Experiential, Neural, and Cognitive Influences on Decision Making in Rats

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Abstract

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All animals have specific mechanisms in place to guide the numerous decisions they face daily. The act of deciding among possible behaviors is a process that involves learning about the relationships between actions and consequences, remembering past outcomes, and evaluating the current internal and external environment to inform an animal of its needs and available choices. The field of neuroeconomics has developed from a joint interest in how the brain guides this decision process that is shared by its parent fields of economics and neuroscience. Other fields provide critical insights into this topic: computer science contributes mathematical models of behavior, and psychology contributes analyses of the behavior itself, particularly in terms of an animal's underlying motivations and cognitive tools. The studies presented in this dissertation explore decision making in rats from both psychological and neuroscientific perspectives. The first study addresses whether and how an unrelated stressful experience affects reward-motivated behavior in a simple value-based foraging task. Rats who experienced an acute, uncontrollable stressful event were subsequently impaired in their ability to optimally update their behavior in response to changing rewards. The next study revealed that optimal performance on a similar value-based decision task does not require the independent contribution of several subregions of the prefrontal cortex. The final study dissociated particular measures of decision making from

performance on other types of tasks, and found that an animal's individual preference for risky rewards was related to its behavioral sensitivity to rewards.

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Chapter I. Background and Introduction

A major goal of neuroeconomics is to identify the brain regions that contribute to and control the decision process. Although there are parallels between human and rodent brain structures that guide decisions (e.g. Balleine & O'Doherty, 2010), the variance in brain size across species means that human decisions have access to a more complex neural processing system than do rodent decisions. However, in order for animals to behave adaptively in an environment in which multiple possible actions are available at each moment, they must all have the ability to complete a particular series of steps that is fundamental to all decisions. Specifically, animals must be able to assess the values of the possible actions and outcomes, to compare these values and select the action with the greatest value, to evaluate the outcome of a choice, and finally to update the representation of that outcome for future use. The general approach to identifying the neural basis of decision making has been to link neural contributions in a particular task to specific components of this fundamental decision process. In order for neuroeconomics to describe an accurate and complete model of decision making in humans, it is necessary to test decision-making models and theories across tasks that vary in complexity and cognitive demand, and across animal species.

The Decision-Making Process

A comprehensive neural and psychological description of how animals make decisions necessarily begins with the identification of the decision process itself. Although intuitively it feels like decisions are events that occur in a particular moment, a decision never occurs in isolation; it is preceded by an assessment and comparison of both the possible actions and the associated outcomes, and it is followed by an evaluation of the resulting outcome so that future

choices may be better informed. This process thus involves several cognitive stages, with distinct underlying neural contributions to each decision phase. The correct identification of these phases will provide the means to understand more complex decision-related questions. For example, certain populations have demonstrated sub-optimal decision making (e.g. drug addicts, adolescents, individuals with mental illness; Ahn et al., 2011; Chambers et al., 2003; MacKillop et al., 2011), and a description of the cognitive components of the decision process is the logical first step in the evaluation of how this process differs in such populations. Further, neuroscientific contributions to the study of human decision making require a breakdown into psychological and behavioral components, in order for experimenters to select appropriate behavioral outcomes when manipulating or measuring neural activity.

One attempt to compartmentalize the decision process identified five basic computations: representation, valuation, action selection, outcome evaluation, and learning (Rangel et al., 2008). During representation, an animal identifies the possible available actions and both the external (environmental) and internal (physiological) states. The animal then assigns value to the possible actions, based either on direct prior experience or on related memories to create a heuristic "best-guess" of overall value. Based on these calculations, the animal then compares the values and selects the action with the greatest value. Finally, after implementing a choice, the animal can then evaluate the consequence of that choice and, if the outcome was unexpected, update (learn) the new information in order to better inform future related choices.

Most attention in neuroeconomic research is directed at the valuation stage, to determine how animals assign value to different actions and outcomes. The current understanding is that mammals use different strategies to assign value (Pavlovian, habitual, and goal-directed), and that these strategies are often in conflict with one another (Dickenson, 1994; Balleine et al.,

2008; Balleine & O'Doherty, 2010). In fact, it has been proposed that dysfunctional competition between valuation systems may underlie certain pathological behaviors (Dayan et al., 2006). The Pavlovian system places value on behaviors that are evolutionarily meaningful (e.g. eating, sexual activity, escape) based on an evaluation of the current stimuli in the environment (Rangel et al., 2008). The habitual and goal-directed systems assign value to a broader range of behaviors. The habitual system learns action values through repeated choice of a particular behavior, such that ultimately a stimulus-response association (S-R) drives behavior. The goal-directed system assigns action values based on response-outcome (R-O) associations, which allows for faster updating of behavior when outcome values are modified. One way to evaluate whether behavior is driven by the habitual or the goal-directed system is to reduce the value of an outcome that is the consequence of a learned behavior (outcome devaluation; first reported by Adams & Dickinson, 1981). After reward devaluation (by pairing a reward with an aversive stimulus or by allowing consumption to satiety) animals driven by R-O associations will subsequently reduce their overall responses that were paired with the devalued outcome. Animals driven by S-R associations will not initially be affected by the devaluation procedure, and will thus take longer to modify their behavior. Habitual actions are also insensitive to changes in the causal relationship between response and outcome: after rewards are presented that are unpaired with the action (which thus reduces the R-O contingency), goal-directed responses will decrease, while habitual responses will not (e.g. Dickinson et al., 1998). The type of valuation system used is sensitive to the amount of training; goal-directed valuation generally dominates early learning, and that overtrained animals are guided more often by habitual systems (Adams and Dickinson, 1981; Packard, 1999; Packard & McGaugh, 1996). Because these systems assign value in unique ways, when in conflict, they promote the choice of distinct

actions, and they can thus help to explain and predict differing behaviors in the presence of the same environmental and physiological states.

Within the valuation phase of decision making, there are additional factors that affect the final value assigned to a particular action. Such modulators of value include the effort it takes to carry out a particular action, the delay between the action and arrival of the outcome, and the uncertainty of whether the outcome will occur following the action (i.e., probabilistic rewards; Platt & Huettel, 2008; Floresco et al., 2008). For animals to determine action values, they must be able to compute and integrate these various factors. Each of these examples represents a cost of a particular action, and their presence thus results in a discounting of the reward value relative to if there were no (or less) cost. Expected utility theory was developed to mathematically characterize rational decision making in the face of uncertainty (Bossaerts et al., 2008; von Neumann & Morgenstern, 1953). According to expected utility theory, potential choices are evaluated based on their relative value (utility) to the decider and the probability of their occurrence. Although expected utility (EU) is still the dominant normative model in decision theory, consistent deviation from its predictions (most famously the Allais and Ellsberg paradoxes) have prompted the development of variants to the EU model. The most influential of these variants is the descriptive model of prospect theory (Kahneman & Tversky, 1979; Tversky & Kahneman, 1992). Prospect theory (PT) maintains the base assumptions of EU, but includes a few modifications to better explain persistent deviations in human choice behavior from EU's predictions. Overall, while both theories predict choices based on comparisons between values of prospects (possible outcomes), EU assigns these values based on objective qualities, while PT assigns values relative to an individual's reference point, typically his or her level of wealth for economic decisions. Specific modifications of decision theory found in PT include: (1)

weighting properties of both value and probability: the value of a potential outcome is weighted by its degree relative to a "reference point" unique to each decider; the probability is weighted by a "decision weight" that allows for differential preference of relative probabilities; (2) risk-aversion in the gain domain (relative to the individual's reference point) versus risk-seeking in the loss domain; (3) loss-aversion (the subjective utility curve is steeper for losses than gains). Thus, an animal's assessments of the quantity and quality of the reward, and of the likelihood of the reward occurrence, are both based on subjective evaluations. The degree of influence on an animal's choices of its internal states and preferences clarify the need for psychological approaches to the design and analysis of decision-making and neuroeconomic experiments. Psychological analysis is critical for grounding economic and computational models in actual behavior, by refining the various cognitive processes involved so that they accurately reflect animals' reward-motivated behaviors.

Experimental Approaches to Reward-Motivated Behaviors

A popular approach in the endeavor to elucidate the neural circuitry and systems underlying experience (e.g. behavior, sensation) is to correlate a particular behavior or stimulus with some physical change in neural activity (e.g. firing rate, blood-oxygen-level dependent activation, chemical concentrations). A region found to be consistently correlated with a particular experience is referred to as a "neural correlate" of that experience. In order to demonstrate the presence of neural correlates, it is first helpful to break down the experience into components more likely to be distinctly represented in the brain. For instance, in decision making, it is reasonable to expect that separate regions (or at least distinct patterns) code for expected value, action selection, and learning about outcomes. Further, the technique to measure

the neural correlate and the behavioral paradigm to create the specific experience both affect the validity of a potential correlation.

With regard to decision making research, a particular challenge in the search for "neural correlates" is that many variables central to the decision process are internal and subjective, and thus not available for direct manipulation or measurement. Several experimental approaches have been developed to measure these variables in order to test for evidence of neural correlates (Corrodo et al., 2008). This type of evidence is necessary for demonstrating the involvement of a region in behavior, because to contribute to a change in behavior (or perception), that region must change from one state to another. However, significant correlation can occur in a structure independent of its direct contribution to a particular task. That is, correlational evidence alone is insufficient to demonstrate direct involvement in a task. Thus, techniques that involve neural manipulations (e.g. lesions, stimulation, drugs, genetic models) must supplement the neural correlate evidence in order to fully demonstrate the involvement of a particular structure or system in a task assessing cognitive function such as decision making.

The advantages and reasons for the popularity of "neural correlate" techniques are numerous, but one general appeal is the lack of directed manipulation. That is, the primary purpose of such techniques is to observe the natural changes in neural activity that best correspond with, and thus potentially control, particular behaviors. In decision-making research, the most commonly used techniques are brain imaging and electrophysiology, specifically fMRI and single-unit recording. This is largely due to the dominance of primate research, in which manipulation techniques are limited by accessibility, cost, and ethics. Although fMRI is a valuable tool in observing real-time activity in human brains during task performance, it is important to consider what the measurement (blood-oxygen-level dependent, BOLD, signal)

represents. For instance, based on correlative evidence of BOLD responses with local field potentials (relative to firing rates), it is now believed that BOLD responses are a measure of input, rather than output, of a specific region (Logothetis et al., 2001). Single-unit recordings provide more temporally and spatially specific information about the activity of individual neurons. They allow an important test of what neurons are capable of responding to, whether or not that response is critical for processing stimuli or producing behavior. Often, a novel integration of current techniques allows for increased measurement potential. For instance, fast-scan cyclic voltammetry, a temporally and spatially sensitive technique of measuring changes in specific neurochemical concentrations, recently has been combined with microarray technology to allow measurement with increased spatial and chemical flexibility in behaving animals (Zachek et al., 2009).

Although it is tempting to assume the direct relevance of a neural correlate to a particular behavior, there are other explanations for correlation that are independent of contribution to a particular task. For instance, dorsal hippocampal activity was correlated with rabbit eyeblink conditioning, which was interpreted as evidence that hippocampus may store the memory trace (Berger et al., 1976), though lesion evidence later indicated that hippocampus is necessary for neither acquisition nor retention of delay eyeblink conditioning (Schmaltz & Theios, 1972). Additionally, in reward-related learning, a neural correlate of a changing reward value (e.g., Glimcher & Rustichini, 2004; Kennerley & Wallis, 2009; Okada et al., 2011; Tremblay & Schultz, 1999) could mean either that the activity is directly tracking the reward value, or that it is associated with indirect responses (e.g. attentional increases to changes in salience, preparatory motor responses). Thus, although measurements of activity changes are useful for determining candidates for relevant neural components, it is critical to supplement such evidence

with alternate techniques.

To avoid this correlational limitation of neural measurement techniques, a large number of directed manipulations exist in neuroscience in which researchers affect one region or system of an animal in order to demonstrate a causal connection between brain activity and behavior. In decision-making research, popular manipulation techniques include lesions or inactivations and drug exposure. Lesion and inactivation techniques include permanent or temporary knock-outs of particular brain regions or neurochemical systems (e.g. lidocaine to block voltage-gated sodium channels, and thus inhibit firing; 6-OHDA to selectively destroy dopaminergic input). These techniques allow a more direct assessment of whether the manipulated region/activity is necessary for a particular behavior. Naturally, these techniques carry their own limitations. For instance, many lesions occur at the time of surgery (e.g. electrolytic, aspiration), and thus animals are provided post-surgery recovery time before testing, which allows for potential neural compensation. In this case, a lack of established necessity (observed intact behavior following selective neural damage) does not preclude typical involvement of the region in an intact brain. Further, chemical inactivation techniques are typically limited in terms of the size of the affected area (extent of diffusion), and the specificity of inactivation to the desired system or region (e.g. lidocaine affects both cell bodies and axons passing through targeted regions). Targeted drug manipulations include agonists and antagonists to specific neurochemical systems, either localized to particular regions, or system-wide. Such manipulations are useful for demonstrating a more causal association between a neurochemical system and behavior, but are often limited in terms of specificity (e.g. to functionally distinct receptor subtypes).

In addition to the relative advantages of particular neural techniques (measurement or manipulation), the behavioral specificity of an experimental paradigm must be considered in

determining the most effective way to evaluate neural contributions to behavior. Because measures of neural correlates are insufficient to prove that neural activity contributes to behavior, manipulation techniques are commonly used in rodents. Thus, one challenge in animal research is to design behavioral paradigms that are appropriate for cross-species comparisons.

In decision-making research in rodents, behavioral paradigms include lever pressing, maze tasks, the 5-choice serial reaction time task (5-CSRTT), and rodent versions of the Iowa gambling task. In both lever pressing and maze tasks, the experimenter can manipulate reward volumes and probabilities, in addition to cost variables including delay and effort (increased press requirements or maze obstacles). In the 5-CSRTT, the rat is required to wait for a cue that indicates the rewarded location, then approach the cued location for the reward. This is designed to assess both attentional capacity (through use of distractors) and inhibitory response control (waiting for the cue). Thus, this task allows dissociation of attentional control from a typical decision-making task (in which the animal chooses between multiple rewarded alternatives). For example, infralimbic cortex is related to impulse control, orbitofrontal and prelimbic cortices control perseveration (avoidance), and anterior cingulate gyrus is related to attention (reviewed in Dalley et al., 2004). For a more direct assessment of rodent decision making, some researchers have developed rodent versions of the Iowa Gambling Task (IGT; e.g. van den Bos et al., 2006; Zeeb et al., 2009). The IGT was originally developed to assess sensitivity to future consequences in patients with prefrontal cortical damage (Bechara et al., 1994). In a task easily conducted in a laboratory, participants repeatedly choose from four decks of cards that differ in terms of long-term payoff (due to variations in probability and amount of gain and loss). Initial observations that most rats and mice learn to maximize payoffs in rodent versions of the IGT (van den Bos et al., 2006; Zeeb et al., 2009) similar to most humans suggest that it is an ideal

model of cross-species decision making. However, one key difference between rodent and human decision tasks is that it is difficult to assign "loss" conditions to a rodent, since rewards are most often immediately consumed. Thus, it is difficult to assess differences in gain versus loss processing (e.g. Kahneman & Tversky, 1979) in rodents.

Neuroeconomic research is ultimately concerned with understanding how (and which) neural processes guide human decision making. A substantial amount of valuable research on this question has come from brain imaging in humans and electrophysiology in non-human primates. However, it is necessary to supplement this work with studies involving manipulations of neural processes if we ultimately want to infer direct relationships and causality. Based on the known similarities in decision-related brain regions of rodents and humans (e.g. Balleine & O'Doherty, 2010), evidence from rodent studies, with reliable behavioral paradigms and a combination of neural measurement and manipulation techniques, has the potential to substantially inform human decision making.

Prefrontal Cortex and Reward-Motivated Behavior

In terms of the neural contributions to decision making, several brain regions have been strongly implicated in various stages of the decision process. As discussed above, confirmation of the normal involvement of a particular region in a behavior should involve multiple measurement and manipulation techniques. Additionally, such confirmation also requires consideration of the neural homology across species when data from non-human subjects are used to inform human behaviors.

The prefrontal cortex (PFC) is one such region that has been extensively investigated for its contributions to decision-related behaviors. Substantial evidence supports its involvement in

several executive functions involved in decision making, including the modulation of attention to environmental and internal stimuli, the planning of behavioral sequences, and the selection of appropriate behaviors based on the current environment. General interest in the prefrontal cortex also stems from its involvement in several clinical syndromes, including schizophrenia, attention deficit hyperactivity disorder, and drug addiction. Although the prefrontal cortex previously was assumed to be unique to primates (Rose & Woolsey, 1948), more recent reviews have concluded that rats have prefrontal cortical regions that can be divided in ways similar to primate PFC subdivisions (e.g. Kesner & Churchwell, 2011; Seamans et al., 2008, Uylings et al., 2003).

In terms of contribution to decision making, the human PFC can be subdivided into three regions: orbitofrontal and ventromedial areas, dorsolateral prefrontal cortex (dlPFC), and the anterior and ventral cingulate cortices (Krawczyk, 2002). The lateral prefrontal area has also been identified as a locus of choice, largely based on evidence from visuo-saccadic tasks in monkeys (Kable & Glimcher, 2009). The rat medial PFC (including ACC and PL/IL) seems to be involved with many functions that are also shared by the primate dlPFC: rule representation, response flexibility, attention, and maintaining information over delays (Seamans et al., 2008). In primates, the anterior cingulate cortex (ACC) is particularly involved with the associations between outcomes and current and past actions. Based on a review of electrophysiological studies in primates, Seamans and colleagues (2008) proposed three general functions of the ACC: (1) selection of and attention to actions; (2) error detection, or conflict monitoring; (3) the maintenance of updated action values based on the integration of previous actions and outcomes. Others have identified a more specific role of the ACC in reward-motivated behavior: the monitoring of effort required to complete a particular action. One review of rat and primate studies concluded that the ACC is particularly concerned with the computation of effort-costs,

and does not seem to be involved in calculating delay-costs (Walton et al., 2007). Because effort is associated with a particular action, the task of monitoring and interpreting effort-related information fits with a system whose overall function centers around associating actions with their consequences (including errors) in order to optimally guide behavior (Rushworth et al., 2004).

The orbitofrontal cortex (OFC) is commonly accepted to be involved with assigning and tracking value to available outcomes. Padoa-Schioppa and colleagues have proposed that not only is the OFC critical for the computation of subjective values in an abstract representation, but that this is the primary role of the OFC (Padoa-Schioppa, 2011; Padoa-Schioppa & Cai, 2011). This assertion is based on a review of evidence from electrophysiological studies and lesion studies in macaques and rats. For example, while macaques performed a task in which they repeatedly chose between two different juice types and volumes, neurons in OFC were found to track several aspects of subjective value, and these value-related measures best accounted for the variance in firing rates of OFC neurons (Padoa-Schioppa & Assad, 2006). Functional imaging studies in humans have supported the notion that OFC encodes subjective value independent of domains, including delay, risk, ambiguity, and gain versus loss (De Martino et al., 2009; Levy et al., 2010; Peters & Büchel, 2009). One lesion study in monkeys aimed to dissociate the roles of the ACC and OFC in computing decision-related values: ACC lesions primarily disrupted action selection, and OFC lesions primarily disrupted stimulus selection (Rudebeck et al., 2008). One prevailing theory of OFC functions is that it allows for the inhibition of undesired behaviors (Kringelbach & Rolls, 2004); however, one recent review of lesion and imaging studies in humans and macaques concludes that the OFC is more broadly concerned with maintaining

previously successful responses, and that subregions within the primate OFC differentially mediate reward credit assignment (Noonan et al., 2012).

Many electrophysiological and lesion studies in rats have been consistent with the functional specialization of the major PFC subdivisions. However, notable exceptions suggest a need for continued evaluation of either the homology between rat and primate PFC or the current descriptions of PFC function. For example, one recent electrophysiological study in rats found that although neural signals relating to upcoming actions were observed in the medial PFC (including ACC), they were only evident immediately before the behavioral choice (Sul et al, 2010). The authors thus suggested that the rat mPFC cannot be responsible for advanced action planning. Further, the claim that individual OFC neurons encode subjective values independent of domain (Padoa-Schioppa, 2011) may not be true in the rat OFC: unlike primates, different populations of OFC neurons have been observed to encode reward magnitude and delay (Roesch et al., 2006; Roesch & Olson, 2005). Finally, the dorsolateral PFC in primates does not seem to have a clear homolog in rats, although many of its proposed functions seem to overlap with those of the rat mPFC (Seamans et al., 2008).

Overall, the ACC is implicated in the maintenance of action-outcome associations and the monitoring of errors between actions and expected outcomes; the mPFC (taken here to collectively include prelimbic and infralimbic cortices, but not ACC) may be required specifically for updating behaviors following a rule shift, and for generally maintaining attention and promoting behavioral flexibility; and the OFC contributes to the evaluation and representation of outcome values. Although this evidence comes from the integration of cross-species results from a broad range of behavioral tasks, if the current functional descriptions are

accurate, then each of these regions should independently contribute to performance on even a simple two-choice reward task that involves a salient change in reward parameters.

The studies presented in this dissertation involve rats behaving on a foraging-based maze task. In the first two studies, the rats repeatedly choose first between two equal rewards, and then between two rewards unequal in volume. Although rats will naturally change their foraging patterns according to this environmental change and begin to choose the larger reward more frequently than they did before the change, rats that were previously exposed to an unrelated stressful experience were significantly impaired in their ability to optimally adapt their behavior in response to the environmental change (Graham et al., 2010; Chapter II). Before it is possible to determine how stress interfered with optimal behavior on this basic foraging task, it is necessary to first determine which brain regions underlie normal (non-stressed) performance. The second study targets this question with an examination of PFC lesion effects on both the maintenance and acquisition of an environmentally-prompted response bias. The absence of significant impairments on behavior following PFC damage suggests that alternate neural mechanisms are sufficient to support reward-related changes in behavior in a simple foraging task.

The final study presented in this dissertation introduces a more complex foraging task in which both reward volume and probability are manipulated to evaluate rat's abilities in a probability discounting task. This study addresses the question of whether there are measures of decision-making performance that are independent of individual ability on a variety of other cognitive measures involved in the overall decision process. That is, when experimenters quantify an animal's "risk preference", for example, is this measure unique or confounded by

other abilities (e.g. working memory, flexibility)? Particularly when there are substantial research efforts focused on identification of the neural correlates of various decision-making variables, it is critical to evaluate the validity of these variables in terms of their distinctness from other psychological measures.

Chapter II. Stress Effects on Reward-Motivated Behavior

Introduction

It is now well documented that exposure to uncontrollable stress can produce alterations in multiple brain–memory systems in humans and animals (Jöels et al., 2006; Kim & Diamond, 2002; Luethi et al., 2008; McEwen & Sapolsky 1995; Shors, 2006). In humans, impairments in long-term, but not short-term, verbal recall tasks have been observed in people with post-traumatic stress disorder (PTSD; Bremner et al., 1995) or Cushing's disease (a hypercortisolemia condition; Starkman et al., 1992) and in healthy individuals subjected to stress (Lupien et al., 1997) or exposed to stress levels of cortisol (Newcomer et al., 1994). In rodents, stress and corticosterone administration interfere with spatial and working memory (de Quervain et al. 1998; Diamond & Rose, 1994; Kim et al., 2001) and potentiate aversive conditioning (Maier et al., 1995; Shors et al., 1992). Further, a number of stress-associated neurobiological changes have been identified (e.g., in hippocampus, medial prefrontal cortex, and amygdala), which affect different memory functions (Arnsten & Goldman-Rakic, 1998; Holmes & Wellman, 2009; Kim & Yoon, 1998; Vyas et al., 2003).

Although stress effects on memory have been well studied, far less is known about whether (and in what manner) stress influences other higher cognitive functions. The present study investigated the effects of acute, uncontrollable stress (60-min restraint + 60 intermittent tailshocks) on subsequent decision-making performance in rats. The stress procedure, in which animals learn that they can neither escape nor predict an aversive experience, was adapted from earlier studies (e.g., Kim et al. 1996; Maier & Seligman, 1976). Decision making was assessed using an automated Figure-8-shaped maze on which rats were motivated to forage for water

rewards in two different locations under equal and unequal quantity conditions. In addition to behavioral stress, we examined the effects of corticosterone administration and inactivation of the amygdala during stress on decision making. Both corticosterone (a glucocorticoid hormone released in response to stress) and the amygdala (a structure crucial in defensive behavior) have been implicated in mediating neurocognitive effects of stress (Kim & Diamond, 2002; McEwen & Sapolsky, 1995).

Methods

Subjects. Experimentally naïve male Charles River Sprague-Dawley rats (initially weighing 275-300 g) were singly housed and maintained on a reverse 12-h light-dark cycle (lights on at 19:00 h). After 7 d of acclimation and for the duration of the experiment, daily water access was restricted to maintain approximately 85% of the animal's body weight. Food was available ad libitum throughout the experiment. All experiments were conducted during the dark phase of the cycle and in strict compliance with the University of Washington Institutional Animal Care and Use Committee guidelines. Animals were divided into four groups: control, stress, amygdalar inactivation plus stress (AMYG), and daily corticosterone (CORT).

Surgery. Under anesthesia (30 mg/kg ketamine and 2.5 mg/kg xylazine, i.p.), amygdala (AMYG) animals were chronically implanted with 26-gauge guide cannulae (Plastics One) bilaterally into the amygdala (from bregma: anteroposterior, -2.3 mm; mediolateral, +/- 5 mm; dorsoventral, -7.7 to -8.0 mm). During 7-10 d of postoperative recovery, each dummy cannula was removed and replaced with a clean one.

Drug Infusion. Muscimol free base (Sigma-Aldrich), dissolved in artificial cerebrospinal fluid (10 mM at pH 7.4), was microinfused into the amygdala (bilaterally) via 33-gauge infusion cannulae that protruded 1 mm beyond the guide cannulae (cf. Kim et al., 2005). An infusion

volume of 0.3 mL (per side) was delivered using a Harvard PHD2000 syringe pump (Harvard Apparatus) over the course of 3 min. Animals were returned to their home cages for 30 min before undergoing the stress procedure. We based the timing of inactivation on previous findings that pre-stress but not immediate post-stress inactivation of the amygdala interferes with stress effects on hippocampal long-term potentiation (LTP) and spatial memory (Kim et al., 2005). Based on studies that examined 3H-muscimol spreading (Krupa et al., 1993; Arikan et al., 2002) in the cerebellum, in which 1 mL diffused a radius of 1.6–2.0 mm, it was estimated that 0.3 mL of muscimol would spread within a radius of approximately 0.5–0.7 mm from the infusion needle tip. Hence, it is likely that infused muscimol would have diffused to the central, lateral, and basal nuclei of the amygdala and possibly to portions of adjacent neighboring structures. The BODIPY TMR-X muscimol conjugate (Invitrogen) was infused in the same manner as muscimol free base (cf. Allen et al., 2008) to image the spread of reversible amygdalar inactivation.

Corticosterone (CORT) animals received three daily subcutaneous injections of 3 mg/kg corticosterone (suspended in sesame oil; Sigma-Aldrich) 30 min prior to bias testing.

Stress. Rats undergoing stress were restrained in Plexiglas tubes and presented with 60 tailshocks (1-mA intensity, 1-sec duration, 5- to 115-sec variable intershock interval) for 60 min (cf. Kim et al., 2005).

Figure-8 Maze. The elevated maze is in the shape of an open square with a center bridge runway that connects the front edge runway with the back edge runway. The maze has four acrylic gates, actuated by air-regulated pneumatic cylinders, that ascend (30 cm above the maze surface) and descend (leveled to the maze surface) to block or allow the rat to pass. The water reward was delivered at three locations (center, left and right runways) via solenoid valves. An

I/O card and an analog video frame grabber card (National Instruments, Austin, TX) were used to control the gates and water delivery and to capture images from a camera over the maze, respectively. The maze system was controlled by a PC, using custom software written in LabView (National Instruments).

Histology. At the completion of behavioral testing, animals were overdosed with urethane and perfused intracardially with 0.9% saline followed by 10% buffered formalin. The brains were removed and stored in 10% formalin overnight and then kept in 30% sucrose solution until they sank. Transverse sections (50 mm) were taken through the extent of the cannulae tract, mounted on gelatin-coated slides, and stained with cresyl violet to verify cannulae placements.

Procedure. Following 2 d of habituation (to transport, maze, and room ambiance), all animals underwent successive shaping and testing phases. During shaping, each rat is placed into the center runway with all four gates in the up position (Figure 2.1A). After 3 sec, the front and one of the side gates drop, until the rat on its own volition moves out of the center and onto the open side runway. At this point, the lowered front and side gates rise (to prevent the rat from going backward), water is delivered to both the open arm and the center spout, and the back gate drops. The rat consumes water from the side arm (0.04 mL), and a new trial begins when he returns to and consumes water from the center arm (0.04 mL). The side-arm rewards occurred pseudo-randomly on 80% of total trials, so that when the rat progressed to free-choice trials in subsequent phases, it would be encouraged to explore both sides of the maze. The reward at the center platform was present only on trials in which a rat received water on a side arm ($p = 0.8$). There was a 3-sec delay between each trial.

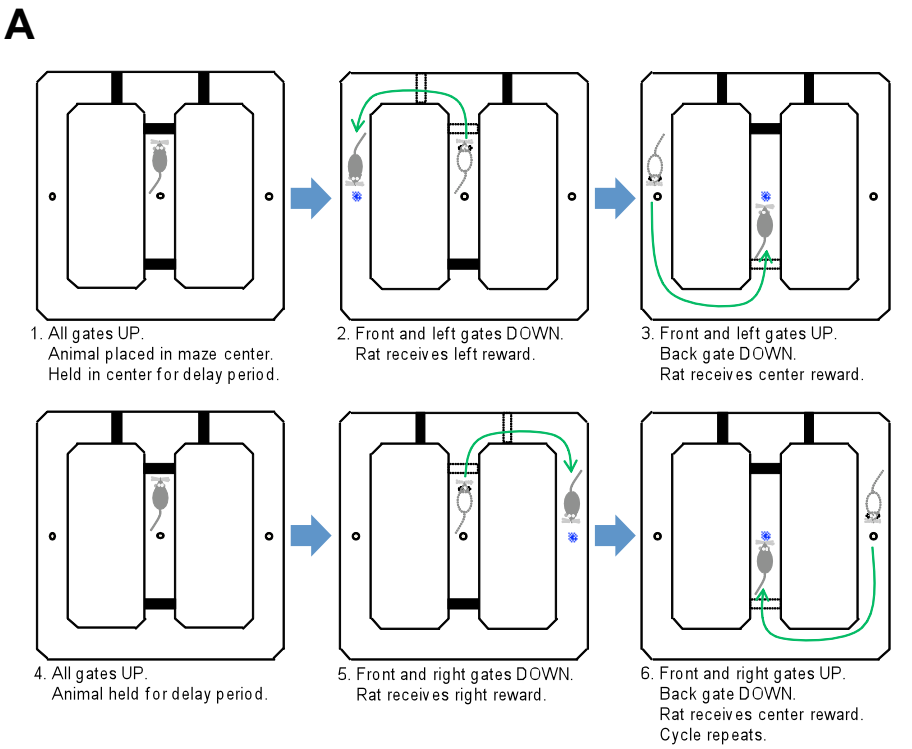

Figure 2.1. Shaping and Baseline procedures. There are four gates represented by rectangles (filled = UP position; blank = DOWN position). Side and center rewards were equal in probability (0.8) and volume (0.04 ml). **(A)** Shaping (forced choice; 40 laps). **(B)** Baseline (free choice; 40 laps).

During shaping, left and right choices were thus forced choices and were presented in a pseudorandom pattern, such that there was an equal number of both in a complete session (40 laps). Here, and in subsequent chapters, "forced choice" refers to trials in which rats are forced to go a single direction, while "free choice" refers to trials in which rats can choose between left or right reward arms. Rats underwent shaping once daily until they met predetermined criteria: completion of 40 laps in less than 30 min, and less than five total back edge errors (i.e., after making a choice, running up the opposite arm instead of going back to the center arm). The automated program controlled the gates and water delivery, according to the rat's position on the maze.

During baseline testing (Figure 1B), the rewards dispensed on left and right arms were equal in both volume (0.04 mL) and probability (0.8). Each rat remained on baseline testing until he demonstrated a stable (i.e. consistent) left/right choice pattern across three consecutive days. If a slight preference to one side was present, the opposite arm would be the increased reward side when bias testing commenced.

Stress and AMYG rats were exposed to restraint + tailshock stress 1 d before their first bias test, and CORT rats were given corticosterone injections 30 min prior to each bias test. During bias testing, the reward value on one side was tripled in volume (0.12 mL), while the value for the other side remained constant (0.04 mL). The probability of the rewards remained equal (0.8). Control, AMYG, and CORT animals were given three consecutive days of bias tests, and stress animals underwent six consecutive days of bias tests.

Data Analysis. The visit number to the left (or right) side of the maze for baseline and bias days were normalized to the mean left (or right) visits across the three baseline days. Statistical comparisons between groups were examined using ANOVA. For a significant

difference ($p < 0.05$), post-hoc comparisons were performed using Tukey's honestly significant difference test.

Results

Thirst-motivated rats readily learned to forage for water on the maze: when left and right sides of the maze provided the same quantity (0.04 mL) and probability (80%) of water, the animals made comparable numbers of left and right visits (during 40 laps daily) that were stable across three baseline days (Figure 2.2A). The 80% probability (a partial reinforcement schedule) was used so that animals frequently explored both sides of the maze. After animals demonstrated stable baseline choices, the volume of water on one side was tripled (0.12 mL at 80%), while the other side remained constant (0.04 mL at 80%). Overall, bias performance (choice of the larger reward) increased across the first three bias test days (repeated-measures ANOVA; main effect of day, $F_{(2,54)} = 78.16$, $p < 0.001$). However, the four groups differentially increased their bias across days (group X day interaction, $F_{(6,54)} = 4.14$, $p < 0.01$). Specifically, stressed rats displayed a significantly slower rate of bias toward the larger reward than did the controls ($p < 0.01$, Tukey). The stressed rats did ultimately develop a bias compared with their baseline choices ($F_{(6,62)} = 8.44$, $p < 0.001$). This bias was first significant on the fourth day of unequal reward testing (day 7 overall; $p < 0.05$, Dunnett t-test relative to average of days 1-3). However, even after 6 d of bias testing, their bias (127 $\pm$ 5.7%, mean $\pm$ SEM) did not reach the level of controls' third day bias (182 $\pm$ 12.2%). Unlike the behavioral stress group, however, animals that received three daily corticosterone injections (3 mg/kg, subcutaneously) prior to testing chose the larger reward side more frequently (173 $\pm$ 6.7%, bias day 3) and did not differ from the control group ($p > 0.05$, Tukey).

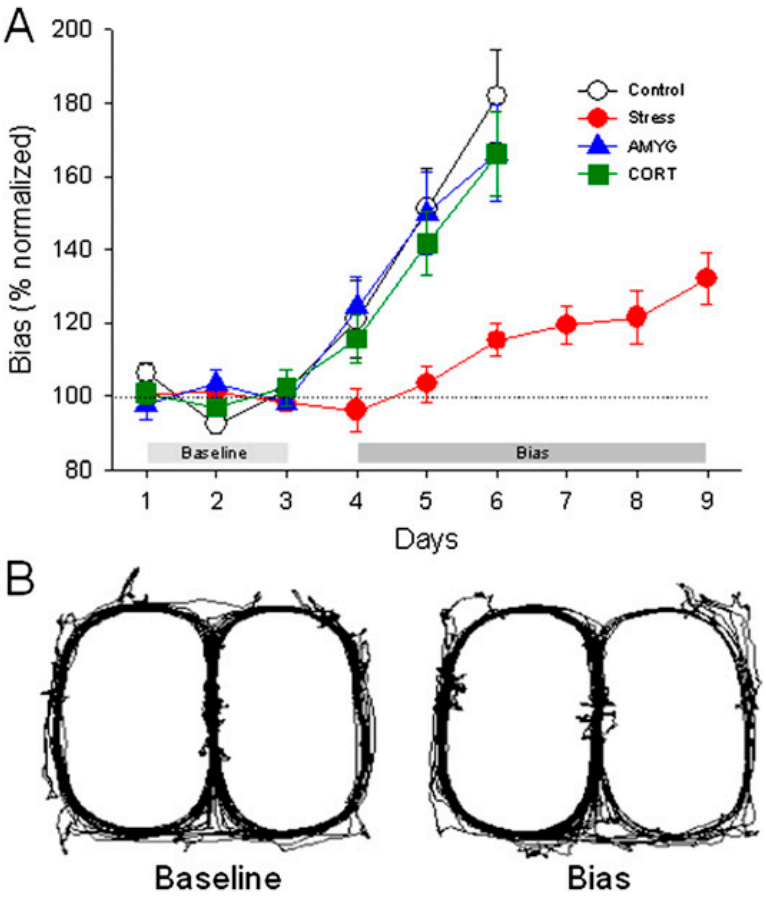

Figure 2.2. Stress effects on decision making. **(A)** All groups of animals showed comparable visits to left and right sides of the maze during the three baseline days. The bias measure is obtained by normalizing each rat's daily percent choice of the larger reward (*Bias*) to his average baseline performance ($\bar{X}$; [*Bias* ÷ $\bar{X}$] x 100). When transitioning from equal to unequal reward trials, stressed rats (n = 7) displayed an impaired ability to bias their responses toward the larger reward side compared with control (n = 10), AMYG (n = 7), and CORT (n = 7) rats. **(B)** Example visit maps of a control rat during baseline and bias days (40 laps each).

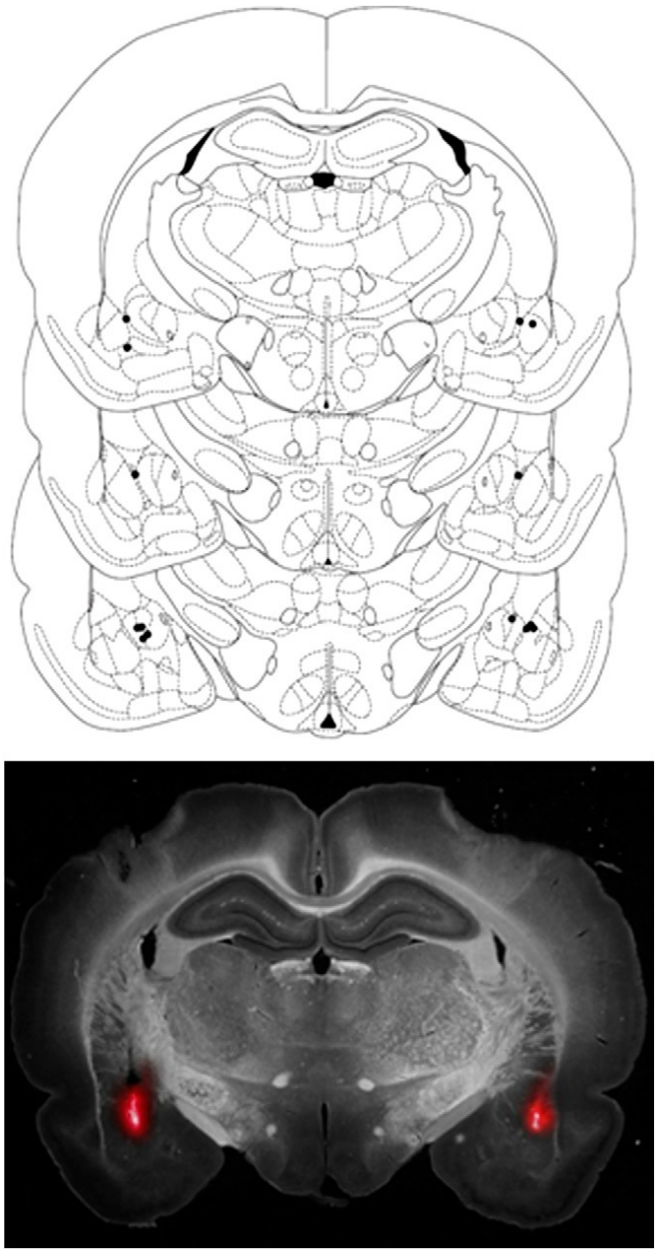

Figure 2.3. *(Top)* Histological reconstruction of injection cannulae placement tips in the amygdala. *(Bottom)* A photomicrograph of fluorophore-conjugated muscimol (0.3 µL over 3 min) spread in the amygdala. The red fluorescence is overlaid with a dark field image.

When the amygdalae were inactivated during stress (Figure 2.3), these animals behaved like controls ($p > 0.05$, Tukey) and increased their visit frequency toward the larger reward side of the maze (174 $\pm$ 13.0%, bias day 3; Figure 2.2A). Although control, CORT, and AMYG, animals developed strong bias responses, they did not exclusively visit the larger reward side of the maze because on 20% of trials they did not receive a reward. That is, they approached an asymptotic rate of responding that was proportional to the rate of reinforcement, as has been observed in other species and paradigms (Herrnstein, 1970).

We then examined whether stress might have produced alterations in motor, motivation, and reference memory performances that hindered the animals' ability to bias their responses toward the larger reward. The latency to complete 40 laps of the first bias test session (Figure 2.4A) did not differ across groups ($F_{(6,54)} = 1.89$, $p > 0.05$). Stress also did not impair the animals' reference memory of the maze (Figure 2.4B). That is, after making a left or right visit, stressed animals readily re-entered the center runway to start the next trial (one-way ANOVA; average baseline and first three bias days, $F_{(3,41)} = 0.20$, $p > 0.05$), whereas control, CORT, and AMYG animals displayed an increased propensity to investigate the other side before re-entering the center, particularly as bias testing progressed (repeated-measures ANOVA; main effect of day, $F_{(2,54)} = 4.84$, $p < 0.05$).

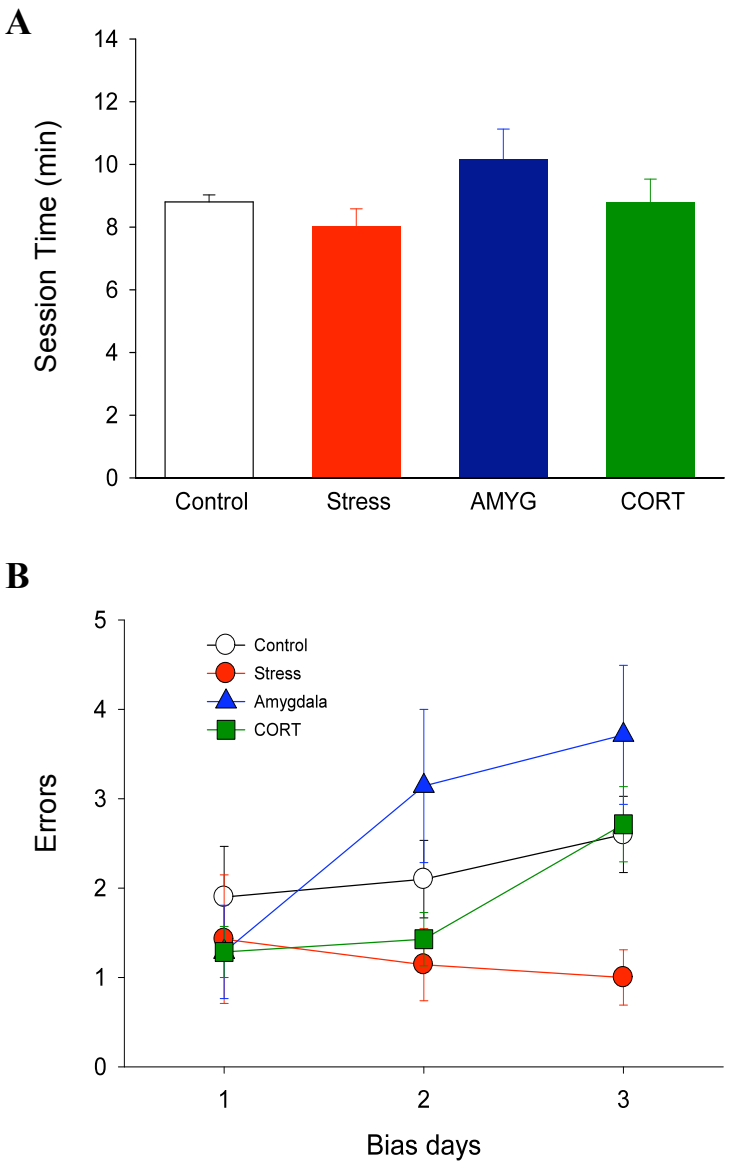

Figure 2.4. Stress effects on motivation and reference memory. **(A)** During bias testing, all groups completed the sessions in similar amounts of time. **(B)** The number of back edge errors (i.e., after making a choice, running up the opposite arm instead of returning to the center arm to begin the next trial) during the three days of bias testing.

Discussion

Our results indicate that rats clearly demonstrate the capacity to change their foraging behavior to acquire a larger water reward when transitioning from equal to unequal quantities, and that such behavioral flexibility is vulnerable to acute, uncontrollable stress. Specifically, rats that experienced 1 h of restraint stress + 60 intermittent tailshocks were significantly impaired in biasing their responses toward the side of the maze with a larger quantity of water. This effect on bias was not due to any lingering post-stress motivational or motor effects, as stress did not increase the latency to complete the bias test. Daily corticosterone injections did not interfere with this task, indicating that corticosterone elevation *per se* cannot reproduce behavioral stress effects on behavioral flexibility. However, similar to previous stress–memory studies (Kim et al., 2001; Waddell et al., 2008), amygdalar inactivation during stress effectively blocked this effect. This suggests that the amygdala plays a crucial role in mediating stress effects across different cognitive domains.

Although stress altered the rats' behavior in our choice-based task, it remains unclear precisely which neural and cognitive systems were affected. For instance, the impairment of behavioral flexibility might be an indirect consequence of stress effects on hippocampal memory functioning. The stress paradigm used here is known to impede LTP in the CA1 hippocampus and to hinder spatial memory (Foy et al., 1987; Kim et al., 2001). However, corticosterone, which also impedes LTP (McEwen & Sapolsky, 1995) and spatial memory when administered 30 min before testing (de Quervain et al., 1998), did not impair behavioral flexibility in the current study. The impairment to choose the larger reward may be due to stress effects on working memory, such that the rats cannot remember (and thus learn) that one reward is larger. However, if true, the stress-induced memory impairment is unusually persistent in our task: rats

were affected through at least 6 d beyond the stress exposure. Because acquisition and retrieval of information are integral components of decision making, the contribution of stress-associated changes in learning and memory cannot be fully excluded. Another possibility is that stressed rats are more likely to use habitual rather than flexible strategies, even when a change in behavior may be optimal. Consistent with this explanation are findings that chronic stress exposure increases habit-based responding, with corresponding atrophy and hypertrophy of goal-directed and habit-based neural circuitry, respectively (Dias-Ferreira et al., 2009). The reliance on habit memory is also increased following anxiogenic drug infusions into the amygdala (Elliott & Packard, 2008), which further implicates amygdalar modulatory activity during and after stress exposure in the decrease of flexible behavior. If the stress experience did increase perseverative choice behavior, this may partially explain previously observed associations between distress and perseveration in humans (Robinson et al., 2006). Alternately, stress may have disrupted the reward circuitry and impaired the ability to discriminate between the two reward values from the two side arms, in which case stress effects on a dopamine-related reward circuit (Schultz et al., 1997) should be explored. However, this cannot be the sole explanation because stress that was experienced after bias acquisition did not affect the animals' subsequent bias behavior toward the larger reward (Table 2.1), and nonstressed rats resume equal arm visits when rewards are returned to baseline values (data not shown).

Table 2.1. Summary of baseline (BL) and bias days for all groups. Post-bias rats (n = 4) received stress exposure (restraint + tailshock, 60 min) after their third bias test and 1 d before their fourth bias test.

	Groups				
	Control	Stress	AMYG	CORT	Post-bias
BL1	107.0±2.9	95.7±3.1	99.7±3.8	97.2±2.8	96.8±4.1
BL2	92.9±2.7	96.0±2.6	100.9±4.4	93.5±2.5	95.5±3.8
BL3	100.2±2.1	93.4±3.5	97.3±1.7	99.2±6.1	107.7±7.8
Bias1	121.5±10.2	91.0±5.2	114.0±10.4	111.8±7.0	120.3±9.7
Bias2	152.1±10.7	98.3±5.6	142.7±16.4	137.5±10.4	152.8±11.3
Bias3	182.8±12.3	109.4±4.8	153.1±20.0	161.2±13.2	180.6±15.5
Bias4		113.2±5.2			185.9±11.5
Bias5		115.1±6.7			193.9±11.7
Bias6		124.7±5.1			217.4±21.3
Bias7					216.1±13.4

Mean ± *SEM*; Bias value > 200 indicates that the post-bias animals had a baseline below 20/40.

The present findings reveal that a single exposure to an acutely stressful experience is enough to affect an animal's behavior on a simple forging task for several days. There is accumulating evidence that exposure to stress increases amygdala and decreases prefrontal activity in both humans and animals (reviewed in Arnsten, 2009) and that even a single stress exposure alters cellular morphology in prefrontal cortex (Izquierdo et al., 2006). This shift in neural activity may promote the use of one cognitive strategy over another (e.g., habitual versus flexible). To address this, future studies need to investigate brain structures implicated in decision making, including the prefrontal and the parietal cortices (Gold & Shadlen, 2007; Lee, 2008), for their susceptibility to stress. Regardless, the present findings, to our knowledge, provide the first direct evidence that acute uncontrollable stress persistently impairs decision-making performance in animals and that this effect is dependent upon amygdalar activity during stress.

Chapter III. Prefrontal Contributions to Reward-Motivated Behavior

Introduction

In humans, other primates, and rodents, particular regions within the prefrontal cortex (PFC) are hypothesized to contribute to distinct aspects of decision making, including error detection, probability discrimination, and outcome valuation. One major role of the PFC is to promote optimal flexible behaviors in the presence of a changing environment (Arnsten, 2009). In the previous chapter, I reported findings that exposure to acute stress disrupts subsequent bias acquisition in rats that are presented with an increase in one of two reward values, and this disruption is dependent on amygdalar activity during the stress exposure (Graham et al., 2010). One explanation for the persistent behavioral disruption is that increased amygdalar activity persists over several days and reduces behavioral flexibility by decreasing PFC activity (e.g., Dias-Ferreira et al., 2009). It has been well-supported that exposure to stress disrupts PFC-dependent behaviors, and that the PFC itself is sensitive to stress effects (for review see Arnsten, 2009; Leuner & Shors, 2012). Thus, as the PFC is both sensitive to stress and implicated in a broad range of decision-making tasks, the stress disruption to optimal reward-motivated behavior may be explained by the amygdalar inhibition of PFC such that one or more aspects of decision making were impaired.

To evaluate the hypothesis that the PFC is critical for either the development or maintenance of a choice pattern based on external reward manipulations, we tested rats' ability to maintain and reverse a biased choice pattern following permanent lesions of particular PFC subregions. Rats were chronically implanted with lesion electrodes into one of three subregions of PFC: medial PFC (*mPFC*), anterior cingulate cortex (*ACC*), or orbitofrontal cortex (*OFC*).

Following recovery from surgery, rats freely foraged for water rewards on the left and right arms of an automated figure-8 maze (cf., Graham et al., 2010). After rats demonstrated stable baseline choices between the left and right rewards, either the left or right reward was increased in volume on every subsequent trial for the next two daily sessions. After bilateral electrolytic lesions of the assigned PFC subregion (*mPFC*, *ACC*, or *OFC*), rats repeated the initial bias test, and then progressed through three days of reversal testing, during which the large reward was switched to the opposite arm. All groups responded optimally during both test phases (that is, they increased their choice of the reward that would lead to the most water available), and the lesion groups did not differ in choice patterns from controls. These results suggest that the mPFC, ACC, and OFC are not independently necessary for updating behavioral responses based on changes in reward values.

Methods

Subjects. Experimentally naïve male Charles River Sprague-Dawley rats (initially weighing 275-300 g) were singly housed and maintained on a reverse 12-h light-dark cycle (lights on at 19:00 h). Rats were handled daily and allowed to acclimate to the home cage environment for 7 d. During the experimental phase, daily water access was restricted to maintain approximately 85% of the animal's body weight. Food was available ad libitum throughout the experiment. All experiments were conducted during the dark phase of the cycle and in strict compliance with the University of Washington Institutional Animal Care and Use Committee guidelines.

Surgery. Rats were assigned to one of four surgical groups: non-surgery control (n = 6), medial prefrontal cortex (mPFC, n = 9), anterior cingulate cortex (ACC, n = 9), and orbitofrontal

cortex (OFC, *n* = 9). Rats were handled daily during 7-10 d of postoperative recovery before beginning behavioral training. Under anesthesia (30 mg/kg ketamine and 2.5 mg/kg xylazine, i.p.), rats in the three PFC groups were chronically implanted with a stainless steel insect pin (#00), insulated with epoxy except for 0.75 mm at the tip bilaterally into the assigned PFC subregion. Target coordinates relative to bregma were as follows: *mPFC* (AP: + 2.8 mm, ML ± 0.5 mm, DV - 5.1 mm); *ACC* (four electrodes total; [1] AP: + 1.7 mm, ML ± 0.5 mm, DV - 3.0 mm; [2] AP: + 0.5 mm, ML ± 0.5 mm, DV - 2.6 mm); *OFC* (AP: + 3.5mm, ML ± 2.4mm, DV - 5.2 mm).

Electrolytic Lesions. Lesions were produced under light halothane anesthesia (a gas mask was placed on the animal while it was gently restrained) by passing constant current (1 mA, 12 s (or 10 s for each ACC target); Grass Medical Instruments) through each electrode. Rats were returned to their home cages, and behavioral testing commenced the following day.

Figure-8 Maze. The maze used was the same as that described in Chapter II.

Procedure. Following 2 d of habituation (to transport, maze, and room ambiance), animals underwent successive shaping and testing phases. During shaping, each rat is placed into the center runway with all four gates in the up position (Figure 2.1A). After 3 sec, the front and one of the side gates drop, until the rat on its own volition moves out of the center and onto the open side runway. At this point, the lowered front and side gates rise (to prevent the rat from going backward), water is delivered to both the open arm and the center spout, and the back gate drops. The rat consumes water from the side arm (0.05 mL), and a new trial begins when he returns to and consumes water from the center arm (0.05 mL). The side-arm rewards occurred pseudo-randomly on 80% of total trials, so that when the rat progressed to free-choice trials in subsequent phases, it would be encouraged to explore both sides of the maze. The reward at the

center platform was present only on trials in which a rat received water on a side arm ($p = 0.8$). There was a 3-sec delay between each trial. During shaping, left and right choices were thus forced choices and were presented in a pseudorandom pattern, such that there was an equal number of both in a complete session (40 laps). Rats underwent shaping once daily until they met predetermined criteria: completion of 40 laps in less than 30 min, and less than five total back edge errors (i.e., after making a choice, running up the opposite arm instead of going back to the center arm). The automated program controlled the gates and water delivery, according to the rat's position on the maze.

During baseline testing (Figure 2.1B), the rewards dispensed on left and right arms were equal in both volume (0.05 mL) and probability (0.8). Each rat remained on baseline testing until he demonstrated a stable left/right choice pattern across three consecutive days. If a slight preference to one side was present, the opposite arm would be the increased reward side when bias testing commenced.

Histology. At the completion of behavioral testing, animals were overdosed with urethane and perfused intracardially with 0.9% saline followed by 10% buffered formalin. The brains were removed and stored in 10% formalin overnight and then kept in 30% sucrose solution until they sank. Transverse sections (50 mm) were taken through the extent of the lesions, mounted on gelatin-coated slides, and stained with cresyl violet to verify extent and location of lesions.

Statistical Analysis. The visit numbers to the left (or right) side of the maze for baseline and bias days were normalized to the mean left (or right) visits across the three baseline days. Statistical comparisons between groups were examined using ANOVA. For a significant

difference ($p < 0.05$), post-hoc comparisons were performed using Tukey's honestly significant difference test.

Results

After histological confirmation, several lesions were either unilateral or missed the target region, so final group numbers were: Control ($n = 6$), mPFC ($n = 8$), ACC ($n = 6$), and OFC ($n = 5$). For an additional control comparison, the rats with inadequate lesions were pooled into a second control group: Miss ($n = 8$). Histological reconstructions of smallest and largest lesions for each experimental group are shown in Figure 3.1.

When the two side rewards were equal in volume and probability (*Baseline*), rats in all groups reached stable left/right choice patterns between 2 and 6 days of *Baseline* sessions. A repeated-measures ANOVA of choices during the four baseline blocks revealed no main effect of group ($F_{(4,28)} = 0.82$, $p > 0.05$). Due to the individual variance across rats during baseline performance (some had innate biases, others chose the two rewards equally), each rat's choices were adjusted based on his average choices during the four baseline blocks. This allowed for bias and reversal test performance to be directly compared across groups. During the pre-lesion *Bias* phase (2 d, blocks 5-8), all groups increased their choices of the large reward: there was a significant main effect of block ($F_{(3,84)} = 42.34$, $p < 0.001$; Figure 3.2).

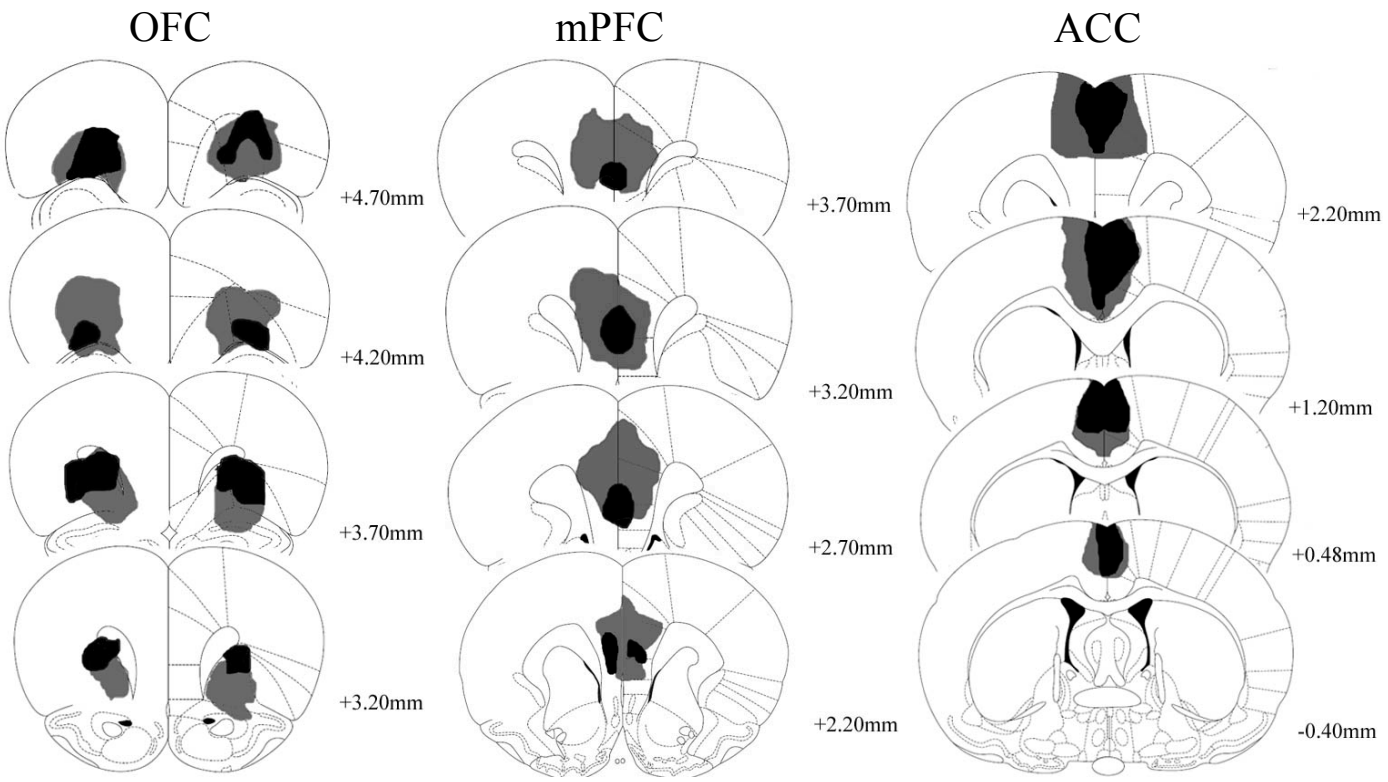

Figure 3.1. Histological reconstruction of smallest (black) and largest (grey) extent of damage at each template (relative to Bregma).

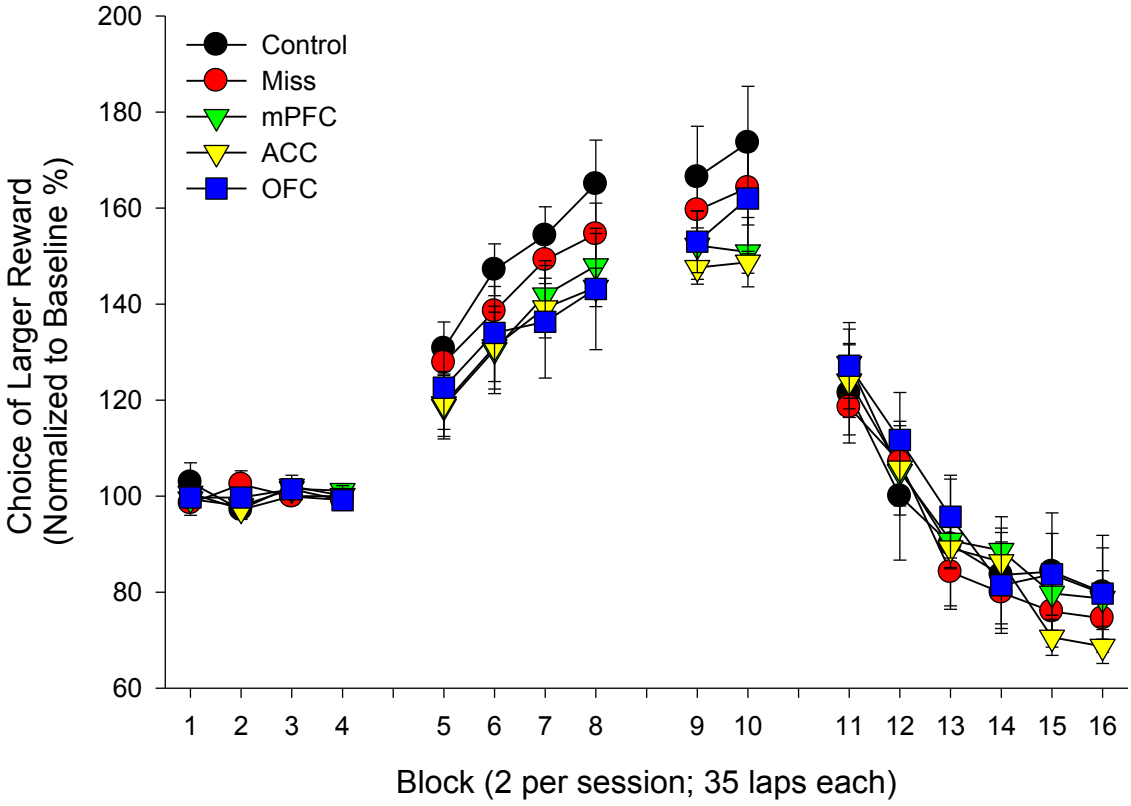

Figure 3.2. Reward Discrimination. Choices of first-biased arm during Baseline (2 d, blocks 1-4), *Bias* (3 d, blocks 5-10), and *Reversal* (3 d, blocks 11-16). All rats had one day off between the second and third *Bias* test day (between blocks 8 and 9); lesion groups underwent the lesion procedure during that day.

During the first two *Bias* days (before the lesion or the controls' day off), there was no main effect of group on choices ($F_{(4,28)} = 0.41$, $p > 0.05$), nor was there an interaction between group and block ($F_{(12,84)} = 0.28$, $p > 0.05$). Thus, all groups were similarly responsive to the first two days of reward-volume change.

The day after the second *Bias* session, control rats remained in their homecages, and all other groups received specific PFC lesions. The following day, rats resumed maze testing with a third *Bias* session, followed by three days of *Reversal* sessions. During these four post-lesion sessions, rats overall changed their choice behavior in response to the changing reward value (repeated-measures ANOVA; main effect of block: $F_{(7,189)} = 249.48$, $p < 0.001$). There was neither a main effect of group ($F_{(4,27)} = 0.09$, $p > 0.05$), nor a group by block interaction ($F_{(28,189)} = 1.05$, $p > 0.05$).

To evaluate whether other factors may have been affected by damage to PFC, we compared session times and reference memory across the groups. Session times did not differ before or after the lesion among all rats (repeated-measures ANOVA, $F_{(1,28)} = 3.71$, $p > 0.05$; Figure 3.3A). Session times also did not differ by group ($F_{(4,28)} = 0.45$, $p > 0.05$), nor was there a group by time interaction ($F_{(4,28)} = 0.60$, $p > 0.05$). Reference memory was measured by the number of back-edge errors (i.e. after making a choice, the rat runs to the other side arm instead of returning to the center arm to begin a new trial). Overall, rats made more back-edge errors during the first four days ($M = 5.39$, $SD = 2.42$) than they made during the second four days ($M = 4.19$, $SD = 2.07$; $F_{(1,28)} = 7.22$, $p < 0.05$; Figure 3.3B). However, there was no difference in overall errors made across groups ($F_{(4,28)} = 0.88$, $p > 0.05$), nor was there a significant interaction between group and time ($F_{(4,28)} = 0.55$, $p > 0.05$).

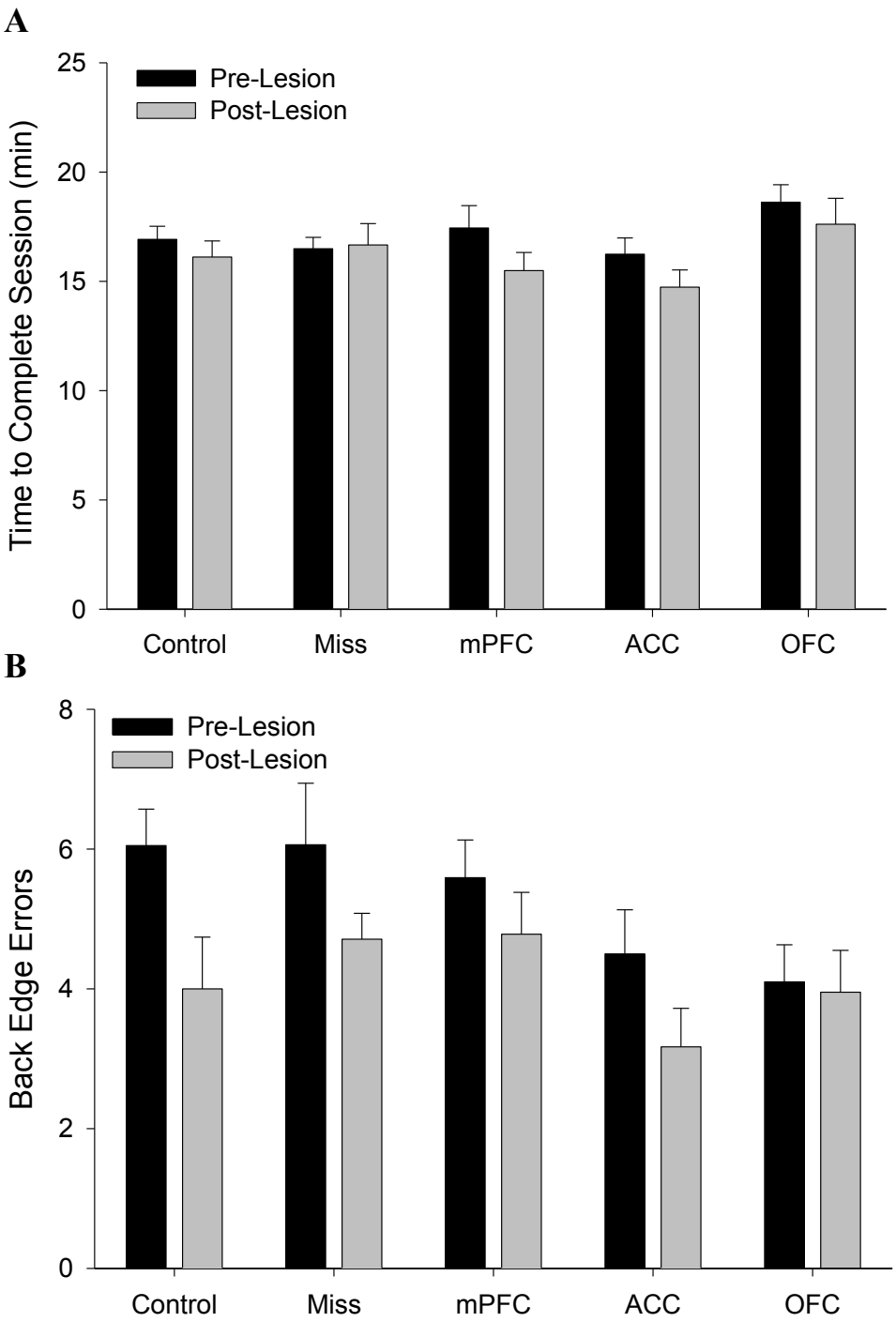

Figure 3.3. Session Times and Reference Memory. **(A)** Total times to complete daily sessions, averaged across four "pre-lesion" sessions (Baseline 2d, Bias 2d) and four "post-lesion" sessions (Bias 1d, Reversal 3d). **(B)** Back-edge errors during daily sessions, averaged across four pre-lesion and four post-lesion sessions. Pre-Lesion and Post-Lesion are named for the experimental groups, which received lesions between Bias days 2 and 3; control rats experienced a day off from testing between Bias days 2 and 3. Bars represent standard error of the mean.

For a final comparison of lesion effects on choice behavior, we looked at lap time averages by group, day (bias day 2, bias day 3, reversal day 1), choice (forced- versus free-choice laps), and reward size (small versus large). For lap-time analyses, we used a 4x3x2x2 repeated-measures ANOVA with one between-subjects factor (group) and three within-subjects factors (day, choice, reward size). There were no main effects of group ($F_{(3,13)} = 0.49$, $p > 0.05$; Figure 3.3A), day ($F_{(2,26)} = 2.35$, $p > 0.05$), or choice ($F_{(1,13)} = 3.88$, $p > 0.05$). Overall, rats took longer on laps with large rewards (12.29 sec $\pm$ 0.84, $M \pm SE$) than they did on laps with small rewards (9.65 sec $\pm$ 0.87; $F_{(3,13)} = 40.09$, $p < 0.001$). Most likely, this difference in lap time is a reflection of the increased time it took rats to consume the larger reward. This effect did not differ by group or choice (no significant interactions; ps > 0.05). However, there was a significant day X reward interaction ($F_{(2,26)} = 4.71$, $p < 0.05$; Figure 3.3B): the relative difference between small- and large-reward lap times varied by test day.

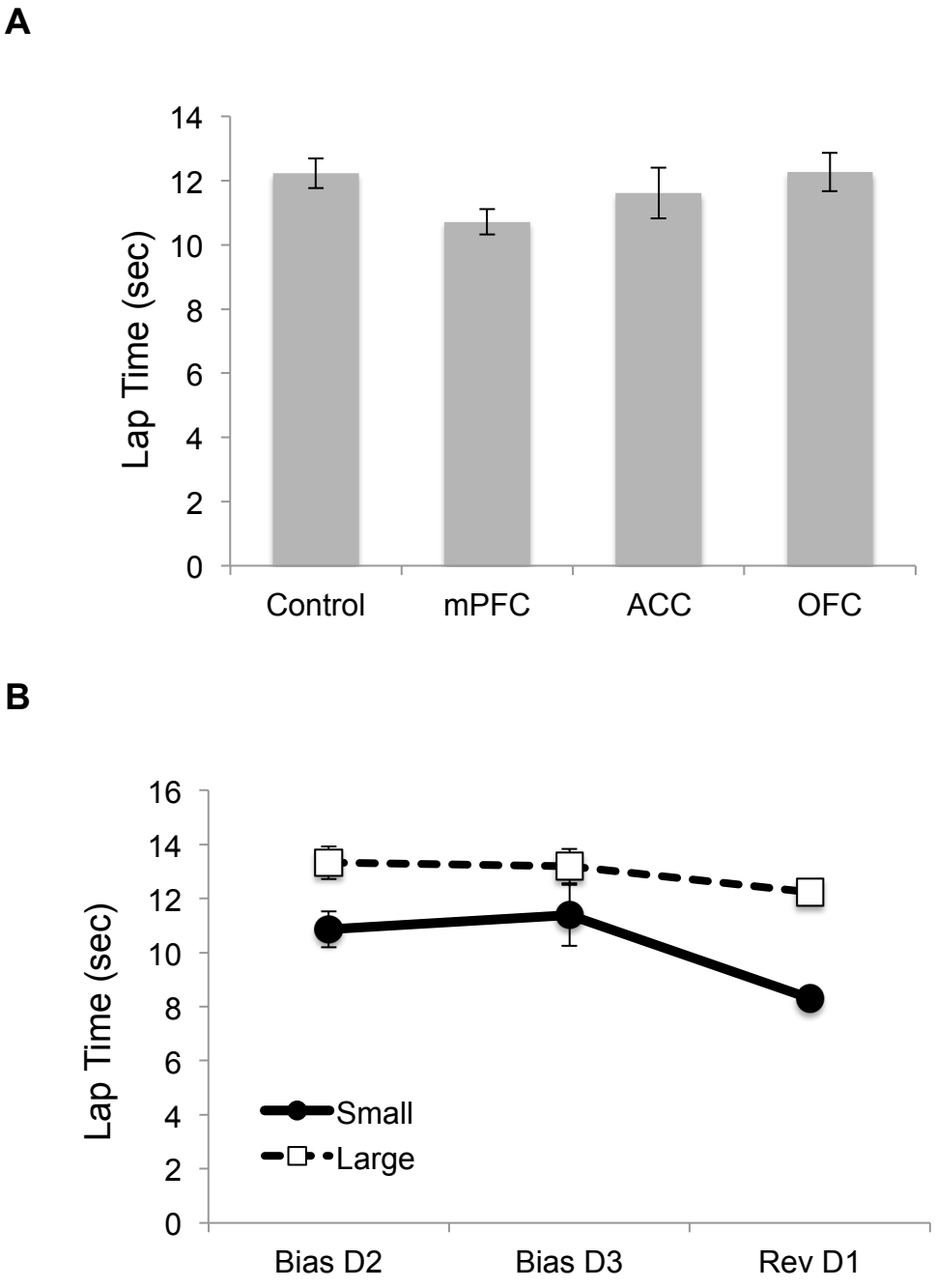

Figure 3.4. Lap Times. **(A)** Lap times averaged across days (Bias Days 2 and 3, Reversal Day 1), choice type (forced, free), and reward type (small, large) for each group. **(B)** Lap times of small versus large reward arms averaged across groups (Control, mPFC, ACC, OFC) and choice type (forced, free) for three days of testing. Bars represent standard error of the mean.

Discussion

The present study evaluated the effects of permanent electrolytic lesions to one of three subregions of the PFC on performance on a basic reward-motivated foraging task. Lesions to either the mPFC, ACC, or OFC did not alter rats' responses to a previously established response bias, nor did they affect rats' ability to respond optimally to a reward reversal. The use of chronic electrode implants allowed for lesion effects to be tested immediately (1d) after damage, rather than after a week of recovery needed when lesions are created during surgeries (Brunzell & Kim, 2001; McCormick et al., 1985). Also, this approach is ideal in minimizing the possible effects of compensation on subsequent behavior, and thus is more likely to assess the normal involvement of the PFC on reward-motivated behavior.

The OFC is believed to underlie the value processing of reinforcing stimuli and the association of reinforcers with stimuli that precede them (Padoa-Schioppa, 2011; Rolls & Grabenhorst, 2008; Schoenbaum et al., 2009). Beyond this general role, it remains unclear what specific reward-related information requires OFC processing. For example, the OFC has been implicated in reversal learning, in which animals must update previously learned stimulus-reinforcer associations (Ragozzino, 2007; Rolls, 2004; Rolls & Grabenhorst, 2008). Macaques with lesions to OFC are impaired at changing their behavior in response to reversal of reward contingencies: they may show perseverance of previously rewarded behaviors (Bohn et al., 2003; Butter, 1969; Jones & Mishkin, 1972), or responses to non-rewarded stimuli (Iversen & Mishkin, 1970). The task used in the present study requires the ability to change a response pattern in response to a reversal of reward contingencies. If the OFC were critical for re-assigning previously learned values in reversal conditions, then rats with lesions to the OFC would be expected to perseverate in their choices of the first-biased arm in the present task. Because OFC-

lesioned rats adapted to the large/small reward change at the same rate as control rats, our data suggest that reversal learning is not dependent on the OFC in rats.

Although it is currently accepted that the OFC is critical for changing previously established behavior in response to unexpected outcomes (Rushworth et al., 2011; Sescouse et al., 2010; Smith et al., 2010), Schoenbaum and colleagues have attributed this general function to the involvement of the OFC in monitoring and signaling expected outcomes, rather than to a role in either response inhibition or to associative learning (Schoenbaum et al., 2009). In fact, a recent study linked the OFC to the dopamine reward-prediction signal: rats with OFC lesions had altered dopamine error signaling, and this alteration appeared to be specific to information about the expected outcome (Takahashi et al., 2011). Thus, the results supported the role of OFC in expected outcome signaling, and suggested that this information is critical to the dopamine signaling believed to underlie reward prediction errors (Schultz et al., 1997; Schultz, 2001). Despite this modified view of how the OFC contributes to changing behavior in the face of unexpected outcomes, the lack of impairment in behavioral changes observed in our current results suggest that this role remains insufficiently characterized.

The involvement of the mPFC and the ACC in reward-motivated behavior has been less well-characterized than that of the OFC. The ACC is currently believed to contribute to the monitoring of outcomes (reinforcement and errors) that follow particular actions (Rushworth et al., 2004). One recent study found a dissociation of behavioral impairments following lesions of mPFC or ACC in rats: chemical lesions of the mPFC increased perseveration (and errors) during early phases of performance, while chemical lesions of the ACC impaired discrimination performance through a general disruption of error-correcting mechanisms (Kosaki & Watanabe, 2011). Another study examined inactivation effects of various PFC subregions in rats and found

that mPFC inactivations (but not OFC or ACC inactivations) altered choices of probabilistic rewards; specifically, rats with inactivated mPFCs chose the larger, riskier reward more often than controls when the reward probabilities decreased across a session (from 100% to 12.5%), but they chose the risky reward less often when probabilities increased across a session (12.5% to 100%; St. Onge & Floresco, 2010). The authors concluded that the mPFC is involved with updating behavior in the presence of changing reward information. Despite the paradigm differences between the discrimination task used by Kosaki and Watanabe (2011) and the probability-discounting task used by St. Onge and Floresco (2010), both studies observed an impairment in behavioral updating following changes to reward information in rats with inactive mPFCs. In contrast, although rats in the current task were required to update their behavior in response to a change in reward values (from the third bias session to the first reversal session), mPFC lesions did not interfere with this ability.

One possibility for the lack of effect of mPFC lesions on behavior in the present results is that although this region is involved in task-switching, or specifically switching between task rules or strategies (Seamans et al., 2008), the rats in the current task have already learned the overall rules of the present task before they experience their lesion. That is, post-lesion, although the rats are required to change their behavioral strategy in response to changing reward parameters, they do not need to apply a new task rule. Our results thus suggest that the neural computations needed to learn and apply a new behavioral strategy do not depend on the rodent mPFC. These results are also consistent with those found by Ragozzino (2007), who observed that rats did not rely on mPFC to learn new behavioral strategies, but did require this region to successfully replace existing strategies with new ones.

One feature of the current experimental design is that all rats are exposed to an initial bias

phase (in which rewards are unequal) before they experience PFC lesions. As discussed above, this means that the rats are not required to learn a new task rule post-lesion, but are only required to update reward values and to adjust their behaviors accordingly. It is possible that the PFC may be necessary for the initial learning of new task rules (including the reversal of reward contingencies), but that it is not necessary for responding to changes in rules after similar changes have already been experienced. One recent study supports this idea: although lesions to the OFC were previously found to disrupt rats' abilities to alter their responses following reward reversal (Boulougouris et al., 2007), rats that were trained on a reversal task were able to successfully adapt their behavior on a future reversal task that occurred after excitotoxic lesions to the OFC (Boulougouris & Robbins, 2009).

Although none of the PFC lesions disrupted overall performance in the current task, we compared performance on other measures of the task to see whether the lesions may have altered less obvious aspects of choice behavior. The groups were all similar in terms of the total time to complete daily sessions, the number of back-edge errors, and the pattern of lap times between forced-and free-choice trials, and between small and large rewards. The absence of lesion effects on session times suggests that the rats did not differ in either motivational or motor-related factors necessary for performance on the maze task. There was also no difference in overall session times between the first four and last four sessions. That is, by the time the experimental groups received their lesions (after the fourth session), general maze performance was stable. The similarities across groups in back-edge errors further supports a lack of lesion influence on another measure of general maze performance, reference memory. That is, groups did not differ in terms of their memory for maze-specific rules. Finally, there were no differences across groups in individual lap times of small versus large rewards or of free-choice versus forced-

choice trials. Thus, PFC lesions did not affect optimal choice behavior (relative to control rats), nor did they affect general performance on the maze.

It is likely that the current paradigm could be modified in ways such that optimal behavior would depend on the PFC. First, if certain cost parameters were introduced (e.g. effort or probability) that varied between the small and large rewards, then PFC lesions would likely alter choice behavior (e.g. St. Onge & Floresco, 2010). Alternately, as discussed above, the PFC may be recruited if the rats did not have previous experience with changes to reward contingencies (i.e. pre-training versus post-training lesions; Boulougouris & Robbins, 2009; but see Ragozzino, 2007). Similarly, a task that required processing of an extra-dimensional shift (e.g. a change in task rules) rather than an intra-dimensional shift (e.g. a change in reward contingencies) may require the PFC (Robbins, 1996). Finally, many of these modifications result in a general increase in task difficulty relative to the original task. It may be that regardless of the specific manipulation used, the resulting increase in difficulty may be sufficient to recruit the PFC for successful performance. As there was no apparent effect of PFC lesions on any observed behavioral measure on the present task, it is most likely that the major difference between the present task and others that are reliant on PFC functioning is the overall simplicity of the task. This should be considered in the context of interpreting PFC functions based on impairments in more complex tasks: our results suggest that it is misleading to claim that the PFC is necessary for such basic tasks as reward value processing, monitoring of outcomes (and errors) associated with actions, and updating behavior based on a changing environment. Rather, these functions likely require PFC contribution only when tasks are sufficiently complex. It remains to be seen which criteria differentiate simple and complex tasks, as well as which regions underlie these critical functions in simple tasks such as the one used in the present study.

Chapter IV. Individual Differences in Probability Discounting

Introduction

Neuroeconomics aims to describe the process by which the brain performs the various steps required to make a decision. Due to the cognitive complexity of the decision process, there is a need for specific and valid measures of decision-making ability or style. This need is particularly clear in studies of complex decisions, in which the behavioral measure may be less explicit due to the increased overall cognitive demands of the task. For example, although a choice between two rewards of the same quality but different quantity may be straightforward, additional modulators of value may complicate an otherwise simple choice. Potential outcomes may vary in terms of the effort required to obtain them, the time before they are available, or the likelihood of their occurrence. Each of these value modulators may influence decisions differently based on the individual and the context. Further, in an environment in which outcomes are not stable, an animal's choices may also reflect its ability to learn and remember new outcome values, and to flexibly adapt to the changed values. Thus, individual choices may reflect substantially more than an animal's underlying preference for particular outcome features; choices also reveal the animal's ability to learn, remember, and adapt to new information.

Because there are several stages to the decision process, it is unsurprising that there are substantial individual differences in decision-making behavior. Individual differences in valuation have been linked to specific personality traits (e.g. impulsivity, neuroticism; Augustine & Larsen, 2011; Richards et al., 1999; Holt et al., 2003) and to particular psychopathologies (e.g. addiction, depression; Bickel & Marsch, 2001; Forbes et al., 2007).

One mechanism proposed to underlie differences in preferences that involve some type of explicit cost (e.g. probability or effort) is variance in dopamine signaling (Treadway et al., 2012). The dopamine signal repeatedly has been observed to track changes in reward value, magnitude, probability, and other cost parameters (e.g. Fiorillo et al., 1999; Knutson et al., 2001; Tobler et al., 2005; Tobler et al., 2008). The initial evidence of this signal led to the proposal that dopamine may signal reward prediction errors (Schultz, 1998; Schultz et al., 1997). The reward prediction error is a critical component of the temporal difference learning model, a computational model of learning in which animals create and modify representations of expected outcomes based on recent experience (Sutton & Barto, 1998). External manipulations of dopamine activity also modulate risk-based decision making: rats tend to choose larger and riskier rewards more often when their dopamine system is up-regulated, and less often when the system is down-regulated (St. Onge & Floresco, 2009; St. Onge et al., 2010). Additional recent studies have confirmed these general results, and further found opposing influences of D1 and D2 receptor activity on risk taking (Simon et al., 2011; St. Onge et al., 2011). Thus, individual differences in dopamine signaling (e.g. from variance in sensitivity to dopamine or from variance in dopamine responsiveness) may underlie some of the observed variance in tolerance to risk, for example.

Despite the growing interest in the neural mechanisms of individual differences in decision making, it remains unclear whether the decision measures used (e.g. risk preference) may reflect some alternate cognitive measure. Knowledge of whether particular decision measures can be predicted by an individual's abilities in another cognitive task will help to inform the nature of individual differences in these measures. In the case of decision-making paradigms that evaluate repeated choices, it is a particular challenge to dissociate learning and

memory processes from other aspects of decision making (e.g. valuation, choice). Depending on the behavioral measure, an animal's atypical performance (due to experimental manipulation or individual differences) may be explained by differences in multiple cognitive factors, including learning-related abilities and valuation strategies. In a different task in which an environmental change occurs (to the context or reward parameters, for example), an animal's performance on subsequent trials additionally reflects its ability to adapt to new information, or its flexibility. Thus, if an animal does not choose the option that would lead to the most overall reward, its sub-optimal choice pattern may be attributed to its abilities in learning, flexibility, or valuation. The goal of the current study is to determine whether two measures of decision-making ability and style (probability discrimination and risk preference) are independent from abilities in other cognitive domains. That is, the study addresses the question of whether discrimination and risk preferences are objective measures of decision making that are independent of general learning-related abilities.

We examined whether individual variance among Sprague-Dawley rats on a discounting decision-making task correlates with individual variance on memory and cognitive flexibility performance. To assess decision-making ability, we used a probability-discounting task, in which animals choose between small/certain and large/uncertain rewards. The larger, uncertain reward had an expected value either 50% higher or 50% lower than the smaller, certain reward during two sequential test phases. This was based on a difference in probability of the larger reward (75% versus 25%) rather than a difference in amount of reward (0.2 mL in both conditions). We quantified individual decision-making performance based on two variables: risk preference (average preference of the large reward under high and low probabilities) and discrimination (the difference in preference of the large reward between high and low

probabilities). We correlated individual performance across several measures to determine whether individual variance in performance on a probability-discounting task could be explained by variance in either working memory or cognitive flexibility. Overall, neither working memory ability nor cognitive flexibility predicts a rat's preference for risky choices or the ability to discriminate between two uncertain outcomes. However, rats' risk preference correlated with their sensitivity to rewarded outcomes (as measured by the "Win-Stay" choice strategy; Bari et al., 2010).

Methods

Subjects. Experimentally naïve male Charles River Sprague-Dawley rats (initially weighing 275-300 g) were singly housed and maintained on a reverse 12-h light-dark cycle (lights on at 19:00 h). After 7 d of acclimation and for the duration of the experiment, daily water access was restricted to maintain approximately 85% of the animal's body weight. Food was available ad libitum throughout the experiment. All experiments were conducted during the dark phase of the cycle and in strict compliance with the University of Washington Institutional Animal Care and Use Committee guidelines.

Figure-8 Maze. The maze used was the same as that described in Chapter II. During the working memory (4d) and flexibility tasks (3d), three visual cues were located on the walls around the maze (front and two side walls). The visual cues were removed before rats began the probability discrimination tests.

Procedure. Following 2 d of habituation (to transport, maze, and room ambiance), all animals underwent successive shaping and testing phases. During shaping, each rat is placed into the center runway with all four gates in the up position (Figure 2.1A). After 3 sec, the front

and one of the side gates drop, until the rat on its own volition moves out of the center and onto the open side runway. At this point, the lowered front and side gates rise (to prevent the rat from going backward), water is delivered to both the side arm (0.05 mL) and the center spout, and the back gate drops. The reward at the center platform (0.05 mL) was present only on trials in which a rat received water on a side arm (p=0.8). The rat consumes water from the open arm, and a new trial begins when he returns to and consumes water from the center arm. There was a 3-sec delay between each trial. During shaping, left and right choices were thus forced choices and were presented in a pseudorandom pattern, such that there was an equal number of both in a complete session (40 laps). Rats underwent shaping once daily until they met predetermined criteria: completion of 40 laps in less than 30 min, and less than five total back edge errors (i.e., after making a choice, running up the opposite arm instead of going back to the center arm). The automated program controlled the gates and water delivery, according to the rat's position on the maze.

Working Memory: After completion of shaping, rats began four days of a delayed-alternation working memory task (cf., Yoon et al., 2008). During all four days, rats ran a total of 40 laps per session. The left and right rewards were each 0.05 mL and were presented on each "correct" decision: the rat was rewarded if it turned to the opposite arm than it chose on the previous trial. The center reward (V = 0.05 mL) also was delivered on each "correct" trial. During the first three days, the delay between trials (during which the rat was contained in the center arm) was 3 seconds; during the fourth and final day, the delay was 30 seconds.

Behavioral Flexibility: After completing four days of the working memory task, rats progressed through three additional days of maze testing: *Rule Shift* (1 d) and *Reversal* (2 d). During both days, rats were only rewarded on a single side (L or R, counterbalanced), and

received a total of 0.1 mL of water every time they chose the rewarded direction (0.05 mL each at the side and center arms). During *Reversal*, the reward was switched to the opposite side.

Probability Discounting: After completion of the memory and flexibility tasks, all rats began the probability discounting task, which progressed in three phases: *Baseline*, *Certain Bias*, and *Uncertain Bias*. During each phase, rats ran a total of 72 laps per session; the first 24 laps were forced-choice trials (one side gate drops, the other remains raised), and the next 48 were free-choice trials. The center platform no longer delivered a reward. During *Baseline*, the rewards dispensed on left and right arms were equal in both volume (0.1 mL) and probability (0.5). Each rat remained on *Baseline* until he demonstrated a stable left-right choice pattern across three consecutive days after at least five days. Stability was defined as a standard deviation of four percent or less across the last three days. After completing *Baseline*, rats began the *Certain Bias* phase, in which the left reward was the small-certain reward (V = 0.1 mL; p = 1.0), and the right reward was the large-uncertain reward (V = 0.2 mL; p = 0.25). Thus, the expected value (EV) for the right arm (EV = 0.05) was less than that for the left arm (EV = 0.1). The term *Certain Bias* reflects this difference: rats will gain the most reward by visiting the small, certain reward more frequently. Rats remained on this phase for 5-15 days, until their left-right choice pattern was stable across the last three days (or until 15 days had passed with no stable pattern). Rats then began the final phase of the probability discrimination task, *Uncertain Bias.* During this phase, the left reward remained the same (V = 0.1 mL; p = 1.0), and the right reward increased in probability (V = 0.2 mL; p = 0.75), so that the expected value of the right reward (EV = 0.15) was greater than that of the left (EV = 0.1).

Data Analysis. Statistical comparisons across sessions were examined using ANOVA. For a significant difference ($p < 0.05$), post-hoc comparisons were performed using Tukey's

honestly significant difference test. For bivariate correlations, the Pearson product-moment correlation coefficient was used.

Results

Working Memory As a group, rats learned the rules of the delayed alternating working memory task to an accuracy of 69.78% (SD = 32.08) by the third day of the three-second delay task (Figure 4.1A). Accuracy fell to 47.86% (SD = 22.99; i.e., chance performance) when the inter-trial delay was increased to 30 s. Overall, a repeated measures ANOVA revealed no significant effect of day on accuracy over the four working memory sessions, ($F_{(3,27)} = 2.58$, $p > 0.05$). Although the range and variance was greatest in the third day of the 3s-delay task among the four working memory sessions, the spread of individual accuracy was most evenly distributed during the 30s-delay task (Figure 4.1B).

Cognitive Flexibility (Rule Shift, Reversal). As a group, rats averaged 55% accuracy (SD = 14.16; i.e., chance performance) during the first test of flexibility, *Rule Shift*, in which rats were only rewarded for turning to one side. For the next two days, the rewarded arm was switched to the other side. Group accuracy was lower the next day, during *Reversal I*, and improved somewhat during the next day's repeated *Reversal II* test (Figure 4.1A). However, the group data violated Mauchly's Test of Sphericity ($p = 0.02$), and with the Greenhouse-Geisser correction to account for an increased likelihood of Type I error, a repeated-measures ANOVA revealed no significant effect of session, ($F_{(1.23, 11.04)} = 3.84$, $p > 0.05$). We evaluated rats' performance during these early test sessions in order to maintain individual variance that would likely diminish with repeated training as the overall group improved. Individual variance in accuracy during the cognitive flexibility tasks is presented in Figure 4.1B.

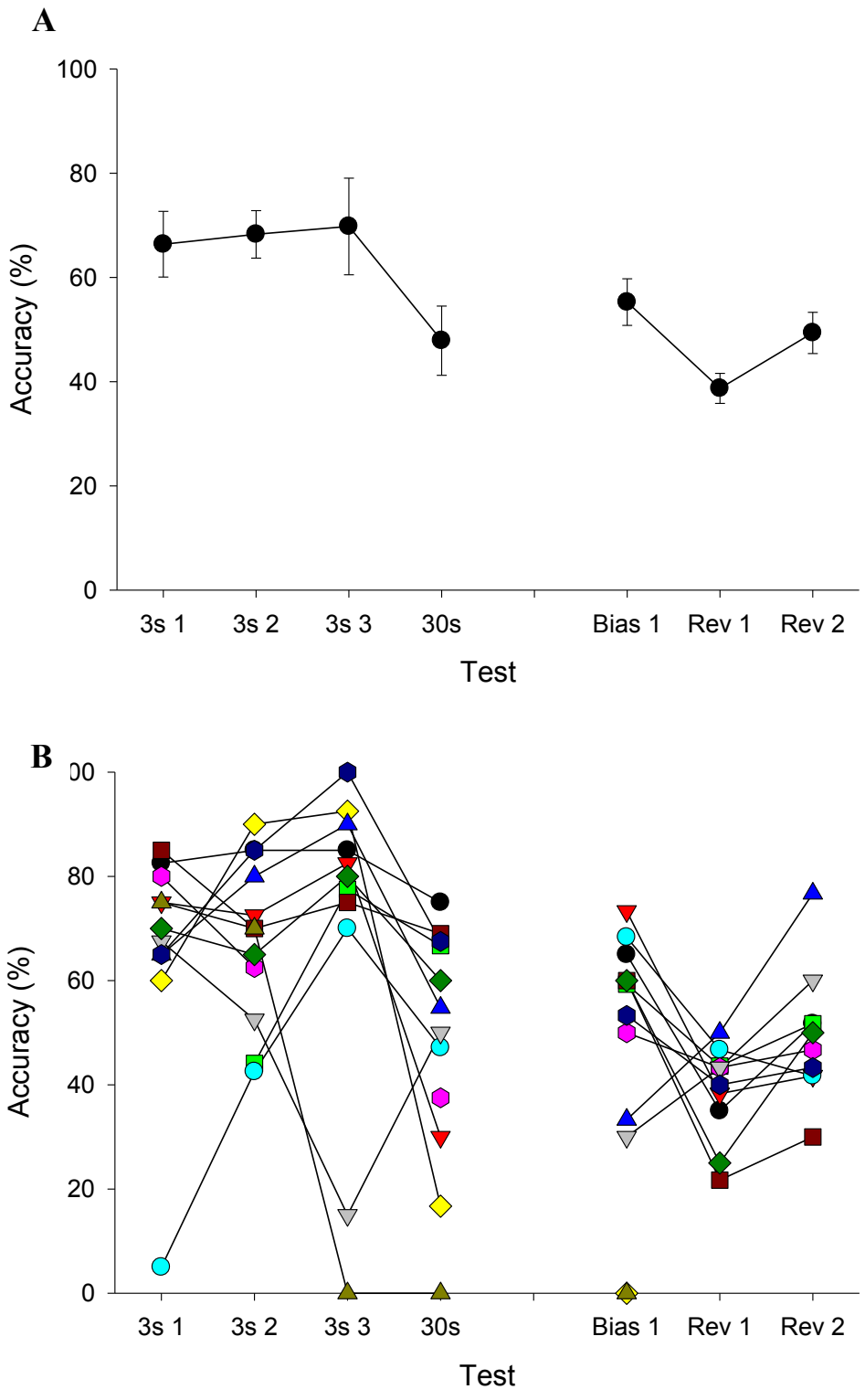

Figure 4.1. Working Memory and Cognitive Flexibility. (A) Group accuracy. Error bars represent standard error of the mean. (B) Individual performance.

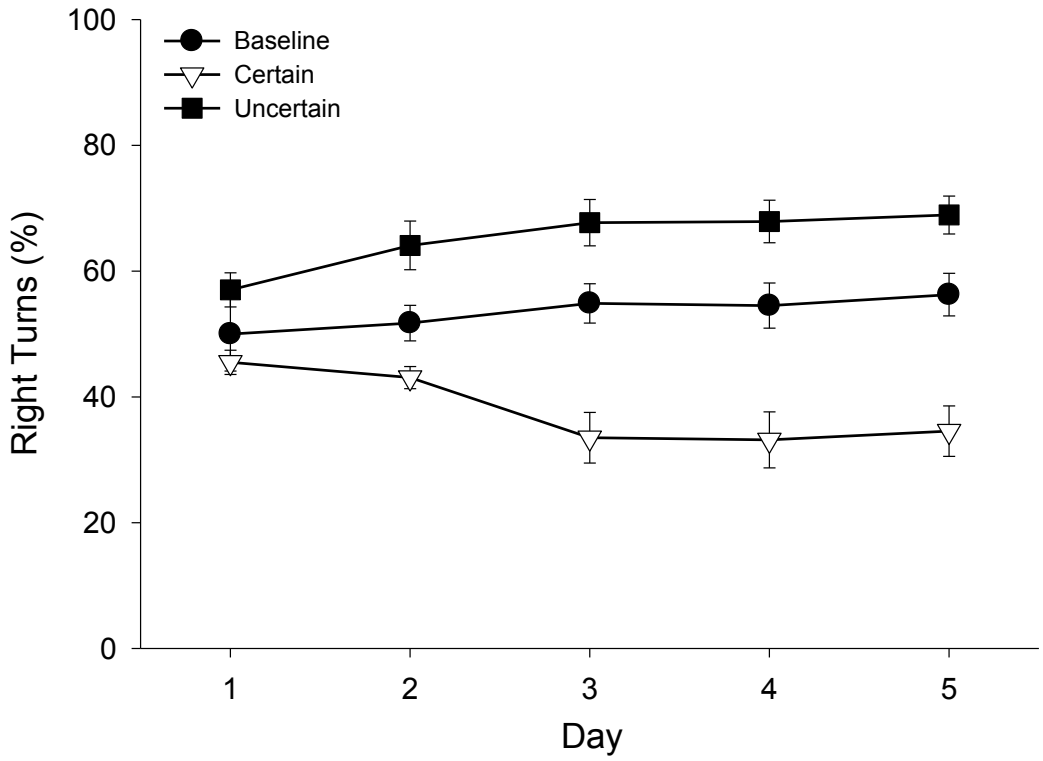

Figure 4.2. Probability Discounting. Group averages of right arm (large reward) choice during the last five days each of *Baseline*, *Certain*, and *Uncertain* phases. Bars represent standard error of the mean.

Probability Discounting. Rats adaptively adjusted their choice behavior in response to changing reward values and probabilities. When the rewards were equal in volume and probability during baseline, rats chose the two rewards approximately equally (percent choice of right arm: 55.21, *SD* = 11.25; Figure 4.2). Rats' choices were subsequently influenced by the reward and probability changes during *Certain* and *Uncertain Bias* phases: there was a significant effect of phase on choice behavior ($F_{(2,11)} = 35.23$, $p < 0.001$). Pairwise comparisons revealed that rats chose the larger reward more frequently during the *Uncertain Bias* phase (*M* = 65.12, *SD* = 4.89) than during the *Certain Bias* phase (*M* = 37.95, *SD* = 5.85; $p < 0.01$), and that choices during the two probabilistic phases were both different than those during baseline (*M* = 53.47, *SD* = 2.54; *p*s < 0.01).

Discrimination and Risk Preference values were calculated for each rat, in order to quantify decision making performance and tendency. Discrimination was defined as the difference between the percent choice of the large, uncertain reward between the final *Uncertain Bias* (X_{Uncert}) and the final *Certain Bias* (X_{Cert}) phase. The higher the difference, the more an animal was optimizing their overall reward levels (assuming that they chose the large reward more often during the *Uncertain* phase than during the *Certain* phase, which was true of all rats). The group mean Discrimination value was 36% (*SD* = 14.18). Risk Preference was defined as the average of each rat's large-reward choices during the two final *Bias* phases ($[X_{Uncert} + X_{Cert}] \div 2$). Rats with high values may be considered risk-preferring, and rats with low risk preference values may be considered risk-averse. As a group, rats had a Risk Preference mean of 50.93% (*SD* = 10.66).

Individual Predictors of Decision Making. Individual performance on the probability discounting task was compared with performance on the working memory and cognitive

flexibility tasks, in order to evaluate whether specific measures of decision-making performance reflect other types of cognitive abilities. All rats chose the large reward more often during the *Uncertain Bias* phase than during the *Certain Bias* phase, and ranged in Discrimination from 20.83% to 66.67%. In terms of individual Risk Preference scores, 58% of the 12 rats had scores between 40 and 60%. The lowest Risk Preference score was 37.50% (X_{Uncert} = 52.08, X_{Cert} = 22.92), and the highest was 69.79% (X_{Uncert} = 83.33, X_{Cert} = 56.25).

Discrimination did not significantly correlate with Risk Preference (r = - 0.31, p >0.05). Neither decision-making measure significantly correlated with any of the accuracies on the working memory and cognitive flexibility tasks (Table 4.1, ps > 0.05). Accuracy during the 30s-delay working memory task positively correlated with accuracy during the Rule Shift task (r = 0.69, p < 0.05; Figure 4.3A), but this relationship is due to two rats who performed both tasks with less than 20% accuracy (each rat primarily or exclusively chose one side during both tasks); when those two rats are removed from the analysis, the correlation is non-significant (r = - 0.13, p > 0.05). Accuracy during the Rule Shift task correlated negatively with accuracy during the Reversal II task (r = - 0.71, p < 0.05; Figure 4.3B). Because these two measures of cognitive flexibility were not positively correlated (and thus do not likely measure the same aspect of flexibility), a third global flexibility variable was created from the sum of the accuracies during the Rule Shift and Reversal II tasks (Flex [RS + Rev]). This additional measure did not significantly correlate with any of the working memory or decision-making measures (Table 4.1, ps > 0.05).

The final individual measures were choice-by-choice analyses of sensitivity to reward feedback. Specifically, we calculated "Win-Stay" and "Lose-Shift" ratios that served as indexes of the sensitivity to positive and negative feedback, respectively (Bari et al., 2010; Stopper &

Floresco, 2011). The Win-Stay measure is the proportion of risky choices that followed a risky win (relative to all risky wins); the Lose-Shift measure is the proportion of safe choices that followed a risky loss (relative to all risky losses). Individual Win-Stay performance positively correlated with individual Risk Preference ($r = 0.85$, $p < 0.01$): rats with higher preference for the large, risky choice were more likely to choose the largereward following a risky win.Because these measures were obtained from performance on the same task, it was possible that there relationship was driving by a third variable. Specifically, the total number of risky wins positively correlated with both Risk Preference and Win-Stay performance (rs = 0.81, 0.65, respectively; ps < 0.05). Thus, both Risk Preference and Win-Stay performance may be independent consequences of choosing the risky reward more frequently. To test this explanation,we ran a partial correlation controlling for each rat's total number of risky wins. Win-Stay performance positively correlated with Risk Preference, even after controlling for risky wins ($r = 0.72$, $p < 0.01$). No other choice-strategy correlations were significant (Table 4.1).

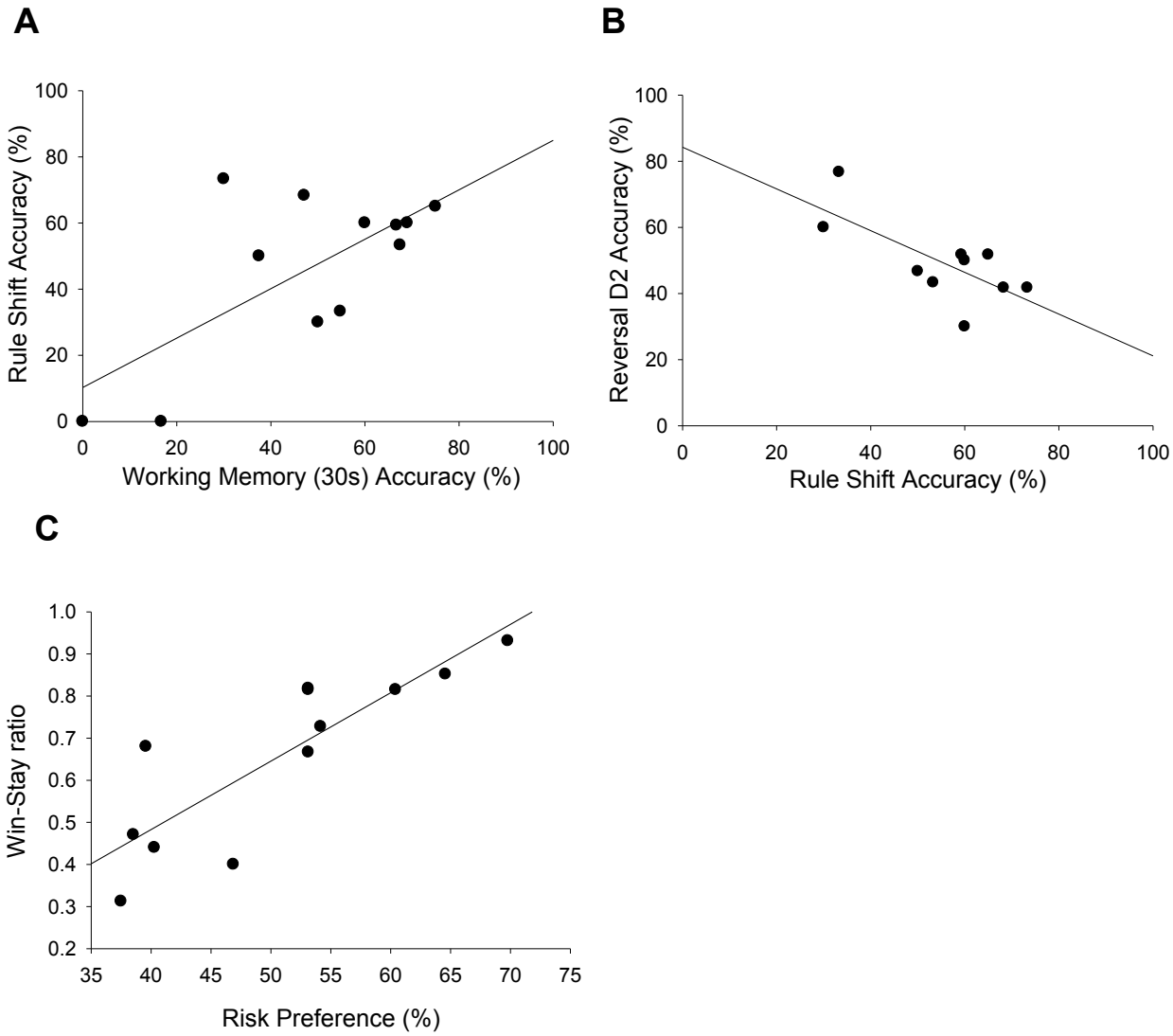

Figure 4.3. Significant correlations of individual performance between (A) the 30s delay working memory task and the Rule Shift flexibility task, (B) the Rule Shift flexibility task and the second day of the Reversal flexibility task, and (C) Win-Stay performance and Risk Preference.

Table 4.1. Summary of bivariate Pearson Correlation values (*r*).

Variable	WM 3s	WM 30s	Rule Shift	Rev Day 2	RS + Rev	Win Stay	Lose Shift	Disc
Working Memory (3s)	1.0							
WM (30s)	0.07	1.0						
Cog Flex (Rule Shift)	-0.10	0.69*	1.0					
Cog Flex (Reversal 2)	0.01	- 0.02	- 0.71*	1.0				
Flexibility (RS + Rev)	- 0.21	- 0.04	0.51	0.24	1.0			
Win-Stay	- 0.34	- 0.13	- 0.26	- 0.09	- 0.08	1.0		
Lose-Shift	- 0.21	0.43	0.44	- 0.01	- 0.22	- 0.48	1.0	
Discrimination	0.33	0.40	0.02	0.44	0.04	0.12	- 0.21	1.0
Risk Preference	- 0.48	- 0.27	- 0.25	- 0.43	- 0.03	0.85*	- 0.44	- 0.36

* $p < 0.05$

Discussion

This experiment evaluated whether individual differences in two measures of decision-making performance on a probability-discounting task correlated with performance in other cognitive domains. Generally, rats' performance on the decision-making task was not predicted by their accuracies in three distinct tasks: a delayed-alternation working memory task, a rule-shift bias task, and a reversal-learning bias task. Although there was a positive relationship between accuracy during the 30s-delay working memory task and accuracy during the rule-shift flexibility task, this relationship was non-significant after the removal of two subjects who performed at less than 20% accuracy on both tasks due to a persistent internal choice bias. Thus, overall there was no predictive relationship between working memory and flexibility performance.

The rats experienced two tests of cognitive flexibility: one that measured responsiveness to a change in task rules ("Rule Shift"), and a second that measured responsiveness to a change in reward variables ("Reversal"). In our tasks, accuracies on the two flexibility tasks were negatively correlated, such that rats who performed better during the Rule Shift task performed worse during the Reversal task. In both tasks, a high accuracy was achieved by frequent selection of the correct reward, which was in the opposite location in the two tasks. Thus, in the current study, the ability to learn and apply a new rule (from previous response-dependent to location-dependent reward) conflicted with the ability to learn and apply new reward contingencies. A common term used in psychology for the ability to learn new task rules is attentional set-shifting. In humans, this can be measured using the Wisconsin Card Sort Task (Berg, 1948). During this task, subjects are asked to sort individual cards into multiple piles, and they have to learn by trial-and-error which rule guides correct responses during different phases

of the task. Performance on this task is impaired in patients with certain clinical conditions (e.g. schizophrenia, Parkinson's disease; Owen et al., 1993; Weinberger et al., 1986). However, one review of the impairments observed in patients with schizophrenia concluded that the deficits are more likely due to a generalized intellectual impairment, rather than to a specific impairment of rule-shift behaviors, or even to a general impairment of executive function (Laws, 1999). This highlights the need for further exploration of the cognitive requirements of such "executive function" tasks, and the present study's assessment of individual performance across multiple tasks suggests that in the case of cognitive flexibility, neither rule-shift nor reversal learning behavior should be used as a sole measure of flexibility in rats.

In the present study, probability discrimination did not correlate with any other behavioral measure. These results suggest that discrimination is not strongly influenced by a rat's abilities in working memory or flexibility, nor is it influenced by a rat's choice strategy in terms of sensitivity to positive and negative feedback (Win-Stay versus Lose-Shift, respectively). The ability to discriminate between probabilities is critical when evaluating an uncertain (risky) reward, which is a necessary step in the process of deciding between probabilistic outcomes. Substantial developments have been made in identifying neural correlates of reward risk (e.g. Bossaerts et al., 2008; Schultz et al., 2011). Although we did not observe a relationship between another cognitive measure and probability discrimination, our results did reveal a broad range of individual discrimination measures (about 20% to nearly 70%). As a group, the rats successfully discriminated between the high and low probability phases (average discrimination was 36%); however, the substantial individual variance in this measure suggests the presence of some moderating factor that differs among individuals. This measure of decision making can be considered as an index of successful performance on this task, because the greater the

discrimination, the more overall reward is received. Thus, the identification of a factor that modulates probability discrimination would contribute insight to what underlies general differences in optimal decision making.

The other measure of decision-making performance used in this study was Risk Preference, or the overall preference of the large, risky reward. As with probability discrimination, this measure did not correlate with accuracies on the working memory or cognitive flexibility tasks, suggesting that it is a stable measure of preference that is not influenced by general learning abilities. However, the choice-by-choice analysis of behavior during the probability discounting task revealed a positive correlation between risk preference and the "Win-Stay" measure, or the likelihood of choosing the risky reward after a risky win. The two choice strategies (Win-Stay and Lose-Shift) were used as indexes of sensitivity to positive and negative feedback, respectively (Bari et al., 2010). The relationship between Win-Stay and Risk Preference remained strong after partialling out a third variable, the total number of risky wins for each rat. Thus, our data suggest that rats who were more strongly influenced to choose the large reward after a large win (i.e., had greater sensitivity to positive feedback) demonstrated a greater overall preference for the large, risky reward. Some recent studies have explored the neural bases of these two choice strategies. Bari and colleagues (2010) manipulated serotonin levels in rats and observed changes in choice strategies dependent on selective-serotonin reuptake inhibitor (SSRI) dose (high versus low) and treatment (acute versus chronic). Overall, acute treatments modulated negative feedback sensitivity, and chronic treatments influenced reward sensitivity. Further, serotonin increases (through SSRI treatment) and decreases (through forebrain degeneration of 5-HT neurons) had opposite influences on reward sensitivity. Floresco and colleagues have observed changes to choice strategies in a lever-

pressing probability discrimination task in rats following manipulations of specific brain regions: a disconnection between the PFC and amygdala reduced Lose-Shift tendencies without affecting Win-stay performance (St. Onge et al., 2012), and inactivations of the nucleus accumbens selectively reduced Win-Stay tendencies without affecting Lose-Shift performance (Stopper & Floresco, 2011). As the current study revealed no relationship between Win-Stay and Lose-Shift performance, and further found a relationship between Risk Preference and Win-Stay (but not Lose-Shift), our results are consistent with the previously observed dissociations between these two choice strategies.

The relationship between reward sensitivity and risk-taking behavior is unclear. Pathological gamblers, who exhibit high levels of risky behavior, have recently been observed to have reduced sensitivity to reward in general, in the context of both delayed and probabilistic rewards (Miedl et al., 2012). Specifically, the authors observed an increase in the discounting of rewards in a delay condition, but a trend toward a decrease in the discounting of probabilistic rewards relative to non-gamblers. The relationship observed in the current findings may thus reflect a cost-specific effect of reward sensitivity on risky behavior. However, one explanation of drug addition is that addicts have developed a reduced sensitivity to reward, such that higher doses are needed to experience the same pleasure (and the same dopaminergic response; Robbins & Everitt, 1999; Volkow et al., 2002). A similar reduction in reward-related neural activity (e.g. in ventral striatum) has been observed in pathological gamblers, relative to control individuals (Reuter et al., 2005). However, it remains unclear whether these differences in reward sensitivity observed in clinical populations were present before they developed behavioral pathologies; possibly, an early hypersensitivity to reward increases choices of higher value but more costly

rewards, and over repeated exposure to high value rewards, the reward system compensates and becomes hypoactive relative to controls.

Recently, one study reported that children have high levels of risk preference compared with adolescents (moderate levels) and young adults (low levels; Paulsen et al., 2011). In the context of the current results, high risk preference may be driven by an increased sensitivity to rewarded outcomes. This explanation is supported by earlier results from a different group, who reported that children with oppositional defiant disorder show an increased preference for large, costly rewards, and that this preference correlated with greater physiological responses to reinforcement (heart rate and skin conductance; Luman et al., 2010). If, as the current results suggest, reward sensitivity is predictive of tendencies toward risky behavior, then individual differences in risky behavior may be driven by differences in the neural processing of reward.

Chapter V. General Conclusions

The studies presented in this dissertation explored the sensitivity of decision-making performance in rats to stress, to manipulations in prefrontal cortex, and to individual abilities in related cognitive domains. In the first study, rats who had experienced an acute, uncontrollable stressor were subsequently impaired at optimally updating their choice behavior in response to a change in reward values. This effect could not be reproduced with injections of the stress hormone corticosterone alone, and it was dependent on amygdalar activity during the stressful experience. In general, the amygdalar-dependent stress effects reflected an increased likelihood that rats would continue their pre-stress behavioral patterns, despite the consequence of obtaining less overall reward than if they had updated their responses. The amygdala is known to directly affect particular brain regions during and after stress exposure, including the hippocampus (Kim & Diamond, 2002) and the prefrontal cortex (Leuner & Shors, 2012; Richter-Levin & Maroun, 2010). The prefrontal cortex is sensitive to stress effects in terms of both structure and transmission (reviewed in Arnsten, 2009; Holmes & Wellman, 2009), and interacts with the amygdala during reward-based decision making (Churchwell et al., 2009; Holland & Gallagher, 2004; Salzman & Fusi, 2010). Based on this background, we next evaluated whether the prefrontal cortex was necessary for optimal performance on a value-based decision task similar to that used in the first study. Electrolytic lesions to either the ACC, mPFC, or OCC did not disrupt rats' abilities to maintain an established preference for a larger reward, nor did they disrupt rats' abilities to change their spatial preference following a reversal of the small and large reward locations. Overall, none of three major subdivisions of the rat PFC are necessary for optimal reward-motivated behaviors on our foraging task.

The decision-making tasks used in the stress and PFC studies evaluated similar abilities of rats to update their behaviors in response to a simple change in reward values. Thus, one possible conclusion from the two studies is that the stress effects observed in the first study were not dependent on major disruptions to PFC functioning. However, the absence of a behavioral effect following a lesion does not preclude that region's normal involvement in the behavior. There is evidence from several common memory tasks (e.g. classical conditioning, spatial memory tests, object recognition) that different memory systems likely interact, and that the manipulation of one neural system may influence the involvement of another system (Kim & Baxter, 2001). In this case, there may be another system that contributes to the behaviors observed in the present reward task such that disruption of that system and the PFC would cause greater impairment than that following disruption of either system independently. Alternately, the PFC may not be a critical region for this particular behavior, but under certain circumstances it may play a modulatory role on another system's control of the behavior. For example, it is possible that during and following the stressful experience, amygdala overactivity resulted in alterations of PFC functioning that were either independently sufficient to disrupt behavior, or that subsequently influenced other regions involved in the task. Thus, several models may account for both the positive stress effects and negative PFC lesion effects on our decision making task. For example, it may be that the PFC is not involved in the task, and that the stressed amygdala acts either directly on reward-based behavior or indirectly through influence on other brain regions (Figure 5.1A).

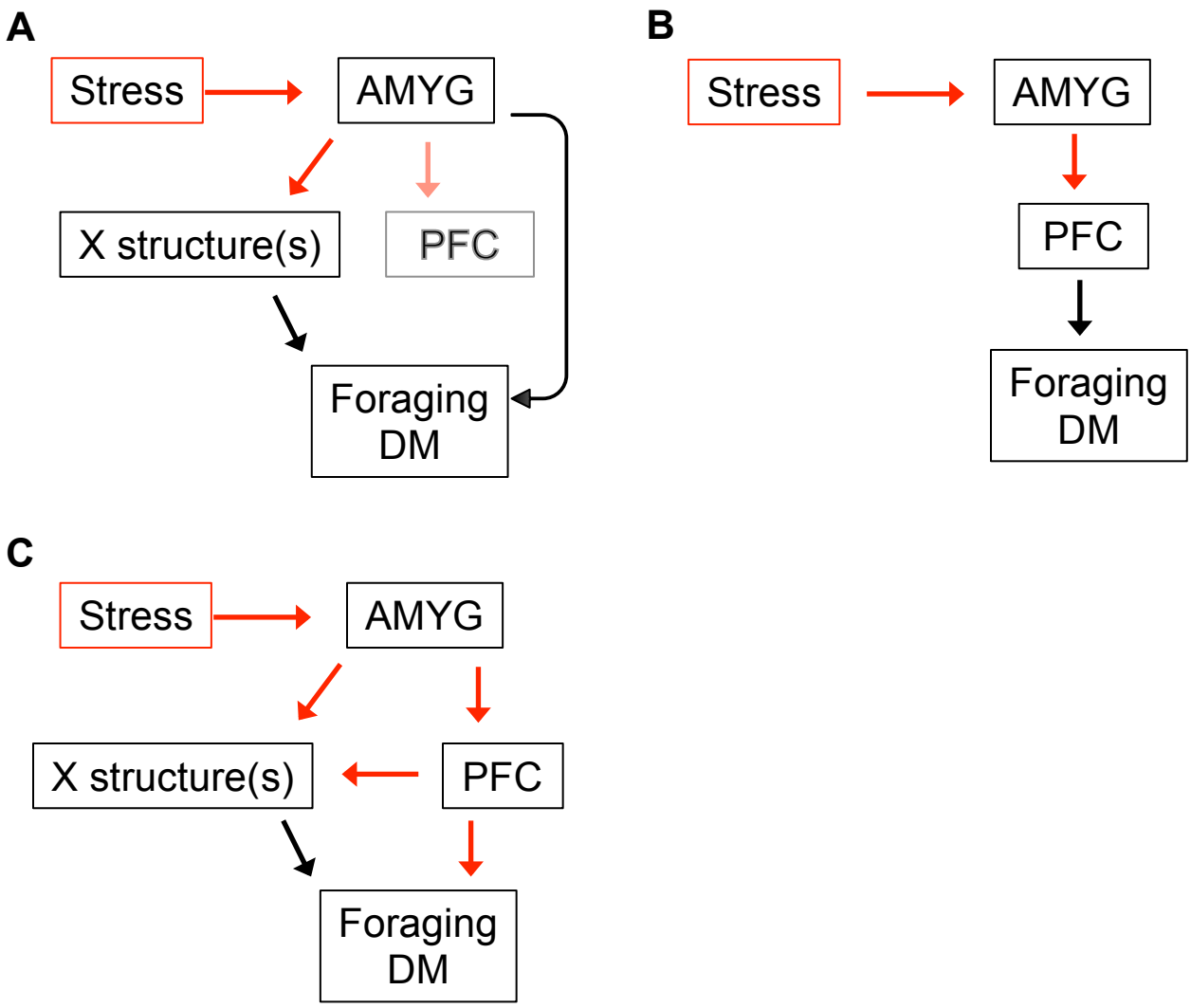

Figure 5.1. Potential models of amygdalar-dependent stress effects on decision-making performance. **(A)** During normal (non-stressed) conditions, some particular neural structures ("X structure(s)"), possibly including the amygdala, guide optimal decision making, and PFC involvement is not necessary for performance. The amygdala is affected by stress, which subsequently leads to behavioral changes via either alterations to non-PFC structures, or through its own direct control of foraging decisions. **(B)** During normal (non-stressed) conditions, the PFC may contribute to foraging decisions, but the absence of individual subregions is insufficient to impair behavior (see text). Here, stress-related changes to either the PFC or alternate structures could subsequently disrupt behavior. **(C)** During normal (non-stressed) conditions, the PFC does not contribute to simple foraging decision making. However, following stress, alterations to PFC activity modulate the effects of other structures on behavior. AMYG, amygdala; PFC, prefrontal cortex; DM, decision making.

Alternately, perhaps damage to individual PFC subregions is insufficient to create a behavioral effect due to compensation from other regions in PFC. In this case, it may suggest either competition between different PFC systems in an intact brain during maze-foraging behavior (Baxter & Kim, 2011), or simply that PFC subregions interact in such a way that in order to cause a behavioral effect in our task, a critical amount of neural tissue must be damaged (i.e., "Law of Mass Action"; Lashley, 1929). This model (Figure 5.2B) predicts that damage to the entire PFC should disrupt behavior on this task, and allows for amygdalar-dependent stress effects to act through the PFC.

A third alternative model that would account for our positive stress effects and negative lesion effects is that the PFC normally plays a modulatory role in foraging decisions, such that in the presence of certain external events (e.g. stressors), its activity affects performance either directly or through other regions (Figure 5.2C). This general effect has been observed in the delay eyeblink conditioning paradigm. In this paradigm, animals are presented with repeated pairings of a conditioned stimulus (CS), often a tone, and an unconditioned stimulus (US), an airpuff to the eye. Specifically, in delay conditioning, the onset of CS precedes the onset of US before they co-terminate (Pavlov, 1927). Animals have learned the CS-US association once they acquire a conditioned response (CR, an eyeblink) to the previously neutral tone. Neurophysiological recording studies have shown that hippocampal neurons exhibit learning-related activity that models the behavioral CR, suggesting that the hippocampus may be crucially involved in delay eyeblink conditioning (Berger et al., 1976). However, lesions to the hippocampus do not affect acquisition of delay eyeblink conditioning, in which the CS and US co-terminate (non-specific lesions, Schmaltz & Theios, 1972; dorsal hippocampus lesions, Shohamy et al., 2000), which indicates that hippocampus is not necessary for the task.

Surprisingly, systemic administration of scopolamine, a muscarinic antagonist that alters hippocampal neuronal activity (e.g. Berry & Thompson, 1979), impairs acquisition of CRs during delay eyeblink conditioning (Solomon & Gotffried, 1981; Solomon et al., 1983), but this effect is prevented with hippocampal lesions (Solomon et al., 1983). These and other studies suggest that the disruption of hippocampal activity (via cholinergic input from the medial septum) affects acquisition of delay eyeblink conditioning, whereas hippocampal lesions do not (reviewed in Christian & Thompson, 2003).

The prefrontal cortex may have a modulatory role in our basic value-based decision-making task that is similar to that of the hippocampus in delay eyeblink conditioning, such that disruption of PFC activity may have a more profound effect on behavior than complete PFC lesions. In this case, a stress-induced disruption of PFC activity may subsequently affect behavior through its altered communication with several potential subcortical structures known to interact with the PFC during decision making (e.g. mediodorsal thalamic nucleus, Izquierdo & Murray, 2010; nucleus accumbens, St. Onge et al., 2012; dorsal striatum, Balleine et al., 2007). This model (Figure 5.1C) generates several testable hypotheses: the behavioral effects of stress exposure should be alleviated following pre-stress (1) lesions to the PFC or (2) functional disconnections of the amygdala and PFC. Also, disruptions to PFC activity without complete lesions should negatively affect behavior in a manner similar to stress.

After further studies identify particular regions that are critical for performance on the stress-sensitive decision task, the model may be further tested by exploring whether stress-induced impairments are dependent on PFC interactions with the critical regions. Currently, this model accounts for both the positive effects of stress on behavior observed in the first study, and the negative lesion effects of PFC on behavior observed in the second study.

The studies presented in this dissertation made use of a water-foraging choice task on an elevated maze to measure the general characteristics of and different influences on decision making in rats. The automated figure-8 maze has been used previously in our lab for the study of working memory function following various neural manipulations (Yoon et al., 2008), and the experiments in this dissertation are evidence for its flexibility in measuring several aspects of decision-making performance in rats.

The maze foraging task has several advantages for the study of rodent decision making over the commonly used operant chamber tasks. The maze task requires animals to physically move around their environment to obtain rewards more than in an operant chamber, in which multiple choices are often together on the same wall of the chamber. This movement more accurately reflects the naturalistic foraging behavior of rodents, so that experiments are more likely to reveal cognitive and neural components of behavior that is ethologically relevant. Further, the maze environment allows for the study of spatial learning and information processing, which is critical to the goal-directed navigation that underlies rodent foraging behavior (reviewed in Penner & Mizumori, 2012).

As with any operant task, one primary limitation of maze paradigms in general is that they require overt responses by the animal. This introduces a need for shaping the animal to the desired response (e.g. running to the reward location then back to the center on our Figure-8 maze), which reduces the naturalistic aspect of any task by enforcing behavioral rules on the animal. However, the use of a maze exploits rats' natural tendency to explore, and is thus not too far removed from behaviors that would be observed in natural settings.

One challenge specific to the current experiments was the initial design of the probability-discounting task. In similar tasks that are performed in operant chambers, rats can

learn to discriminate between rewards that vary in probability between blocks within individual sessions (e.g. St. Onge & Floresco, 2010). That is, rats learn to lever-press optimally in a task when reward probabilities increase or decrease predictably within a session, and they demonstrate stable choice preferences across repeated sessions. On the present maze task, rats that were trained on similar within-session discounting paradigms tended to show reduced probability discrimination as training continued (data not shown), suggesting that they were modifying an overall valuation of the large, risky choice based on all previous encounters, rather than on those experienced within a single block of trials. Thus, in order to measure rats' overall discrimination ability and risk preference, it was necessary to expose them to each contingency (large/low probability versus large/high probability) in a continuous manner until their choice behavior was stable. Because we also observed an averaging effect of previously experienced probabilities when repeating sessions (e.g. repeatedly alternating probabilities between sessions), the rats' first exposure to each contingency was the best measure of both discrimination and preference. The final successful paradigm thus has some particular disadvantages. First, it requires many days of training on each phase before rats demonstrate stable choices, and the duration of training is unique to each rat (ranging from 3 to 15 days). This is a challenge of convenience and cost for the experimenter, but it also precludes the ability to test the effects of a single neural manipulation on preferences during multiple probability phases. Repeated manipulations (e.g. temporary chemical inactivations of neural activity or drug treatments to influence neurotransmitter activity) are thus necessary to evaluate effects on multiple phases, and such repeated manipulations may have different effects with subsequent treatments.

The maze can be adapted for additional decision-making tests beyond those used in the present studies. For example, cost parameters other than risk can be introduced by either

imposing a delay before the animal can obtain the chosen reward (in the current maze, this would require additional barriers immediately before the side reward locations) or by manipulating the physical effort required to obtain the rewards (e.g. prevent one side gate from dropping completely so that the rat has to climb over it, or introduce an alternate physical barrier before the reward). Such tests would be a useful complement to risk-based decision tasks, in order to determine whether behavioral characteristics are specific to probability-related decisions or are general to decisions that involve analysis of any explicit cost.

The results presented in this dissertation produce a number of questions that may be addressed by future studies. Several additional techniques would extend the current findings. For example, although complete lesions of PFC subregions did not disrupt decision making in the current foraging task, one of the models proposed earlier (Figure 5.1C) suggests that alterations to PFC functioning may affect task performance. A number of such alterations are possible; in the context of the current studies, one approach is to mimic some of the previously observed stress effects on PFC activity. For example, the PFC is subject to alterations in catecholamine release (particularly norepinephrine and dopamine) following stress (Finlay et al., 1995; Roth et al., 1988), and the activity of PFC neurons is affected by such changes (reviewed in Arnsten, 2009). Further, treatment with antagonists of particular norepinephrine receptors has been found to block stress-induced cognitive impairments in both rats (Birnbaum et al., 1999) and humans (Alexander et al., 2007). Thus, it would be interesting to see whether and how the manipulation of catecholamine activity (via infusion of dopamine or norepinephrine agonists and antagonists) in the PFC affects rats' abilities to update their behavior in response to altered reward values. Measurement techniques would be useful in addressing similar questions: microdialysis could be used to measure catecholamine levels in the PFC before and after stress,

and fast-scan cyclic voltammetry (with greater temporal precision) could address whether norepinephrine or dopamine activity in the PFC in response to rewards obtained on the maze changes after exposure to stress.

In addition to measuring specific neurotransmitter levels during maze performance, electrophysiological recordings of particular regions would provide more information about how the intact brain functions during this decision-making task. This would be particularly useful to test one hypothesis from the first study: if the stress-induced impairment was a result of amygdala-induced bias toward a subcortical "habit system" and away from a "flexible system", we may expect to see a stress-induced decrease in activity in regions associated with these behavioral strategies (e.g. a decrease of activity in mPFC and dorsomedial striatum, and an increase of activity in dorsolateral striatum; Balleine & O'Doherty, 2010). These regions have shown stress-induced morphological changes consistent with this idea following chronic stress in rats (Dias-Ferreira et al., 2009); but it is unclear whether an acute stressor may have similar effects on general activity of these regions.

The final study presented in this dissertation addressed the underlying cognitive components of decision-making measures in a probability-discounting task. One finding in particular from this study would be interesting to explore further: the positive correlation observed between win-stay performance (an index of reward sensitivity) and risk preference. First, it would be useful to validate the win-stay index by measuring reward sensitivity in another way. For example, rats with higher win-stay indices would be expected to have a greater dopaminergic response to a reward than rats with lower win-stay indices. This could be evaluated by recording neural activity in ventral tegmental area, the primary source of dopamine into the nucleus accumbens, and by measuring dopamine levels in nucleus accumbens

immediately following reward exposure (through electrophysiological recording and fast-scan cyclic voltammetry, respectively). Also, the current findings are based on a correlation between two variables, and thus do not address causality. One prediction from the positive correlation is that greater sensitivity to reward leads to an increase in risk-taking behavior. This prediction could be tested by manipulating the dopaminergic signal during reward exposure (via microstimulation of VTA neurons or DA agonist treatment into nucleus accumbens) and measuring subsequent risk-taking behavior.

Finally, many of the proposed studies could be carried out in different paradigms (maze versus operant chamber) and modified for different species (macaques and humans) to develop a more complete understanding of the neural and cognitive bases of decision making.

References

Ahn WY, Rass O, Fridberg DJ, Bishara AJ, Forsyth JK, Breier A, Busemeyer JR, Hetrick WP, Bolbecker AR, O'Donnel BF (2011) Temporal discounting of rewards in patients with bipolar disorder and schizophrenia. *Journal of Abnormal Psychology* 120:911-921.

Alexander JK, Hillier A, Smith RM, Tivarus ME, Beversdorf DQ (2007) Beta-adrenergic modulation of cognitive flexibility during stress. *Journal of Cognitive Neuroscience* 19:468-478.

Allen TA, Narayanan NS, Kholodar-Smith DB, Zhao Y, Laubach M, Brown TH (2008) Imaging the spread of reversible brain inactivations using fluorescent muscimol. *Journal of Neuroscience Methods* 171:30–38.

Arikan R, Blake NM, Erinjeri JP, Woolsey TA, Giraud L, Highstein SM (2002) A method to measure the effective spread of focally injected muscimol into the central nervous system with electrophysiology and light microscopy. *Journal of Neuroscience Methods* 118:51–57.

Arnsten AF (2009) Stress signaling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience* 10:410–422.

Arnsten AF, Goldman-Rakic PS (1998) Noise stress impairs prefrontal cortical cognitive function in monkeys: Evidence for a hyperdopaminergic mechanism. *Archives of General Psychiatry* 55:362–368.

Augustine AA, Larsen RJ (2011) Affect regulation and temporal discounting: interactions between primed, state, and trait affect. *Emotion* 11:403-412.

Balleine B, Daw N, O'Doherty J (2008) Multiple forms of value learning and the function of dopamine. In: *Neuroeconomics: Decision Making and the Brain* (pp. 367-387) Ed. PW Glimcher, CF Camerer, E Fehr, RA Poldrack, New York: Academic Press.

Balleine BW, Delgado MR, Hikosaka O (2007) The role of the dorsal striatum in reward and decision-making. *The Journal of Neuroscience* 27:8161-8165.

Balleine BW & O'Doherty JP (2010) Human and rodent homologies in action control: coticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology* 35:48-69.

Bari A, Theobald DE, Caprioli D, Mar AC, Aidoo-Micah A, Dalley JW, Robbins TW (2010). Serotonin modulates sensitivity to reward and negative feedback in a probabilistic reversal learning task in rats. *Neuropsychopharmacology* 35:1290-1301.

Bechera A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50:7-15.

Berg EA (1948) A simple objective technique for measuring flexibility in thinking. *The Journal of General Psychology* 39:15-22.

Berger TW, Alger B, Thompson RF (1976) Neuronal substrate of classical conditioning in the hippocampus. *Science* 192:483-485.

Berry S, Thompson R (1979) Medial septal lesions retard classical conditioning of the nictitating membrane response in rabbits. *Science* 205:209-211.

Bickel WK, Marsch LA (2001) Toward a behavioral economic understanding of drug dependence: delay discounting processes. *Addiction* 96:73-86.

Birnbaum SG, Gobeske KT, Auerbach J, Taylor JR, Arnsten AFT (1999) A role for norepinephrine in stress-induced cognitive deficits: α-1-adrenoceptor mediation in prefrontal cortex. *Biological Psychiatry* 46:1266-1274.

Bohn I, Giertler C, Hauber W (2003) Orbital prefrontal cortex and guidance of instrumental behavior in rats under reversal conditions. *Behavioral Brain Research* 143:49-56.

Bossaerts P, Preuschoff K, Hsu (2008) The neurobiological foundations of valuation in human decision making under uncertainty. In: *Neuroeconomics: Decision Making and the Brain* (pp. 353-365) Ed. PW Glimcher, CF Camerer, E Fehr, RA Poldrack, New York: Academic Press.

Boulougouris V, Dalley JW, Robbins TW (2007) Effects of orbitofrontal, infralimbic and prelimbic cortical lesions on serial spatial reversal learning in the rat. *Behavioral Brain Research* 179:219-228.

Boulougouris & Robbins (2009) Pre-surgical training ameliorates orbitofrontal-mediated impairments in spatial reversal learning. *Behavioral Brain Research* 197:469-475.

Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delany RC, McCarthy G, Charney DS, Innis RB (1995) MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *The American Journal of Psychiatry* 152:973–981.

Brunzell DH, Kim JJ (2001) Fear conditioning to tone, but not to context, is attenuated by lesions of the insular cortex and posterior extension of the intralaminar complex in rats. *Behavioral Neuroscience* 115:365-375.

Butter CM (1969) Perseveration in extinction and in discrimination reversal learning following selective frontal ablations in *Macaca mulatta. Physiology & Behavior* 4:163-171.

Caraco T (1981) Energy budgets, risk and foraging preferences in dark-eyed juncos (Junco hyemalis). *Behavioral Ecology and Sociobiology* 8:213-217.

Chambers RA, Taylor JR, Potenza MN (2003) Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *The American Journal of Psychiatry* 160:1041-1052.

Christian KM, Thompson RF (2003) Neural substrates of eyeblink conditioning: acquisition and retention. *Learning & Memory* 10:427-455.

Churchwell JC, Morris AM, Heurtelou NM, Kesner RP (2009) Interactions between the prefrontal cortex and amygdala during delay discounting and reversal. *Behavioral Neuroscience* 123:1185-1196.

Corrodo GS, Sugrue LP, Brown JR, Newsome WT (2008) The trouble with choice: Studying decision variables in the brain. In: *Neuroeconomics: Decision Making and the Brain* (pp. 463-480) Ed. PW Glimcher, CF Camerer, E Fehr, RA Poldrack, New York: Academic Press.

Croy MI, Hughes RN (1991) Effects of food supply, hunger, danger and competition on choice of foraging location by the fifteen-spined stickleback, Spinachia spinachia L. *Animal Behavior* 42:131-139.

Dalley JW, Cardinal RN, Robbins TW (2004) Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. *Neuroscience & Biobehavioral Reviews* 28:771-784.

Dayan P, Niv Y, Seymour B, Daw ND (2006) The misbehavior of value and the discipline of the will. *Neural Networks* 19:1153-1160.

De Martino B, Kumaran D, Holt B, Dolan RJ (2009) The neurobiology of reference-dependent value computation. *The Journal of Neuroscience* 29:3833-3842.

de Quervain DJ, Roozendaal B, McGaugh JL (1998) Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature* 394:787–790.

Diamond DM, Rose GM (1994) Stress impairs LTP and hippocampal-dependent memory. *Annals of the New York Academy of Sciences* 746:411–414.

Dias-Ferreira E, Sousa JC, Melo I, Morgado P, Mesquita AR, Cerqueira JJ, Costa RM, Sousa N (2009) Chronic stress causes frontostriatal reorganization and affects decision-making. *Science* 325:621–625.

Dickenson A (1994) Instrumental conditioning. In Mackintosh, N.J. (Ed.) *Animal Cognition and Learning.* Academic Press, London, pp. 4-79.

Dickinson A, Squire S, Varga Z, Smith JW (1998) Omission learning after instrumental pretraining. *Quarterly Journal of Experimental Psychology Section B* 51:271-286.

Elliott AE, Packard MG (2008) Intra-amygdala anxiogenic drug infusion prior to retrieval biases rats toward the use of habit memory. *Neurobiology of Learning and Memory* 90:616–623.

Finlay JM, Zigmond MJ, Abercrombie ED (1995) Increased dopamine and norepinephrine release in medial prefrontal cortex induced by acute and chronic stress: effects of diazepam. *Neuroscience* 64:619-628.

Fiorillo CD, Tobler PN, Schultz W (2003) Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* 299:1898-1902.

Floresco SB, St Onge JR, Ghods-Sharifi S, Winstanley CA (2008) Cortico-limbic-striatal circuits subserving different forms of cost-benefit decision making. *Cognitive, Affective, & Behavioral Neuroscience* 8:375-389.

Forbes EE, Shaw DS, Dahl RE (2007) Alterations in reward-related decision making in boys with recent and future depression. *Biological Psychiatry* 61:633-639.

Foy MR, Stanton ME, Levine S, Thompson RF (1987) Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behavioral and Neural Biology* 48:138–149.

Glimcher PW, Rustichini A (2004) Neuroeconomics: The consilience of brain and decision. *Science* 306:447-452.

Gold JI, Shadlen MN (2007) The neural basis of decision making. *Annual Review of Neuroscience* 30:535–574.

Graham LK, Yoon T, Kim JJ (2010) Stress impairs optimal behavior in a water foraging choice task in rats. *Learning & Memory* 17:1-4.

Herrnstein RJ (1970) On the law of effect. *Journal of the Experimental Analysis of Behavior* 13:243-266.

Holland PC, Gallagher M (2004) Amygdala-frontal interactions and reward expectancy. *Current Opinion in Neurobiology* 14:148-155.

Holmes A, Wellman CL (2009) Stress-induced prefrontal reorganization and executive dysfunction in rodents. *Neuroscience & Biobehavioral Reviews* 33:773– 783.

Holt DD, Green L, Myerson J (2003) Is discounting impulsive? Evidence from temporal and probability discounting in gambling and non-gambling college students. *Behavioral Processes* 64:355-367.

Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB, Thurmon JJ, Marinelli M, DiLeone RJ (2006) Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron* 51:801-810.

Iversen SD, Mishkin M (1970) Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Experimental Brain Research* 11:376-386.

Izquierdo A, Murray EA (2010) Functional interaction of medial mediodorsal thalamic nucleus but not nucleus accumbens with amygdala and orbital prefrontal cortex is essential for adaptive response selection after reinforcer devaluation. *The Journal of Neuroscience* 30:661-669.

Izquierdo A, Wellman CL, Holmes A (2006) Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. *The Journal of Neuroscience* 26:5733–5738.

Joels M, Pu Z, Wiegert O, Oitzl MS, Krugers HJ (2006) Learning under stress: How does it work? *Trends in Cognitive Sciences* 10:152–158.

Jones B, Mishkin M (1972) Limbic lesions and the problem of stimulus-reinforcement associations. *Experimental Neurology* 36:362-377.

Kable JW, Glimcher PW (2009) The neurobiology of decision: consensus and controversy. *Neuron* 63:733-745.

Kahneman D, Tversky A (1979) Prospect theory: An analysis of decision under risk. *Econometrica* 47:263-291.

Kennerley SW, Wallis JD (2009) Evaluating choices by single neurons in the frontal lobe: outcome value encoded across multiple decision variables. *European Journal of Neuroscience* 29:2061-2073.

Kesner RP, Churchwell JC (2011) An analysis of rat prefrontal cortex in mediating executive function. *Neurobiology of Learning and Memory* 96:417-431.

Kim JJ, Baxter MG (2001) Multiple brain-memory systems: the whole does not equal the sum of its parts. *Trends in Neurosciences* 24:324-330.

Kim JJ, Clark, RE, Thompson, RF (1995) Hippocampectomy impairs the memory of recently, but not remotely, acquired trace eyeblink conditioned responses. *Behavioral Neuroscience* 109:195–203.

Kim JJ, Diamond DM (2002) The stressed hippocampus, synaptic plasticity and lost memories. *Nature Reviews Neuroscience* 3:453–462.

Kim JJ, Foy MR, Thompson RF (1996) Behavioral stress modifies hippocampal plasticity through N-methyl-D-aspartate receptor activation. *Proceedings of the National Academy of Sciences of the United States of America* 93:4750–4753.

Kim JJ, Lee HJ, Han JS, Packard MG (2001) Amygdala is critical for stress-induced modulation of hippocampal long-term potentiation and learning. *The Journal of Neuroscience* 21:5222–5228.

Kim JJ, Koo JW, Lee HJ, Han JS (2005) Amygdalar inactivation blocks stress-induced impairments in hippocampal long-term potentiation and spatial memory. *The Journal of Neuroscience* 25:1532–1539.

Kim JJ, Yoon KS (1998) Stress: Metaplastic effects in the hippocampus. *Trends in Neurosciences* 21:505–509.

Knutson B, Adams CM, Fong GW, Hommer D (2001) Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *The Journal of Neuroscience* 21:1-5.

Krawczyk DC (2002) Contributions of the prefrontal cortex to the neural basis of human decision making. *Neuroscience and Biobehavioral Reviews* 26:631-664.

Krügel U, Schraft T, Kittner H, Kiess W, Illes P (2003) Basal and feeding-evoked dopamine release in the rat nucleus accumbens is depressed by leptin. *European Journal of Pharmacology* 482:185-187.

Krupa DJ, Thompson JK, Thompson RF (1993) Localization of a memory trace in the mammalian brain. *Science* 260:989–991.

Lashley KS (1929) *Brain Mechanisms and Intelligence: A Quantitative Study of Injuries to the Brain.* Chicago, IL: University of Chicago Press.

Laws KR (1999) A meta-analytic review of Wisconsin Card Sort studies in schizophrenia: General intellectual deficit in disguise? *Cognitive Neuropsychiatry* 4:1-35.

Lee D (2008) Game theory and neural basis of social decision making. *Nature Neuroscience* 11:404–409.

Leuner B, Shors TJ (2012) Stress, anxiety, and dendritic spines: What are the connections? *Neuroscience*, http://dx.doi.org/10.1016/j.neuroscience.2012.04.021.

Levy I, Snell J, Nelson AJ, Rustichini A, Glimcher PW (2010) Neural representation of subjective risk and ambiguity. *Journal of Neurophysiology* 103:1036-1047.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature*412:150-157.

Luethi M, Meier B, Sandi C (2008) Stress effects on working memory, explicit memory, and implicit memory for neutral and emotional stimuli in healthy men. *Frontiers in Behavioral Neuroscience* 2:1–9.

Luman M, Sergeant JA, Knol DL, Oosterlaan J (2010) Impaired decision making in oppositional defiant disorder related to altered psychophysiological responses to reinforcement. *Biological Psychiatry* 68:337-344.

Lupien SJ, Gaudreau S, Tchiteya BM, Maheu F, Sharma S, Nair NP, Hauger RL, McEwen BS, Meaney MJ (1997) Stress-induced declarative memory impairment in healthy elderly subjects: Relationship to cortisol reactivity. *The Journal of Clinical Endocrinology & Metabolism* 82:2070–2075.

MacKillop J, Amlung MT, Few LR, Ray LA, Sweet LH, Munafo MR (2011) Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology* 216:305-321.

Maier SF, Seligman MEP (1976) Learned helplessness: Theory and evidence. *Journal of Experimental Psychology* 105:3–46.

Maier SF, Busch CR, Maswood S, Grahn RE, Watkins LR (1995) The dorsal raphe nucleus is a site of action mediating the behavioral effects of the benzodiazepine receptor inverse agonist DMCM. *Behavioral Neuroscience* 109:404–412.

McCormick DA, Steinmetz JE, Thompson RF (1985) Lesions of the inferior olibary complex cause extinction of the classically conditioned eyeblink response. *Brain Research* 359:120-130.

McEwen BS, Sapolsky RM (1995) Stress and cognitive function. *Current Opinion in Neurobiology* 5:205–216.

Miedl SF, Peters J, Büchel C (2012) Altered neural reward representations in pathological gamblers revealed by delay and probability discounting. *Archives of General Psychiatry* 69:177-186.

Newcomer JW, Craft S, Hershey T, Askins K, Bardgett ME (1994) Glucocorticoid-induced impairment in declarative memory performance in adult humans. *The Journal of Neuroscience* 14:2047–2053.

Noonan MP, Kolling N, Walton ME, Rushworth MFS (2012) Re-evaluating the role of the orbitofrontal cortex in reward and reinforcement. *European Journal of Neuroscience* 35:997-1010.

Okada K, Nakamura K, Kobayashi Y (2011) A neural correlate of predicted and actual reward-value information in monkey pedunculopontine tegmental and dorsal raphae nucleus during saccade tasks. *Neural Plasticity* 2011: doi:10.1155/2011/579840.

Owen AM, Roberts AC, Hodges JR, Summers BA, Polkey CE, Robbins TW (1993) Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain* 116:1159-1175.

Packard MG (1999) Glutamate infused posttraining into the hippocampus or caudate-putament differentially strengthens place and response learning. *Proceedings of the National Academy of Sciences of the United States of America.* 96:12881-12886.

Packard MG, McGaugh JL (1996) Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiology of Learning and Memory* 65:65-72.

Padoa-Schioppa, C (2011) Neurobiology of economic choice: a good-based model. *Annual Review of Neuroscience* 34:333-359.

Padoa-Schioppa C, Assad JA (2006) Neurons in the orbitofrontal cortex encode economic value.*Nature* 441:223-226.

Padoa-Schioppa C, Cai X (2011) The orbitofrontal cortex and the computation of subjective value: consolidated concepts and new perspectives. *Annals of the New York Academy of Sciences* 1239:130-137.

Paulsen DJ, Platt ML, Huettel SA, Brannon EM (2011) Decision-making under risk in children, adolescents, and young adults. *Frontiers in Psychology* 2:72 doi:10.3389/fpsyg.2011.00072

Pavlov, IP (1927) *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex. Translated and Edited by GV Anrep.* London: Oxford University Press.

Pedigo SF, Song EY, Jung MW, Kim JJ (2006) A computer vision-based automated Figure-8 maze for working memory test in rodents. *Journal of Neuroscience Methods* 156:10–16.

Penner MR, Mizumori SJY (2012) Neural systems analysis of decision making during goal-directed navigation. *Progress in Neurobiology* 96:96-135.

Peters J, Büchel C (2009) Overlapping and distinct neural systems code for subjective value during intertemporal decision making. *The Journal of Neuroscience* 29:15727-15734.

Platt ML, Huettel SA (2008) Risky business: the neuroeconomics of decision making under uncertainty. *Nature Neuroscience* 11:398-403.

Ragozzino M (2007) The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. *Annals of the New York Academy of Sciences* 1121:355-375.

Rangel A, Camerer C, Montague PR (2008) A framework for studying the neurobiology of value-based decision making. *Nature Reviews Neuroscience* 9:545-556.

Reuter J, Raedler T, Rose M, Hand I, Glascher J, Büchel C (2005) Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nature Neuroscience* 8:147-148.

Richards JB, Zhang L, Mitchell SH, de Wit H (1999) Delay or probability discounting in a model of impulsive behavior: effect of alcohol. *Journal of the Experimental Analysis of Behavior* 71:121-143.

Richter-Levin G, Maroun M (2010) Stress and amygdala suppression of metaplasticity in the medial prefrontal cortex. *Cerebral Cortex* 20:2433-2441.

Robbins TW (1996) Dissociating executive functions of the prefrontal cortex. *Philosophical Transactions of the Royal Society B* 351:1463-1471.

Robbins TW, Everitt BJ (1999) Drug addiction: bad habits add up. *Nature* 398:567-570.

Robinson MD, Wilkowski BM, Kirkeby BS, Meier BP (2006) Stuck in a rut: Perseverative response tendencies and the neuroticism-distress relationship. *Journal of Experimental Psychology: General* 135:78–91.

Roesch MR, Olson CR (2005) Neuronal activity in primate orbitofrontal cortex reflects the value of time. *Journal of Neurophysiology* 94:2457-2471.

Roesch MR, Taylor AR, Schoenbaum G (2006) Encoding of time-discounted rewards in orbitofrontal cortex is independent of value representation. *Neuron* 51:509-520.

Rose JE, Woolsey CN (1948) The orbitofrontal cortex and its connections with the mediodorsal nucleus in rabbit, sheep and cat. *Research Publications – Association for Research in Nervous and Mental Disease* 27:210-232.

Roth RH, Tam S-Y, Ida Y, Yang J-X, Deutch AY (1988) Stress and the mesocorticolimbic dopamine systems. *Annals of the New York Academy of Sciences* 537:138-147.

Rudebeck PH, Behrens TE, Kennerley SW, Baxter MG, Buckley MJ, Walton ME, Rushworth MFS (2008) Frontal cortex subregions play distinct roles in choices between actions and stimuli. *The Journal of Neuroscience* 28:13775-13785.

Rushworth MFS, Walton ME, Kennerley SW, Bannerman DM (2004) Action sets and decisions in the medial frontal cortex. *Trends in Cognitive Sciences* 8:410-417.

Salzman CD, Fusi S (2010) Emotion, cognition, and mental state representation in amygdala and prefrontal cortex. *Annual Review of Neuroscience* 33:173-202.

Schultz W (1998) Predictive reward signal of dopamine neurons. *Journal of Neurophysiology* 80:1-27.

Schultz W (2001) Reward signaling by dopamine neurons. *Neuroscientist* 7:293-302.

Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. *Science* 275:1593–1599.

Schultz W, O'Neill M, Tobler PN, Kobayashi S (2011) Neuronal signals for reward risk in frontal cortex. *Annals of the New York Academy of Sciences* 1239:109-117.

Schmaltz LW, Theios J (1972) Acquisition and extinction of a classically conditioned response in hippocampectomized rabits (*Oryctolagus cuniculus*). *Journal of Comparative and Physiological Psychology* 95:322-330.

Seamans JK, Lapish CC, Durstewitz D (2008) Comparing the prefrontal cortex of rats and primates: insights from electrophysiology. *Neurotoxicity Research* 14:249-262.

Sesscousse G, Redouté J, Dreher JC (2010) The architecture of reward value coding in the human orbitofrontal cortex. *The Journal of Neuroscience* 30:13095-13104.

Shohamy D, Allen MT, Gluck MA (2000) Dissociating entorhinal and hippocampal function in latent inhibition. *Behavioral Neuroscience* 114:867-874.

Shors TJ (2006) Significant life events and the shape of memories to come: A hypothesis. *Neurobiology of Learning and Memory* 85:103–115.

Shors TJ, Weiss C, Thompson RF (1992) Stress-induced facilitation of classical conditioning. *Science* 257:537–539.

Simon NW, Montgomery KS, Beas BS, Mitchell MR, LaSarge CL, Mendez IA, Banuelos C, Vokes CM, Taylor AB, Haberman RP, Bizon JL, Setlow B (2011) Dopaminergic modulation of risky decision-making. *The Journal of Neuroscience* 30:17460-17470.

Smith DV, Hayden BY, Truong TK, Song AW, Platt ML, Huettel SA (2010) Distinct value signals in anterior and posterior ventromedial prefrontal cortex. *The Journal of Neuroscience* 30:2490-2495.

Solomon PR, Gottfried KE (1981) The septohippocampal cholinergic system and classical conditioning of the rabbit's nictitating membrane response. *Journal of Comparative and Physiological Psychology* 95:322-330.

Solomon PR, Solomon SD, Vander Shaaf E, Perry HE (1983) Altered activity in the hippocampus is more detrimental to classical conditioning than removing the structure. *Science* 220:329-331.

Starkman MN, Gebarski SS, Berent S, Schteingart DE (1992) Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biological Psychiatry* 32:756–765.

St. Onge JR, Abhari H, Floresco SB (2011) Dissociable contributions by prefrontal D1 and D2 receptors to risk-based decision making. *The Journal of Neuroscience* 31:8625-8633.

St. Onge JR, Floresco SB (2009) Dopaminergic modulation of risk-based decision making. *Neuropsychopharmacology* 34:681-697.

St. Onge JR, Floresco SB (2010) Prefrontal cortical contribution to risk-based decision making. *Cerebral Cortex* 20:1816-1828.

St. Onge JR, Stopper CM, Zahm DS, Floresco SB (2012) Separate prefrontal-subcortical circuits mediate different components of risk-based decision making. *The Journal of Neuroscience* 32:2886-2899.

Stopper C, Floresco SB (2011) Contributions of the nucleus accumbens and its subregions to different aspects of risk-based decision making. *Cognitive, Affective, & Behavioral Neuroscience* 11:97-112.

Sul JH, Kim H, Huh N, Lee D, Jung MW (2010) Distinct roles of rodent orbitofrontal and medial prefrontal cortex in decision making. *Neuron* 66:449-460.

Symmonds M, Emmanuel JJ, Drew ME, Batterham RL, Dolan RJ (2010) Metabolic state alters economic decision making under risk in humans. *Public Library of Science ONE* 5:e11090. doi:10.1371/journal.pone.0011090

Takahashi Y, Roesch MR, Wilson RC, Toreson K, O'Donnell P, Niv Y, Schoenbaum G (2011) Expectancy-related changes in firing of dopamine neurons depend on orbitofrontal cortex. *Nature Neuroscience* 14:1590-1597.

Thompson RF, Kim JJ (1996) Memory systems in the brain and localization of a memory. *Proceedings of the National Academy of Sciences of the United States of America* 93:13438-13444.

Tobler PN, Christopoulos GI, O'Doherty JP, Dolan RJ, Schultz W (2008) Neuronal distortions of reward probability without choice. *The Journal of Neuroscience* 28:11703-11711.

Tobler PN, Fiorillo CD, Shultz W (2005) Adaptive coding of reward value by dopamine neurons. *Science* 307:1642-1645.

Tremblay L, Schultz W (1999) Relative reward preference in primate orbitofrontal cortex. *Nature* 398:704-708.

Tverksy A, Kahneman D (1992) Advances in prospect theory cumulative representation of uncertainty. *Journal of Risk and Uncertainty* 5:297-323.

Uylings HBM, Groenewegen HJ, Kolb B (2003) Do rats have a prefrontal cortex? *Behavioral Brain Research* 146:3-17.

van den Bos R, Lasthuis W, den Heijer E, van der Harst J, Spruijt B (2006) Toward a rodent model of the Iowa gambling task. *Behavioral Research Methods* 38:470-478.

Volkow ND, Fowler JS, Wang GJ, Goldstein RZ (2002) Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. *Neurobiology of Learning and Memory* 78:610-624.

von Neumann J, Morgenstern O (1953) *Theory of Games and Economic Behavior* (3rd ed.) Princeton, NJ: Princeton University Press.

Vyas A, Bernal S, Chattarji S (2003) Effects of chronic stress on dendritic arborization in the central and extended amygdala. *Brain Research* 965:290-294.

Waddell J, Bangasser DA, Shors TJ (2008) The basolateral nucleus of the amygdala is necessary to induce the opposing effects of stressful experience on learning in males and females. *The Journal of Neuroscience* 28:5290-5294.

Walton M, Rudebeck P, Bannerman D, Rushworth MFS (2007) Calculating the cost of acting in frontal cortex. *Annals of the New York Academy of Sciences* 1104:340-356.

Weinberger DR, Berman KF, Illowsky BP (1986). Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. *Archives of General Psychiatry* 43:114-135.

Wunderle JM, Jr, Castro MS, Fetcher N (1987) Risk-averse foraging by bananaquits on negative energy budgets. *Behavioral Ecology & Sociobiology* 21:249-255.

Yoon T, Okada J, Jun MW, Kim JJ (2008) Prefrontal cortex and hippocampus subserve different components of working memory in rats. *Learning & Memory* 15:97–105.

Zachek MK, Takmakov P, Park J, Wightman RM, McCarty GS (2010) Simultaneous monitoring of dopamine concentration at spatially different brain locations *in vivo*. *Biosensors and Bioelectronics* 135:1556-1563.

Zeeb FD, Robbins TW, Winstanley CA (2009) Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. *Neuropsychopharmacology* 34:2329-2343.

VITA

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