ASSESSING THE IMPACT OF PAIN ON DECISION-MAKING IN A RAT GAMBLING

TASK (RGT)

by

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Abstract

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(RGT)

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Recent clinical assessments using the Iowa Gambling Task have revealed pain can negatively affect decision-making processes, leading to risky or poor decisions. Despite the gain these models have made in further elucidating the cognitive components of pain, they fail to fully address neurobiological factors of decision-making on behavior. As a result, there remains significant limitation in assessing the extent of how acute or chronic pain and the relief of pain with analgesics can affect cognitive abilities. Therefore, we examined the effect of acute and chronic pain on decision processing and the impact of morphine on that decision processing.

In this study, forty-four Sprague Dawley rats were presented with a rodent version of the Iowa Gambling Task (RGT). On Day One testing, animals were injected with Complete Freund's Adjuvant (CFA) (or saline) to induce an inflammatory pain condition in the left hindpaw. Thirty minutes after, animals were given an injection of either 3 mg/kg morphine or saline and allowed to habituate for thirty minutes. Animals were tested using the RGT where percent choice and omission percentage were used to assess the animals' cognitive performance for acute pain. Thus, the conditions were as followed: saline/saline, saline/morphine, CFA/saline, CFA/morphine. After testing, animals were subjected to a Place Escape/Avoidance Paradigm (PEAP) testing. On the tenth day, animals were given the same drug injection as Day One testing and allowed to habituate for 30 minutes. Afterward, animals were subjected to a Day Ten testing using the RGT. Again, the animals were assessed, but for chronic pain cognitive

performance, using percent choice and omission percentage of the RGT and again were subjected to another PEAP testing. Surprisingly, RGT data revealed no differences in best choice option ability regardless of pain, drug, or time conditions. However, results of PEAP testing did reveal a significant difference in pain affect for pain conditions, but not across time, suggesting pain affect does not change within acute to chronic conditions. Thus, the results of this study suggest that specific patterns of decreased cognitive performance were not seen for subcutaneous inflammatory conditions, but did maintain responding in a measure of pain affect. Future studies should seek to further assess the relationship between pain and cognition in order to obtain a comprehensive understanding of pain behaviors, specifically pertaining to the underlying biological mechanisms that that influence cognitive pain-behaviors. Approaches such as this can provide critical information that can ultimately translate to clinical populations and lead to improvements in understanding pain and its cognitive component.

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Chapter 1

INTRODUCTION

Pain is a subjective, perceptual, and multidimensional phenomenon that has biological, psychological, and social implications (Melzack and Casey, 1968; Rainville, 2002; Gatchel, Peng, Peters, Fuchs, & Turk, 2007). As a homeostatic emotion, pain is also adaptive, in that is creates an unpleasant state needing to be resolved (Craig, 2003). This in turn motivates an organism to maintain internal stability by reacting or behaving in favor of survival. This adaptive type of pain is acute pain, which is short in duration, self-limited, and deficient in psychosocial or biological changes disproportionate to the pain intensity. However, if pain persists beyond tissue damage repair or removal of the noxious stimulus, pain is regarded as chronic and no longer serves its adaptive evolutionary advantage. Chronic pain is characterized as lasting over 6 months in duration and has distinct sensory, emotional, and behavior changes (Grichnik & Ferrante, 1991; Hart, Martelli, & Zasler, 2000).

At any given time within a 6-month period, 25.3 million American adults are experiencing pain (Nahin, 2015). Additionally, over 100 million Americans experience chronic pain costing Americans over half a trillion annually in lost-wages, medical care, and quality of life (Gregory et al 2013). Unfortunately, these statistics do not account for acute pain, which prevalence and cost could be similarly high.

1.1 The Multidimensionality of Pain

Historically, pain research has predominantly focused on quantifying the sensory component of pain (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). However, with the introduction of Melzack and Wall's (1965) publication of the gate control theory, the importance of physiological and psychological properties of pain was established. Researchers' view of pain shifted into a multidimensional one, where affective-motivational, sensory-discriminative, and

cognitive-evaluative components serve as the major determinants. Due to and under these constructs, pain has thus been defined as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Melzack and Casey, 1968; Merskey & Bogduk, 1994). Subsequent research has investigated these dimensions and indeed revealed these trends supporting this multi-modality.
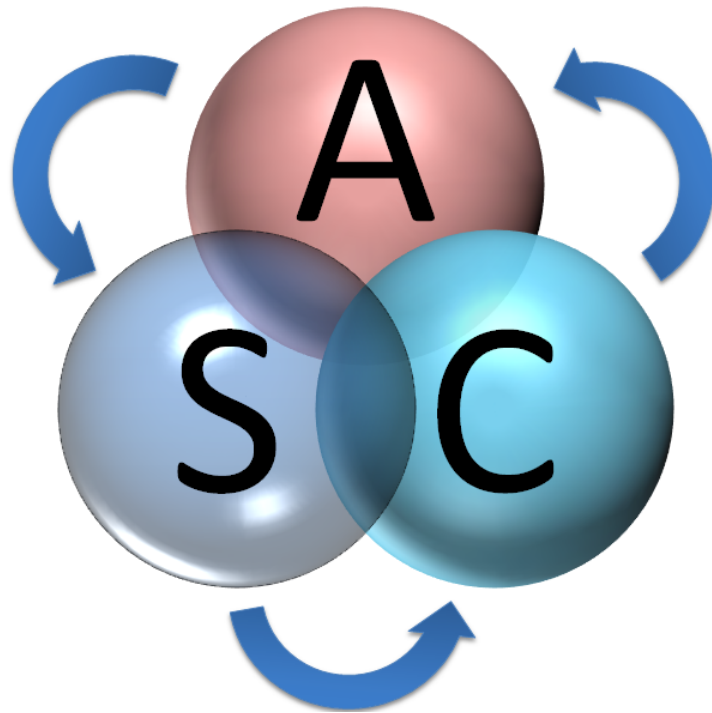

Figure 1-1: The multi-dimensionality of pain; A, affective-motivational; S, sensory-discrimative; C, cognitive-evaluative

1.1.1 Sensory Component of Pain

The sensory component of pain involves the size, location, and intensity of pain via inputs of sensory neurons stimulation, which ascends to the dorsal horn and then to the thalamus. These projections are sent to cortical areas, such as the somatosensory cortex for sensory processing and provides information on the location of sensory and tactile stimulus (Bushnell & Apkarian, 2006; Craig, 2003). Current preclinical assessments, which quantify the sensory component, include mechanical paw withdrawal threshold testing and thermal paw withdrawal latency.

1.1.2 Affect Component of Pain

Pain affect is described as the emotional response of how unpleasant or aversive pain is perceived (Melzack & Casey, 1968; Craig, 2003). In addition, pain affect is considered to be a homeostatic drive, meaning a response is required to resolve or maintain homeostasis (Craig, 2003). This mechanism can be used to understand the importance of how an organism is motivated to remove a painful stimulus, specifically by means of either escape or avoidance (LaBuda & Fuchs, 2000). Some of current preclinical assessments of affect include conditioned place avoidance (CPA), conditioned place preference (CCP), and place escape-avoidance paradigm (PEAP).

1.1.3 Cognitive Component of Pain

Formally posited as central control determinants, the cognitive-evaluative component of pain has been described as the "complex function(s) of identification, evaluation, and selective input modulation" (Melzack & Casey, 1968). The dimension can also be separated from the other components of pain in that it can selectively influence sensory processing and motivational mechanisms (Melzack & Casey, 1968). Essentially, this dimension is important for understanding how stimulus information is processed and is then conveyed into a response or

output. Additionally, cognitions (attitudes, beliefs, and expectations) can act directly upon and influence or alter the pain experience (Turner and Chapman, 1982).

1.2 Cognition and Pain

Cognition is a "generic term embracing the quality of knowing, which includes perceiving, recognizing, conceiving, judging, sensing, reasoning, and imaging" (Stedman's Medical Dictionary, 1976; Weisenburg, 1999). Cognition allows for the exploration, evaluation, and perception of the real world, along with defining future and alternative possibilities (Dessimoz, 2016). Under this umbrella lie more simple and complex forms of attention, learning, memory, and decision-making. Subsequent research has revealed lower and higher order cognitive deficits associated with pain, including attention (Boyette-Davis, Thompson, & Fuchs, 2008), learning and memory (Hu et al., 2010), and decision-making (Pais-Vieira, 2009). These models attribute these effects to be driven by either one of two factors: either cognitive deficits are a direct result of pain or pain indirectly causes cognitive effects (a full schema can be shown to represent this relationship with Figure 1-2). The former assumes pain is a cognitive state that can disrupt other cognitive functioning due to cognitive overload, while the latter reasons cognitive deficits result from a mediator, and if the mediator is resolved, cognitive functioning can be restored (Apkarian et al., 2004; Buenaver et al., 2012). However because the direct and indirect effects of pain and cognition can overlap, the tangible cause of impairments may be too ambiguous.
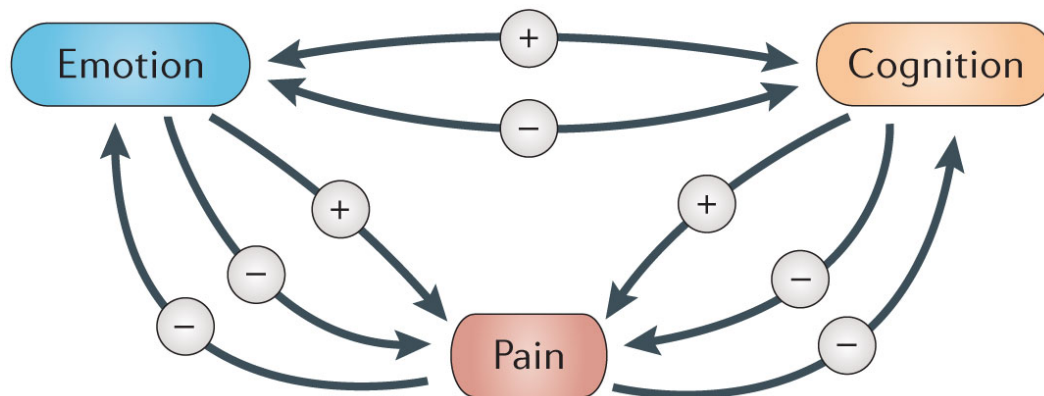
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Figure 1-2: The relationship between pain, cognition, and emotion. Pain can influence both emotion and cognition negatively, whereas emotion and cognition can have a negative or positive influence on pain and on each other (Bushnell, Ceko, & Low, 2013).

Yet, despite of the attributed effects of cognitive impairments, models have successfully quantified explicit behavioral cognitive functioning under pain. Validated paradigms include, but are not limited to probe testing in humans (Veldhuijzen et al. 2006) and the 5-Choice Serial Reaction Time Task (5CSRTT) in rats (Boyette-Davis, Thompson, Fuchs, 2008) for attention, the WAIS-III digit-symbol test in humans (Lee et al., 2010) and Morris Water Maze in rats (Hu et al., 2010) to assess memory and learning, and the Iowa Gambling task (IGT) in humans (Apkarian et al., 2004) and the rat-version of the IGT (RGT) (van den Bos et al. 2006; Pais-Viera et al., 2009; Rivalan et al. 2009; Potenza, 2009; Zeeb et al., 2009; Zeeb & Winstanley, 2011) have been used to reveal decision-making.

1.3 Decision-Making Deficits

Decision-making is considered a higher order of cognition that is important for everyday functioning. Normal decision-making is influenced by both emotional and cognitive processes to assess long-term consequences (Bechara et al., 1994; Bechara, Damasio, & Damasio, 2003). As a result, the benefits, costs, and consequences are assessed in order to obtain a decision (Fishburn, 1970; Hsu et al., 2005). Yet when these processes are disrupted, decision-making becomes impaired and leads to risky or poor long-term decision-making behaviors (Bechara, 2004, Bechara et al. 2005; Bechara & Damasio, 2005.) Previous clinical studies have shown poor decision-making behaviors in numerous psychiatric disorders such as Attention Deficit Hyperactivity Disorder (ADHD) (Garon, Moore & Waschbush, 2006), substance abuse (Bechara et al., 2001; Bechara and Damasio, 2002; Bechara et al., 2002; Barry & Petry, 2008), gambling (Cavedini et al., 2002; Brand et al., 2005), and most recently, chronic pain (Apkarian et al., 2004; Verdejo-García et al., 2009).

1.4 Iowa Gambling Task

To examine emotion-based decision-making behaviors, Bechara et al. (1994) introduced the Iowa Gambling Task (IGT). This task assesses real-life decision-making by implementing factors of uncertainty and outcomes of reward and punishment (Bechara et al. 1994; Bechara, Damasio, & Damasio, 2003; Van den Bos et al. 2006). Essentially, the task involves four decks of cards, two "good" decks and two "bad" decks. Cards in the "good" stack yield lower immediate gain, but smaller long-term losses, while "bad" decks yield high immediate gain, but larger long-term losses (Figure 1-1; Bechara et al. 1994.) Unlike normal patients, patients with damage to the amygdala or orbitofrontal cortex tend to choose cards more from the "bad" deck, suggesting these impaired areas enhance the decision to choose high-risk options (Apkarian et al. 2004;

Bechara, 2004; Bechara & Damasio, 2005; Bechara, Damasio, & Damasio, 2003, Bechara et al.

1994). This paradigm has been useful in validating the somatic marker hypothesis, providing

evidence that certain brain areas involved in emotion and cognition, in addition to exteroceptive

and interoceptive information concerning somatic states are necessary for decision-making

processes (Bechara, 2003).

The Iowa Gambling Task

	"Bad" decks		"Good" decks	
	A	B	C	D
Gain per card	$100	$100	$50	$50
Loss per 10 cards	$1250	$1250	$250	$250
Net per 10 cards	−$250	−$250	+$250	+$250

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Figure 1-3 Schematic of the Human Iowa Gambling Task (IGT) (Bechara et al., 2005)

1.5 Rodent Versions of the Iowa Gambling Task

Like the IGT, the RGT is also designed to assess emotion-based decision-making (van

den Bos et al. 2006; Pais-Viera et al., 2009; Rivalan et al. 2009; Potenza, 2009; Zeeb et al.,

2009; Zeeb & Winstanley, 2011). Similarly, this paradigm uses economy, but of foraging, which tends to earn criticism on the use of appetitive reward (obtaining food) and losses (not obtaining food) to serve as the equivalent of monetary rewards and losses for humans (de Visser, 2011; van de Bos et al., 2014). Regardless of such, similar trends have been translated from clinical to preclinical models.

Currently, there are five paradigms, including the novel version presented later in this proposal, each differing in characteristics including immediate and overall reward amount, punishment duration or quinine punishment, number of choices, and chronic pain conditions or lesion placement (Table 1, de Visser, 2011).

Table 1-1: Main features and comparison of the human and rodent gambling tasks (de Visser et al., 2011)

Table 1 | Main features of the human and rodent gambling tasks.

Task features	IGT	RGT_reward or quinine	RGT_reward probabilities	RGT_one session reward and time-out	RGT_reward or time-out
Original references	Bechara et al. (1994)	van den Bos et al. (2006)	Pais-Vieira et al. (2007)	Rivalan et al. (2009)	Zeeb et al. (2009)
Apparatus	Computerized card game	Manually operated maze	Manually/automated arena	Automated operant chamber	Automated operant chamber
No. of choice options	4	4	2	4	4
Reward	Monetary gain	Sucrose pellets	Sucrose pellets	Palatable food pellets	Sucrose pellets
Reward occurence	Each trial	Alternate with punishment	Alternate with punishment	Each trial	Alternate with punishment
Punishment	Monetary loss	Quinine pellets	No reward	Time-outs	Time-outs
Conflict immediate rewards	100 (A and B) vs. 50 (C and D)	3 (A) vs. 1 (B)	3 (A) vs. 1 (B)	2 (A and B) vs. 1 (C and D)	3;4 (A and B) vs. 1;2 (C and D)
Conflict long-term payoff	Per 10 cards −250 vs. +250	Per 10 trials 3 vs. 8 pellets ratio = 2.7	Per 10 trials 9 vs. 8 pellets ratio = 0.9	Total test: 60 vs. 300 pellets ratio = 5	Total test: 353 vs. 117 (average) ratio = 3
Task duration	Single session (100 trials)	10 daily sessions (10–20 trials)	Single session	Single session (1 h)	25 daily sessions for stability (approximately 100 trials per 30 min session)
Pre-training procedure	None	10-min habituation	20–25 days	5–7 days	10–15 days incl. 7 forced-choice sessions
Prior knowledge of contingencies	No	No	No	No	Yes
Motivational aspects	n/a	90–95% of FFW	80% of FFW	95% of FFW	85% of FFW

Values for the conflict long-term payoff are hypothetical calculations for RGT_one session reward or time-out and RGT_reward and time-out (based on a fixed trial duration of 9 or 5s, respectively). FFW, free-feeding weight.

1.6 Purpose

Although previous clinical studies have revealed that chronic pain negatively impacts cognitive processing, these studies fail to fully explain decision-making processes in gambling tasks (Pais-Vieria et al., 2009; Van de Bos et al., 2006; Van de Bos et al., 2014; de Visser et al, 2011). Thus, this limitation has presented the need for animal models to further explore underlying mechanisms behind gambling tasks (Potenza, 2009). Current animal models have investigated pain-induced cognitive deficits, but the research appears to be minimal and has not yet investigated how acute versus chronic inflammatory pain and analgesics influence decision-making processes (Van de Bos et al., 2006; Van de Bos et al., 2014; de Visser et al, 2011; Gi et al., 2010; Pais-Vieria et al., 2009; Pais-Vieira,et al, 2012). Therefore, the aim of this study is to elucidate the relationship between acute and chronic pain, analgesics, and decision-making. Based off of Apkarian et al. (2004) ideas that pain is a cognitive state and knowing that pain is a multi-dimensional phenomenon which includes affective-motivational aspects, we anticipate that acute and chronic pain will impair decision-making (Melzack & Casey, 1968). Even further, when pain is eliminated or reduced using an analgesic like morphine, decision-making processes should return to normal or similar to baseline testing within the RGT, regardless of the presence of acute or chronic pain.

Chapter 2

2.1 METHODS

2.1.1 Subjects

Forty-five Sprague Dawley rats (*n* = 10-12 per group) randomly chosen from the

University of Texas at Arlington vivarium were used in this study. Animals were single housed

and maintained on 12:12 dark/light cycle on a food-controlled diet until 85% of original weight

was achieved with unlimited water throughout the study. Animals were weighed daily and fed on

a variable time schedule to ensure reward-seeking behavior. All procedures were approved by

the University of Texas at Arlington Institutional Animal Care and Use Committee and in

accordance with the guidelines of the International Association for the Study of Pain.

2.1.2 Procedure

Animals were subjected to a baseline mechanical paw withdraw threshold (MPWT) to

assess the presence of tactile allodynia in the right and left hindpaws. If animals showed no

hypersensitivity, animals were trained to successfully lever press for sucrose pellet reward

distributed via a food hopper first for a single lever, then dual levers. RGT testing occurred once

daily for 30 minutes until animals successfully lever-press for 80% of trials for three consecutive

sessions. The three sessions were averaged and the average was used as a baseline

assessment. On the Day One, an acute inflammatory pain condition was be induced with a .05

mL of Complete Freund's Adjuvant (CFA) injection or saline into the left hindpaw and was

allowed to develop for 30 minutes. Animals were then given an injection of either 3 mg/kg of

morphine or saline and allowed to habituate for 30 minutes. Animals were then tested using the

RGT. Afterwards, animals were subjected to plethsymometer testing, MPWT, and PEAP testing.

On the tenth day (nine days after the Day One testing), animals were tested (Day Ten) again in

the RGT, 30 minutes after the drug/vehicle injection and again, subjected to plethysmometer, MPWT, and PEAP testing.

Thus, animals were randomly assigned to one of four of the following conditions: saline/saline, saline/morphine, CFA/saline, CFA/morphine. Experimental design is displayed in Figure 2.
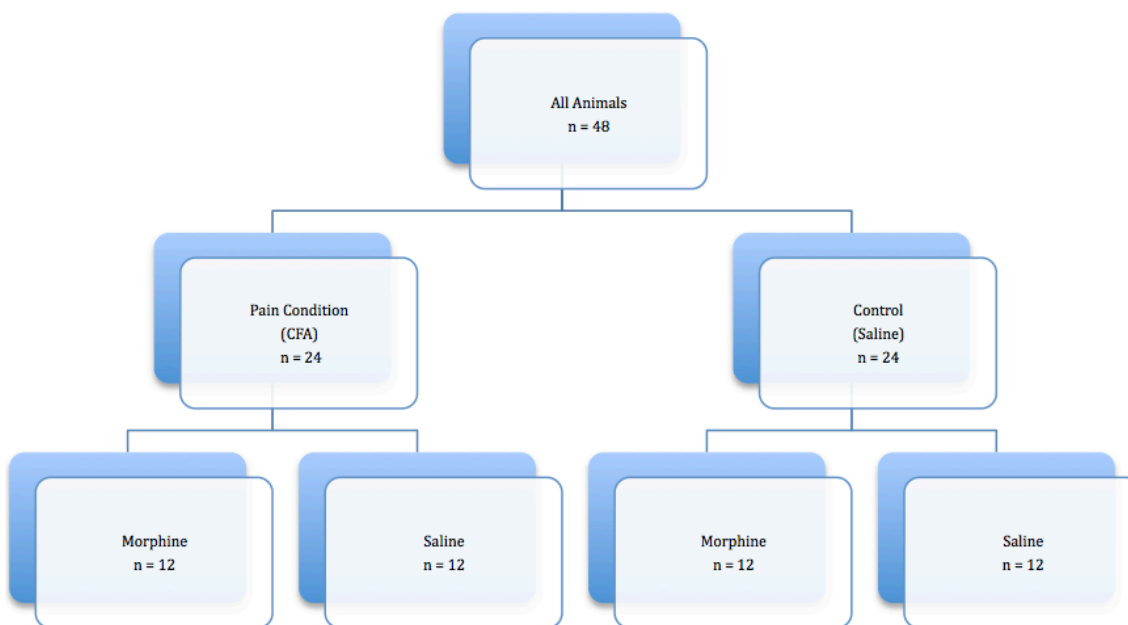
Figure 2-1: Experimental Design for the RGT

2.1.3 Mechanical Paw Withdrawal Testing (MPWT)

Animals were placed into Plexiglas chambers, placed atop a mesh screen in order to access the hind paws for tactile stimulation. Subjects were left to habituate for ten minutes. Tactile sensitivity was measured using the up/down method to the plantar portion of the hind paws using a set of von Frey monofilaments (3.85, 5.68, 9.74, 18.39, 39.42, 77.3, 135.3, and 251.34 mN). Each trial of testing began with the 9.74 mN von Frey filament delivered to the left

hind paw for approximately 1 second, then to the right paw, or vice versa depending on orientation of the animal. If no withdrawal response was observed (i.e. paw withdrawal or licking), the next highest force was used, whereas the next lowest force was delivered if a response was observed. This procedure was repeated until no response was made at the highest force (251.34 mN) or until five stimuli were administered in total. The 50% paw withdrawal threshold for each trial was calculated using the following formula: $[Xth]log = [vFr]log + ky$, where $[vFr]$ is the force of the last von Frey used, $k = 0.2593$ is the average interval (in log units) between the von Frey monofilaments, and y is a value that depends upon the pattern of withdrawal responses. If an animal did not respond to the highest von Frey monofilament (251.34 mN), then $y = 1.00$ and the 50% mechanical paw withdrawal response for that paw was calculated to be 456.63 mN. This test was conducted three times and the scores from each trial was averaged to determine the mean threshold to tactile stimulation for the right and left paws for each animal (Dixon, 1960).

MPWT testing occurred prior to training (baseline), after Day One (acute pain), and Day Ten testing (chronic pain).

2.1.4 Operant training

Animals were placed in standard Med Associates Inc. operant chambers and trained to press a single lever for one sucrose reward. Animals were randomly assigned to learn either the left or right lever first. Once animals were successfully trained to single lever-press, animals were trained with both levers until no more than 65% of lever presses were occurring at a single lever and animals had also achieved 80% of successful lever-presses or no more than 20% omissions. Animals varied on the number of days training, but had a minimum of six days before meeting criteria for Day One testing. Inclusion criteria to advance to the next phase of testing are described in Table 2.

Table 2-2: Criteria and Procedure for RGT

Table 2

Criteria and Procedure for RGT

Daily	Procedure	Inclusion Criteria
Weigh/Feed	Food-Controlled Diet	Training begins at 85% of free access weight
Weigh/Feed	Baseline MPWT	No sensitivity in hind paws
Weigh/Feed	Manual Training Phase 1 Right Shape (counterbalanced)	Must retrieve pellet from hopper
Weigh/Feed	Manual Training Phase 2 Right Train (counterbalanced)	Must achieve 80% of presses
Weigh/Feed	Automatic Training Right Train (counterbalanced)	Must achieve 80% of presses
Weigh/Feed	Dual Training	Must achieve 80% of presses 65% unbiased pressing
Weigh/Feed	RGT	Must achieve 3 session within the paradigm at 80% active trials (**Average of the 3 days serves as baseline for RGT testing**)
Weigh/Feed	**Day One** Baseline Plethysmometer Test	Baseline measures of normal paw volume
	Saline or CFA Injection	Randomly assigned
	Saline or Morhine Injection	Randomly assigned
	RGT Test Post Plethysmometer Test	Ensure effectiveness of CFA and ineffectiveness of saline for inflammation
	Test Day MPWT	Assess sensory components of pain in CFA and saline conditions
	PEAP Testing	Assess affetive components of pain in CFA and saline conditions
Weigh/Feed	**Day Ten** Morphine or Saline Injection	10 days post initial Day One testing Randomly assigned
	RGT Posttest Post Plethysmometer Test	Ensure effectiveness of CFA and ineffectiveness of saline for inflammation
	Test Day MPWT	Assess sensory components of pain in CFA
	PEAP Testing	Assess affetive components of pain in CFA and saline conditions

2.1.5 Unilateral Left Inflammatory Condition (CFA)

Once animals successfully reached criteria for Day One testing, animals were randomly assigned a subcutaneous injection to the plantar surface of the left hindpaw with either CFA or normal saline. A second MPWT was conducted after PEAP testing (described in 2.1.7) after the injection to ensure the effectiveness of the CFA inflammatory condition to induce mechanical hypersensitivity. A third MPWT was also conducted after PEAP testing on Day Ten testing day.

2.1.6 Operant RGT testing

Decision-making was assessed using the RGT once daily for 30-minutes. The test utilized both left and right lever bars in an operant chamber to measure preference for infrequent high amount of food with long next-trial wait and low long-term success compared to a more frequent, lower amount of food with short next-trial wait and high long-term gain. Thus, animals were presented with the opportunity to choose between 1 of the 3 following options in the Rat Iowa Gambling task (RIGT) (see Figure 2-2):

> Option 1: (best outcome) gives 2 pellets; 10s time out; .9 probability of obtaining reward; and 216 hypothetical max pellets
>
> Option 2: (worst outcome) gives 4 pellets; 40s time out; .4 probability of obtaining reward; and 96 hypothetical max pellets
>
> Option 3: Omit trial
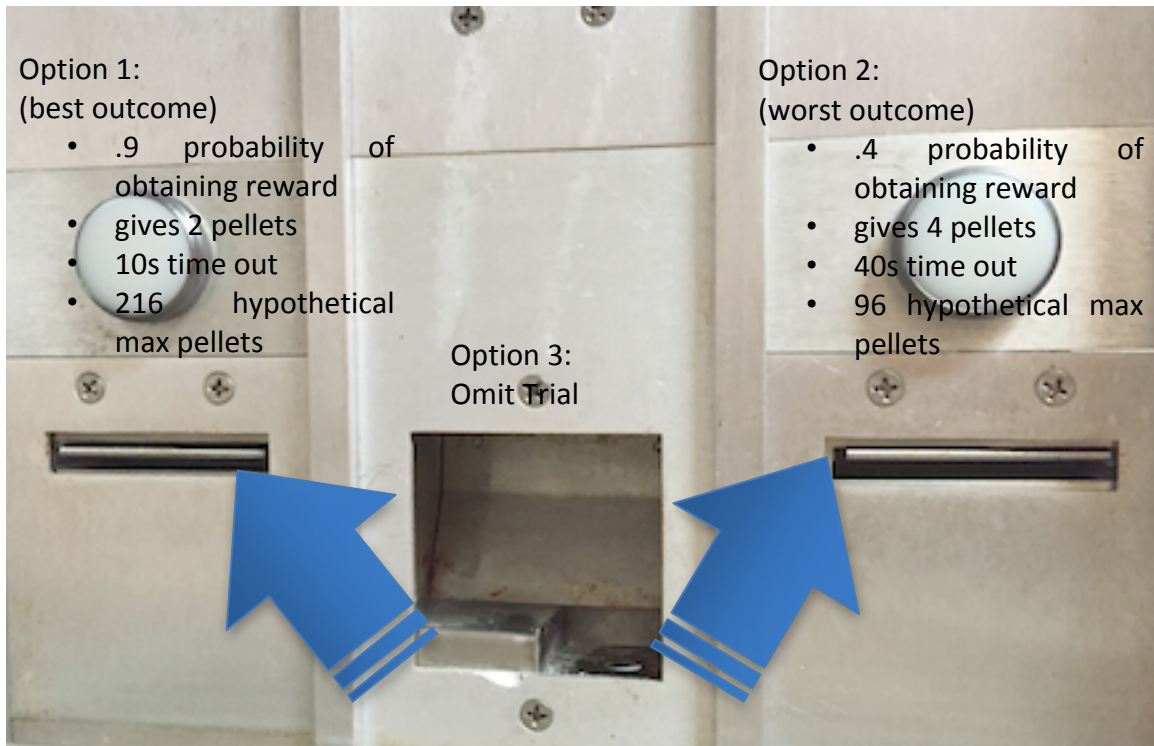
Figure 2-2: Lever set-up for RGT and three possible options

Options were presented on left or right levers depending on the randomization of the

lever training for the animal, where half received best option and the other half received the

worst option on the lever which training began. Percentage of trials yielding responses in each

option and omissions were recorded via MED-PC operant coding by Med Associates for at least

three training days (serves as baseline), Day One testing (acute pain), and Day Ten (10 days

post injection/chronic pain). Percent preference was calculated by using the number of lever

presses for the best option divided by the total number of lever-press responses where 1

indicated constant preference for the best option and 0 referred to preference for the worst

option. Percent omission was also assessed and was calculated using the number of omissions divided by total number of trials.

2.1.7 Place Escape Avoidance Paradigm (PEAP) Testing

PEAP testing occurred after placing subjects into a half light/half dark chamber (40.5 x 30.5 x 15.5 cm) atop raised wire mesh. During the 30 minute test, the plantar surfaces of the hind paws were stimulated every 15 seconds with a suprathreshold Von Frey filament (476mN of force). Stimulation was applied to the injected left hind paw while in the dark side of the chamber, which is inherently preferable to rats, while stimulation was applied to the right/unaffected, hind paw when in the light side of the chamber. Subjects indicated unpleasantness of a condition by spending more time in the light side of the chamber. The wire mesh platform and chamber were cleaned between test subjects to minimize scent cues and subjects were randomly assigned to placement of the light side of the chamber on either the right or left side of the mesh. Subjects that did not cross over to both sides of the chamber during the first 5 minutes were excluded. This occurred after RGT testing on both Day One and Day Ten.

Chapter 3

RESULTS

3.1 Paw Volume and Paw by Pain Condition

To assess the efficacy of CFA on paw volume for the left paw over baseline (three day average, Day One, and Day Ten testing times, a 2(pain condition) x 3(time) mixed-model repeated measures ANOVA was used. Data revealed there was a significant main effect of pain condition, $F(1, 43) = 21.043$, $p < .001$, suggesting higher paw volumes for CFA compared to saline animals. There was also a significant main effect of time, $F(2, 86) = 65.480$, $p < .001$,

suggesting paw volume was significantly higher on Day One and Day Ten test days compared to baseline testing. Main effects were qualified by a significant group by time interaction, $F(2, 86) = 67.940$, $p < .001$.

To ensure the inflammatory pain condition is isolated to the left side and did not affect the right paw, a 2(pain condition) x 3(time) mixed-model repeated measures ANOVA was used. There was no significant main effect of pain condition, $F(1, 43) = 1.749$, $p = .193$ or main effect of time, $F(2, 86) = 2.087$, $p = .130$ (data not shown). This suggests thresholds for the right paw were not affected by the unilateral pain condition.
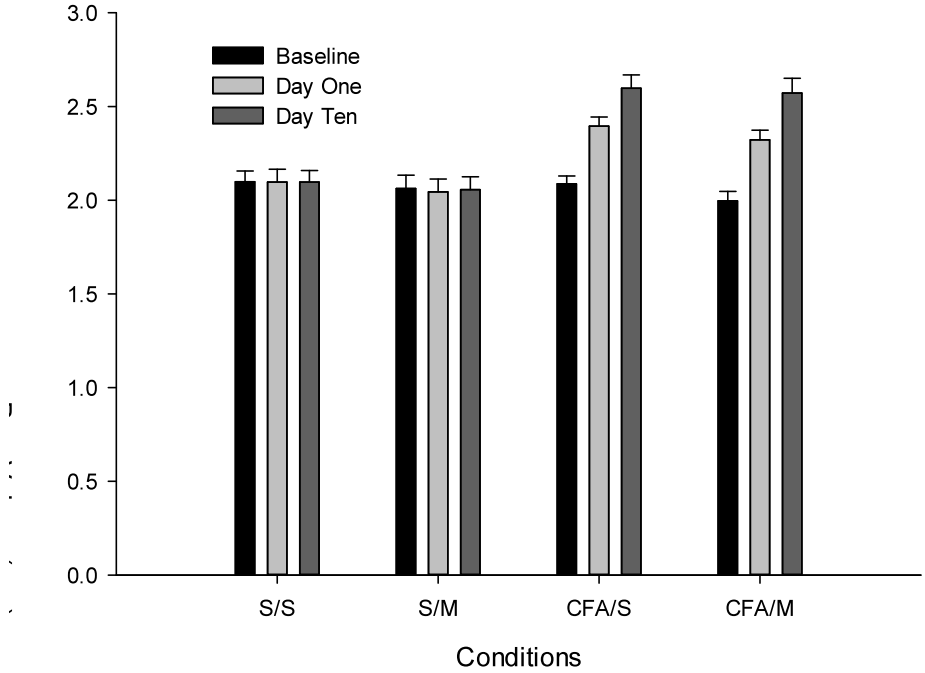

Figure 3-1: Paw volume across conditions for left hindpaw. As expected, there were increased paw volumes for the inflammatory condition, CFA, for all animals and increased across time.

3.2 Mechanical Paw Withdrawal Threshold (MPWT) and Paw by Pain Condition

To assess the efficacy of CFA on sensory pain using MPWT for the left paw over time, a 2(pain condition) x 3(time) mixed-model repeated measures ANOVA was used. Data revealed there was a significant main effect of pain condition, $F(1, 43) = 19.098$, $p < .001$, suggesting lower paw withdrawal thresholds for CFA animals compared to saline. There was also a significant main effect of time, $F(2, 86) = 613.264$, $p < .001$, such that paw withdrawal thresholds were significantly lower on Day One and Day Ten testing days compared to baseline testing. These main effects were qualified by a significant condition by time interaction, $F(2, 86) = 9.998$, $p < .001$.
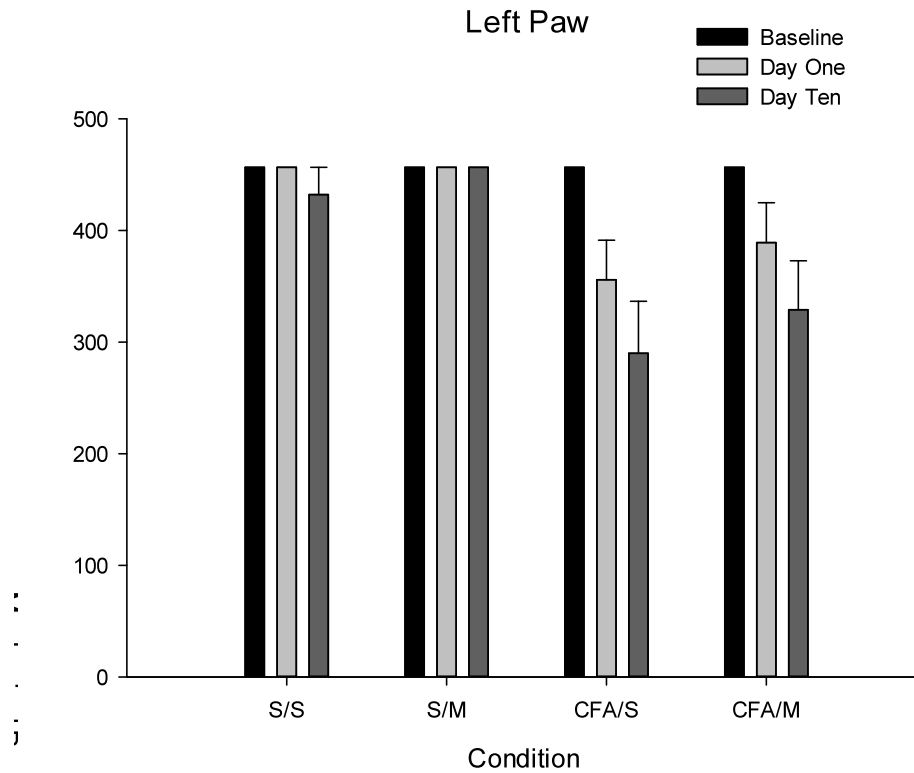
Figure 3-2: Mechanical paw withdrawal thresholds across conditions within the left hindpaw. As expected, the inflammatory condition, CFA, induced hypersensitivity and increased over time.

To ensure the inflammatory pain condition is isolated to the left side and did not affect the right paw, a 2(pain condition) x 3(time) mixed-model repeated measures ANOVA was used. As expected, there was not a significant main effect of pain condition, $F(1, 43) = .263$, $p = .611$ or main effect of time, $F(2, 86) = .616$, $p = .543$, suggesting thresholds for the right paw were not affected by the unilateral pain condition (data not shown).

3.3 Place Escape Avoidance Paradigm (PEAP) by Pain and Drug Conditions

A 2(pain condition) x 2(drug condition) x 3(time) mixed-model repeated measures ANOVA was used to assess pain affect via the use of avoidance measures denoted by amount of time spent on the light side of the chamber for Day One and Ten.

For Day One, there was significant main effect of pain condition, $F(1, 41) = 5.623$, $p = .023$, that revealed increased preference for the light side of the chamber for CFA (CFA/S and CFA/M) animals compared to saline (S/S and S/M). Unexpectedly, there was not a significant main effect of drug condition, $F(1, 41) = .514$, $p = .447$, suggesting that morphine did not change avoidance behavior. There was also no significant main effect of time, $F(5, 205) = 1.747$, $p = .125$.

For Day Ten, there was a significant main effect of pain condition, $F(1, 41) = 6.498$, $p = .015$, but no significant main effect of drug condition, $F(1, 41) = 2.158$, $p = .149$, or time, $F(5, 205) = .480$, $p = .791$.
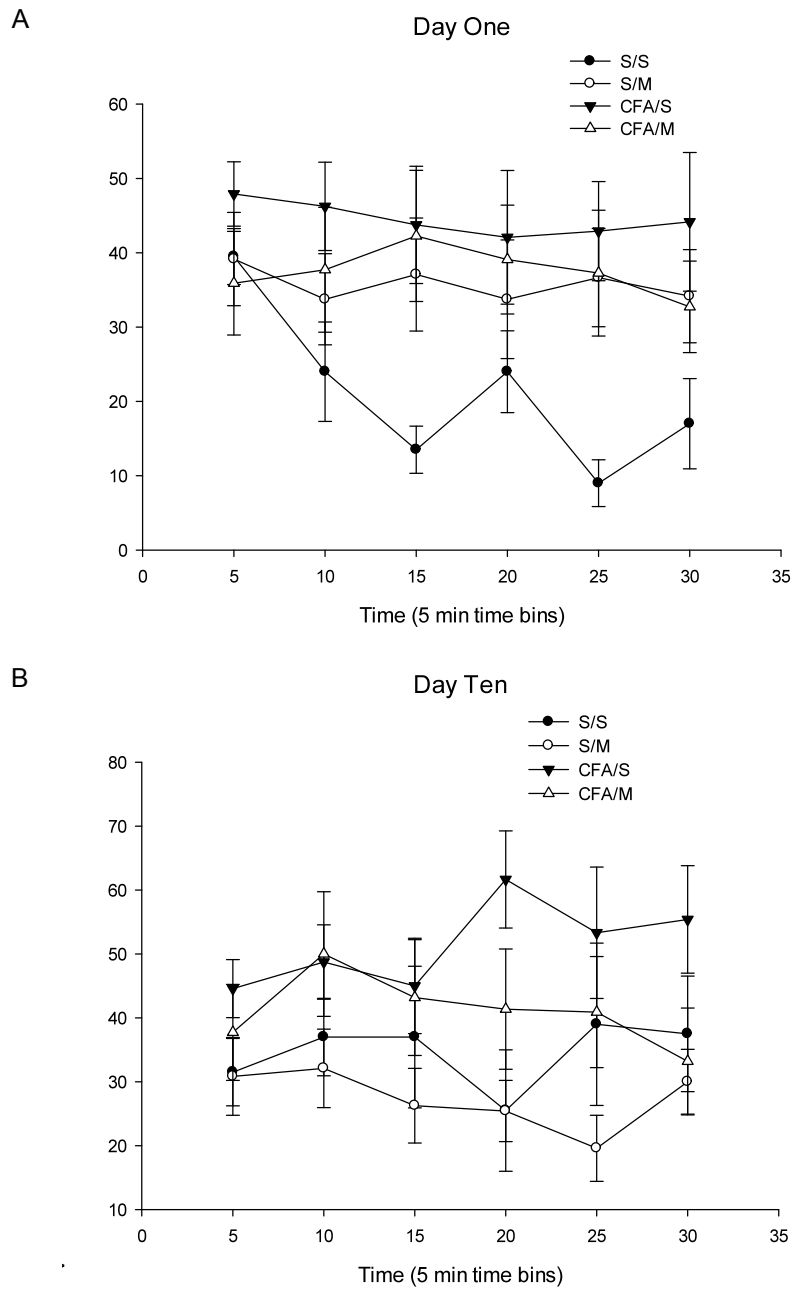
A — Day One

B — Day Ten

Figure 3-3: PEAP Testing: Amount of time spent on the light side of the chamber (i.e. avoidance behavior for (A) Day One and (B) Day Ten, where more time spent in the light side translated to more avoidance behavior) across time for each condition.

3.4 Percent Preference for Best Outcome by Condition

A 2(pain condition) x 2(drug condition) x 3(time) mixed-model repeated measures ANOVA was used to assess group differences in percent preference for best outcome across time. Unexpectedly, there was no significant main effect of pain condition, $F(1, 41) = .068$, $p = .795$, no significant main effect of drug condition, $F(1, 41) = 3.206$, $p = .081$. There was however, a significant main effect of time, $F(2, 82) = 3.258$, $p = .043$.
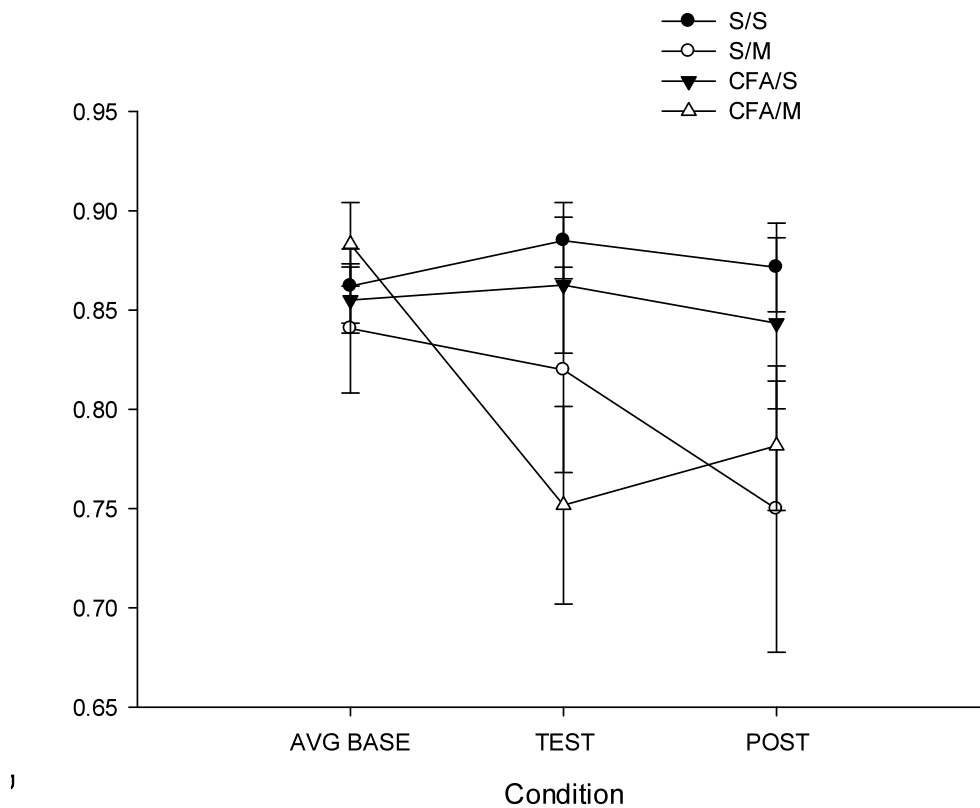
Figure 3-4: Percent choice across time where percent choice was calculated as the number of best choice lever presses divided by total lever press choices (best and worst total number of lever presses).

3.5 Percent Omitted by Condition

A 2(pain condition) x 2(drug condition) x 3(time) mixed-model repeated measures ANOVA was used to assess group differences in percent omitted for each session (baseline, Day One, Day Ten). Unexpectedly, there was no significant main effect of pain condition, $F(1, 41) = .881.$, $p = .353$. However, there was a significant main effect of drug condition, $F(1, 39) = 12.624$, $p = .001$, where morphine animals omitted significantly more than saline animals. There was also a significant main effect of time, $F(2, 82) = 8.263$, $p < .001$, where Day Ten animals omitted more than on Day One testing, while Day One testing omitted more than baseline average.
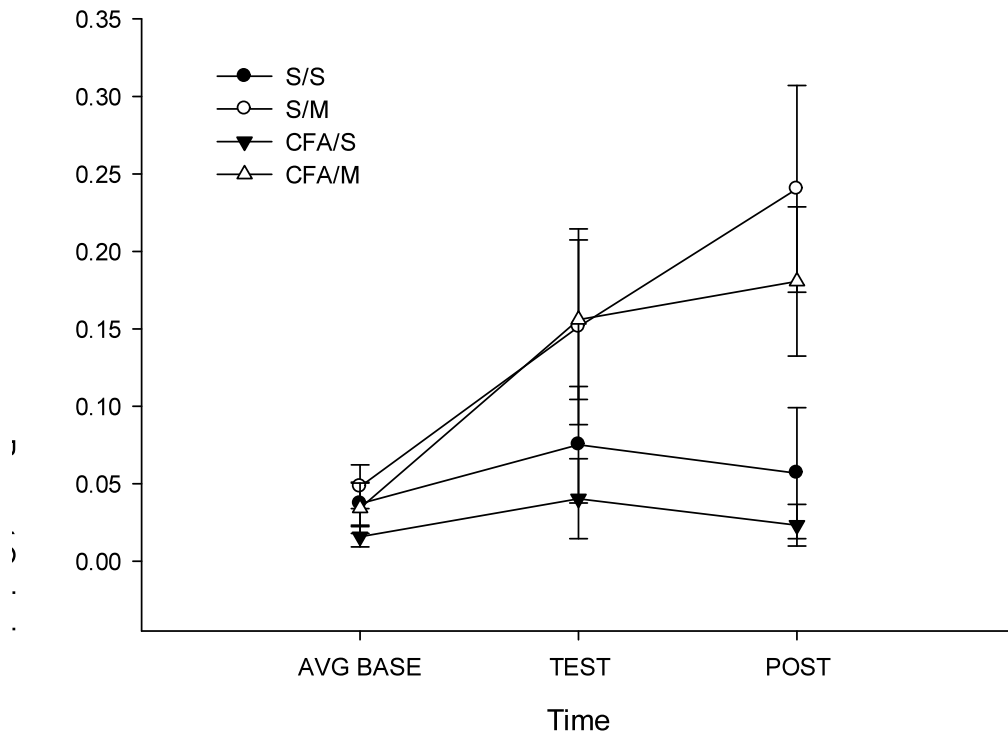

Figure 3-5: Percent omission across time, where percent omission was calculated as number of omissions divided by the total of combined score of best, worst, and omission amounts.

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Chapter 4

DISCUSSION

4.1 Study Summary

The purpose of this study was to examine the effect of pain on decision-making. Based on previous literature, it was first hypothesized that acute and chronic pain would similarly disrupt decision making such that CFA/Saline animals would perform worse on the RGT (i.e. choose the best option less and worst option more) compared to animals in the Saline/Saline, Saline/Morphine, or CFA/Morphine conditions. Unexpectedly however, results of this study revealed that pain was not associated with decision-making deficits. The lack of poor decision-making performance in the RGT indicates that the relationship between decision-making and pain is complex and suggests additional factors are critical in order to elicit poor or risky behaviors.

One of these potential factors, for example, might be the type of pain. Previous studies showing a significant increase in poor decision-making behavior utilized an invasive arthritic model within the knee joint (Pais-Viera et al., 2012). However, in the current study, the pain model involved a CFA-induced inflammatory condition localized to the left hindpaw. Since the inflammatory condition was isolated to the plantar surface of the paw, rather than the knee joint, it may be less intense and as a result, cognitive processes might be differentially altered (Apkarian et al, 2004; Pais-Vieira et al, 2009; Ji et al, 2010; Pais-Vieira et al, 2012; Verdejo-García et al, 2009). Nonetheless, CFA did cause significant enlargement of left paw volume (i.e. inflammation) and a significant increase in avoidance behavior in the PEAP, with slightly significant enhancement of mechanical allodynia. This lack of more pronounced hypersensitivity may reflect a loss of physiological function of the nerve endings within the hindpaw due to a robust inflammatory response and tissue damage from CFA (Cao et al., 1998; Smith-Edwards et

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al., 2016). Due to this possible confound, future studies should utilize inflammatory conditions that will result in both significant enlargement in paw volume and hyperanalgesia without the possibility of damage or disruption of normal pain physiological function.

We also hypothesized that the administration of an analgesic would restore cognitive processes and decision-making to levels prior to the onset of pain and in pain-free animals. However, our results revealed that morphine caused a slight decrease in decision-making behavior compared to saline groups suggesting that morphine itself causes cognitive disruption. This was quite surprising given that Boyette-Davis, Thomson, & Fuchs (2008) reported an increase in attentional mechanisms with the use of low dose of morphine (3 mg/kg) compared to high (6mg/kg) and no drug animals. It is possible that morphine alters different aspects of cognition with a slight impairment on decision-making within a positive impact on attention. Future studies could incorporate other doses and possibly, other analgesics to assess when and if decision-making is altered.

Morphine was also associated with increase omissions of the RGT, which increased across from Day One to Day Ten. This finding might reflect a frustration effect (Stout, Boughner, Papini, 2003). For morphine treated animals, the morphine "reinforcement" was greater reward than the food reinforcement so that morphine animals reduced their responses and increased omissions, regardless of pain condition. However, saline animals had no reward value from the "drug" so lever-press responses were increased while omissions decreased in order to pursue reward fulfilment. As a result, we observed a greater response in lever-presses after non-reinforcement (saline) than reinforcement (morphine). Thus, future studies should be designed to solve this potential confound between levels of cognition within the RGT and learn to tease out different components of cognition in order to unveil effects of pain and cognition.

4.2 Conclusion

Pain is a complex, unpleasant sensory and emotional experience and serves in both an advantageous and disadvantageous role, when either acute or chronic, respectively (Merskey & Bogduk, 1994). Because of its diverse nature, pain is also remains to be the most common experience that affects Americans, surpassing diabetes, heart disease, and cancer combined ("Yesterday, Today & Tomorrow: NIH Research Timelines", 2013). Yet, despite the current knowledge of pain, it is apparent there remains the need for it to be studied extensively. As previously mentioned, pain is costly and will only grow larger than the already estimated half a trillion dollars annually due to lost wages and healthcare costs (Gregory et al., 2013). In addition, possible emotional and cognitive responses may result from the trauma of pain, adding as a strong possibility for decreased quality of life (Gatchel et al., 2007).

The ambiguity of pain, however, lies within its complex and subjective qualities, which is difficult to quantify effectively due to differences across individuals. Furthermore, "to consider only one component of pain… is to look at only part of the problem" and so the multidimensionality of pain must also be considered (Casey & Melzack, 1968). Pain research has looked primarily at the sensory component of pain, but as the importance of the multi-modality surfaced, research on pain affect and cognition increased greatly and must continue in order to address pain as a whole.

Thus the significance of the cognitive component of pain becomes apparent when looking at the impairment of decision-making in response to pain. The cognitive-evaluative component of pain reflects the way pain stimulus information is processed and then conveyed into a response or output. These responses, or outputs, must be determined via decision-making, which is a construct under the umbrella of both the cognitive-evaluative component of both pain and cognition (Melzack & Casey, 1968). Decisions are used constantly in life. Similarly to pain, decisions can be advantageous and disadvantageous. Good decisions are needed for

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the advancement of the individual in means of reproduction and survival, whereas bad or risky decisions may instead hinder that chance of survival (Bechara et al. 1994; Bechara, Damasio, & Damasio, 2003).

In means to quantify the cognitive-evaluative and the effect of pain on decision-making, paradigms, such as the IGT and the RGT, have been designed (Apkarian et al. 2004; Bechara, 2004; Bechara & Damasio, 2005; Bechara, Damasio, & Damasio, 2003, Bechara et al. 1994, van den Bos et al. 2006; Pais-Viera et al., 2009; Pais-Viera et al., 2012; Rivalan et al. 2009; Potenza, 2009; Zeeb et al., 2009; Zeeb & Winstanley, 2011). These tasks assess real-life decision-making and gauge the likelihood of poor or risky decision-making behavior. Current preclinical and clinical trends in respect to chronic pain patients show a decrease in good decisions and an increase in poor or risky behaviors, similar to individuals with brain damage to certain areas that govern higher order cognitive abilities, as well as, gambling and drug addicts (Apkarian et al. 2004; Bechara, 2004; Bechara & Damasio, 2005; Bechara, Damasio, & Damasio, 2003, Bechara et al. 1994). Yet these cognitive responses to pain have been studied briefly despite the overwhelming need to understand this relationship for the millions of pain sufferers. In addition, the effects of drugs on pain for decision-making, along with the effects of acute pain have never been assessed regardless of numerous Americans using opiates as pain relief, which often leads to addiction and major cause for the current overdosing epidemic (Manchikanti et al., 2012).

Therefore, this type of paradigm is imperative for relaying over how decision-making can occur especially in humans and how they may respond cognitively in both chronic and acute pain conditions. Although the current study revealed conflicting data in comparison to previous literature, it did provide suggestions that possible quantity and/or quality of pain and the amount of analgesics are important factors within the RGT that can significantly alter outcomes of decision-making. Future studies should include further validation of the RGT in acute pain

paradigms and further assess the differences between acute and chronic pathways as well as determine the effect of morphine on decision-making deficiencies. The need to examine the neural underpinnings is also paramount so that acute pain pathways may be explicated for eventual relief in acute pain populations.

Appendix A

Med PC Notation for Novel Rodent Gambling Task

```
\Dual lever
\Written by C. Salcido/J. Beyor (Med Associates)




\ INPUTS
^LeftLever = 7
^RightLever = 6




\ OUTPUTS
^LeftLever = 7
^RightLever = 6
^Dispenser  = 8
^LeftLight = 10
^RightLight  = 9
^HouseLight = 12




\ CONSTANTS



\ A() = Control Variables with Assigned Aliases as Defined
Var_Alias Session Time (min)                = A(0)  \ Default = 30
Var_Alias Right Lever Reward (# of pellets)     = A(1)  \ Default = 4
Var_Alias Left Lever Reward (# of pellets)      = A(2)  \ Default = 1
Var_Alias Right Lever Time Out (sec)          = A(3)  \ Default = 40
Var_Alias Left Lever Time Out (sec)          = A(4)  \ Default = 5
Var_Alias Time to respond (sec)          = A(5)  \ Default = 10
Var_Alias Omission Time Out (sec)           = A(6)  \ Default = 10



^Session  = 0
^RLR     = 1
^LLR     = 2
^RLTO    = 3
^LLTO    = 4
^TTR     = 5
^OTO     = 6
```

```
\ B = Trial by Trial data
\ B(E)   = Trial number
\ B(E+1) = Left Lever Presses
\ B(E+2) = Right Lever Presses
\ B(E+3) = Rewards
\ B(E+4) = Omissions




\ C(I) = Left Lever Latency
\ D(O) = Right Lever Latency



\ F = Reward counter
\ G = Total Rewards
\ H = Total Omissions
\ J = Trials
\ L = Total Left Lever presses
\ R = Total Right lever presses
\ S = Session Time
\ T = Latency Timer
\ X = List #



LIST Y = 1,1,1,1,1,1,1,1,1,2
LIST Z = 1,1,1,1,2,2,2,2,2,2



DIM A = 6
DIM B = 10000
DIM C = 10000
DIM D = 10000




DISKVARS = A,B,C,D,G,H,J,L,R,S



\*************************************************
\               DEFAULTS
```

```
\*************************************************


S.S.1,
S1,
 0.01": SET A(^Session) = 30, A(^RLR) = 2, A(^LLR) = 4, A(^RLTO) = 10, A(^LLTO) =
40;
     SET A(^TTR) = 10, A(^OTO) = 10;
     SET B(E) = -987.987;
     SET C(I) = -987.987;
     SET D(0) = -987.987 ---> S2




S2,    \ First Statement: Wait for START signal, turn HouseLight and
       \ associated stimulus ON.
       \
       \ Second Statement: Update screen display with default values
       \ for Control Variables.  This will show any changes made via
       \ the "Configure | Change Variables" Window prior to START.
  #START: CLEAR 1,200 ---> S3
  1": SHOW 1,Session,A(^Session), 2,RL Rewards,A(^RLR), 3,LL Rewards,A(^LLR);
     SHOW 4,RL Time Out,A(^RLTO), 5,LL Time Out,A(^LLTO), 6,Respond
Time,A(^TTR), 7,Omission TO,A(^OTO)---> SX




S3,    \ Time Session Length
  0.01": SET S = S + 0.01; SHOW 1,Session,S ---> SX
  #Z32: ---> S4




S4,    \ Wait for Screen Update and end with
       \ STOPABORTFLUSH for Automatic Data Saving
  2": ---> STOPABORTFLUSH






\*************************************************
\              MAIN PROGRAM
\*************************************************
S.S.2,
S1,
  #START: SET A(^RLTO) = A(^RLTO) * 1", A(^LLTO) = A(^LLTO) * 1";
       SET A(^TTR) = A(^TTR) * 1", A(^OTO) = A(^OTO) * 1" ---> S2
```

S2,
 0.01": ON ^HouseLight, ^LeftLight, ^RightLight, ^LeftLever, ^RightLever;
 ADD J; SET B(E) = 0, B(E+5) = -987.987, B(E) = J; Z4 ---> S3

S3,
 A(^TTR)#T: OFF ^HouseLight, ^LeftLight, ^RightLight, ^LeftLever, ^RightLever; ADD
B(E+4), H; Z3 ---> S4
 #R^LeftLever: OFF ^LeftLight, ^RightLight, ^LeftLever, ^RightLever; ADD B(E+1), L; Z1
---> S5
 #R^RightLever: OFF ^LeftLight, ^RightLight, ^LeftLever, ^RightLever; ADD B(E+2), R;
Z2 ---> S7

S4,
 A(^OTO)#T: IF S/60 >= A(^Session) [@T, @F]
        @T: Z32; ---> S1
        @F: SET E = E + 5 ---> S2

S5,
 #Z5 ---> S6
 #Z7 ---> S2

S6,
 A(.01")#T: IF S/60 >= A(^Session) [@T, @F]
        @T: Z32; ---> S1
        @F: SET E = E + 5 ---> S2

S7,
 #Z6 ---> S8
 #Z8 ---> S2
S8,
 A(.01")#T: IF S/60 >= A(^Session) [@T, @F]
        @T: Z32; ---> S1
        @F: SET E = E + 5 ---> S2

```
\*************************************************
\            Lever Rewards
\*************************************************
S.S.3,
S1,
 #START: ---> S2



S2,
 #Z1: RANDD X = Z; IF X =1 [@T, @F]
              @T: ON ^Dispenser; ADD F, G, Z7 ---> S3 \ LEFTLEVER
              @F: Z5 ---> S2
 #Z2: RANDD X = Y; IF X =1 [@T, @F]
              @T:ON ^Dispenser; ADD F, G, Z8---> S5 \ RIGHTLEVER
              @F: Z6 ---> S2



S3,
 0.05": OFF ^Dispenser;
     IF F >= A(^LLR) [@Done, @More]
       @Done: SET B(E+3) = F, F = 0 ---> S2
       @More: ---> S4



S4,
 0.5": ON ^Dispenser; ADD F, G ---> S3



S5,
 0.05": OFF ^Dispenser;
     IF F >= A(^RLR) [@Done, @More]
       @Done: SET B(E+3) = F, F = 0 ---> S2
       @More: ---> S6



S6,
 0.5": ON ^Dispenser; ADD F, G ---> S5




\*************************************************
```

```
\          Latency Timer
\**************************************************
S.S.4,
S1,
  #START: ---> S2




S2,
  #Z4: SET T = 0 ---> S3




S3,
  #R^LeftLever: SET C(I) = T, C(I+1) = -987.987; ADD I ---> S2
  #R^RightLever: SET D(O) = T, D(O+1) = -987.987; ADD O ---> S2
  #Z3: ---> S2
  0.01": SET T = T + 0.01 ---> SX




\**************************************************
\          Display Update
\**************************************************
S.S.5,
S1,
  #START: ---> S2




S2,
  .01": SHOW 2,LeftL Presses,L, 3,RightL Presses,R, 4,Rewards,G, 5,Omissions,H,
6,Trial #,J ---> SX
```

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