TRANSSITUATIONAL TRANSFER OF TOLERANCE TO FRUSTRATION STRENGHTENED BY OPIOID BLOCKAGE

by

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TABLE OF CONTENTS

LIST OF FIGURES

Incentive Relativity

Mammals are capable of forming expectations about rewards and demonstrate changes in behavior when expected rewards deviate from the actual rewards received under similar conditions. Tinklepaugh (1928) was one of the first to report that monkeys are capable of developing expectations about rewards. A monkey was trained to look, in different trials, for a piece of lettuce or banana under one of two cups. The other cup was empty. In this case, the banana was preferred over the lettuce; however, if the monkey was hungry, it would eat the lettuce. In a training trial, the monkey could watch the experimenter place the food reward, banana or lettuce, under one of the two cups, and then a screen was lowered during a retention interval lasting a few seconds. When the screen was raised, the monkey could choose a cup, and was allowed to consume the reward. During occasional test trials, the monkey watched a banana being placed under the cup, but the banana was replaced by lettuce during the retention interval, while the screen was lowered. However, when the monkey discovered the less preferred reward of lettuce under the cup rather than the expected banana, it searched under the cup, presumably for the missing banana, and occasionally emitted shrieks of anger and left the lettuce uneaten. The rejection of the less preferred lettuce reward is best understood by assuming an expectation of a more preferred reward, the banana, had been formed and that finding the lettuce instead of the banana had violated this expectation.

Elliott (1928) reported a similar study with rats trained in a complex maze. The study consisted of two rewards, a preferred wet cereal mixture and a less preferred (but acceptable) sunflower seeds. Rats were first trained to run the maze with a wet cereal reward or a sunflower seed reward delivered in the goal box. Wet cereal animals were then shifted to receive the less desirable reward of sunflower seeds. In subsequent trials, downshifted rats ran through the maze

with more errors and with a longer latency to reach the goal compared to those that had always received the sunflower seed reward in previous trials. Elliot (1928, p. 29) concluded that the "rats had learned to expect a specific reward," and that the increase in running time and number of errors was due to the animals searching for the missing food reward causing significant changes in behavior.

Both Tinklepaugh's and Elliott's experiments involved manipulating the qualitative value of rewards and monitoring the behavioral changes that followed. However, the quantitative value of rewards can likewise be manipulated with similar changes in behavior. Crespi (1942) manipulated the quantitative value of rewards (grams of solid food) in a runway procedure. In this study, rats demonstrated significant reductions in running speeds when downshifted from a large reward to a small reward compared to that of unshifted control animals. Conversely, when rats were shifted from small rewards to large rewards, they seemed to showed an increase in running speeds, relative to preshift running speeds (although large-reward unshifted controls were not included in Crespi's study). These effects were referred to as "depression" and "elation," respectively, and were proposed to be due to the emotional responses resulting from violations of reward expectancies.

These findings suggested that the Thorndikian view of reward magnitude directly affecting learning was insufficient and prompted the notion that reward magnitude influences incentive motivation and affects behavior independently of learning (Flaherty, 1996). Crespi (1942) suggested that the value of the incentive needed to be viewed both quantitatively and qualitatively in relation to the expected versus obtained value. It was Crespi's early research that led to the definition of incentive relativity. Flahtery (1996, p. 10) defined incentive relativity as the "effect of a given reward in behavior [being], in part, relative to the animal's experience with

rewards of different amounts or qualities." The notion of incentive relativity suggests that incentives are not simply valued by their own properties. The absolute value refers to the physical properties of an incentive, such as the caloric content, magnitude, or intensity. The relative value refers to setting the value of an incentive on the basis of experience with incentives of different absolute value (Flahtery, Krauss, Rowan, & Gibson, 1994).

The terms "positive contrast" and "negative contrast" were first used by Zeaman (1949) in reference to the behavioral changes witnessed when increasing and decreasing, respectively, the magnitude of the cheese reinforcer in his runway experiments. When the cheese reinforcer was decreased from a 2.4 g reinforcer to a 0.6 g reinforcer for traveling down a runway, Zeaman found animals took significantly longer to reach the goal compared to animals consistently rewarded with a small reinforcer (negative contrast). Likewise, when animals were upshifted from a smaller reward to a larger reward, they took significantly less time to travel to the goal compared to animals that received the larger reward continuously (positive contrast). Here the term "contrast" refers to the comparison of reward values, and "positive" and "negative" refers to the direction of the shift (whether the change in reward values was upward or downward). Bower's (1961) later research added the terms "successive" and "simultaneous" into the contrast repertoire. Successive contrast refers to instances in which different rewards are presented one after another, usually involving a single shift, as in the rat studies described thus far, whereas simultaneous contrast occurs when animals receive both reward values within the same session, but in different contexts. Bower trained rats to expect large rewards when running in a black alley, and to expect small rewards in a white alley, and compared their latencies to those of animals that received only large or only small rewards regardless of alley brightness. Rats that had been taught to discriminate between the two alleys ran faster in the alley associated with the

large reward and slower in the alley associated with the small reward when compared to the respective control groups. These effects are known as positive and negative simultaneous contrast, respectively.

The experiments of Elliott (1928), Crespi (1942), and Zeaman (1949) measured the behavior of animals that were searching for the incentive and are thus referred to as instrumental successive negative contrast (iSNC). Vogel, Mikulka, and Spear (1968) developed a model illustrating SNC based on consummatory behavior (cSNC). Rats were given access to 32% sucrose solution for 11 daily trials (preshift), 5 min per trial and then downshifted to a 4% sucrose solution for 6 trials (postshift). This downshift from a higher concentration of sucrose solution to a lower concentration produced significantly fewer licks than control animals that had received only 4% sucrose. The reduction in the licking response was acute on the first downshift trial, but, over the subsequent trials, downshifted animals began to show a recovery of their consummatory behavior, until they eventually did not differ from the control group.

Flaherty (1996) described the downshift phase as triggering a two-stage process (see Figure 1). Stage 1 occurs on the first downshift trial, when animals detect the change in incentive values; they reject this change; and they engage in searching behavior to either find the missing, preferred, incentive or to escape the less desirable incentive. Stage 2 occurs during the subsequent daily trials following the initial downshift. Animals experience a conflict because they cannot find the preferred incentive, but they also reject the available incentive; however, they are food deprived and therefore need the calories that the 4% sucrose solution provides. Consummatory behavior then recovers to the level of unshifted controls always exposed to the 4% solution.

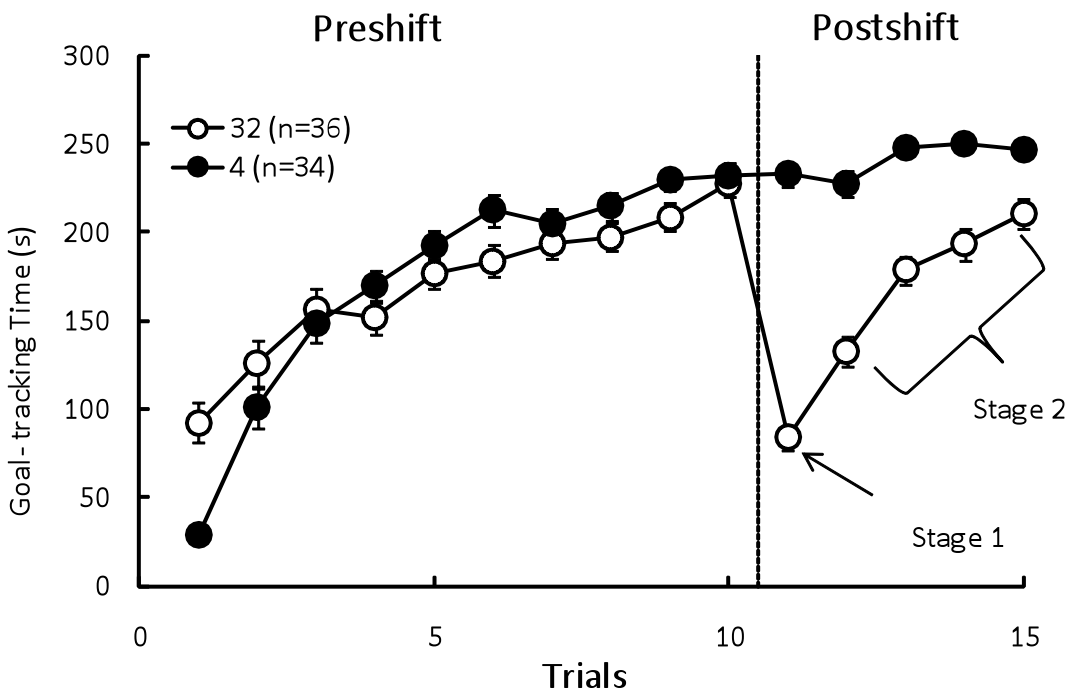

Figure 1. Example of cSNC obtained by averaging the performance of animals from different experiments treated in a similar manner. The dependent variable is the cumulative time in contact with the sipper tube, goal-tracking, expressed in seconds (error bars are ± SEM).

Frustration Theory

An alternative way to examine incentive downshift is in terms of Amsel's (1992) frustration theory. Frustration theory is based on the notion that a negative emotional reaction occurs when an animal experiences a negative discrepancy between an expected reward and the presentation of a lesser reward (e.g., incentive downshift), or nonreward (e.g., appetitive extinction). According to Amsel, this negative discrepancy occurrs when an animal first experiences a surprising nonreward triggers an unconditioned internal state called primary frustration. An association then develops between the external cues and the animal's internal

state of primary frustration, whose product is an aversive anticipatory state of frustration, termed secondary frustration.

Amsel (1992) suggested that primary frustration had several properties. First, the unconditional reaction to a frustrating event is drive inducing and typically leads to a temporary increase in responding in both Pavolvian (Dudley & Papini, 1995; Papini & Dudley, 1997) and instrumental (Hall & Marr, 1969; Stout, Boughner, & Papini, 2003) procedures. This energizing property is illustrated in instrumental procedures in Hall and Marr's (1969) double runway study where rats were given differential reward magnitudes depending on which alley runway they were being trained. Results revealed rats ran at the same speed when upshifted to larger reward than they were originally trained to receive upon completing the runway, but rats ran faster after being downshifted to a smaller reward compared to running speeds in an unshifted control alley. Dudley and Papini (1995) demonstrated the energizing property of primary frustration using a Pavlovian procedure. Rats exposed to light-food pairing in an autoshaping procedure, lever pressed at higher rates after light-only nonreinforced trials than after reinforced trials. Moreover, rats lever pressed more following nonreinforced trials relative to control animals that experienced the reinforcement presentations but in an unsignaled fashion. Rats also exhibited an energizing of lever pressing following nonreinforcement and decreases in two different incentives: The omission of sucrose and the decrease of 5 pellets to 1 pellet.

Second, primary frustration is hedonically aversive and, if given the opportunity, animals will learn to escape from a context associated with nonreward (Daly, 1974; Norris, Pérez-Acosta, Ortega & Papini, 2009). In an escape from frustration training situation, an animal is allowed to move out of the context where they have experienced the incentive downshift and into a neutral context (Daly, 1974). In Norris et al's (2009) study, animals were never explicitly rewarded for

leaving the downshifted context, but nonetheless consistently did so faster than unshifted animals, supporting the notion that escaping from the aversive context was rewarding itself. Third, primary frustration has stimulus properties and triggers behavior, such as, aggression (Gallup, 1965) or suppression of aggressive behaviors (Mustaca, Martínez, & Papini, 2000), emission of odor (McHose & Ludvigston, 1966), increased locomotion (Gallup & Altomari, 1969; Flaherty, Troncoso, & Dreschu, 1979; Flaherty, Krauss, Rowan & Grigson, 1994), and distress vocalizations (Amsel, Radek, Graham, & Letz, 1977).

Secondary frustration results when stimuli associated with primary frustration begin to trigger an expectation of frustration (Amsel, 1992). This anticipatory effect results from an association forming between the stimuli that previously predicted a high value reward being paired with primary frustration. Eventually, the cues become ambiguous by activating conflicting expectations of reward and frustration. This discrepancy results in an approach-avoidance conflict. The animal wants to avoid the frustration experience, but also wants to approach in order to obtain the reward. Secondary frustration may also lead to persistence in behavior when paired with reward. The pairing reward and secondary frustration leads to the development of tolerance to frustration through counterconditioning. This counterconditioning leads to a hedonic shift of secondary frustration from an aversive to an appetitive state, resulting in an increase in behavioral persistence in regards to goal approach. This is best illustrated in terms of the partial reinforcement extinction effect (PREE). Animals that have previously been trained under a partial reinforcement schedule demonstrate greater resistance to extinction, through the persistence of the lever-pressing behavior, than animals trained under a continuous reinforcement schedule.

Likewise, counterconditioning, through partial reinforcement reduces the cSNC effect (Pellegrini, Muzio, Mustaca, & Papini, 2004). Rats trained under a 50% partial reinforcement schedule received 32% sucrose (reward) or distilled water (nonreward) during a 20 trial preshift (where half of the trials were reinforced) demonstrated a reduced initial consummatory suppression and faster recovery, relative to animals trained under continuous reinforcement of 32% sucrose. This partial reinforcement effect was eliminated when nonreinforced trials, during the preshift, were preceded by administration of the benzodiazepine anxiolytic chlordiazepoxide (CDP; Pellegrini et al., 2004), and was also modulated by the delta opioid receptor agonist [D-Pen2,D-Pen5]enkephalin (DPDPE) (Wood, Daniel, & Papini, 2005). Thus, the effects of frustration can be modulated via pharmacological manipulation (more on this in the pharmacological section).

Amsel's (1992) frustration theory can also be applied to cSNC (see Papini, 2003; Wood, Daniel, & Papini, 2005). Frustration theory (Amsel, 1992) assumes that during the preshift phase of cSNC (Trials 1-10 in a typical cSNC experiment), animals form an expectation of obtaining the 32% sucrose solution when in the context of the cSNC box. The context of the cSNC box, in turn, triggers the drinking response. On the first downshift trial (Trial 11), when the animal encounters the surprising reduced reward (4% sucrose), the discrepancy between the expected 32% and the actual 4% solution is detected. This induces the unconditional aversive internal state of primary frustration. An association then develops between external cues of the cSNC context and the internal state of primary frustration leading to the aversive anticipatory state of secondary frustration. Now, the cSNC box context has both the ability to trigger the drinking response and to elicit an avoidance response that accompanies the anticipatory state of secondary frustration. Through subsequent pairings of secondary frustration and the less valued incentive of 4%

sucrose, two dissociable processes are induced. First, appetitive reinforcement while under the state of frustration (either primary, secondary, or both) leads to the counterconditioning of frustration, which reduces the avoidance component of the conflict, thus promoting recovery from cSNC. This counterconditioning mechanism is central to the type of transsituational effect studied in the present experiment. Second, experiencing the new, 4% sucrose solution triggers new learning. Through this process, the expectation of the larger reward is weakened and replaced by an expectation of the new incentive. Both the formation of the new incentive expectancy and the weakening of the expectation of the old incentive (32%) contribute to the recovery of consummatory behavior during subsequent postshift trials.

Factors Affecting Incentive Downshift

There are many factors affecting behavior in incentive downshift situations. For instance, Papini and Pellegrini (2006) found that the detection of the reward downshift was controlled by a discrepancy ratio between the concentrations of sucrose received during postshift trials and the expected concentration based on preshift trials (except when the concentrations were extreme). Equal postshift/preshift ratios resulted in similar levels of suppression, even when the absolute values and the absolute difference of the concentrations were different. This suggests that a scaling effect (i.e., constant proportionality) modulates emotional reactivity following the detection stage of Flaherty's (1996) model and presumably primary frustration in Amsel's (1992) theory has scaling property.

Empirical evidence for searching for the missing incentive is evident in increased ambulatory and rearing behaviors for downshift rats compared to the unshifted control groups in the usual contrast box (Pellegrini & Mustaca, 2000), in the open field situations (Flaherty, Blitzer, & Collier, 1978), in increased exploration of arms in the radial arm maze (Flaherty et al.,

1994), and in the elevated plus maze (Pecoraro, Timberlake, & Tinsley, 1999). However, it is unclear whether animals are searching for the missing reward or searching for an exit from that location. Thus, it is uncertain whether rats are searching, attempting to escape from the situation, or both.

Prior exposure to partial reinforcement has been demonstrated to attenuate cSNC and facilitate the recovery process (Pellegrini et al., 2004). In Pellegrini et al.'s (2004) study, rats were trained either under continuous or partial reinforcement with two sucrose solutions: 32% or 4%, in a typical cSNC paradigm for 20 daily trials. Animals in the continuous reinforcement condition were presented with either 32% or 4% solution (depending on group assignment) in every preshift trial; the partial reinforcement groups were presented with their respective solution in half the trials (reinforced trials) and with distilled water in the remaining 10 trials (nonreinforced trials). For the postshift trials, all animals received 4% sucrose solution. Results revealed that animals in the downshift partial reinforcement condition demonstrated reduced cSNC compared to the continuously reinforced downshift animals. Likewise, the downshifted partially reinforced animals showed a faster recovery of consummatory behavior compared to that of the downshifted continuously reinforced group. Amsel's (1992) frustration theory suggests that this attenuation and faster recovery from cSNC in the partially reinforced animals is due to the counterconditioning of secondary frustration that occurred during the rewarded preshift trials.

Ross (1964) conducted an experiment to test whether the counterconditioing that occurs during partial reinforcement in one context could be transferred to another context, even after animals had more recently undergone continuous reinforcement training in the second context. Of specific interest here is the hypothesis that behavioral responses (running, jumping, and

climbing) that are “compatible” with each other should elicit similar resistance to extinction compared with behaviors that are “incompatible”. Ross believed that jumping and running were “compatible”, whereas climbing and running were “incompatible”. This characterization led to the prediction that animals that experienced counterconditioning for a response compatible with running (i.e., jumping) during the first acquisition phase should experience a transfer of resistance to extinction, whereas, animals that experienced an incompatible response to running (i.e., climbing) should experience response competition between the earlier trained counterconditioning response of climbing and the newly acquired continuously reinforced response of running. Thus, Ross predicted there would be a transfer of resistance to extinction from jumping to running, but not from climbing to running.

To test this hypothesis, rats were first trained to either run, jump, or climb to obtain a reward at the end of a runway (runway A) under partial (50% reward delivery) or continuous reinforcement (100% reward delivery). After completion of the first acquisition phase, animals were then trained to run down a different runway (runway B) under a continuous reinforcement schedule. Following this second acquisition phase, animals underwent extinction in runway B, where they had only experienced continuous reinforcement. As predicted, animals that learned to jump in runway A under partial reinforcement demonstrated greater persistence in the extinction of running in runway B. However, rats that learned to climb in runway A under partial reinforcement showed faster extinction of running in runway B. Frustration theory (Amsel, 1992) argues the persistence in behavior seen in animals with previous exposure to partial reinforcement is the result of counterconditioning that occurred during the first acquisition phase of training that was reactivated by the extinction in the second phase of training. Thus, the theory suggests that the previous counterconditioning of frustration allows for transfer across situations

and behaviors. The previous counterconditioning of frustration inoculates the animal against the disrupting effects of other frustrating events across time and contexts.

Psychopharmacology

Pharmacological manipulations have been extensively used to examine the neural basis underlying cSNC. The main conclusion from these studies is that some drugs have trial-selective effects, that is, they affect cSNC when administered before one specific trial. It was this trial selectivity of some drugs (e.g., benzodiazepine anxiolytics) that led Flaherty (1996) to suggest the multistage model for incentive downshift. Four types of drugs tapping on relatively selective classes of receptors and found to modulate incentive downshift are: hormones (corticosterone, ACTH, and testosterone), anxiolytics (including benzodiazepines and ethanol), opioids, and the memory enhancer D-cycloserine (an N-Methyl-D-aspartate receptor partial agonist).

Stress hormones. Corticosterone and the adrenocorticotropic hormone, ACTH, are the stress hormones of interest to examine in the cSNC paradigm. Corticosterone has been widely associated with both acute and chronic stress responses (e.g., McEwen, 2007). It is produced in the adrenal cortex and is a component of the hypothalamic-pituitary-adrenal (HPA) axis (Herman, 2009). The release of corticosterone is controlled by ACTH, which is produced in the anterior pituitary gland, and, in turn, is modulated by the hypothalamus. The HPA axis is a key mechanism that allows for behavioral and physiological adjustments in response to relatively intense environmental changes (Pecoraro & Dallman, 2009). Stress hormones have a variety of effects, including acting on membrane receptors in the hippocampus, dentate gyrus, central nucleus of the amygdala, cerebellum, and the hypothalamus (Rossie, Jaychandran, & Meisel, 2006).

Two avenues of research provide evidence for stress hormones being involved in cSNC. The first revealed that plasma levels of corticosterone and ACTH were higher in rats undergoing cSNC compared to animals in the unshifted control group after Trial 11 and before and after Trial 12 (Flaherty, Becker, & Pohorecky, 1985; Mitchell & Flaherty, 1998; Pecoraro, de Jong, & Dallman, 2009). Flaherty et al's (1985) early work suggested that corticosterone was selectively released on Trial 12, but not on Trial 11. However, Pecoraro et al.'s (2009) recent work provides evidence that corticosterone levels peak after the first downshift trial and then decrease after the second downshift trial, thus suggesting HPA axis activation may also occur in Stage 1 of Flaherty's (1996) model. This result is consistent with an account of cSNC frustration based on frustration theory (Papini, 2003), since the enhanced released of stress hormones is consistent with an emotional reaction of primary frustration during the first downshift trial.

However, there were some procedural differences that may account for the discrepancy in results obtained between these studies. Flaherty et al. (1985) and Mitchell and Flaherty (1998) conducted the cSNC testing in a separate apparatus rather than in the animals' home cage (Pecoraro et al., 2009). Previous research suggests the cSNC boxes may have served as a predictor for the delivery of sucrose and therefore may have weakened the HPA axis outflow, for the first trial of downshift, and then became a predictor of a less valuable incentive, the 4% sucrose, thus enhancing the HPA axis outflow for the second trial of downshift (Pecoraro et al., 2009). However, this hypothesis is unlikely. Pecoraro et al. (2009) tested the predictive context hypothesis in two ways: (1) by testing the animals in their home cages vs. a separate cSNC apparatus, and (2) by using distinctive contexts which predicted whether or not sucrose would be delivered. Both tests yielded the same results: ACTH and corticosterone levels were higher on the first downshift trial and decreased after the second downshift trial. Moreover, although the

external context can be manipulated to yield a cSNC effect, contextual control over licking is rather weak (Daniel, Wood, Pellegrini, Norris, & Papini, 2008). Also, Pecoraro et al. (2009) employed a 12-day preshift period with 5.5-min trials as opposed to a 10-day preshift and 5-min trials used in the other studies (Flaherty et al., 1985; Mitchell & Flaherty, 1998). Perhaps the prolonged preshift period provided a more stressful downshift experience in the Pecoraro et al. (2009) study.

The second avenue of evidence linking corticosterone to cSNC involved its administration immediately after Trial 11. Posttrial 11 administration of corticosterone results in prolonged consummatory suppression in later trials (Bentosela, Ruetti, Muzio, Mustaca, & Papini, 2006). Interestingly, this effect was observed in successive, but not anticipatory contrast, it was found to depend on a large reward downshift, and it could not be explained in terms of conditioned taste aversion (Ruetti, Justel, Mustaca, & Papini, 2009). These results suggest that corticosterone facilitates the encoding of an emotional memory of the frustrative reaction (Ruetti et al., 2009), as it is known to do in other aversive situations (McGaugh, 2000; Roozendaal, 2000).

Testosterone. Testosterone binds to androgen receptors located throughout the brain. Fernandez-Guasti and colleagues (1989) illustrated that sexual behavior elicits an anxiolytic-like effect of reducing the effect of stressors. Previous research has recently shown that testosterone's anxiolytic-like effects also attenuate the cSNC effect (Justel, Ruetti, Bentosela, Mustaca, & Papini, 2012). In this study, gonadectomized animals were trained in a typical cSNC paradigm and testosterone (or saline) was administered before Trial 5 and continued until Trial 15. Results revealed that animals treated with testosterone demonstrated a reduced cSNC effect and had a

faster recovery, relative to saline controls. These results are similar to those to be discussed next for benzodiazepine anxiolytics.

Anxiolytics. Two classes of anxiolytics proved effective in modulating cSNC: benzodiazepine anxiolytics and ethanol. Both of these neurochemicals act at the GABA (gamma-aminobutyric acid) receptor throughout the brain. GABA receptors are found in high concentration in the cerebral cortex, hippocampus, thalamus, basal ganglia, cerebellum, and brainstem (Young & Chu, 1990).

Both ethanol and benzodiazepines share in common that they do not affect cSNC before the first downshift trial (usually Trial 11), but they reduce the cSNC effect when administered before the second downshift trial (Trial 12; Flaherty, 1996). The GABAergic system, then appears to be related to Flaherty's Stage 2 (1996), a conclusion suggested by the effects of the administration of benzodiazepine anxiolytics on cSNC. There are two subtypes of GABA receptors: $GABA_A$ and $GABA_B$. Benzodiazepines are allosteric neuromodulators that enhance the effectiveness of $GABA_A$ receptors rather than directly mimicking the neurotransmitter. In the absence of GABA, benzodiazepines do not work. To explain the trial selectivity of benzodiazepine anxiolytics, Flaherty (1996) hypothesized that after the cSNC effect occurs, an endogenous recovery process is triggered involving $GABA_A$ receptors.

To test whether chlordiazepoxide (CDP), a drug that selectively binds to the benzodiazepine site of the $GABA_A$ receptor, is ineffective on the first downshift trial because the GABA circuit has not yet been activated, Flaherty (1996) injected muscimol, a direct GABA agonist, into the lateral ventricles of rats on Trial 11 followed by a systemic injection of CDP. Animals that received both muscimol and CDP treatments showed no signs of the cSNC effect on Trial 11, whereas animals that received only CDP showed significant signs of the cSNC

effect. These results are consistent with the hypothesis that GABAergic activity needs to be present in order for the benzodiazepine anxiolytics to reduce the cSNC effect.

Ortega, Glueck, Daniel, White, and Papini (2012) found that CDP has a dual effect on cSNC depending on the timing of its administration. When CDP is administered immediately posttrial 11, it enhanced the cSNC effect on subsequent trials, whereas administration prior to Trial 12, as mentioned above, leads to a reduction of the cSNC effect. These results suggest that $GABA_A$ receptors play a complex role in cSNC. Pretrial, CDP leads to anxiolytic effects without effecting memory, but posttrial CDP administration modulates memory consolidation.

Feldon and Gray (1981) investigated the effects of chronic administration of CDP on the partial reinforcement extinction effect (PREE). In this study, animals were treated with CDP prior to acquisition and extinction training (Experiment 1) or prior to extinction training only (Experiment 2) in a straight alley. Results revealed that when animals were injected with CDP throughout training, the PREE was reduced. Interestingly, the PREE was reduced by decreasing the persistence in partially reinforced animals and by increasing persistence in continuously reinforced animals. However, when animals were only treated with CDP only during extinction trials, there was increased resistance to extinction in both CR and PR animals. Thus it appears that CDP modulates the behavioral effects of stimuli and contexts associated with frustrating nonreward (Amsel, 1962).

D-cycloserine and other memory enhancers. N-methyl-D-aspartate (NMDA) receptors are generally thought of as the classic learning and memory receptors for their role in memory consolidation (Riedel, Platt, & Micheau, 2003). NMDA receptors are ioniotropic channels with a voltage-dependent magnesium channel-binding site. These receptors also contain other modulatory binding sites for glutamate and glycine. As neurotransnmitters binds to the NMDA

receptor and a voltage change releases the magnesium channel blocker, calcium flows into the cell. This in turn sets off a cascade of events involved in memory consolidation (Meyer & Quenzer (2005).

Memory consolidation is a time-dependent process and can best assessed by postrial pharmacological administration (McGauch, 2002). Because drug administration occurs after training, the drug does not directly affect behavior. Additionally, subsequent behavioral testing typically occurs the day following drug administration, after the drug has been metabolized, the trial drug effect can be assumed to be affecting memory consolidation rather than motivation, motor, or attention during training (Norris, Ortega, Papini (2011).

Norris, Ortega, and Papini (2011) tested the memory enhancing effects of D-cycloserine in the cSNC paradigm and found that when it was administered after Trial 11, it enhanced the aversive memory of the downshifted reward and retarded the typical recovery process from the downshift. Similar results were found when D-cycloserine was administered prior to Trial 11. Interestingly, the effect was specific to the aversive downshift memory, as it did not disrupt consummatory behavior in the unshifted control animals.

Norepinephrine was also thought to have a role in memory modulation of aversive memories via the amygdala (McGaugh, Ferry, Vardarjanova, & Roozendall, 2000). Unlike norepinephrine's apparent role in aversive memory modulation, Flaherty's (1996) review of some published and unpublished findings suggested that cSNC is resistant to adrenergic manipulation. There was no detectable effect on cSNC when either α or β-adrenergic receptors were antagonized. This suggests a difference in the neurochemical mechanisms of aversive procedures such as passive avoidance and cSNC. The aversive memory consolidation following passive avoidance learning is modulated by the manipulation of norepinephrine levels, via

epinephrine administration, and by posttrial administration of opioids (Izquierdo & Dias, 1983, 1985). Neither of these manipulations has been shown to modulate cSNC (Daniel, Ortega, & Papini, 2009; Flaherty, 1996).

Based on previous research on passive avoidance (Taylor, 1990) and on iSNC (Salinas, 1997), it was predicted that cholinergic neurotransmission would be involved in the memory consolidation of reward loss, which occurs during cSNC. Bentosela, D'Ambros, Altamirano, Muzio, Baratti, and Mustaca (2005) administered a cholinergic antagonist (atropine) and an acetylcholinesterase inhibitor (physostigmine) immediately after the first downshift trial (Trial 11) and immediately after the last preshift trial (Trial 10), in different experiments. They reported no detectable effects of any of these treatments on subsequent postshift trials, concluding that cholinergic neurotransmission is not involved in memory consolidation processes in the cSNC situation.

Opioids. Opioids are neuroactive peptides that bind to four receptor types: μ, δ, κ and ORL-1 (Papini & Ortega, 2011). These receptors are widely, but differentially distributed in the mammalian brain (Mansour, Fox, Akil, & Watson, 1995; Sim-Selley, Vogt, Childers, & Vogt, 2003) and occur at high densities in the presubiculum, amygdala, cortical amygdaliod nucleus, external plexiform layer, caudate-putamen, nucleus accumbens, olfactory tubercle, medial amygdaliod nucleus, cingulated cortex, insular cortex, perirhinal cortex, piriform cortex, hippocampus, thalamus, preoptic area, anterior and superior colliculi, interpeduncular nucleus, nucleus ambiguous, nucleus tractus solitarius, and the substantia gelatinosa (Papini & Ortega, 2011).

Nonspecific opioid receptor agonists and antagonist have been found to modulate both stages of Flaherty's (1996) model. cSNC is attenuated when the nonselective opioid-receptor

agonist morphine is administered prior to Trials 11 or 12 in the downshifted animals only (Rowan & Flaherty, 1987). However, this effect is only observable when used in low to moderate doses (0.5 to 8.0 mg/kg); at larger doses (16 mg/kg) morphine also depressed consummatory performance in unshifted control animals. Additionally, the attenuating effect of morphine is eliminated when the nonselective competitive opioid antagonist naloxone is coadministered thereby blocking opioid receptors. Interestingly, Rowan and Flaherty (1987) reported no discernible effects of naloxone when administered alone. However, it was later discovered that naloxone did affect contrast when administered at a higher dose (Pellegrini, Wood, Daniel, & Papini, 2005). Moreover, rats that showed a slower rate of recovery from reward downshift also demonstrated a higher sensitivity to naloxone administration before an activity test compared to animals that experienced a faster rate of recovery.

Papini (2009) hypothesized that the results of blocking opioid receptors could be attributed to four potential processes: (a) modulation of the downshift experience via an amplification of the rejection process or by reducing incentive value of sucrose; (b) disruption of downshift detection process; (c) enhanced consolidation of the memory of the downshift event; and (d) induction of a conditioned taste aversion to the downshifted solution. Daniel, Ortega and Papini (2009) tested the detection, memory consolidation, and taste aversion hypotheses with the following conclusions. Naloxone shifted the comparison from a ratio-based to a difference based-comparison, thereby modulating the comparison process triggered by the incentive downshift. Thus, when the antagonist blocked the opioid receptors, the consummatory suppression was enhanced as a direct function of the absolute difference between the preshift and postshift solution concentrations. Additionally, they found that the posttrial administration of naloxone had no detectable effects on subsequent trials. This suggests that opioid receptors do

not play a part in memory consolidation of the downshift event. Daniel et al. (2009) also reported that naloxone administration failed to induce conditioned taste aversion to a novel 4% sucrose solution under conditions similar to those used in cSNC experiments, but without the downshift event. These results allowed for the tentative rejection of the memory consolidation and taste aversion hypotheses. More research is still needed to examine the role opioids potentially play in the amplification of the rejection and/or the reduction of the incentive value of sucrose.

There is evidence suggesting that specific opioid receptors are involved in the different stages of Flaherty's (1996) multistage theory. Wood, Daniel, and Papini (2005) administered the selective δ opioid receptor agonist DPDPE prior to Trials 11 or 12 in the cSNC paradigm. DPDPE reduced consummatory suppression followed administration prior to Trial 11 (first downshift), but had no effect during Trial 12 (second downshift). To investigate the role of the δ opioid receptors further, naltrindole, a selective δ opioid antagonist, was administered prior to Trials 11 and 12 with the expected result of enhancing the suppression of consummatory behavior on Trial 11, but having no effect on Trial 12 (Pellegrini et al., 2005). These results support the hypothesis that stage 1 of Flaherty's theory of the rejection process selectively involves the δ opioid receptor.

The second stage of Flaherty's theory can be pharmacologically manipulated by administering drugs immediately after Trial 11 and prior to Trial 12. Wood, Norris, Daniel, and Papini (2008) reported that κ opioid receptors are differentially involved in the modulation of stage 2. When U-50,488H, a κ opioid receptor agonist, is administered prior to Trial 11 or 12, no drug effects were detected for Trial 11 and complex dose-dependent effects occurred on Trial 12. A low dose (1 mg/kg) attenuated cSNC while higher doses (3 and 10 mg/kg) enhanced cSNC. When a 3 mg/kg dose of U-50,488H was administered immediately after Trial 11, cSNC was

enhanced. However, when the low dose of 1 mg/kg was administered, no effect was observed. The enhancing effects of the 3 mg/kg dose of U-50, 488H were eventually explained as a drug-induced condition taste aversion to the 4% solution. These results suggested that κ opioid receptors are involved in the conflict and recovery stage of cSNC, but only in low doses.

Current Research

The purpose of the current research was to further explore Amsel's (1992) hypothesis that previous exposure to counterconditioning leads to a tolerance to frustration across contexts and behaviors (cf. Ross, 1964). In order to investigate the tolerance to frustration hypothesis, I exposed animals to a surprising reward reduction (e.g., incentive downshift), enhanced counterconditioning to the reward reduction via naloxone administration (which is known to increase the size of the cSNC effect; Daniel et al., 2009; Pellegrini et al., 2005), and examined the tolerance to frustration in these same animals via the partial reinforcement acquisitions effect (PRAE). The PRAE is defined as higher response rate under partial rather than continuous reinforcement (Goodrich, 1959). If Amsel's (1992) hypothesis about tolerance to frustration is correct, then animals exposed to surprising reward reduction (e.g., downshift) in one paradigm should show reduced behavioral persistence, elimination of the PRAE, in a subsequent behavioral test, despite the differences in the external conditions and response requirements.

All animals in this experiment were originally part of a larger study designed to explore the effects of bilateral electrolytic lesions of the central nucleus of the amygdala (CeA) and naloxone administration on incentive downshift. However, the surgical side of the research did not yield the expected results. Histology results indicated that none of the animals had detectable brain lesions. I believe that the electrode used for the electrolytic lesions was responsible for the failure to produce visible lesions. Still, as will be shown later, there were interesting results in

the groups that had received sham lesions and were exposed to treatment with naloxone vs. saline. To error on the conservative side, I decided to use only animals that had been subjected to sham surgery.

Method

Subjects

Forty Wistar male rats (*Rattus norvergicus*) were used for this experiment. The animals were bred at the Texas Christian University vivarium and were derived from breeders purchased from Charles River Laboratories (Wilmington, MA). The subjects were 90 days old at the start of the experiment and maintained at 81-84% of their free food weight. Animals were housed individually in wire-bottom cages with a rodent retreat for enrichment in each cage. Animals had free access to water while in their cage. Animals were kept under a 12 h light/12 h dark schedule (light on at 07:00 h) in a noise-controlled room with a constant room temperature (22-23 °C) with the humidity kept between 50 and 65%. They were fed with standard laboratory rat chow administered at least 15 min after the end of training trails.

Surgical procedure

Animals used in this study were originally part of a project involving electrolytic lesions to the central nucleus of the amygdala. At the age of 90 days, rats received bilateral sham surgeries. Sham surgery involves everything done with animals subjected to brain lesions, including electrode insertion, except that no electric current is administered. Animals were deeply anesthetized by intraperitaneal injection of ketamine (50 mg/kg) and xlyazine (2.61 mg/kg). Animals were positioned in a stereotaxic frame with blunt-tipped ear bars. A midline incision was made in the scalp and two burr holes were drilled 2.4 mm posterior to bregma, ± 4.2 mm lateral to bregma, and – 8.0 D/V (coordinates from Paxinos & Watson, 2007) and a 0.3-mm

electrode was inserted. To attenuate pain associated with surgery, 0.1 mL of bupornophrin (.4 mg/mL) was administered subcutaneously to all animals immediately after surgery. Rats were allowed 8 days to recover from surgery. Antibiotics were applied as need. Food and water were continuously available in the cage.

After recovery, rats were food deprived to 81-84% of their free-food weight. Behavioral training started 14 days after surgery.

Behavioral Testing Procedures

Following recovery from surgery and food deprivation, animals began behavioral testing. All animals experienced the same order of testing: cSNC and autoshaping. The order of the testing was kept constant in order to test for transfer effects from cSNC to autoshaping.

The rationale behind the current design was provided by Amsel's (1992) frustration theory. The central hypothesis is that the counterconditioning of secondary frustration in one situation should lead to positive transfer to other situations that also induce secondary frustration. Amsel (1992) has shown that partial reinforcement is theoretically connected to SNC and Wood et al. (2005) have specifically extended Amsel's theory to the case of cSNC. Thus, the present study tested whether an experience with incentive downshift in the cSNC situation and the counterconditioning that occurs during subsequent pairings of the 4% sucrose solution and secondary frustration, would generate the conditions necessary to affect performance in the PRAE situation. According to Amsel's theory, partial reinforcement should have an effect relative to continuous reinforcement. The counterconditioning experienced during the recovery of consummatory behavior in cSNC should elevate the energizing responding during acquisition (PRAE). Thus, anything that reduces or enhances cSNC should likewise reduce or enhance the PRAE in an autoshaping paradigm (Papini, 2003). There is no information on the effects of

previous exposure to frustration across the reward downshift preparations used in the present experiment. Furthermore, I have used opioid blockage via naloxone administration to enhance the effects of incentive downshift in the cSNC situation. Frustration theory predicts that enhancing the effects of frustration should lead to stronger counterconditioning and, thus, enhance the transfer effect from cSNC to the PRAE situation. Thus, the present experiment used naloxone as a tool to enhance the behavioral transfer effect.

Two types of control conditions were included in this experiment. First behavioral controls involved groups that were not exposed to reward downshift in the consummatory situation (i.e., always given 4% sucrose; unshifted control), or to nonreward in the autoshaping situation (i.e., continuous reinforcement). Second, saline controls were administered saline rather than naloxone on Trials 11 and 12.

cSNC Testing

Apparatus. cSNC training was conducted in 8 conditioning boxes (MED Associates, St. Albans, VT) made of aluminum and Plexiglas (29.3 × 21.3 × 26.8 cm, L × W × H). The floor consisted of steel rods running perpendicular to the feeder wall. A bedding tray filled with corncob bedding was placed below the floor to collect feces and urine. Against the feeder wall was an elliptical hole, 1 cm × 2 cm (W × H), and 3.5 cm from the floor. A sipper tube, 1 cm in diameter, was inserted through this hole. When fully inserted, the sipper tube was flush against the wall. A computer located in an adjacent room controlled the presentation and retraction of the sipper tube, and detected contact with the sipper tube via a circuit involving the steel rods in the floor. Each conditioning box was in a sound-attenuating chamber that contained a house light, a speaker that delivered white noise, and a fan for ventilation. Together, the speaker and fan produced noise with an intensity of 80.1 dB (SPL, Scale C).

General Procedure. At the age of 90 days, rats received sham surgeries. After recovery, rats were food deprived to 81-84% of their free-food weight (4-6 days). Upon reaching deprivation weight, rats were randomly assigned to one contrast condition: downshifted (32-to-4% sucrose) or unshifted (4-to-4% sucrose). Rats received 10 trials (1 trial/day) of access to a 32% sucrose solution (w/w, 32 g of sucrose for every 68 g of distilled water) or 4% sucrose solution (w/w, 4 g of sucrose for every 96 g of distilled water), depending on the contrast condition. This was followed by 5 trials (1 trial/day) in which all animals received 4% sucrose.

Animals were assigned to two drug conditions: saline (unshifted saline, downshift saline) or naloxone (unshifted naloxone, downshift naloxone); based on consummatory behavior on Trials 1-10, and equally balanced across conditions. Naloxone (2 mg /kg) or saline (equal-volume injection) was administered via an intraperitoneal injection 20 min prior to Trials 11 and 12. This injection schedule was based on Pellegrini et al. (2005), who reported that naloxone administration before Trials 11 and 12 enhanced cSNC. Each trial lasted 5 min from the first contact with the sipper tube. Trials were administered at about the same time each day (09:00 and 15:00 h). Drinking time was automatically recorded by a computer and measured in terms of time in physical contact with the drinking spout (in units of 0.01 s).

Autoshaping

Apparatus. Four standard operant chambers (MED Associates, St. Albans, VT) each enclosed in a sound-attenuating chamber were used. Each box was 20.1 x 28 x 20.5 cm (W x L x H), with a grid floor consisting of stainless steel bars 0.4 cm in diameter and spaced 1.6 cm apart. Underneath the grid floor was a pan filled with corncob bedding. The food cup was located on the front wall of the chamber, 2 cm above the floor. Two retractable levers were located 1 cm to the right and left of the feeder, and 6 cm above the floor. Pellet dispensers delivered 45-mg food

pellets (Bio-Serv, Frenchtown, NJ). Food pellets contain protein (18.8%), fat (5.0%), carbohydrate (61.5%), fiber (4.6%), ash (4.4%), and moisture (5.0%), and provided 3.68 kcal/g. The sound-attenuating chambers were equipped with a light (GE 1820) that provided diffuse illumination, a speaker that administered white noise, and a fan for air circulation. Background masking noise (speaker and fan) registered 80.1 dB (SPL, scale C).

General Procedure. This test followed Thomas and Papini's (2001) procedure. It provided data on the basic learning phenomena: acquisition. Autoshaping training started the day after the final trial of cSNC (Trial 15). Rats were kept at 81-84% of their ad libitum weight throughout the autoshaping phase. There were 10 sessions of acquisition at 1 session/day. In each session there were 10 trials, each involving the presentation of a lever for 10 s. Trials were separated by variable intervals averaging 90 s (range: 60-120 s). A reinforced trial ended with the retraction of the lever and the delivery of five 45-mg pellets at a rate of one pellet every 0.25 s. A nonreinforced trial ended with the retraction of the lever. During acquisition, each trial was reinforced for continuous reinforcement groups (CR), but only a random 50% of the trials were reinforced for partial reinforcement groups (PR). A computer controlled the administration of events and the recording of lever-pressing responses. Although rats did not have to press the lever to obtain food, they nonetheless came to approach and make contact with the lever (a phenomenon called "autoshaping").

Histology

When all behavioral testing was finished (after the open-field test), animals were sacrificed using CO_2. The brains were removed and stored in 10% formaldehyde for at least 48 h and then transferred to a 30% sucrose solution for at least another 48 h. Using a cryostat, 80 μm coronal sections were sliced, mounted on gelatin coated glass slides, and stained with thionin. An

experimenter blinded to the behavioral outcomes performed histological analysis under 40X magnification to determine whether any brain damage was present, other than that created by the insertion of the electrode.

Results

Results were analyzed using mixed-model analyses of variance (ANOVA) with trials or sessions as the repeated-measure factor, and an alpha value set at the 0.05 level.

cSNC

Trial averages for each group are shown in Figure 2. During the preshift phase, animals learned to drink the sucrose solutions at similar rates whether having access to 32% or 4% sucrose. A Contrast (32, 4) x Trial (1-10) ANOVA yielded a significant effect of trial, $F(9, 324) = 62.01$, $p < 0.001$. The contrast and contrast by trial interaction were not significant, Fs < 1.10, ps > 0.15.

Figure 2 also shows the results of the postshift trials (11-15). A visual inspection revealed that animals in the 32/Nlx condition suppressed consummatory behavior more than animals in the 32/Sal condition on Trials 11 and 12. This enhanced suppression of consummatory behavior was limited to animals that had experienced a downshift and received naloxone (32/Nlx) administration relative to saline controls (32/Sal). Animals that received naloxone, but did not experience a downshift (4/Nlx) did not exhibit suppression of consummatory behavior relative to saline controls (4/Sal). I concentrated on Trials 11-14 because this yielded the best statistical results; however, when the analysis included Trials 11-15, there was a marginal but not significant triple interaction, $F(4, 144) = 2.35$, $p = 0.057$. A Contrast (32, 4) x Drug (Nlx, Sal) x Trial (11-14) ANOVA yielded a significant triple interaction, $F(3, 108) = 3.80$, $p < 0.05$, a trial by contrast interaction, $F(3, 108) = 18.05$, $p < 0.001$, and a trial by drug interaction, $F(3, 108) =$

9.61, $p < 0.00$. In addition, there were significant main effects of trial $F(2, 72) = 39.99$, $p < 0.001$, and contrast, $F(1, 36) = 8.02$, $p < 0.01$. All other effects were not significant, Fs < 2.60, ps > 0.05.

The source of the significant triple interaction was determined with post hoc LSD tests. Group 32/Sal showed a significant decrease in consummatory behavior on Trial 11 compared to Group 4/Sal, $F(1, 36) = 10.34$, $p < 0.01$. However, Groups 32/Nlx and 4/Nlx showed a significant difference on Trial 11, $F(1, 36) = 20.22$, $p < 0.001$, and Trial 12, $F(1, 36) = 11.31$, $p < 0.01$. Thus, naloxone (32/Nlx vs. 4/Nlx) lengthened the cSNC effect by one trial, relative to the saline controls (32/Sal vs. 4/Sal). Furthermore, a similar analysis conducted to investigate the difference between the contrast conditions yielded a significant suppression of consummatory behavior for Trial 11, $F(1, 36) = 7.18$, $p < 0.05$, and Trial 12 $F(1, 36) = 10.12$, $p < 0.01$, for downshifted naloxone animals compared to downshifted saline animals (32/Nlx vs. 32/Sal). There were no significant differences between unshifted animals (4/Nlx vs. 4/Sal) in any of the postshift trials, Fs$(1, 36) < 1.16$, ps > 0.05.

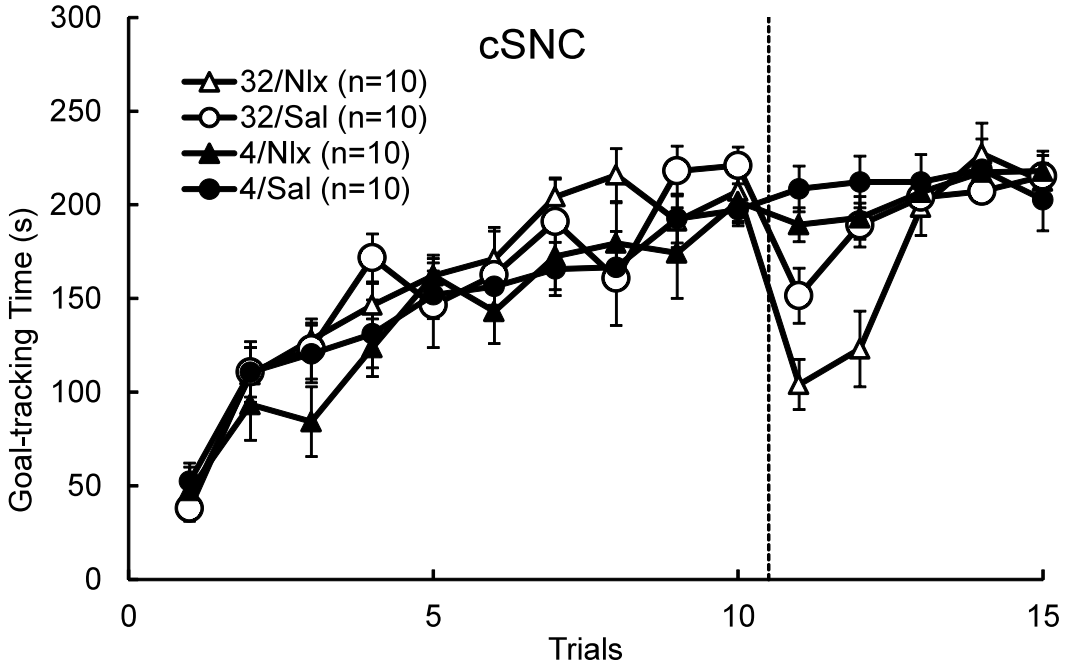

Figure 2. The dependent measure is the group average for the cumulative time in contact with the sipper tube, goal-tracking time, and expressed in seconds (error bars are ± SEMs). The dotted line represents the division between preshift (Trials 1-10) to postshift (Trials 11-15). Animals received ip naloxone (Nlx, 2 mg/kg) or saline (Sal, equal volume) injections 20 min prior to the start of Trials 11 and 12.

Autoshaping

Of specific interest in this phase of the experiment was whether previous exposure to a frustrative event in cSNC affected subsequent behavior in autoshaping acquisition and extinction under continuous or partial reinforcement (CR, PR). Therefore the results were analyzed by dividing the groups in terms of their previous cSNC conditions (32: downshift animals; 4: unshifted animals). Session averages for acquisition data can be seen in Figure 3 for the previously downshifted (*a*) and previously unshifted animals (*b*).

The acquisition of lever-pressing behavior under CR and PR schedules is illustrated in Figure 3a for previously downshift animals (32/Nlx and 32/Sal). The PRAE (higher response rate in PR than CR animals during acquisition training) was present in the previously downshifted saline animals, but not in previously downshifted naloxone animals. A Schedule (CR, PR) x Drug (Nlx, Sal) x Session (1-10) ANOVA revealed a significant triple interaction, $F(9, 144) = 1.97$, $p < 0.05$, and a significant main effect of session, $F(9, 144) = 16.75$, $p < 0.001$. All other effects were not significant, Fs < 1.88, ps > 0.05, for the acquisition data.

The source of the significant triple interaction was determined with post hoc LSD tests. Several comparisons are relevant for a test of transfer effects:

(1) A comparison of CR/Sal vs. PR/Sal establishes whether the PRAE occurred in animals that experienced a regular cSNC effect. Such comparison indicated that PR/Sal animals showed higher response rate during autoshaping acquisition on Session 10 F (1, 16) = 5.18, ps < 0.05, relative to CR/Sal animals. Although there were no other significant difference in rate of responding across acquisition sessions between the PR/Sal and CR/Sal animals, there was a trend for the PR/Sal animals to demonstrate an increase in responding relative to CR/Sal animals, Fs$(1,16) < 3.90$, ps > 0.05.

(2) A comparison of CR/Nlx vs. PR/Nlx groups establishes whether the PRAE occurred in animals that experienced a cSNC effect enhanced by the administration of naloxone; in these animals, counterconditioning is assumed to be stronger and therefore a greater tolerance to the effects of frustration was expected during autoshaping acquisition than in animals that experienced a regular cSNC effect.

Consistent with these predictions, Groups CR/Nlx and PR/Nlx did not differ in any of the autoshaping acquisition sessions, $F(1,16) = .09, p > 0.05$.

(3) A comparison of Groups PR/Nlx vs. PR/Sal would indicate the extent to which the enhanced cSNC experience reduced responding during partial reinforcement autoshaping training. The statistical analysis indicated that PR/Sal animals showed a higher responding rate during autoshaping acquisition on Session 10, $F(1,16) = 5.62$, $p < 0.05$, relative to PR/Nlx animals. Although the results did not yield a statistical difference in responding between any other acquisition sessions, there was a trend for the PR/Sal animals to demonstrate more responding relative to the PR/Nlx animals.

(4) Finally, a planned pair-wise comparison between Groups PR/Nlx vs. CR/Sal would also indicate the extent to which the enhanced cSNC effect made the behavior of the former group more like that of the latter during autoshaping acquisition, $F(1,9) = 1.77, p > 0.05$.

The acquisition of lever-pressing behavior under CR and PR schedules is illustrated in Figure 3b for the previously unshifted animals (4/Nlx and 4/Sal). A Schedule (PR, CR) x Drug (Nlx, Sal) x Session (1-10) analysis revealed a significant effect of session, $F(9, 144) = 11.15$, $p < 0.001$. All other effects were not significant, Fs < 2.28, ps > 0.05. While no other statistically significant effects, there was a trend for unshifted animals to demonstrate the PREA in acquisition. Previous exposure to naloxone had no detectable effect on the PRAE in previously unshifted animals, relative to saline controls, which occurred in both pairs of CR vs. PR groups. Therefore, the effect on the PRAE required both a downshift experience and its enhancement by naloxone during the cSNC phase of training.

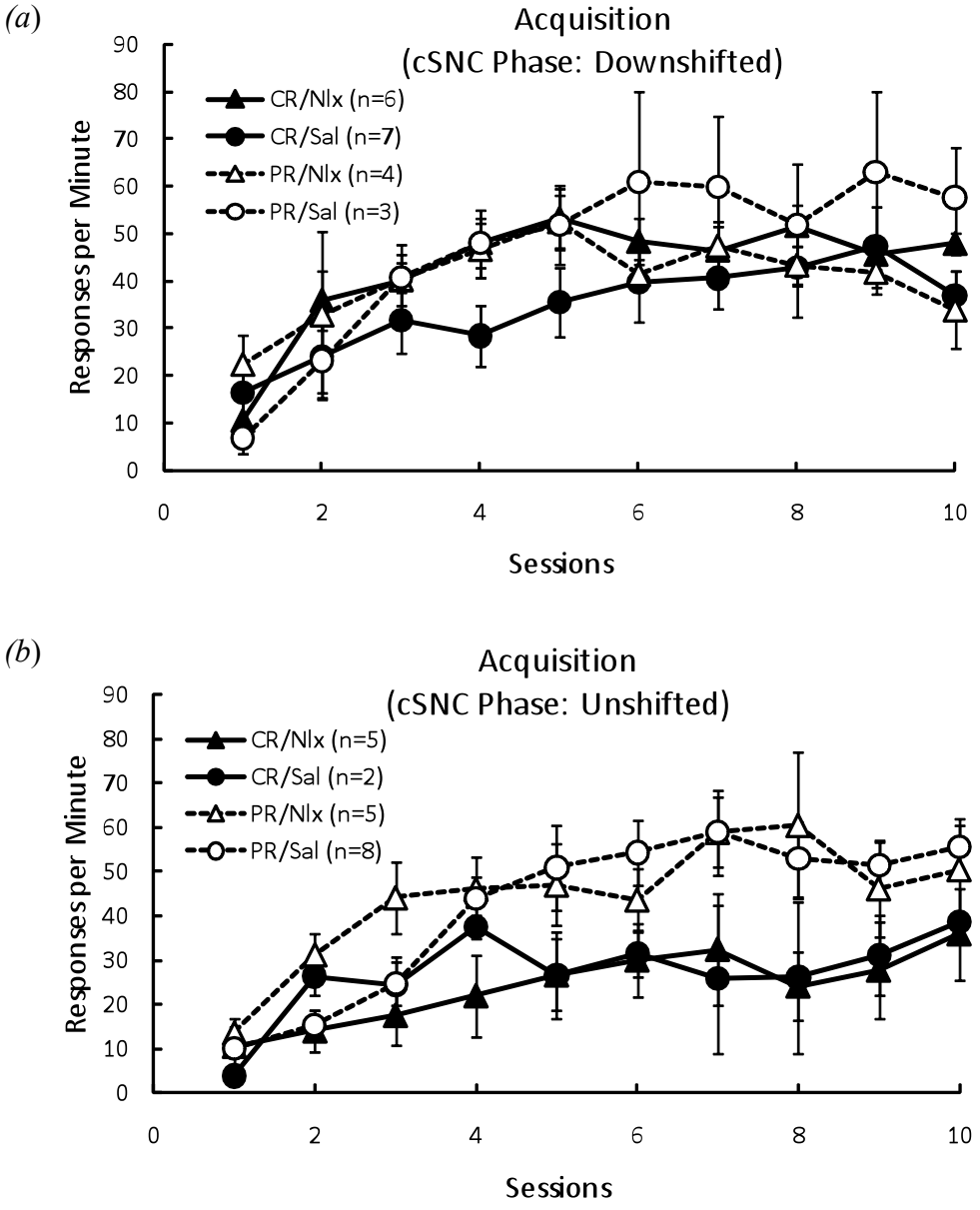

Figure 3. The dependent measure is the group average of number of lever press responses per minute for animals that experienced a downshift in cSNC (*a*) and for unshifted animals (*b*) (error bars are ± SEMs). Each session consisted of 10 trials and animals ran one session per day. Animals received ip naloxone (Nlx, 2 mg/kg) or saline (Sal, equal volume) injections 20 min

prior to the start of Trials 11 and 12 during the cSNC phase. No naloxone or saline was administered during the course of the autoshaping acquisition sessions shown in this figure.

General Discussion

The current experiment examined Amsel's (1992) tolerance to frustration hypothesis. Animals were exposed to a surprising reward reduction (e.g., incentive downshift) with the negative experience intensified and enhanced via naloxone administration, followed by additional PR training and extinction. Frustration theory predicted that the counterconditioning of secondary frustration in the cSNC situation (which should have been stronger in naloxone-treated, downshifted animals) would be reactivated by partial reinforcement in the autoshaping situation, thus resulting in reduced PRAE. The results can be summarized as follows: (1) Naloxone enhanced the cSNC effect, and lengthened the cSNC effect by one trial, but had no effect on unshifted animals. (2) Previous exposure to the downshift enhanced by naloxone eliminated the PRAE, whereas there was a trend where the regular downshift experience and unshifted training, whether with saline or naloxone, had no effect on the PRAE, which was occurred in these three conditions.

Consider first the results from the cSNC phase. Animals administered naloxone showed enhanced consummatory suppression and an extended cSNC effect, lasting an additional trial. Conversely, naloxone had no effect on unshifted animals. These findings extended previous results from our lab (Pellegrini et al., 2005; Daniel et al., 2009), confirming under the usual conditions of the cSNC situation that blocking opioid receptors leads to an enhancement of the negative experience of incentive downshift (32/Nlx), but has no effect on consummatory behavior in unshifted animals (4/Nlx). This suggests that the naloxone effect is limited to the incentive downshift experience. The results of the present and previous experiments are

consistent with the hypothesis that opioid blockage enhances the negative emotional experience of the downshift without affecting directly the consolidation of the memory of that event (Papini, 2009).

According to the application of frustration theory to the special case of cSNC (Papini, 2003; Wood et al., 2005), access to the postshift solution retrieves the memory of the preshift solution. This, in turn, triggers a comparison between the current and previous incentives, and this negative discrepancy induces an aversive internal state of primary frustration. Primary frustration has two effects: it leads the animal away from the current incentive and it triggers the conditioned anticipatory state of secondary frustration. While primary frustration is believed to be involved in the initial suppression of consummatory behavior on Trial 11, secondary frustration is assumed to be responsible for the suppression of consummatory behavior that occurs following Trial 12. Additionally, the recovery process is believed to be the result of conditioning that occurs as the animals begins to form a new expectation for the postshift solution. It was previously suggested by Pellegrini et al. (2005) that the opioid system is normally activated during a surprising reward reduction event.

Next, consider the results of the autoshaping phase. Previously downshifted animals that were administered naloxone showed no evidence of the PRAE, whereas animals that were downshifted and given saline injections demonstrated the PRAE. These results suggest that the counterconditioning experienced by the downshifted saline animals was insufficient to induce tolerance of frustration across paradigms; however, naloxone administration appears to have intensified the counterconditioning such that tolerance was induced.

Frustration theory (Amsel, 1992) argues that once the internal state of frustration is conditioned, it can be reactivated by similar experiences even if they occur at different times and

contexts. However, the current results suggest that such a transfer from cSNC to PRAE can occur only when the frustrative experience in the cSNC situation is enhanced beyond its normal occurrence (in the present experiment, via naloxone administration). A possible reason for the lack of transfer in downshifted/saline animals in the current experiment would assume that five trials of postshift training are insufficient to induce a strong enough counterconditioning of secondary frustration that would allow for a transfer effect from the cSNC to the PRAE situation. Although plausible, this explanation is unlikely to be correct in light of another study recently conducted in our lab.

I autoshaped 40 female Wistar rats under CR (n = 20) or PR (n = 20) for 10 trials per day for 10 days (identical to the autoshaping acquisition phase in the current study). After completing the 100 trials, animals were divided based on their autoshaping performance into 4 cSNC groups: 32/CR, 32/PR, 4/CR, 4/PR. Animals were then trained in typical cSNC procedure (10 preshift trials and 5 postshift trials, one trial per day). If more counterconditioning occasions were required to induce tolerance to frustration in the 32/Sal animals in the previous study, then animals exposed to 100 trials of counterconditioning, in the PR group, should have demonstrated tolerance to frustration via a significant reduction of consummatory behavior on Trial 11 and or shown attenuated recovery during Trials 12-15.

Figure 4 shows the results of the acquisition of lever-pressing behavior during the autoshaping phase. Results were analyzed using a mixed-model ANOVA with sessions or trials as the repeated-measure factor, and an alpha level set at the 0.05 level. A Schedule (CR, PR) x Session (1-10) ANOVA yielded a significant interaction for session by schedule, $F(9, 342) = 44.68$, $p < 0.001$, and a significant effect for session, $F(9, 342) = 38.14$, $p < 0.001$, and schedule, $F(1, 38) = 259.86$, $p < 0.001$. PR animals demonstrated an invigoration of the lever-pressing

behavior, relative to the lever-pressing demonstrated by the CR animals. Thus, there was a significant PRAE.

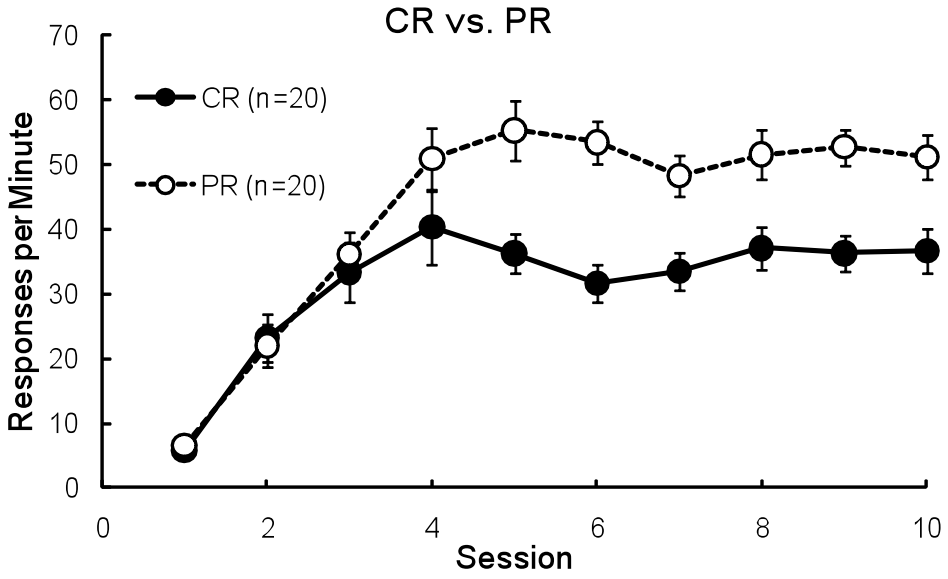

Figure 4. The dependent measure is the group average of number of lever-pressing responses per minute from the autoshaping phase (error bars are ± SEMs). Each session consists of 10 trials.

Group trial averages for the preshift phase of cSNC are illustrated in Figure 5. A visual inspection revealed that animals in the 32/PR condition engaged in consistently less goal-tracking behavior compared to the 32/CR group. A Schedule (CR, PR) x Sucrose (32, 4) x Trial (1-10) ANOVA revealed significant interactions of trial by sucrose, $F(9, 324) = 4.70$, $p < 0.001$, schedule by sucrose, $F(1, 36) = 4.38$, $p < 0.05$, and significant effect of trial, $F(9, 323) = 39.70$, $p < 0.001$. All other effects were not significant, Fs < 1.01, ps > 0.05.

Figure 5 also shows the results of the postshift trials (11-15). A visual inspection of the results revealed that both 32% groups showed identical levels of consummatory suppression on Trial 11 and nearly identical recovery during the subsequent trials (12-15). A Schedule (CR, PR) x Sucrose (32, 4) x Trial (11-15) ANOVA revealed a significant interaction of trial by sucrose,

$F(4, 144) = 18.39$, $p < 0.001$, and significant effects for trial, $F(4, 144) = 26.90$, $p < 0.001$, and sucrose, $F(1, 36) = 46.36$, $p < 0.001$. All other effects were not significant, Fs < .32, ps > 0.05.

Results from this study did not yield evidence of tolerance to frustration in animals previously receiving PR training in autoshaping and later exposed to the incentive downshift in the consummatory situation. Animals in the 32/PR groups had 100 trials of counterconditioning, compared to the current study that had only 5 trials. Therefore, it seems unlikely the lack of tolerance to frustration demonstrated in the current study was due to animals only having experienced 5 trials of counterconditioning. Interestingly, the 32/PR animals demonstrated less goal-tracking behavior during the preshift phase compared to 4/PR animals and the 32/CR animals. These results suggest that PR training altered the palatability of the 32% sucrose solution such that these animals drank less compared to the 4/PR and 32/CR animals.

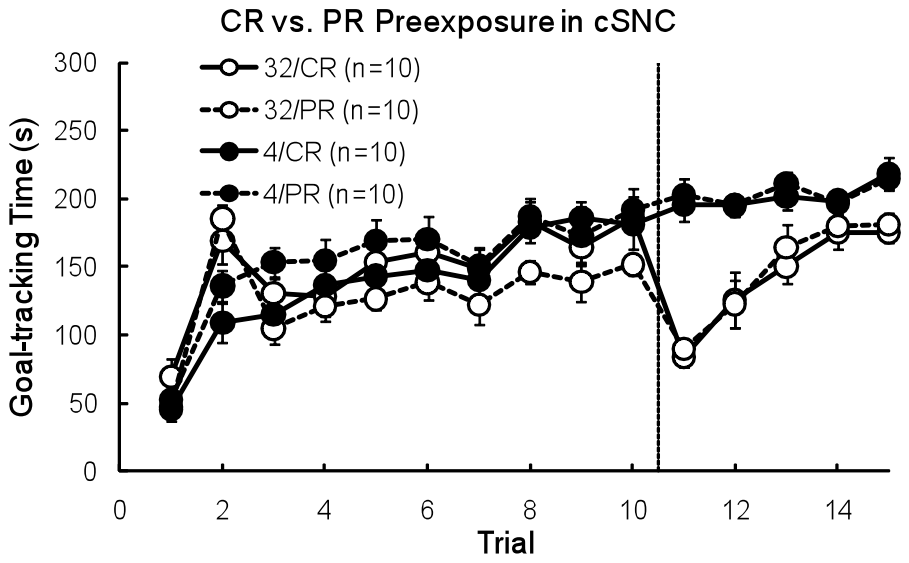

Figure 5. The dependent measure is the group average for the cumulative time in contact with the sipper tube, goal-tracking time, and expressed in seconds (error bars are ± SEMs). The dotted line represents the division between preshift (Trials 1-10) to postshift (Trials 11-15).

Another possibility is that the transfer effect induced by a large cSNC effect in naloxone-treated animals might have intensified the counterconditioning of secondary frustration, thus inducing the transfer effect from cSNC to PRAE. However, this explanation seems unlikely based on another study conducted in our lab recently. I autoshaped 39 female Wistar rats under PR and administered either naloxone (Nlx, 2 mg/kg) (n = 20) or saline (Sal, equal volume) (n = 19) 20 minutes prior to each acquisition session, under identical acquisition procedures as in the current study. After completing autoshaping acquisition training, the animals were divided in to 4 groups: 32/Nlx, 32/Sal, 4/Nlx, 4/Sal, based on prior autoshaping performance, and run through a typical cSNC phase. If naloxone intensified the counterconditioning experience in the present experiment thus facilitating transfer across paradigms, then after 100 trials in autoshaping, tolerance to frustration should be expressed as a smaller cSNC effect on Trial 11, less suppression of consummatory behavior compared to saline controls, and with attenuated recovery.

Figure 6 shows the results of the lever-pressing behavior (responses per min) from the acquisition autoshaping phase. A visual inspection revealed that Nlx animals showed less lever-pressing responses early in training, relative to Sal controls, but eventually achieved the same terminal level of performance. A Drug (Nlx, Sal) x Session (1-10) ANOVA yielded a significant interaction of session by drug, $F(9, 333) = 1.95$, $p < 0.05$, a significant effect of session, $F(9, 333) = 50.17$, $p < 0.001$, and a moderate, but not significant effect of drug, $F(1, 37) = 4.04$, $p = 0.05$. The implication is that counterconditioning should have been enhanced by naloxone in the PR/Nlx condition, relative to the PR/Sal condition.

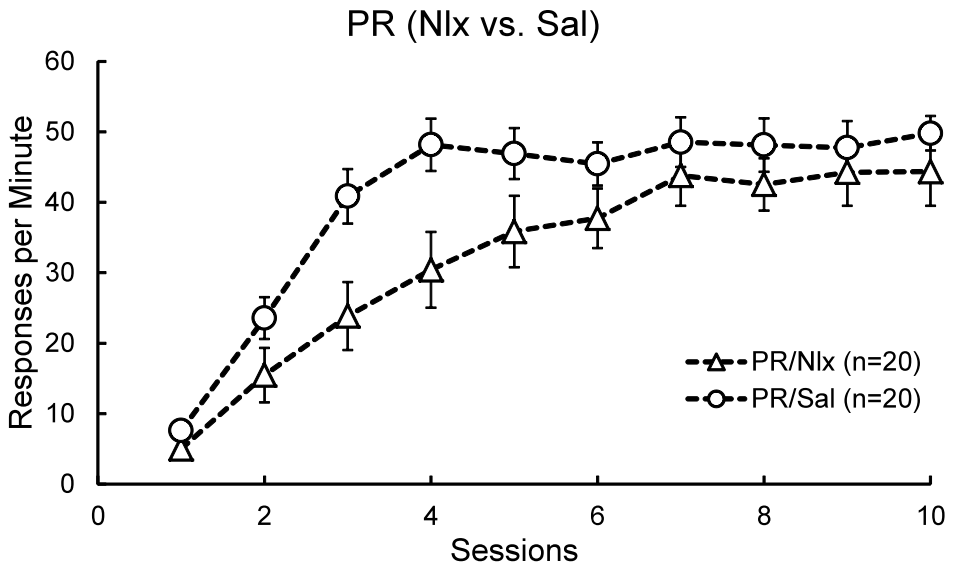

Figure 6. The dependent measure is the group average of number of lever-pressing responses per minute from the autoshaping phase (error bars are ± SEMs). Each session consists of 10 trials. Animals received ip naloxone (Nlx, 2 mg/kg) or saline (Sal, equal volume) injections 20 min prior to the start of Sessions 1-10.

The results of the preshift phase of cSNC are illustrated in Figure 5. A visual inspection of the data revealed there were little differences in goal-tracking times between the 32/Nlx and 32/Sal groups, and this was similar to the behavior observed in the 4% conditions. However, the 32% sucrose animals goal-tracked for significantly less time compared to the 4% sucrose animals. This result replicated the previous autoshaping-to-cSNC results (see Figures 4 - 5 above). A Sucrose (32, 4) x Drug (Nlx, Sal) x Trial (1-10) ANOVA yielded significant effects of trial, $F(9, 315) = 40.56$, $p < 0.001$, and sucrose, $F(1, 35) = 21.73$, $p < 0.001$. All other effects were not significant, Fs$(9, 315) < 1.09$, ps > 0.05. Thus, animals that had prior partial reinforcement training goal tracked the 32% sucrose significantly less than animals with similar experience given access to 4% sucrose, regardless of previous drug administration.

Figure 7 also shows the results for the postshift phase of cSNC. A visual inspection revealed little differences between the 32/Nlx and the 32/Sal groups, and this was similar for the 4% conditions. A Trial (11-15) x Drug (Nlx, Sal) x Sucrose (32%, 4%) ANOVA yielded a significant interaction of trial x sucrose, $F(4, 140) = 5.70$, $p < 0.001$, and significant effects of trial, $F(4, 140) = 21.71$, $p < 0.001$, and sucrose, $F(1, 35) = 33.58$, $p < 0.001$. All other effects were not significant, Fs < 1.92, ps > 0.05.

These results failed to demonstrate the transfer of tolerance to frustration from partial reinforcement training in autoshaping to the postshift phase in the cSNC situation—the opposite sequence to that administered in the present experiment. These results support the previous observation that PR training seems to alter the palatability of the 32% sucrose solution such that animals display less consummatory behavior compared to 4% controls. However, the lack of transfer of frustration during the postshift phase in the 32/Nlx group suggests the naloxone administration does not intensify the counterconditioning experience such that the second hypothesis could be responsible for the lack of tolerance of frustration exhibited in the current study.

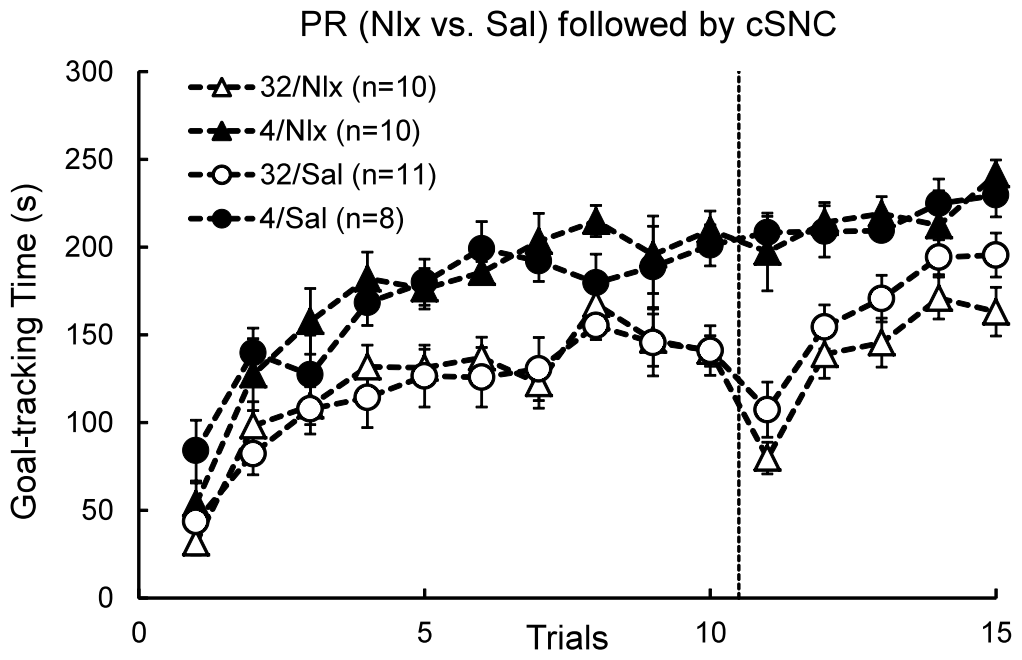

Figure 7. The dependent measure is the group average for the cumulative time in contact with the sipper tube, goal-tracking time, and expressed in seconds (error bars are ± SEMs). The dotted line represents the division between preshift (Trials 1-10) to postshift (Trials 11-15). Animals received ip naloxone (Nlx, 2 mg/kg) or saline (Sal, equal volume) injections 20 min prior to the start of Sessions 1-10 during the autoshpaing phase.

It is also possible that transfer of tolerance to frustration did not occur in the present experiment and in saline treated animals due to a lack of "compatibility" between the consummatory behavior of goal tracking and the anticipatory behavior of lever pressing. This hypothesis stems from Ross' (1964) finding that animals trained in "compatible" behaviors demonstrated a transfer of tolerance to frustration across contexts and behaviors. Therefore, it is possible that transfer failed to occur in the 32/Sal animals because of lack of "compatibility" between behavioral measures. However, this explanation seems unlikely because animals in the 32/Nlx group demonstrated a transfer of tolerance to frustration. Therefore, it seems unlikely that

incompatible behaviors are responsible for the lack of transfer in the saline-treated animals of the current study.

Conclusions

The current study shows that the enhancement of the downshift experience via naloxone administration in the cSNC situation leads to a transfer effect in autoshaping, as indexed in terms of a reduced PRAE.

The current study has a limitation. Groups were not evenly distributed such that there were an equal number of animals in each condition. However, it is important to note that even with the small sample size in some groups, there were still significant statistical effects. This suggests that additional replications are warranted in order to further investigate transfer of tolerance to frustration.

The reasons for an asymmetrical transfer of tolerance to frustration shown across studies (i.e., the current study vs. the two studies discussed above) remain unclear. One possibility is that transfer of tolerance to frustration across cSNC and partial reinforcement situations may not be as Amsel (1992) previously predicted. It seems that animals need more than experience with the internal state of frustration in order to transfer tolerance across paradigms and behaviors.

Further research is needed to explore the asymmetry of the transfer of frustration seen across cSNC and partial reinforcement experiences. One possible study could be to match the incentives used in both paradigms as a means of establishing greater similarity across contexts. Instead of sucrose solution and food pellets, sucrose could be used in both cSNC and autoshaping. It would also be interesting to further investigate the within-trial data for the current study. Previous research has found that animals do not detect the change in incentive values early in trial (within the first 100 s), but typically show suppression during the last 100 s of a 300 s

trial (Norris, Daniel, & Papini, 2009). Therefore, there is the possibility that animals are demonstrating a transfer of tolerance to frustration, but it is occurring within the trial. Additionally, more research is needed to further investigated of the decreased palatability of larger incentives following PR training. For example, after animals complete acquisition training, a test could be performed where preferences for various sucrose concentrations are measured.

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Ortega, L.A., Uhelski, M., Glueck, A.C., Fuch, P.N., & Papini, M.R. (2011, November) Lesions of the ventro-lateral ordital cortex, but not of the medial prefrontal cortex, impair adjustment to incentive downshifts. Poster presented at Society for Neuroscience annual convention. Washington, D.C.

Ortega, L.A., Glueck, A.C., Daniel, A.M., Prado, M.A., & Papini, M.R. (2011, August) Reinterperting the Role of Chlordiazepoxide n Reward Downshift: Emotion, Memory, or Both? Poster presented at American Psychological Association annual convention. Washington, D.C.

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ABSTRACT

TRANSSITUATIONAL TRANSFER OF TOLERANCE TO FRUSTRATION STRENGHTENED BY OPIOID BLOCKAGE

by Amanda C. Glueck, 2012
Department of Psychology
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Thesis Advisor: Mauricio R. Papini, Professor of Psychology

The present experiments were designed to study transfer of tolerance to frustration through paradigms. Animals were exposed to a surprising reward reduction via consummatory successive negative contrast (cSNC), enhanced counterconditioning to the reward reduction via naloxone (Nlx) administration, and tolerance to frustration was examined in these same animals via the partial reinforcement acquisition effect (PRAE), the partial reinfocement extinction effect (PREE), and anxiety induced open-field activity. The results revealed Nlx enhanced and lengthened the cSNC effect while having no effect on unshifted animals. Previously downshifted animals with previous Nlx administration in cSNC showed an elimination of the PRAE , while Nlx had no effect on the PRAE in previously unshifted animals or on PREE in all animals. Nlx exposure to previously unshifted continuously reinforced animals demonstrated an increase in ambulation in the open-field apparatus.