation manipulation. Overall, these data suggest that basic stimulus- reward learning and the attribution of incentive value can be prevented by the administration of MK-801 post-session. Furthermore, based on the methods used, the administration of MK-801 after a reactivation session, where one or four presentations of a targeted stimulus was presented, demonstrated there were no effects in disrupting memory reconsolidation.

The first set of data fits with literature demonstrating that the administration of MK-801 post-session can disrupt Pavlovian learning, more specifically PCA (Bevins & Bardo, 1999; Blaiss & Janak, 2007). However, the data concerning memory reconsolidation prompts discussion about the protocols used. First, when presenting a previously conditioned stimulus, whether it an aversive or appetitive CS-US pairing, during the reactivation phase raises the issue of when does reactivation become extinction learning and whether or not these two processes are dissociable (de la Fuente et al., 2011). If reactivating a memory is extinction learning, than the disruption of the memory during reconsolidation should prevent extinction learning. However, a recent study by Merlo and colleagues (2014) examined how the gradual increase in presentations of a previously conditioned fear stimulus can affect the behavioral and molecular transitions between reconsolidation and extinction. The results of the aforementioned study demonstrated that by increasing the number of CS presentations during reactivation a

gradual shift towards extinction learning occurs. Furthermore, this shift from reactivation to extinction is associated with an increase in calcineurin, a protein phosphatase linked to the consolidation of fear memory (Ikegami & Inokuchi, 2000). While this is an example of reactivation versus extinction in aversive conditioning, the data suggests that too many presentations of the conditioned stimulus during reactivation could lead to extinction learning. While, there was no molecular data collected in this present study, the similar results from one presentation versus four presentations, where both saline and MK-801 treated rats extinguished at similar rates, suggest that there was no blockade of any possible extinction learning.

Interestingly, present results from the attempt to disrupt memory reconsolidation relate to the results that Blaiss and Janak (2007) found, where goal-tracking responses to a tone and light CS+ combination for a sucrose solution were unaltered by post-session treatments of anisomycin. While, this study had a tone CS to elicit goal-tracking, the administration of MK-801 post-session did not have any effect, similar to the effects observed herein. However, a recent study by Reichelt and Lee (2013) did demonstrate a disruption of memory reconsolidation in goal-tracking behavior. In this particular study, rats were had to discriminate a CS+ tone from a CS- tone for three sucrose pellets over three, six, or twelve days of training with 10 presentations each followed by a reactivation, during which three presentations of the CS+ were presented. It was found that at three days, when treatments were administered prior to reactivation sessions, saline-treated animals were unable to discriminate the CS+ and CS- thus suggesting that extinction learning occurred during the reactivation session. However, MK-801 treated animals following the three days of CS+ and CS- discrimination task were still able to

make the distinction, suggesting that MK-801 prevented the CS+ from undergoing extinction learning during the reactivation task. However, at six days it was found that discrimination for CS+ and CS- was only impaired in the drug treated animals, suggesting goal-tracking memories were disrupted. Finally, following the twelve days of training, it was shown that the pre-session administration of MK-801 during the reactivation session had no effect on the CS+ and CS- discrimination task. One thing to note in the study by Reichelt and Lee (2013) is that pre-session administration of MK-801 was used instead of the typical post-session administration that has been demonstrated to work in other Pavlovian conditioning paradigms (Kelley et al., 2007; Sadler et al., 2007; Milton et al., 2008). Another difference between the present study and Reichelt and Lee (2013) is that 60 pairings of each conditioned stimulus (CS+ and CS-) were presented during the initial training, with 3 presentations during reactivation; in contrast, in the present study there was greater initial conditioning of two appetitive stimuli, where there were 224 pairings of each stimulus, with 1 or 4 presentations of each during reactivation. Thus, the resistance of sign- and goal-tracking to a lever CS and tone CS, respectively, to the disruption in reconsolidation herein supports the possibility of enhanced memory strength for each stimulus.

Memory strength has been shown to be correlated with the extent of training. In aversive learning, it has been shown that the number CS-US pairings of a fear stimulus can affect the number of CS presentations required during reactivation to disrupt memory. Furthermore, the number of reactivation presentations might not have any effect when the number of conditioned responses elicited by the CS-US pairings reach an asymptote, where the memory is, in a sense, fully consolidated, and where training

beyond that could lead to over-training (Di Ciano et al., 2001; Wang et al., 2009). Moreover, following over-training, an extended period of abstinence from CS-US training (30 days; Wang et al., 2009) was required in order to disrupt memory reconsolidation. While there has been little study in over-trained appetitive memories, strong appetitive memories for cocaine-associated cues can be disrupted (Lee et al., 2006). Within the 2-CS model, the lever CS associated with sign-tracking is theoretically representative of a strong appetitive memory, where the incentive value attributed to it can influence the memory formed and make it stronger to start off with. However, when the lever CS and tone CS, a stimulus absent of incentive value, underwent disruption during memory reconsolidation, neither stimulus showed any evidence of memory disruption. This suggests that it is quite possible that in the present study, the strength of the Pavlovian memories could be resistant to memory destabilization due to an over-training effect.

Overall, the present study demonstrated the importance of the NMDA receptor in the consolidation of reward-associated stimuli, where both general stimulus-reward learning and stimulus-reward learning with attribution of value were impeded. While, the results for the attempts to modulate a pre-existing memory did not show any significant effects, it is clear that the methods to successfully modify a PCA memory require a lot more consideration. The concept that over-training could be influencing the results seen during the attempt to disrupt memory reconsolidation for both the lever CS and tone CS provokes thought about the different neurobehavioral mechanisms that drive sign- and goal-tracking. Stimulus-response (S-R) relationships have been proposed to drive sign-tracking repertoires, while learned action-outcome (A-O) relationships have been

proposed to drive goal-tracking repertoires (Clark et al., 2012; Dezfouli & Balleine, 2012). These proposed mechanisms suggest sign-tracking should be more habit-like, while the goal-tracking is more goal-directed (Dayan & Berridge, 2014). With sign-tracking being habit-like, it has been hypothesized and demonstrated that sign-tracking behavior is less sensitive to changes in the CS-US relationship, where under extinction conditions or the application of an omission contingency sign-tracking behavior continues to persist longer than goal-tracking behavior which is goal-directed, making it more malleable and sensitive to changes in contingency (Beckmann & Chow, submitted). If sign-tracking repertoires are reflective of a habit-like learning system, and goal-tracking is not, than theoretically the formation of these memories could also differ in the time it takes for the two response types to become over-trained.

Collectively, the data from the present study and the discussion mentioned above suggest that memory profiles behind sign-tracking and goal-tracking repertoires could be different. However, current procedures used for training the different stimuli could influence the overall memory. In all, different procedural methods could provide insight into whether or not stimuli attributed with incentive value have different memory profiles than normal reward-predictive stimuli.

Figure 2.1

Mean (± SEM) response rate (responses/second; r/s) for (A) sign-tracking, (B) goal-tracking, (C) goal-tracking 8s before the presentation of a stimulus, and (D) difference in response probability, where 1.00 guarantees a sign-tracking response every trial and -1.00 guarantees a goal-tracking response every trial.

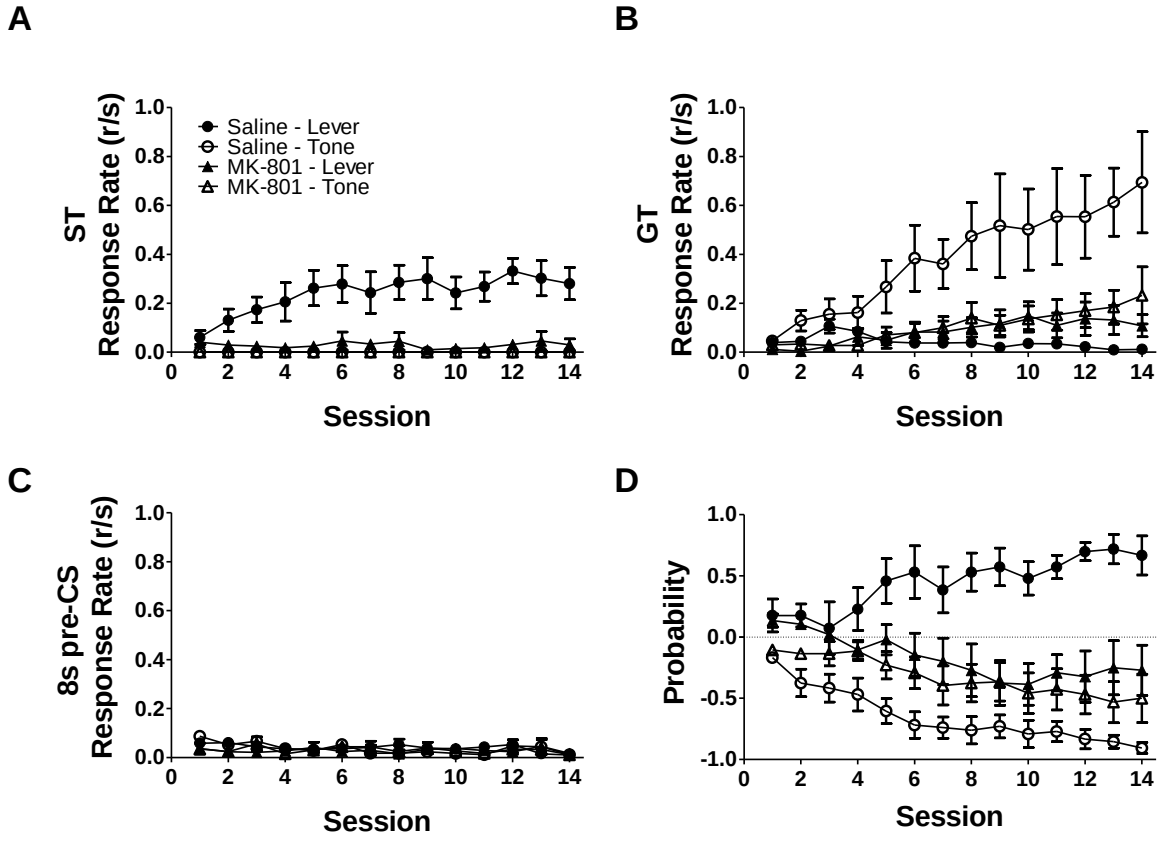


Figure 2.2

Mean (± SEM) response rate (responses/second; r/s) for (A) sign-tracking and (B) goal-tracking for the matched groups.

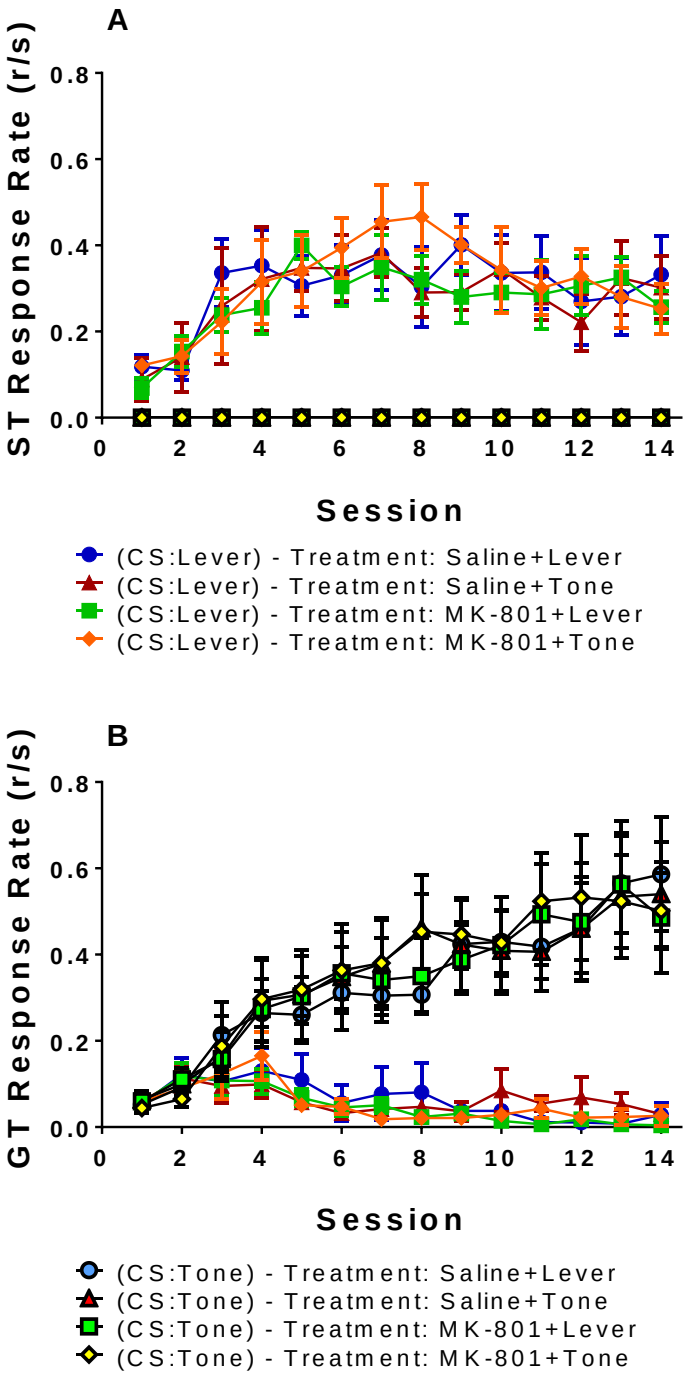


Figure 2.3

Mean (± SEM) response rate (responses/second; r/s) for (A) sign-tracking and (B) goal-tracking and mean (± SEM) probability of obtaining a response for (C) sign-tracking and (D) goal-tracking. (CS: Lever vs. Tone) indicates the stimulus being responded on, while (Treatment: Saline vs. MK-801 + Lever vs. Tone) indicates what stimulus and drug were used during the memory reconsolidation manipulation.

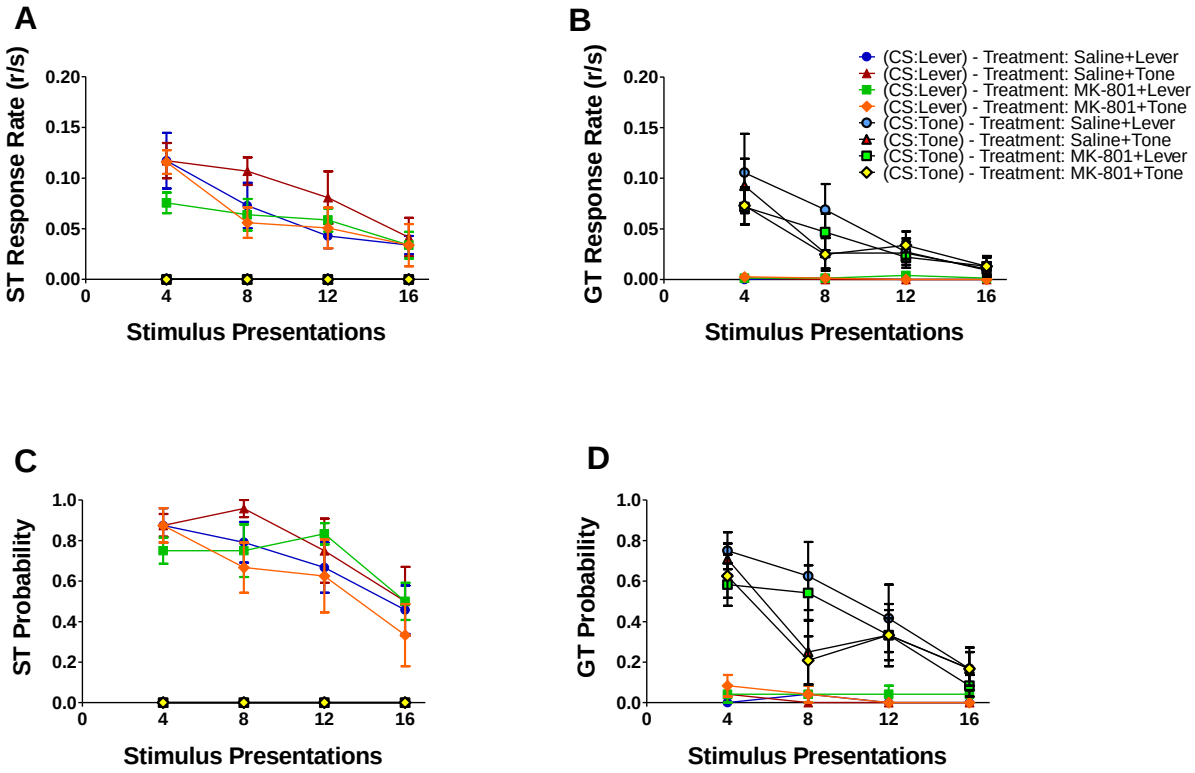


Figure 3.1

Mean (± SEM) response rate (responses/second; r/s) for (A) sign-tracking and (B) goal-tracking for the matched groups.

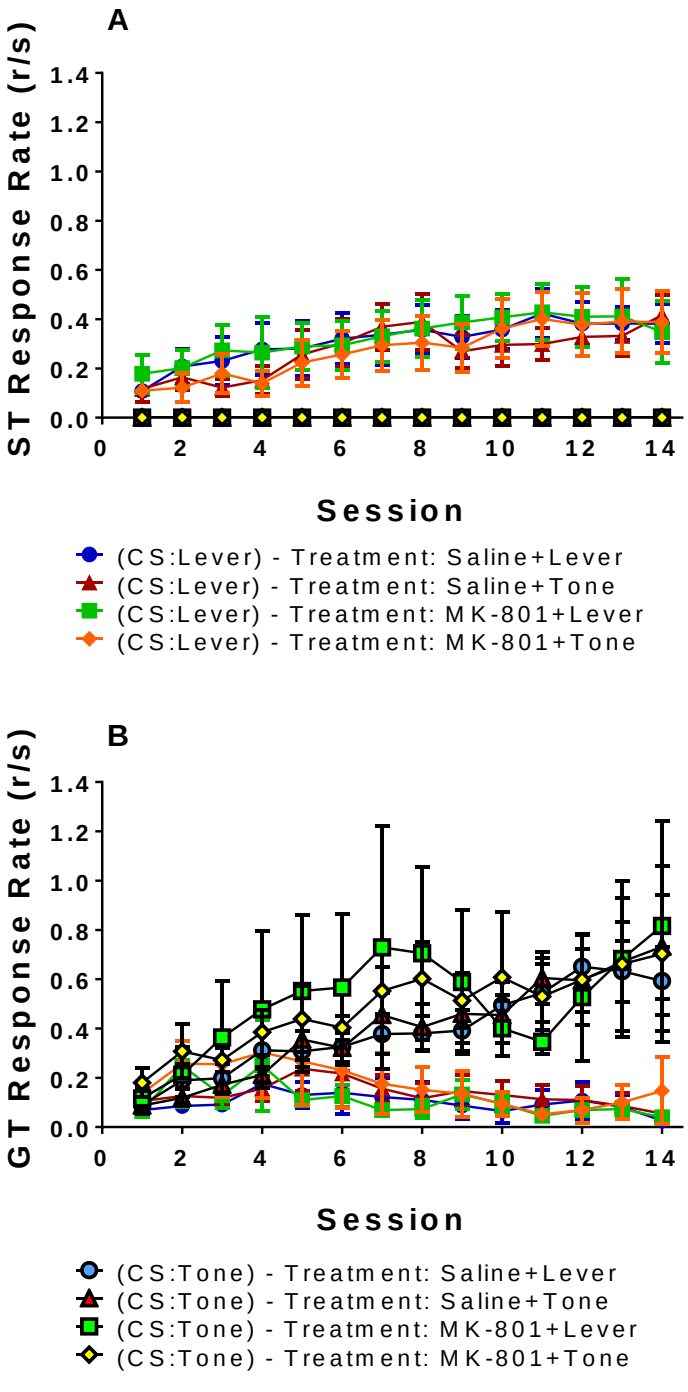
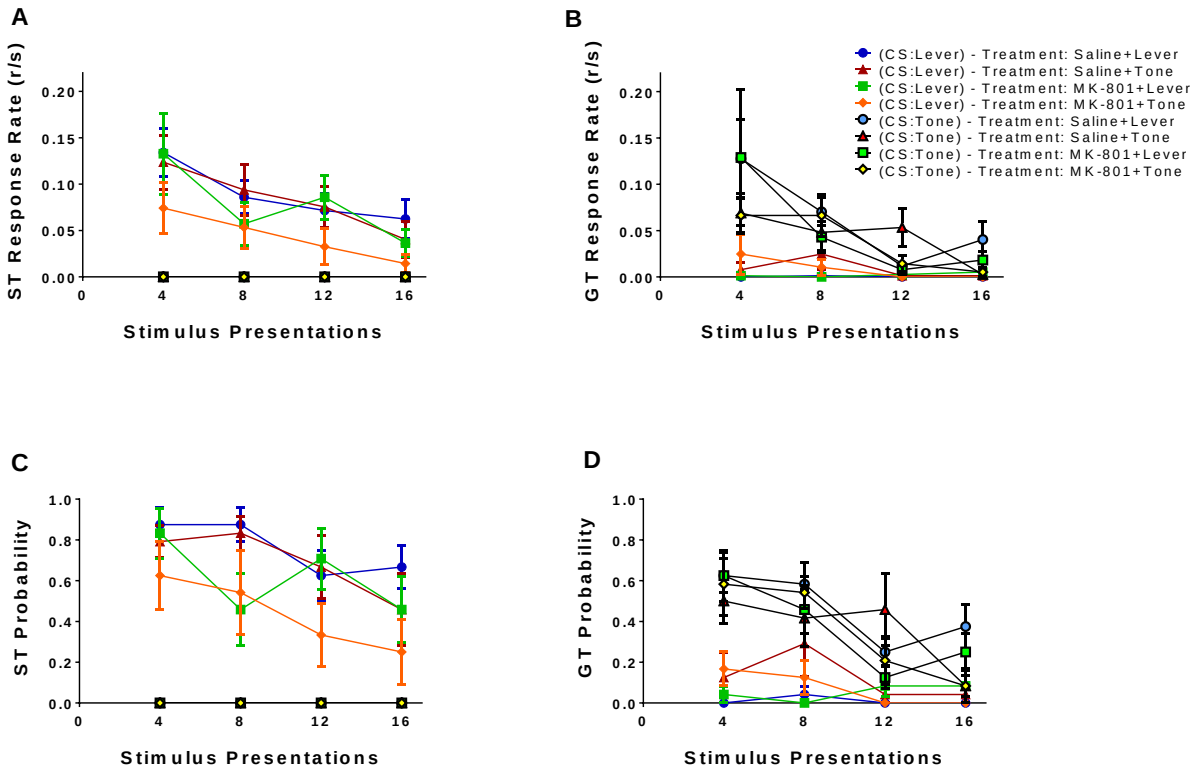


Figure 3.2

Mean (± SEM) response rate (responses/second; r/s) for (A) sign-tracking and (B) goal-tracking and mean (± SEM) probability of obtaining a response for (C) sign-tracking and (D) goal-tracking. (CS: Lever vs. Tone) indicates the stimulus being responded on, while (Treatment: Saline vs. MK-801 + Lever vs. Tone) indicates what stimulus and drug were used during the memory reconsolidation manipulation.



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Publications

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Oral Presentations

Pavlovian Valuation: A Look at Reversal Learning (2014, May) *27th TriState Conference on Animal Learning and Behavior*, Windsor, Ontario Canada.

Pavlovian Valuation Systems – (2014, May) *Center for Ecology, Evolution and Behavior*, Lexington, KY.

The Role of Glutamate in Pavlovian Valuation – (2014, May) *Midwestern Psychology Assocation Annual Conference*, Chicago, IL.

Poster Presentations

Chow, J. J., Darna, M., & Beckmann, J. S., (2014, November). The role of D1 and D2 receptors in Incentive Value Attribution. Poster session presented at *2014 Society for Neuroscience*, Washington D.C.

Chow, J. J. & Beckmann, J. S., (2014, June). The Role of Glutamate on Incentive Value Attribution: Acquisition and Expression. Poster session presented at *2014 CPDD*, San Juan, PR.

Chow, J. J., Scott, R. J., & Beckmann, J. S., (2014, May). Pavlovian Valuation: Lever vs Tone Choice. Poster session presented at *2014 Midwestern Psychology Association Annual Conference*, Chicago, IL.

Scott, R. J., Chow, J. J., & Beckmann, J. S., (2014, April). Modeling Pavlovian Conditioned Approach Using a Drug Reinforcer. Poster session presented at *2014 National Conference of Undergraduate Research*, Lexington, KY.

Chow, J. J. & Beckmann, J. S., (2013, November). Dissociating sign- and goal-tracking function using a 2-CS Pavlovian conditioned approach task. Poster session presented at *2013 Society for Neuroscience*, San Diego, CA.

Chow, J. J., Beckmann, J. S., & Bardo, M. T., (2013, June). Strain differences in sign-tracking and goal-tracking as an indicator of abuse vulnerability in rats. Poster session presented at *2013 CPDD*, San Diego, CA.

Chow, J. J., Beckmann, J. S., & Bardo, M. T., (2012, October). The Role of D1 and D2 Dopamine Receptors on Incentive Salience Attribution and Subsequent Cocaine Acquisition. Poster session presented at the *2012 Society for Neuroscience*, New Orleans, LA.

Chow, J. J., Beckmann, J. S., & Bardo, M. T., (2012, April). The role of D1 and D2 dopamine receptors on incentive salience attribution and cocaine self-administration. Poster session presented at the *2012 Undergraduate Research Showcase*, Lexington, KY.

Chen, H.-T., Lorch, R. F., Chow, J., Carter, N., Crispin, R. (2011, May). Effects of Signals on Outlining. Poster session presented at the *2011 Midwestern Psychology Association Annual Conference*, Chicago, IL.

Lorch R. F., Chen H.-T., Chow J., Carter N., Crispin R. (2011, July). Effects on Outlining of Signaling Topics in Printed and Spoken Texts. Poster session presented at the *Annual Meeting of the Society for Text & Discourse*, Poitiers, France.

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Christian Soares – Fall 2014

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Michael T. Bardo & Jonathan Chow
NCUR - Oral Presentation Proctor — April 2014