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ADAPTATION OF CHOICE BEHAVIOR IN CONCURRENT CHAINS SCHEDULES AND THE ROLE OF THE BASOLATERAL AMYGDALA

by

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ABBREVIATIONS

AP – anterior-posterior
B – basal amygdala
BLA – basolateral amygdala
CCM – contextual choice model
CeL – central nucleus of the amygdala, medial
CeM – central nucleus of the amygdala, medial
CeN – central nucleus of the amygdala
COD – change over delay
CR – conditioned response
CS – conditioned stimulus
DLS – dorsolateral striatum
DMS – dorsomedial striatum
DRT – delay reduction theory
DV – dorsoventral
ec – external capsule
FI – fixed interval
FR – fixed ratio
FT – fixed time
GABA - γ-amino-butyric acid
LA – lateral nucleus of the amygdala
ML – mediolateral
MR – mixed ratio
NTS – nucleus of the solitary tract
NAc – nucleus accumbens
OFC – orbitofrontal cortex
PBS – phosphate-buffered saline
PIT – Pavlovian-instrumental transfer
PRE – pre-training surgery group
POST – post-training surgery group
US – unconditioned stimulus
VI – variable interval
VR – variable ratio

ABSTRACT

When a light predicts food that is subsequently devalued by pairing its consumption with a lithium chloride injection, rats avoid the food source in the presence of the light, although the food itself is absent. This behavioral adaptation is blocked by lesioning the BLA before, but not after, light-food training. To evaluate the generality of this finding, and whether the BLA allows the sensory properties of reinforcers to influence preference, this thesis aimed to measure changes in choice when various attributes of the consequences of behavior were systematically manipulated. Rats were trained to choose between a large and a small sucrose reinforcer. The delay to reinforcer delivery included tones, the frequency of which indicated the forthcoming reinforcer magnitude. After rats' preference for the large reinforcer side was stable, the frequency of the tone preceding the large reinforcer was shifted toward that preceding the small reinforcer, its onset was delayed, or quinine was added to the large reinforcer. The rats were insensitive to these manipulations across all five levels of each independent variable. In the second experiment, reversing the reinforcer magnitudes, the tones, or both, decreased preference for the originally large reinforcer side. As in previous reports, pre- but not post-training lesions of the BLA retarded behavioral adaptation to changes in reinforcer value, here measured by choice behavior and accomplished by reversing the magnitudes. The lesions did not affect preference acquisition, or the effect of reversing the magnitudes on subsequent baseline preference. The data agree with previous reports that the BLA is involved in behavioral adaptation. This role for the BLA can now be generalized to choice behavior in complex reinforcement schedules for which reinforcer

GENERAL INTRODUCTION

Choice behavior

The behavior of animals varies in magnitude and directionality, the latter of which is the concern of this thesis. Why does an animal move to the left, rather than the right? Why does it spend time in one location rather than another? Insofar as, for example, pressing a left lever and pressing a right lever are distinct behaviors, one can also ask why animals perform one behavior instead of another. Outside the laboratory, animals must balance foraging and mating with avoidance of predators. When they are not being threatened, however, what principles guide their choice between sources of food?

This question was first studied with rodents running through mazes. Hull (1932) described a maze in which food was placed in goal boxes perpendicularly displaced from the start box. After exiting the start box and traversing a straight alley, a right turn leads to food after a short path, and a left turn leads to food after a longer path. Rats prefer the shorter path. Researchers have taken different theoretical positions in discussing this problem. Hull argued that stimuli in the environment elicit the behavior leading to food. His goal gradient hypothesis states that the proximity of stimuli to food determines the strength with which stimuli elicit food-directed responses. The start box does not provide differential stimulation, so the excitatory strengths of the first differential stimuli experienced in the two alleys determine which alley is chosen. A shorter distance to food means a stronger response elicited by the stimulus, and preference for the short alley.

For Tolman (1938), in contrast, such a description was unsatisfactory as an explanation of behavior. According to Tolman, it is an impossible task to exhaustively

describe the factors influencing the proportion of trials on which a subject chose the left alternative (B_L) relative to all left and right choices ($B_L + B_R$). Tolman advocated using intervening variables to explain the relationship between operationalized independent variables, such as reinforcement schedule, and the dependent variable, response allocation, i.e. $B_L/(B_L + B_R)$. For example, Tolman, Ritchie, and Kalish (1946) proposed that animals anticipate the consequences of their actions, and behave in order to produce particular outcomes. Since animals transfer their learning about the location of a reinforcer in a water maze to a dry maze, Tolman (1938) suggested that Hull's explanation of maze preference in terms of stimuli eliciting responses was unsatisfactory (p. 14). Instead, Tolman argued that animals expect a reinforcer at particular location, and are flexible in the methods by which they obtain it.

The matching law

The experimental project of describing the factors that determine response allocation, $B_L/(B_L+B_R)$, was advanced when Skinner introduced an automated chamber for measuring responses, presenting stimuli, and controlling reinforcer delivery, as described by Ferster and Skinner (1957). The operant chamber provides several advantages over mazes. First, it is automated so that researchers do not need to handle the animal, replenish the reinforcer, and record the behavior at the end of each trial. As a result, more trials can be conducted per session than with labor-intensive maze protocols. Researchers can therefore train animals with reinforcement schedules that might be ineffective in the few trials afforded by a maze protocol, e.g., probabilistic schedules requiring many trials of exposure. Measuring preference over a greater number of

reinforcers also decreases the error associated with the measurement. That is, a rat that chooses one alternative on 3 of 4 trials may be said to have 75% preference, but certainly we are more confident in this percentage if the rat chooses one alternative on 8 of 12, or 75 of 100 trials. An "alternative" refers to one of two concurrently presented schedules of reinforcement toward which an animal might direct its responding. Another method of increasing confidence is to test more subjects and state the number of subjects choosing one alternative over the other even in a single trial (e.g., Tolman & Gleitman, 1949).

Despite these disadvantages, maze protocols are still used in some laboratories (e.g., Floresco & Ghods-Sharifi, 2006). Reinforcement in mazes may be delivered after performance that requires control of behavior by spatial stimuli and so mazes are often used to study memory for spatial configurations (Morris, 1981). For example, a rat may be reinforced for moving in the direction of a poster on the wall outside of the maze, so that accurate performance requires that the rat discriminate the poster from other stimuli in the space outside of the maze.

When animals are presented with two levers or keys in a chamber, responding on each of which results in different schedules of reinforcement, their relative frequency of choice between the two alternatives tends to match the ratio of the obtained reinforcement (Herrnstein, 1961). Reinforcement is most frequently food, grain for pigeons and food pellets or sucrose for rats. These are called primary reinforcers because their effects on behavior are due to unlearned consequences of the reinforcer; pigeon's exhibit innate physiological responses to grain consumption. In contrast, conditioned reinforcers are initially neutral and arbitrary stimuli, such as lights or tones, which acquire the capacity to reinforce behavior because they predict a primary reinforcer.

Herrnstein (1961) presented pigeons with a red and a white key. If they pecked a key after a variable interval (VI) of time had passed, grain was delivered. The VI schedule for one key was shorter than the other, making it a richer source of reinforcement. Herrnstein varied the pairs of concurrent VI schedules between the red and a white key every 16-45 sessions and observed a linear relationship between percent of responses on the red key and the percent of reinforcers delivered to that key. This observation, known as the matching law, has broad applicability. For example, it describes humans' allocation of verbal contributions during a conversation: more comments are directed toward people delivering a greater frequency of approbation, e.g., "that's a good point" (Conger & Killeen, 1974). The initial observations of matching launched decades of studies addressing the mechanisms by which matching occurs and identifying the reinforcer variables and other factors that contribute to matching (for a review, see Davison & McCarthy, 1988).

Deviations from matching are common. To accommodate deviations from perfect matching, Baum (1974b) proposed the generalized matching equation:

$$\log (B_1/B_2) = b \log (R_1/R_2)^a$$

When the ratio of responses (B_1/B_2) and the ratio of reinforcement (R_1/R_2) are plotted on log-log coordinates with at least five levels of the independent variable, the y-intercept and slope of this function vary (e.g., Hollard & Davison, 1971; Baum & Rachlin, 1969); because slope is a property of a line through several data points, a greater number of data points results in a more accurate estimate. Five points is acceptable for this type of

research (Davison & McCarthy, 1988). The y-intercept reflects bias (b), which is responding that is independent of relative reinforcement. Equal reinforcement can result in a preference for one alternative over the other if the subject is biased. Unmeasured asymmetries in the apparatus, animal, or reinforcement schedule contribute to bias, e.g., position preference, handedness or reinforcer quality (Baum, 1974b). The slope indicates sensitivity to reinforcement (a), or the degree to which B_1/B_2 matches R_1/R_2, with $a = 1$ for perfect matching. Undermatching ($a < 1$) refers to a B_1/B_2 ratio that is less extreme than R_1/R_2, and overmatching ($a > 1$) refers to a B_1/B_2 ratio that is more extreme than R_1/R_2.

Variables that affect matching include the shape of the distribution of VI values. Pigeons approximate perfect matching more closely when the reinforcers are delivered according to VI schedules generated from an exponential relative to an arithmetic progression, possibly because of the greater variance in former (Taylor & Davison, 1983). Also, switching between the alternatives resulting in few responses per bout is related to undermatching (Baum, 1979).

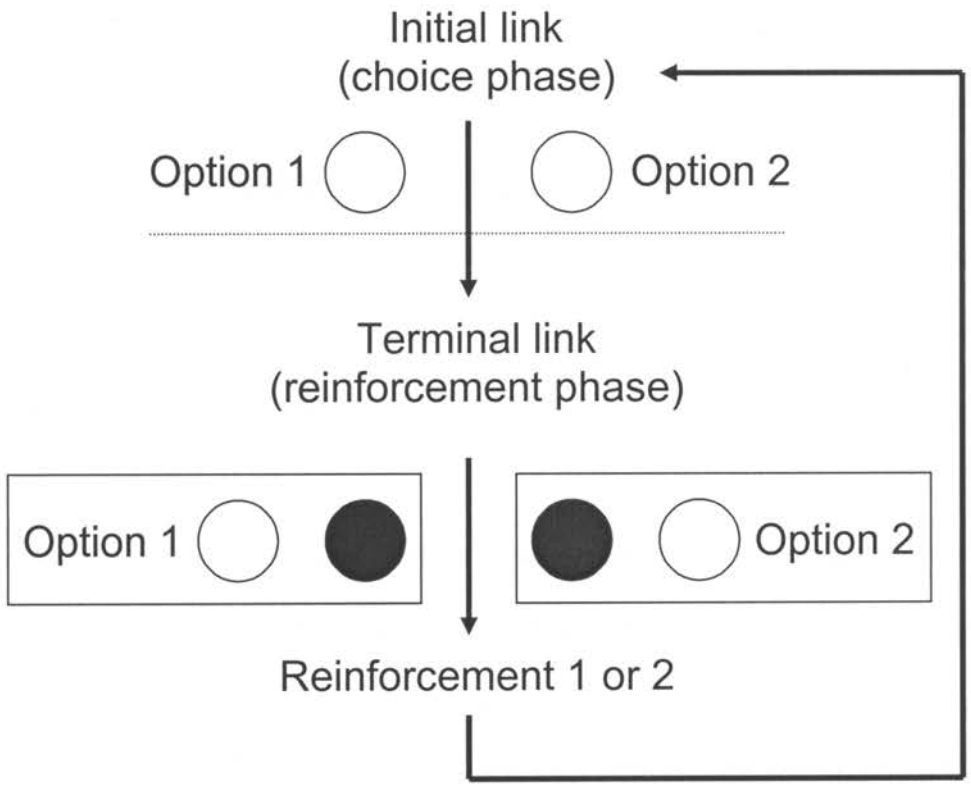
Concurrent schedules

The generalized matching equation accurately describes choice between two alternatives after many sessions of training (Davison & McCarthy, 1988). Animals' relative responding generally matches relative reinforcement between alternatives varying along many dimensions, indicating that animals are sensitive to various properties of reinforcers. For example, approximate matching occurs to the ratio of reinforcer frequency (VI VI schedules, Herrnstein, 1961). When one alternative is a VI

schedule, matching occurs when the other alternative delivers reinforcers after a variable number of responses (VI variable ratio (VR), Herrnstein & Heyman, 1979) or after a fixed, rather than variable, time period (VI fixed interval (FI), Trevett, Davison, & Williams, 1972).

Combinations of reinforcer variables, such as amount and delay, influence choice behavior, such that measures of preference are used to infer overall reinforcer value as determined by its various properties (Baum & Rachlin, 1969; Mazur, 1987). Animals are

Figure 1. Flow diagram of concurrent chains schedules of reinforcement. In the initial link (choice phase), subjects choose between responding on different concurrent schedules (options 1 and 2). Once the reinforcement schedule is satisfied, subjects enter the terminal link (reinforcement phase). The terminal link is usually a single, rather than concurrent, schedule of reinforcement, the parameters of which depend on the initial link chosen. After a reinforcer is delivered, the initial link is reinstated, sometimes after a time out during which responding has no scheduled consequences. Open circles refer to illuminated keys for which pecking is reinforced and closed circles refer to non-illuminated keys for which pecking has no consequences.


Initial link
(choice phase)
Option 1
Option 2
Terminal link
(reinforcement phase)
Option 1
Option 2
Reinforcement 1 or 2

sensitive to the immediacy of a reinforcer (Chung, 1965), reinforcer quality (Hollard & Davison, 1971), and amount as modulated by reinforcer duration (Catania, 1963), or combinations of reinforcer frequency and rate (Todorov, 1973). That matching occurs to all of these reinforcer properties implies that they converge on common neural systems supporting choice behavior (Shizgal, 1997). Understanding the processes underlying sensitivity to different reinforcer properties and how they converge to influence valuation and choice behavior is central to understanding normal and maladaptive choice behavior.

Concurrent chains schedules

In concurrent chains schedules (Autor, 1960, 1969), choices are measured during the initial link, or choice phase, during which subjects respond in order to gain access to a terminal link, or reinforcement phase (Figure 1). The terminal links are usually, but not always (e.g. Baum, 1974a), mutually exclusive. If the schedules during the initial links are independent, the subjects can switch alternatives at any time during the initial link and possibly enter the terminal link. For example, if the initial links are independent VI 16 s schedules, two independent timers allow responding on either schedule to result in terminal link entry. Suppose that one alternative is strongly preferred because it delivers immediate reinforcement while the other delivers delayed reinforcement in the terminal link. Subjects may obtain a greater frequency of reinforcers from the preferred alternative such that both reinforcer frequency and immediacy must be considered when accounting for preference. This additional variable can be eliminated by applying a single VI schedule to both initial link alternatives, controlling the number of terminal link

entries, and therefore reinforcers, for each alternative (dependent scheduling: Stubbs & Pliskoff, 1969).

In simple concurrent schedules, subjects' responses produce primary reinforcers. Relative responding is used to measure preference. The contingencies can, however, affect responding in a way that confounds measures of preference. For example, in concurrent schedules, rats respond more frequently on a fixed ratio (FR) 35 than a mixed ratio (MR) 1 or 99 schedule (Rider, 1983). Relative response rate would imply that the FR 35 schedule is preferred. Rider (1983) showed, however, that in concurrent chains schedules for which the terminal links are FR 35 and MR 1 or 99, the MR schedule is preferred as measured by initial link choice. Responding in the initial links of concurrent chains schedules is therefore dissociated from how the reinforcement schedule influences response patterns in the terminal link. Response requirements in the terminal links generally do not influence preference in the initial links (e.g., Neuringer, 1969). Omino & Ito (1993) reported different numbers of responses for FI versus fixed-time (FT) terminal links, but initial link preference did not differ.

Concurrent chains schedules may be the most widely used reinforcement schedule for studying conditioned reinforcement (Williams, 1994). A conditioned reinforcer is a previously neutral stimulus that supports learning when it is a consequence of behavior. In concurrent chains schedules, when an animal enters a terminal link, a stimulus change typically occurs. If the stimuli introducing each terminal link are unique, they may be conditioned reinforcers due to their temporal relationship to reinforcer delivery (Kelleher & Gollub, 1962). Assuming that conditioned reinforcers are like primary reinforcers, influencing the probability of behavior upon which they are contingent, this aspect of

concurrent chains schedules should be a factor determining preference. When differential terminal link stimuli do not occur, choice may still deviate from indifference, but preference is weaker when the terminal links are unsignaled (Ploog, 2001). Stimuli that differentially signal the terminal links appear to influence the acquisition of preference because of their temporal relationship with reinforcer delivery, and are therefore conditioned reinforcers (Williams & Dunn, 1991; Grace, 2002b). After pigeons showed a stable preference, Grace (2002b) reversed the locations of initial links leading to short and long FI terminal links. He reported that pigeons required fewer sessions to acquire preference for the initial link leading to a shorter FI schedule if the terminal link stimulus-FI relationships were maintained, rather than switched, during the reversal. In another study, when different FI terminal links were assigned to random locations after VI 60-s initial links, using a white key light for both FI schedules resulted in lower preference for the initial link leading to the shorter FI than if differential key light colors signaled the FI schedules (Williams & Fantino, 1978). The magnitude of initial link preference in concurrent chains is therefore affected by stimuli signaling the terminal links. Compared to concurrent schedules, concurrent chains schedules therefore allow dissociation of the effects of conditioned and primary reinforcers on choice.

Models of concurrent chains choice

Concurrent chains schedules are clearly more complex than concurrent schedules. The matching law requires that relative choice proportions be a constant function of relative reinforcement. When reinforcer ratios and initial link durations are held constant, but the absolute duration of the terminal links increase, preference for the more valuable

alternative becomes more extreme (MacEwen, 1972), which is inconsistent with the matching law. Preference between schedules delivering equal rates of reinforcement also becomes more extreme when initial link duration is reduced (VI terminal links: Fantino, 1969; FI terminal links: Wardlaw & Davison, 1974; FT terminal links: Davison, 1983). For example, Wardlaw and Davison (1974) presented pigeons with equal VI initial links of 27, 38, 49, or 115 s, leading to FI terminal links. One terminal link was always FI 5 s, and the other was FI 5, 7.5, 10, 15, 30 s. A particular combination of VI initial links and FI terminal links occurred until preference stabilized (18-47 sessions), and then the conditions changed. Initial link preference was more extreme with shorter VI schedules. Conversely, lengthening the initial links drives preference toward indifference (Fantino, 1969; Squires & Fantino, 1971; Fantino & Davison, 1983).

Preference is therefore influenced by variables other than the initial or terminal link reinforcement schedule, and these influences are known as context effects (Grace, 1993). Context effects are not included in the generalized matching law or its variants that have been applied to concurrent chains schedules (Davison, 1983). A model that accounts for preference in concurrent chains schedules must include terms describing the effects of the temporal context provided by initial and terminal link duration.

Fantino's (1969) incorporated temporal context into a matching law formulation with his delay reduction theory (DRT):

$$\frac{B_L}{B_L + B_R} = \frac{T - t_L}{(T - t_L) + (T - t_R)}$$

In this equation, the subscripts L and R refer to the left and right alternatives, respectively. B refers to initial link response rate, T is the mean time between initial link onset and reinforcement, and t is the mean terminal link duration. DRT states that preference is determined by conditioned reinforcer value, which is determined by the reduction in expected time to reinforcement signaled by the onset of one terminal link relative to the other. According to DRT, preference depends on the proportion of the delay to reinforcement from initial link onset occurring in the terminal link. DRT accounts for many context effects on concurrent chains preference. Decreasing initial link duration effectively decreases T, time to reinforcer delivery from initial link onset. As a result, terminal link (t) encompasses a greater proportion of the time to reinforcement, and initial link preference increases. According to the model, the reduction in time to reinforcer delivery from initial link onset influences preference via conditioned reinforcers (Squires & Fantino, 1971).

The original DRT can be modified to include reinforcer rate as a variable by adding r, indicating reinforcer rate for each alternative, external to each set of parentheses to the right of the equivalence sign.

$$\frac{B_L}{B_L + B_R} = \frac{r_L(T - t_L)}{r_L(T - t_L) + r_R(T - t_R)}$$

In this modified form, DRT reduces to the matching law when the terminal links are 0 s. The theory provides a more accurate account of preference in concurrent chains than simply considering relative reinforcer rate (Fantino, Preston, & Dunn, 1993). It is unique in that overall delay of reinforcement influences preference as opposed to just the

delay to primary reinforcement in the presence of the stimulus (Killeen, 1982). The theory therefore incorporates context effects into an extension of the matching law.

DRT cannot predict exact choice probabilities or intransitivity in preference. For example, when subjects are indifferent between concurrent FI and VI schedules, preference would be intransitive if the FI schedule were preferred to a third schedule to the same extent that the VI schedule is preferred to that third schedule. Intransitivity occurs (Navarick & Fantino, 1972) and cannot be accounted for by delay reduction theory (Grace, 1993).

Grace (1994) took a similar approach to DRT in accounting for context effects on concurrent chains choice. He extended the matching law by including an exponent that affects all terminal link variables:

$$\frac{B_L}{B_R} = b\left(\frac{R_L}{R_R}\right)^{a_1}\left[\left(\frac{1/D_L}{1/D_R}\right)^{a_2}\left(\frac{X_L}{X_R}\right)^{a_x}\right]^{(T_t/T_i)^k}$$

In the contextual choice model (CCM), subscripts L and R refer to the left and right alternatives, respectively. The symbols B_L and B_R refer to initial link response rates, R_L and R_R refer to terminal link entry rates, D_L and D_R refer to delays to reinforcement from terminal link entry, T_t and T_i refer to the mean terminal and initial link duration per reinforcement. The variable X is any measurable reinforcer property that differs between the alternatives, such as reinforcer magnitude. The parameters in the model are bias (b), sensitivity to initial link conditioned reinforcement (a_1) and terminal link primary reinforcement (a_2, a_x), and k, the context scaling parameter. The CCM accounted for

more than 90% of the variance in mean initial link preference over 19 data sets (Grace, 1994). In this analysis, $k < 1$ if the terminal links included non-differential stimuli, suggesting that the effects of temporal context are influenced by stimuli in the terminal link.

Like DRT, CCM reduces to the generalized matching law when terminal link duration is 0 s. The theories account for the same qualitative effects of varying initial and terminal link duration on preference, but the CCM makes quantitative predictions and is applicable to various procedures (Grace, 1994). The primary difference between the CCM and DRT is how they account for stimulus effects on preference. DRT claims that terminal link stimulus value depends on the context. On the other hand, the CCM claims that terminal link stimulus value does not depend on the context, but the efficacy of a stimulus with a particular value is determined by context. While the details of these models will continue to be specified, overall they provide a fairly comprehensive account of steady-state preference in concurrent chains.

Concurrent schedules – choice in transition

The models above describe preference between reinforcement schedules that have been stable for many sessions. Researchers have recently turned their attention toward understanding how preference is acquired and how choice changes immediately after the consequences are manipulated, i.e., choice in transition. In rapidly changing environments, animals must be sensitive to variations in reinforcement contingencies. When animals adjust their choices to reflect the current reinforcement contingencies, they will more efficiently obtain reinforcers. For example, a rich reinforcement schedule may

switch to non-reinforcement, or extinction. The sooner an animal detects and adapts to this change, the sooner it can direct effort toward richer schedules of reinforcement. On the other hand, such non-reinforcement may reflect local variability and not an overall change in reinforcement contingencies, in which case it would be disadvantageous for the animal to prematurely adapt its choices.

Davison & McCarthy (1988) described preference between concurrent schedules as being influenced by current and past relative reinforcement contingencies:

$$\log\left(\frac{B_{1n}}{B_{2n}}\right) = a_0 \log\left(\frac{R_{1n}}{R_{2n}}\right) + a_1 \log\left(\frac{R_{1(n-1)}}{R_{2(n-1)}}\right) + \ldots + a_9 \log\left(\frac{R_{1(n-9)}}{R_{2(n-9)}}\right)$$

In this formula, B_1 and B_2 refer to response rates at two separate alternatives, R_1 and R_2 refer to their respective reinforcer rates, and the subscripts n and n-1 or n-9 refer to the reinforcer rate ratio for the preceding session or nine sessions past, respectively. The contribution of each past reinforcer ratio to the current response ratio is quantified by a, the sensitivity parameter from the generalized matching law. The equation states that response allocation between two alternatives is a function of both past and present reinforcer ratios. For example, if an animal chooses between concurrent schedules yielding a 2:1 ratio of reinforcer frequency for several sessions, the animal should allocation approximately twice as many responses to the richer schedule. If the ratio reverses suddenly, the animal will not immediately reverse its preference. Rather, the animal must learn about the new contingencies and adjust its choices. Initially, the animal's choices will reflect the 2:1 reinforcer ratio and show little sensitivity to the

current reinforcer ratio, 1:2. Over time, the sensitivity parameter, a_1, will decrease and a_0 will increase.

Davison & Hunter (1979) provided an early example of this phenomenon, varying concurrent VI schedules every six sessions. On average, the sensitivity parameter was .48 when response ratios were plotted against reinforcer ratios for the current session, but declined to .28 when reinforcer ratios from the previous condition were used in the calculation. Hunter & Davison (1985) varied the concurrent VI schedules every session according to a 31-step pseudo-random binary sequence. Response ratios in the current session showed decreasing sensitivity to reinforcer ratios from previous sessions, with little influence from reinforcer ratios six or more sessions in the past.

Mazur (1995) explored the processes influencing the control of past reinforcement contingencies on current preference. He trained pigeons with equal dependent concurrent VI schedules, varying the proportion of reinforcers delivered to one alternative among values ranging from .10 and .90. Six minutes into the first transition session, the values reversed and were maintained for the next four sessions. Preference changed across each session, but Mazur noticed that at the start of a session, response ratios resembled those from past sessions more than response ratios from the end of the immediately preceding session. That is, he detected evidence of spontaneous recovery of response allocation reflecting temporally distant reinforcer ratios, rather than the most recent ratios. Since spontaneous recovery decreased across the four post-transition sessions, Mazur's data suggest that subjects' response ratios are determined by a weighted moving average of reinforcer ratios from several past sessions.

As with many learning phenomenon the neural plasticity necessary for behavioral expression of learning about recent changes in reinforcement contingencies may undergo a period of consolidation (Hernandez, Sadeghian, & Kelley, 2002). In the first minutes or hours after training, blocking protein synthesis, among other treatments, can prevent the later expression of learning; consolidation refers to the molecular processes disrupted by such treatments that are necessary for the synaptic plasticity that presumably underlie learning (Dudai, 2004). Rates of consolidation could explain spontaneous recovery and the rate at which preference adapts to changes in reinforcement contingencies. For example, in Mazur's protocol, if learning about the reinforcement contingencies consolidated very rapidly after a session, one might expect less spontaneous recovery of preference reflecting contingencies from several sessions in the past. The biological mechanisms underlying spontaneous recovery in a matching context have not been investigated.

It is possible that spontaneous recovery simply reflects a regression of preference toward indifference. To test whether spontaneous recovery reflects a regression of preference toward sensitivity to past contingencies, Mazur (1996) trained pigeons for an unpredictable number of baseline sessions with equal, dependent concurrent VI schedules for which 50% of the reinforcers were delivered to each alternative. For 1-3 transition sessions, a greater percentage of reinforcers were delivered to one alternative, after which the baseline conditions were reinstated. When the baseline conditions were restored, Mazur observed spontaneous recovery of preference that reflected the differential reinforcer percentages. Spontaneous recovery was greater when the transition percentage was 90% compared to 70%. If spontaneous recovery was simply a drift in preference

toward indifference, it should occur to a similar extent whether the subject has been exposed to a more or less asymmetrical ratio of reinforcement percentages. Past reinforcement, rather than regression toward indifference, influenced spontaneous recovery. With a greater number of transition sessions, spontaneous recovery was also greater in terms of magnitude and the number of recovery sessions over which it was observed. Furthermore, passage of time between the transition and restoration of baseline conditions influenced the degree of spontaneous recovery in Mazur's (1996) second experiment, suggesting that time-dependent neural processes not requiring stimulus input affect spontaneous recovery.

Mazur (1997b) later used a similar protocol to Mazur (1996) to show that the more rapidly contingencies change, the more sensitive pigeons are to these changes. Two alternatives delivered equal reinforcement percentages for 5, 6, or 7 baseline sessions. Then for 3 sessions, 70 or 90% of the reinforcers were delivered to one alternative. When reinforcers occurred more frequently (VI 15 s compared to VI 180 s), the pigeons acquired a preference for the richer alternative three times faster, in terms of the number of reinforcers. Overall reinforcer rate therefore affects the rate of preference acquisition, perhaps because more information about the new contingencies is provided over a shorter period of time. In a second experiment, Mazur (1997b) showed that pigeons' preference adjusted more rapidly when reinforcement percentages changed after 1-2 instead of 7-9 sessions. The range of past reinforcer ratios influencing current preference therefore varies, with one factor being the stability of past reinforcement.

Davison and Baum have conducted studies examining the effects of changes in reinforcer ratios (2000, 2002, 2003). They changed the reinforcer rate or magnitude

every 10 reinforcers to a randomly selected value. The change was not signaled and a blackout intervened between contingency changes. With every reinforcer, preference increasingly reflected the current reinforcer rate (Davison and Baum, 2000, 2002) or magnitude (Davison & Baum, 2003) ratio. As the duration of the blackout occurring between contingency changes increased from 1 to 120 s, the influence of the immediately preceding reinforcer ratio on current preference declined (Davison & Baum, 2002), implying that decay of memory for past contingencies may have allowed the pigeons to be more sensitive to the current reinforcer ratios. Past reinforcement contingencies may be less reliable with the passage of time. This is the opposite of spontaneous recovery, which refers to the strengthening of control of behavior by past contingencies after time has passed. The effect described by Davison and Baum (2002) also occurs over a time scale of seconds rather than hours, and therefore probably reflects different neurobiological processes.

Krägeloh and Davison (2003) used the same protocol as Davison & Baum (2000, 2002, 2003) to evaluate the effects of signaling the changes in reinforcement contingencies on the rate of preference change. In some conditions, the magnitude of the reinforcer rate ratio was signaled by how long a key light was illuminated, while in others, the components were not differentially signaled. The signal allowed pigeons' responding to favor the richer alternative even before the first reinforcer was delivered, approaching asymptote after only 2-3 reinforcers. Without a signal, pigeons' preference was biased toward the side that was richer in the previous component until the first reinforcer was delivered. Thus, stimuli signaling the current reinforcer ratio influenced pigeons' response allocation even before they had sampled the new contingencies.

Overall, research on choice in transition in concurrent schedules suggests that preference can change rapidly, particularly if reinforcer ratios change frequently (Mazur, 1997b; Gallistel et al., 2001), the overall rate of reinforcement is high (Mazur, 1997b), and the contingencies are signaled (Krägeloh & Davison, 2003). When reinforcer ratios change, preference seems to reflect a weighted moving average of past reinforcer contingencies (Mazur, 1996, 1997b), which is affected by the passage of time (Devenport & Devenport, 1994; Mazur, 1996; Davison & Baum, 2002). These data suggest that the nervous system learns to predict contingency changes and that the associated memory mechanisms are affected by time-dependent neurobiological processes.

Concurrent chains schedules – choice in transition

While relatively few studies exist regarding choice in transition in concurrent schedules, even fewer have been conducted for choice in transition in concurrent chains schedules. Mazur, Blake, and McManus (2001) provided the first report about choice in transition in concurrent chains schedules. In separate conditions, Mazur et al. (2001) reversed the terminal link delays or the percentage of reinforcement delivered to each alternative every 9-13 sessions. Presumably, a change in the percentage of reinforcers delivered to each alternative will only be detected after many trials because percentage is a global property of reinforcement contingencies. In contrast, pigeons should detect a change in reinforcement delay at its first occurrence. Contrary to Mazur et al.'s prediction, the pigeons' choices adapted more rapidly to reversal of the reinforcement percentages compared to the delays. One counterintuitive interpretation is that subjects'

ability to discriminate the schedule change is not a factor influencing choice in transition. In this study, choice changed gradually when reinforcement schedules changed.

Grace (2002b, Experiment 2) studied the effects of terminal link stimulus-reinforcer relations on choice in transition in concurrent chains schedules. The pigeons chose between pecking left and right keys that were illuminated white. After a VI 15-s initial link elapsed, the center key changed its color to red or green. The color indicated whether a peck would be reinforced after an 8- or 16-s delay (FI, 8 or 16 s). After preference for the shorter terminal link stabilized, Grace reversed the positions of the initial links. The side previously associated with the long delay was now associated with the short delay. In one condition, if pecking the left key changed the center key red during baseline, this same stimulus arrangement was in place after the delays were reversed. As a result, the red key might signal an 8-s delay during baseline, but a 16-s delay after the reversal, and vice versa for the green key. The pigeons shifted their preference toward the shorter terminal link, approaching asymptote after approximately 6.5 sessions. When the center key colors and FI terminal links were reversed, so that the color signaled the same FI value as during baseline, pigeons acquired asymptotic preference in approximately 4 sessions. Grace argued that the terminal link stimuli were conditioned reinforcers, i.e., Pavlovian conditioned stimuli that had acquired value via their temporal relationship with reinforcer delivery. An alternative interpretation, however, is that when only the FI values are reversed, the schedule is more similar to baseline than when both the delays and stimulus colors are reversed. It is unclear, therefore, whether the more rapid adjustment of preference when terminal link stimulus-FI values were the same during baseline and reversal is due to generalization or

consistent conditioned reinforcement. Regardless of the interpretation, the data suggest that preference can adjust fairly rapidly when reinforcer variables are manipulated in concurrent chains schedules and terminal link stimuli contribute to changes in choice.

Grace, Bragason, and McLean (2003) presented pigeons with more rapid changes in contingencies in concurrent chains schedules. The left terminal link was always FI 8 s, but the right terminal link FI values were 4 or 16 s, changing each session according to a pseudorandom binary sequence. Response ratios changed more rapidly when the right FI was 16 s, even though the ratios were always balanced at 2:1 (4 and 8 s or 8 and 16 s). For some pigeons, the response ratio changed 3-fold change in favor of the short delay from the first to the second twelfth of a session. The pigeons barely changed their preference when the schedules were changed to FI 4-s and FI 8-s. Grace et al. (2003) suggest that this could reflect a context effect, i.e. longer terminal links result in greater preference between initial links (MacEwen, 1972), or avoidance of long, 16 s delays.

In a second experiment, Grace et al. (2003) used a wider range of right FI values, varying them pseudorandomly between 2 and 32 s, with 32 and 29 values less and greater than 8 s, respectively. When the FI was greater than 8 s, response ratios changed more rapidly. Pigeons' sensitivity to the current FI values was not, however, greater than when the right terminal links were only two values, FI 4 s and FI 16 s. Thus, although the FI values used by Grace et al. are usually discriminable to pigeons, discrimination of individual FI ratios did not appear to control changes in preference. Instead, the pigeons appeared to discriminate categorically based on whether the variable terminal link was greater than FI-8 s. This result was replicated in a later study directly comparing pigeons' sensitivity to terminal link schedules with minimal or maximal variation in FI

values (Grace & McLean, 2006). These data suggest that pigeons do not remember every delay to reinforcement, but make their choices based on whether the current FI value is greater than the average remembered value. A comparison of changes in preference using the same protocol in simple concurrent (Schoefield and Davison, 1997) and concurrent chains schedules (Grace et al., 2003) indicates that preference changes more slowly with concurrent chains schedules. Grace et al. (2003) suggested that how quickly terminal link stimulus values change could be a source of this difference. Presumably reducing the initial link to 0 s should eliminate differences in the rate of preference change between concurrent and concurrent chains schedules. This has not been investigated.

Studies of choice in transition in concurrent chains schedules have examined somewhat different independent variables than studies of choice in transition in concurrent schedules. Mazur et al. (2001), Grace et al. (2003), and Grace and McLean (2006) collected data that provide information about the decision rule pigeons use to adapt their preference to changes in reinforcement contingencies. Like Krägeloh and Davison (2003) using concurrent schedules, Grace (2002b) showed that stimulus conditions contribute changes in preference in concurrent chains. Given that only a few studies of choice in transition in concurrent chains have been conducted, all with pigeons as subjects, additional research is needed to understand why preference changes more slowly in concurrent chains schedules and how the terminal link stimulus is involved in choice in transition.

Models of choice in transition

Using mathematical models, researchers have attempted to describe how preference is acquired, or how preference changes when reinforcement schedules change. The most common type is the linear operator model. Linear operator models propose that reinforcement history influences behavior via changes in stimulus value, which update with each reinforcer as a function of the current and asymptotic value of the stimulus (e.g. Bush & Mosteller, 1955; Pearce & Hall, 1980; Rescorla & Wagner 1972). The rate or magnitude of behavior, or preference, is used to estimate stimulus value.

Typically, a trial consists of a single reinforcer, so it is possible to describe how the value of an alternative changes with each reinforcer. The strength of a response alternative increases with each reinforcer and decreases with each nonreinforcement according to Mazur's (1992) model:

$$\text{Reinforcement:} \quad \Delta V_i = r(1 - V_i)$$

$$\text{Non-reinforcement:} \quad \Delta V_i = n(-V_i)$$

The proportion of responses allocated to one alternative, i.e., preference, is determined by its relative value. The reinforcement and nonreinforcement parameters r and n, respectively, vary from 0 to 1. These are equivalent to learning rate parameters in Rescorla and Wagner's (1972) model of changes in conditioned responding in Pavlovian conditioning. The change in conditioned responding (ΔV) is determined by the difference between asymptotic conditioned responding (λ) and responding supported by the sum strengths of each CS present (ΣV):

$$\Delta V = \alpha\beta\left(\lambda - \sum V\right)$$

The learning rate parameters, α and β, modify the degree to which discrepancies between asymptotic conditioned responding and responding supported by the current value of each CS affect changes in behavior on each trial. The parameters refer to features of the CS (α) such as salience and the unconditioned stimulus (US, β) such as magnitude. The US has the same physiological definition as a reinforcer, but could also be a punisher like foot shock. Likewise, the learning rate parameter in Mazur's (1992) formulation, (r), determines the extent to which each reinforcer increases or decreases the value of an alternative. Mazur's model can account for spontaneous recovery if V_i is computed at the start of each session but reflects the average V_i from previous sessions; preference at the start of a session would reflect reinforcer ratios from preceding sessions (Mazur, 1995, 1996).

In contrast to linear operator models, memory-representational models propose that the reinforcement delays for each alternative are sampled prior to a choice; animals choose the alternative with a shorter remembered delay (e.g., rate expectancy theory: Gallistel & Gibbon, 2000). Grace (2002a) compared linear-operator accounts of choice in transition with memory-representational models, arguing that linear-operator models describe acquisition preference and choice in transition. This is consistent with Grace and McLean's (2006) proposal that pigeons use a categorical decision rule rather than extensive memory sampling for each alternative to direct their choice.

Linear operator models provide an important step toward quantitative descriptions of learning and changes in behavior, although their mathematical forms are simple and

descriptive. These models do not explain how preference is acquired, or how preference changes following shifts in reinforcement contingencies. As revealed in the above discussion, clearly many factors influencing choice in transition are omitted from the linear operator formulations, such as whether reinforcement changes are signaled. One is left feeling a bit like Tolman, desiring more intervening variables. It remains to be seen whether these models can be elaborated in a satisfactory manner. In any case, it is worth noting that the same mathematical form has been used to describe acquisition of Pavlovian conditioning (Rescorla & Wagner, 1972; Pearce & Hall, 1980), preference and choice in transition (e.g., Mazur, 1992). It may be that common learning mechanisms underlie these types of behavioral changes.

Behavioral momentum theory

In contrast to the factors influencing changes in preference when reinforcement contingencies change, the factors affecting changes in the rate of responding on a single reinforcement schedule of have been extensively investigated. Behavioral momentum theory (for a review, see Nevin, 1992) takes off from a physics metaphor, likening response rate to the velocity of a physical body, and response strength to its mass. Mass is measured by the momentum of behavior when it is disrupted, e.g., by reinforcer omission. The less a behavior changes when disrupted, the greater its momentum. Behavioral momentum is a function of the history of reinforcement, whereas response rate is a function of the reinforcement schedule. Like linear operator models, behavioral momentum theory claims that reinforcement history is represented via stimulus value (Nevin & Grace, 2000).

The data supporting behavioral momentum theory are generally collected with reinforcement schedules that alternate (multiple schedules), rather than being presented concurrently. For example, Nevin et al. (1990) reinforced pigeons' pecking according to a VI schedule in the presence of one key color. After 3 minutes, the key color changed, and pecking was reinforced on the same VI schedule except that reinforcers were also delivered freely. To test for behavioral momentum, the pigeons were satiated before the test or the reinforcer was omitted. Pigeons' response rates changed less (i.e., had more momentum) in the presence of the color that had been associated with a higher rate of reinforcement, which was the alternative with the free reinforcers. Nevin and Grace (2000) suggested that similar processes determine behavioral momentum and preference, i.e., Pavlovian stimulus-reinforcer relationships that allow past reinforcement to influence current behavior. An important question is how the stimulus value of conditioned reinforcers, or terminal link stimuli, influence preference and animals' changes in preference when the primary and conditioned reinforcer contingencies are manipulated.

The amygdala

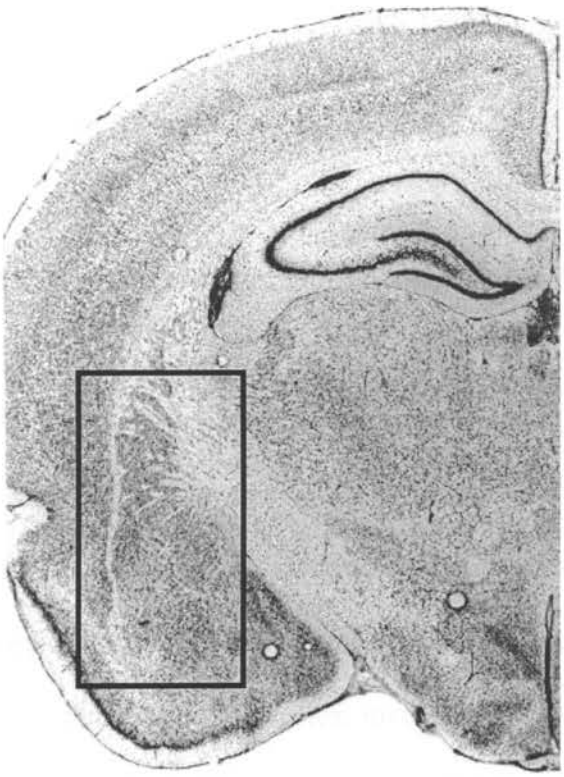
After decades of research on the variables influencing steady-state preference between reinforcement schedules, researchers have just begun studying the factors affecting changes in preference when reinforcement schedules change. Every study conducted so far has examined behavioral variables, e.g., reinforcer rate, the discrepancy between the schedules, and the rate of schedule change. No studies of choice in transition have considered what areas of the brain may be involved. This is an important link because it could provide information about the neurobiological mechanisms of

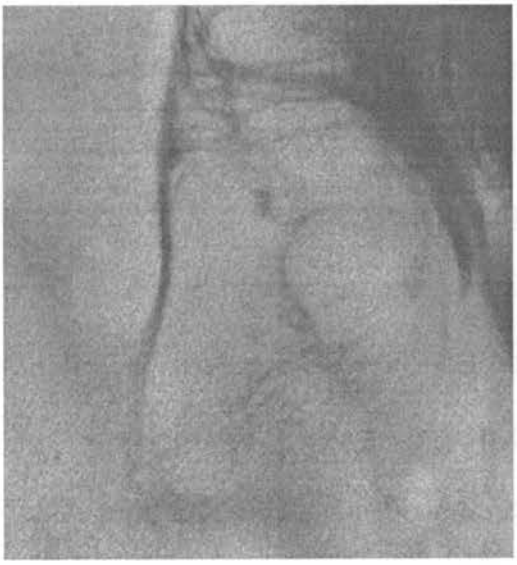
maladaptive choice, which occurs in many psychiatric disorders from drug addiction to depression (Evenden, 1999). The amygdala is one brain area that is likely to be involved. Before reviewing the evidence, I will provide an overview of how the amygdala is connected with the rest of the brain.

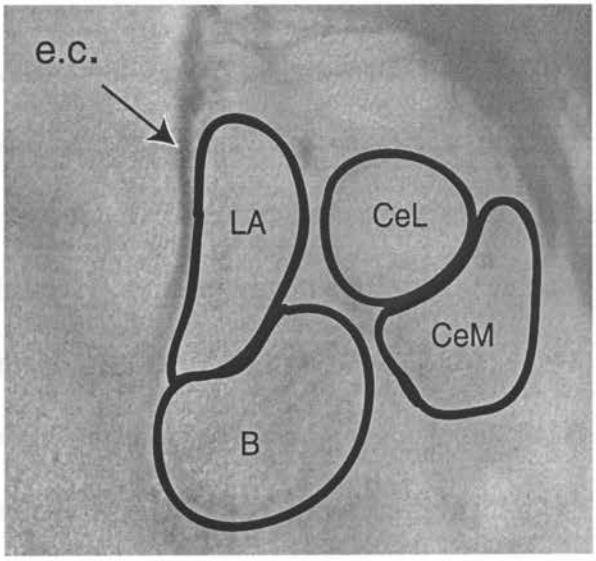
The amygdala is a collection of nuclei in the medial temporal lobe first described by Burdach around 1820 (referenced by Swanson & Petrovich, 1998) and dissected into six distinct nuclei by Johnston (1923): central, medial, cortical, basal, accessory basal, and lateral nuclei. In the mid-19th century, Meynert described Burdach's amygdala, the basolateral amygdala (BLA) as the deepest layer of the cerebral cortex (Swanson, 2003). The mammalian amygdala contains two broad groups of neurons: 1) a cortex-like basolateral nuclear group consisting of the lateral, basal and accessory basal nuclei (basolateral nuclear complex) and 2) a non-cortex-like corticomedial group, consisting of the central (CeN), medial, cortical and lateral olfactory tract nuclei (McDonald, 1992). Like cortical projection neurons, cortex-like neurons in the amygdala are pyramidal in shape and produce glutamate; like striatal medium-sized projection neurons, non-cortex-like amygdala neurons are medium-sized and spiny, and use the inhibitory γ-amino-butyric acid (GABA) as a neurotransmitter (Gerfen & Wilson, 1996). Unlike adjacent striatal areas, the CeN has extensive intrinsic connections (De Olmos, Beltramino, & Alheid, 2004). Figure 2 illustrates the relative placement of amygdala nuclei in rats (Sah et al., 2003), which served as subjects for this thesis.

The CeN and BLA are dissociated based on their inputs and outputs, which determine the significance of these regions for learning. Amygdala afferents and efferents are numerous and varied between the nuclei, with extensive connectivity

Figure 2. Photomicrograph of the rat amygdala illustrating the spatial relationship between the basolateral (lateral, LA; basal, B) and central nuclei (central medial, CeM; central lateral, CeL; external capsule, ec); the accessory basal nucleus is immediately ventral to the basal nucleus (Sah et al., 2003). The rectangle in the top section roughly outlines the regions magnified in the lower sections.






e.c.
LA
CeL
CeM
B

between them (McDonald, 1992). In general, areas with cortex-like neurons such as the BLA (basal, accessory basal, and basolateral nuclei) are heavily interconnected and project to non-cortex-like nuclei such as the CeN. The BLA projects to the central nucleus and the superficial cortical nuclei. The CeN, on the other hand, projects only very weakly back to the BLA (McDonald, 1992).

Amygdala afferents and efferents – basolateral and central nucleus

BLA Afferents

The BLA receives extensive afferents from thalamic and cortical regions that process sensory stimulation from several of modalities (McDonald, 1982). Reciprocal connections exist between the BLA and structures sensitive to multimodal stimulation, including the hippocampus, prefrontal cortex, perirhinal, and entorhinal cortex (McDonald, 2003). The association cortex, involved in high-level sensory processing, is a source of many amygdaloid afferents (Pitkänen, 2000). The lateral amygdala also receives projections from thalamic nuclei, themselves getting input from structures that respond to sensory input (LeDoux, Farb, & Ruggiero, 1990). The massive inputs from structures involved in sensory processing supports the idea that the basolateral amygdala is involved in behavioral control by conditioned stimuli (Everitt et al., 2003). The BLA also strongly reciprocates dense input from the gustatory cortex (Ottersen, 1982).

Most BLA afferents are glutamatergic, or cholinergic if originating in the nucleus basalis part of the cholinergic basal forebrain (Power, 2004). Dopaminergic input from the substantia nigra pars compacta and ventral tegmental area densely innervates neurons bordering the basal and lateral nuclei, and moderately innervates the parvicellular ("small

cells") and magnocellular ("large cells") neurons of the basal amygdala (Fallon & Ciofi, 1992). Noradrenergic input from the locus ceruleus, pons, and medulla in the brain stem densely innervates the basal nucleus, and moderately innervates other amygdala nuclei. Dense serotonergic input from the medial and dorsal raphé innervates most of the amygdala, particularly the magnocellular and parvicellular basal amygdala and lateral nucleus.

CeN Afferents

The CeN receives information via its lateral portion about sensory input from the cortex (medial prefrontal: Ottersen, 1982; McDonald, Mascagni, & Guo, 1996), and thalamus (LeDoux, Farb, & Ruggiero, 1990; Price, 2003). Many inputs to the CeN arise from within the amygdala itself, especially from the BLA (Phillips, Ahn, & Howland, 2003), but many also originate from within the CeN (de Olmos et al., 2004). In addition, the CeN receives information regarding taste stimuli directly from the first primary taste relay in the medulla, the nucleus of the solitary tract (NTS; Zardetto-Smith & Gray, 1990), which is sensitive to taste inputs from cranial nerves VII, IX, and X, the subdiaphragmatic vagus nerve in the gastrointestinal tract and the area postrema, which are primary sensory organs for taste. The CeN also receives taste information from the lateral parabrachial nucleus, an output nucleus of the NTS (Sakai & Yamamoto, 1999). Indirect taste information arrives in the CeN from the gustatory cortex and parabrachial nucleus, which also provides nociceptive input (Norgren, 1976; Bernard et al., 1990).

The CeN is the primary amygdala nucleus receiving sensory input from the brain stem and midbrain (Ottersen, 1980). The CeN receives dopamine input from the

midbrain ventral tegmental area and substantia nigra pars compacta (Fallon & Moore, 1978). Dopaminergic input to the lateral CeN is moderate, but denser in the medial CeN, which controls the output of the CeN and also receives dense epinephrine input from the medulla (Fallon & Ciofi, 1992). The brain stem pons, medulla, and locus ceruleus provide noradrenergic input densely to the medial CeN, but all areas of the CeN receive moderate norepinephrine projections. The medial and dorsal raphé provide dense serotonergic input to the medial central nucleus and weak input to the lateral nucleus. The input sources of the CeN are consistent with its ability to control Pavlovian conditioned responses to CSs independently of the BLA (Balleine & Killcross, 2006).

BLA Efferents

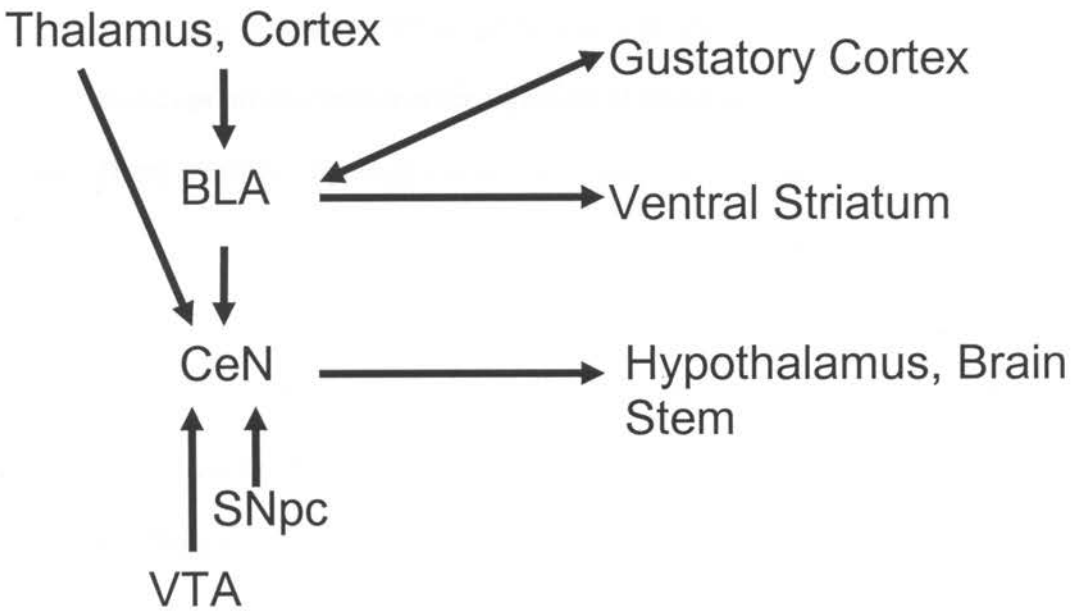
The BLA sends topographical glutamate projections to the striatum (Kelley, Domesick, & Nauta, 1982; Kita & Kitai, 1990) and the cortex, including anterior cingulate, primary motor, and gustatory cortex (Sripanidkulchai, Sripanidkulchai, & Wyss, 1984). The anterior BLA innervates the nucleus accumbens (NAc) shell, whereas the posterior BLA innervates the medial NAc core (Swanson, 2003). The glutamate projection from the BLA to the NAc is dense, and the terminals are proximal to terminals from midbrain dopamine neurons (Kelley et al., 1982; Johnson et al., 1994; Wright, Beijer, & Groenewegen, 1996). Stimulation of the BLA increases dopamine in the NAc via activation of glutamate receptors (Floresco et al., 1998; Howland, Taepavarapruk, & Phillips, 2002). Dopamine in the NAc is implicated in the control of behavior by conditioned reinforcers (Robbins & Everitt, 1992) and adaptation of behavior when reinforcement contingencies reverse (Cools et al., 2006; Goto & Grace, 2005). Midbrain

dopamine afferents to the NAc change their activity in accordance with linear operator models such as the Rescorla-Wager model (Schultz, 1997, 2005). For example, reinforcers initially increase midbrain dopamine neuron activity and subsequently dopamine release in the NAc. With training, these responses shift from the reinforcer to the CS predicting the reinforcer. With further training, neither the CS nor the reinforcer influences these responses until something about the conditioning situation changes, e.g., the reinforcer is omitted. Similarly, the Rescorla-Wagner model states that associative strength is constant at asymptotic learning until something about the conditioning situation changes, such as the reinforcer properties. The ability of the BLA to regulate NAc dopamine is therefore consistent with the hypothesis that the BLA is involved in CS-control of behavior.

CeN Efferents

The CeN, via its medial portion, projects widely to brain stem areas (nucleus of the solitary tract and the parabrachial nucleus, ventral tegmental area, locus coerulus, dorsal raphé), the lateral hypothalamus, periaqueductal gray, and the pontine reticular nucleus (Price & Amaral, 1981; Swanson & Petrovich, 1998). The outputs of the CeN are consistent with pharmacological and lesion work indicating that this structure controls CRs expressed through autonomic and defensive behavior systems, modulating reactions such as autonomic arousal, heart rate, blood pressure, hypoalgesia, stress hormone release, and startle (LeDoux, 2000). The CeN also projects to midbrain dopamine neurons (Fudge & Haber, 2000), and the bed nucleus of the stria terminalis and substantia innominata (Price & Amaral, 1981). CeN activity appears to regulate NAc dopamine,

Figure 3. Schematic illustration of basolateral amygdala (BLA) and central nucleus of the amygdala (CeN) neural connectivity. VTA, ventral tegmental area; SNpc, substantia nigra pars compacta.


Thalamus, Cortex
Gustatory Cortex
BLA
Ventral Striatum
CeN
Hypothalamus, Brain Stem
SNpc
VTA

since inactivation of this area increases dopamine levels (Phillips et al., 2003). Whereas the CeN is anatomically positioned to mediate behavioral responses to threats, it may also regulate appetitive behavior.

Experimental techniques

A common technique for inferring the function of brain nuclei in behavior is experimental ablation. Many early studies accomplished this electrolytically, by passing a current through the neurons comprising the region of interest, or by cutting with a knife. Modern techniques involve site-specific injection of neurotoxins that selectively destroy neurons. There are three important caveats to consider when interpreting amygdala lesion studies, especially those conducted pre-1980s. First, electrolytic or aspiration lesions destroy fibers passing through the amygdala from the gustatory cortex to the brain stem and hypothalamus (Dunn & Everitt, 1988) so that behavioral deficits cannot be attributed only to amygdala damage. Second, the various amygdala nuclei have different functions (McDonald, 1992) so lesioning the entire amygdala could disrupt multiple behavioral processes. Older data are valuable for illustrating the range of behaviors that may involve the amygdala, but the technique and extent of lesion must be considered when comparing across studies. Third, primates have a more complex frontal cortex than rats, and some researchers (e.g., Swanson & Petrovich, 1998) believe that the basolateral amygdala in rodents is an extension of their minimal cortex.

The role of the amygdala in punishment and reinforcement

Textbook treatments describe the function of the amygdala as supporting emotion, or the attribution of significance to external stimuli (LeDoux, 1996). If an animal survives a close encounter with a predator or some other threat, it may not be so lucky next time. In order to prevent dangerous situations from recurring, the systems supporting learning about potential threats act very rapidly. Pavlovian fear conditioning is the most widely used preparation for studying this type of learning, which often occurs in a single trial in the laboratory. Such experiments use aversive stimuli, such as foot shock, as the US. Once paired with foot shock, a CS will elicit an array of CRs: freezing, potentiated startle, increased blood flow to the muscles, stress hormone release, increased heart rate, blood pressure, and rate of respiration, analgesia, and ultrasonic vocalizations (LeDoux, 2000). These changes prepare the animal to escape or defend itself in the face of threats.

The CeN is involved in the acquisition of all of the above-mentioned CRs (Kim & Jung, 2006) and may be the locus of neural plasticity necessary for long-term expression of these CRs (Schafe, Doyère, & LeDoux, 2005). Lesions of the CeN, with its connections to the brain stem, hypothalamus, and bed nucleus of the stria terminalis, prevent conditioning of all foot-shock CRs (heart rate: Kapp et al., 1979; startle potentiation: Davis, 1992; for a review, see LeDoux, 1996, 2000).

Investigations of amygdala function have most often used aversive USs. The amygdala also has a role in conditioning with positive reinforcers (Everitt & Robbins, 1992). Rats will perform a response in order to receive stimulation of the amygdala, particularly regions of the central nucleus; stimulation of portions of the basolateral amygdala tends to be punishing (Wurtz & Olds, 1963), but this is by no means consistent

(Richardson, 1973). Early researchers noticed that amygdala damage decreased animals' emotional responses to aversive and appetitive stimuli: monkeys for which the entire temporal lobe was damaged were tame, changed their diets, orally examined objects more readily, were hypersexual and appeared to lack knowledge about the significance of objects (Klüver and Bucy, 1939). Whereas non-lesioned monkeys were fearful and violent toward the researchers, Weiskrantz's (1956) lesions that were restricted to the amygdala, rather than the entire medial temporal lobe, produced immediate and striking tameness. Lesioned monkeys rejected familiar foods until forcibly reintroduced, and exhibited impaired acquisition, but more rapid extinction, of conditioned avoidance learning. Weiskrantz concluded that subjects with amygdala lesions "are altered in their adaptation to emotional stimuli" (p. 389), and suggested, "the effect of amygdalectomy is to make it difficult for animals to identify reinforcing stimuli" (p. 390).

The role of the amygdala in Pavlovian conditioning

Researchers later suggested that the amygdala did not support sensitivity to reinforcement in general, but the association between stimuli and reinforcers (Gaffan & Harrison, 1987). In this regard, the CeN and BLA have distinct functions (Balleine & Killcross, 2006). Post-training amygdala lesions disrupt the expression of preference for a location paired with sucrose consumption, i.e., conditioned place preference (Everitt et al., 1991). Lesions also disrupt the acquisition and expression of amphetamine-induced conditioned place preference (Hiroi & White, 1991; White & McDonald, 1993). Burns et al. (1993) showed that excitotoxic lesions of the BLA before or after training impaired the acquisition of approach to a CS and acquisition of a new response when the CS was

the reinforcer. Berglind et al. (2006) used a test in which CS efficacy is measured by its ability to reinstate extinguished cocaine self-administration. Antagonizing dopamine D_1 or D_2 receptors in the BLA before Pavlovian conditioning between an initially neutral CS and cocaine infusions prevented that CS from later reinstating the extinguished response.

The claim that the amygdala associates CSs with USs is too simplistic. Certain classes of CRs can still be acquired after amygdala lesions. Lesions of the CeN prevent acquisition of CRs that are specific to the modality of the CS, rearing to a visual CS and startling to an auditory CS. Lesions of the CeN do not, however, affect food cup approach, known as US-generated behavior (Gallagher, Graham, & Holland, 1990). Since animals with CeN lesions approach the food cup when the CS is presented, some type of association between the CS and US occurs independently of the CeN. Only the modality-specific control of a CR by a CS requires the CeN. Furthermore, the ability of a CS to potentiate feeding is not affected by CeN lesions (Gallagher & Holland, 1992; Holland & Gallagher, 2003). The CeN is therefore only necessary for some CRs generated by CS-US associations.

Gallagher and Holland (1992) attempted to identify the associative process supported by activity of the CeN using a blocking protocol (Kamin, 1968, 1969). Blocking occurs when acquisition of a CR to one element of a compound CS is retarded because the other element was previously trained with the US, so that the US is no longer surprising. For example, Gallagher and Holland (1992) presented rats with a light followed by food. A tone was subsequently conditioned in compound with the light, and then responding to the tone was measured. Both intact and CeN-lesioned rats showed

impaired acquisition of responding to the tone, indicating blocking (Holland & Gallagher, 1993b).

Blocking is prevented, or "unblocked", if the compound conditioning co-occurs with a change in the reinforcer properties (Holland, 1988). Presenting the light and tone together with an increase or decrease in US magnitude (Holland, 1984), or US omission (Dickinson, Hall, & Mackintosh, 1976) prevents blocking. Gallagher and Holland (1992) showed that CeN lesions prevent this effect except when the US magnitude is increased, or when a surprising extra reinforcer is presented (Holland, 2006). That is, CeN lesions prevent unblocking of US-generated behaviors with down-, but not up-, shifts in reinforcer magnitude or value. As mentioned above, CeN lesions usually impair CS-generated behaviors, but spare US-generated behavior. Gallagher and Holland (1994) argue that the CeN positively modulates attention to CSs when the associated US changes. CeN lesions do not affect normal blocking (Holland & Gallagher, 1993b). Nor do CeN lesions affect latent inhibition, which is the retardation of CR acquisition after pre-exposure to the CS in the absence of the US (Holland & Gallagher, 1993a). Holland and Gallagher interpret these data to mean that the CeN is necessary only for increases, not decreases, in attention to CSs. The term attention could be substituted with CS salience, or the learning rate parameter, α, in the Rescorla-Wagner model.

The unblocking protocol and choice in transition may be different ways of assessing the same underlying phenomenon, changes in learned behavior when the US, reinforcer, or some other aspect of the contingencies changes. By changing reinforcer properties, the associative strength or the value of an alternative adjusts (ΔV in the Rescorla-Wagner model and Mazur's model), resulting in changes in conditioned

responding or preference. The CeN is necessary for the acquisition of some CRs, and for changes in the US to affect CR acquisition in the blocking protocol. It is unknown whether the CeN is involved in changes in CRs when the US is omitted or modified. Whether the CeN is involved in choice in transition has not been investigated.

A role for the CeN in CS attention is also suggested in protocols for which properties of the CS are manipulated. Holland and Gallagher (1993a) presented rats with light immediately followed by a tone and then food. The light and tone could be called a serial compound stimulus. For one group, the tone was omitted on half the trials. The other group experienced the serial compound stimulus preceding the US on all trials. When acquisition of conditioned responding to the light was measured, the group for which the tone was omitted on half the trials showed more rapid acquisition than the group experiencing the light-tone compound on every trial. Either the surprise of omitting the tone or enhanced associability of the CS increased the rate of learning. The Rescorla-Wagner model by could account for this if the associative strength of the light decreased when it was presented without the US, so that the difference between current and asymptotic associative strength is greater for the omission group, resulting in more rapid learning during test trials. Whatever the explanation for this effect, it is prevented by CeN lesions. The CeN clearly has a complex role in changes in Pavlovian CRs.

The role of the amygdala in reinforcer devaluation

The role of the BLA in Pavlovian conditioning is also complex. Unfortunately, the effects of BLA lesions on blocking and unblocking, or on the enhanced CR acquisition following omission of an expected component of a compound stimulus, are

unknown. The reinforcer devaluation protocol, however, has been used to assess the neural systems underlying changes in CRs or operant behavior when reinforcer value is manipulated. As an example of this protocol, Adams and Dickinson (1981) delivered sucrose or food pellets to rats. One reinforcer was delivered response-contingently and the other independent of responding. After the rats consumed one of the reinforcers in the experimental chamber when the lever was retracted, they were injected with saline or lithium chloride, inducing gastric malaise. The rats decreased their consumption of the reinforcer paired with lithium chloride, eventually rejecting the devalued reinforcer. When given the opportunity to press the lever during extinction, the rats suppressed their lever pressing only if the reinforcer contingent upon responding had been devalued. Analogous results occur in Pavlovian conditioning preparations (e.g., Holland & Rescorla, 1975), which involve no operant contingencies.

Hatfield and colleagues (1996) first reported that the approach behavior of rats with BLA, but not CeN, lesions failed to adapt after food-lithium chloride pairings, even though the lesioned rats refused to consume the devalued reinforcer. However, Pickens et al. (2003) showed that the devaluation effect was still observed when the lesions were made after initial training during which a light predicted food delivery. Only pre-training lesions of the BLA prevent the adaptation of CRs to changes in reinforcer value. Balleine et al. (2003) conducted the instrumental conditioning version of Hatfield et al.'s (1996) experiment, reporting that pre-training BLA lesions disrupted behavioral adaptation to reinforcer devaluation accomplished via sensory-specific satiety, which consists of feeding subjects copious amounts of one of the reinforcers before the test session. These

data suggest that processes occurring in the BLA during acquisition allow behavior to adapt to subsequent changes in stimulus value.

It is worth noting the commonalities between the four protocols: unblocking, CR acquisition after surprising omission of the CS, reinforcer devaluation, and choice in transition. Although this may not be an inclusive list, each of the above protocols involves manipulating the CS or reinforcer, and measuring changes in behavior. If the function of the CeN or BLA mapped onto the difference component ($\lambda - \Sigma V$) of the linear operator models, one would expect lesions to disrupt changes in behavior in each of the protocols. In addition, one would predict deficits in the acquisition of responding. Both CeN and BLA lesions disrupt acquisition under only specific conditions. In addition, CeN and BLA lesions have different effects in the four protocols, although not all of the experiments have been completed. The selective effects of CeN and BLA lesions imply that these structures have distinct and complex functions that may support the adaptation of behavior to contingency manipulations. These functions are not readily imaginable from the simple mathematical models proposed so far, although the models provide a useful starting point for discussing the processes involving learning that may be affected by neurobiological manipulations.

The most recent theories of BLA function emphasize incentive learning. In the incentive learning protocol, the animal consumes the reinforcer in a sated state, and so reinforcer value is decreased. For example, Wang et al. (2006) trained rats to press one lever for food pellets and to press another lever for sucrose. The rats were free fed on their maintenance diet, and then allowed to consume either pellets or sucrose, thereby devaluing one of the reinforcers. Control rats decreased their responding on the lever that

was associated with the devalued reinforcer during training. However, rats that had a protein synthesis inhibitor injected into their BLA prior to consuming the reinforcer did not. It is unlikely that the protein synthesis inhibitor disrupted behavior during the choice test or damaged the BLA because when the rats were re-exposed to the reinforcer in the sated state without the protein synthesis inhibitor, they exhibited normal changes in choice during a subsequent test. Balleine and Killcross (2006) propose that the BLA is necessary for the sensory features of stimuli, perhaps even reinforcers themselves, to reflect the current value of the reinforcer.

The hypothesis put forth by Balleine and Killcross (2006) resembles hypotheses put forth about the amygdala almost 50 years ago. As the physical features of a stimulus become increasingly discrepant from those present during training, behavioral control decreases according to a smooth gradient (Honig & Urcuioli, 1981). Schwartzbaum & Pribram (1960) hypothesized that amygdala lesions disrupt this generalization of stimulus control. Baxter & Murray (2002) suggested that the BLA is required for behavioral adjustment following changes in stimulus value. These ideas point to the hypothesis that the BLA supports behavioral adaptation when the sensory properties of stimulus-reinforcer relationships change. In other words, BLA activity may contribute to the shape of conditioned reinforcer generalization gradients when sensory properties or stimulus value changes.

How the BLA is involved in changes in choice when reinforcement contingences change is a natural extension of these investigations, but is so far unstudied. Because preference in concurrent chains schedules is determined by conditioned and primary reinforcement contingencies, they provide a useful model for these studies. The effects

of neurobiological treatments on changes in preference can be measured after manipulating features of the stimuli, the reinforcers, or their relationship in the same protocol.

This hypothesis could be tested using a variety of methods. If the Skinner box had not been invented, I might use a t-maze. Primary and conditioned reinforcer contingencies could be set up by presenting stimuli while the rat waits to enter a portion of the maze containing the sucrose. However, it is difficult to approximate interval schedules of reinforcement using a t-maze. After a rat turned in one direction, I would need to return it to the start box for the next choice, and so on. After the interval elapsed, the conditioned reinforcer could be presented. It is unclear that a rat would continue making choices under these circumstances. Rats perform many responses when reinforced with interval schedules, so one's confidence in a measured choice proportion is high. In a t-maze, it is not possible to allow the rats to make as many choices. Each t-maze choice takes longer than a single lever press. In addition, relocating the rat after each response could introduce bias or stress as confounds. If the Skinner box had not been invented, it is unlikely that researchers would have found much interest in interval schedules of conditioned reinforcement, and we would know little about how behavior is controlled by these important reinforcement contingencies. Since variability is a fundamental feature of the natural world, interval schedules of reinforcement are likely to be an important problem for animals. For example, multiple factors may affect how long it takes a food source to replenish so that animals experience variability in time to reinforcer is availability. In this case, an animal may check various sources of food multiple times before reinforcement occurs.

Rationale

The first part of this thesis tests a behavioral protocol for evaluating generalization of the control of preference by components of terminal link stimulus and reinforcer contingencies in concurrent chains schedules in rats. The first set of experiments evaluates changes in preference after systematic manipulation of the taste of the primary reinforcer, the sensory properties of the terminal link stimulus, and the delay to onset of the terminal link stimulus. The rats were insensitive to the subtle manipulations in the first experiment, so more extreme manipulations were tested in the next experiment. The second part of this thesis evaluates the effect of pre- and post-training basolateral amygdala lesions on changes in choice during one of the extreme manipulations, reinforcer magnitude reversal.

Studies of steady-state choice behavior have most often used pigeons as subjects for a very good reason: pigeons live for up to 12 years and instrumental experiments often include many conditions each lasting more than 20 daily sessions. Pigeons provide a long-lived re-usable research subject. Studies of choice in transition are generally briefer so that subjects other than pigeons may be used. To make the experiments in this thesis comparable to previous studies of the neurobiology of learning and memory, rats were used as subjects. The neural systems influencing choice are beginning to be evaluated in pigeons (e.g., Kalenscher et al., 2005), but there is evidence that pigeons and rats respond differently to variables influencing choice behavior such as initial link duration and reinforcer delay (Green et al., 2004; Mazur, 2000, 2005). Such species differences introduce the possibility that studies with pigeons and rats will not illuminate

behavioral and neural processes occurring in humans. One cannot know a priori to what extent principles uncovered via rodent experimentation will inform us about humans. As mammals, however, rodents are phylogenetically more similar to humans than are pigeons. Although most concurrent chains studies using rats as subjects do not suggest species differences in sensitivity to schedule parameters (e.g., Ito & Asaki 1982; Ito, 1985; Preston, 1994; Ito & Oyama, 1996; Williams, 1997; Ito, Takatsuru, & Saeki, 2000), relatively little attention has been directed toward this issue.

This thesis makes the assumption that the fundamental learning mechanisms and the neural structures supporting them are similar between pigeons, rodents and other mammals. This assumption is justified since the topic of investigation is the amygdala, a highly conserved system of nuclei that have been helping animals prepare for potential threats for millions of years (LeDoux, 1996). In rats and primates the structure and connectivity of the amygdala are highly similar, with a couple of exceptions. In primates, but not rodents, the amygdala projects back to primary sensory cortices (Price, 2003). The entorhinal cortex, which receives input from multimodal association cortices, directly and heavily innervates each nucleus of the rodent amygdala, but these afferents are weak in primates, and possibly passed through the perirhinal cortex (McDonald, 1998). What this means for behavioral differences between rats and primates is currently unclear.

CONCURRENT CHAINS CHOICE IN TRANSITION: REINFORCER AND TERMINAL LINK STIMULUS VARIABLES

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Running head: Concurrent chains transition in rats

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ABSTRACT

Most concurrent chains studies use pigeons, but the neural systems supporting choice are primarily studied with rodent mammalian models. Few studies have measured rats' preference in concurrent chains schedules. None have assessed choice in transition. Rats were trained using concurrent chains schedules with dependent variable-interval 16-s initial links and fixed-time 16-s terminal links. A 2 s tone occurred in the first and last 2 s of each terminal link; its frequency indicated the reinforcer magnitude delivered to a consistent location during training. After initial link preference stabilized, in Experiment 1, rats did not change their preference during parametric manipulations on the large reinforcer side: 1) the terminal link stimulus frequency was shifted toward the frequency preceding the small reinforcer, 2) quinine (10, 20, 40, 80, 160 μM) was added to the large reinforcer, and 3) the time between terminal link entry and stimulus onset was increased (2, 4, 6, 8, 10 s). In Experiment 2, most rats decreased their preference for the large reinforcer side when reinforcer magnitude, terminal link stimulus frequencies, or both, were reversed during single sessions. Preference change was uncorrelated across different types of contingency change, suggesting that different behavioral and biological processes determine sensitivity.

Animals' choices between two alternatives tend to match the ratio of obtained rates of reinforcement (Herrnstein, 1961; Baum, 1974b). Choice behavior is also sensitive to features other than the relative schedules or reinforcement, such as reinforcer amount (Catania, 1963; Neuringer, 1967; Ito, Takatsuru, & Saeki, 2000), immediacy (Chung & Herrnstein, 1967; Williams & Fantino, 1978), quality (Hursh, 1978) and rate of conditioned reinforcers (Shahan, Podlesnik, & Jimenez-Gomez, 2006). The factors influencing choice at steady state are well known (Davison & McCarthy, 1988). Less is known about how choice changes when reinforcement schedules change.

In concurrent schedules of reinforcement, pigeons' choices are influenced by current and past reinforcer ratios. For example, when concurrent variable-interval (VI) schedule ratios shifted every six sessions, pigeons' choices were sensitive to reinforcer ratios three, but not six, sessions in the past (Davison & Hunter, 1979). Research on choice in transition using concurrent schedules suggests that the sensitivity of choice to current reinforcer ratios is positively influenced by the frequency (Mazur, 1997b; Davison & Baum, 2003) and range (Landon & Davison, 2001) of reinforcement contingency changes, the overall rate of reinforcement (Mazur, 1997b), and signaling the schedule change (Mark & Gallistel, 1994; Krägeloh & Davison, 2003).

In concurrent chains schedules (Autor, 1960), subjects choose between two concurrent schedules (initial links) leading to mutually exclusive schedules of primary reinforcement (terminal links). Preference is measured by allocation of responding between the two initial links. Only a few studies have addressed choice in transition in concurrent chains schedules. For example, Grace (2002b, Experiment 2) assigned left and right keys as initial links. The center key color (red or green) signaled the onset of

the terminal link, fixed-interval (FI) 8- or 16-s. After preference stabilized, Grace reversed the FI schedules, maintaining the relationship between initial link location and center key color: the color previously indicating FI 8-s now indicated FI 16-s, and vice versa. Pigeons' preference for the shorter FI reached 75% of the new asymptote after approximately 6.5 sessions. When both the center key colors and the delays were reversed, so that the color signaled the same FI value as during baseline, asymptotic preference occurred in 4 sessions. Choice proportions shifted by about 10% per session in both conditions. The relationship between the terminal link stimuli and reinforcers therefore influenced changes in choice when contingencies were manipulated.

As another example of concurrent chains choice in transition, Mazur (2002) trained pigeons with VI 45-s initial links and FT 1- or 20-s terminal links. Every 5-9 sessions, the percentage of reinforcers delivered to the left side shifted (10, 30, 70, or 90%). Neither the terminal link duration nor the magnitude of change in reinforcement percentages influenced the time to asymptotic preference, which was approximately one 40-minute session. Grace, Bragason, and McLean (2003, Experiment One) trained pigeons using a concurrent chains schedule with VI 10-s initial links and FI terminal links. One terminal link was FI 8-s and the other terminal link was FI 4- or 16-s, varying pseudo-randomly across sessions (Hunter & Davison, 1985) for 93 sessions. The pigeons became more sensitive to reinforcement contingencies in the current session as training proceeded; preference was mostly influenced by contingencies in the current session by the third set of 31 sessions.

The following experiments aimed to assess steady state and transitional performance in concurrent chains schedules in a mammalian model, rats, as a precursor

to neurobiological studies. The neural systems influencing choice are beginning to be evaluated in pigeons (e.g., Kalenscher et al., 2005), but pigeons and rats may respond differently to variables that affect preference including initial link duration and reinforcer delay (Mazur, 2000, 2005). In Experiment One, changes in preference were measured as features of both the primary reinforcer and the terminal link stimulus (conditioned reinforcer) were manipulated parametrically. These experiments preceded neurobehavioral studies evaluating the effects of lesioning the basolateral amygdala with a similar protocol. Concurrent chains schedules were used because both primary and conditioned reinforcers contribute to initial link preference, and the basolateral amygdala is important for conditioned reinforcers to affect behavior (Everitt et al., 2003).

EXPERIMENT ONE

METHOD

Subjects

Six male Long-Evans rats (Charles River, Raleigh, NC) were obtained at 50-55 days of age (225-250 g). The animals habituated to the temperature (21 ± 1°C) and light-controlled vivarium (12:12-hr light-dark cycle with lights on at 6:00 am) for 6-7 days. The rats were then food-deprived to 90% of their free-feeding weights and weighed daily for 6-7 days, after which training commenced. For the remainder of the experiment, rats were maintained at 90% of their free-feeding body weights by supplemental feeding of lab chow following experimental sessions. Daily sessions occurred during the light cycle, 5-7 days per week. Water was freely available. Care followed the guidelines

provided by the Oregon Health & Science University Department of Comparative Medicine. The Institutional Animal Care and Use Committee approved all procedures.

Apparatus

Behavior was measured in 4 identical Med-Associates (St. Albans, VT) operant chambers housed in sound-attenuating ventilated boxes with a 60 dB background noise level. One panel contained three equally spaced nose poke response units: left and right head-entry devices contained a liquid reinforcer cup, but the center did not. Horizontal infrared beams broke when the animal poked its nose 0.64 cm into any response unit. A stainless steel pipe protruded from the rear of each liquid reinforcer cup to which was fit a length of plastic tubing. The tubing was attached to 60-ml syringes. The syringes were filled with 25% (w/v) sucrose dissolved in deionized water and secured in Med-Associates pumps (60.2 μl/s).

A single response lever was set above both the left and the right reinforcer cup. A stimulus light was set 5.7 cm above each lever, and a house light was set 14 cm above the center head-entry device. The panel opposite the levers contained a speaker connected to a multiple tone generator. Lever presses and reinforcer deliveries were recorded with an IBM-compatible computer using Med-PC software.

Procedure

The rats were trained in 6 phases, summarized in Table 1, which also lists the performance criteria for each phase and the number of sessions required for each rat to

Table 1. Reinforcement contingencies and sessions to criterion[1] for each subject during the six phases of training.

Phase	Contingency Changes[2]	Rat						
		1	2	3	4	5	6	Mean ± SEM
1[3]	Independent concurrent chains: fixed-ratio 1-fixed-time 2-s	19	11	25	15	17	21	18.00 ± 1.98
2	Interdependent concurrent chains: variable-interval 8-s-fixed-time 2-s	5	5	3	4	3	3	3.83 ± .40
3	2.5-s change over delay	5	2	2	3	4	7	3.83 ± .79
4	10-s time out	2	2	3	4	3	2	2.68 ± .33
5[4]	Terminal links increase by 2 s every 8 trials to fixed-time 16-s	1	1	1	1	1	1	1.00 ± 0
6	Variable interval 16-s fixed-time 16-s	7	17	12	6	9	19	11.68 ± 2.19

[1] criteria for Phases 1-4 were achieved for two consecutive sessions; Phase 1, 64 lever presses in ≤ 30 min; Phases 2-4, 64 trials in ≤ 45 min; Phase 5, one session; Phase 6, 5 consecutive sessions with stable preference; [2] changes in each phase were retained in subsequent phases; [3] reinforcer magnitude was 150 µl for both alternatives until Phase 5; [4] a 1.0 or 15.0 kHz tone occurred in the first and last 2 s of intervals > 4 s; the frequency indicated the reinforcer magnitude to be delivered (50 or 150 µl).

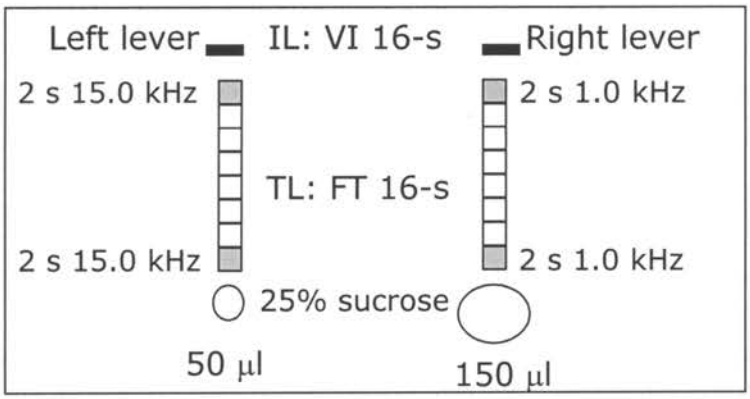
satisfy the criterion. The changes introduced during each phase of training were retained in subsequent phases. Phase 1 was lever-press training. A reinforcer was delivered 2 s after each lever press (fixed-time 2 s, FT 2 s). In Phase 2, concurrent chains schedules were introduced. The initial links were dependent variable- interval (VI)-8 s schedules (Stubbs & Pliskoff, 1969), and the terminal links were FT 2-s delays to sucrose delivery. Both stimulus lights shut off, but the house light stayed on, at the onset of each terminal link. Thirty-two 150-µl reinforcers were delivered to each reinforcer cup per session; four to each cup every 8 trials in a random order. The VI initial links consisted of 12 randomly selected intervals from an exponential progression (Fleshler & Hoffman, 1962). In Phase 3, a change over delay (COD) was introduced to maximize preference (e.g. Leung & Winton, 1985) so that decreases in preference during the manipulations would be readily noticeable. After the initial link VI schedule elapsed, the terminal link occurred after the next press to the lever assigned for reinforcement if 1) it was the first press since the onset of the initial link or 2) 2.5 s elapsed since the rat switched from the other lever. In Phase 4, a 10-s time out occurred between reinforcer delivery and the start of the next initial link. During the time out, all the lights shut off. Responses were recorded, but not reinforced. At the end of the time out, the house and stimulus lights were illuminated to signal the beginning of the next trial. Phase 5 was a single session during which one of the reinforcer magnitudes was decreased to 50 µl and both terminal links incremented to FT 16-s, 2 s every 8 trials from 2 to 16 s. Tones were presented upon terminal link entry and in the 2 s preceding reinforcer delivery. The tones therefore overlapped with 2-s delays and occurred at the end of 4-s delays. Each tone frequency (kHz) consistently preceded delivery of a specific reinforcer magnitude (µl): Rats 1,2 and

5, 15 kHz before 50 μl and 1 kHz before 150 μl; Rats 3, 4 and 6, 1 kHz before 50 μl and 15 kHz before 150 μl.

For the final schedule (Figure 4), the initial links were interdependent VI 16-s, and included a 2.5-s COD. The terminal links were FT 16-s terminal links, segmented by a tone in the first and last 2 s. The frequency of the tones signaled the magnitude of sucrose to be delivered. Every 8 trials, 4 50-μl and 4 150-μl reinforcers were delivered in a random order, but to consistent locations for each rat. A 10-s time out occurred after each reinforcer. Sessions lasted 64 trials or 90 minutes, whichever occurred first. Preference was measured as the mean percent of initial link presses to the lever leading to 150-μl sucrose. The rats were trained on the final concurrent chains schedule until preference was stable. Stability was attained when the percent of initial link lever presses to the large reinforcer lever in the most recent session deviated by <10% from preference each of the past five sessions. Neither the first nor the last value in a series could differ from the next greatest or smallest value by more than 1%. For example, the series 67, 61, 65, 61, 67 is stable because each value differs from the most recent by <6.7%. If the first value in the series had been 69, however, the series would not be considered stable because 69-67 > 1; such a series implies a trend toward decreasing preference.

Once stable preference was obtained, two consecutive test sessions occurred, after which baseline was reacquired for a single session prior to the next test session. The criterion for reacquisition of baseline was as follows: the difference between choice percentages for the baseline session immediately preceding and following the last set of test sessions had to be < 10%. This criterion was chosen as a compromise between establishing baseline preference before each manipulation and expediency. A one-year

Figure 4. The final reinforcement schedule was concurrent chains with interdependent variable-interval (VI) 16-s initial links (IL) with a 2.5-s change over delay and fixed-time (FT) 16-s terminal links (TL), followed by a 10-s time out. In the first and last 2 s of the terminal links, 2 s tones were presented (gray squares). Tone frequency predicted the reinforcer magnitude (50 or 150 μl), delivered at a consistent location. The frequency-magnitude pairings varied across subjects. Each reinforcer magnitude was delivered 32 times per session: every 8 trials, 4 reinforcers of each magnitude were delivered in a random order.


Left lever
IL: VI 16-s
Right lever
2 s 15.0 kHz
2 s 1.0 kHz
TL: FT 16-s
2 s 15.0 kHz
2 s 1.0 kHz
25% sucrose
50 µl
150 µl

experiment comprises at least one-quarter of a rat's life, spanning a range of developmental stages that might confound the results.

Table 2 lists the order of conditions for each rat, which followed a randomized block design, and the number of preceding baseline sessions. The frequencies of the tone preceding the 150-µl reinforcer resembled those used by Armony et al. (1997) to demonstrate generalization of lever press suppression from a 19.55 kHz stimulus conditioned with foot shock. Quinine was added to the 150-µl sucrose reinforcer in concentrations discriminable in bitterness to laboratory technicians not involved with the experiment.

Results and Discussion

Appendix 1 lists individual rats' preference for the large reinforcer initial link during each baseline and test session after stability was first attained. The number of sessions to stable preference was slightly fewer than typically reported for concurrent chains research using pigeons (e.g., Grace, 2002b: ≥20 sessions). The rats preferred the initial link lever on the large reinforcer side even within the first 64 trials of the final reinforcement schedule (mean ± SEM: 63.76 ± 2.31). The mean (±SEM) percent of initial link lever presses to the large reinforcer side prior to the first manipulation was 66.89 ± 1.96. This percent choice under-matches the reinforcer ratio of 3:1 (150-50 µl); for perfect matching, percent choice would be 75% (Baum, 1979), with sensitivity values of approximately 0.89. The sensitivity value indicate how closely the response ratio matches the reinforcer ratio, where 1 reflects perfect matching. This slight under-matching is also seen in concurrent schedules, for which sensitivity to reinforcer

Table 2. Order of manipulations for the large reinforcer terminal link interspersed with baseline (BL) sessions in Experiment One.

Terminal Link Stimulus Frequency (kHz)		Quinine (μM) Concentration in Large Reinforcer		Delay (s) to Terminal Link Stimulus Onset	
Rat 1	Rat 2	Rat 3	Rat 6	Rat 4	Rat 5
BL (6)	BL (17)	BL (12)	BL (19)	BL (6)	BL (9)
2.5	2.5	40	10	6	6
2.5	2.5	40	10	6	6
BL (5)	BL (19)	BL (1)	BL (7)	BL (9)	BL (15)
5	12	10	80	2	6
5	12	10	80	2	6
5	BL (1)	BL (5)	BL (7)	BL (1)	BL (1)
15	9	20	40	4	10
15	9	20	40	4	10
BL (3)	BL (1)	BL (2)	BL (1)	BL (10)	BL (2)
12	5	160	20	8	8
12	5	160	20	8	8
BL (1)	BL (2)	BL (3)		BL (3)	BL (1)
9	15	80		10	2
9	15	80		10	2
BL (4)		BL (3)		BL (1)	BL (1)
15		160		4	10
15		160		4	10

Table 2: continued

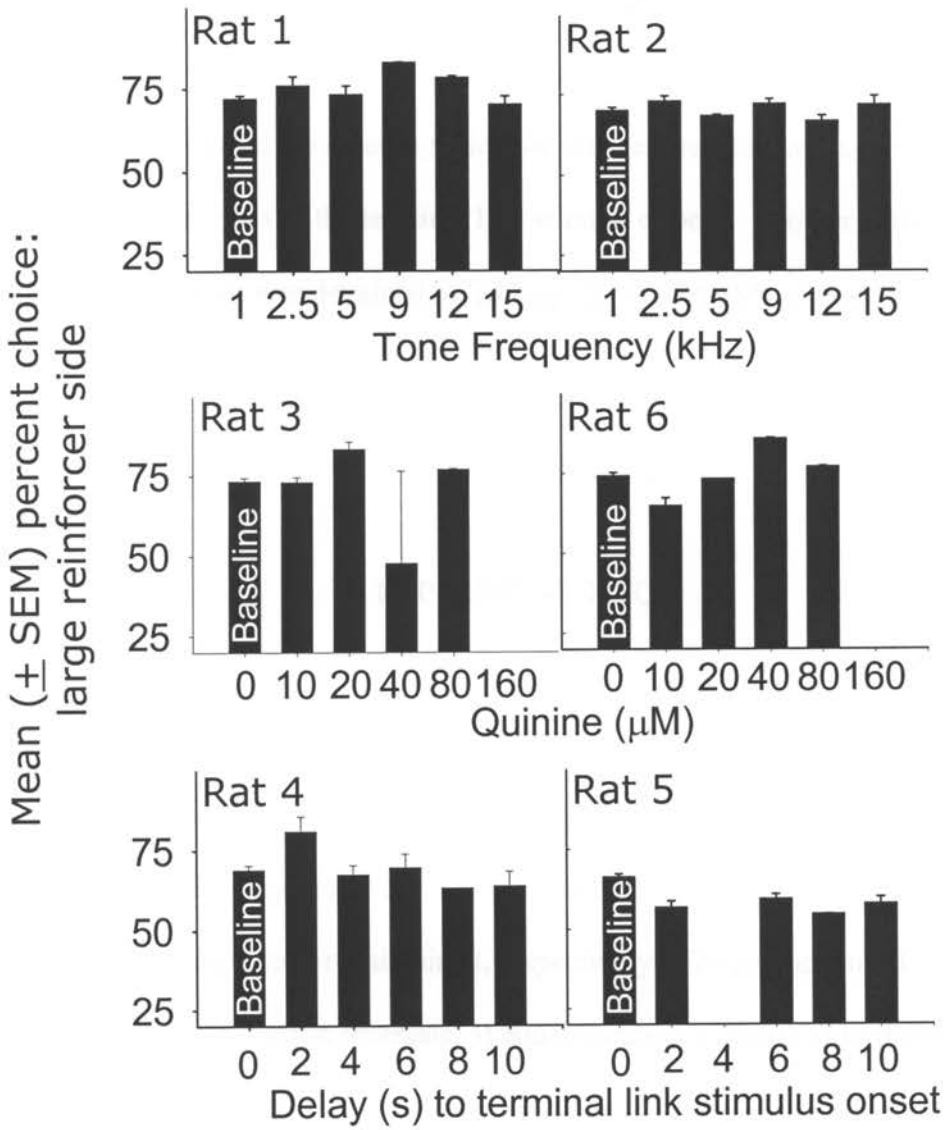
BL (1)		BL (3)
5		2
5		2
BL (3)		
12		
12		
BL (1)		
2.5		
2.5		

The number in parentheses refers to the number of baseline sessions preceding the next manipulation. Rats 1 and 2 were trained with a 1 kHz tone preceding delivery of 150 µl sucrose and a 15 kHz tone preceding delivery of 50 µl sucrose, then the frequency of the tone preceding the large reinforcer was manipulated; Rats 3 and 6 were trained with 50 and 150 µl sucrose without quinine, then concentrations of quinine were added to the large reinforcer; Rats 4 and 5, terminal link stimulus onset was delayed from terminal link entry; blank condition labels indicate baseline.

magnitude ratios after acquisition of stable preference ranges from 0.70 to 0.87 (Landon, Davison and Elliffe, 2003).

Figure 4 illustrates the main result of Experiment One: none of the parametric manipulations systematically affected initial link preference. For the frequency manipulations at least, this cannot be attributed to a failure of discrimination since a previous study demonstrated generalization of conditioned suppression (Armony et al., 1997) using the same stimuli and species (rats, Sprague-Dawley). A protocol in which the terminal links occurred at random locations may have resulted in greater behavioral control by the tone frequencies (e.g., Ploog, 2001). In the current protocol, the rats' choices could have been directed by the lever and reinforcer locations. The ineffectiveness of delaying the terminal link stimulus preceding the large reinforcer onset was not due to rats' failure to discriminate the onset of the terminal link, since both stimulus lights shut off to signal the event. The failure of quinine to decrease preference for the large reinforcer was not due to lack of exposure; no sucrose remained in the troughs at the end of any session, suggesting that the rats always consumed the reinforcer. Preference in

Figure 5. Experiment One. Mean (± SEM) initial link preference for the large reinforcer side during all baseline sessions and parametric manipulations to the large reinforcer side occurring as in Table 2. Initial links were interdependent VI 16-s with a 2.5-s change over delay. Terminal links were FT 16-s delays with 2-s tones occurring in the first and last 2 s of the delay. During baseline, 1.0 kHz preceded 150 μl and 15 kHz preceded 50 μl sucrose for Rats 1 and 2. The experiment was terminated before data was collected for each condition.


Rat 1
Rat 2
Rat 3
Rat 6
Rat 4
Rat 5
Baseline
75
50
25
1 2.5 5 9 12 15
Tone Frequency (kHz)
0 10 20 40 80 160
Quinine (μM)
0 2 4 6 8 10
Delay (s) to terminal link stimulus onset
Mean (± SEM) percent choice: large reinforcer side

concurrent chains is controlled by many factors (Grace, 1994), however, so relatively subtle manipulations of only one schedule feature may be insufficient to alter preference.

To demonstrate that rats are sensitive to changes in terminal link characteristics, the same rats from Experiment One were tested in Experiment Two, but with more extreme manipulations of the same characteristics altered in Experiment One. During test sessions, we reversed the sides to which the different reinforcer magnitudes were delivered, the frequencies of the terminal link stimuli, or both. In other manipulations, the large reinforcer link was devalued by adding 320 or 480 μM quinine or a long delay to terminal link stimulus onset.

EXPERIMENT TWO

Experiment Two was modeled after Grace (2002b, Experiment Two), who reversed the location of the initial links leading to long and short FI terminal links. We included switched and consistent reversals, in which the terminal link stimulus-schedule relationships were disrupted or maintained, respectively. The protocol used 1) rats rather than pigeons, 2) single-session reversals, 3) equal duration terminal links differing in reinforcer magnitude (50 or 150 μl sucrose), and 4) auditory, rather than visual, terminal link stimuli. Rats 1 and 2 were trained with concurrent chains VI 16-s FT 32-s terminal links, and the effect of delaying onset of the first 150-μl terminal link stimulus by 12- and 24-s was assessed. The quality of the large reinforcer was first manipulated by adding

high concentrations of quinine, then five rats experienced four consecutive sessions during which the 150-µl sucrose concentration was 25%, 5%, 30%, or 0%.

METHODS

Subjects

The subjects used in Experiment One were also used in Experiment Two.

Procedure

After the last manipulation from Experiment One, the terminal link was increased to 32 s for Rats 1 and 2, and this became their new baseline schedule. All rats were trained with the baseline reinforcement schedule until their percent of presses to the large reinforcer lever in the initial link differed by <10% of the most recent session for five consecutive sessions. Table 3 lists the conditions for each session in their order of occurrence, and the number of baseline sessions preceding each manipulation. The manipulations occurred in a pseudo-random order. In order to streamline the procedure, the conditions were distributed across rats, so every rat was exposed to a subset of conditions. After completing the conditions in Table 3, the rats were used for a pharmacological experiment during which they received 6-8 injections of low doses of a dopamine receptor antagonists (data not shown) under the same behavioral protocol. Stable preference was then reacquired, and changes in preference were assessed when the concentration of sucrose in the 150-µl reinforcer was 25%, 5%, 30%, or 0%, in that order, over four consecutive sessions (Rats 1-4, and 6). Rats 1-4 and 6 experienced, respectively, 92, 91, 113, 100, and 131 sessions between cessation of Experiment One,

the pharmacological manipulations, and reacquisition of stable preference before the first session for which sucrose concentration was manipulated.

Results and Discussion

In contrast to Experiment One, baseline preference (mean ± SEM: 75.80 ± 22.61) approximated perfect matching (Figure 5, striped bars). The additional training after Experiment One may have increased rats' sensitivity to the reinforcer magnitude ratio. Also in contrast to Experiment One, the manipulations in Experiment Two decreased the percent of initial link lever presses to 150-μl lever in 24 of 25 manipulations shown in Figure 5. The decreases in preference were greater in Experiment Two not because the rats had extensive training but because the manipulations were more extreme. Subsequent experiments in our lab (data not shown) indicate similar, if not greater, decreases in preference after reinforcer magnitude reversal with 20 or fewer baseline sessions.

Repeated measures ANOVA with session type (baseline, manipulation) as a within-subjects factor revealed a significant effect of magnitude reversal, $F(1, 4) = 32.35$, $p = 0.005$, frequency reversal, $F(1, 5) = 49.44$, $p = 0.001$, and magnitude and frequency reversal, $F(1, 3) = 13.42$, $p = 0.035$. The decrease in preference for the large reinforcer side when quinine was added did not reach significance at 320 μM, $F(1, 2) = 2.37$, or 480 μM, $F(1, 2) = 1.90$. Only two rats experienced 12- and 24-s terminal link stimulus delays, so these data were not analyzed, although Figures 5 and 6 suggest a similar decrease in preference with both delays. Figure 5 shows that, similar to Grace (2002b), preference decreased more when the terminal link stimulus-reinforcer relationship

Table 3. Order of conditions for the large reinforcer side in Experiment Two.

Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6
BL (9)	BL (6)	BL (6)	BL (10)	BL (19)	BL (15)
24 s	24 s	Freq	480	320	Freq
BL (4)	BL (4)	BL (5)	BL (9)	BL (1)	BL (2)
Mag	Mag	Mag	320	480	M&F
BL (4)	BL (5)	BL (8)	BL (1)	BL (4)	BL (4)
12 s	12 s	M&F	Freq	Freq	Mag
BL (4)	BL (1)		BL (1)		
Freq	320		Mag		
BL (5)	BL (1)		BL (5)		
M&F	480		M&F		
	BL (8)				
	Freq				

BL, the first baseline constituted five consecutive sessions for which preference in the most recent sessions differed from the previous sessions by < 10%; subsequent baseline conditions continued until preference in the current session differed from the last session by < 10%; parentheses refer the number of baseline sessions preceding the following manipulation; 12 and 24 s, terminal link stimulus onset delayed by 12 or 24 s; Mag, reinforcer magnitude locations were reversed; Freq, frequencies of the terminal link stimuli preceding the large and small reinforcer were reversed; M&F, terminal link stimulus frequencies and reinforcer magnitudes were reversed; 320 and 480, refers to the μM quinine added to the large reinforcer.

Figure 6. Experiment Two. Percent choice of the large reinforcer side during baseline (*stripes*) and manipulation (*solid*) sessions for individual subjects. The lower left panel shows mean ± SEM change in preference. Panels showing individual subject data have the same x-axis labels (order: Mag, Freq, Mag & Freq, 12 s, 24 s, 320 μM, 480 μM). The manipulations occurred as in Table 3, which shows that not every subject experienced each manipulation. The initial links were interdependent VI 16-s with 2.5-s change over delay and the terminal links were FT 16-s. Tones (2 s) occurred in the first and last 2 s of the delay. Mag, 150- and 50-μl reinforcers reversed; Freq, 1.0 and 15 kHz tones reversed; Mag & Freq, reinforcer magnitudes and tones reversed; 12 and 24 s, first terminal link stimulus onset delayed by 12 or 24 s; 320 and 480, refers to the μM quinine added to the 150-μl reinforcer. * $p < 0.01$.

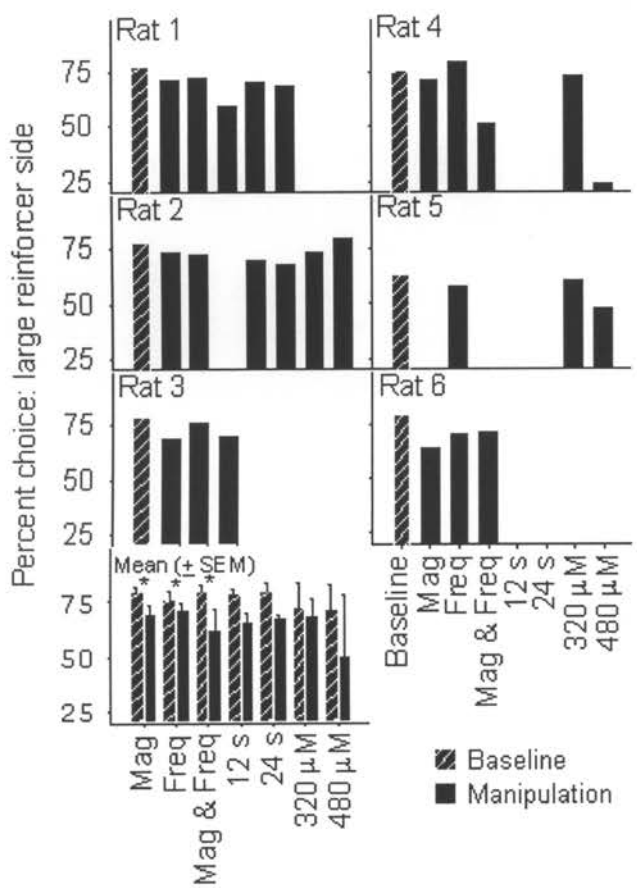
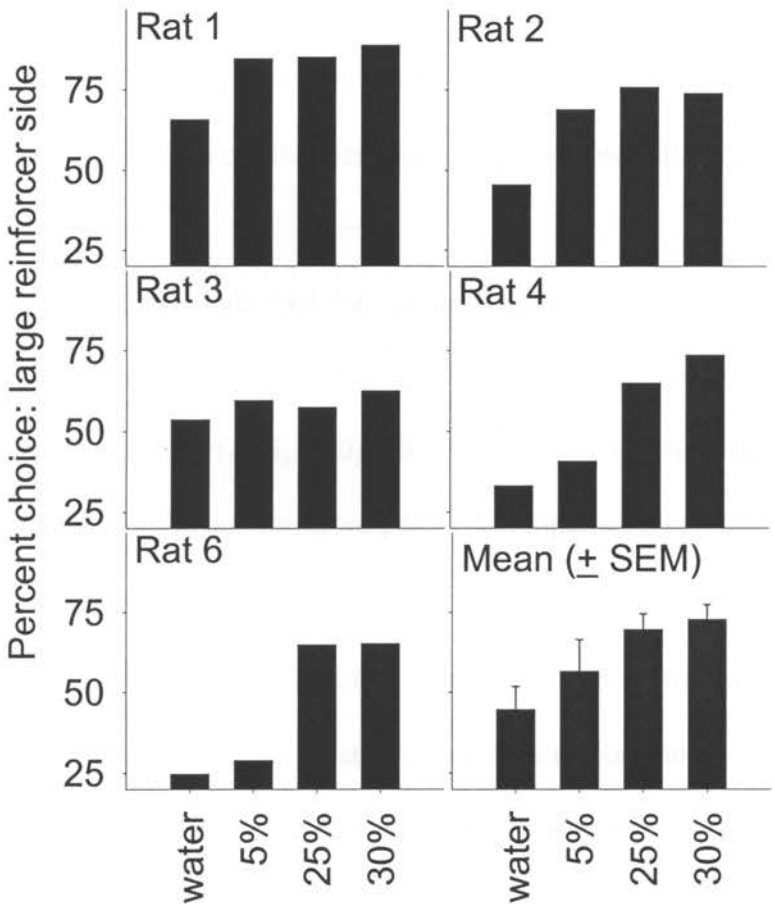

Rat 1
Rat 2
Rat 3
Rat 4
Rat 5
Rat 6
Mean (+ SEM)
Percent choice: large reinforcer side
75
50
25
Baseline
Mag
Freq
Mag & Freq
12 s
24 s
320 µM
480 µM
Baseline
Manipulation

Figure 7. Experiment Two. Individual and mean (± SEM) initial link preference for the large reinforcer side in concurrent chains as a function of sucrose concentration. Interdependent VI 16-s schedules with a 2.5-s change over delay constituted the initial links. Terminal links were FT 16-s delays. Percent choice measures are from single sessions during which the 150-µl reinforcer sucrose concentration was 25% (baseline), then 5%, 30% then 0% (water); the 50-µl reinforcer was 25% sucrose.


Rat 1
Rat 2
Rat 3
Rat 4
Rat 6
Mean (± SEM)
Percent choice: large reinforcer side
75
50
25
water
5%
25%
30%

was maintained compared to when it was disrupted, although this pattern occurred only in 2/4 rats (Rats 1 and 4, not 3 and 6).

Perfect matching would require that rats deliver one quarter of their lever presses to the previously large reinforcer side after the reversal (Baum, 1979). The rats never approached perfect matching in a single session: preference usually decreased by < 10% over 64 trials. This is similar to Grace's (2002b) Figure 3, in which preference changed little over the first 72-trial session, then shifted by approximately 10% in subsequent sessions until asymptote.

Experiment Two also indicated that rats are sensitive to the concentration of sucrose on the large reinforcer side, as indicated by a main effect of concentration in a repeated measures ANOVA, $F(1.85, 7.40) = 9.99$, $p = 0.009$ (Huyhn-Feldt-corrected degrees of freedom). Bonferroni-corrected pairwise comparisons revealed that preference for 150 µl 0% sucrose was almost ($p = .052$) significantly lower than preference for 150 µl 30% sucrose. Of all the manipulations, rats decreased their preference the most when water was substituted for 25% sucrose on the larger reinforcer side (Figure 6). Although replacing 25% sucrose with water dramatically shifted preference, rats did not exclusively choose the alternative containing sucrose (50 µl, 25%), suggesting that past reinforcement contingencies may have contributed to preference during the test session.

GENERAL DISCUSSION

These are the first data addressing rats' changes in choice with different schedule transitions in concurrent chains. In Experiment One, preference was not affected by parametrically manipulating the 1) terminal link stimulus tone frequency, 2) delay to terminal link onset, or 3) concentration of quinine added to the sucrose on the large reinforcer side. In Experiment Two, rats' choices were sensitive to reversals of the 1) location of the initial link leading to the large reinforcer, 2) frequencies of the terminal link auditory stimuli preceding delivery of the large and small reinforcers, and 3) reversal of both reinforcer magnitude and terminal link stimulus frequency.

The magnitude of preference decrease in Experiment Two was similar to that observed in pigeons. For example, Mazur, Blake, and McManus (2001) trained pigeons with concurrent-chains interdependent VI 45-s initial links and FT terminal links (5 and 20 s, 2 and 18 s). After at least nine baseline sessions, the terminal link delays were unpredictably switched, maintaining the switched assignments for 9-13 40-minute sessions. In the first 40 minutes, preference switched by almost 10%, and by the eighth 20-minute block (about 4 sessions), changes in response percentages decelerated toward an asymptote. Grace (2002b, Experiment 1) trained pigeons over 27 baseline sessions, then reversed FI 10- and 20-s terminal link schedules; pigeons' preference approached a new asymptote within 9 sessions. The current rat data, in addition to the pigeon data reported by Mazur et al. (2001) and Grace (2002b), suggest that when reinforcement contingencies change infrequently, preference is slow to adjust. Indeed, Mazur (1997b) reported that preference changed more rapidly concurrent schedules when reinforcement percentages shifted after 1-2 sessions compared to after about 8 sessions.

The sensitivity of choice to changes in reinforcer magnitude has been assessed in concurrent schedules for which the dependent measure is a in Baum's (1974b) generalized matching equation. This measure indicates how closely the response ratio matches the reinforcer ratio, where $a = 1$ reflects perfect matching. Davison and Baum (2003) adjusted the reinforcer magnitude ratios randomly seven times per session for 10 reinforcers per ratio. Sensitivity to the reinforcer ratio was 0.22 to 0.31 after 9 reinforcers. Using the same range of reinforcer magnitude ratios, Landon et al. (2003) reported sensitivities to reinforcer magnitude ratio of 0.70 to 0.87 for the last 50 of 65 sessions per condition. Therefore, after 9 reinforcers, Davison and Baum (2003) reported sensitivity one-quarter to one-third that obtained after 65 80-trial sessions, suggesting a rapid change in preference when the contingencies shifted. The rats in the current experiment adjusted their preference by about 10% in a single session, whereas a 50% adjustment (75% to 25%) would have constituted a complete reversal of preference upon reinforcer magnitude reversal. Assuming a linear change in preference per session if the test condition was continued, this data predicts that our rats would approach perfect matching in five sessions, with one-fifth of maximal sensitivity occurring after 64 trials. By this estimate, our rats adjusted their preference at a much slower rate than Davison and Baum's (2003) pigeons. Assuming that Davison and Baum's pigeons increased their sensitivity linearly, they would approach perfect matching in 30-50, rather than 320, trials. How frequently reinforcer magnitude ratios shift appears influence the rate of preference adjustment.

Comparing individual differences in preference change across Figures 5 and 6, it is apparent that sensitivity to sucrose concentration does not correlate with sensitivity to

the manipulations in Experiment Two. For example, while Rat 1 exhibited the most systematic decreases in preference in Figure 5, it was nearly insensitive to changes in sucrose concentration in Figure 6. Rats 4 and 6 exhibit the greatest sensitivity to sucrose concentration in Figure 6; Rat 4 was primarily sensitive to the magnitude and frequency reversal and to the addition of quinine to the large reinforcer, whereas preference is nearly stable across all the manipulations for Rat 6 (Figure 5). Our data suggest that changes in preference with different types of contingency manipulations are not necessarily correlated. Perhaps rats use different neural systems to detect changes in, for example, reinforcer concentration and magnitude. Experience with greater variability in reinforcement along one dimension could result in greater sensitivity to changes, and therefore faster changes in preference. Future experiments could assess whether sensitivity to different manipulations involves different neurobiological substrates.

Identifying the factors that affect choice in transition is fundamental to understanding normal choice behavior and conditions in which choice behavior may be disrupted, such as impulsivity and drug addiction. Our rats were sensitive to extreme, but not subtle, manipulations of features of the reinforcement contingencies. Future studies could investigate the neurobiological systems necessary for behavior to change with different types of contingency change. Such data would contribute to our understanding of clinical conditions associated with impulse control and decision making impairments.

Appendix 1

Table 4. Order of conditions (left) and initial link preference (right) for the large reinforcer side for each session in Experiment One.

Terminal Link Stimulus Frequency (kHz)			Quinine (μM) Concentration in Large Reinforcer			Delay (s) to Terminal Link Stimulus Onset			
	Rat 1	Rat 2		Rat 3	Rat 6		Rat 4		Rat 5
	61	72		61	60		58		69
	67	68		68	67		61		72
	60	64		69	64		60		64
	61	70		76	61		58		69
	60	64		66	64		57		69
	67	74		68	56		61		64
2.5	73	51		78	66	6	73		75
2.5	70	64		78	79	6	65		76
	72	60		80	82		62		71
	72	58		78	73		62	6	73
	69	60		79	75		64	6	76
	76	65		78	61		68		72
	76	72	40	77	68		69		64
5	69	74	40	19	68		69		62
5	71	74		78	72		81		70
5	72	76	10	72	66		81		68

Table 4: continued

15	65		69	10	74		67		78		71
15	67	2.5	75		68		75		77		65
	65	2.5	71		76		65		73		76
	73		73		72	10	62	2	76		70
	77	15	69		78	10	67	2	86		64
12	80		77		80		73		74		61
12	77		75	20	73		62	4	75		67
	74		76	20	73		73	4	64		66
9	83		64		78		73		67		74
9	83		71		71		72		80		67
	84		75	160	74		67		74	6	61
	82		66	160	73		72		87	6	58
	77		71		65	80	77		77		62
	76		77		69	80	77		73	10	55
15	76		83		74		81		73	10	60
15	73		72	80	72		76		66		58
	76		78	80	67		83		65		58
5	72		79		69		80		67	8	54
5	81		74		76		85	8	63	8	54
	83		69		73		81	8	63		59
	73		78	160	81		88		62	2	52

Table 4: continued

	77		76	160	81	40	86		67	2	57
12	79		71			40	86		67		60
12	78	12	65				86	10	68	10	54
	78	12	68			20	86	10	59	10	63
2.5	81		71			20	81		65		55
2.5	80	9	71					4	62		60
		9	75					4	68		60
			72							2	62
		5	68							2	57
		5	69								
			68								
			66								
			65								
		15	69								
		15	77								

Rats 1 and 2 were trained with a 1 kHz tone preceding delivery of 150 µl sucrose and a 15 kHz tone preceding delivery of 50 µl sucrose, then the frequency of the tone preceding the large reinforcer was manipulated; Rats 3 and 6 were trained with 50 and 150 µl sucrose without quinine, then concentrations of quinine were added to the large reinforcer; Rats 4 and 5, terminal link stimulus onset was delayed from terminal link entry; blank condition labels indicate baseline.

Table 5. Order of conditions[1] and initial link preference for the large reinforcer side for each session in Experiment Two.

Rat 1		Rat 2		Rat 3		Rat 4		Rat 5		Rat 6	
	80		72		78		50		67		86
	74		78		83		75		68		84
	72		78		82		61		67		82
	78		75		81		66		61		82
	74		79		82		68		64		85
	80		77		82		71		68		78
	80	24 s[2]	68	Freq[3]	76		75		69		74
	78		82		80		73		67		80
	80		79		80		72		66		83
	84		81		78		75		63		74
24 s	69		79		82	480	24		62		78
	84	Mag[3]	73		81		85		56		75
	79		77	Mag	69		93		69		79
	79		77		76		76		57		76
	81		83		76		95		65		78
Mag	71		78		76		79		68	Freq	71
	75		78		74		79		66		80
	75	12 s	70		79		81		64		78
	79		77		75		83		60	M&F[4]	71
	81	320[5]	74		76		81	320	60		73

Table 5: continued

12 s[6]	62		80		83	320	73		59		77
	70	480[7]	80	M&F	69		82	480	47		82
	75		76			Freq	79		57		81
	78		73				79		55	Mag	64
	78		78			Mag	72		62		
Freq	54		71				77		62		
	72		74				75	Freq	58		
	73		84				81				
	78		80				78				
	82		78				80				
	80	Freq	73			M&F	51				
M&F	59										

[1] Baseline conditions are indicated by blank cells; [2] 24 s, terminal link stimulus onset delayed by 24 s; [3] Freq, frequencies of the terminal link stimuli preceding the large and small reinforcer were reversed; [3] Mag, reinforcer magnitude locations were reversed; M&F, terminal link stimulus frequencies and reinforcer magnitudes were reversed; [5] 320, 320 μM quinine was added to the large reinforcer; [6] 12 s, terminal link stimulus onset delayed by 12 s; 480, 480 μM quinine was added to the large reinforcer

BASOLATERAL AMYGDALA LESIONS DISRUPT THE ADAPTATION OF PREFERENCE AFTER REINFORCER MAGNITUDE REVERSAL

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Running Head: Reinforcer magnitude reversal - basolateral amygdala

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ABSTRACT

Previous studies show that the basolateral amygdala (BLA) is required for behavior to adjust when the value of a reinforcer decreases due to gastric illness or satiation. We evaluated the effect of excitotoxic BLA lesions on changes in preference for a different type of contingency change, reinforcer magnitude reversal. Rats were trained to press two levers during a variable-interval choice phase to produce a 16-s delay to sucrose reinforcement. During baseline, one lever produced 50 and the other 150 μl sucrose to consistent locations, 32 of each per session. Once preference stabilized, the locations of the reinforcer magnitudes were unpredictably reversed for a single session. Lesions induced prior to training disrupted changes in preference when the reinforcer magnitudes reversed. Lesions induced after stable preference was acquired, but prior to reinforcer magnitude reversal, did not affect changes in choice behavior. These results parallel data from reinforcer devaluation protocols, extending the role of the BLA to updating of response allocation in choice procedures when reinforcer magnitudes change.

Introduction

The basolateral amygdala (BLA) has been repeatedly implicated in the control of behavior by Pavlovian stimulus-reinforcer relationships (for a review, see Everitt et al., 2003), and behavioral adaptation to decreases in reinforcer value or reinforcer omission (Hatfield et al., 1996; Burns et al., 1999; Fuchs et al., 2002; Pickens et al., 2003; Balleine et al., 2003). For example, when rats are trained to approach a food source in the presence of a stimulus, and then the food is devalued by pairing its consumption with nausea induced by lithium chloride injection, normal rats decrease their rate of approach in the presence of the trained stimulus (Colwill & Motzkin, 1994). However, for rats with pre- (Hatfield et al., 1996) but not post- (Pickens et al., 2003) training BLA lesions, the stimulus continues to elicit approach to the food source. The types of reinforcer variables manipulated in previous studies are limited. For example, the role of the BLA in behavioral adaptation to increases in reinforcer value has not been investigated. It is unclear whether the BLA supports behavioral adjustment following changes in reinforcer properties such as magnitude.

Animals' choices are sensitive to variety of reinforcer properties. When presented with two sources of reinforcement, animals allocate their behavior to match the ratio of reinforcement schedules (Herrnstein, 1961; Baum, 1974b), and other reinforcer variables such as amount (Catania, 1963; Neuringer, 1967; Ito, Takatsuru, & Saeki, 2000), immediacy (Chung & Herrnstein, 1967; Williams & Fantino, 1978), and the relative rate of conditioned reinforcers (Shahan et al., 2006). Although the factors determining steady-state preference are well described (Davison & McCarthy, 1988), how preference changes when different reinforcement properties change is poorly understood.

Research has shown, however, that both current and past experiences with reinforcement influence preference (Killeen, 1981; Shettleworth & Plowright, 1992). For example, Davison and Baum (2000, 2003) presented pigeons with concurrent schedules of reinforcement that differed in magnitude, shifting the magnitudes for each alternative after ten reinforcers, seven times per session. Pigeons' ratio of responding between the two alternatives was sensitive to the current ratio of reinforcer magnitudes, and to a lesser extent, past reinforcer ratios. The results are similar when reinforcer delays shift between two alternatives (Schofield & Davison, 1997; Grace, Bragason, & McLean, 2003).

Changes in choice have most often been studied using concurrent schedules of reinforcement. In contrast, in concurrent *chains* schedules (Autor, 1960, 1969), subjects choose between two concurrent schedules (choice phase, or initial links) providing access to mutually exclusive schedules of primary reinforcement (reinforcer phase, or terminal links). Choice behavior in the initial links is influenced by stimuli in the terminal links (Grace, 2002b). These stimuli probably affect choice as conditioned reinforcers (e.g. Dunn, Williams, & Royalty, 1987) because they precede reinforcer delivery and can acquire conditioned value.

The BLA has a well-known role in conditioned reinforcement. Disruption of BLA activity decreases the ability of Pavlovian conditioned stimuli to reinforce new behavior (Cador et al., 1989; Burns et al., 1993) and to sustain responding in second-order schedules (Burns et al., 1999; DiCiano & Everitt, 2004). Concurrent chains schedules may be useful for studying the role of the BLA in sensitivity to changes in reinforcer variables because the contribution of primary and conditioned reinforcers can be dissociated.

We aimed to develop a protocol for assessing the role of the BLA in the adaptation of preference when conditioned and primary reinforcer properties are manipulated using concurrent chains schedules. We expected normal acquisition of preference, since previous studies have shown that these lesions do not affect the acquisition of operant behavior (Balleine et al., 2003). Since pre- (Hatfield et al., 1996; Balleine et al., 2003), but not post-training (Pickens et al., 2003) BLA lesions decrease behavioral changes after reinforcer devaluation, we hypothesized that pre-training, but not post-training, BLA lesions would disrupt changes in choice behavior when the reinforcer magnitudes were reverse. This study fits into a long-term project of identifying how the BLA contributes to changes in choice when different attributes of conditioned and primary reinforcers are manipulated. Such data will provide information regarding the role of the BLA in sensitivity to combinations of reinforcer properties, i.e. value, as measured by relative choice behavior.

Materials and Methods

Subjects and apparatus

Forty-three male Long-Evans rats (Charles River, Raleigh, NC) obtained at 50-55 days of age (225-250 g) served as subjects. The rats were split into groups of 23 and 20 rats that were run in serially conducted experiments. Subjects in Experiment 1 underwent pre-training surgery (PRE) and Experiment 2 subjects underwent surgery after initial behavioral training (POST). Table 6 outlines the time course of the protocol for both groups. The PRE group required 54-77 days to complete the protocol, and the POST group required 65-102 days. Upon arrival, the animals were habituated to the

temperature (21 ± 1°C) and light-controlled vivarium (12:12-hr light-dark cycle with lights on at 6:00 am), then weighed and handled daily. During recovery from surgery, the rats were free-fed, then food restricted to 90% of their free-feeding body weights prior to training and maintained at 90% of free-feeding weight with supplemental feeding of lab chow following experimental sessions. Sessions occurred during the light cycle, 5-7 days per week. Water was freely available. Care followed the guidelines provided by the Oregon Health & Science University Department of Comparative Medicine. The Institutional Animal Care and Use Committee approved all procedures.

Behavior was measured in 4 identical Med-Associates (St. Albans, VT) operant chambers (ENV-008) housed in sound-attenuating ventilated boxes (60 dB). Nose pokes, lever presses and reinforcer deliveries were recorded using an IBM-compatible computer running Med-PC software. The panel to the left of the door contained three equally spaced nose poke response units (ENV-254): left and right, but not the center (ENV-114BM), head-entry devices contained a liquid reinforcer cup (ENV-200R3BM). Horizontal infrared beams were broken when the animal poked its nose 0.64 cm into any response unit. A stainless steel pipe protruded from the rear of each liquid reinforcer cup to which was fit a length of plastic tubing (PHM-122). The tubing was attached to 60-ml syringes. Syringes were filled with 25% (w/v) sucrose dissolved in deionized water and secured in Med-Associates pumps (PHM-100; 3.33 RPM, 60.2 µl/s).

Table 6. Outline of the protocol for rats receiving pre- or post-training excitotoxic lesions of the basolateral amygdala including the sessions or, if appropriate, mean ± SEM days or sessions of training, for each stage of the protocol.

	Surgery Group	
Protocol	Pre-Training (PRE)	Post-Training (POST)
Habituation	5.91 ± 0.06	5
Weigh/Handle	7.43 ± 0.34	10
Food Restriction	—	6
Training – Stable Preference	—	38.5 ± 1.91
Surgery	1	1
Recovery	5.96 ± 0.20	2
Food Restriction	5.74 ± 0.17	4
Training	36.7 ± 1.99	21.39 ± 0.99
Sacrifice		

A response lever (ENV-110M) was set above each head-entry device. A stimulus light (ENV-221M) was set 5.7 cm above each lever, and a house light (ENV-215M) was set 14 cm above the center head-entry device. The panel to the left of the door contained a speaker (ENV-224BM) connected to a multiple tone generator (ENV-223).

Surgical procedures

At the time of surgery, PRE (N=23) and POST (N=20) rats weighed (mean ± SEM), respectively, 347.10 ± 3.30 g and 318.75 ± 2.75 g; only POST rats were food-deprived at the time of surgery. PRE rats were anesthetized with ketamine hydrochloride (mean ± SEM: 130.21 ± 8.89 mg/kg, i.p.) and xylazine (8 mg/kg, intraperitoneally, i.p.). POST rats were anesthetized with isoflurane gas. After the rats were secured in a stereotaxic frame (Cartesian) with incisor and ear bars, the scalp was cut to expose the skull. Holes were drilled above the BLA [basal, lateral, accessory basal nuclei: coordinates relative to bregma, mm; antero-posterior (AP), -2.9; mediolateral (ML), ± 5.0; dorsoventral (DV), -8.1]. For lesions, rats received bilateral injections of 0.50 µl (0.05 µl/min + 4 min diffusion) of 0.09 M quinolinic acid (Sigma) dissolved in phosphate-buffered saline (PBS, pH 7-7.4) using a 1 µl Hamilton syringe (Hamilton, Reno, NV). Rats in the control group underwent similar treatment except that PBS, rather than quinolinic acid, was injected. Buprenorphine, ketoprofen, and warm sterile saline were administered after surgery to prevent pain, inflammation, and dehydration, respectively.

Histological procedures

When the experiment was completed, rats were injected with a lethal overdose of sodium pentobarbital or ketamine HCl and perfused transcardially with 0.9% saline followed by 10% formaldehyde solution in PBS (formalin). The brains were stored for 24 h each in solutions of 10%, 20%, and 30% sucrose in PBS. Frozen coronal sections (40 μm) were cut through the BLA using a cryostat. Every fourth section was mounted on a glass slide, stained with thionin, and inspected under a light microscope. The brains of animals for which sham and BLA lesions were intended were compared by an observer blind to the behavioral data at -1.88, -2.30, -2.80, -3.30, and -3.80 mm posterior from bregma. A 2 x 2 mm grid was placed over drawings of coronal sections (Paxinos & Watson, 1998) at each coordinate. The squares containing damage as shown in the photomicrograph were marked. The proportion of squares in a region that appeared damaged when compared to sham sections indicated the percent of neuronal loss. Rats for which the average of the left and right damage was >30% were included in the behavior analyses. This criterion was chosen based on the magnitude of the lesions in order to include a sufficient number of subjects in the lesion groups.

Behavioral procedures

Each rat was assigned to a single experimental chamber for the duration of the experiment, with box assignments balanced among the groups.

Instrumental acquisition. The rats were trained in 6 phases (Table 7). In Phases 1-4, rats advanced to the next phase by obtaining 64 reinforcers in 60 minutes or less for

Table 7. Reinforcement contingencies during the six phases of training.

Training Phase	Reinforcement Contingency Changes[1]
1	Concurrent schedules: fixed-ratio 1-variable-time 120-s
2	Dependent concurrent chains: variable-interval 8-s-fixed-time 2-s
3	2.5-s change over delay
4	10-s time out
5	Terminal links increase by 2 s every 8 trials to fixed-time 16-s
6	Variable interval 16-s fixed-time 16-s

[1] Schedule changes in each phase were retained in subsequent phases.

two consecutive sessions. Contingency changes in each phase were preserved across subsequent phases. In Phase 1, 150 µl 25% sucrose was delivered immediately after a left or right lever press. Sucrose was also delivered according to a variable-time (VT) 120-s schedule. When sucrose was delivered, the house light and the stimulus light above the reinforced cup shut off for 2 s. In Phase 2, the concurrent chains schedule was introduced. The initial link VI 8-s schedules were randomly selected from 12 intervals generated from an exponential progression (Fleshler & Hoffman, 1962). After the VI elapsed, if the rat pressed the lever assigned for reinforcement, sucrose was delivered after a fixed-time (FT) 2-s terminal link. Unlike Phase 1, reinforcer delivery co-occurred with both stimulus lights shutting off, but the house light remained illuminated. After the reinforcer was delivered, the lights came back on and the initial link VI schedule restarted. The initial links were interdependently scheduled (Stubbs & Pliskoff, 1969) so the rats experienced an equal number of reinforcers from each side per session: every 8 reinforcers, 4 were delivered to the left, and 4 to the right, in a random order. In Phase 3, a change over delay (COD) was introduced. Once the initial link VI interval elapsed, the next press to the lever assigned for reinforcement resulted in terminal link entry if a) it was the first press to that lever during the trial, or b) a 2.5 s COD had elapsed after the rat switched from the other lever. This COD was used in preliminary experiments with this protocol, and is similar to those used for pigeons (Stubbs, Pliskoff, & Reid, 1977). Since greater switching between alternatives is associated with a lower magnitude of preference, the COD was used to decrease switching and maximize preference (Leung & Winton, 1985) thereby increasing our ability to detect decreases in preference. In Phase 4, a 10-s time out occurred after reinforcer delivery to allow time for sucrose

consumption before the next initial link. During the time out, all the lights shut off; head entries and lever presses were recorded but inconsequential. The lights came back on after the time out to signal onset of the initial link. Phase 5 was a single session during which terminal link durations incremented 2 s every 8 trials from fixed-time (FT) 2- to 16-s. One of the reinforcer magnitudes was reduced to 50 µl, while the other was still 150 µl. In Phase 5, both the left and right stimulus lights shut off at the onset of the terminal link. Tones occurred in the first and last 2 s of terminal links greater than FT 6 s; a tone occurred in the first 2 s of FT 2- and 4-s terminal links. The tone segmented the delay because longer duration stimuli may be less efficacious conditioned reinforcers (Mazur, 1997a). The frequency of the tone (1 or 15 kHz, 75 dB) indicated the reinforcer magnitude to be delivered. The magnitude location-tone-frequency assignments were counterbalanced across sham and lesion groups.

Phase 6 training continued until preference was stable, but for at least 14 sessions. Preference was measured as the total number of initial link lever presses to the large reinforcer lever divided by the total number of initial link presses per session. There are many techniques for assessing stable preference (e.g., Killeen, 1978). Stability was acquired when, in a series of five sessions, the percent of initial link lever presses to the large reinforcer lever in the most recent session deviated by <10% from the previous sessions. Also, the first and last percent choice values in the series could differ from the next smallest or largest value by no more than 1%, i.e., an absence of increasing or decreasing trends in preference. For example, the series 70, 73, 71, 69, 73 would be considered stable because the difference between 73 and every other value is less than 7.3; 70 is the lowest value, but is not > 1% different from 71.

Reinforcer magnitude reversals. After preference was stable, the locations to which the large and small reinforcers were delivered were reversed during the next session, and returned to the baseline condition at the start of the following session. The magnitudes were reversed and restored three times per subject. So that rats could not predict when the magnitudes would be reversed, a series of 3 or 4 baseline sessions intervened between the reversal sessions, the order of the two series being randomly determined. Three baseline sessions followed the third reversal. Davison & McCarthy (1988) estimated that reinforcer ratios more than 3 sessions in the past exert almost no influence on choice. Their estimate was based on pigeon data from concurrent VI schedules for which the reinforcer ratio could not be predicted from previous session values, and so their conclusions may not completely generalize to our protocol. We expected preference to approximate baseline values within the 3 or 4 sessions following a reversal. Due to scheduling errors for PRE rats only, 1 lesioned rat experienced 6 instead of 5 sessions during the first series of baseline sessions, and a sham rat experienced 5 instead of 4 baseline sessions during the second series. For 1 sham rat, 4 baseline sessions intervened between each reversal session, and on one occasion, 2 rats were exposed to the reversed reinforcer magnitudes for 2 consecutive sessions. Omitting these subjects did not alter the outcomes of statistical analyses of the primary dependent measure (i.e., preference) and so they were included in the analyses after omitting the extraneous sessions.

Statistical Analysis

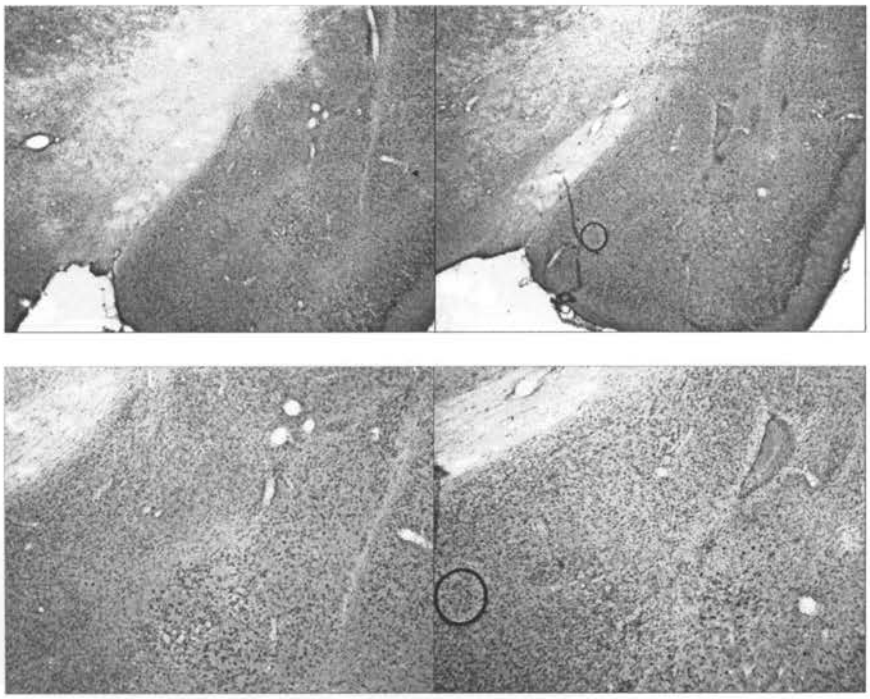
All measures were evaluated with 2 (PRE, POST) x 3 (sham, partial lesion, lesion) mixed factor ANOVAs that. Huynh-Feldt corrections were used when repeated factors were included; adjusted degrees of freedom are cited throughout the manuscript. Main effects and interactions were evaluated with Bonferroni-corrected pairwise comparisons. For all analyses, alpha was .05.

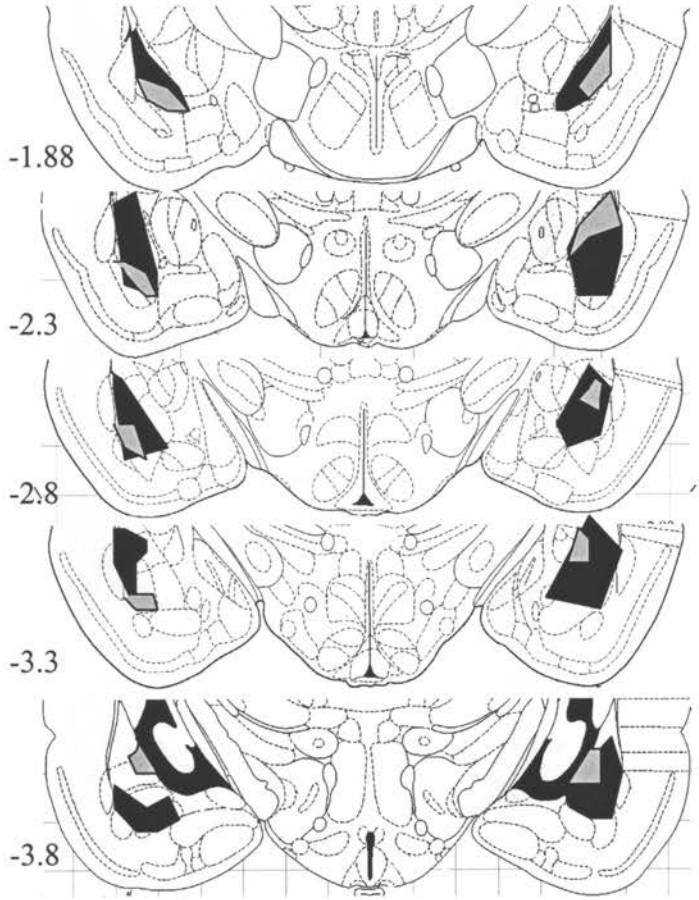
Results

Figures 8A and 8B show representative photomicrographs of sham and BLA lesions and diagram the least and greatest extents of lesion throughout the rostrocaudal extent of the BLA for PRE and POST subjects, respectively. The lesions matched our criterion for 7/12 PRE and 6/11 POST rats. On average (± SEM), 50.0 ± 2% and 53.6 ± 6.9% of the basal and lateral amygdala was damaged bilaterally in PRE and POST rats, respectively. The lesions for POST rats were slightly more extensive, resulting in minor unilateral damage to the central nucleus; researchers typically include subjects with unilateral central nucleus damage in the behavior analysis (e.g., Burns et al., 1993).

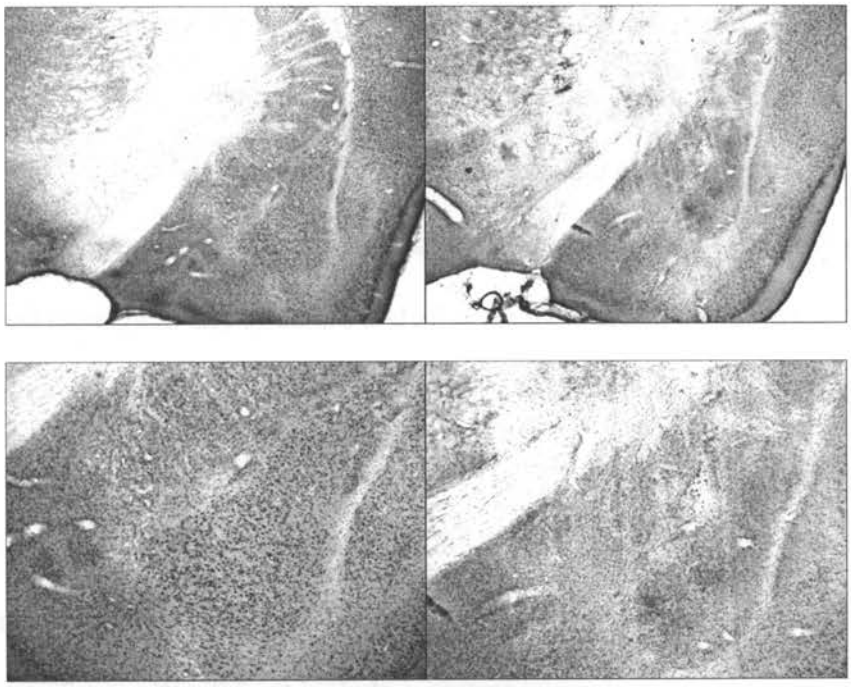
Identical lesion protocols were used for PRE and POST rats (after Balleine et al., 2003), except that ketamine anesthesia was used for the former and isoflurane gas for the latter, both of which are common anesthetics in behavioral neuroscience research about learning. It is worth noting that all, and only, the rats anesthetized with isoflurane gas and microinjected with quinolinic acid exhibited seizures approximately 30 minutes after surgery, lasting < 24 h. Minor and unilateral central nucleus damage occurred in three POST rats with acceptable BLA lesions. One POST rat had 50% damage to the left

Figure 8. Representative photomicrographs (*top*) and diagrams of coronal sections (*bottom*) demonstrating the least (*lighter*) and greatest (*darker*) extent of lesion in rats for whom bilateral quinolinic acid or PBS infusions were aimed at the BLA. The photomicrographs demonstrate sham (left) and lesion (right) sections from –2.8 mm posterior from bregma at 2.5x (top) and 5x (bottom) magnification. The extent of lesion drawings are from subjects with lesions meeting the criterion for inclusion in the data analysis, with the numbers indicating the mm posterior from bregma which the drawing illustrates. A) pre-training lesions; B) post-training lesion.





A



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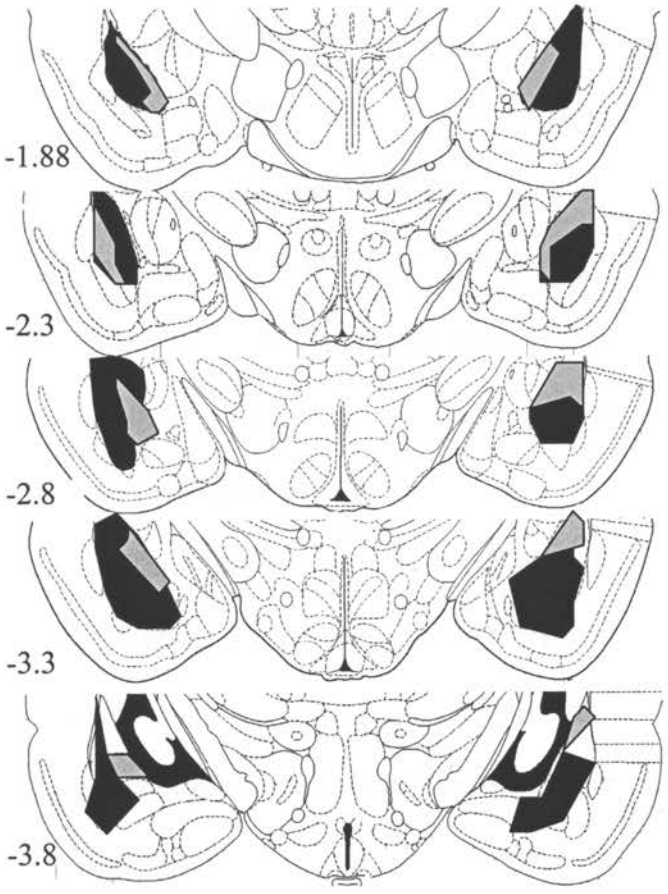


central nucleus and a complete lesion of the right central nucleus and was omitted from the analysis. One POST sham rat had >10% bilateral damage to the BLA and was excluded from the analyses because the quality of damage may have differed from rats with partial lesions induced by quinolinic acid. Otherwise, none of the PRE or POST sham rats had damage to any structure and all were included in the analyses. Rats with partial BLA lesions, which averaged (± SEM) 11.14 ± 4.70 and 17.23 ± 1.63% of the BLA for PRE (N=5) and POST (N=5) rats, respectively, were compared to the sham (PRE, N=11; POST, N=8) and lesion (PRE, N=7; POST, N=5) groups. The lesions occupy similar locations in PRE and POST rats, although they may be somewhat more medial in POST rats. We did not include a control lesion to refute the argument that damage to any part of the brain could have produced our effects because many studies have shown quite specific effects of BLA lesions when compared with lesions of other sites including the medial prefrontal cortex, dorsal striatum, fimbria fornix, hippocampus, central nucleus, and orbitofrontal cortex (OFC; e.g., Burns et al., 1993; McDonald & White, 1993; White & McDonald, 1993; Winstanley et al., 2004).

As shown in Figure 9, BLA lesions did not affect the mean (± SEM) sessions to criterion performance during the 6 phases of concurrent chains training. Phases 1-4 were analyzed independently of Phases 5 and 6 because of the different performance criteria. Sessions to criterion in each phase was analyzed with 2 (PRE, POST) x 3 (sham, partial lesion, lesion) mixed factor ANOVAs. There were no main effect or interactions, indicating that the groups acquired the task after a similar number of sessions.

In Phase 5, the delay to both reinforcer magnitudes was incremented to 16 s. The groups were compared with respect to several performance measures with 2 (PRE,

Figure 9. Mean (± SEM) number of sessions to criterion across the six phases of concurrent chains training described in Table 7. Pre-training surgery (PRE) occurred before Phase 1 and post-training surgery (POST) occurred after Phase 6. The rats received excitotoxic lesions of the BLA or sham lesions; the performance of rats with partial lesions of the BLA is also shown.

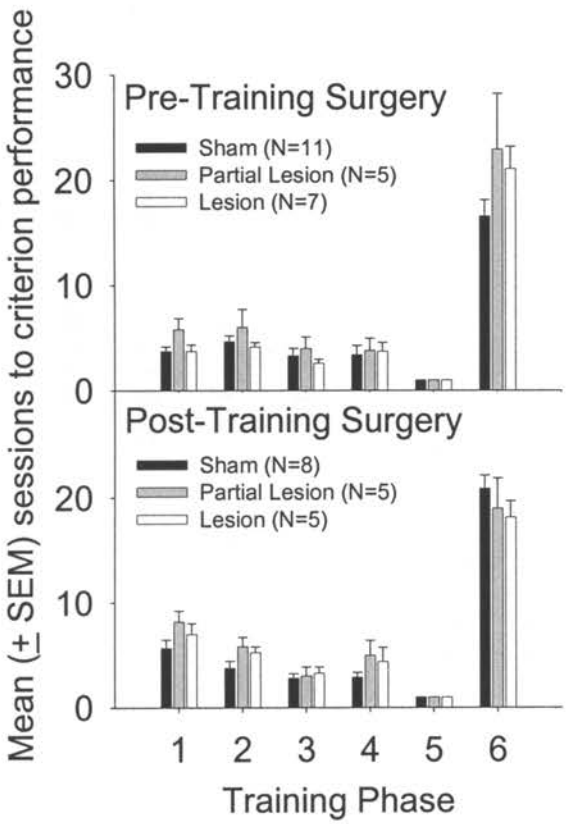

Mean (± SEM) sessions to criterion performance
30
20
10
0
Pre-Training Surgery
Sham (N=11)
Partial Lesion (N=5)
Lesion (N=7)
Post-Training Surgery
Sham (N=8)
Partial Lesion (N=5)
Lesion (N=5)
20
10
0
1
2
3
4
5
6
Training Phase

Table 8. Mean (± SEM) performance measures for Phase 5 and 6 training.

	Phase 5					
	Pre-Training Surgery			Post-Training Surgery		
Measure	Sham	Partial Lesion	Lesion	Sham	Partial Lesion	Lesion
Trials Completed	55.00 ± 2.52	64.00 ± 3.34	61.43 ± 2.82	62.50 ± 2.64	64.00 ± 3.34	63.40 ± 3.34
Session Time	4309 ± 278	3731 ± 412	4520 ± 349	4403 ± 326	3948 ± 412	3924 ± 412
Total Presses	420 ± 34	504 ± 52	432 ± 44	474 ± 40	442 ± 52	484 ± 52
Total Nose Pokes	653 ± 49	646 ± 73	616 ± 62	636 ± 58	584 ± 73	737 ± 73
	Phase 6					
Trials Completed[1]	31.35 ± 4.24	49.76 ± 6.29	41.51 ± 5.32	38.49 ± 4.97	29.79 ± 6.29	47.15 ± 6.29
Session Time (s)	5337 ± 76	5009 ± 113	5168 ± 96	5293 ± 89	5360 ± 113	5345 ± 113
Total Presses	279 ± 50	495 ± 74	390 ± 63	332 ± 59	495 ± 75	397 ± 74
Total Nose Pokes	493 ± 76	655 ± 113	663 ± 95	590 ± 89	457 ± 113	829 ± 113

[1] Interaction between PRE/POST and group (sham, partial lesion, lesion): $F(2, 35) = 3.35$, $p = .047$

POST) x 3 (sham, partial lesion, lesion) ANOVAs, which revealed no main effects or interactions. The top of Table 8 shows the number of trials completed, session time, total lever presses, and total nose pokes for the three groups. Pre-training BLA lesions did not affect any measures of performance during Phase 5.

In Phase 6 (Figure 9), the trend toward lesioned PRE rats (mean ± SEM: 23.14 ± 2.45) requiring a greater number of sessions to criterion than sham PRE rats (mean ± SEM: 17.45 ± 1.75) was not statistically significant, $t(16) = 1.94$, $p = 0.07$. As in Phase 5, sham, partially lesioned, and lesioned rats from the PRE and POST groups did not differ in session time, total lever presses, or total nose pokes (Table 8, bottom). PRE partial lesion rats completed more trials than POST partial lesion rats, as indicated by a significant interaction from a 2 (PRE, POST) x 3 (sham, partial lesion, lesion) ANOVA. For all groups, performance generally declined from Phase 5 to 6 because the overall duration of both the initial and terminal links increased in Phase 6, decreasing reinforcer rate (e.g., Mazur, 2002). Baseline preference was acquired in approximately 20 sessions, which is consistent with previous studies using concurrent chains schedules (Grace, 2002b).

Figure 10 illustrates the acquisition of preference for the large reinforcer side across the first 14 sessions of Phase 6. Figure 10 also shows the mean preference across the first set of five stable baseline sessions, and the post-surgery baseline sessions for POST rats. Fourteen is the minimum number of sessions within which stability could have been attained. For PRE and POST rats, the percent of initial link lever presses to the large reinforcer side increased across sessions as indicated by a main effect of session from a 2 (PRE, POST) x 3 (sham, partial lesion, lesion) x 14 (session) mixed factor

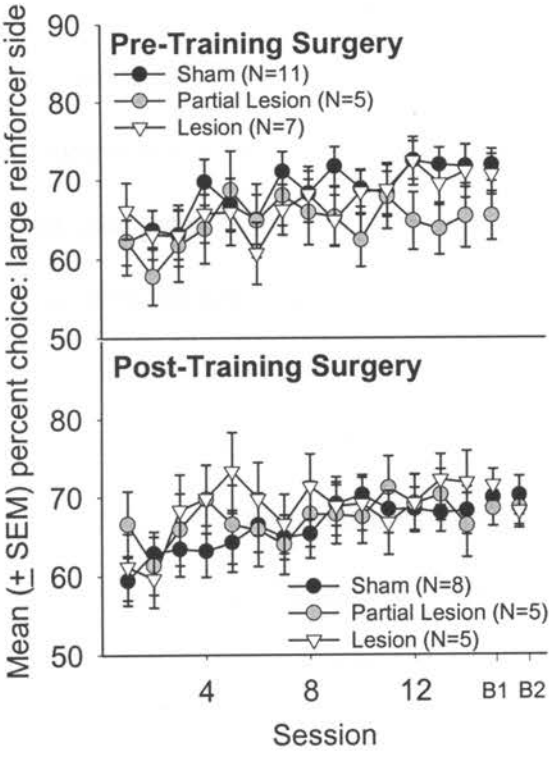
ANOVA, $F(12.44, 448.00) = 2.88, p = 0.01$). There were no other significant main effects or interactions.

Mean (± SEM) baseline preference across the first five stable sessions did not differ between the groups according to a 2 (PRE, POST) x 3 (sham, partial lesion, lesion) ANOVA; there were no main effects or interactions. The number of sessions required for reacquisition of stable preference after surgery, including the second set of five stable sessions, was (mean ± SEM) of 7.37 ± 0.63, 11.40 ± 2.62, and 8.20 ± 1.60 for POST sham, partially lesioned, and lesioned rats, respectively; the groups did not differ according to a one-way ANOVA. To assess the effect of surgery on baseline preference for POST rats, stable baseline preference before surgery was compared with preference acquired after surgery with a 3 (sham, partial lesion, lesion) x 2 (pre-surgery, post-surgery) mixed factor ANOVA. This analysis revealed an interaction between the factors, $F(2.00, 15.00) = 4.51, p = 0.029$, but the interaction was not due to a single groups' baseline preference changing significantly after surgery.

According to the matching law, perfect matching of initial link lever presses to the 3:1 terminal link reinforcer ratio would be 75% (Baum, 1979). As shown in Figure 10, preference slightly undermatched (0.87-0.95) the reinforcer magnitude ratio, which is consistent with stable preference between concurrent schedules differing in reinforcer magnitude (Landon et al., 2003).

We analyzed nose poking during the terminal link to assess control of behavior by the terminal link stimuli. First, we counted the number of nose pokes to the large and small reinforcer cups during each large reinforcer terminal link. Accuracy was measured as the percent of nose pokes to the large reinforcer side. The rats nose poked almost

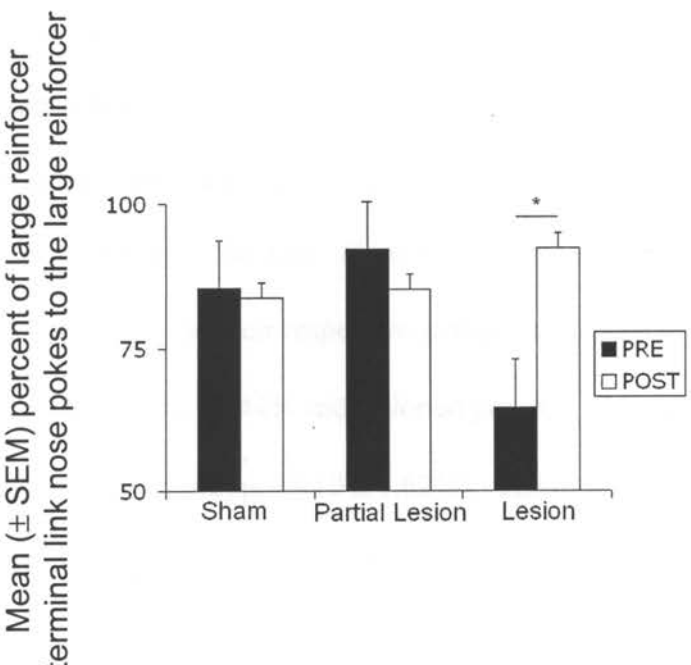
Figure 10. Mean (± SEM) percent choice of the large reinforcer side during initial links across the first 14 sessions of concurrent chains training. After a 16-s delay, 150-or 50-μl 25% sucrose solution was delivered to the troughs underlying the large and small reinforcer levers, respectively. Rats received an equal number of large and small reinforcers each session. Pre-training surgery (*top*) occurred prior to any training and post-training surgery (*bottom*) occurred after stable preference was acquired; the data in the bottom panel are from non-operated rats. B1, preference over the first five stable sessions; B2, post-surgery baseline preference.


Pre-Training Surgery
Sham (N=11)
Partial Lesion (N=5)
Lesion (N=7)
Post-Training Surgery
Sham (N=8)
Partial Lesion (N=5)
Lesion (N=5)
Mean (± SEM) percent choice: large reinforcer side
90
80
70
60
50
80
70
60
50
4
8
12
B1
B2
Session

exclusively during the first, second, and last 2 s of the terminal link, so accuracy was assessed within these time bins. A 2 (PRE, POST) x 3 (group: sham, partial lesion, lesion) x 3 (time: first 2 s, second 2 s, last 2 s of the terminal link) mixed-factor ANOVA revealed a three-way interaction, $F(4, 56) = 3.61$, $p = 0.01$, a PRE, POST x group interaction, $F(2, 28) = 6.12$, $p = 0.006$, and a main effect of time, $F(2, 56) = 28.56$, $p < 0.001$. Three lesioned and 4 sham PRE rats failed to nose poke during either the first or last 2 s and were therefore excluded from the analysis. We never observed sucrose in the reinforcer cups at the end of the session, suggesting that these rats consumed the reinforcer, but did not put their noses in the cup before it was delivered. The rats directed a greater percentage of their nose pokes to the reinforced side during the first relative to the second and last 2 s of the terminal link (mean ± SEM: first 2 s, 94.4 ± 2.3%, second 2 s, 80.0 ± 2.2%, last 2 s, 77.3 ± 2.9%). The PRE, POST x group interaction reflected that PRE lesioned rats directed a lower percentage of their nose pokes to the reinforced cup than POST lesioned rats, which did not differ from any other group (Figure 11). This suggests that pre-training lesions may have disrupted the acquisition of behavioral control by the terminal link stimuli. The three-way interaction reflected that PRE lesioned rats had the lowest percentages during the second and last 2 s of the terminal link. The groups did not differ in the rate of terminal link nose pokes per session.

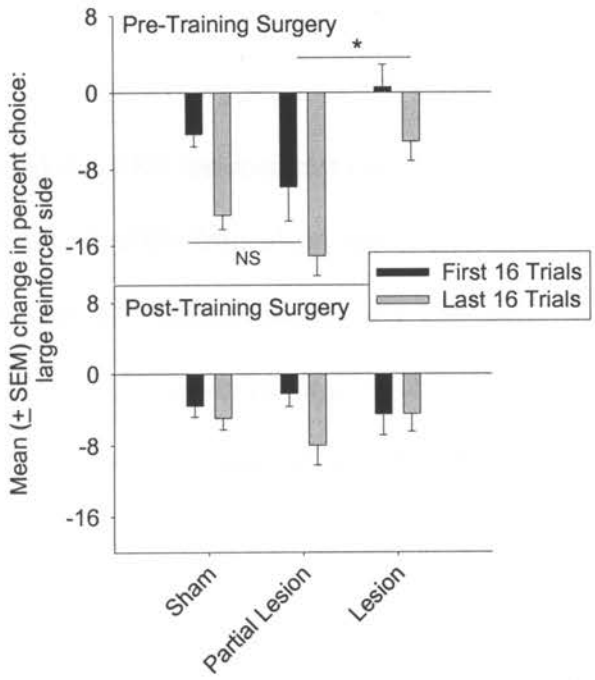
Appendix 2 lists individual rats' preference for the large reinforcer initial link during each baseline and reversal session. To analyze the changes in preference during reinforcer magnitude reversal, we calculated percent choice of the large reinforcer side

Figure 11. Mean (± SEM) percent of nose pokes to the large reinforcer side during seconds 1-2, 3-4 and 15-16 of the 16-s terminal link preceding delivery of the large reinforcer. * $p < 0.05$


Mean (± SEM) percent of large reinforcer terminal link nose pokes to the large reinforcer
100
75
50
*
PRE
POST
Sham
Partial Lesion
Lesion

during the first and last 16-trial bins completed by each subject during each reversal session. Eight trials is the smallest unit over which the assigned number of reinforcers was equal between the alternatives. Preference tended to change non-monotonically when measured locally (i.e., 8-trial bins), which is consistent with previous analyses (e.g., Grace & McLean, 2006). Greater regularity in the patterns of time-dependent changes in preference emerged when 16-trial bins, rather than 8-trial bins, were analyzed. One lesioned and one sham PRE rat were excluded from this analysis because they completed fewer than 16 trials for some reversals (trials completed for reversals 1-3 for the lesioned rat and sham rat, respectively: 15, 10, 21 and 20, 13, 22). Excluding these two individuals was necessary for analyzing changes in preference over time, but unlikely to alter the conclusions drawn from the data. These two subjects exhibited overall changes in preference that were similar to their respective groups (mean ± SEM change in preference: lesioned individual, –2.44% and lesioned group, –1.31 ± 2.10%; sham individual, –14.25% and sham group, –8.10 ± 1.62%). The mean (± SEM) trials completed averaged over the three reversal sessions for each subject did not differ between the groups (PRE groups: sham, 47.64 ± 4.14, 45.00 ± 5.00, 53.73 ± 3.86; partial lesion, 59.40 ± 6.14, 61.20 ± 7.41, 56.80 ± 5.72; lesion, 46.57 ± 5.19, 50.57 ± 6.26, 52.14 ± 4.84; POST groups: sham, 52.67 ± 2.65, 50.00 ± 5.69, 51.44 ± 6.85; partial lesion, 48.00 ± 6.14, 42.60 ± 7.41; 37.60 ± 5.72; lesion, 55.64 ± 3.08, 52.36 ± 4.33, 46.36 ± 6.51). The reinforcer magnitudes were reversed three times, but the data were collapsed across the three repetitions because a 2 (PRE, POST) x 3 (sham, partial lesion, lesion) x 3 (repetition) x 2 (first and last 16-trial bin) mixed factor ANOVA for preference indicated no main effects or interactions involving repetition. Preference during each 16-trial bin

Figure 12. Mean (± SEM) decrease in percent of initial link lever presses to the originally large reinforcer lever after the 150- and 50-μl reinforcer magnitudes were unpredictably reversed for a single session, collapsed across the three repetitions of the reversal. Preference during the reversal session was calculated from the first and last 16-trial and subtracted from mean preference across all completed trials from the immediately preceding baseline session. Rats received excitotoxic or sham lesions of the BLA before any training (*left*; sham, N=11; partial lesion, N=5; lesion, N=7) or after stable baseline preference was acquired, but before reinforcer magnitude reversals (*right*; sham, N=8; partial lesion, N=5; lesion, N=5). The horizontal lines are used to illustrate differences between the groups; PRE BLA-lesioned rats decreased their preference less than PRE partially lesioned rats, but partially lesioned rats did not differ from sham rats (*, significant; NS, not significant).


Pre-Training Surgery
Post-Training Surgery
Mean (± SEM) change in percent choice: large reinforcer side
8
0
-8
-16
*
NS
First 16 Trials
Last 16 Trials
Sham
Partial Lesion
Lesion

was subtracted from preference during the preceding baseline session to produce Figure 12.

Preference changed more during the last than the first set of 16 trials as indicated by a main effect of trial bin, $F(2, 33) = 10.79, p = 0.002$. Changes in preference over time were unique to reversal sessions and not observed during baseline sessions. Although Figure 12 suggests that POST lesioned rats did not follow this pattern, there were no significant interactions involving trial bin. An interaction between experiment (PRE, POST) and group, $F(2, 33) = 3.86, p = 0.03$, and Bonferroni-corrected pairwise comparisons, indicated that PRE lesioned rats changed their preference less than partially lesioned rats, which did not differ from sham rats. PRE partial lesion subjects' decrease in preference was greater, although not statistically, than PRE sham subjects, so that the difference between PRE partial lesion and lesion subjects reached significance. That the difference between PRE sham and lesioned subjects did not reach significance is probably due to measurement error resulting from small sample size. This suggests that only lesioning the BLA prior to training blunted changes in preference when the reinforcer magnitudes were reversed. No other pairwise comparisons were significantly different; apparent differences in preference change between the experiments are therefore due to random error rather than systematic treatment differences.

Table 9 lists the left and right lesion sizes, mean lesion sizes, and change in preference in the first and last 16 trials for PRE and POST rats. Pearson's correlations indicated that mean lesion size did not correlate with change in preference during the first 16 trials of the reversal session for PRE rats ($r^2 = 0.44, p = 0.11$), but did for POST rats

Table 9. Lesion size, approximate location within the basolateral amygdala, and change in preference from baseline to reversal of reinforcer magnitudes for each subject.

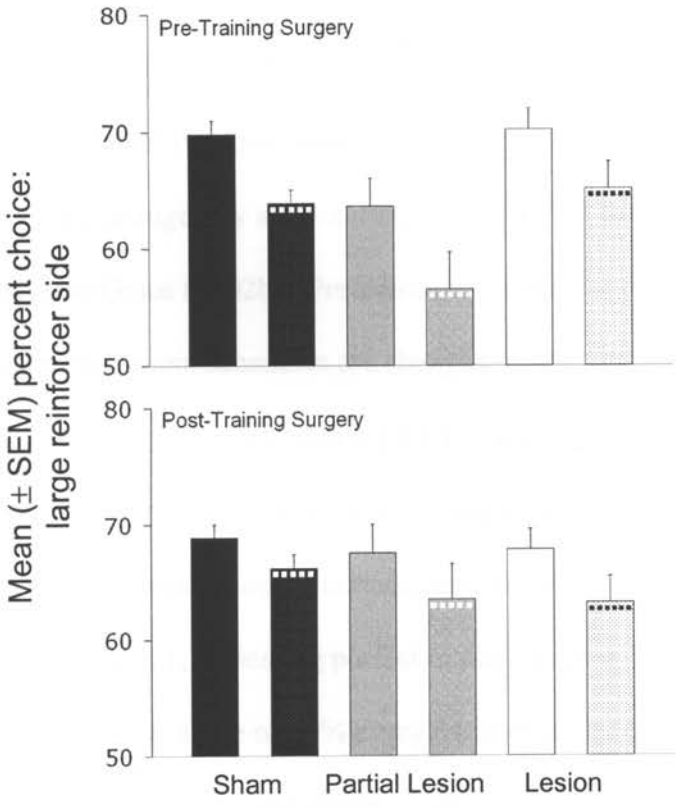
Rat	Lesion Size			Lesion Location	First 16 Trials	Last 16 Trials
	Left	Right	Mean			
Pre-Training Surgery						
I2	25%	80%	52.5%	Anteroventral	3.79	6.11
J9	21%	87%	54.0%	Anteroventral	11.62	-4.55
K2	49%	47%	48.0%	Anteroventral	4.83	-19.07
K10	23%	87%	55.0%	Posterior	3.57	-7.15
K12	9%	87%	48.0%	Posterior	-2.44	—
K15	27%	69%	48.0%	Anteroventral	-5.83	1.88
K16	24%	65%	44.5%	Anterior	-1.58	-9.39
Post-Training Surgery						
M3	85%	57%	71.0%	Ventral	5.63	.45
M12	58%	89%	73.5%	Throughout	6.53	-.04
M13	71%	39%	55.0%	Anteroventral	-5.55	-3.24
M15	46%	17%	31.5%	Posterior	-21.94	-17.29
M20	29%	48%	38.5%	Dorsomedial	-7.26	-2.34

—, completed < 32 trials

($r^2 = 0.88, p = 0.02$). Scatterplots indicated that for POST rats, smaller lesions were associated with a greater change in preference in the first 16 trials of the reversal session. If lesion size was related to the magnitude of preference change after reinforcer magnitude reversal, the relationship should be maintained through the last 16 trials completed by each subject. This was not the case, however (PRE: $r^2 = 0.08$; POST, $r^2 = 0.61$), suggesting that the significant correlation between lesion size and change in preference for the first 16 trials was spurious. One would usually expect larger, not smaller, lesions to have the greatest effect on behavior. The significant correlation seems to reflect variability in the POST lesion sample that is not actually due to the lesion treatment, since their performance overlapped with sham and partial lesion subjects. There is no clear relationship between the approximate lesion location and the change in preference when the reinforcer magnitudes were reversed, nor is there a relationship between asymmetries in lesion size and this measure (Table 9). Most of the lesions for PRE rats were in the anterior BLA and somewhat focused on the ventral portions. The lesions for POST rats were spread evenly throughout the BLA.

Reinforcer ratios from previous sessions have been shown to affect subsequent preference (Schofield & Davison, 1997). Baseline preference during the sessions immediately preceding and following the reinforcer magnitude reversal was analyzed with a 2 (PRE, POST) x 3 (sham, partial lesion, lesion) x 2 (session type: pre-reversal, post-reversal) x 3 (repetition) mixed factor ANOVA. Only the main effect of session type was significant, $F(1.00, 34.00) = 59.04, p < 0.001$, as pre-reversal baseline preference was greater than post-reversal baseline preference (Figure 13).

Figure 13. Mean (± SEM) percent of initial link lever presses to the originally large reinforcer lever before (solid) and after (stippled) the 150- and 50-μl reinforcer magnitudes were unpredictably reversed for a single session, collapsed across the three repetitions of the reversal. Rats received excitotoxic or sham lesions of the BLA before any training (*top*; sham, N=11; partial lesion, N=5; lesion, N=7) or after stable baseline preference was acquired, but before reinforcer magnitude reversals (*bottom*; sham, N=8; partial lesion, N=5; lesion, N=5).


Pre-Training Surgery
Post-Training Surgery
Mean (± SEM) percent choice: large reinforcer side
80
70
60
50
Sham
Partial Lesion
Lesion

The absence of group differences indicates that neither pre- nor post-training BLA lesions affected the processes by which past reinforcer ratios influence current preference.

Discussion

This is the first report about the effects of BLA lesions on learning in concurrent chains schedules. Despite the complexity of the reinforcement schedule, BLA lesions did not impair learning, which is consistent with previous reports employing simple chain or concurrent schedules of reinforcement (e.g., Balleine et al., 2003).

Preference changed by approximately 10% by the last 16 trials of the reversal session, similar to Grace (2002b). Preference changed less than when the reinforcer magnitudes for concurrent schedules are changed every 10 trials (Davison & Baum, 2000). Davison and Baum report that pigeons increasingly matched their response ratios to the ratio of reinforcer magnitudes, approaching sensitivity values of .2-.4 after 10 trials. Assuming a constant rate of increase in sensitivity with each reinforcer, sensitivity values would approach 1, indicating perfect matching, after 25 to 50 trials (Baum, 1969). If preference changes at a rate of 10% every 64 trials in the current protocol, the rats should approach perfect matching approximately four sessions after the magnitude reversal, or in 256 trials. This time scale of preference change would be similar to pigeons' changes in preference in concurrent chains schedules when the terminal link FI schedules reverse (Grace, 2002b).

Only lesions induced prior to any training blunted changes in preference when reinforcer magnitudes reversed. PRE lesioned rats changed their preference to some extent, suggesting that they might eventually completely reverse their preference, but

after a greater number of trials than non-lesioned rats and rats with lesions induced after baseline training. The difference in preference change between PRE and POST rats parallels the results of Hatfield et al. (1996) and Pickens et al. (2003). In their protocol, after Pavlovian conditioning between a light and food, the food was devalued by pairing its consumption with an injection of lithium chloride. When the BLA was lesioned after Pavlovian conditioning, the rats decreased their conditioned responding to the light, as did non-lesioned rats (Pickens et al., 2003). When the BLA was lesioned before Pavlovian conditioning, the rats failed to decrease their conditioned responding to the light (Hatfield et al., 1996). Pre-training BLA lesions also impair decreases in instrumental responding for a reinforcer with which rats have been satiated, known as sensory-specific satiety (Balleine et al., 2003). These data extend previous reports indicating that the BLA is involved in behavioral adaptation to decreases in reinforcer value by showing that the BLA supports changes in choice behavior, in this case after changes in reinforcer magnitude.

Reversing the magnitudes decreased preference for the large reinforcer side even after the original contingencies were reinstated. Baseline preference after the reversal was lower than baseline preference before the reversal for all the groups. This suggests that the BLA does not contribute to rats' estimation of past reinforcement used to determine current preference. The reversal was detected by PRE lesioned rats, but expression of this reversal in behavior was delayed, perhaps because distinct neural processes support changes in preference and the carryover of past reinforcement to current preference.

All of these conclusions must be qualified by acknowledging that only half of the BLA was lesioned on average. Figure 8 indicates that the lateral amygdala was lesioned most often, whereas the basal and accessory basal nuclei were mostly, but not completely, spared. Future experiments are needed to address the effects of larger BLA lesions, and whether pharmacological treatments in the lateral amygdala could dose-dependently impair changes in preference when reinforcer properties are manipulated.

These data suggest, however, that the BLA performs a specific function in supporting changes in preference when reinforcer magnitudes reverse. Only pre-training BLA lesions disrupted changes in preference, implying that the BLA might engage neural systems during learning that mediate behavioral adaptation to changes in reinforcement. For example, during acquisition and reversal of odor discriminations, communication between the BLA and OFC contributes to the differential firing of BLA neurons when odors predicting sucrose or quinine are presented; communication with the OFC also supports changes in BLA neuron firing when the odor-outcome relationships are reversed (Saddoris, Gallagher, & Schoenbaum, 2005). Disconnection of the BLA and OFC prevented monkeys from adapting their choices when satiated on one of the reinforcers (Baxter et al., 2000), and OFC lesions prevented rats from changing their approach behavior when a reinforcer was devalued with lithium chloride (Pickens et al., 2003). Future studies could address whether an interaction between the OFC and BLA also supports behavioral adaptation when value is manipulated by changing the physical properties of the reinforcer rather than the animal's motivation.

The reinforcer devaluation protocol, using lithium chloride-induced conditioned taste aversion or sensory-specific satiety, has been used in a series of lesion studies to

map the circuits underlying behavioral adaptation to changes in reinforcer value. Implicated structures include the NAc core (Corbit, Muir, & Balleine, 2001), dorsal striatum (Yin, Knowlton, & Balleine, 2004; Yin et al., 2005), BLA (Balleine et al., 2003), prelimbic medial prefrontal cortex (Balleine & Dickinson, 1998a; Corbit & Balleine, 2003), gustatory cortex (Balleine & Dickinson, 2000), and mediodorsal thalamus (Corbit, Muir, & Balleine, 2003) (for a review, see Balleine, 2005). It is possible that the BLA lesions in the current study disrupted processing in downstream regions, such as the NAc or OFC, and that these regions are critical for the adaptation of choice to reinforcer magnitude reversal. Future studies are necessary to determine whether lesions to downstream structures disrupt changes in choice when reinforcer magnitudes reverse.

Researchers have assumed that studies of choice in transition will provide information about both the processes supporting preference acquisition and animals' matching of response allocation to reinforcers between concurrent schedules of reinforcement (e.g., Grace, 2002a). With respect to the former, our data show that pre-training BLA lesions do not affect preference acquisition, but do affect rats' changes in choice behavior after reversal of the reinforcer magnitudes. In addition, the lesions did not affect the influence of past reinforcement contingencies on current choice. This suggests that unique processes underlie preference acquisition, the influence of past reinforcement contingencies, and preference change. BLA activity appears to support the latter, perhaps by allowing animals to learn about various attributes of reinforcers that provide a basis for rapid discrimination of changes.

When the BLA is lesioned during acquisition, the reinforcing effects of sucrose are intact, but rats may fail to learn about sensory input associated with the reinforcer,

e.g., oral sensations, that also change when the magnitudes reverse. For example, a Pavlovian CS paired with food pellets or sucrose increases rats' lever pressing for either reinforcer (Pavlovian-instrumental transfer), an effect that is disrupted by CeN but not BLA lesions (Corbit & Balleine, 2005). Lever pressing is increased more if the CS was paired with the same reinforcer that is a consequence of lever pressing, an effect that is disrupted by BLA but not CeN lesions (Corbit & Balleine, 2005). In order for Pavlovian-instrumental transfer to be reinforcer specific, the reinforcers must be discriminated. Since the transfer itself does not require the BLA, this suggests that the BLA is specifically involved in associating attributes of sensory stimulation with reinforcement that provide a basis for discrimination. In the current study, the BLA may not be involved in the discrimination of magnitude reversal itself, since post-training lesions did not retard changes in preference when the reinforcer magnitudes were reversed. Rather, the BLA needed to be present during learning in order for the rats to learn about the sensory differences between the reinforcers that would later be reversed. This predicts that normal performance on any task requiring a discrimination of primary or conditioned reinforcers will require an intact BLA when the reinforcer is presented.

What features of the reinforcers provided a basis for discriminating the reversal is unclear. A pilot investigation (data not shown) indicated that reversing just the tone frequencies decreased preference for the large reinforcer side, indicating that the tone is probably a factor influencing preference in this protocol. Our data suggest that the BLA lesions may have prevented rats from learning the tone frequency-sucrose magnitude relationship, since PRE lesioned rats nose poked less accurately during the terminal link. The passage of time, however, also served as a stimulus that may have controlled nose

poke accuracy, although there is no evidence that the amygdala is involved in timing. The BLA is, however, well known for its role in conditioned reinforcement, which relies on stimulus-reinforcer relationships (Everitt et al., 2003). Pre-training BLA lesions may therefore have decreased rats' learning about the tone-reinforcer relationship, and prevented them from discriminating changes in this relationship that could have contributed to changes in choice in normal rats. Future studies could compare the role of the BLA in changes in preference when properties of the conditioned and primary reinforcers change independently.

The selectivity of the lesion effects suggests that distinct neural systems underlie preference acquisition, memory for past reinforcement, and sensitivity to contingency changes. Variability in reinforcement contingencies is a fundamental feature of the natural world to which animals seem exquisitely sensitive. Identifying the neural bases for the control of behavior by reinforcement contingencies when they are stable and following a disruption is a basic problem. The answers to this problem could inform the causes of disorders of choice behavior. Overall, the BLA appears to support behavioral adaptation under various training conditions and changes in reinforcer properties, which suggests that the BLA has a prominent role in decision making involving the evaluation of alternatives along multiple dimensions, such as incentive value (Balleine et al., 2003; Wang et al., 2005), immediacy (Winstanley et al., 2004), possibly reinforcer quality (Schoenbaum et al., 2003) and magnitude, as suggested by the current data.

Appendix 2

Table 10. Percent of initial link lever presses to the large reinforcer side during post-surgery baseline (BL) sessions, and during the three repetitions of the reinforcer magnitude reversal (Rev) for sham and partially lesioned rats experiencing surgery prior to training.

	Sham											Partial Lesion				
Rat	J2	J3	J5	J8	K1	K3	K5	K6	K7	K11	K14	G2	G5	J1	J6	K4
BL	75.8	65.8	82.0	62.2	78.0	70.7	64.4	82.6	73.1	71.8	77.2	62.9	72.0	48.0	72.6	71.2
BL	68.9	61.0	73.8	63.5	72.1	73.0	61.7	75.4	73.7	74.4	79.2	62.2	74.7	46.5	77.0	66.9
BL	77.1	65.2	78.2	60.1	76.2	66.0	67.7	81.4	77.0	70.6	80.1	68.0	69.3	44.5	76.6	64.1
BL	71.7	66.2	74.5	65.0	76.3	63.3	65.9	77.8	74.6	67.5	79.7	62.8	67.9	49.3	71.7	75.5
BL	71.8	66.6	67.8	61.8	79.3	68.5	63.3	82.5	73.9	69.3	76.8	69.0	72.6	46.5	75.6	69.0
Rev-1	71.4	59.4	67.8	61.7	84.8	60.5	53.1	70.6	67.8	52.6	71.5	62.7	57.9	38.3	77.5	58.8
BL	67.1	59.3	64.3	58.3	76.4	61.5	48.5	64.1	75.5	55.5	64.8	57.5	54.4	44.0	65.3	54.5
BL	67.2	66.6	70.6	53.8	75.0	55.9	49.5	73.9	71.7	59.6	75.8	67.4	62.7	47.7	71.0	68.4
BL	61.9	65.4	74.4	52.4	73.9	59.6	57.2	76.2	74.3	61.9	65.2	66.0	64.6	54.2	73.4	68.6

Table 10: continued

BL		72.2	77.8	53.6	62.0		60.5	76.8	74.3	66.1		66.0				
Rev-2	56.1	61.9	63.2	60.7	59.7	61.2	51.8	60.2	69.9	54.2	61.6	591	48.3	38.7	64.2	54.0
BL	67.1	66.9	72.2	61.0	64.0	65.4	44.9	65.8	65.4	54.1	70.1	57.6	61.8	44.9	67.8	61.7
BL	52.9	67.0	73.1	69.5	61.2	61.3	61.2	70.2	62.7	74.7	75.7	62.2	62.4	45.2	69.5	66.5
BL	58.3	74.2	77.3	66.8	76.6	59.8	62.3	71.5	65.8	66.9	82.0	66.6	52.8	43.5	74.3	69.7
BL	63.9			70.5		65.3					81.6		56.1	53.9	78.2	69.9
Rev-3	70.7	61.7	56.9	50.5	74.0	59.8	57.4	62.3	69.6	54.7	80.5	59.7	53.6	36.7	75.1	56.9
BL	69.2	61.9	66.7	61.4	70.2	66.5	61.3	64.4	70.3	66.0	58.9	71.0	53.7	46.6	69.7	62.5
BL	75.0	64.4	61.6	57.6	60.3	69.4	76.4	69.5	64.3	70.0	70.7	66.7	50.2	52.3	69.5	52.9
BL	-	70.5	67.0	61.3	54.8	68.2	64.8	72.6	60.6	76.4	54.0	66.5	51.8	40.0	59.9	63.9

Table 11. Percent of initial link lever presses to the large reinforcer side during post-surgery baseline (BL) sessions, and during the three repetitions of the reinforcer magnitude reversal (Rev) for lesioned rats.

	Lesion						
Rat	I2	J9	K2	K10	K12	K15	K16
BL	68.9	63.0	68.7	75.5	78.7	64.7	72.0
BL	68.1	63.0	68.5	83.7	78.6	55.7	78.7
BL	70.5	68.3	72.3	75.5	81.0	64.3	75.3
BL	60.4	63.4	73.3	81.2	79.8	64.5	71.3
BL	61.1	63.1	68.3	81.0	78.2	61.4	72.8
Rev-1	53.9	68.0	64.1	80.7	77.3	60.4	62.9
BL	56.4	48.8	57.5	72.2	79.1	53.0	68.0
BL	57.1	56.1	68.3	73.1	82.4	61.8	70.9
BL	42.9	57.5	64.1	80.4	89.7	64.9	66.8
BL	43.3	56.9	66.1	81.4			69.8
Rev-2	48.2	60.2	57.4	73.9	81.0	63.7	68.7
BL	52.7	51.9	55.3	82.5	82.9	65.0	76.0
BL	46.8	63.2	57.1	78.0	82.2	65.6	72.7
BL	50.0		58.1	72.8	80.1	74.8	74.6
BL					76.7	67.3	
Rev-3	54.9	60.2	50.7	73.3	77.6	64.2	64.2
BL	53.0	53.7	58.7	78.4	65.6	57.0	82.9
BL	-	65.5	50.9	70.6	67.5	56.6	78.2
BL	-	63.1	50.5	77.2	75.3	55.4	75.6

Table 12. Percent of initial link lever presses to the large reinforcer side during baseline (BL) pre-surgery sessions, post-surgery sessions, and during the three repetitions of the reinforcer magnitude reversal (Rev) for sham, partially lesioned, and lesioned rats experiencing surgery after attaining stable baseline preference.

	Sham								Partial Lesion					Lesion				
Rat	M1	M5	M6	M7	M11	M16	M17	M18	M4	M9	M10	M14	M19	M3	M12	M13	M15	M20
								Pre-Surgery										
BL	68.5	73.2	68.5	62.6	73.3	85.7	54.8	63.6	67.9	74.3	72.9	73.8	73.1	76.8	67.8	75.9	64.8	77.7
BL	65.2	71.8	72.8	61.7	65.6	83.5	58.2	59.3	71.7	68.1	72.4	77.6	70.9	75.3	67.5	71.2	70.0	75.7
BL	68.1	68.1	67.0	62.5	69.0	79.5	56.2	62.9	66.4	68.5	73.0	71.8	72.3	74.6	71.1	69.0	68.7	74.2
BL	74.3	71.0	70.2	55.8	72.5	85.3	55.7	63.5	67.2	72.5	74.3	72.5	67.8	75.5	66.3	74.1	69.2	77.1
BL	71.8	68.7	70.2	60.9	71.3	85.2	56.0	62.3	72.4	73.5	73.8	73.4	67.7	76.2	71.3	76.1	64.9	77.0
								Post-Surgery										
BL	68.7	63.0	79.2	64.2	75.1	75.0	59.6	62.1	69.3	73.8	63.2	61.8	72.7	79.6	66.3	75.5	69.1	82.8
BL	67.8	67.4	76.9	66.1	73.2	67.4	58.0	47.5	63.1	73.8	50.0	63.9	65.1	74.6	60.0	75.4	68.2	78.2
BL	68.7	69.9	74.6	69.6	74.3	71.2	57.8	61.5	61.0	71.7	62.2	70.7	62.6	64.3	61.7	70.1	69.8	75.5

Table 12: continued

BL	67.5	79.6	78.3	61.8	68.8	72.9	73.7	63.4	65.5	74.3	59.7	56.7	64.0	65.3	64.4	75.0	66.0	74.5
BL	75.4	74.0	73.1	64.2	71.0	79.2	71.8	58	61.4	71.8	73.8	70.0	56.5	70.4	61.7	73.9	61.6	73.3
BL	70.1	74.0	68.5		70.1	78.8	66.8	52.8	67.2		57.4	71.4	59.6	72.2	60.8		62.7	72.5
BL		76.2	74.6			81.1	70.3	57.9	73.2		60.0	65.8	61.7	70.8			65.2	71.1
BL		75.0				84.6	60.5		66.6		61.0	80.7					72.2	69.1
BL		73.8				85.6	67.2		69.5		56.8	76.0					63.9	69.4
BL							64.7		68.8		51.7	75.0					65.7	
BL											61.9	75.9					61.8	
BL											55.6	74.7					64.3	
BL											65.4	74.5					69.3	
BL											63.1	72.4					67.1	
BL											66.4	78.7						
BL											75.3	66.3						
BL											64.0	71.6						

Table 12: continued

BL											69.0								
Rev-1	64.5	78.7	70.9	61.0	61.9	75.8	69.9	46.7	62.1	65.6	65.0	69.8	57.6	74.5	66.2	77.9	58.5	68.0	
BL	66.6	71.8	66.0	70.4	83.8	77.9	63.1	53.8	66.1	61.1	68.3	69.2	50.7	71.6	63.4	66.1	58.7	58.1	
BL	66.4	74.9	70.5	64.1	71.8	80.1	67.4	52.3	64.9	76.3	63.0	65.9	53.6	73.2	67.3	70.9	62.9	65.2	
BL	74.6	79.3	71.9	59.8	70.5	81.8	65.3	55.5	66.0	69.9	66.4	71.7	63.2	71.3	73.7	74.6	58.3	66.6	
BL	70.4	79.1		59.7		80.4									70.0	67.3	60.8	70.8	
Rev-2	53.6	71.9	73.2	57.7	68.6	77.8	61.2	55.5	59.9	63.7	67.3	61.2	60.4	64.6	70.3	67.1	52.4	64.3	
BL	59.4	75.6	69.7	67.1	76.5	81.2	63.4	56.1	67.6	58.0	62.8	66.5	67.0	63.6	59.7	63.4	56.3	73.3	
BL	64.2	72.0	69.2	65.6	67.2	80.4	54.3	66.0	58.1	63.2	64.7	69.7	64.3	70.5	67.1	64.4	60.3	62.2	
BL	67.3	77.7	74.9	64.0	66.8	77.8	65.3	63.6	69.8	66.0	62.2	72.8	70.2	62.5	74.0	66.4	55.8	72.2	
BL			68.7		66.0		55.4	61.3	64.5	67.3	55.3	72.9	73.3	67.0					
Rev-3	58.5	71.9	68.9	59.1	58.3	63.8	52.1	66.2	55.9	60.3	60.4	70.1	50.4	74.4	61.1	64.6	50.6	63.5	
BL	64.0	73.5	64.6	67.4	61.5	78.9	45.9	60.9	61.8	63.7	55.2	66.5	67.5	68.1	65.4	62.1	51.1	66.8	
BL	69.7	76.0	63.2	68.1	60.5	77.0	46.3	54.5	55.7	71.3	61.2	67.2	62.4	67.3	65.1	58.0	52.6	64.4	

Table 12: continued

BL	67.7	81.6	72.0	63.5	63.1	80.2	46.8	59.3	60.9	76.9	60	69.6	68.8	73.3	63.1	52.9	52.4	61.2

GENERAL DISCUSSION

The data in this thesis are the first addressing choice in transition in concurrent chains schedules in rats. The few previous studies have used pigeons. In addition, these are the first studies investigating the neural systems supporting preference acquisition and choice in transition in concurrent chains schedules. Concurrent chains schedules approximate the schedules of reinforcement supporting much of human behavior, which usually involves chains of responses ending in conditioned reinforcement, and eventually a primary reinforcer. For example, modern humans generally work for money. Most of the things necessary for us to live, including food and shelter, are obtained by exchanging money. Money has no intrinsic value; its value is learned as we practice exchanging it for goods and services. Thus, human choices take place in an economic environment for which primary reinforcers are only infrequently the outcome. Using concurrent chains schedules to evaluate the neural systems involved in choice in transition in rodents may provide information about how humans adjust their choices when contingencies change in the complex schedules supporting much of our behavior.

Since choice in transition in concurrent chains schedules had not been studied in rodents, the first set of experiments evaluated rats' sensitivity to changes in reinforcement contingencies. The independent variables were designed for follow-up studies with BLA lesions, and therefore aimed to evaluate theories about BLA function. Researchers have argued that the BLA allows the sensory features of "emotional events", including primary and conditioned reinforcers, to selectively influence behavior (e.g., Blundell et al., 2001; Balleine & Killcross, 2006). Primary and conditioned reinforcers influence initial link

preference in concurrent chains schedules (Ploog, 2001; Grace, 2002b). The protocol used in this thesis allowed changes in choice to be measured following manipulation of various features of primary and conditioned reinforcers using the same protocol. The features that were parametrically manipulated included 1) the terminal link stimulus (conditioned reinforcer) frequency, 2) the immediacy of the stimulus from terminal link entry, and 3) the reinforcer taste.

The rats were trained until they exhibited stable preference in a concurrent chains schedule for which the terminal links delivered large or small sucrose reinforcers. In one condition, I modulated the kHz value of the terminal link stimulus preceding the large reinforcer to approximate the kHz value preceding the small reinforcer. In other conditions, I delayed onset of the terminal link stimulus preceding the large reinforcer, and added various concentrations of a bitter substance, quinine, to the large reinforcer. I predicted that the greater the deviation of the independent variable level from baseline, the more preference should shift away from the large reinforcer side. I hypothesized that BLA lesions would flatten the generalization gradient. This was to be a strong test of the hypothesis that the BLA encodes the sensory attributes of reinforcing alternatives. However, before I could conduct the lesion studies I found that the rats were strikingly insensitive to all of these manipulations.

My protocol was inspired by Armony et al. (1997), who measured the suppression of lever pressing for food in the presence of an auditory CS predicting shock as the CS increasingly deviated from its training frequency. Armony et al. showed a systematic generalization gradient that was not affected by auditory cortex lesions. Omitting the auditory cortex requires that all auditory input to the amygdala arise from the auditory

thalamus. Auditory thalamus neurons are broadly tuned, i.e., indiscriminate with respect to variations in stimulus properties; auditory cortex neurons, on the other hand, are more discriminating. Contrary to previous theories (Jarrell et al., 1987; LeDoux, 1996), auditory cortex lesions did not disrupt discrimination and generalization of CS control. Armony et al. suggested that the auditory cortex may contribute only when stimuli are more complex, and that coordinated neuronal activity may have allowed the relatively indiscriminate neurons of the auditory thalamus to support frequency discrimination. The amygdala is a downstream target of the auditory thalamus and a structure supporting conditioned suppression (e.g., Selden et al., 1991; Lee, Dickinson, & Everitt, 2005), and should therefore be sensitive to variability in CS properties. Indeed, neurons in the BLA respond to conditioned stimuli that predict cocaine (e.g., Carelli, Williams, & Hollander, 2003). How BLA neuron responses change as CS properties vary has not been studied.

I aimed to replicate Armony et al.'s (1997) generalization gradient in concurrent chains schedules by varying the terminal link stimulus frequency. In natural environments, the physical properties of stimuli or animals' perception of them vary. For example, a particular foraging patch may look different depending on the time of day or seasonally as the landscape shifts. Animals that fail to generalize are at a disadvantage: any change in the sensory properties of a foraging stimulus could disrupt its control over foraging behavior. On the other hand, animals that generalize with too shallow a gradient are also at a disadvantage, choosing according to reinforcement contingencies signaled by a stimulus only vaguely resembling the one present and therefore not currently available. In actuality, animals probably must be sensitive to variations in both the sensory properties of stimuli and their associated contingencies.

Rats' insensitivity to any of the three manipulations in the first experiment could be explained by several factors. Most obviously, these factors may be unimportant for choice behavior. Armony et al.'s (1997) generalization gradient for conditioned suppression may have been possible because CSs predicting threats strongly control behavior, as it may be necessary for survival in the short-term (one-trial learning: e.g., Liang et al., 1982). Appetitive behavior, however, is also controlled by differential sensory stimuli. As the wavelength of a key light deviates from the training stimulus, pigeons' response rates generalize (Blough, 1967). This also occurs when illumination is the consequence of key pecking rather than a discriminative stimulus indicating which response to perform (Thomas & Caronite, 1964). Rats discriminate between the amplitudes of 10 kHz tones predicting saccharin or nonreinforcement (Watanabe et al., 2001). Rats can also use noise pulse rates to navigate through a maze to obtain food reward, which affects neuronal response properties in the auditory cortex (Bao et al., 2004). It is likely, therefore, that the rats could perceive the tones used in the first study, and that these are capable of influencing choice behavior. Other procedural factors may have prevented the generalization of preference.

First, the rats' history with stable reinforcement contingencies may have prevented them from adapting to the manipulations. Acquisition of preference in concurrent chains required 20 or more training sessions. With a constant reinforcement schedule, animals' sensitivity to contingency changes is likely to be low; choice adapts faster when contingencies change more frequently (Mazur, 1997b). Perhaps preference was changing, but could not be detected within only two 64-trial sessions. This seems unlikely because rats' preference changed in a single session in the second experiment

and since studies of choice in transition typically show negatively accelerated shifts in preference toward a new asymptote, so that preference changes most dramatically immediately after the schedule change (e.g., Grace, 2002b; Mazur et al., 2001). Grace (2002b) used about 20 training sessions, reversed the terminal link FI schedules, and preference changed by approximately 10% by the first or second 72-trial session, with decreasing increments of preference change in later sessions, comparable to the second manuscript. Variability in the number of baseline sessions, rather than the number of tests sessions, more likely contributed to rats' insensitivity to the frequency manipulations.

Second, baseline preference was reacquired between manipulations for the first experiment. A variable number of sessions therefore occurred between each manipulation. The contribution of past reinforcement to current preference appears to be determined by an exponentially weighted moving average (Killeen, 1981; Devenport and Devenport, 1994; Mazur, 1996). If so, varying the number of intervening baseline sessions could have increased the variability in rats' perception of reinforcement contingencies from the recent past and therefore the background against which changes in contingencies were compared. In the second experiment, however, rats' preference changed under these conditions. The manipulation parameters rather than the baseline conditions were probably responsible for rats' insensitivity in the first experiment.

Insofar as terminal link stimulus value influences initial link preference in concurrent chains schedules (Williams & Fantino, 1978; Dunn & Fantino, 1982), delaying the stimulus onset should decrease preference similar to delaying primary reinforcement (Chung, 1965; Ainslie, 1975; Snycerski, Laraway, & Poling, 2005).

Delaying terminal link stimulus onset did not systematically affect preference. The rats could discriminate the onset of the terminal link since both lights above the levers shut off. Overall, the data seem to suggest that the terminal link auditory stimuli had very little influence on choice, a conclusion that is contradicted by data from the second experiment. Since the location of reinforcer delivery was constant throughout training, spatial stimuli may have overshadowed behavioral control by the tone. A protocol in which terminal link location is either constant (e.g., change-over protocol; Findley, 1958) or varies randomly (Ploog, 2001), could result in increased control by auditory stimuli so that delaying their onset for one alternative affects preference.

Perhaps most surprising was the failure of quinine to devalue the large reinforcer, since the solutions were bitter and discriminable according to human judgment. Slawecki and Samson (1998) reported very little change in consumption of 10% sucrose with the addition of 10, 50, or 100 μM quinine in male Long-Evans rats, but a large decrease in consumption when the sucrose concentration was decreased to 3% with 100 μM quinine, at least during the first presentation. Even increasing the concentration of quinine to 480 μM did not, however, consistently decrease preference for 25% sucrose. The sucrose concentration used in the first experiment (25%) is more than 8 times the concentration used by Slawecki and Samson, but the quinine concentration is not quite five times as great. Quinine concentrations approaching 1000 μM may be required to decrease the value of 25% sucrose in rats. The lack of change in preference with these manipulations prompted the second experiment, in which relatively extreme manipulations of the contingencies were introduced in an attempt to modify preference.

In the second experiment of the first manuscript, preference for the originally large reinforcer side decreased significantly when the reinforcer magnitudes, terminal link stimulus frequencies, or both, were reversed unpredictably for a single session. The magnitude of preference decreases did not differ between these treatments. Like Grace (2002b), however, maintaining the stimulus-reinforcer relationships by reversing both the reinforcer magnitudes and the tone frequencies tended to result in greater changes in preference. Reversing the tone frequencies decreased preference for the large reinforcer side, indicating that the terminal link stimuli also contributed to choice, but not for every rat. The second experiment therefore shows that conditioned and primary reinforcers contributed to initial link preference. An additional experiment indicated that rats' initial link preference was influenced by an additional property of the reinforcer, sucrose concentration. Reversing the reinforcer magnitudes had the most consistent effect, so the effects of BLA lesions on this manipulation were evaluated in the next set of experiments.

Once the protocol was established, the effects of BLA lesions could be assessed. But first, the lesions themselves had to be evaluated. The BLA receives multimodal sensory input from thalamic and cortical structures, and projects to the nucleus accumbens, a structure involved in modulating response output; it also has extensive connections with the prefrontal cortex (Sah et al., 2003). A survey of published images of BLA lesions reveals variability in the appearance of excitotoxic lesions. For example, Winstanley et al. (2004) illustrate an intact BLA approximately –2.80 mm posterior from bregma, but show a lesioned BLA from –1.88 mm; representative sham and lesioned images are usually taken from the same AP coordinate. The shape of the BLA differs

greatly at these two coordinates, so an uneducated viewer would be convinced that a lesion was present. In my view, Winstanley et al.'s image shows a small lesion of the BLA, mainly the medial portion, although they claim that the lesions encompassed the entire basolateral amygdala. Blundell et al. (2003) provide a clear illustration of an excitotoxic BLA lesion with obliterated borders and a loss of cell bodies, but compared to the sham image, the central nucleus also appears obliterated. The photomicrographs in this thesis most resemble those of Corbit and Balleine (2005), which show a loss of cell bodies and some distortion of shape in the BLA. In some studies, e.g. Touzani and Sclafani (2005), the BLA retains its shape but exhibits decreased cell density. The procedural factors that influence variability in lesion appearance are unclear. In general, however, the rate of successful lesions in this thesis is consistent with the published literature, although the lesions are somewhat smaller than typically reported.

In two separate experiments, rats received sham or excitotoxic BLA lesions before training (PRE) or after acquiring stable baseline preference (POST). The lesion sizes varied slightly between the experiments, with the primary difference being minor and unilateral damage to the central nucleus in the second experiment. The differential size of the lesions is probably due to using different anesthetics. Ketamine was used in the first experiment. Ketamine affects the NMDA binding site at the glutamate receptor and has been shown to protect neurons from glutamate toxicity and reduce the size of excitotoxic lesions (e.g., Lees, 1995). Quinolinic acid is a selective agonist at N-methyl-d-aspartate (NMDA)-type glutamate receptors (Stone, 1993). Neuronal swelling and degeneration, i.e., excitotoxicity, is caused by excessive release of excitatory amino acid neurotransmitters such as glutamate after NMDA receptors are stimulated (Choi, 1988).

In the second experiment, the rats were anesthetized with isoflurane, and every rat infused with quinolinic acid exhibited seizures after reviving from the anesthetic. The seizures were primarily facial, only occasionally involving the forelimbs or entire body. The seizures subsided within 24 hours. In the first experiment, for which ketamine was the anesthetic, none of the rats had seizures. In humans, amygdalotomy was initially used as a treatment for temporal lobe epilepsy, among other disorders including aggression and depression (Andersen, 1978). Stimulation of the amygdala with a protocol known as kindling can cause seizures, and is an animal model for epilepsy (McIntyre, 1979). Amygdala neurons are especially disposed toward generating seizures (Sarter & Markowitsch, 1985), which may cause retrograde amnesia (McDonough & Kesner, 1971). Pre- and post-surgery preference did not differ for the BLA-lesioned anesthetized with isoflurane suggesting that amnesia was not a factor in their performance.

On average, half of the BLA was damaged bilaterally for lesioned subjects in both experiments. Figure 12 in the second manuscript demonstrates that, relative to partially lesioned rats, rats with pre-training BLA lesions were retarded in adjusting their preference for the large reinforcer side during the sessions for which the small reinforcer was delivered to that location. Figure 12 and the supporting statistical analyses also show that rats with partial lesions of the BLA did not differ from intact rats, decreasing their preference when the reinforcer magnitudes were reversed to the same degree. When lesions were induced after baseline preference was acquired, preference shifted in all subjects to a similar degree. In order for the data to most convincingly reflect the pattern of data reported by Hatfield et al. (1996) and Pickens et al. (2003), PRE lesioned rats

should differ significantly from sham rats. This did not occur probably because of a lack of power. In addition, POST lesioned rats should decrease their preference for the large reinforcer side significantly more than PRE lesioned rats when the magnitudes are reversed. This also did not occur, probably because the magnitude of preference decrease for POST rats was generally less than for PRE rats, as discussed next.

The magnitude of preference change in sham and partially lesioned rats was somewhat greater for PRE relative to POST rats, although differences between them were not statistically significant. The reason for this variability is unclear, but may be traced to differences in the timing of the protocols shown in Table 4. POST rats necessarily experienced a greater number of training sessions than PRE rats because they attained stable baseline preference both before and after surgery. Having a greater number of baseline sessions could have decreased POST rats overall sensitivity to changes in reinforcement, so that the effects of group were evaluated within a narrower range of preference change compared to PRE rats. Mazur (1997b) showed that the number of baseline sessions influences pigeons' sensitivity to changes in reinforcement percentages; when they changed every 1-2 sessions, pigeons adjusted their preference more quickly than when they changed every 7-9 sessions. The protocol may be improved by obtaining stable preference twice in PRE rats, including a break during which free-feeding occurs in order to equate number of training sessions prior to reinforcer magnitude reversals for PRE and POST rats.

Nevertheless, the data from this thesis suggest three main conclusions. First, pre-training BLA did not affect preference acquisition. The rats with pre-training BLA lesions, however, directed a lower percentage of their nose pokes to the large reinforcer

cup during terminal links for which the large reinforcer was to be delivered, implying impaired stimulus control relative to the other groups. Second, pre-training, but not post-training, BLA lesions retarded the adaptation of choice behavior with reinforcer magnitude reversal. By the last 16 trials of the reversal session, PRE lesioned rats' preference for the originally large reinforcer side decreased, but was still significantly smaller than the magnitude of preference change apparent in partially lesioned PRE rats, which did not differ from sham rats. That preference changed slightly implies redundancy, albeit limited, in the circuits that support changes in choice, or could reflect variability in lesion size. Third, reversing the reinforcer magnitudes decreased baseline preference in the next session for which the magnitudes were returned to their original locations. This carryover of past reinforcer ratios to current preference did not differ between the groups. Thus, the processes involved in acquisition, carry-over, and behavioral adaptation to changes in consequences can be dissociated, with the BLA contributing to the latter.

That BLA lesions did not affect acquisition of preference is consistent with previous reports, since most reports have shown that the BLA is not critical for learning. Those suggesting that the BLA is necessary for the acquisition of CRs have used aversive USs (e.g., LeDoux, 2000). Even so, a CS predicting an aversive US can control behavior without the BLA. Killcross, Robbins, and Everitt (1997) demonstrated that CeN, but not BLA, lesions disrupted the suppression of operant responding for food in the presence of a CS previously paired with foot shock. In contrast, BLA, but not CeN, lesions disrupted avoidance of a lever that, when pressed, delivered a CS paired with foot shock (Killcross et al., 1997).

The BLA is involved in learning, however, when CSs are used as reinforcers (i.e., conditioned reinforcement) or when sensory stimuli must be used to predict the reinforcement contingencies (Balleine et al., 2003; Blundell et al., 2001; Corbit & Balleine, 2005). BLA lesions impair learning with conditioned reinforcement (e.g., Cador et al., 1989; Hatfield et al., 1996; Whitelaw et al., 1996; Burns et al., 1999; Parkinson et al., 2001) and second-order Pavlovian conditioning (Setlow et al., 2002). The data suggest that basic learning processes are intact when the BLA is damaged, but that the BLA has a specific role when a sensory stimulation such as a CS predicts a reinforcer. If, in the second manuscript, terminal link location had been randomized so that only the terminal link auditory stimuli predicted the upcoming reinforcer, the BLA lesions may have prevented rats from acquiring a preference for the initial link leading the large reinforcer.

To account for the role of the BLA in conditioned reinforcement but not reinforcement and learning in general, researchers have proposed that the BLA allows the sensory properties of motivational events to affect behavior (Balleine & Killcross, 2006). Sensory properties, in contrast to reinforcing efficacy or value, allow reinforcers to be discriminated. For example, I will pay $4.50 for a burrito. This suggests that the value, or utility, of a burrito and $4.50 are equivalent (e.g., Shizgal, 1997), but clearly they differ along several important dimensions. One of them can be lunch; the other is just paper and metal. The products humans typically consume vary along subtle dimensions, e.g., brands of toothpaste or yogurt, but we are able to discriminate among them and make choices reflecting relative valuation. Manufacturers sometimes try to increase the value of a product by manipulating a few attributes, e.g., cola with cherry. While

presumably the sensory attributes of a reinforcer contribute to its value, research with rodents indicates that these dimensions have separable influences on behavior and are supported by distinct neural substrates.

Pavlovian-instrumental transfer (PIT) refers to the increase in instrumental responding induced by presentation of a CS (Estes, 1948; Edgar, Hall, & Pearce, 1981). If the reinforcers associated with a CS and instrumental response are identical, responding is increased even more (Kruse et al., 1983). Lesions of the BLA prevent this effect but not PIT generally, and the opposite is true for CeN lesions (Blundell et al., 2001; Corbit & Balleine, 2005). The *reinforcing* properties of stimuli allow CSs to have a general motivational influence on instrumental behavior via the CeN. The *sensory* properties of stimuli allow CSs to have a specific influence on instrumental behavior via the BLA. The BLA therefore contributes to discrimination of reinforcers with similar values but different sensory properties (e.g., sucrose and food pellets, cookies with and without raisins), but the CeN supports their reinforcing efficacy.

Rats with BLA lesions are impaired at discriminating reinforcers that are equal in value, as measured by their ability to support learning, but differ in sensory attributes (Balleine et al., 2003). More specifically, when reinforcer type (food pellets or maltodextrin) is used to signal which of two responses will be reinforced, rats with pre-training BLA lesions perform fewer of the reinforced response, indicating impaired discrimination, although the reinforcers are equally efficacious in supporting instrumental acquisition. The rats in this thesis with pre-training BLA lesions were capable of discriminating the reinforcing efficacy of 150 and 50 µl sucrose since they acquired preference normally. I suggest that they were unable to discriminate other reinforcer

attributes, but that discrimination of these attributes would have contributed to behavioral adaptation to reinforcer magnitude reversal.

What are the other attributes of the sucrose reinforcers that may have been discriminated, providing a basis for detecting the reinforcer magnitude reversal? Some possibilities include caloric value, or the touch sensation; a large amount of sucrose may have felt different from a small amount in the rat's mouth. Proprioceptive stimulation caused by differential motor patterns during consumption of the small and large reinforcers may have provided a basis for discriminating the magnitude reversal. For example, perhaps the rats took longer or emitted more licks when consuming the large reinforcer.

The alternatives could also be discriminated based on the frequency of the tones preceding the large and small reinforcer. The rats clearly discriminated between the tones, since reversing the frequencies decreased preference for the large reinforcer side in the first manuscript. When the reinforcer magnitudes reversed, the relationship between tone frequency and reinforcer magnitude was disrupted, possibly contributing to changes in choice.

Most obviously, the reinforcers differed in spatial location, and BLA lesions do not affect the use of spatial stimuli in mazes (Ito et al., 2006). Pre-training BLA lesions may have prevented the rats from learning about other, non-spatial sensory attributes of the reinforcers. This would explain why the pre-training lesioned rats were only retarded at changing their preference, rather than completely impaired. Certain salient attributes, such as spatial location, were learned and used to discriminate the change in reinforcement. The rats may have learned about this attribute without the BLA via the

hippocampus, which supports learning about spatial stimuli (Morris et al., 1982). Other studies have indicated that multiple aspects terminal links in concurrent chains schedules can be used to discriminate changes. Grace (2002b) reported that preference changed faster when both the terminal link FI schedules and their respective stimuli were reversed, compared to when just the schedules were reversed.

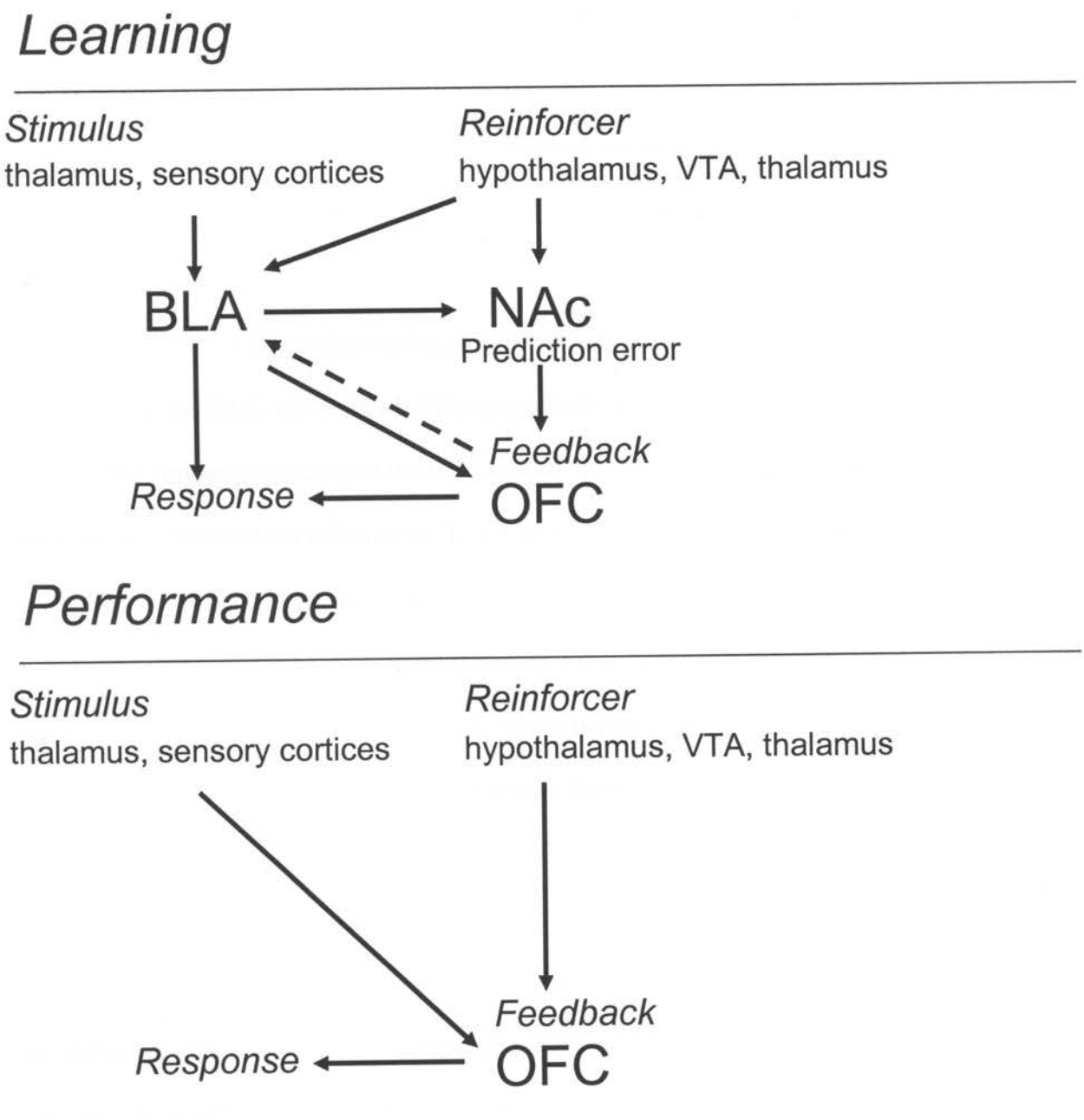
Donahoe and Burgos (2000) and Balleine and Killcross (2006) argued that the neural structures sensitive to reinforcer properties send feedback to structures that receive sensory input and modulate response output (i.e., BLA). They suggest that this feedback is critical for behavior to adapt to changes in reinforcer value. A diagram of this model incorporating the specific influence of the BLA during learning (top), but not performance (bottom), is shown in Figure 14. The separation of the diagram into circuits underlying learning and performance follows from the data in this thesis and other reports. In order for behavior to adapt to changes in reinforcer value, the BLA must be present during learning (Hatfield et al., 1996; Figure 12, top), but it is not necessary during performance (Pickens et al., 2003; Figure 12, bottom). In contrast, damage to the orbitofrontal cortex (OFC) before (Gallagher et al., 1999) or after (Pickens et al., 2003) learning disrupts behavioral adaptation. Communication between these structures during learning is apparently required for the behavior to subsequently adapt, since pre-training disconnection of these structures by lesioning the BLA on one side and the OFC on the other disrupts behavioral adaptation (Baxter et al., 2000).

Saddoris, Gallagher, & Schoenbaum (2005) evaluated the interaction between OFC and BLA in a series of neurophysiology studies. Rats were trained that one odor predicted quinine and another odor predicted sucrose; the rats received quinine or sucrose

only if they poked their noses into a trough within 3 seconds after the odor was presented. Lesions of the OFC (Schoenbaum et al., 2002) and BLA (Schoenbaum et al., 2003) disrupt only reversal, but not acquisition, of odor discrimination. The researchers measured neuronal activity in the OFC and BLA when the odor was presented and during the delay to outcome delivery. Activity concurrent with odor presentation was assumed to reflect stimulus-reinforcer relationships, and activity during the delay was assumed to reflect response-reinforcer relationships. Once the rats were trained to asymptote, the BLA neurons fired to the outcome predicted by the odor, but not the odor itself, and rapidly reversed their firing when the odor-outcome assignments were reversed (Schoenbaum et al., 1999). This reversal was impaired when the OFC was lesioned (Saddoris, Gallagher, & Schoenbaum, 2005). Conversely, lesioning the BLA decreased outcome-specific odor responding in OFC neurons (Schoenbaum et al., 2003). BLA lesions did not affect the number of OFC neurons that exhibited outcome-specific firing during the delay (Schoenbaum et al., 2003), although OFC lesions decreased the outcome-specific firing of BLA neurons during the delay (Saddoris et al., 2005). Holland and Gallagher (2004) summarize these results: the "BLA is crucial to the representation of stimulus-reinforcer expectancies in OFC, and OFC is needed for the representation of response-reinforcer expectancies in BLA" (p. 150). During acquisition, the BLA appears to teach OFC neurons about stimulus-reinforcer relationships so that behavior can adapt when the reinforcer changes, i.e. the OFC guides behavior according to the value of reinforcers.

Thus, there appears to be two possible explanations for why pre-training BLA

Figure 14. Schematic of the neural circuits underlying the learning (*top*) and performance (*bottom*) involved in the adaptation of behavior with reinforcer devaluation based on the model of Balleine & Killcross (2006). Top: During learning, the basolateral amygdala (BLA) receives information about stimuli and reinforcers, so that stimulus input produces a prediction about the upcoming reinforcer that is sent to the nucleus accumbens (NAc). During learning, the BLA can mediate behavioral output. The BLA sends information about the sensory properties of the predictive stimuli to the orbitofrontal cortex (OFC), from which it receives information about whether the actual reinforcer matched the predicted reinforcer. Bottom: After learning, stimuli predicting reinforcement bypass the BLA, directly influencing the OFC. The OFC compares the predicted reinforcer with the actual reinforcer and mediates behavioral output.


Learning
Stimulus
thalamus, sensory cortices
Reinforcer
hypothalamus, VTA, thalamus
BLA
NAc
Prediction error
Feedback
Response
OFC
Performance
Stimulus
thalamus, sensory cortices
Reinforcer
hypothalamus, VTA, thalamus
Feedback
Response
OFC

lesions disrupt changes in behavior when reinforcer value is manipulated. First, pre-training BLA lesions result in sparse encoding of the sensory properties of reinforcers, rendering changes more difficult to discriminate. Second, the BLA provides a critical link between cortical areas sensitive to reinforcement (e.g., OFC) and structures mediating motor output (e.g., striatum) that is absent when the BLA is lesioned. In fact, these may be the same explanation stated in different terms. The latter may describe how the former is enacted in neural circuitry. Encoding the sensory properties of reinforcers, or associating CSs with reinforcement, may require BLA to communicate with cortical areas such as the OFC, which is what the neurophysiology data above suggests.

The connections between the BLA and striatal structures mediating motor output may be less important for behavioral adaptation to changes in reinforcement, since post-training BLA lesions do not prevent adaptation. It appears that the OFC can mediate behavioral adaptation to changes in reinforcement if it has acquired sensitivity to sensory features via communication with the BLA, which is supported by the neurophysiology data. It is unknown whether BLA lesions disrupt the behavior of OFC neurons that have previously acquired reinforcer-specific CS responses. Future studies combining neurophysiology and behavior analysis will help to answer this question.

In order to test a proposed neural circuit underlying behavior, one approach is to systematically lesion each structures in the circuit and assess its effects on behavior, as has been done with Pavlovian fear conditioning with auditory stimuli (LeDoux, 2000). This project has mostly been completed with respect to the circuit in Figure 14 using a protocol in which reinforcers are devalued with lithium chloride or sensory-specific satiety. Pre-training lesions to the BLA (Hatfield et al., 1996; Balleine et al., 2003), OFC

(Gallagher et al., 1999), and the NAc (Corbit et al., 2001) disrupt behavioral adaptation to decreased reinforcer value. Post-training lesions of the OFC but not the BLA (Pickens et al., 2003, 2005) disrupt behavioral adaptation, which warrants omission of the BLA from the performance portion of Figure 14. The effect of post-training lesions of the NAc has not been tested.

Excitotoxic lesions are irreversible, so that lesions present during learning are also present during performance, necessitating a second experiment in which lesions are induced after training, as in this thesis. Reversible lesions, e.g., infusion of tetrodotoxin (e.g., Fuchs & See, 2002) or muscimol (e.g., Wellman, Gale, & Malkova, 2005), allow disruption of activity in the BLA during training, but then restoration of BLA function during performance. This technique is challenging because it requires an infusion for each day of training, which would likely produce mechanical tissue damage because of repeated injection. If the BLA is only involved in learning as shown in Figure 14, however, adaptation to reinforcer devaluation should be disrupted even if BLA function is restored after training. Researchers may eventually bypass the challenges of repeated injections with inducible gene knockouts. Once we have identified the receptors in the BLA that are active during learning that support adaptation to reinforcer devaluation, these receptors can be targeted with genetic techniques.

It is unknown whether lesions to the neural systems processing sensory stimuli present during learning (e.g., inferior colliculus, auditory thalamus, or sensory cortices) prevent behavioral adaptation to decreases in reinforcer value. Insofar as the behavior is stimulus controlled, one would anticipate impairment unrelated to whether the reinforcer had been devalued. The effects of lesioning structures that provide inputs regarding the

obtained reinforcer, including the VTA and hypothalamus, have not been examined, possibly because such lesions might interfere with the behavior being measured by disrupting feeding or locomotion. Techniques that allow precise identification of the neurons from the hypothalamus and VTA that mediate activity of neurons in the NAc during adaptation to changes in reinforcer value could result in specific lesions that do not produce general behavioral impairments. For example, one might use a combination of retrograde fluorescence and measurement of the immediate-early gene c-fos to identify NAc neurons that are active when reinforcer value changes and that receive inputs from the VTA or hypothalamus.

To further test a circuit, one must identify which anatomical connections are necessary for the behavior. The only connection so far investigated is between the BLA and OFC: disconnection disrupts behavioral adaptation to decreased reinforcer value in rhesus monkeys (Baxter et al., 2000). The same results would be expected for rats. Pharmacological disconnection of the BLA and NAc disrupts responding for cocaine when a stimulus predicting cocaine is the consequence of behavior (Di Ciano & Everitt, 2004). Since this presumably reflects impaired learning about specific features of the stimuli predicting the reinforcer, and it includes the BLA, which is only required for the learning that supports behavioral adaptation to decreased reinforcer value, a functional connection between the BLA and NAc is likely involved only in the learning component of Figure 14. Future studies should assess how disconnection of the NAc and OFC, and VTA and OFC, affect animals' adaptation to decreases in reinforcer value. The bottom portion of Figure 14 predicts that the OFC supports behavioral adaptation during

performance because it receives information from the hypothalamus and VTA. A post-training disconnection study would be necessary to evaluate this prediction.

Figure 14 excludes several structures that, when lesioned, affect behavioral adaptation to decreased reinforcer value. For example, different components of the dorsal striatum have distinct roles in behavioral adaptation. When trained to respond with interval schedules of reinforcement, rats with lesions of the dorsolateral striatum (DLS) adapt their behavior to reinforcer devaluation, whereas sham rats do not (Yin et al., 2004). In contrast, lesions of the posterior, but not anterior, dorsomedial striatum (DMS) decrease adaptation to reinforcer devaluation (Yin et al., 2005). Whereas the CeN appears to have no role in behavioral adaptation when reinforcers are devalued (Hatfield et al., 1996), connections between the CeN and DLS, via the substantia nigra pars compacta, support the learning and performance, respectively, of conditioned orienting to a CS (Han et al., 1997). For at least a decade, the DLS has been implicated in "stimulus-response" or habit learning, i.e., animals' performance of a response in the presence a stimulus irrespective of the consequence (e.g., Packard & McGaugh, 1996); nobody has evaluated the effects of CeN lesions on the maze protocol used to infer the role of the DLS in habit learning. Lesioning the DLS appears to disrupt habit learning, allowing the rats' behavior to be sensitive to changes in reinforcer value (Yin et al., 2004). When the DLS is functioning, it appears to prevent animals from adjusting their behavior, even if the reinforcer has changed. The role of the DLS in stimulus-response learning may be related to its inputs from the CeN, which controls orienting towards CSs irrespective of whether the orienting increases or decreases the probability of reinforcement (Holland, Han, & Winfield, 2002).

Balleine's (2005) circuit juxtaposes the differential connections between the DLS and DMS. He emphasizes the former's inputs from sensorimotor cortex and outputs to the structures mediating motor output (i.e., globus pallidus), and the latter's connections with cortical areas including the anterior cingulate, medial precentral, and prelimbic cortices, and the BLA and NAc. The purpose of Balleine's circuit is to juxtaposes the neural systems he believes underlie the learning and performance of habitual (i.e., insensitive to changes in consequences) versus "goal-directed" (i.e., sensitive to changes in consequences) behavior. Many researchers currently believe that animals learn, in parallel, behaviors that are insensitive and sensitive to changes in reinforcement. Another view, implicit in Figure 14, is that insensitivity and sensitivity are supported by the same neural circuits but represent quantitatively different connection strengths, e.g., from structures providing feedback about changes in reinforcement to structures mediating motor output (Donahoe & Burgos, 2000).

How does one evaluate whether habits and "goal-directed" behaviors are qualitatively or quantitatively different? A qualitative distinction predicts that the same behavior may be habitual or "goal-directed" under different circumstances in which the behavior is mediated by different neural circuits. For example, perhaps lever pressing reinforced with ratio schedules is "goal-directed" (Dickinson, Nicholas, & Adams, 1983) and mediated by the BLA, NAc, and OFC, whereas lever pressing reinforced with interval schedules may be habitual (Dickinson et al., 1983) and mediated by the CeN, sensorimotor cortex, and DLS. A quantitative distinction predicts that the same neural circuits mediate lever pressing reinforced according to ratio or interval schedules, but the magnitude of feedback from structures sensitive to reinforcement (hypothalamus, VTA,

NAc) to those intervening between stimulus input and response output (BLA, OFC) varies. It may be that additional structures, such as the DLS, are recruited to inhibit the feedback, so that the quantitative distinction between habitual and "goal-directed" behaviors merges with the qualitative distinction.

In the Introduction to this thesis, I suggested that the BLA, with its role in stimulus-reinforcer relationships (Everitt et al., 2003), might support behavioral momentum, which may also be supported by stimulus-reinforcer relationships (Nevin, 1992). Multiple schedules are typically used to measure behavioral momentum. One might argue that PRE lesioned rats' blunted changes in preference when the reinforcer magnitudes reversed in was due to enhanced behavioral momentum. Since behavioral momentum is influenced by stimulus-reinforcer relationships, such an explanation would imply that stimuli acquired stronger value for BLA-lesioned rats. This conclusion is inconsistent with many other studies showing BLA lesions impair learning about stimulus-reinforcer relationships (Everitt et al., 2003). It appears that blunted changes in preference in PRE lesioned rats cannot be interpreted as enhanced behavioral momentum because the processes assumed to mediate momentum are impaired, not enhanced, by BLA lesions.

On the other hand, I also assessed the extent to which reversing the reinforcer magnitudes influenced baseline preference in the following session. Greater momentum would be implied by increased carryover from the reversal session to the subsequent baseline session. Assuming that this is an adequate measure of behavioral momentum, the data in this thesis indicate that the BLA has no role. All the groups exhibited similar amounts of carryover. Preference for the large reinforcer side was lower in the session

after the reversal, relative to the baseline session before the reversal. This suggests that structures other than the BLA may support acquisition of stimulus value that could contribute to behavioral momentum. The role of the CeN in PIT (Corbit & Balleine, 2005) suggests that this structure allows CSs to affect behavior with respect to the efficacy of their paired reinforcers. Future studies could evaluate whether the CeN contributes to behavioral momentum, perhaps using more traditional protocols. I predict that CeN lesions would decrease behavioral momentum so that responding would be more susceptible to disruptors.

The data in this thesis and in many other reports suggest that the BLA, and the CeN (Gallagher & Holland, 1992; Holland & Gallagher, 1993a), have distinct contributions to the acquisition of behavior and its adaptation when aspects of the conditioning situation change (e.g., reinforcer value or the CS surprisingness). The failure of the parametric protocol in the first manuscript is unfortunate, since it would have provided a strong test of the hypothesis that the BLA encodes the sensory attributes of reinforcing alternatives. Identifying the neural systems that allow reinforcers to be richly encoded with respect to multiple attributes is important for understanding how reinforcers are compared, and how changes in reinforcers affect preference.

Although the mathematical models for Pavlovian CR acquisition (e.g., Rescorla & Wagner, 1972) and choice in transition (e.g., Mazur, 1992) are formally equivalent, the biological systems that could eventually map onto these formulae may differ, at least qualitatively. On the other hand, the same function may describe changes in synaptic strength between the BLA (feedback units) and motor units influencing behavior (Donahoe & Burgos, 2000) during acquisition and reinforcer revaluation. Furthermore,

both acquisition and behavioral adaptation (e.g., changes in responding after reinforcer omission) both follow negatively accelerated curves (Rescorla, 2001). What neurobiological process accounts for this quantitative similarity between behavioral acquisition and adaptation remains to be seen, but appears not to involve the BLA, because this structure seems to have a specific role in behavioral adaptation.

Neurons in the NAc are activated by events preceding reinforcer delivery and decrease their activity when an expected reinforcer is omitted (Schultz et al., 1992, 1997). The activity of NAc neurons seems to reflect an error signal for reinforcer prediction, and is therefore a neurophysiologic analogue to the difference component of mathematical models describing changes in behavior during acquisition or in transition (Schultz, 2005). How changes in the sensory properties of CSs or reinforcers would affect NAc neuron activity is unknown, but such changes would likely be mediated by the BLA. BLA neurons are sensitive to CS presentation (Pratt & Mizumori, 1998) and the BLA modulates NAc activity (Floresco et al., 2001). Pharmacological disconnection studies indicate that communication between the BLA and NAc core supports responding in second-order schedules, for which conditioned reinforcement maintains behavior (Di Ciano & Everitt, 2004). Communication between the BLA and NAc is therefore likely to be an important component of the neural systems supporting changes in preference when consequences change. Across species, the OFC sends projections to NAc sites also receiving input from the BLA, so a circuit involving these three structures may be central to the neural mechanisms for behavioral adaptation to changes in reinforcement (Schoenbaum, Roesch, & Stalnaker, 2006), perhaps each contributing to distinct behavioral processes.

The data in this thesis fit into a research program to identify the behavioral and neurobiological factors underlying the sensitivity of behavior to changes in consequences. The opposite of sensitivity to changes in consequences may be habitual behavior. This problem is fundamentally important. "When we look at living creatures from an outward point of view, one of the first things that strike us is that they are bundles of habits" (James, 1890/1950, p.104). The problem is also practically important. The seeking and taking of drugs of abuse is initially sensitive to changes in consequences, but becomes increasingly habitual, resulting in addiction (Everitt & Robbins, 2005). Identifying how behavior changes when different aspects of reinforcement contingencies change, and what neural substrates support these changes, may inform us about the processes disrupted in addiction.

Summary

In a concurrent chains protocol designed to test the hypothesis that the BLA encodes the sensory properties of reinforcers, rats were insensitive to manipulations of the terminal link stimulus properties or reinforcer taste. The rats were sensitive to unpredictable reversal of the reinforcer magnitudes, terminal link stimulus frequencies (kHz), or both. Pre-training, but not post-training, excitotoxic lesions of the BLA retarded changes in preference when reinforcer magnitudes reversed. This finding parallels data from Pavlovian conditioning protocols in which reinforcers are devalued with lithium chloride or sensory-specific satiety. The lesions did not affect the acquisition of preference, or the extent to which reversing the magnitudes decreased preference in the following baseline session. Pre-training BLA lesions may have

prevented rats from learning about terminal link stimulus-reinforcer relationships. Rats with these lesions directed a lower percentage of their nose pokes to the reinforced side during the terminal link. This interpretation is consistent with the view that the BLA supports learning about the sensory properties of reinforcers. Rats that did not learn about the terminal link stimulus-reinforcer relationship would be unable to discriminate its disruption when the reinforcer magnitudes reversed, and would be slower to change their preference.

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